Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part I

Introduction to Series, Methods, and Tolterodine vs. Oxybutynin Systematic Review

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Abbreviations/Glossary

ADL	activities of daily living
AE	adverse event
CDR	Common Drug Review
CI	confidence intervals
CR	controlled release
d	day
DARI	darifenacin
DB	double blind
ER	extended release
FESO	fesoterodine
h	hours
IR	immediate release
IIQ	Incontinence Impact Questionnaire
ITT	intention-to-treat
LOCF	last observation carried forward
M	muscarinic
MD	mean difference
MCID	minimal clinically important difference
NRS	non-randomized studies
NDA	new drug approval (U.S. FDA)
OAB	overactive bladder syndrome
OXY	oxybutynin
PP	per protocol
PPBC	Patient perception of bladder condition
PSD	Pharmaceuticals Service Division
PSUR	Periodic Safety Update Report
QoL	quality of life
RCT	randomized, controlled trial
RR	relative risk
SAE	serious adverse events
SD	standard deviation
SOL	solifenacin
TDS	transdermal system
TOL	tolterodine
TROS	trospium
UDI	Urogenital Distress Inventory
UTI	urinary tract infection
UI	urinary incontinence
UUI	urge urinary incontinence
WDAE	withdrawals due to adverse events

Glossary

Term	Definition
Continence	Absence of any involuntary leakage of urine, usually measured over a 3 day or 7 day period of time (as recorded in a bladder diary)
Cystometry	Measurement of the pressure/volume relationship of the bladder during filling and/or pressure flow study during voiding.
Detrusor	Bladder smooth muscle that contracts on voiding and relaxes upon filling of the bladder
Detrusor overactivity	Involuntary detrusor contractions during filling cystometry (normally, there is little or no change in detrusor pressure and no involuntary phasic contractions) i.e., a diagnosis made by urodynamics. May or may not be accompanied by symptoms (e.g., urgency or urgency incontinence).
Idiopathic detrusor overactivity	Detrusor overactivity with no known neurogenic cause.
Lower urinary tract symptoms (LUTS)	Includes urinary storage symptoms and voiding symptoms
Mixed urinary incontinence	Incontinence associated with urgency, and also with effort or physical exertion or on sneezing or coughing
Neurogenic detrusor activity	Detrusor overactivity and evidence of a relevant neurological cause.
Nocturia	Waking at night to void
Overactive bladder syndrome	Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection or other obvious pathology
Post-void residual volume	Volume remaining in bladder immediately after voiding
Stress urinary incontinence	Involuntary loss of urine on effort or physical exertion (or on sneezing or coughing)
Urgency	A sudden compelling desire to pass urine, which is difficult to defer
Urge or urgency incontinence	Involuntary loss of urine associated with urgency; 'Urgency' has recently replaced 'urge' as the accepted terminology to distinguish urgency associated with OAB, which is maximal and episodic, from normal urge (Haylen 2010; Chapple 2005)
Urge or Urgency predominant mixed urinary incontinence	Mixed urinary incontinence with predominant, more frequent symptoms of urgency urinary incontinence
Urinary incontinence	Involuntary loss of urine
Urodynamics	Functional study of the lower urinary tract; Usually involves free (no catheter) uroflowmetry and postvoid residual urine volume measurement prior to filling and voiding (with catheter) cystometry.

Overview Executive Summary

Antimuscarinic Drugs for Overactive Bladder Syndrome

Introduction

Pharmaceutical Services Division requested a review of the antimuscarinic drug class for the treatment of overactive bladder syndrome (OAB) as part of the Clinical Evidence Review Program. Currently, oxybutynin immediate release (IR) is the only drug in this class that is a regular benefit of PharmaCare for the treatment of OAB.

The primary objective of the clinical review series is to analyze the comparative effectiveness (harms and benefits) of antimuscarinic drugs to determine if any drug has a therapeutic advantage over oxybutynin IR, or each other, for the treatment of OAB. Additional objectives are to assess the comparative effects of these drugs on cognition, particularly in the elderly, and to determine whether there is new evidence available since the Common Drug Review (CDR) for drugs that have undergone the CDR process.

Background

Condition: Overactive bladder syndrome is defined as urgency with or without urgency incontinence, usually accompanied by frequency (increased daily number of voids) and nocturia (waking up at night to void) (Abrams 2002). The syndrome is a diagnosis of exclusion and does not imply a specific etiology. The traditional view of OAB has focused on overactivity of the detrusor muscle, the bladder smooth muscle that controls urination. However, urodynamic findings of detrusor overactivity are not necessarily associated with symptoms, and individuals who have symptoms may not have urodynamically confirmed evidence of detrusor overactivity.

Standardization of International Continence Society (ICS) terminology in 2002 greatly expanded the numbers of people identified as having OAB, and shifted emphasis from urgency incontinence to the symptom of urgency (Abrams 2002, Haylen 2010). Based on a systematic review of 15 mainly industry-sponsored studies, an estimated 15% of women met OAB criteria, 8% with urgency incontinence (Hartmann 2009). Prevalence increases with age but the influence of age on urgency incontinence is not as strong as it is on OAB overall (Hartmann 2009). Prevalence rates in a recent independently conducted study are lower than the rates reported in industry-sponsored literature (Tikkinnen 2012). The age-standardized prevalence, obtained by survey of a random sample of the Finnish population aged 18-79, is 6.5% in men and 9.3% in women (Tikkinnen 2012). In this study, 0.7% of men and 2.4% of women had OAB with urgency incontinence.

Treatment goals are to reduce symptoms that lead to distress and interfere with quality of life. Urgency incontinence affects quality of life to a greater extent than urgency or frequency alone and resolution or reduction of incontinence remains a key treatment aim. Non-pharmaceutical options exist and should be tried before considering drug treatment. These include reducing caffeinated drinks, control of fluid intake, weight loss, and bladder training. Pharmacological therapy includes antimuscarinic drugs and the recently approved beta-adrenoceptor agonist mirabegron. Intravesical botulinum toxin has also been used.

Antimuscarinic drugs: Antimuscarinic drugs bind to muscarinic receptors and prevent the action of acetylcholine in contracting the detrusor smooth muscle in the bladder. Acetylcholine-mediated signals to the brain, which result in impulses to initiate voiding, are also inhibited. There are five subtypes of muscarinic receptors that are widely distributed throughout the body and available antimuscarinic drugs bind to all receptor subtypes. The M3 receptor is thought to be the key target in the bladder although other receptors are also present in the detrusor muscle and other bladder structures.

The following antimuscarinic drugs and formulations are being considered in this review:

- Oxybutynin IR (Ditropan), oxybutynin ER (Ditropan XL®), oxybutynin CR (Uromax®), oxybutynin transdermal (Oxytrol™), oxybutynin gel (Gelnique™)
- Tolterodine IR (Detrol™), tolterodine ER (Detrol LA™)
- Trospium IR (Trosec®)
- Darifenacin (Enablex®)
- Solifenacin (Vesicare®)
- Fesoterodine (Toviaz®)

Overview of efficacy - drug class

All antimuscarinic drugs have modest efficacy when compared with placebo. This is reflected in outcomes of a Cochrane systematic review pooling trials across all drugs in the class (Nabi 2006) and a systematic review pooling placebo effects (Lee 2009).

- 42% of participants reported improvement or cure with placebo; an additional 15% reported improvement or cure with active drug (Nabi 2006);
- Incontinence episodes were reduced by an average of 1.2 episodes per 24 hours on placebo (Lee 2009); an additional 0.5 episodes per 24 hours occurred with active drug (Nabi 2006);
- Micturition frequency was reduced by around 1.3 episodes per 24 hours on placebo (Lee 2009) and an additional mean of 0.7 episodes per 24 hours with active drug (Nabi 2006).

A more recent systematic review has confirmed that improvement over placebo is modest, corresponding to an absolute risk difference of < 20% across drugs (Shamliyan 2012).

In RCTs, patients on antimuscarinic drugs have three times the rate of dry mouth and two to three times the rate of constipation as patients on placebo (Meek 2011; Nabi 2006). This translates to an average of around one in five additional patients experiencing dry mouth (31% on OAB antimuscarinics vs. 10% on placebo) and around an extra one in 20 experiencing constipation (9% on OAB antimuscarinics vs. 4% on placebo). There were differences by drug in the proportion of patients with dry mouth in placebo-controlled trials, with the highest rates observed for oxybutynin IR, and large differences between trials for individual drugs, with the highest rates in trials with active data collection (e.g. where patients were asked if they had specific AE). These and other effects such as blurred vision and central nervous system effects are associated with the anticholinergic properties of the drugs. Because all the available antimuscarinic drugs have dose-limiting adverse effects related to their anticholinergic activity, the only definitive way to distinguish the drugs in terms of benefits and harms is to conduct well-designed and adequately powered head-to-head direct comparator trials that include an appropriate harms evaluation framework.

Research questions addressed in this review

The aim of this drug class systematic review is to analyze the comparative effectiveness (harms and benefits) of antimuscarinic drugs available in BC, to determine if any drug has a therapeutic advantage over oxybutynin IR or each other for the treatment of OAB. The drugs under review are: Oxybutynin IR; Oxybutynin transdermal patch (Oxytrol™); Oxybutynin gel (Gelnique™); Oxybutynin ER or CR (Ditropan XL®; Uromax®); Tolterodine (Detrol™, Detrol LA™); Trospium (Trosec™); Darifenacin (Enablex™); Solifenacin (Vesicare®); and Fesoterodine (Toviaz®). Three specific questions were addressed:

Q1. In adults, including the frail elderly, do the antimuscarinic drugs under review provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) and to each other, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz*) or oxybutynin gel (Gelnique) provide improved clinically relevant outcomes or a better safety profile compared to oxybutynin IR?

Q3. In adults, particularly the elderly, does trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz®), oxybutynin gel (Gelnique™), oxybutynin transdermal patch (Oxytrol™) or other formulations of oxybutynin have less effect on cognition when compared to oxybutynin IR or to each other?

Methods

We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included as supplemental information on harms if they exclusively enrolled elderly populations or assessed cognition. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities. We included controlled and uncontrolled cohort analyses of ≥ 12 weeks' duration with samples >1000, case-control studies, case series, and case reports.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all cause mortality and serious adverse events including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth, constipation, urinary retention and cognitive effects were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Subgroup analyses were also conducted to explore heterogeneity if enough studies were included to all for this. All

meta-analyses were carried out using the Review Manager Computer Program (RevMan) version 5.2 (Review Manager 2012).

Risk of bias for RCTs was assessed according to standardized Cochrane Risk of Bias criteria and helped to inform conclusions. These criteria were developed based on evidence of influence on study outcomes. (Higgins 2011) RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included evaluation of techniques used to reduce confounding, patient and control selection criteria, blinding of outcome assessment, and completeness of follow-up and reporting.

RCT data were combined for each outcome if clinical populations, interventions, outcome assessment, and study methodology, were deemed sufficiently similar to warrant pooling. For continuous data, the summary outcome measure is the mean difference (MD), using an inverse variance fixed effects model. Standardized mean difference was used where appropriate. Dichotomous data are presented as risk ratios and risk differences, using a Mantel-Haenszel fixed effects model. If statistical heterogeneity was present, a random effects model was used instead. Sensitivity analyses were conducted to determine the robustness of the results in the presence or absence of poorer quality studies.

If direct comparator trials with oxybutynin IR were not available, the feasibility and appropriateness of use of indirect comparisons within a network meta-analysis were assessed, with a view to ensuring that network meta-analysis could provide reliable comparisons. This took into account the extent of similarity of patient populations between trials, interventions (including dose equivalence), the magnitude of change from baseline on placebo, trial quality/ risk of bias, and assessed outcomes. If the degree of heterogeneity and/or proportion of trials at high risk of bias precluded network meta-analysis, summary narrative analysis based on tabulation of results of direct comparisons was used to draw overall conclusions.

A qualitative synthesis was conducted on non-randomized studies to supplement RCT data, including an assessment of whether such evidence was consistent with the available RCT data, and the most important additional signals on infrequent harmful effects and effects in the elderly. Priority was given to controlled cohort analyses and case-control studies over uncontrolled cohort analyses, case series and case reports, as the latter can only provide exploratory signals of effect.

Results

Database searches identified 2362 unique records for the review series across all drugs, which were screened at the title/abstract level. Full text versions were obtained for 621 potentially relevant articles, which were further assessed for eligibility. A PRISMA flowchart detailing the flow of primary empirical studies for this review is provided on page 84.

In total, there are 41 comparative RCTs for all drug-drug comparisons considered in this review, 27 of which were comparisons between oxybutynin IR and other formulations of oxybutynin, tolterodine (IR or ER), darifenacin, solifenacin, or trospium (IR). Table 1 provides a summary overview of the available trials. With the exception of one trial comparing darifenacin with solifenacin, all other trials included either oxybutynin or tolterodine as a comparator.

Table 1. Number of RCTs for each pairwise comparison

Drug	Oxy IR	Oxy ER or CR	Oxy TDS	Oxy Gel	Tol IR	Tol ER	Feso	Dari ER	Soli	Tros IR	Total
Oxy IR	X	5	1	1[a]	10	1	0	2	1 + 2[a]	2 + 2[a]	**27**
Oxy ER		X			1	1		1[a]			**3**
Oxy TDS			X			1					**1**
Oxy Gel				X							**0**
Tol IR					X	1			3		**4**
Tol ER						X	3		2		**5**
Feso							X				**0**
Dari CR								X	1		**1**
Soli									X		
Trospium IR										X	
Total		5	1	1	11	4	3	3	9	4	**41**

[a] elderly volunteers, outcome cognition; CR= controlled release; dari= darifenacin; ER= extended release; feso=fesoterodine; IR=immediate release; oxy= oxybutynin; soli= solifenacin; tol= tolterodine; tros= trospium; TDS= transdermal system
Table does not include placebo RCTs that were included in this review in the absence of direct comparator RCTs.

For further information on harms, 13 additional trials are included. These were placebo-controlled RCTs that exclusively enrolled the elderly, or RCTs that specifically assessed cognition but were either placebo-controlled or direct comparator trials that involved a formulation that was not included in this review (trospium ER) (Pfizer Protocol A0221049; Pfizer NCT0041137; Allergan NCT01178827; Sand 2010; Wagg 2013a; Kay 2012; Lackner 2008; Chapple 2007; Kay 2006; Lipton 2005; Diefenbach 2005; Katz 1998; Herberg 1997).

A total of 33 non-randomized studies (study design other than case reports) were included:

- 4 controlled cohort analyses (Gomes 2011; Jumadilova 2006; Moga 2013; Sink 2008);
- 23 uncontrolled cohort analyses (Abrams 2001; Amarenco 1998; Appell 2001; CONTROL 2012; Diokno 2002; Elinoff 2006; Garely 2006; Geller 2012; Haab 2005; Haab 2006; Isik 2009; Kreder 2002; Layton 2001; Michel 2002; Michel 2005; Michel 2008; Movig 2001; Newman 2008; Sand 2012; Schneider 2010; Staskin 2010; Wagg 2013b; Zinner 2011);
- 2 uncontrolled before-after studies (Hussain 1996; Monnot 2012); and
- 4 case series (Alzayer 2010; Gish 2009; Jonville 1992; 't Veld 1998).

A total of 15 case reports (1 to 3 cases each) were also identified and are briefly described, as they can provide additional information on rare serious or unanticipated adverse events (Asajima 2008; Bilici 2010; Bryan 2010; Colucci 1999; Edwards 2002; Juss 2005; Madewell 2008; Mason 2008; Pemmaraju 2008; Salvatore 2007; Shalders 2007; Schlienger 2002; Taylor 2006; Tsao 2003; Womack 2003).

Systematic reviews

We identified six potentially relevant systematic reviews in a search strategy designed to identify higher quality reviews from high-yield databases (Chapple 2008; Hartmann 2009; McDonagh 2009; Madhuvrata 2012; Semla 2011; Shamliyan 2012). Three of these reviews met AMSTAR

quality criteria (Shea 2007). These were Madhuvrata 2012, a Cochrane systematic review, Shamliyan 2012, an Agency for Healthcare Research and Quality (AHRQ) review and Mcdonagh 2009, Drug Effectiveness Review Project (DERP, Oregon). We compare our results to Madhuvrata 2012 and Shamliyan 2012 throughout this review, but chose to carry out our own meta-analysis due to differences in inclusion/exclusion criteria and research questions addressed. For example, Shamliyan 2012 only includes treatment of OAB in women.

Two published reports describe a single network meta-analysis for anti-muscarinic drugs for OAB (Kessler 2011; Buser 2012). This network meta-analysis is seriously flawed, both in the lack of attention to methodological strength and risk of bias of included studies and the use of a framework for assessment of comparative harm and overall ratio of benefit versus harm that is unlikely to provide accurate or reliable results. Additionally, the manufacturer of one of the drugs being compared (oxybutynin gel) has sponsored this network meta-analysis. Consistent with previous research on effects of industry sponsorship of direct comparisons within a class (Bero 2007), the sponsor's drug is among those judged to have the best benefit to harm ratio.

In the analysis carried out of direct comparator trials for the systematic reviews of each included drug within this report, we found that a large proportion of RCTs had serious methodological shortcomings, or had such poor reporting that risk of bias could not be fully assessed. Additionally, outcomes were not always reported for the entire randomized treatment arm (e.g. intention-to-treat approach) or in a form that could be incorporated into meta-analysis, or failed to reflect full patient experience (e.g. reporting of subsets of adverse events judged to be treatment-related). Given the potential magnitude of influence on indirect comparisons and rankings of drugs within the class, a network meta-analysis was judged likely to produce unreliable results. An additional problem in this data set is the heterogeneity of included trials, in terms of patient populations and comparator choice. Network meta-analysis depends on the assumption of 'transitivity': that if A is compared with B and B is compared with C, one can learn something about A versus C. A particular problem within this data set is that choices to include more or less severely affected patients, and specific comparators and doses have not been made at random; higher doses or an IR versus an ER comparator are frequent examples. These systematic (versus random) forms of heterogeneity seriously compromise the transitivity assumption behind network meta-analysis (Salanti 2012). Due to the high risk of bias in included studies, and the systematic nature of heterogeneity of trials, results of network meta-analysis are likely to be unreliable.

Meta-analyses of direct comparisons have been tabulated and discussed in a narrative synthesis. Each individual drug report and associated executive summary provides additional detail on outcomes. The following is a brief overview of the results, in response to the key research questions (1-3). We have also included a supplementary analysis synthesizing results per evaluated health outcome at the end of this executive summary (see page 32).

Q1 Comparative benefits and harm

Q1. In adults, including the frail elderly, do the antimuscarinic drugs under review provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) and to each other, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

Comparisons with at least one direct comparator RCT are discussed below.

Q1a. Tolterodine versus comparators

Tolterodine IR versus Oxybutynin IR

- 10 RCTs (n=1986), duration 3 to 12 weeks (9 providing data for analysis) (Abrams 1998; Altan-Yaycioglu 2005; Appell 1997; Drutz 1999; Giannitsas 2004; Lee 2002; Leung 2002; Malone-Lee 2001; Qiu 2002; Xia 2001)
- There was no evidence of an efficacy advantage
- Tolterodine IR resulted in fewer withdrawals due to adverse events (WDAE)
    - RR=0.57 (95% CI 0.43 – 0.76); absolute difference 7%
- Tolterodine IR resulted in fewer adverse events in total (total AE)
    - RR=0.78 (95% CI 0.69-0.89); absolute difference 17%
- There was less dry mouth with tolterodine IR
    - RR=0.54 (95% CI 0.49 – 0.60); absolute difference 32%

Comments:
These differences may be due to dose non-equivalence and a higher anticholinergic effect for the dose of oxybutynin IR most commonly used in these trials, 15mg/day (5 mg t.i.d.) as compared with the dose used for tolterodine, 4mg/day (2mg b.i.d.) (CDER FDA 20-771) Therefore a therapeutic advantage cannot be claimed for tolterodine IR over oxybutynin IR.

Tolterodine ER vs. Oxybutynin ER

- 1 RCT compared tolterodine ER with oxybutynin ER (n=790) (Diokno 2003)
- Doses were non-equivalent: tolterodine ER 4mg/day (maximum recommended) vs. oxybutynin ER 10mg/day (lower end of recommended doses)
- Fewer patients on tolterodine ER experienced resolution of incontinence at week 12; Fewer patients on oxybutynin ER experienced dry mouth.

Comments:
These results are consistent with dose non-equivalence. There is insufficient data available to compare these treatments.

Tolterodine ER vs. Oxybutynin TDS

- 1 RCT compared tolterodine ER 4mg/day with oxybutynin TDS 3.9mg/day (n=361) (Dmochowski 2003)
- Tolterodine ER resulted in fewer withdrawals due to adverse events, mostly due to application site reactions
    - RR=0.15 (95% CI 0.03 =0.66); absolute difference 6.6%

Tolterodine vs. Oxybutynin: IR vs. ER formulations

- 2 RCTs, one comparing tolterodine ER with oxybutynin IR (n=608) (Homma 2003), one tolterodine IR vs. oxybutynin ER (n=378) (Appell 2001a)

- Comparisons of ER with IR formulations does not allow differentiation of drug effect, from effects of the formulation (less fluctuation of drug plasma levels with ER formulations)
- More dry mouth occurred in the IR arm of each trial.

Comments:
There is limited evidence comparing tolterodine ER with formulations of oxybutynin other than oral oxybutynin IR. The finding that IR formulations of each drug led to more dry mouth in the two trials that compared ER formulations with IR formulations suggests that extended-release products may be associated with less dry mouth due to the reduced fluctuations in drug levels.

Q1b. Fesoterodine versus comparators

Fesoterodine vs. Tolterodine ER

- 3 RCTs compared fesoterodine with tolterodine ER (n=1927) (Chapple 2007; Herschorn 2010; Kaplan 2010); most comparisons were between fesoterodine 8mg/day, tolterodine ER 4mg/day; no differences vs. tolterodine ER observed for patients on fesoterodine 4mg/day (1 trial; n=271)
- More patients experienced serious adverse events on fesoterodine
  - RR=1.84 (95% CI 1.1 – 3.1); absolute difference 1%
- More patients experienced adverse events in total
  - RR=1.24 (95% CI 1.2 – 1.3); absolute difference 10%
- More patients experienced dry mouth (RR 1.91; 95% CI 1.7 – 2.2; absolute increase, 14%); constipation (RR=1.41; 95% CI 1.0 to 1.9; absolute increase 1%) and dyspepsia (RR = 1.85; 95% CI 0-2%; absolute increase 1%)
- More patients reported improvement or cure with fesoterodine (3-day diary)
  - RR = 1.11 (95% CI 1.1-1.2); absolute difference 7%
- Greater reduction in incontinence episodes with fesoterodine
  - Mean difference = -0.20 episodes (95% CI -0.04 to -0.036)
- Greater reduction in urgency with fesoterodine
  - Mean difference = -0.29 (95% CI 0.30 – 0.87)

Comments:
There were no differences in beneficial or harmful outcomes between fesoterodine 4mg/day and tolterodine ER 4mg/day. At 8mg/day, 7% more patients on fesoterodine reported improvement or cure. In total, patients experienced one fewer urgency episode per 3.4 days, one fewer urgency incontinence episode per 5 days, and one fewer nocturia episode per 11 days. These modest differences in benefit fail to outweigh increased harm. In general, these differences are consistent with a stronger antimuscarinic effect from fesoterodine 8mg/day vs. tolterodine ER 4mg/day.

Q1c. Solifenacin versus comparators

Solifenacin vs. oxybutynin IR

- 1 RCT compared solifenacin 5mg/day with oxybutynin IR 5mg t.i.d. (15mg/day) (n=132) (Herschorn 2010)
- Solifenacin 5mg/day had fewer WDAE (absolute risk difference 15%), fewer total AE (absolute risk difference 15%), and less dry mouth (absolute risk difference 48%) than oxybutynin IR;
- Oxybutynin was more efficacious on patient self-rated benefit (patient perception of bladder condition); mean difference 0.5 points on a 6-point scale, uncertain clinical meaning

Comments:
This trial was of low quality, with a differential early patient withdrawals and a per protocol analysis only; 83% of patients experienced dry mouth on oxybutynin IR 15mg/day. The trial raises concerns about this dose and formulation of oxybutynin. There are no trials comparing oxybutynin ER with solifenacin. This is a more appropriate comparison, given solifenacin's long half-life.

Solifenacin vs. tolterodine ER
- 2 RCTs compared solifenacin 5 or 10mg/day with tolterodine ER 4mg/day (n=1275) (Ho 2010; Chapple 2005)
- There was no difference in withdrawals due to adverse events or total AE
- More patients had dry mouth with solifenacin than tolterodine ER
    - RR=1.27 (95% CI 1.05-1.53); absolute difference 6%
- More patients on solifenacin had constipation than on tolterodine ER
    - RR=2.60 (95% CI 1.47-4.58); absolute difference 4%
- More patients on solifenacin achieved dryness (3-day rate)
    - RR=1.19 (95% CI 1.04-1.35); absolute difference 9%
- 1 trial indicates a difference in incontinence; the other not (meta-analysis not possible)
    - mean difference -0.59 episodes/day (95% CI -0.93 to -0.25) (Chapple 2005; n=743)
- Urgency was reduced on solifenacin
    - Mean difference -0.44 episodes / day (95% CI -0.84 to -0.04)

Comments:
Patients on solifenacin had a reduction in incontinence episodes by 0.6 / day and an additional 9% achieved continence. On the other hand more 6% more patients on solifenacin experienced dry mouth and 4% more experienced constipation. There was both a modest benefit, in terms of efficacy, and a modest degree of additional harm, in terms of higher anticholinergic adverse event rates. The strength of evidence for this comparison is moderate.

Solifenacin vs. tolterodine IR
- 3 RCTs compared solifenacin with tolterodine IR (n=1585); all with separate treatment arms of solifenacin 5mg or 10mg vs. tolterodine 4mg (Choo 2008; Chapple 2004a; Chapple 2004b)
- There was no difference in withdrawals due to adverse events or total adverse events
- Solifenacin 5mg was associated with less dry mouth; no difference for solifenacin 10mg
    - RR=0.64 (95% CI 0.46 to 0.88); absolute risk difference 7%
- Solifenacin was associated with more constipation than tolterodine IR

  - RR 2.91 (95% CI 1.49 to 5.68); absolute difference 5% for solifenacin 5mg
  - RR 3.63 (95% CI 1.89 to 6.97); absolute difference 7% for solifenacin 10mg
- Solifenacin 5mg (n=298) reduced incontinence episodes compared with tolterodine; the difference was not significant for solifenacin 10mg (n=315)
  - Mean difference 0.5 episodes/day

Comments:
Overall, there is more dry mouth with tolterodine IR vs. solifenacin but less constipation, with a similar magnitude of effect for each adverse event. The magnitude of differences in efficacy outcomes is small. The overall strength of evidence is moderate.

Solifenacin vs. darifenacin
- 1 open-label RCT compared solifenacin 5mg vs. darifenacin 7.5mg CR in women (But 2012; n=77)
- the lack of blinding leads to a high risk of bias; there was a 21% withdrawal rate and only a per protocol analysis was reported; AE are incompletely reported. No outcomes are identified as predefined or primary.

Comments:
Conclusions cannot be drawn for this comparison due to the methodological limitations of this study. There is insufficient evidence to determine whether solifenacin has a therapeutic advantage over darifenacin.

Q1d. Darifenacin

Darifenacin ER vs. oxybutynin IR
- 2 short (1-2 week) crossover RCTs compared darifenacin ER 15mg with oxybutynin IR 5mg t.i.d. (15mg/day) (n=100)(Zinner 2005; Chapple 2005)
- Withdrawals due to adverse events and total adverse events did not differ
- There was significantly less dry mouth with darifenacin in 1 trial (Zinner 2005); absolute difference 23%; not significant in the second trial (meta-analysis not possible)
- Reduction in incontinence and other efficacy outcomes did not differ, based on one trial measuring those outcomes, per protocol analysis only (n=58)

Comments:
Overall the evidence is insufficient to conclude a therapeutic advantage for darifenacin ER, incorporating both benefit and harm. A more suitable comparator would have been an extended release formulation of oxybutynin.

Darifenacin ER vs. tolterodine IR
- 1 RCT compared darifenacin ER 15mg with tolterodine IR 2mg b.i.d. (4mg/day) (Novartis 2006; unpublished; n=335)
- There was no difference in efficacy outcomes
- Withdrawals due to adverse events, total adverse events and dry mouth did not differ

- More patients on darifenacin experienced constipation than on tolterodine
    - RR=1.99 (95% CI 1.24 to 3.19); absolute difference 12%

Comments:
With no difference in efficacy outcomes and a 12% higher rate of constipation on darifenacin ER than on tolterodine IR, this unpublished trial found a therapeutic disadvantage for darifenacin ER.

Darifenacin ER vs. solifenacin

- See solifenacin section above; there are insufficient data available for this comparison.

Q1e. Trospium

Trospium IR vs. Oxybutynin IR

- 2 RCTs, 12 weeks and 52 weeks in duration, compared trospium IR 40 to 90mg/day with oxybutynin IR (7.5 to 15mg/day) (n=2015) (Zellner 2009; Halaska 2003)
- There were fewer withdrawals due to adverse events with trospium IR
    - RR=0.69 (95% CI 0.50 to 0.95); absolute difference 3%
- Fewer patients had one or more AE on trospium IR
    - RR = 0.85 (95% CI 0.75 to 0.97); absolute difference 5%
- Efficacy outcomes did not differ, but reporting was limited.

Comments:
Overall, incorporating both benefit and harm, trospium IR had a therapeutic advantage over oxybutynin IR, based on similar reductions in incontinence episodes and better tolerability. The strength of evidence was low. Trospium IR exposure included doses that exceeded the maximum recommended dose, versus the mid to low range dose for oxybutynin IR. However, given the direction of dose non-equivalence, the findings of higher adverse event rates with oxybutynin IR are likely to be robust.

Trospium IR versus Tolterodine IR

- 1 RCT compared trospium IR with tolterodine IR (n=153 on active drug; placebo-controlled; 3 week duration) (Madaus AG 2001 Study MP94D2.15)
- The trial was underpowered for serious adverse events and withdrawals due to adverse events
- Total adverse events and dry mouth did not differ
- There was no difference in reduction of incontinence episodes
- Trospium was slightly better at lessening restrictions of work/everyday activities, recreational activities, eating/drinking but not social gatherings (difference ~15mm on a 100mm visual analogue scale. The clinical meaningfulness of these differences is unclear.

Comments:
There is insufficient evidence to conclude a therapeutic advantage for trospium IR over tolterodine IR or placebo in this trial. There was no difference in micturition frequency, the trial's primary

outcome, between trospium and placebo. The trial remains unpublished although the study report dates to 2001, likely due to the lack of effectiveness for trospium versus placebo.

Q1f. Comparisons between different formulations of the same drug

Oral oxybutynin ER versus oxybutynin IR

- 5 RCTs of 2 – 12 weeks compare oxybutynin ER with oxybutynin IR (n=658) (Anderson 1999; Barkin 2004; Birns 2000; Minassian 2007; Versi 2000)
- Serious adverse events, withdrawals due to adverse events and total AE did not differ
- Fewer patients on oxybutynin ER than oxybutynin IR experienced dry mouth
    - RR 0.86 (95% CI 0.75 to 0.98); absolute risk difference 8%
- There was no difference in reduction in incontinence episodes or in urgency
- There was less improvement on condition-specific quality of life on oxybutynin ER than IR on UDI scores ; mean difference 0.23 points [95% CI 0.03 to 0.44] (a 6% difference)

Comments:
An advantage has not been established for oxybutynin ER versus oxybutynin IR based on the available clinical trial evidence. There was an increase in dry mouth with oxybutynin IR (number needed to harm = 13) but condition-specific quality of life improved less on oxybutynin ER.

Oxybutynin Transdermal Patch (TDS) vs. Oxybutynin IR

- 1 RCTs compared oxybutynin TDS (1 to 8mg/day) with oxybutynin IR (5-22mg/day) (n=76) (Davila 2001)
- The trial was underpowered for serious adverse events; withdrawals due to adverse events did not differ; no data are provided on total AE
- Fewer patients experienced dry mouth on oxybutynin TDS
    - RR=0.39 (95% CI 0.26 – 0.59); absolute difference 59%
- Fewer patients experienced constipation or nausea on oxybutynin TDS
    - RR = 0.42 (95% CI 02.1 to 0.84), absolute difference 29% (constipation)
    - RR=0.30 (95% CI 0.09 to 1.01), absolute difference 45%; statistical significance marginal (nausea)
- Fewer patients experienced somnolence on oxybutynin TDS
    - RR = 0.29 (95% CI 0.14 to 0.59); absolute difference 45%
- Reporting on application site reactions was incomplete, with only erythema at patch site reported; total rate unknown (15% more erythema, incomplete)
- There was no difference in continence (dryness) or reduction of incontinence
- no data on urgency or nocturia

Comments:
Dose ranges for oxybutynin TDS and oxybutynin IR in this trial were not comparable, and the lower rates of anticholinergic adverse events with oxybutynin TDS could have been due to the lower anticholinergic dose. This trial was designed as an equivalence trial and failed to show equivalence of oxybutynin TDS with oral oxybutynin for the *a priori* primary outcome, the percentage of patients who were responders. A response was defined as a ≥ 30% reduction from baseline in incontinence episodes. There is insufficient evidence, based on this trial, to conclude a therapeutic advantage of oxybutynin TDS over oxybutynin IR.

Tolterodine ER versus Tolterodine IR

- 1 RCTs compared tolterodine ER 4mg/day with tolterodine IR 2mb b.i.d. (4mg/day) and placebo (n=508) (Kerrebroeck 2001)
- Serious adverse events and withdrawals due to adverse events did not differ; total adverse events were not reported
- There was less dry mouth with tolterodine ER
    - RR=0.77 (95% CI 0.62 to 0.94; absolute difference 7%
- There was no difference in reduction of incontinence episodes; urgency and nocturia are not reported; quality of life is not compared between drugs;

Comments:
This trial provides insufficient evidence on harms and efficacy outcomes to conclude a therapeutic advantage for tolterodine ER.

Q1 Drug to drug comparisons: evidence from observational studies
We included non-randomized studies for additional evidence on infrequent harmful effects and outcomes in patient groups not included in RCTs, such as the elderly and those with serious co-morbidities, as well as effects of anti-muscarinic drugs in the longer term. We did not include assessment of beneficial drug outcomes as double-blind RCTs provide much more accurate and reliable evidence than observational studies.

Of the included observational studies, only two controlled cohort studies comparing drugs in this review could provide secondary evidence on comparative benefit and harm (Gomes 2011; n=81,126; Jumadilova 2006; n=26,386). Both were population-based comparative cohort analyses that examined the rates of fractures among patients taking oxybutynin or tolterodine, using propensity score matching to adjust for confounding. Neither found a difference in the rate of fractures. Gomes 2011 also assessed rates of serious falls and delirium, in patients with a mean age of 78, over a 90-day period, and neither differed between oxybutynin and tolterodine.

Jumadilova 2006 found a 1.5% higher rate of depression on oxybutynin IR than tolterodine ER, with no difference between oxybutynin ER and tolterodine ER. Urinary tract infections also occurred more often on oxybutynin (ER or IR) than tolterodine ER. However, this study reports on three unrelated outcomes, fractures, depression and urinary tract infections. There is no published protocol and selective reporting is likely, which can be especially problematic in an observational study of this type, as many different outcomes may be tested, making chance associations more likely. Discontinuation was not taken into account, a serious flaw for a one-year study, given that

most persistence studies indicate high rates of discontinuation on antimuscarinics for OAB. The study was funded by Pfizer, the manufacturer of tolterodine.

Gomes 2011 found a 0.6% higher rate of all-cause hospitalization and a 0.3% higher rate of death among patients on oxybutynin than tolterodine. The most likely cause is residual confounding, with a patient population that is generally in poorer health and more elderly, despite the attempt to address confounding through propensity score matching, and the authors judge this outcome to be exploratory only.

Additional data on fractures is non-comparative within the class, but highlights the potential for harm within the class. Moga 2013 (n=6,594) assessed the rate of hip fractures and total fractures among patients on antimuscarinics compared with non-users. For oxybutynin IR, the hazard ratio for hip fracture was 4.89 (95% CI 1.79 to 13.44); for all users the hazard ratio for hip fracture was 3.67 (95% CI 1.46 to 9.34). Risks for any fracture were also elevated. The authors calculated a number needed to harm at 90 days of 36 (95% CI 12-209) for hip fractures among all users.

Most were taking IR formulations, with oxybutynin IR the most frequently used drug. The sample was 96% male. Patients were followed for up to 8 years, with censoring on discontinuation, and the sample was propensity-matched. Rates of hip fracture were nearly as high as rates of at least partial resolution of incontinence (number needed to treat 32). The lack of large margin between the rate of hip fracture and partial improvement in urinary incontinence in this largely male elderly population with a high level of comorbidity raises a strong signal of the potential that harm may outweigh benefits.

Comments:
Results of the two comparative cohort studies are judged to be exploratory only, with a low strength of evidence. The lack of difference in falls and fractures, replicated in two settings, provides some evidence of comparable risk levels, especially given the direction of differences in evidence suggestive of incomplete adjustment for confounding in Gomes 2011 (e.g. oxybutynin users in poorer health; given the hypothesis of more falls and fractures with oxybutynin). Due to serious methodological limitations of Jumadilova 2006, results should be considered exploratory only. Increased deaths and hospitalizations with oxybutynin in Gomes 2011 most likely reflect incomplete adjustment for confounders, but further research is needed in case this is a true signal of effects on total serious morbidity and mortality. A more recent study, Moga 2013, highlights the need for additional longer-term population-based research for the entire drug class. Oxybutynin IR, and a mix of anti-muscarinic drugs, were associated with a large increase in hip fracture rates in a largely frail elderly male population, over an 8-year period. Whether this is a class or a drug-specific effect remains unknown, and whether it extends to women or to patient populations with fewer serious co-morbidities.

Q2. New Evidence since the Common Drug Review Clinical Evidence Reports

Is there new evidence since the Common Drug Review Clinical Evidence reports that trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz) or oxybutynin gel (Gelnique) provide improved clinically relevant outcomes or a better safety profile compared to oxybutynin IR?*

Common Drug Reviews were available for the five drugs with dates of review:

- Fesoterodine (Toviaz)
- Oxybutynin gel (Gelnique)
- Solifenacin (Vesicare)
- Darifenacin (Enablex)
- Trospium (Trosec)

Common Drug Review (CDR) reports were not available for: oxybutynin IR (Ditropan); oxybutynin transdermal patch (Oxytrol™); oxybutynin ER (Ditropan XL®); oxybutynin CR (Uromax®); tolterodine IR (Ditropan); tolterodine ER (Detrol LA™).

For each drug, new evidence that was considered included direct comparator trials, placebo-controlled trials on elderly, trials that assessed cognitive effects in patients with OAB or healthy volunteers, non-randomized studies and post market surveillance data, as outlined in Q1.

Fesoterodine

CDEC Final Recommendation (October 18, 2012): list fesoterodine in the same manner as extended-release tolterodine.

Evidence in this review: no substantive new evidence was identified that would lead to a difference in recommendation as compared with the CDR review, either with respect to comparative effectiveness or safety versus other antimuscarinic drugs.

- No new direct comparator RCTs were identified

- One new placebo-controlled, crossover RCT was identified that assessed multiple-dose (steady-state) cognitive effects of fesoterodine 4mg and 8mg/day (Kay 2012). This was a 6-day RCT that enrolled 20 cognitively intact, healthy volunteers aged ≥ 65 years (mean age 72, range 65 to 85). A battery of computerized tests to assess cognitive ability, including reaction time following fesoterodine or an acutely sedating high dose of alprazolam, a benzodiazepine. The only conclusion from this study is that fesoterodine, in the short-term, does not impair the ability to carry out cognitive tasks to the same extent as a high dose of a benzodiazepine. The study provides no information on potential effects on cognition from chronic use of fesoterodine, or comparative effects with other antimuscarinic drugs.

- Two uncontrolled cohort analyses were identified in this review that were not part of the CDR review as the latter is restricted to RCTs only (Sand 2012; Wagg 2013b). Both were post-RCT extension studies. Withdrawals due to adverse events, total adverse events, dry mouth and constipation occurred more frequently in patients who had previously taken placebo. These differences were most pronounced among patients aged 75+, suggesting that the strongest selection effects in patients previously randomized to fesoterodine occurred in this population group. These studies cannot be used to draw conclusions about any therapeutic advantage of fesoterodine and do not modify the conclusions of the CDR review.

- The available Periodic Safety Update Report (PSUR) (April 2011 to April 2012) reveals a qualitatively similar adverse event profile as other antimuscarinic drugs and cannot be used to draw conclusions about the relative rate of adverse events for fesoterodine versus comparator drugs. The WHO Monitoring Centre in Uppsala published a signal of gastrointestinal (GI)

hemorrhage with fesoterodine (Hill 2012) based on 7 reports in their international database. Gastrointestinal hemorrhage has also been previously reported with tolterodine, the drug most closely related to fesoterodine.

Oxybutynin chloride gel

CDEC Final Recommendation (May 24, 2012): do not list. Reasons cited were 1) the uncertain comparative clinical benefit in the absence of any RCTs that directly compare it to other pharmacological treatment, and 2) the absence of RCTs comparing the incidence of anticholinergic adverse effects (such as cognitive and neurological) between oxybutynin chloride gel and other oxybutynin products, particularly in the elderly.

One placebo-controlled 12-week RCT (Staskin 2009, corresponding to Study OG05009) was included in the CDR clinical review. The submission also included subgroup analyses from that trial that showed the results for patients > 65 years did not differ between oxybutynin gel and placebo in reducing incontinence frequency or micturition. This is in contrast to the product monograph that states there were no observed differences in safety or effectiveness between older and younger patients.

Evidence in this review: no substantive new evidence was identified. There is insufficient evidence available with which to assess whether oxybutynin gel has a therapeutic advantage over oxybutynin IR or other comparators. This is consistent with the CDR review results and the rationale behind the CDEC recommendation.

- No new direct comparator trials were identified in patients with overactive bladder.

- The only new direct comparator RCT was an 8-day, parallel group trial on healthy volunteers aged 60 or older (N=153) that compared short-term cognitive effects of oxybutynin gel to oxybutynin IR (Kay 2012b). This study provides insufficient evidence to conclude a therapeutic advantage for oxybutynin gel. This trial compared oxybutynin gel to oxybutynin IR and did not reveal a difference between formulations for the primary outcome, delayed recall on the name-face association test. The emphasis on name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008). Conclusions cannot be drawn on secondary outcomes or post hoc analyses, which are hypothesis-generating only. The issue of dose equivalence in this study is unresolved, limiting interpretation of the data.

- No new trials were identified that exclusively enrolled the elderly, either direct comparator trials or placebo-controlled trials.

- No non-randomized studies were identified in the current review. The available post market data in a Periodic Safety Update covers a few months of post market experience only, and the Canada Vigilance Adverse Reaction Online Database contains few cases. These additional data do not provide information on the relative safety. Qualitatively, the adverse event profile is similar to other oxybutynin products (and includes central nervous system effects) and other antimuscarinic drugs.

Solifenacin

CDEC Final Recommendation (May 20, 2009): list for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and in a similar manner as drug plans list tolterodine.

Evidence in this review: no substantive new evidence was identified that would lead to a difference in recommendation as compared with the CDR review, either with respect to comparative effectiveness or safety relative to other antimuscarinic drugs

- In the current review, we identified three additional direct comparator RCTs and one additional subanalysis of an RCT:
  - Wagg 2013 (solifenacin vs. oxybutynin IR), 3-week crossover trial assessing cognition in the elderly (N=26);
  - Ho 2010, (solifenacin vs. tolterodine ER), open-label 12-week parallel group trial (N=75);
  - Chapple 2007 (solifenacin vs. tolterodine ER), predefined subanalysis of the STAR trial at 4 weeks, a time point when all participants in the solifenacin group were taking 5mg/day;
  - But 2012 (solifenacin vs. darifenacin ER), open-label, 12-week parallel group RCT (N=77)

  Ho 2010 is a non-blinded trial that compared a fixed dose of solifenacin 5mg/day with tolterodine ER 4mg/day. But 2012 is also an open-label trial that compared solifenacin 5mg/day versus darifenacin 7.5mg. Both are of poor quality and do not provide sufficient evidence to draw conclusions on the relative efficacy or safety of the comparisons assessed because of their methodological limitations.

  The additional RCT data do not provide evidence that would modify the conclusions of the CDR 2009 review.

- One new trial was identified that assessed cognitive effects (Wagg 2013). This 21-day crossover trial was identified that compared the cognitive effects of solifenacin 5 mg daily with oxybutynin 5 mg b.i.d (10 mg total/day) and placebo in 26 men and women, aged 75 years or older, who had mild cognitive impairment, at steady state. This trial provides insufficient evidence upon which to draw conclusions about the relative short-term cognitive effects of solifenacin versus oxybutynin IR. At estimated peak dose level for each drug, there were no statistically significant changes from baseline in cognitive function when each drug was compared with placebo. The authors did not carry out any statistical analyses directly comparing the two active drugs. Post hoc analyses were performed pooling time points but are exploratory only. Drug levels were not measured.

- In the current review, no comparative non-randomized studies were identified. The available uncontrolled cohort analyses did not provide information that would modify the CDR conclusions.

- Signals highlighted in the available Periodic Safety Update included a signal for muscle weakness and a possible signal for Parkinson's disease. Events targeted for further monitoring by the manufacturer also include cardiac events such as arrhythmias, and interstitial lung disease. Because of the limitations of voluntary reporting systems, such data can be used for signal detection only and not incidence rates.

- The current review found no evidence to support the CDEC recommendation in populations who were refractory to or intolerant of oxybutynin. Furthermore, a refractory population or an insufficient response to oxybutynin was not defined in any of the trials or observational studies.

- A clinical update submission was provided by the manufacturer for the current review. All identified studies in the clinical update were included in the literature database and screened for Q1. The majority were placebo-controlled trials and not eligible for this review.

Darifenacin

There have been two CDR reports, one based on the original submission, dated September 2006, and a resubmission report in 2009

CDEC Final Recommendation (April 16, 2009): list darifenacin for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and to list in a similar manner as drug plans list tolterodine.

Evidence in this review: no substantive new evidence was identified that would lead to a difference in recommendation as compared with the CDR review, either with respect to comparative effectiveness or safety versus other antimuscarinic drugs.

- One new direct comparator, open-label parallel-group RCT (77 patients) was identified that compared darifenacin ER with solifenacin (But 2012). This trial is the only identified RCT that compares darifenacin ER with another long-acting drug in OAB patients. Solifenacin shows some selectivity for the M3 receptor subtype although not to the same extent as darifenacin. The trial failed to meet its recruitment goal and was termed ‘exploratory’ by its investigators. It provides insufficient evidence for a therapeutic advantage for either drug, and is weak methodologically.

- No new trials were identified that exclusively enrolled the elderly in either direct comparator or placebo-controlled trials. The current review also did not identify new comparator or placebo-controlled RCTs that assessed cognitive function.

- No direct comparator trials were identified that assess darifenacin in a population that is refractory to or intolerant of oxybutynin.

- Two uncontrolled cohort analyses identified in the current review (Schneider 2010; Haab 2006), fail to provide adequate information to assist in the assessment of darifenacin’s adverse effects, either in the elderly, in patients in general with overactive bladder syndrome.

- A Periodic Safety Update Report was not made available for the current review. Based on FDA documentation and records in the Canada Vigilance Adverse Reaction Online Database, the adverse event profile is qualitatively similar to other antimuscarinic drugs.

Trospium

CDEC Final Recommendation (dated July 26, 2006): list trospium for patients who cannot tolerate immediate-release oxybutynin and in a similar manner as drug plans list tolterodine.

The CDR review based its conclusions on efficacy predominantly on 3 RCTs that were ≥ 12 weeks long, two placebo-controlled and one active comparator trial (Halaska 2003). Trospium improved quality of life over placebo in two trials but this was not assessed relative to an active control. Several micturition frequency and incontinence outcomes were significantly improved versus placebo. In the 52-week trial, efficacy was not significantly different than oxybutynin (Halaska 2003). For conclusions on harms, all available trials were assessed. Trospium was not significantly different from oxybutynin or tolterodine although more AE occurred with trospium versus placebo. In the 52-week study, fewer patients on trospium were noted to experience dry mouth than oxybutynin.

Evidence in this review: The available new evidence does not modify the CDR conclusions substantively. Although there are additional studies in an older age group, the available evidence is insufficient to conclude trospium IR is safer than oxybutynin IR for cognition in the short-term. One study is suggestive that trospium in the extended-release formulation (rather than trospium IR, which is the drug included in this review) crosses the blood-brain barrier to a lesser extent than usual doses of oxybutynin IR. The ER formulation results in lower drug exposure and narrower fluctuations of drug levels in the bloodstream than trospium IR so that these findings cannot be directly extrapolated to use of trospium IR.

In the current review, the following additional RCT was identified:

- ***Trospium IR vs. oxybutynin IR:*** Zellner 2009 (a 12-week parallel group trial on trospium IR vs. oxybutynin IR – note this trial used a trospium dose range [45-90mg total/day] above the recommended dose range in Canada [40mg total/day])

  The current review's conclusions are based on Zellner 2009 and the 52-week trial, Halaska 2003. Trospium IR was similar to oxybutynin IR for efficacy but had lower rates of WDAE and total AE. Because only a subset of specific AE judged by investigators to be treatment-related were reported, rather than all specific AE, we did not base conclusions on specific AE data.

  Zellner 2009 provided quality of life outcomes, which were similar for both drugs. The strength of evidence for this outcome is insufficient in part because about 30% of participants were on more than double the recommended dose of trospium IR.

- ***Trospium IR vs. tolterodine IR:*** There were no new data for this comparison (One study, Novartis 2006, Study MP94D2.15, unpublished). This trial provides insufficient evidence to conclude a therapeutic advantage (incorporating benefit and harm) for trospium IR over tolterodine IR or placebo. The full study report of the 3-week trial comparing trospium IR vs. tolterodine IR reported impact of each drug on aspects of quality of life using visual analogue scales but not a validated quality of life scale, and the clinical meaningfulness of the differences between trospium IR and tolterodine IR was not addressed. These results do not change the CDR review conclusions substantively.

- No direct comparator trials wren identified that compare trospium with another antimuscarinic drug in a population that is refractory to or intolerant of oxybutynin IR.

- In the current review, supplemental information on cognition included studies on trospium IR, both in healthy volunteers:
    - Herberg 1997 (a 7-day multiple-dose RCT on trospium IR vs. oxybutynin IR in healthy volunteers aged 35 to 70; translated from German)
    - Diefenbach 2005 (a single-dose crossover RCT on trospium IR vs. oxybutynin IR, tolterodine IR or placebo in healthy volunteers aged ≥ 50 years)

  Herberg 1997 presents few data with all cognitive outcomes described as showing no difference between trospium IR 20 mg b.id. and oxybutynin IR 5 mg t.id. Diefenbach 2005 is a single-dose study similar to one included in the CDR Review but in an older age group. It was largely on sleep architecture with total daily doses of oxybutynin IR, tolterodine IR and trospium IR administered as a single high dose, limiting its applicability. Oxybutynin and tolterodine but not trospium showed a decrease of about 15% in rapid-eye-movement (REM) sleep.

- Studies that compared trospium ER versus oxybutynin IR were also considered for cognition in the current review:
    - Allergan NCT 01178827 Study (unpublished direct comparator RCT, multiple doses, trospium ER (10 days) vs. oxybutynin IR (2 days) in OAB patients ≥ age 60, mean age 72 years)
    - Staskin 2010 (non-randomized uncontrolled study, trospium ER)
    - Geller 2012 (non-randomized uncontrolled study, trospium ER)

  NCT 01178827 results are posted on clinicaltrials.gov but a full study report is not available. The primary outcome was cerebrospinal fluid levels of drug with secondary outcomes of cognitive tests. No statistical analyses were reported for the cognitive tests but in an exploratory analysis for this review, the Hopkins Verbal Learning Test-Revised Total Recall Score and other test scores, did not show a statistically significant difference between drugs or versus placebo. Trospium was not detected in CSF but it is questionable whether this may in part be due to dose non-equivalence.

- No non-randomized observational studies on trospium IR were identified in the current review.

- The available post market surveillance data, including PSUR data (both IR and ER formulations) includes reports of disorientation (with a positive dechallenge) and other central nervous system events that suggest trospium is able to penetrate the blood-brain barrier. There was also one case of aggravation of Parkinson's disease. These data cannot be used to draw conclusions on comparative safety.

Q3. Cognition

In adults, particularly the elderly, does trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz®), oxybutynin gel (Gelnique™), oxybutynin transdermal patch (Oxytrol™) or other formulations of oxybutynin have less effect on cognition when compared to oxybutynin IR or to each other?

Tolterodine

- There is insufficient evidence available to assess the magnitude of tolterodine's effects on cognition, versus oxybutynin.

- There are no published RCTs comparing tolterodine with oxybutynin that assessed cognition. It is not appropriate to rely solely on voluntary reporting for cognitive changes as patients may be unaware of such changes or may not attribute them to drug treatment, and none of the identified short-term trials specifically measured cognitive effects. The available trials were under-powered for CNS effects and information on these effects was not systematically collected.

- One unpublished, short-term RCT was identified that assessed cognitive effects of tolterodine ER vs. oxybutynin ER in the elderly (clinicaltrials.gov NCT00411437) was identified. A brief summary of the placebo-controlled trial is in the PSUR documentation but dosages of the drugs are not provided, and without further information on the methods and a full study report, the trial cannot be critically appraised. Results are therefore not presented. The final study report has been requested.

- No non-randomized studies are available that provide direct comparative data on the cognitive effects of oxybutynin and tolterodine.

- Based on case reports and data submitted to regulators, there is evidence of adverse cognitive effects associated with tolterodine, but insufficient research to assess the frequency of effects or how this compares to oxybutynin.

Fesoterodine

- The available evidence is insufficient to draw conclusions about the cognitive effects of fesoterodine compared with other antimuscarinic drugs.

- No direct comparator RCTs were identified that compared the short- or long-term cognitive effects of fesoterodine with oxybutynin or any other antimuscarinic drug. The available 12-week RCTs on patients with OAB syndrome were under-powered to detect differences in central nervous system effects and none actively assessed cognition.

- One 6-day placebo-controlled, crossover RCT enrolled 20 healthy volunteers aged 65 years or older (mean age 72, range 65 to 85) and tested the cognitive effects of steady state fesoterodine 4mg/day or 8mg/day (Kay 2012). All volunteers had normal cognition on a Mini-Mental Status Examination at baseline. A battery of computerized tests was used to assess cognitive ability, including reaction time, following fesoterodine or an acutely sedating high dose of alprazolam

(1mg, 4-fold higher than the usual starting dose in the elderly). The latter was used as a positive control. There were no differences in change from baseline between either dose of fesoterodine and placebo. The high dose of alprazolam showed deterioration in scores. The only conclusion from this study is that fesoterodine, in the short-term, does not impair the ability to carry out cognitive tasks to the same extent as a high dose of a benzodiazepine.

- Based on post market surveillance and regulatory data, there is evidence of adverse cognitive effects and other central nervous system effects associated with fesoterodine.

- There are no long-term studies on potential effects on cognition from chronic use of fesoterodine.

Solifenacin

- There are no studies of solifenacin in OAB patients that were adequately powered for central nervous system effects or actively assessed cognition. In particular, there are no studies that compare the longer-term effects of solifenacin with oxybutynin IR, or any other antimuscarinic drug.

- Two placebo-controlled crossover trials were identified that compared the effect of solifenacin and oxybutynin IR on cognitive function in elderly volunteers (Wagg 2013; Wesnes 2009).

  A three-way crossover pilot study, tested cognitive function before and after single doses of solifenacin 10 mg, oxybutynin IR 10 mg and placebo in 12 healthy, elderly volunteers (Wesnes 2009). The dose of oxybutynin IR is twice the recommended maximum single dose and is therefore an inappropriate dose for comparative analysis.

  Wagg 2013 compared the cognitive effects of solifenacin 5 mg daily with oxybutynin 5 mg b.i.d (10 mg total/day) and placebo in elderly men and women aged 75 years or older (N=26), who had mild cognitive impairment, at steady state (21 days of treatment). At estimated peak dose level for each drug, there were no significant changes from baseline when each drug was compared with placebo. The authors did not carry out any statistical analyses directly comparing the two active drugs. Post hoc analyses were performed pooling time points but are exploratory only. Drug levels were not measured. This trial provides insufficient evidence upon which to draw conclusions about the relative short-term cognitive effects of solifenacin vs. oxybutynin IR.

Darifenacin (ER)

Darifenacin is relatively M3-receptor selective and has been hypothesized to have less effect on the brain because M1 and M2 receptors may be of particular importance in learning and memory.

- No comparative RCTs in patients with OAB were identified. Data on cognition were obtained from two RCTs in healthy volunteers, one comparative and the other, placebo-controlled.

- There is no evidence with which to conclude darifenacin has less effect on cognition than oxybutynin IR.

- Based on one short-term (3-week) RCT in healthy volunteers, there is insufficient evidence to conclude darifenacin ER has less effect than oxybutynin ER.

- There are no RCTs that compared darifenacin to other drugs included in this review.
- No RCTs in any population have assessed the cognitive effects of chronic use of darifenacin. We also did not identify any observational studies that assessed long-term cognitive effects.

Available studies are described below.

Darifenacin ER vs. Oxybutynin ER

- One three-week parallel group, placebo-controlled trial assessed effects of darifenacin ER and oxybutynin ER on cognition (Kay 2006).

  150 healthy volunteers ≥ age 60 were enrolled (mean age 66-68 years) and given a battery of computerized cognitive tests at baseline and weeks 1, 2 and 3. Participants on oxybutynin ER received 10mg/day week 1, 15 mg/day week 2 and 20mg/day week 3 whereas participants on darifenacin received 7.5mg/day for 2 weeks, than 15 mg/day for week 3.

  In total, 144 different comparisons in cognition scores are reported on, without adjustment for multiple comparisons, and with 48 comparisons each for weeks 1-3. Little published data exist on test parameters.

  The identified primary outcome measure was delayed recall on the name-face association test. In week 2, participants on darifenacin ER 7.5mg/day did significantly better than those on oxybutynin ER 15mg/day. In week 3, participants on darifenacin 15mg did significantly better than participants on oxybutynin ER 20 mg/day: mean difference 1.23 points (95% CI 0.4 to 2.1). These differences were adjusted for baseline score, age and sex. The clinical meaning of a 1.23 point difference is unknown.

  Although the name-face association test at week 3 is identified as the primary outcome measure in the published report, this primary outcome was first reported in a protocol amendment on www.clinicaltrials.gov on May 24, 2006, one year after trial completion. Thus it is unlikely to have been identified *a priori* as the primary outcome measure.

  In total, participants on oxybutynin ER did worse than those on darifenacin in 2 (4.2%) comparisons and did worse than placebo in 4 (8.3%). Participants on darifenacin did worse than those on oxybutynin ER on one comparison (2.1%) and did worse than placebo on one comparison (2.1%). Thus there was a trend towards participants on oxybutynin ER experiencing more effects on cognition than those on darifenacin.

  The study was at high risk of bias for incomplete outcome data as it had differential withdrawal rates in treatment arms, and reported a per protocol analysis. It was also at high risk of bias for selective outcome reporting because of the amendment to disclose the primary outcome one year after trial completion.

The lack of information provided on maximum test scores or on established minimal clinically important differences in scores limits interpretability. The emphasis on the name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008).

This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome, or to patients with any degree of underlying cognitive impairment.

Placebo-controlled RCTs

- One placebo-controlled RCT on cognition was identified. Lipton 2005 is a three-period crossover trial, in which healthy volunteers were randomized to 2-week periods of drug treatment, with 1 week in between. Volunteers received 3 of 5 treatments: 3.75mg, 7.5mg, or 15mg of darifenacin ER; darifenacin IR 15mg; and placebo.

  The authors identify three domains as primary cognition function variables: memory scanning sensitivity; choice reaction speed; and delayed word recognition sensitivity. There were no significant differences at $p<0.05$ in any of these measures versus placebo. A trend was seen in reduced speed in choice reaction time for the two higher dose groups (darifenacin 15mg/ day – either extended-release or immediate-release), with the lower doses (3.75mg/day and 7.5 mg/day ER) and placebo exhibiting improvements in speed over time, as would be expected with a practice effect.

  The authors identified an additional five domains as secondary cognitive function variables: simple reaction time; digit vigilance task – speed; digit vigilance task – accuracy; memory scanning speed; and word recognition scanning speed. For recommended doses of darifenacin, there were no significant differences versus placebo.

  It is not clear whether the differences between primary and secondary outcomes were established *a priori*, as the rationale for the sample size calculation is not provided.

  The study is at high risk of bias for incomplete outcome reporting because the analyses were per protocol. There was also high risk of bias for selective outcome reporting.

  This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome. It is also unclear whether primary outcome measures on cognition tests were determined *a priori*, or whether a minimal clinically important difference was identified for cognition scores.

  Additionally, because patients with serious comorbidities and with dementia, depression, or other psychological disorders were excluded, the trial results are unlikely to be applicable to the frail elderly with multiple morbidities.

Trospium (IR)

- Trospium's physicochemical properties (quaternary amine) suggest it might penetrate the intact blood-brain barrier to a lesser extent than other antimuscarinic drugs. In addition to available

data on trospium IR, we included as supplemental information, data on the extended-release formulation of trospium even though it is not a drug under review.

- There is insufficient evidence to conclude trospium IR is safer, in the short-term, than oxybutynin IR for cognition. In healthy volunteers, a multiple-dose study (7 days of treatment) reported no differences between trospium IR (40mg total/day) and oxybutynin IR (15mg total/day). A single-dose healthy volunteer study (mean age 60) also reported no difference between trospium IR and oxybutynin IR, when a total daily amount was given in a single dose (45mg trospium IR and 15mg oxybutynin IR), with cognitive testing one hour later. This time point is unlikely to have coincided with the peak plasma concentration for trospium (about 5 hours).

- Available evidence on 16 patients with OAB, and an unspecified degree of age-related cognitive impairment (mild cognitive impairment), suggests that usual doses of *extended-release* formulation of trospium penetrate the blood-brain barrier less than oxybutynin IR. Cognitive testing did not reveal statistically significant between-treatment differences in the change from baseline between active drugs or placebo. This result cannot be applied to trospium IR because the IR formulation results in higher overall drug exposure compared to the extended-release formulation (Silver 2010).

- No RCTs in any population have assessed the cognitive effects of chronic use of trospium IR (or ER). There are also no observational studies on trospium IR that have assessed long-term cognitive effects.

Trospium IR vs. Oxybuytnin IR

- No RCTs were identified that compared the cognitive effects of trospium IR to oxybutynin IR or other antimuscarinic drugs in patients with OAB.

- Two RCTs on healthy volunteers were identified that compared trospium IR versus oxybutynin IR (Herberg 1997; Diefenbach 2005) and tolterodine IR (Diefenbach 2005).

  A multiple-dose, double-blind parallel-group RCT on 36 healthy volunteers, aged 35 to 70 years, evaluated psychomotor function, including reaction time, after 7 days of treatment with trospium IR 20mg b.i.d. (40 mg/day total) or oxybutynin IR 5mg t.i.d. (15 mg/day total) (Herberg 1997, translated). Outcomes included precision of visual orientation, concentration, vigilance, motor co-ordination, reaction in stress situations and word match list using computerized tests. Few data are presented in the study with all outcomes described as showing no differences between trospium IR and oxybutynin IR.

  A single-dose RCT in healthy volunteers $\geq$ age 50 (N=24, mean age 60) also provides insufficient evidence that trospium IR is safer than oxybutynin IR or tolterodine IR in terms of cognitive effects. The single doses used were an entire daily dose for each drug: 45mg trospium IR (slightly higher than the recommended Canadian dose of 40mg total/day) 15mg oxybutynin IR, and 4mg tolterodine IR. The study primarily analyzed sleep architecture by polysomnography but included two cognitive tests, a number-combination test that evaluated information-processing capacity and working velocity (expressed as a reaction time), and the d2 test of attention for assessing individual sustained attention and concentration. The d2 test measures processing speed, rule compliance and quality of performance. Results are expressed

as number of items completed and mistakes/missed target items; the latter need to be interpreted with caution as they could be due to accommodation disturbances (Diefenbach 2003).

The timing of cognitive testing, 1 hour after administration, does not coincide with the peak plasma concentration for trospium IR (~5 hours for a single dose of trospium 20mg). The timing of peak drug exposure with the single dose was not verified by plasma levels; these were not measured beyond 1 hour because this was primarily a sleep study and the dose was given at night. No differences were detected in the two cognitive tests between active drugs or placebo. The study provides no information on steady state conditions and has limited generalizability. Sleep structure is an insufficient proxy for cognition and the clinical meaningfulness of a ~15% reduction in REM sleep with a higher-than recommended single dose of oxybutynin IR or tolterodine IR was not discussed.

Trospium ER vs. Oxybutynin IR

- Studies that evaluated trospium ER, a formulation not under consideration in this review, were included for supplemental information on harms.

- One comparative single-blinded, parallel group RCT was identified (NCT01178827). The trial evaluated cognitive effects of trospium ER versus oxybutynin IR in OAB patients who had age-related cognitive impairment (not further specified). The trial could not be critically appraised because a full study report was not available. Results are presented as posted on clinicaltrials.gov.

  Twenty patients 60 years or older (mean age 72 ± 8 years) were randomized to trospium ER 60mg once daily x 10 days (N=6), oxybutynin IR 5mg t.i.d. x 2 days (N=10) or oxybutynin IR placebo x 2 days (N=4). Drug levels were measured in both cerebrospinal fluid (CSF) and plasma after the last dose. Trospium ER was undetectable in CSF at a time point when the plasma concentration was 1470 pg/ml. In contrast, oxybutynin (OXY) and its major metabolite N-desethyl-oxybutynin (DEO) were detected in CSF (OXY=59.7 ± 30.9 pg/ml; DEO=386 ± 235 pg/ml) when the plasma concentrations of OXY and DEO were 8800 pg/ml ± 2840 pg/ml and 47,000 pg/ml ± 11,200 pg/ml, respectively.

  The plasma levels of oxybutynin were much higher than trospium ER, and although penetration into the brain is complex and multifactorial, depending in part on the physicochemical properties of each drug (with increased propensity of oxybutynin to cross the blood-brain barrier), the use of non-equivalent doses may have contributed to the disparity seen. Furthermore, extended-release formulations are known to result in lower plasma drug levels and overall drug exposure so the results for trospium ER cannot be extrapolated to trospium IR.

  Cognitive tests were HVLT-R (recognition and recall), and the Brief Visuospatial Memory Test-Revised (BMVT-R), a test that measures the ability to learn. Statistical analyses are not provided by the investigators for cognitive tests. Oxybutynin IR had greater negative changes on HVLT-R and BMVT-R scores, but the differences were not statistically significant based on our exploratory calculations (paired t-test). Changes did not meet the minimal threshold for reliable change indices that had previously been identified for each score (Staskin 2010).

This study's findings cannot be directly extrapolated to trospium IR because drug exposure is higher with the immediate-release formulation (Silver 2010) and this may affect blood-brain barrier crossing as well as clinical effects. In addition, information is needed on time points.

- An additional non-randomized, uncontrolled 10-day study in cognitively intact healthy volunteers did not detect trospium ER in CSF (Staskin 2010). HVLT-R scores were also below reliable change indices but the BVMT-R results were invalid as they showed a practice or training effect. A second 12-week observational study on trospium ER in women only (Geller 2012) is unreliable due to use of per protocol analyses and the high withdrawal rate (30%).

Oxybuytnin

- One direct comparator trial (Minassian 2007) measured mini-mental status examination scores in women > age 75, comparing oxybutynin ER vs. oxybutynin IR. This was the only trial identified in patients with OAB. An additional RCT in healthy volunteers compared oxybutynin gel versus oxybutynin IR (Kay 2012). Taken together, these studies do not provide sufficient evidence with which to conclude one formulation of oxybutynin has a therapeutic advantage in terms of cognitive effects in the elderly.

- No RCTs were identified that assessed long-term cognitive effects of any formulation of oxybutynin.

Available studies are described below.

RCTs

Oxybutynin ER vs. Oxybutynin IR:

- A 12-week, parallel-group trial (N=72) compared oxybutynin ER (5-10mg/day) to oxybutynin IR (7.5-15mg/day) (Minassian 2007). It was terminated early due to recruitment difficulties after an interim analysis indicated that a much larger sample size than initially planned would be needed to detect a significant difference between formulations. The only cognitive outcome was MMSE, which did not show statistically significant differences between formulations. However, this screening tool is not likely to be sensitive to mild differences in cognition.

Oxybutynin gel vs. oxybutynin IR:

Direct Comparator RCTs

- No direct comparator trials were identified in patients with OAB.
- One 8-day, parallel group, placebo-controlled RCT (N=152; mean age 67-68) assessed the effects of oxybutynin topical gel (100mgday) and oxybutynin IR (15mg/day) on cognition (Kay 2012). Participants had normal MMSE scores (~30). The identified primary outcome was delayed recall on the name-face association test (NFAT). In a pairwise analysis versus placebo, there was no significant effect of either oxybutynin gel or oxybutynin IR. The Misplaced Objects Test, a secondary outcome, showed a decline from baseline with oxybutynin IR whereas other groups showed an improvement (consistent with a practice effect). More participants on oxybutynin IR met or exceeded the minimal difference for reliable change (decline in score > 6 points) on HVLT-R immediate recall. However, on exploratory analyses (paired t-test) there were no statistically significant differences between oxybutynin IR and

placebo or oxybutynin gel. Conclusions cannot be drawn on these post hoc analyses, which are hypothesis-generating only.

More participants on oxybutynin IR withdrew due to an AE: 5.8% vs. 0 on gel or placebo. Dry mouth was also much more frequent on oxybutynin IR: 73% vs. 6% on oxybutynin gel, risk difference 67% (53% to 81%).

Placebo-controlled RCTs

- Lackner 2008 was a 4-week trial comparing oxybutynin ER 5mg/day with placebo. Cognitively impaired women residing in nursing home, aged > 65 (mean age 89 ± 6.2 years), and with OAB were enrolled. Participants had MMSE scores of 5 to 23 and randomization was stratified on the basis of MMSE score (11-23 and 5-10). The study primary outcome was mean change in the Confusion Assessment Methods (CAM) algorithm, used to measure delirium. No patient experienced delirium during the study. No difference was detected in median changes in MMSE before or after adjustment for potential confounders such as age and other medication use, but MMSE has poor sensitivity for mild CNS effects.

  This study used the lowest recommended dose of oxybutynin ER, 5mg/day, and the changes assessed predominantly pertain to delirium, not all potential CNS effects. Risk of bias was unclear or high for most domains.

- Katz 1998 enrolled 12 healthy volunteers aged >65 in a single-dose, double-blind, placebo-controlled crossover trial vs oxybutynin IR 5mg or 10mg and an antihistamine (diphenhydramine 50mg). The higher dose is greater than the maximum recommended single dose. Washout period was 7 days between treatments. Significant oxybutynin effects ($P < 0.05$) were identified on 3 of 15 cognitive measures, all indicating some degree of impairment, after correcting for multiple comparisons. Diphenhydramine had no significant effects. This trial had methodological drawbacks such as lack of adequate blinding (drugs given in orange juice; taste may have been affected).

Non-randomized studies

- An additional non-randomized study**,** Moga 2003, a controlled cohort analysis among residents of U.S. Veterans Administration long-term care facilities, compared initial users of antimuscarinic drugs with non-users. The majority of patients were elderly males, with 21-22% over the age of 85. 10% had moderate to severe cognitive impairment at baseline; 75% of users were on oxybutynin IR. A cognitive performance scale that is highly correlated with the mini-mental state exam (MMSE) was used to assess cognition; range in scores 0 (intact) to 6 (very severe impairment). No difference was observed between patients on antimuscarinics and non-users. However, the scale is not likely to be sensitive to mild differences in cognition.

The addendum on the next page presents results for all comparisons by health outcome. Further details on each drug comparison are provided in executive summaries for the individual reports on each drug comparison.

Addendum to Executive Summary

Comparative outcomes – anti-muscarinic drug class
Health outcomes are organized as a hierarchy with outcomes of greatest importance to patient health situated higher in the hierarchy. Both potential beneficial and harmful effects of drug treatment are included within this hierarchy of health outcomes, in order to assess net benefit. Note: The tables below include only rows and columns for which there is at least one direct comparator trial assessing the relevant outcome. Bolded outcomes are significant.

1. All cause mortality: The included trials were underpowered and too short in duration to assess this outcome.

2. Non-fatal serious adverse events (SAE)

Table 2[1] presents an overview of the evidence from direct comparator RCTs that provided data on non-fatal SAE. In most cases, no difference was seen between comparators, but the trials were underpowered and were too short in duration (mainly 12 weeks) to assess this outcome. The single exception was the comparison between tolterodine ER (3 trials; n=3873 in total) and fesoterodine. Patients on fesoterodine were more likely to experience SAE : RR = 1.84 (95% CI 1.10 to 3.08), absolute risk difference 1% (95% CI 0% to 2%).

Table 2: Serious adverse events – results of comparative RCTs

Drug	**Oxybutynin IR**	**Tolterodine IR**	**Tolterodine ER**	**Fesoterodine**
Oxybutynin ER/CR	3 trials (n=460) equivalent/ underpowered			
Tolterodine IR	4 trials (n=1061) equivalent/ underpowered			
Tolterodine ER		1 trial (n=1021) equivalent/ underpowered		3 trials (n=3873) Tol > Feso **- 1%**
Tolterodine ER & IR combined	5 trials (n=1547) equivalent/ underpowered			
Darifenacin CR	2 trials (n=108) equivalent/ underpowered	1 trial (n=355) equivalent/ underpowered		
Solifenacin	1 trial (n=132) equivalent/ underpowered	3 trials (n=1585) equivalent/ underpowered	1 trial (n=1200) equivalent/ underpowered	
Trospium IR	2 trials (n=2015) equivalent/ underpowered	1 trial (n=153) equivalent/ underpowered		

CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system> = better than; Equivalent = any observed differences not statistically significant; underpowered = sample size too small and/or duration too short to adequately evaluate differences between drugs in this outcome.

[1] For all comparative results tables (Table 2 – 11a), blank cells indicate that there were no comparisons between the row and column drug. If an entire row or column was blank it was deleted (i.e. omitted drugs do not have comparative data on this outcome.

SAE rates were also reported for placebo-controlled trials in the AHRQ systematic review (Shamliyan 2012). No significant differences in SAE were reported between oxybutynin, tolterodine, fesoterodine or darifenacin and placebo, but the trials were underpowered for this outcome. Only mortality, not fatal SAE, are reported for solifenacin (no difference) and no data on SAE were available for trospium. Similarly to direct comparator trials, these trials were underpowered to assess this outcome, and the strength of evidence is generally judged to be low to moderate.

3. Cognitive adverse events:
Because the included RCTs were generally of short duration, ≤ 12 weeks, were not actively evaluating cognition, and these trials were underpowered to assess infrequent cognition-related SAE no relevant data are available from the included active comparator RCTs in patients with OAB. See section below on Q3 (cognition) for details on this outcome from placebo-controlled cognition trials and trials in healthy volunteers.

Shamliyan 2012 (AHRQ review) describes CNS adverse events among women with overactive bladder on anti-muscarinic drugs, versus placebo, including dizziness, somnolence, fatigue, and headache. Most differences were not significant due to the infrequency of events. Significantly more patients experienced fatigue on tolterodine (2%; 95% CI 1% to 3%), on fesoterodine (2%; 95% CI 1% to 4%) and solifenacin (1%; 95% CI 0 to 3%). This outcome was not reported for the other included drugs. The only other CNS event occurring significantly more often on drug than placebo was headache, experienced by 3%more patients darifenacin than placebo (95% CI 1% to 6%).

4. Quality of life (QoL):
Table 3 reports on the results of comparisons of validated measures of overall quality of life measures such as SF-36. The advantage of such QoL measures over condition-specific QoL is that a general measure of health can capture both benefit and harm from treatment, whereas condition-specific QoL measures tend to focus primarily on disease-specific outcomes.

In total, there were only six drug-to-drug comparisons (four versus oxybutynin IR) of general quality of life measures. Neither tolterodine, (IR or ER & IR in combination), solifenacin nor trospium improved general QoL to a greater extent than oxybutynin IR. One trial comparing trospium IR with tolterodine IR found that patients did better by around 15 cm on a 100 cm VAS (visual analogue scales) for three of four scales assessing social integration or activities: work, hobbies, and eating/drinking. This was the only significant difference in overall quality of life noted between drugs.

Table 3: Quality of life – general

Drug	Oxybutynin IR	Oxybutynin (all formulations)	Tolterodine IR	Tolterodine ER
Tolterodine IR	1 trial (n=277) equivalent/ insufficient evidence*			
Tolterodine ER & IR combined		2 trials (n=480) equivalent		
Darifenacin CR				1 trial (n=355) equivalent

Solifenacin	1 trial (n=125) equivalent			
Trospium IR	1 trial (n=1659) equivalent/ insufficient§ (tros dose > approved)		1 trial (n=153) Tros > Tol **15/100 cm VAS** work, hobbies, eat/drinking	

CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifenacin; soli=solifenacin; TDS=transdermal system
VAS = visual analogue scales
> = better than; equivalent = any observed differences not statistically significant.
*SF-36 reported as showing no difference between drugs; insufficient information provided on this outcome.
§ includes a higher than approved dose for trospium; therefore results should be interpreted with caution – evidence considered insufficient.

Condition-specific QoL

Table 4 summarizes direct comparisons for condition-specific QoL measures. We also include results for patient perception of benefit on this table, as a secondary subjective measure of treatment benefits. Nearly all results for drug-drug comparisons were equivalent (darifenacin CR vs. tolterodine IR; trospium IR vs. tolterodine IR; trospium IR vs. oxybutynin IR; solifenacin vs. tolterodine IR) or were of small magnitude below published thresholds for minimal clinical significance: fesoterodine vs. tolterodine ER; solifenacin vs. oxybutynin IR; solifenacin vs. tolterodine ER).

Table 4: Condition-specific quality of life or patient-reported improvement or cure (where specified)**

Drug	**Oxybutynin IR**	Oxybutynin ER/CR	Tolterodine IR	Tolterodine ER
Oxybutynin IR		2 trials (n=159) Oxy IR > Oxy ER; 0.23 points UDI §		
Fesoterodine				3 trials (n=3492) Feso > Tol -4.6/100 pt ; marginal*;
Darifenacin CR			1 trial (n=355) equivalent	
Solifenacin	1 trial (n=111) Soli > Oxy** 0.5/6 pt; likely marginal*		3 trials (n=852) equivalent ¶	2 trials (n=1252) Soli > Tol 0.17/6 pt; marginal*
Trospium IR	2 trials (n=1880) equivalent** 1 trial (n=1659) equivalent (KHQ)		1 trial (n=153) equivalent**	

CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system
KHQ = King's Health Questionnaire, a condition-specific QoL scale
> = better than; equivalent - any observed differences not statistically significant.
*marginal = difference below threshold for clinical relevance
** measure of patient reported perception of improvement or cure
§ clinical meaning of this degree of difference unclear.
¶ results could not be combined in meta-analysis; either no difference or differences below minimal clinically relevant levels in all 3 trials.

5. Withdrawals due to adverse events (WDAE)

The rate of withdrawals due to adverse events (WDAE) provides a summary measure of drug tolerability that can be applied across all conditions and drug classes. As shown in Table 5, there were significant differences between drugs in tolerability. Differences in rates of WDAE ranged from 2% to 15% of patients. The latter estimate is likely to be unreliable, as it is based on one trial that compared a low dose of solifenacin (5mg/day) with a relatively high dose of oxybutynin IR (15mg/day). These doses are unlikely to be equivalent, and the higher rate of withdrawals due to adverse event on oxybutynin is likely to reflect stronger anticholinergic effects at this dose level. There were no comparisons between oxybutynin IR and solifenacin at equivalent doses. The largest reliable estimate of differences in WDAE between oxybutynin IR and a comparator is for tolterodine IR: RR for tolterodine IR vs. oxybutynin IR 0.57 (95% CI 0.43-0.76). Solifenacin had equivalent rates of WDAE to tolterodine IR, based on 3 trials (n=1700), indirectly lending weight to the likelihood that a 15% difference versus oxybutynin IR is an overestimate.

Tolterodine ER led to fewer WDAE than oxybutynin TDS or fesoterodine. There were no differences in the rates of WDAE between tolterodine IR or tolterodine ER and oxybutynin ER/CR, tolterodine IR and darifenacin CR or solifenacin, or tolterodine ER and solifenacin. For three comparisons for which no difference in WDAE was observed, sample sizes were too small to assess this outcome: darifenacin vs. oxybutynin IR, darifenacin vs. solifenacin, and trospium IR vs. tolterodine IR.

Table 5: Withdrawals due to adverse events (estimates drug tolerability)

Drug	**Oxy IR**	Oxy ER/CR	Oxy TDS	Tol IR	Tol ER	Soli	Feso
Oxybutynin ER/CR	5 trials (n=658) equivalent						
Tolterodine IR	6 trials (n=1061) Tol > Oxy **-7%**	1 trial (n=378) equivalent					
Tolterodine ER		1 trial (n=790) equivalent	1 trial (n=361) Tol >Oxy **-7%**				3 trials (n=3873) Tol > Feso **- 2%**
Darifenacin CR	1 trial (n=24) equivalent /insuffic			1 trial (n=355) equivalent		1 trial (n=77) equivalent/ insuffic.	
Solifenacin	1 trial (n=132) Soli > Oxy **-15%***			3 trials (n=1700 equivalent	2 trials (n=1275) equivalent		
Trospium IR	2 trials (n=2015) Tros > Oxy **- 3%**			1 trial (n=153) equivalent /insuffic.			

CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system
> = better than; Equivalent = any observed differences not statistically significant; insuffic: insufficient evidence to assess this outcome (1 trial, small sample size).

Shamliyan 2012 provides an overview of the rates of withdrawals due to adverse events in the class as compared with placebo in women with overactive bladder. Oxybutynin (combined formulations), fesoterodine, solifenacin and trospium were all associated with a higher rate of WDAE than placebo, with no significant differences seen for tolterodine or darifenacin. Table 5a presents an overview of these comparisons.

Table 5a, Withdrawals due to adverse events versus placebo

Drug	Absolute Risk Difference [95% CI]
Oxybutynin	5 trials (n=1483) 6% [1% to 13%] NNH=17
Tolterodine	10 trials (n=4466) 1% [- 1% to 3%], NS
Fesoterodine	4 trials (n=4433) 3% [1% to 6%]NNH=32
Solifenacin	7 trials (n=9808) 1% [0 to 3%] NNH=77
Darifenacin	7 trials (n=3138) , 0 [- 1% to 2%], NS
Trospium	6 trials (n=3936) 2% [2% to 3%] NNH=55

NNH= numbers needed to harm; NR= not reported; NS= non-significant at $p<0.05$
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, http://www.ncbi.nlm.nih.gov/books/NBK92960/, and Shamliyan 2012, Appendix Table.

6. Mean reduction in incontinence episodes per 24 hours:
Reduction or elimination of incontinence is a key treatment aim and arguably the most important treatment aim. Reduction in the frequency of incontinence was measured and reported in many more trials than the proportion of patients who had become dry or continent. An overview of results of comparative trials is presented in Table 6.

There were significant differences observed for 4 comparisons, two of which reflect mixed results. Overall there was no difference in frequency of incontinence episodes between tolterodine IR and oxybutynin IR. However, if two trials that contribute to considerable heterogeneity are removed from the analysis, oxybutynin IR led a reduction of 0.4 more incontinence episodes per day. This is an exploratory subanalysis but it may reflect differences in response between different demographics. The two excluded trials enrolled younger Asian patients (Lee 2001; Xia 2002). In one trial, patients on solifenacin 5mg had a reduction of an additional 0.5 episodes per day compared with tolterodine IR; patients in the same trial on solifenacin 10mg did not have a significant difference in reduction in frequency of incontinence episodes, although there was a similar direction of numerical difference. Patients on solifenacin also experienced a reduction of an additional 0.6 episodes per day as compared with tolterodine ER. (Chapple 2005) Fesoterodine also led to 0.2 fewer episodes per day than tolterodine ER, based on a meta-analysis of results of 3 trials. (Chapple 2007; Herschorn 2010, Kaplan 2010.

These differences in frequency of incontinence are modest, ranging from around 1 less

incontinence episode per 2 days to 1 less episode per 5 days. A number of other comparisons did not find a difference in frequency: oxybutynin TDS vs. oxybutynin IR and versus tolterodine ER; oxybutynin ER/CR vs. oxybutynin IR; darifenacin vs. oxybutynin IR and versus tolterodine ER; solifenacin vs. oxybutynin IR, and trospium vs. tolterodine IR.

Table 6. Reduction in incontinence episodes

Drug	Oxybutynin IR	Tolterodine IR	Tolterodine ER
Oxybutynin IR		6 trials (n=912) equivalent *subanalysis:* 4 trials (n=767)* Oxy>Tol **-0.4/day**	
Oxybutynin ER/CR	5 trials; data useable for 1 (n=94)§ equivalent		
Oxybutynin TDS	1 trial (n=72) equivalent		1 trial (n=361) equivalent
Fesoterodine			3 trials (n=3525) Feso >Tol **-0.2/day**
Darifenacin CR	1 trial (n=58) equivalent		1 trial (n=355) equivalent
Solifenacin	1 trial (n=111) equivalent	1 trial (n=298;Soli 5mg); Soli > Tol **-0.5/day** 1 trial (n=315 on Soli 10mg);Soli 10mg/ equivalent	1 trial (n=743) Soli > Tol **- 0.6/day****
Trospium IR	2 trials (n=358; n=1658, meta-analysis not possible) equivalent (both)	1 trial (n=153) equivalent	

CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system
> = better than; Equivalent = any observed differences not statistically significant; insuffic: insufficient

The pooled difference in reduction in urinary incontinence for all the drugs in this class versus placebo, based on a Cochrane systematic review, was -0.51 incontinence episodes/day (95% CI -0.66 to -0.37) (Nabi 2006) Table 6a provides an overview of two related outcomes versus placebo, differences in percent of patients who became continent and patient perception of improvement, among women with OAB (Shamliyan 2012). Different formulations of oxybutynin and tolterodine are considered jointly. Of note in this analysis, patient perception of improvement did not differ between trospium and placebo, based on a meta-analysis of two trials measuring this outcome (n=1176). Four trials assessed the proportion of patients who had achieved continence, and found an 11% increase on trospium (95% CI 8% to 14%) versus placebo.

Table 6a. Antimuscarinic Drugs vs. Placebo: outcomes by drug from AHRQ 2012 Review

Drug	Oxybutynin (N) [95% CI]	Tolterodine (N) [95% CI]	Fesoterodine (N) [95% CI]	Solifenacin (N) [95% CI]	Trospium (N) [95% CI]	Darifenacin (N) [95% CI]

Continence	4 trials (992) **RR 1.7** [1.3 to 2.1] **RD 11%** [6% to 16%]	4 trials (3404) **RR 1.2** [1.1 to 1.4] **RD 9%** [4% to 13%]	2 trials (2465) **RR 1.3** [1.1 to 1.5] **RD 13%** [6% to 20%]	5 trials (6304) **RR 1.4** [1.4 to 1.6] **RD 11%** [6% to 16%]	4 trials (2677) **RR 1.7** [1.5 to 2.0] **RD 11%** [8% to 14%]	NA
Patient perception of improvement	9 trials (1244) **RR 1.5** [1.2 to 1.9] **RD 17%** [10% to 24%]	7 trials (6119) **RR 1.3** [1.1 to 1.4] **RD 10%** [4% to 15%]	2 trials (1896) **RR 1.3** [1.2 to 1.5] **RD 10%** [6% to 15%]	2 trials (1507) **RR 1.5** [1.0 to 2.1] **RD 18%** [10% to 26%]	2 trials (1176) RR 1.1 [0.6 to 2.0] RD 8% [-10% to 25%	3 trials (1011) **RR 1.3** [1.2 to 1.5] **RD 12%** [6% to 17%]
N= number of patients; NA= not applicable (no RCTs report this outcome); RD= risk difference; RR=relative risk; Bolded results are statistically significant Data from Shamliyan 2012						

7. Urgency:

No differences were observed for urgency for any of the comparisons with oxybutynin IR; comparator drugs were oxybutynin ER/CR, Tolterodine IR, darifenacin, solifenacin and trospium. There was less urgency with solifenacin than tolterodine IR or ER, and less with fesoterodine than tolterodine ER, mainly with differences of less than 1 urgency episode per day. Darifenacin did not differ from tolterodine IR.

Table 7: Number of urgency episodes

Drug	Oxybutynin IR	Tolterodine IR	Tolterodine ER
Oxybutynin ER/CR	1 trial (n=94) equivalent		
Tolterodine IR	1 trial (n=106) equivalent		
Fesoterodine			3 trials (n=3525) Feso > Tol **0.3/day**
Darifenacin CR	1 trial (n=58) equivalent	1 trial (n=355) equivalent	
Solifenacin	1 trial (n=111) equivalent	1 trial (Soli 5mg, n=514; 10mg, n-511) Soli > Tol **0.8 – 1/day**	2 trials (n=1190) Soli > Tol **0.4/day**
Trospium IR	1 trial (n=358) equivalent		
CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system > = better than; Equivalent = any observed differences not statistically significant; insuffic: insufficient			

8. Nocturia:

Few trials reported on treatment effects on nocturia. Fesoterodine reduced nocturia episodes by a mean of 0.09 per night (95% CI 0.18 to 0.0), compared with tolterodine ER, based on meta-analysis of 3 trials. (Chapple 2007; Herschorn 2010; Kaplan 2010) This degree of difference is unlikely to be clinically meaningful as it represents one less visit to the toilet in the night per 11 days.

Table 8: Reduction in nocturia (mean # fewer episodes/night)			
Drug	Oxybutynin IR	Tolterodine IR	Tolterodine ER
Fesoterodine			3 trials (n-3593) Feso > Tol -0.09/night
Solifenacin	1 trial (n=111) equivalent	2 trials (n=379; n=118; meta-analysis not possible) equivalent	1 trial (n=975) equivalent
CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifenacin; soli=solifenacin; TDS=transdermal system > = better than; Equivalent = any observed differences not statistically significant.			

9. Total adverse events (AE):

Many of the included RCTs failed to report the number of patients in total in each treatment arm who had experienced one or more adverse event. Table 9 provides an overview of the comparative evidence.

More patients on oxybutynin IR experienced AE than patients on tolterodine IR, solifenacin or trospium, and more patients on fesoterodine experienced AE than patients on tolterodine ER.

There were no statistically significant differences in rates of total AE between oxybutynin ER/CR or darifenacin and oxybutynin IR; between solifenacin and tolterodine IR or tolterodine ER, or between trospium and tolterodine IR.

Table 9: Total adverse events (AE)				
Drug	**Oxybutynin IR**	Tolterodine IR	Tolterodine ER	Fesoterodine
Oxybutynin ER/CR	2 trials (n=193) equivalent			
Tolterodine IR	7 trials (n=1613) Tol > Oxy **-17%**			
Tolterodine ER				3 trials (n=3873) Tol > Feso **-10%**
Darifenacin CR	2 trials (n=69; n=24; no meta-analysis) equivalent		1 trial (n=355) equivalent	
Solifenacin	1 trial (132) Soli > Oxy **-20%**	3 trials (n=852 5mg; n=839 10mg) equivalent*	2 trials (n=1275) equivalent	
Trospium IR	2 trials (n=2015) Tros > oxy **-5%**	1 trial (n=153) equivalent		
CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifienacin; soli=solifenacin; TDS=transdermal system > = better than; Equivalent = any observed differences not statistically significant; insuffic: insufficient evidence to assess this outcome (1 trial, small sample size). *meta-analyses carried out separately for solifenacin 5mg and 10mg; equivalent for both				

Table 9a, below, provides an overview of total adverse event rates versus placebo in women with overactive bladder, as reported in the AHRQ review. (Shamliyan 2012) This comparison includes combined formulations.

Drug	Absolute Risk Difference versus placebo in women with overactive bladder (95% CI)
Oxybutynin	3 trials (n=821) 10.1% (- 5% to 26%), NS
Tolterodine	15 trials (n=4162) 7.9% (5% to 11%)
Fesoterodine	6 trials (n=4145) 15.3% (11% to 19%)
Solifenacin	6 trials (n=1713) 18% (9% to 27%)
Darifenacin	5 trials (n=1495) 18.3% (12% to 25%)
Trospium	5 trials (n=2967) 11.6% (8% to 15%)

Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, plus Supplement 9 http://www.ncbi.nlm.nih.gov/books/NBK92960/; and Shamliyan 2012, Appendix Table.

10. Dry mouth:

Nearly all comparisons between other drugs and formulations and oxybutynin IR found a lower rate of dry mouth with the comparator, ranging from an 8% difference for oxybutynin ER/CR, to a 59% difference for oxybutynin TDS. The latter was based on active solicitation of information on adverse events from patients, in a questionnaire on 10 anticholinergic AE, which was used as a basis for dose titration decisions. Adequacy of blinding was not assessed in this trial and the high reported AE rates (for both treatment arms but especially oxybutynin IR) may have led to a loss of blinding, which could affect both subsequent reporting and titration decisions. It is also possible that trials relying on passive AE reporting, with fewer rates of dry mouth and smaller magnitudes of difference between treatment arms are under-reporting patient experience with this AE, as it is considered an expected outcome of anti-muscarinic treatment.

Tolterodine ER was also associated with less dry mouth than Oxy ER/CR, solifenacin and fesoterodine, with differences ranging from 6 to 14%. Conversely a comparison between solifenacin 5mg and tolterodine IR found a 7% lower rate of dry mouth with solifenacin; there was no significant difference between solifenacin 10mg and tolterodine IR among the 839 patients in the trial included in this comparison. Thus the difference at 5mg is likely to reflect dose-related differences rather than product characteristics per se.

Table 11. Dry mouth						
Drug	Oxy IR	Oxy ER/CR	Oxy combined	Tol IR	Soli	Feso
Oxybutynin ER/CR	5 trials (n=652) Oxy ER> IR **-8%**					
Oxybutynin TDS	1 trial (n=71) Oxy TDS>IR **-59%**			1 trial (n=361) equivalent		
Tolterodine IR	7 trials (n=1410)					

	Tol > Oxy **-32%**					
Tolterodine ER		1 trial (n=790) Tol > Oxy **- 7%**			2 trials (n=1275) Tol > Soli **-6%**	3 trials (n=3873) Tol > Feso **-14%**
Tolterodine IR and ER combined			10 trials (n=3521) Tol > Oxy **-19%**			
Darifenacin CR	2 trials (n=69; n=24) no meta-analysis equivalent			1 trial (n=355) equivalent		
Solifenacin	1 trial (n=132) Soli> Oxy **-48%**			3 trials (n=852 soli 5mg; 839,10mg) Soli 5 > Tol **-7%** Soli 10 equivalent		
Trospium IR				1 trial (n=153) equivalent		
CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifenacin; soli=solifenacin; TDS=transdermal system > = better than; Equivalent = any observed differences not statistically significant.						

11. Constipation

Table 11 presents an overview of the comparative results for constipation. Tolterodine ER led to less constipation than fesoterodine, solifenacin and darifenacin, with the largest magnitude of difference seen with darifenacin (12%) and the least with fesoterodine (1%). One trial including 76 patients compared oxybutynin TDS with oxybutynin IR and found that a large difference in rates of constipation between the two formulations (29% fewer patients on oxybutynin TDS experienced constipation, 95% CI -49% to -8%).(Davilo 2001) The difference between estimations of constipation rates in this study and the other studies under review is that patients were asked to fill in a questionnaire regularly about a set of 10 symptoms, with results used to titrate dosage. It is likely that active solicitation of this information led to higher reported rates (21% on oxybutynin TDS, 50% on oxybutynin IR) than in other studies that relied on passive reporting. The confidence intervals around this estimate are wide, due to small sample size, and the lack of placebo treatment arm makes results more difficult to interpret results.

Table 11. Constipation					
Drug	**Oxy IR**	Oxy combined	Dari	Soli	Feso
Oxybutynin ER/CR	2 trials (n=230) equivalent				
Oxybutynin TDS	1 trial (n=76) **Oxy TDS>IR -29%**				
Tolterodine ER			1 trial (n=355)	2 trials	3 trials

			Tol> Dari -12%	(n=1275) **Tol > Soli - 4%**	(n=3873) **Tol > Feso -1%**
Tolterodine IR and ER combined		5 trials (n=2276) equivalent			
Darifenacin CR	2 trials (n=61; n=24) equivalent/ insuffic*				
CR=controlled release; ER=extended release; IR=immediate release; oxy= oxybutynin; tol= tolterodine; feso=fesoterodine; dari=darifenacin; soli=solifenacin; TDS=transdermal system > = better than; Equivalent = any observed differences not statistically significant; insuffic: insufficient evidence to assess this outcome					

In comparison the AHRQ review (Shamliyan 2012) found that the increase in constipation rates versus placebo ranged from 1% to 8%, with tight confidence intervals around most estimates and a strength of evidence judged to be high. (See Table 11a) Oxybutynin (IR and ER formulations combined) was the only drug not associated with a significant increase in constipation rates, but the strength of evidence is considered moderate rather than high for this comparison.

Table 11 a. Product-specific rates of constipation vs. placebo in women with overactive bladder*

Drug	Absolute Risk Difference vs. placebo [95% CI]
Oxybutynin	7 trials (n=1743); 3% [-1% to 9%], NS
Tolterodine	14 trials (n=9592); 1% [0 to 2%]
Fesoterodine	7 trials (n=7695); 4% [0 to 10%]
Darifenacin	5 trials (n=2239); 8% [2% to 15%]
Trospium	5 trials (n=3335); 7% [5% to 9%]
Solifenacin	8 trials (n=11765); 7% [5% to 10%]

*data from Shamliyan 2012 (AHRQ review)

Other Adverse events

A number of other adverse events are associated with anti-muscarinic drugs for overactive bladder, but these occur too infrequently to assess comparative frequency between drugs. These include other gastro-intestinal adverse events such as dyspepsia, ocular adverse events, most often blurred

vision and accommodation difficulties, and urinary retention. The included RCTs were not adequately powered to assess frequency of these AE.

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Chapter 1. Introduction and Background to the Series

Introduction

PSD Request

Pharmaceutical Services Division (PSD) requested a comparative drug class review, involving a series of clinical evidence reviews, on oxybutynin and its antimuscarinic drug class comparators for the treatment of overactive bladder syndrome (OAB). Currently, oxybutynin immediate release (IR) is the only drug in this class that is a regular benefit of PharmaCare for the treatment of OAB.

The following questions were received from PSD:

1. What is the comparative clinical effectiveness, safety and cost-effectiveness of drugs under review to oxybutynin immediate-release (IR) for the treatment of overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms?

2. In addition to the Common Drug Review Clinical Evidence reviews, is there further evidence that trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™) and fesoterodine (Toviaz*) demonstrate improved clinically relevant outcomes, a better safety profile and/or optimized cost-effectiveness when compared with oxybutynin IR?

3. Elderly patients may be more prone to the anticholinergic adverse effects especially the central nervous system from the antimuscarinic agents used in overactive bladder. What is the safety evidence that trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz®), oxybutynin gel (Gelnique™), and oxybutynin transdermal patch (Oxytrol™) have less effect on cognition than oxybutynin IR?

In further discussions, PSD requested that Question 1 be expanded to include comparisons of each comparator drug with each other. The research questions are listed in the Methods Chapter on page 77.

Organization of the report

This report is divided into a background, methods, results and discussion section. The results section is organized by drug comparison, with Q1-3 listed consecutively for each drug comparison. Each review of a drug-drug comparison is a separate chapter in the series. These are followed by a summary chapter on cognition and a final chapter integrating the evidence for the drug class.

Background

Overactive Bladder (OAB) Syndrome: Definition and Prevalence

Overactive bladder syndrome (OAB) is primarily defined as a set of symptoms including urgency, “a sudden compelling desire to pass urine, which is difficult to defer”, urgency incontinence (involuntary leaking of urine associated with a feeling of urgency), nocturia (waking in order to void in the middle of the night) and frequency of voiding (Abrams 2002). The first standardized definition of OAB as a constellation of symptoms of urgency with or without associated

incontinence, frequency and nocturia, dates from 2002 (Abrams 2002). Attention had previously focused primarily on urinary incontinence associated with urgency.

Terminology was further standardized by the replacement of term urge incontinence with urgency incontinence in 2010, to distinguish urgency from the normal sensation associated with a full bladder (Haylen 2010).

The main mechanism by which OAB occurs is hypothesized to be overactivity of the detrusor muscle, the bladder smooth muscle that controls urination. When relaxed, the detrusor allows the bladder to fill with urine; contraction squeezes the bladder and leads to urination. Dysfunctions include involuntary contractions that cause urine to leak and inadequate contractions associated with incomplete voiding. Detrusor overactivity is characterized as idiopathic if no cause has been identified; if caused by a neurological condition it is called neurogenic. However, although a proximate mechanism is hypothesized via detrusor muscle instability, OAB is symptom-based only with no requirement for prior urodynamic investigations or link to a specific cause. Madersbacher estimates that only 50% of patients with OAB have detrusor overactivity on urodynamic examination, and conversely many patients with urodynamically established detrusor overactivity fail to have clinical symptoms (Madersbacher 2005). OAB is a diagnosis of exclusion, as a person is considered to have OAB when urinary tract infections and pathologies leading to similar symptoms are ruled out.

The definition of OAB introduced in 2002 greatly expanded the number of affected patients as compared with urge incontinence. In their systematic review for the U.S. Agency for Healthcare Research and Quality (AHRQ), Hartmann et al. state that, “momentum toward a very broad definition in marketing was a factor in the updated consensus definition…”, with specific reference to the role of U.S. direct-to-consumer advertising (Hartmann 2009). A number of studies have examined population-based prevalence rates. Reported rates vary depending on how criteria for OAB are defined, whether respondents are asked about symptoms over specific time periods, and whether or not they are asked if they are bothered by symptoms. The threshold for urinary frequency is usually set at $\geq$8 micturitions within a 24 hour period. This threshold is characterized as arbitrary, and is based on an average of around 6 micturitions/24 hours in healthy adults (Milsom 2001).

Herschorn 2007 carried out a survey on random sample of 1000 Canadian adults (mean age 44; response rate not stated), in which respondents were first asked if they had a urinary or bladder control problem and then about specific symptoms. In total 8.9% (5.4% of men, and 12.2% of women) stated that they had a bladder control problem, with the most common type being stress incontinence in women, not urgency (Herschorn 2007). If symptom prevalence is reported instead, 43% of men and 57% of women reported at least one symptom, most commonly nocturia (36%), defined as $\geq$ 1 void per night. The authors report a 13.9% rate of OAB with no significant differences between men and women. This is not controlled for whether the respondent believed he or she had a problem. Urge incontinence occurred more frequently in women than men: 7.1% vs. 3.3%, p=0.007.

A previous Canadian population-based survey had reported an 18.1% OAB rate (Corcos 2004), a European survey 16.6% (Madersbacher 2005), a U.S. survey 16.0% (Stewart 2003), a Japanese survey 12.4% (Homma 2005), and a joint European/Canadian survey 11.8% (Irwin 2007), with prevalence rates increasing with age. None of these surveys adequately account for symptom

severity or whether respondents identified themselves as needing treatment. A 2012 report notes that nearly three quarters of epidemiological studies of OAB were funded by drug manufacturers (Tikkinen 2012a). This includes all of the surveys listed above. The AHRQ 2009 systematic review on OAB in women identified 15 studies (N=64,528 women) on OAB prevalence in 16 distinct populations (Hartmann 2009). Data collection was mainly through questionnaire surveys. Estimates of OAB prevalence in women ranged from 8 to 31%, with an average estimate of 15% meeting OAB criteria (excluding the highest and lowest estimates), with 8% of those surveyed having OAB with a component of urgency incontinence. A total of 48 studies looked at urgency incontinence, 28 before the 2002 standardization of criteria. Average urge incontinence was 10% in the U.S., 11% in Europe and 10% in Asia. Of note, the influence of age was less pronounced for urgency incontinence than for OAB prevalence.

A more recent, independent population-based prevalence study of OAB reports lower rates. Tikkenen et al. surveyed a random sample of the Finnish population aged 18-79 (N=3727; 62% participation rate) (Tikkinen 2012b). The age-standardized prevalence of OAB, based on International Continence Society definitions, was 6.5% (95% CI 5.5% to 7.6%) in men and 9.3% (95% CI 7.9% to 10.6%) in women. In this study, 0.7% of men and 2.4% of women had OAB with urge incontinence.

If men with benign prostatic hyperplasia (BPH) are excluded, the prevalence of OAB in men is 5.6% (Tikkenin 2012b). BPH should be excluded as symptoms overlap with OAB, but etiologies differ, and anti-muscarinic drugs are ineffective against obstruction due to prostate enlargement. A legal case launched in 2007 by 22 U.S. states and the District of Columbia under the False Claims Act claims that Pfizer carried out illegal off-label promotion of tolterodine for men with BPH, a use for which the product had not been approved nor found to be effective (U.S. District Court District of Massachusetts 2010).

There have been few studies on the natural history of OAB. A 2009 systematic review on OAB in community-dwelling women reported that 23 to 25% of cases resolve over a year's time (Hartmann 2009). No studies on the lifetime natural history of OAB were identified in that review.

Treatment Goals and Options

The goals of treatment are to reduce symptoms that are distressing to the patient and that interfere with quality of life. As pointed out by Hartmann et al., the symptoms are not de facto harmful, though consequences such as sleep interruption or risks of falls and fractures from rushing to the toilet might be (Hartmann 2009). In community dwelling ambulatory women, the most distressing symptom is urgency incontinence. A 50 to 70% reduction in incontinence episodes from baseline has been identified as an important improvement to the patient but may in part depend on the type of incontinence (Shamliyan 2012).

Achieving continence is also a key goal for individuals who are dependent on others for caregiving as incontinence is often a factor in caregiver decision-making about long-term placement. Although meaningful to the patient, few studies report 'cure' or continence, suggesting selective outcome reporting bias in clinical trials (Madden 2012).

Treatment options include non-pharmacological or lifestyle measures. Available pharmacological agents target the cholinergic (anticholinergic or antimuscarinic drugs) or adrenergic nervous systems.

Mirabegron, a β adrenoceptor agonist, was approved in Canada this year (Health Canada Summary of Basis of Decision Myrbetriq 2013). Summarized clinical trial results in Health Canada's Summary Basis of Decision report a reduction of around 0.4 incontinence episodes per 24 hours in 12-week trials, as compared with placebo. Mirabegron's adverse event profile includes hypertension, QT prolongation, and cardiac arrhythmias (Mirabegron Product Monograph).

Procedural treatments such as botulinum-A toxin injections into the detrusor muscle (approved in Canada for neurogenic but not idiopathic detrusor overactivity) or intravesical instillation of drugs have been used in patients refractory to conservative and other pharmacological treatments. Percutaneous tibial nerve stimulation and sacral neuromodulation have also been used.

Non-Pharmaceutical Treatment Options

Patients with OAB may be treated with conservative measures such as reduction in caffeinated drinks, control of fluid intake and recommendations for weight loss (Rai 2012). The most common non-drug approach is bladder training. Patients keep a bladder chart to record volumes voided and the interval between each micturition, and are encouraged to gradually increase time between voids. Pelvic floor training exercises are used in patients with mixed incontinence (stress and urge) or in stress incontinence alone. There is only limited information about habit retraining or other conservative measures (e.g., prompted voiding) in the context of caregiving for the frail elderly or people who have cognitive impairment (Ostaszkiewicz 2004).

Antimuscarinic Drugs

The most commonly used pharmacological agents are antimuscarinic drugs. Until 2004, the only drugs approved were oxybutynin and tolterodine. There are eleven drugs or different formulations under review and available in BC. These include five different formulations of oxybutynin (IR, ER, controlled release (CR), transdermal gel, transdermal patch), two formulations of tolterodine (IR, ER), fesoterodine, darifenacin ER, solifenacin and trospium IR. Table 1 provides the approval year in Canada for the eleven drugs or formulations under review, and the CDEC recommendations for the five drugs that have undergone a Common Drug Review.

Table 1. Drug Approval Dates in Canada and CDEC Recommendations

Drug	Manufacturer	Approval Year	CDEC Date Year-month-day	CDEC Recommendation
Oxybutynin IR (Ditropan)	Now generic	1981	NA	NA - (regular benefit in British Columbia)
Oxy ER (Ditropan XL)	Janssen	2001	NA	NA
Oxy CR (Uromax)	Purdue	2006	NA	NA

Tolterodine IR (Detrol)	Pfizer	1998	NA	NA
Tolterodine ER (Detrol LA)		2002	NA	NA
Oxy transdermal (Oxytrol)	Watson	2004	NA	NA
Trospium IR (Trosec)	Oryx/Sunovian	2006	2006-08-24	List for patients who cannot tolerate IR-oxybutynin and in a similar manner as drug plans list tolterodine.
Darifenacin (Enablex)	Novartis	2005	2009-04-16 (Resubmission) 2006-10-19	List for patients who cannot tolerate or have insufficient response to an adequate trial of IR-oxybutynin, and in a similar manner as drug plans list tolterodine. Do not list.
Solifenacin (Vesicare)	Astellas	2006	2009-06-17 (Resubmission) 2007-01-17	List for patients who cannot tolerate or have insufficient response to an adequate trial of IR-oxybutynin, and in a similar manner as drug plans list tolterodine. Do not list.
Oxy gel (Gelnique)	Watson	2011	2012-05-24	Do not ist
Fesoterodine (Toviaz)	Pfizer	2012	2012-10-18	List in similar manner as tolterodine ER.
NA=not available (pre-dated Common Drug Revieq); CDEC=Common Drug Expert Committee; TPD=Therapeutics Product Directorate				

Tables 2-3 provide an overview of dosing and administration for each of the included drugs, and requirements for dose adjustments for the elderly and patients with renal and hepatic impairment. For most of the included drugs and formulations, there are no specific labeled requirements for dose adjustment in the elderly. Oxybutynin IR labeling recommends beginning at the lowest dose in patients over 65; oxybutynin CR includes a caution about use in elderly, debilitated patients. In Canada, 5 mg is the lowest dose mentioned in the oxybutynin IR product monograph; the U.S. package insert specifically states that 2.5 mg should be used (Oxybutynin IR Product Monograph; Ditropan U.S. Package Insert).

Table 2. Dose, Frequency and Administration of Antimuscarinic Drugs for OAB

Drug	Usual Dose	Administration (oral unless otherwise stated)
Oxybutynin IR	5 mg bid-tid; max. 5 mg qid (20 mg/day)	Best if taken on empty stomach
Oxybutynin ER	5-10 mg once daily; max. 30 mg once a day	Must be swallowed whole Can be taken without regard to meals. Dose titration no faster than weekly intervals
Oxybutynin CR	10-15 mg once daily; max. 20 mg/day	Must be swallowed whole
Oxybutynin TDS	3.9 mg/day patch applied every 3-4 days	Apply to dry, intact skin on abdomen, hip or buttocks; Apply each patch to a new site; avoid reapplying to same site within 7 days.
Oxybutynin Gel	10% gel in 1 gm applied daily	Apply to abdomen, upper arms/shoulders, or thigh once daily. Rub into skin until dry. Avoid open flame (flammable) until dry.

Tolterodine IR	1-2 mg bid	Can be taken with food Food intake increases bioavailability by a mean of 53% but does not affect levels of 5-HMT so no dose adjustment required; Administer a minimum of 2 weeks before relief can be expected; **Use 1 mg bid for patients taking concurrent CYP3A4 inhibitors.**
Tolterodine ER	2-4 mg once daily; max. 4 mg	Must be swallowed whole; No clinically relevant changes with food; **Use 1 mg bid for patients taking concurrent CYP3A4 inhibitors.**
Fesoterodine	4 mg daily; max. 8 mg daily	Must be swallowed whole; May be taken without regard to food;
Darifenacin ER	7.5 mg -15 mg daily	Must be swallowed whole; May be taken without regard to food; Increase to 15 mg daily no sooner than 2 weeks after starting
Solifenacin	5 mg once daily; max. 10 mg daily	May be taken without regard to food
Trospium IR	5 mg bid-tid (max. 5 mg qid)	Take on an empty stomach
Modified from Semla 2011; bid=twice a day; CR=controlled release; ER=extended release; gm=grams; mg=milligrams; IR=immediate release; max=maximum; tid=three times a day; qid=four times a day; Note: Extended-release formulations may be variously called XL, ER or CR.		

Table 3. Dose adjustments for Special Populations

Drug	Elderly > age 65	Renal Impairment	Hepatic Impairment
Oxybutynin IR	In elderly and debilitated patients, it is advisable to initiate treatment at the lowest recommended dosage and to increase the dosage carefully according to tolerance and response	should be used with caution	should be used with caution
Oxybutynin ER[1]	No adjustment	use with caution; no recommended adjustment	use with caution; no recommended adjustment
Oxybutynin CR[2]	Use with caution in debilitated patients; no recommended dosage adjustment	Use with caution; no recommended adjustment	Use with caution; no recommended adjustment
Oxybutynin TDS	No adjustment	Use with caution; no recommended adjustment	Use with caution; no recommended adjustment
Oxybutynin Gel	No adjustment	Has not been tested	Has not been tested
Tolterodine IR	No adjustment	CrCl 10-30 mL/min: 1 mg bid	1 mg bid
Tolterodine ER	No adjustment	CrCl 10-30 mL/min: 2 mg daily	2 mg once daily
Fesoterodine	No adjustment	CrCl < 30 mL/min: max. 4 mg daily	Moderate impairment:no adjustment Severe: not recommended
Darifenacin ER	No adjustment		Moderate impairment: max. 7.5 mg daily
Solifenacin	No adjustment	CrCl < 30 mL/min: max. 5 mg daily	Moderate impairment: maximum dose 5 mg daily. Avoid if severe impairment

Trospium IR	No adjustment	CrCl < 30 mL/min: 20 mg once daily at bedtime[3]	Use with caution in moderate and severe hepatic dysfunction
[1] Ditropan XL; [2] Uromax; [3] Diurnal variation occurs with decreased exposure for evening doses; CrCl=creatinine clearance; CR=controlled release; IR=immediate release; ER=extended release; max=maximum			

Mechanism of Effect: anti-muscarinic activity

Antimuscarinic drugs bind to and block the activation of muscarinic receptors. By doing so, they act as competitive antagonists of the neurotransmitter acetylcholine. There are five subtypes of muscarinic receptors, all of which are widely distributed throughout the body (Abrams 2006) (Table 4).

Table 4. Distribution of muscarinic receptor subtypes

Subtype	General distribution
M1	Brain (cortex, hippocampus), glands (e.g., salivary), sympathetic ganglia
M2	heart, hindbrain, smooth muscle (e.g., bladder, gastrointestinal tract)
M3	smooth muscle (e.g., bladder, eye), glands (e.g., salivary), brain
M4	brain (forebrain, striatum)
M5	brain (substantia nigra), eye
Modified from Andersson 2004	

The urinary bladder has two functions, storage of urine and voiding. Storage of urine requires the bladder to relax and to fill without a large increase in intravesical pressure. This is achieved by the sympathetic (adrenergic) nervous system relaxing the bladder wall and contracting the bladder outlet. Voiding requires the coordinated contraction of the detrusor smooth muscle with simultaneous relaxation of the bladder outlet and urethra. Adenosine triphosphate (ATP) initiates detrusor contraction during voiding while acetylcholine acts on muscarinic receptors to maintain contraction and completely empty the bladder. Nitric oxide is the main neurotransmitter to relax the bladder outlet (Sellers 2012).

Parasympathetic (cholinergic) nerves release acetylcholine, and there are also non-neuronal sources of acetylcholine in the bladder wall (Sellers 2012; Andersson 2011). An increase in non-neurogenic acetylcholine release occurs with age and in distended bladder. It is debated whether the release of non-neurogenic acetylcholine normally functions as a negative feedback mechanism. Other excitatory transmitters exist, and are increased in OAB and in obstructed bladder.

All five muscarinic receptor subtypes are expressed in various structures of the bladder (Table 5). The receptors are functionally coupled to G proteins. The signal transduction pathways that are activated vary and can be inhibitory or excitatory. M3 receptors mainly mediate detrusor contraction. M2 receptors are more abundant and are inhibitory receptors. They are also likely involved in detrusor overactivity, opposing detrusor relaxation mediated by the sympathetic nervous system (Andersson 2011; Abrams 2007; Andersson 2004). Activation of muscarinic receptors in the bladder urothelium induces the release of many factors including ATP and nitric oxide. Muscarinic receptors located on presynaptic nerve terminals regulate neurotransmitter release.

Table 5. Muscarinic receptor subtypes: effects relevant in pathophysiology of OAB

Subtype	Function
M1	Facilitates release of acetylcholine in the bladder
M2	Contributes to muscarinic receptor-mediated detrusor contraction
M3	Main contributor to muscarinic receptor-mediated detrusor contraction
M4	Role unclear
M5	Role unclear
Modified from Andersson 2004	

Muscarinic receptors or their functions are modified in bladder disorders associated with OAB. The effects of antimuscarinic drugs may therefore vary depending on the pathophysiologic state of the bladder.

Antimuscarinic drugs competitively block M3 muscarinic receptors on the detrusor muscle to relax the bladder. When used in OAB at doses that do not cause urinary retention, the drugs act mainly during the storage or filling phase to increase bladder capacity and decrease urgency. Ongoing basal release of acetylcholine is increased from nerves or non-neurogenic sources such as the urothelium in conditions associated with detrusor overactivity. The released acetylcholine directly or indirectly stimulates afferent nerves (leading to the brain) to generate signals that initiate the micturition reflex or enhance the spontaneous contraction of the detrusor. Antimuscarinic drugs prevent the generation of the afferent signals to the brain (Andersson 2011).

All available antimuscarinic drugs have dose-limiting adverse effects related to their anticholinergic activity. Commonly reported adverse events such as dry mouth and constipation are in part mediated by blocking the M3 receptor, the same receptor important in bladder contraction. Cardiovascular effects are attributable to blocking M2 receptors, and central cognitive effects likely involve M1 and M2 receptor blockade (Table 6). All have similar contraindications, warnings and precautions.

Table 6. Muscarinic receptor subtypes and association with adverse events

Adverse effect	Receptor subtype likely involved
Dry mouth	M1 and M3 receptors control secretion in salivary glands
Constipation	M2 and M3 receptors
Eye (blurred vision)	M3 and M5 receptors
Cardiac (heart rate, QT prolongation)	M2 receptors
Central Nervous System	M1 and M2 receptors for cognition but all 5 subtypes expressed

Manufacturers of some antimuscarinic drugs claim their products have functional tissue selectivity (e.g. selectivity for bladder over salivary glands), based on preclinical models and in vitro data. This phenomenon is unrelated to receptor subtype selectivity. Evidence for tissue or end organ selectivity is weak and may reflect differences in the magnitude of activation of the end organ for technical reasons. It has been noted that the apparent organ selectivity might be model specific and is not necessarily valid to humans (Abrams 2007).

Antimuscarinic drugs differ in their structure, relative receptor selectivity, duration of action, and metabolism. Genetic variation in metabolism can alter the ratio of parent compound to active metabolite(s) for some drugs (e.g., tolterodine). Modification of this ratio may have implications for clinical responses including adverse events. The ratio of active metabolite to parent compound

may also depend on mode of administration (e.g., transdermal formulations of oxybutynin may have lower plasma concentrations of active metabolite than oral oxybutynin IR).

A key question is whether an antimuscarinic drug can selectively relax the bladder without causing unwanted effects of dry mouth, constipation, blurred vision and more serious but less common cardiovascular and central nervous system effects. M3 selectivity is proposed to minimize adverse effects such as dry mouth. The relative M2:M3 receptor binding affinity has been proposed to be associated with the overall efficacy/adverse event profile, with those agents having a lower ratio being associated with a higher risk of dry mouth and constipation than those with a higher ratio (Chancellor 2012). An M3:M1 ratio has also been proposed to predict the type and severity of adverse events. However, the only definitive way to distinguish the drugs in terms of benefits and harms is to conduct adequately powered, head-to-head direct comparator trials that include an appropriate harms evaluation framework.

Pharmacokinetic features and other select characteristics of each drug are highlighted in Appendix B. Features of the drugs that are relevant to central nervous system effects are discussed below. Darifenacin is the only agent considered to have moderate selectivity for the M3 muscarinic receptor subtype based on binding affinities to human cloned receptors. Oxybutynin and solifenacin are considered to havea modest degree of M3 selectivity over M2 receptors. None of the drugs under review are clinically selective for the bladder. Different formulations of the same drug have different pharmacokinetic features that may influence clinical effects, as discussed in Appendix B. The drugs also differ in metabolism (Appendix B Table). Some are affected by genetic variations in CYP 2D6 enzyme (tolterodine, fesoterodine, darifenacin) (Appendix B Table). All are contraindicated in the presence of urinary retention, gastric retention, uncontrolled narrow-angle glaucoma, and in patients with hypersensitivity to active or inert ingredients in a product.

Cognition, the Elderly and Antimuscarinic Drugs

The cholinergic system, mediated by acetylcholine, is a major neurotransmitter system in the central nervous system. It is involved in memory storage and retrieval, arousal, perception and attention (Abrams 2006). Cholinergic function is reduced in Alzheimer's dementia and in cognitive impairment, and is blocked by antimuscarinic drugs.

All five muscarinic receptor subtypes are expressed in the brain, with different distribution for each subtype. For example, M1 receptors are abundant in the neocortex, which is responsible for higher cognitive functions. In the brain, muscarinic receptors activate signalling pathways important for modulation of neuronal excitability, synaptic plasticity and feedback regulation of acetylcholine release (Abrams 2006). Studies on receptor gene knockout mice or M1 receptor agonists suggest M1 receptors are involved in higher cognitive processes such as learning and memory (Anagnostaras 2003). M2 receptors, which are more widely expressed, improve memory, and are required for behavioral flexibility and learning (Tzavara 2003; Seeger 2004).

All of the OAB drugs under review are included in the 2012 updated Beers criteria list for potentially inappropriate medication use in older adults, due to the CNS effect of delirium and other non-CNS adverse events (American Geriatrics Society 2012).

The CNS effects of antimuscarinic drugs used for OAB are likely due to the blockade of multiple receptors, including M1, because none of the drugs selectively act on only one receptor subtype.

Theoretically, OAB drugs differ in their ability to cross the blood brain barrier. However, central nervous system effects have been reported in clinical studies or in post marketing experience for all drugs under review (Table 7). Cognitive effects include acute global effects such as delirium as well as chronic impairment.

Overall, the concentration of a drug in the CNS depends on the equilibrium between drug penetration of the blood brain barrier, efflux or transport away from the CNS, and the pharmacokinetics, distribution and metabolism of the drug (Staskin 2010). Drug transport across an intact blood brain barrier can be passive or active (Chancellor 2012). Passive transport involves diffusion along a concentration gradient (into the brain) and is enhanced by a small molecular weight (< 400 kDA), a neutral charge at physiological pH (determined by ionization constant pKa) and lipid solubility (Table 7). Oxybutynin is the only OAB drug with a molecular weight < 400 kDa. Most OAB drugs are tertiary amines and are not charged at physiological pH; these cross the blood brain barrier more readily than trospium, a positively charged quaternary amine. The degree of protein binding influences how much drug gets into the brain because only free unbound drug crosses the blood brain barrier (Chancellor 2012). Drugs also differ in the rate at which they are cleared from the brain. Some antimuscarinic drugs are substrates for carrier-mediated active transport out of the brain. For example, darifenacin, fesoterodine and trospium are substrates for the permeability-glycoprotein (p-gp), which actively pumps the drug back into the bloodstream. A drug like trospium, which has a low ability to cross an intact blood brain barrier and is also actively transported out of the brain, would be considered less likely to accumulate to high concentrations in the brain. However, the activity of transporter proteins varies, as does the integrity of the blood brain barrier. The only definitive way of determining which drugs are least likely to have CNS effects is to measure clinical effects.

Table 7. Drug properties that may affect blood brain barrier crossing and CNS effects.

Drug	oxybutynin	tolterodine	fesoterodine	darifenacin	solifenacin	trospium
Theoretical ability to cross the blood brain barrier	moderate/high	low	very low	high	moderate	almost none
Lipophilicity	moderate	low	very low	high	moderate	no (hydrophilic)
M3:M1 receptor binding affinity ratio	1.5 (Non-selective)	0.9 (Non-selective)	1.1 (Non-selective)	9.2 (Mainly M3)	2.5 (Mainly M3)	1.5 (Non-selective)
Polarity at physiological pH (7.2-7.4)	neutral	neutral	neutral	neutral	neutral	positively charged
Active metabolites	DEO –smaller and more negatively charged than parent compound, CNS effects unknown	5-HMT – larger and less lipophilic than parent compound	5-HMT	some but little known	Very low concentration of 4R-hydroxy metabolite, little known about CNS effects	None
pKa (determines whether there is a neutral charge at physiological pH)	~8	9.28, 9.87	9.28	9.2	8.5	~7 (ionization at neutral pH)

Molecular weight (kDa)	357	475.6	411.6	507.5	480.6	428
P-gp substrate	no	no	yes	yes	no	yes
Nervous system or 'psychiatric' effects listed in Canadian product monographs § (other than special senses such as vision, taste and smell, and effects that are secondary to overdose**)	• somnolence headache • convulsions confusion • agitation, hallucinations • psychotic disorder • memory impairment • dizziness** • insomnia^^ • nervousness^ • depression^^	• headache, • fatigue • ability to drive and use machinery, • hallucinations, • disorientation • memory impairment, • worsening of symptoms of dementia (e.g., confusion, disorientation, delusion) in patients on cholinesterase inhibitors • vertigo/ dizziness^	• insomnia • dizziness	• dizziness* • headache* • asthenia, • insomnia, • somnolence, • thinking abnormal	• somnolence, • fatigue, • dizziness*** • depression*** • headache, • confusional state, • delirium, • disorientation, • hallucinations	• headache, • migraine, • hallucinations, • delirium

§ Adverse events listed in the product monographs may in part reflect differences in the extent or duration of postmarketing experience for individual drugs. For oxybutynin IR , the U.S. Package Insert was the source of listed AE. **Anticholinergic overdose signs and symptoms include central nervous system excitation (e.g., restlessness, tremor, irritability, convulsions, delirium and hallucinations.)
Table modified from Chancellor 2012.
* incidence in clinical trials similar to placebo; ** listed in clinical trials for gel; *** listed in clinical trials; ^ incidence in clinical trials similar to placebo and to oxybutynin IR; ^^ in clinical trials compared with XL vs. IR;

The elderly are more susceptible to the CNS effects of antimuscarinic drugs than younger adults for several reasons. These include increased permeability of the blood brain barrier, reduced density of muscarinic receptors in the brain or altered receptor distribution, an increased anticholinergic load due to multiple medications, and non-CNS parameters such as age-related changes in drug elimination (Chancellor 2012).

In addition to advanced age, loss of integrity of the blood brain barrier occurs in a variety of conditions such as diabetes, multiple sclerosis, stroke, vascular dementia, and Alzheimer's disease (Chancellor 2012). Stress has also been shown to affect the integrity of the blood brain barrier. This means that irrespective of their physicochemical properties, all antimuscarinic drugs have the potential to cross the blood brain barrier. Because of the changes that occur with age and comorbidities, it is important to evaluate central nervous system effects in older populations most likely to be prescribed the drugs.

A wide range of drugs, in addition to those used for OAB, have anticholinergic effects. These include antidepressants, bronchodilators, antihistamines, antiarrhythmics and other drugs. Most studies that have assessed cognition in the elderly in relation to anticholinergic drugs have not separated out types of drugs on the basis of therapeutic class but have measured overall anticholinergic load. This is of importance because older people are prescribed a diverse spectrum of anticholinergic medications.

Longitudinal studies have reported an association of anticholinergic drugs with impairment of cognition (Koyama 2013; Whalley 2012; Campbell 2001; Boudreau 2011; Sittironnarit 2011). Not all studies, however, have reported an association with progression of dementia, and people with different degrees of cognitive impairment may be affected differently (Whalley 2012; Ancelin 2006; Sink 2008). People with pre-existing cognitive impairment may be particularly vulnerable because of reduced receptor density.

Cholinesterase inhibitors are used to treat Alzheimer's disease and increase (postsynaptic) acetylcholine by inhibiting the enzyme that degrades it. The increase in acetylcholine results in greater muscarinic receptor activity. These drugs therefore oppose the action of antimuscarinic drugs that block activation of postsynaptic muscarinic receptors. However, rather than merely cancelling the effect of each other, there is some evidence to suggest that their concomitant use can result in more complex effects due to up- or downregulation of receptors and signalling pathways. Patients receiving both may be particularly susceptible to adverse events, which may include adverse CNS effects upon withdrawal of a centrally acting anticholinergic drug (Piecoro 1998).

Concomitant use of cholinesterase inhibitors with anticholinergic drugs has been reported in populations of community-dwelling individuals as well as residents in long-term care (Boudreau 2011; Modi 2009; Teramura-Gronblad 2011; Roe 2002). A study on Indiana Medicaid nursing home residents (N=3251) reported 47% of the total population were receiving combinations of cholinesterase inhibitors and anticholinergic drugs for a variety of indications including OAB. Of the total population, 6% were receiving tolterodine and 7% were receiving oxybutynin in combination with cholinesterase inhibitors (Modi 2009). In another U.S. health management administrative database study (N=5625 adults aged 50 or older), 37% of cholinesterase inhibitor users also received anticholinergic drugs (Boudreau 2011).

A population-based cohort study on adults over the age of 65 with dementia in Ontario (N=44,884) reported that individuals who are prescribed cholinesterase inhibitors are more likely to subsequently receive an antimuscarinic drug for incontinence compared with those who are not prescribed cholinesterase inhibitors, after adjusting for potential confounders (adjusted hazard ratio 1.55 [95% CI 1.39 to 1.72]) (Gill 2005). Although increased urinary incontinence is associated with dementia, cholinesterase inhibitors can also precipitate urgency and urinary incontinence (Gill 2005; Hashimoto 2000; Starr 2007; Donepezil Product Monograph). In this setting, antimuscarinic drug use is an example of an unnecessary prescribing cascade.

A prior systematic review on the CNS effects of antimuscarinic drugs in OAB patients included placebo-controlled trials (Paquette 2011). Most potentially eligible trials (77%) did not measure or report CNS outcomes. Of the 72 included trials, only one administered a cognitive test. In the other trials, it was not possible for the review authors to discern whether CNS symptoms were systematically measured or collected based on voluntary reporting. This highlights the need for properly designed, conducted and reported trials that measure CNS effects. Such studies must include active surveillance methods that assess memory and other cognitive functions rather than rely on voluntary reporting of adverse events.

Antimuscarinic Drugs versus Placebo

The Placebo Effect

It is well-recognized that patients taking placebo in OAB trials improve markedly, with only modest differences detected between active and placebo treatment across all drugs.

Two industry-supported systematic reviews have quantified the placebo effect in OAB (Lee 2009; Mangera 2011). Lee 2009 reported on three commonly used outcomes in trials: incontinence episodes, frequency, and volume voided (Lee 2009). Thirty-six studies were identified as having a placebo arm. The placebo arms from studies that reported useable data (approximately half of the studies) were pooled and meta-analyzed to obtain a more precise estimate of the placebo effect. The number of patients in the placebo groups ranged from 13 to 508 (mean 164). Improvement in all three outcomes was substantial, statistically significant, and highly heterogeneous. For all three outcomes, the larger the study, the greater the statistical significance of the placebo response.

Table 8. Placebo response – pooled effect estimates for commonly reported outcomes

Outcome	Incontinence episodes per day	Micturitions per day	Mean volume voided
Baseline (mean)	3.16 (SD 1.00)	11.8 (SD 0.9)	163.1 mls (42.9)
Change (MD)	-1.15 [95% CI -1.34 to -0.96]	-1.27 [95% CI -1.51 to -1.03]	12.4 mls [95% CI 9.3 to 15.5]
No. of studies (N)	17 (3479)	18 (3549)	15 (3121)
CI=confidence intervals; mls=milllimeters; SD=standard deviation; MD=mean difference; N=number of patients			

The mean number of incontinence episodes was 3.16 (SD 1.00) episodes per day at baseline. At study end, incontinence episodes were reduced by 1.15 episodes/day (95% CI -1.34 to -0.96) in the pooled placebo treatment arms. The greater the severity of incontinence at baseline, as measured by number of episodes, the greater the improvement with placebo (correlation coefficient r = 0.69). No relationship was detected between the magnitude of the placebo response and the ability to detect a statistically significant difference between active drug and placebo (defined as the success of the study).

The mean number of micturitions per day at baseline was 11.8 (SD 0.9). Placebo reduced the frequency per day by 1.27 [95% CI -1.51 to -1.03] micturition episodes. Similar to the results with incontinence episodes, the greater the frequency at baseline, the greater the change in frequency in the placebo arm.

Variation in study outcomes was high in the Lee 2009 meta-analyses (Lee 2009). Heterogeneity in OAB trials may be attributable to multiple factors such as: differences in study populations (e.g., inclusion of mixed types of incontinence); sample size; use of subjective endpoints; changes in study methodology and types of patients recruited over time; the type of bladder diary (electronic or paper) and length of time over which patients had to recall subjective endpoint data (Lee 2009). Because the analysis was performed on aggregate data at the study level, individual patient characteristics that might affect the placebo response (e.g., age or sex) were not explored.

A second systematic review confirmed improvements from baseline with placebo for incontinence episodes, frequency, and mean micturition volume (Mangera 2011). Study size, however, was not found to influence the magnitude of change, in contrast to previous results. A reduction in urgency episodes occurred with placebo but was not statistically significant. Few studies were available to assess urgency, which showed a reduction of about one episode per day.

Mangera et al. have pointed out there are many possible explanations for the effects observed with placebo in OAB. These include regression to the mean, patient or assessor expectations,

"experimental subordination" (the patient responding in a way they believe they should so as not to disappoint their physician), response to additional attention during the study, or a bladder training effect from the use of a bladder diary (Mangera 2011). OAB trials comparing drugs to either an active comparator or placebo have not, to date, included a 'no treatment' or 'nondrug' arm and investigators have assumed there would be no change in the absence of placebo or active treatment. The inclusion of such an arm (in which patients fill out a bladder diary) could help elucidate whether the placebo effect is arising from patient or physician expectations or whether it may be attributable to bladder training secondary to the use of a bladder diary (Mangera 2011).

The influence of study duration on the placebo response has not been assessed because the majority of available OAB trials (that reported appropriate data) were 12 weeks long.

The documented, substantive placebo response in OAB studies warrants the inclusion of a placebo arm in active comparator trials as improvement in outcomes in active drug groups may be of the magnitude of that seen with placebo, depending on the particular population and circumstances (Center for Drug Evaluation and Research NDA 20-771). The variability of the placebo response across trials is also a compelling reason to use caution in interpreting indirect comparisons in the absence of head-to-head comparator trials.

Antimuscarinic Drugs vs. Placebo

A systematic review for the Cochrane Collaboration compared anticholinergic drugs vs. placebo for the treatment of OAB (Nabi 2006). Forty-one parallel group trials, included neurogenic as well as idiopathic detrusor overactivity, were considered for meta-analysis. All drugs of interest to this review were included with the exception of fesoterodine. The review also included parallel group trials of two drugs that are not of interest. All drugs and dosage regimens were pooled. Because heterogeneity was low for efficacy outcomes (and trials on drugs not of interest made a small contribution to these), we present the overall pooled results in Table 9.

Table 9. Antimuscarinic Drugs (Pooled) vs. Placebo

Outcome	No. of trials (N)	Relative Risk/Risk Difference or Mean Difference [95% CI]
QoL condition-specific (KHQ)	3 (2113)	MD -6.95 [95% CI -10.36 to -3.53]
Patient Perception of Improvement or Cure	8 (2742)	RR 1.39 [95% CI 1.28 to 1.51] RD 14% [95 % CI 11% to 18%]
Incontinence Episodes per day	12 (1482)	MD -0.51 [95% CI -0.66 to -0.37]
Micturitions per day	12 (5979)	MD -0.68 [95% CI-0.84, -0.52]
Urgency Episodes	NR	NR
Nocturia	NR	NR
Dry mouth*	27 (9372)	3.00 [95% CI 2.70 to 3.34]
Dry mouth tolterodine vs. placebo	14 (6042)	3.37 [95% CCI 2.90 to 3.90]
Dry mouth oxybutynin vs. placebo	7 (719)	2.41 [95% CI 2.02 to 2.87]
Dry mouth solifenacin vs. placebo	3 (2213)	3.62 [95% CI 2.29 to 5.74]
Dry mouth trospium vs. placebo§	4 (1011)	2.66 [95% CI 1.98 to 3.55]

KHQ=King's Health Questionnaire; MD=mean difference; N=number; NR=not reported; RD=absolute risk difference; RR=relative risk *heterogeneity I^2 87%; § two trials overlap with other subgroups for dry mouth

When eight trials were pooled, 41% of participants in the placebo group reported cure or improvement in symptoms. Only an additional 15% of participants reported that they were

improved or cured on active drug. The difference in improvement between drug and placebo groups was on average about four less leakage episodes per week (half an episode a day) and five less voids per week in favour of active drug. As the authors point out "while the difference between the groups in micturition and leakage episodes is statistically significant (the confidence intervals are tight), the issue is their clinical significance" (Nabi 2006). WDAE were numerically higher but not statistically significant. However, there was a three-fold higher risk of dry mouth with active drug.

A more recent review for AHRQ on community-dwelling women only, included all drugs of interest for this review and reported treatment effects for each drug vs. placebo separately (pooling different dosage regimens and formulations) as presented in Table 10, below (Shamliyan 2012). That review also concluded modest efficacy for all drugs. The drugs were more effective than placebo in achieving continence and in improving incontinence, but the degree of benefit was low for all drugs, corresponding to an absolute risk difference of < 20% compared with placebo.

Table 10. Antimuscarinic Drugs vs. Placebo: outcomes by drug from AHRQ 2012 Review

Drug	Oxybutynin (N) [95% CI]	Tolterodine (N) [95% CI]	Fesoterodine (N) [95% CI]	Solifenacin (N) [95% CI]	Trospium (N) [95% CI]	Darifenacin (N) [95% CI]
Continence	4 trials (992) **RR 1.7** [1.3 to 2.1] **RD 11%** [6% to 16%]	4 trials (3404) **RR 1.2** [1.1 to 1.4] **RD 9%** [4% to 13%]	2 trials (2465) **RR 1.3** [1.1 to 1.5] **RD 13%** [6% to 20%]	5 trials (6304) **RR 1.4** [1.4 to 1.6] **RD 11%** [6% to 16%]	4 trials (2677) **RR 1.7** [1.5 to 2.0] **RD 11%** [8% to 14%]	NA
Patient perception of improvement	9 trials (1244) **RR 1.5** [1.2 to 1.9] **RD 17%** [10% to 24%]	7 trials (6119) **RR 1.3** [1.1 to 1.4] **RD 10%** [4% to 15%]	2 (1896) **RR 1.3** [1.2 to 1.5] **RD 10%** [6% to 15%]	2 (1507) **RR 1.5** [1.0 to 2.1] **RD 18%** [10% to 26%]	2 trials (1176) RR 1.1 [0.6 to 2.0] RD 8% [-10% to 25%	3 trials (1011) **RR 1.3** [1.2 to 1.5] **RD 12%** [6% to 17%]

N= number of patients; RD= risk difference; RR=relative risk; Bolded results are statistically significant
Data from Shamliyan 2012

Data on harms from meta-analyses of placebo-controlled trials

The systematic review by AHRQ on treatments for urinary incontinence in women (Shamliyan 2012) represents the most complete overview to date of data on harms from placebo-controlled trials. Although criteria for inclusion differ from the current review, results are broadly applicable as most studies of anti-muscarinic drugs for OAB mainly or solely include women. The AHRQ pooled analyses are presented here, by outcome, in order to provide an overview of evidence on evidence of harms from placebo-controlled trials.

Table 1. Serious adverse events *

Pooled analyses, AHRQ 2012: Antimuscarinic Drugs vs. Placebo for OAB in women						
Drug	**# RCTs**	**Total N**	**SAE Drug**	**SAE Placebo**	**Absolute Risk Difference (95% CI)**	**Strength of evidence****
Oxybutynin	3	1,393	3.7%	2.0%	2% (- 2% to 15%), NS	Moderate

Tolterodine	5	3,550	1.8%	3.1%	- 1% (- 2% to 0), NS	Moderate
Fesoterodine	2	1,905	1.8%	1.9%	0 (- 1% to 1%), NS	Low
Darifenacin	2	655	1.2%	2.1%	- 1% (- 2% to 1%), NS	Low
Solifenacin§	2*	1,411	1/920	0/491	0.1% (0 to 1%), NS	Insufficient

*not reported for trospium
§ fatal serious adverse events (deaths) only reported; judged insufficient due to incomplete reporting
** AHRQ rating scale on strength of evidence: **High**= high confidence a true effect, future research unlikely to change estimate; **Moderate**= moderate confidence; further research may change confidence or the estimate; **Low**= low confidence, further research likely to change confidence and the estimate; **Insufficient** = evidence is unavailable or does not permit a conclusion.
NR= not reported; **NS**= non-significant at p<0.05; **SAE**= serious adverse events
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, http://www.ncbi.nlm.nih.gov/books/NBK92960/, and Shamliyan 2012, Appendix Table.

Table 3. Withdrawals Due to Adverse Events

Pooled analyses, AHRQ 2012 Antimuscarinic Drugs vs. Placebo for OAB in women						
Drug	**# RCTs**	**Total N**	**WDAE Drug**	**WDAE Placebo**	**Absolute Risk Difference [95% CI]**	**Strength of evidence***
Oxybutynin	5	1,483	10%	5%	**6% [1% to 13%] NNH=17**	High
Tolterodine	10	4,466	4%	3%	1% [- 1% to 3%], NS	High
Fesoterodine	4	4,433	6%	3%	**3% [1% to 6%] NNH=32**	High
Solifenacin	7	9,808	5%	4%	**1% [0 to 3%] NNH=77**	High
Darifenacin	7	3,138	5%	3%	0 [- 1% to 2%], NS	High
Trospium	6	3,936	6%	4%	**2% [2% to 3%] NNH=55**	High

*AHRQ rating scale on strength of evidence: **High**= high confidence a true effect, future research unlikely to change estimate; **Moderate**= moderate confidence; further research may change confidence or the estimate; **Low**= low confidence, further research likely to change confidence and the estimate; **Insufficient** = evidence is unavailable or does not permit a conclusion.
NNH= numbers needed to harm; **NR**= not reported; **NS**= non-significant at p<0.05; **WDAE** = withdrawals due to adverse events; bolded results are significant at p<0.05
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, http://www.ncbi.nlm.nih.gov/books/NBK92960/, and Shamliyan 2012, Appendix Table.

Table 4. Total Adverse Events

Pooled analyses, AHRQ 2012: Antimuscarinic drugs vs. Placebo for OAB in women*					
Drug	**# RCTs**	**Total N**	**Total AE Drug**	**Total AE Placebo**	**Absolute Risk Difference (95% CI)**
Oxybutynin	3	821	27.7%	15.1%	10.1% (- 5% to 26%), NS
Tolterodine	15	4,162	44.7%	38.1%	**7.9% (5% to 11%) NNH=13**
Fesoterodine	6	4,145	51.5%	37.8%	**15.3% (11% to 19%) NNH=7**
Solifenacin	6	1,713	51.9%	36.3%	**18% (9% to 27%) NNH=6**
Darifenacin	5	1,495	57.0%	43.2%	**18.3% (12% to 25%) NNH=5**
Trospium	5	2,967	40.5%	28.7%	**11.6% (8% to 15%) NNH=9**

Note: results reported per drug only if they were listed in the AHRQ review (e.g., trials meeting their inclusion criteria had examined total AE)
*Strength of evidence not reported by AHRQ for this outcome.
AE= adverse event; **NNH**=number needed to harm; **NR**= not reported; **NS**= non-significant at $p<0.05$;
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, plus Supplement 9 http://www.ncbi.nlm.nih.gov/books/NBK92960/; and Shamliyan 2012, Appendix Table.

Table 5. Central Nervous System (CNS) Adverse Events*

Pooled analyses, AHRQ 2012: Antimuscarinic Drugs vs. Placebo for OAB in women						
Drug	**# RCTs**	**Total N**	**CNS Event Drug %**	**CNS Event Placebo %**	**Absolute Risk Difference [95% CI]**	**Strength of evidence****
CNS disorders - total						
Trospium	2	1,217	3.9%	3.8%	0 [- 2% to 3%], NS	NR
Dizziness						
Oxybutynin	5	1,541	2%	1.7%	1% [0 to 3%], NS	Moderate

Tolterodine	6	5,257	2%	2%	0 [0 to 1%], NS	High
Fesoterodine	2	3,138	1.2%	0.9%	0 [- 1% to 1%], NS	Low
Solifenacin	2	1,411	3%	2%	1% [- 1% to 3%], NS	Low
Somnolence						
Oxybutynin	3	1,412	0.9%	0.8%	0 [- 1% to 2%], NS	Low
Tolterodine	2	1,869	1%	1%	0 [- 1% to 2%]	Low
Fatigue						
Tolterodine	4	3,234	1.9%	0.7%	**2% [1% to 3%] NNH=50**	High
Fesoterodine	2	1,905	2.0%	0.3%	**2% [1% to 4%] NNH=50**	Low
Solifenacin	2	1,507	2%	1%	**1% [0 to 3%] NNH=83**	Low
Headache						
Oxybutynin	3	1,299	4%	4.5%	- 1% [-3% to 1%], NS	Moderate
Tolterodine	11	6,766	4%	4%	1% [0% to 3%], NS	High
Darifenacin	3	1,155	4%	1%	**3% [1% to 6%] NNH=34**	Moderate
Trospium	4	2,771	3%	4%	-1% [-2% to 1%], NS	High
Solifenacin	4	2,481	3%	4%	- 1% [- 2% to 1%], NS	Moderate
Fesoterodine	5	5,230	7%	6%	0% [-1% to 2%], NS	High

*note: results reported per drug only if they were listed in the AHRQ review (e.g. trials meeting their inclusion criteria had examined this AE).
** AHRQ rating scale on strength of evidence: High = high confidence a true effect, future research unlikely to change estimate; Moderate = moderate confidence; further research may change confidence or the estimate; Low = low confidence, further research likely to change confidence and the estimate; insufficient = evidence is unavailable or does not permit a conclusion.
CNS= central nervous system; **NNH**=number needed to harm; **NR**= not reported; **NS**= non-significant at $p<0.05$;
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, plus Supplement 9 http://www.ncbi.nlm.nih.gov/books/NBK92960/; and Shamliyan 2012, Appendix Table.

Table 6. Other Specific AE*

Pooled analyses, AHRQ 2012: Antimuscarinic Drugs vs. Placebo for OAB in women						
Review drug	**# RCTs**	**Total N**	**Adverse Event Drug %**	**Adverse Event Placebo %**	**Absolute Risk Difference [95% CI]**	**Strength of evidence****
Urinary Retention						
Oxybutynin	3	1,287	3.2%	0.5%	4% [- 1% to 16%],NS	Moderate
Solifenacin	2	747	2.4%	0.8%	3% [- 1% to 12%], NS	Low
Constipation						
Oxybutynin	7	1,743	7.3%	5.5%	3% [-1% to 9%], NS	Moderate
Tolterodine	14	9,592	4%	3%	**1% [0 to 2%] NNH=83**	High
Fesoterodine	7	7,695	11%	3%	**4% [0 to 10%] NNH=24**	High
Darifenacin	5	2,239	14.6%	5.7%	**8% [2% to 15%] NNH=13**	High
Trospium	5	3,335	9.3%	2.6%	**7% [5% to 9%] NNH=14**	High
Solifenacin	8	11,765	11%	3%	**7% [5% to 10%] NNH=14**	High
Urinary Tract Infection						
Tolterodine	5	4,465	2%	3%	0 [- 1% to 1%], NS	High
Fesoterodine	2	1,896	2%	2%	1% [- 1% to 5%], NS	Low
Darifenacin	2	655	2.9%	2.3%	1% [- 1% to 4%], NS	Low
Trospium	3	2,248	2.6%	1.3%	1% [0 to 3%], NS	Moderate
Dry mouth						
Oxybutynin	9	2,238	34%	15%	**35% [16% to 54%]**	High

					NNH=3	
Tolterodine	14	7,637	18.4%	6.7%	**14% [10% to 18%] NNH=7**	High
Fesoterodine	5	6,674	27%	7%	**20% [16% to 24%] NNH=5**	High
Solifenacin	7	11,098	21%	5%	**17% [12% to 23%] NNH=6**	High
Darifenacin	5	2,382	22.0%	5.6%	**16% [7% to 27%] NNH=17**	High
Trospium	6	3,490	15.1%	4.5%	**11% [7% to 14%] NNH=9**	High
Dyspepsia						
Oxybutynin	3	613	12.1%	3.3%	**8% [3% to 16%] NNH=12**	Moderate
Tolterodine	8	3,525	3%	2%	**2% [0% to 5%] NNH=45**	High
Solifenacin	5	1,663	3.4%	0.4%	**4% [2% to 6%] NNH=27**	Moderate
Darifenacin	7	1,772	4.4%	1.3%	**3% [1% to 6%] NNH=32**	High
Abdominal pain						
Trospium	3	2,113	1.7%	0.7%	**1% [0 to 2%] NNH=100**	High
Dry eye						
Fesoterodine	4	4145	2%	1%	**3% [1% to 6%] NNH=36**	High
Trospium	2	1590	1.7%	0.2%	**1% [0 to 3%] NNH=71**	Low
Abnormal vision						
Fesoterodine	1	1,094	0.3%	1.0%	- 1% [- 1% to 0], NS	Insufficient
Blurred vision						

Oxybutynin	5	663	10.4%	9.1%	**10% [2% to 19%] NNH=10**	Moderate
Tolterodine	2	608	1.3%	3.0%	- 3% [- 2% to 3%], NS	Low
Solifenacin	9	12,922	4%	2%	**2% [1% to 3%] NNH=59**	High

*note: results reported per drug only if they were listed in the AHRQ review (e.g. trials meeting their inclusion criteria had examined this AE)
AHRQ rating scale on strength of evidence: **High= high confidence a true effect, future research unlikely to change estimate; **Moderate**= moderate confidence; further research may change confidence or the estimate; **Low**= low confidence, further research likely to change confidence and the estimate; **Insufficient** = evidence is unavailable or does not permit a conclusion.
NNH=number needed to harm; **NR**= not reported; **NS**= non-significant at $p<0.05$; **WDAE**= withdrawals due to adverse events
Adapted from: AHRQ 2012 Systematic Review Table F47 p F339 – 375, plus Supplement 9 http://www.ncbi.nlm.nih.gov/books/NBK92960/; and Shamliyan 2012, Appendix Table.

Persistence with Antimuscarinic Drugs

There is good evidence from observational studies that patients in usual clinical care discontinue treatment with antimuscarinic drugs at much higher rates than the clinical trials indicate. Pharmacological treatment is intended for long-term use when continence and symptomatic relief are not achieved with non-pharmacologic approaches. Persistence refers to the duration of time a person continues a medication, and can be a marker for whether the patient felt better or worse on the drug. Poor persistence can indicate that, from the patient's perspective, the drug did not provide symptomatic relief sought or that adverse events outweigh perceived benefits. Other factors affecting persistence include perceived affordability and physician-initiated switching or discontinuation.

Sexton 2011 conducted a systematic review of persistence in patients with OAB treated with antimuscarinic drugs and compared rates of discontinuation based on randomized, clinical trials and observational studies (Sexton 2011). Among 129 included articles, there were 77 trials, and 14 observational studies that used administrative data. Studies using administrative data found that 43% to 83% of patients discontinued therapy within the first 30 days of treatment, higher than the 4% to 31% discontinuation reported in 12-week clinical trials.

For tolterodine, discontinuation rates at one year were as high as 88% (Shaya 2005) among the studies using administrative data vs. 36% in extension studies that follow clinical trial participants for a period of time after a trial is completed (Sexton 2011). Discontinuation by 12 weeks ranged from 8% to 19% for tolterodine in clinical trials. This large discrepancy can be explained by the highly select nature of the population enrolled in clinical trials versus routinely treated patients represented in administrative studies. Additionally, extension studies only enroll trial completers. Among those previously randomized to the active treatment arm, any patient who fails to tolerate the drug is excluded.

Five of the 14 studies included in Sexton 2011 that used administrative data investigated IR and ER formulations of oxybutynin and tolterodine and found that persistence was low for both drugs, although results generally favored ER formulations over IR, and tolterodine over oxybutynin. In a study using a large U.S. pharmacy claims database, Lawrence 2000 found that 59% of those prescribed oxybutynin IR and 54% of patients prescribed tolterodine had discontinued medication completely by 6 months while 19% and 14% respectively had switched to another drug (Lawrence 2000). Most patients who discontinued either drug did so within the first 30 days.

Newer anticholinergic agents (e.g., trospium, darifenacin, solifenacin) had similar rates of overall discontinuation as older drugs (e.g., tolterodine, oxybutynin) in clinical trials (Sexton 2011). A recent administrative claims data study also reports low persistence among users of all the drugs (Wagg 2013). Comparisons reported in this study are likely to be unreliable as some drug user samples were very small (e.g. darifenacin; N=23) and because of methods used to identify treatment initiation and discontinuation.

The studies of persistence described above are mainly pharmaceutical industry-sponsored, and the systematic review by Sexton et al. was sponsored by a medical device company (Sexton 2011).

A more recent population-based study in Norway (Mauseth 2013) compared initial prescriptions and switching among users of tolterodine, solifenacin, darifenacin and fesoterodine. All Norwegian women over the age of 18 who initiated use of one of these four products from January 2006 to December 2009 inclusive and were still alive one year following initiation were included in the study (N=32,178). This study was based on a database of all prescriptions filled in Norwegian pharmacies (Norwegian Prescription Database). Patients in hospital or long-term care were not included.

The authors report that 0.94% of the Norwegian population filled prescriptions for an anticholinergic drug for OAB in 2010. This was a 25% increase since 2004, without age adjustment. Use was highest in women: 1.3% vs. 0.6% of men. The age group of 80-89 year-old women had the highest use rate, 5.2%.

In total, 38% of women (12,238) were persistent for at lest one year. Per drug, this was 39.0% for tolterodine, 39.4% for solifenacin, 34.3% for darifenacin, 29.1% for fesoterodine. Differences in persistence were correlated with the proportion of treatment initiators who discontinued use without first switching to another anti-muscarinic for OAB. This ranged from 49% for tolterodine to 61% for fesoterodine. The authors note that persistence was lowest among 19-39 year-olds (21%) and increased sharply with increasing age, 43% of those ≥80.

The authors do not report on demographics of users per drug. The most commonly prescribed drug was solifenacin over the 4-year period (42.5%) followed by tolterodine (38.5%) with 13.7% of prescriptions for darifenacin and 5.3% for fesoterodine. The latter was the most recently launched (in June 2008, midway through the study) and had the most rapid growth in use. There was a rapid decline in tolterodine initiations over the study period, from 4500/ year in 2006 to <2000/year by 2009.

Persistence on tolterodine versus solifenacin did not differ in this study: risk ratio 0.99 (95% CI 0.96 to 1.02), p=0.6. [unadjusted exploratory analysis, RevMan, Mantel-Haenszel risk ratio analysis].

The authors note that persistence was lowest for fesoterodine and darifenacin, both of which "were accompanied by significant marketing campaigns focusing on better effect and lower risk of adverse reactions when they were launched". The authors interpret their results as being inconsistent with these marketing claims. It is also possible that on average physicians prescribed the drugs to patients with milder problems. Both drug and patient characteristics would be expected to affect persistence.

Mauseth 2013 was publicly funded (Norwegian University of Science and Technology), without any industry funding or sponsorship reported. It provides a note of caution that differences in persistence per product can reflect a range of factors, particularly among new products within a competitive drug class.

Because of the range of methods used to assess persistence, reliability of study results vary. However, data from a range of clinical settings indicates that the majority of patients discontinue use of antimuscarinics within the first few months after treatment initiation.

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Chapter 2. Methods

Objectives of the review:

1) Analyze the comparative effectiveness (harms and benefits) of antimuscarinic drugs available in BC, to determine if any drug has a therapeutic advantage over oxybutynin IR or each other for the treatment of OAB.
2) Determine whether additional information is available since the CDR review for any drug under review.
3) Assess the cognitive effects of the drugs under review and determine which, if any, has less effect on cognition when compared with oxybutynin IR or each other

Research Questions

In order to carry out a series of systematic reviews to answer question one above, the question was reformulated into 'PICO' format (Patients, Intervention, Comparator, Outcomes).

Q1. In adults, including the frail elderly, do the antimuscarinic drugs under review provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) and to each other, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

The drugs under review are: Oxybutynin IR; Oxybutynin transdermal patch (Oxytrol™); Oxybutynin gel (Gelnique™); Oxybutynin ER or CR (Ditropan XL®; Uromax®); Tolterodine (Detrol™, Detrol LA™); Trospium (Trosec™); Darifenacin (Enablex™); Solifenacin (Vesicare®); and Fesoterodine (Toviaz®).

The second two questions will be informed by the results of the systematic reviews carried out for question 1. These are discussed for each drug-drug comparison, with a summary of the analyses and overall conclusions at the end of the report.

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz*) or oxybutynin gel (Gelnique) provide improved clinically relevant outcomes or a better safety profile compared to oxybutynin IR?

Q3. In adults, particularly the elderly, does trospium (Trosec™), solifenacin (Vesicare®), darifenacin (Enablex™), tolterodine (Detrol™, Detrol LA™), fesoterodine (Toviaz®), oxybutynin gel (Gelnique™), oxybutynin transdermal patch (Oxytrol™) or other formulations of oxybutynin have less effect on cognition when compared to oxybutynin IR or to each other?

Selection criteria for studies included in this review ('PICOS' format)

Population

- Adults (men and women) including the frail elderly
- Community dwelling or institutionalized populations

Conditions

- Overactive bladder syndrome with symptoms of urinary frequency, urgency or urgency incontinence, or any combination of these symptoms
- Urge predominant mixed urinary incontinence

Exclusions:

- Children
- Patients with neurogenic causes of bladder overactivity (unless reported separately or comprising < 20% of population)
- Patients in the immediate postoperative period

Interventions/Comparators

- Oxybutynin IR
- Tolterodine (Detrol™, Detrol LA™)
- Trospium (Trosec™)
- Darifenacin (Enablex™)
- Solifenacin (Vesicare®)
- Fesoterodine (Toviaz®)
- Oxybutynin transdermal patch (Oxytrol™)
- Oxybutynin gel (Gelnique™)
- Oxybutynin ER or CR (Ditropan XL®; Uromax®)

The main comparison of interest is of oxybutynin IR versus each of the other comparators (tolterodine, trospium, darifenacin, solifenacin and fesoterodine, and other formulations of oxybutynin). Secondly, trials directly comparing each of these comparator drugs with one another were examined.

Outcomes

Health outcomes are organized as a hierarchy with outcomes of greatest importance to patient health situated higher in the hierarchy. Both potential beneficial and harmful effects of drug treatment are included within this hierarchy of health outcomes, in order to assess net benefit.

1. All-cause mortality

2. Non-fatal serious adverse events (SAE) – includes:
   - CNS (short and long-term cognition – validated outcomes)
   - Cardiovascular (includes conduction abnormalities)

- Acute urinary retention
- Falls and fractures

3. Quality of life (generic and condition-specific instruments validated in target population)

4. Patient perception of improvement or cure

5. Drug tolerability / withdrawals due to adverse events

6. Incontinence / continence

- Quantification of incontinence episodes (change in mean number and severity of episodes over 24 hours, change in number of pads used; proportion of patients with resolution or improvement)
- Restrictions of activities of daily living associated with incontinence
- Subjective patient assessment of symptoms

7. Nocturia

8. Urgency

9. Total adverse events

10. Specific ('non-serious') adverse events of interest
- Common anticholinergic events e.g., dry mouth;
- Other

11. Mean volume voided per micturition

12. Clinician/urodynamic measures: maximum cystometric capacity; volume at first contraction; residual volume

Study design

For the review of efficacy outcomes and frequent short-term adverse events, only evidence from comparative randomized controlled trials (RCTs) and systematic reviews of RCTs were considered.

For populations not included in RCTs, especially the elderly, and patients with co-morbidities and for the review of serious and less frequent adverse events, a broader range of study designs were considered.

The following study designs were included:

- Comparative cohort analyses;
- Case-control studies
- Uncontrolled cohort analyses
- Before-after studies
- Cross-sectional studies
- Case series

Exclusion criteria:

- Controlled or uncontrolled cohort studies and before-after studies with a duration of follow-up of < 12 weeks;
- Cohort studies, before-after studies, cross-sectional studies and case series with N < 500;

Note: Studies specifically designed to assess cognitive adverse events, other serious adverse events, or adverse events in the elderly are not subject to these exclusion criteria.

We defined case series as groups of more than ten cases, and case reports as one to ten cases. Case reports on cognitive adverse events, serious adverse events, unanticipated events or adverse events in the elderly were briefly summarized.

Search Strategy

See Appendix C for search strategies. We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date. A targeted search was initially conducted in higher-yield databases with the aim of identifying high quality, recent systematic reviews. A comprehensive literature search for primary studies was subsequently conducted and supplemented by a search specifically for adverse events related to cognition or the central nervous system. Initial searches were conducted January 10-16, 2013 with regular updates obtained from PubMed until June 26, 2013.

Database searches were further supplemented by a grey literature search that included regulatory agency websites, periodic safety updates, and clinical trial registry data through the WHO International Clinical Trials Search Portal.

Assessment of study quality

For RCTs, quality assessment included the Cochrane risk of bias tool for the assessment of internal validity, using one assessment across outcomes for each study if appropriate (Higgins and Green 2011). Quality assessment also included an assessment of applicability and consideration of methodological features. Observational studies were assessed for strength of study design and methods using the taxonomy in the Cochrane Handbook, with attention to application of methods that reduce risk of bias (e.g., adjustment, stratification, matching or propensity scores).

Data analysis

Results are summarized using the hierarchy of outcomes listed above, and by study design. RCT data were combined for each outcome if clinical populations, interventions, outcome assessment, and study methodology, are deemed sufficiently similar to warrant pooling. For continuous data, the summary outcome measure is the mean difference (MD), using an inverse variance fixed effects model. Use of a standardized mean difference was considered where appropriate. Dichotomous data are presented as risk ratios and risk differences, using a Mantel-Haenszel fixed effects model. If statistical heterogeneity is present, a random effects model was used instead. Sensitivity analyses were conducted to determine the robustness of the results in the presence or absence of poorer quality studies. To explore heterogeneity in the presence of sufficient numbers of studies, subgroup analyses were conducted. The following factors were considered for subgroup analyses: drug dosages; baseline severity (incontinence), age, ethnicity, sex, duration of treatment or quality of study. However, few subgroup analyses were feasible due to small numbers of studies for each comparison. All meta-analyses were carried out using the Review Manager Computer Program (RevMan) version 5.2 (Review Manager 2012).

If direct comparator trials with oxybutynin IR are not available, the use of indirect comparisons or network meta-analyses was considered. Consideration of the feasibility and appropriateness of conducting network meta-analyses took into account the extent of similarity between trials in terms of patient population, interventions and assessed outcomes. Factors that were considered included, for example, baseline severity of condition, follow-up time, trial setting, methodological comparability and the comparability of interventions.

The strength of RCT evidence overall was assessed as follows: high= high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect; moderate= moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate; low= low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; Insufficient Evidence either is unavailable or does not permit a conclusion.

A qualitative synthesis was conducted on non-randomized studies to supplement RCT data, and an assessment made whether such evidence was consistent with the available RCT data.

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Chapter 3. Overall Search Results

Database searches identified 2361 unique records for the review series across all drugs, which were screened at the title/abstract level. Full text versions were obtained for 621 potentially relevant articles, which were further assessed for eligibility. A PRISMA flowchart detailing the flow of primary empirical studies for this review is provided on page 84.

In total, there are 41 comparative RCTs for all drug-drug comparisons considered in this review, 27 of which were comparisons between oxybutynin IR and other formulations of oxybutynin, tolterodine (IR or ER), darifenacin, solifenacin, or trospium (IR). Table 1 provides a summary overview of the available trials. With the exception of one trial comparing darifenacin with solifenacin, all other trials included either oxybutynin or tolterodine as a comparator.

Table 1. Number of RCTs for each pairwise comparison

Drug	Oxy IR	Oxy ER or CR	Oxy TDS	Oxy Gel	Tol IR	Tol ER	Feso	Dari ER	Soli	Tros IR	Total
Oxy IR	X	5	1	1[a]	10	1	0	2	1 + 2[a]	2 + 2[a]	**27**
Oxy ER		X			1	1		1[a]			**3**
Oxy TDS			X			1					**1**
Oxy Gel				X							**0**
Tol IR					X	1			3		**4**
Tol ER						X	3		2		**5**
Feso							X				**0**
Dari CR								X	1		**1**
Soli									X		
Trospium IR										X	
Total		5	1	1	11	4	3	3	9	4	**41**

[a] elderly volunteers, outcome cognition; CR= controlled release; dari= darifenacin; ER= extended release; feso=fesoterodine; IR=immediate release; oxy= oxybutynin; soli= solifenacin; tol= tolterodine; tros= trospium; TDS= transdermal system
Table does not include placebo RCTs that were included in this review in the absence of direct comparator RCTs.

Also included are an additional 13 trials, which were placebo-controlled RCTs that exclusively enrolled the elderly or RCTs that specifically assessed cognition but were either placebo-controlled trials or direct comparator trials that involved a formulation that was not included in this review (trospium ER) (Protocol A0221049; Pfizer NCT0041137; Pfizer NCT01178827; Sand 2010; Wagg 2013a; Kay 2012; Lackner 2008; Chapple 2007; Kay 2006; Lipton 2005; Diefenbach 2005; Katz 1998; Herberg 1997).

A total of 33 non-randomized studies (study design other than case reports) were included:

- 4 controlled cohort analyses (Gomes 2011; Sink 2008; Jumadilova 2006; Moga 2003);
- 23 uncontrolled cohort analyses (Abrams 2001; Amarenco 1998; Appell 2001; CONTROL 2012; Diokno 2002; Elinoff 2006; Garely 2006; Geller 2012; Haab 2005; Haab 2006; Isik 2009; Kreder 2002; Layton 2001; Michel 2002; Michel 2005; Michel 2008; Movig 2001; Newman 2008; Sand 2012; Schneider 2010; Staskin 2010; Wagg 2013b; Zinner 2011);

- 1 uncontrolled before-after study (Monnot 2012); and
- 4 case series (Alzayer 2010; Gish 2009; 't Veld 1998; Jonville 1992).

A total of 15 case reports (1 to 3 cases each) were also identified and are briefly described, as they can provide additional information on rare serious or unanticipated adverse events (Salvatore 2007; Tsao 2003; Womack 2003; Juss 2005; Madewell 2008; Bryan 2010; Schlienger 2002; Shalders 2007; Taylor 2006; Colucci 1999; Edwards 2002; Asajima 2008; Pemmaraju 2008; Mason 2008; Bilici 2010).

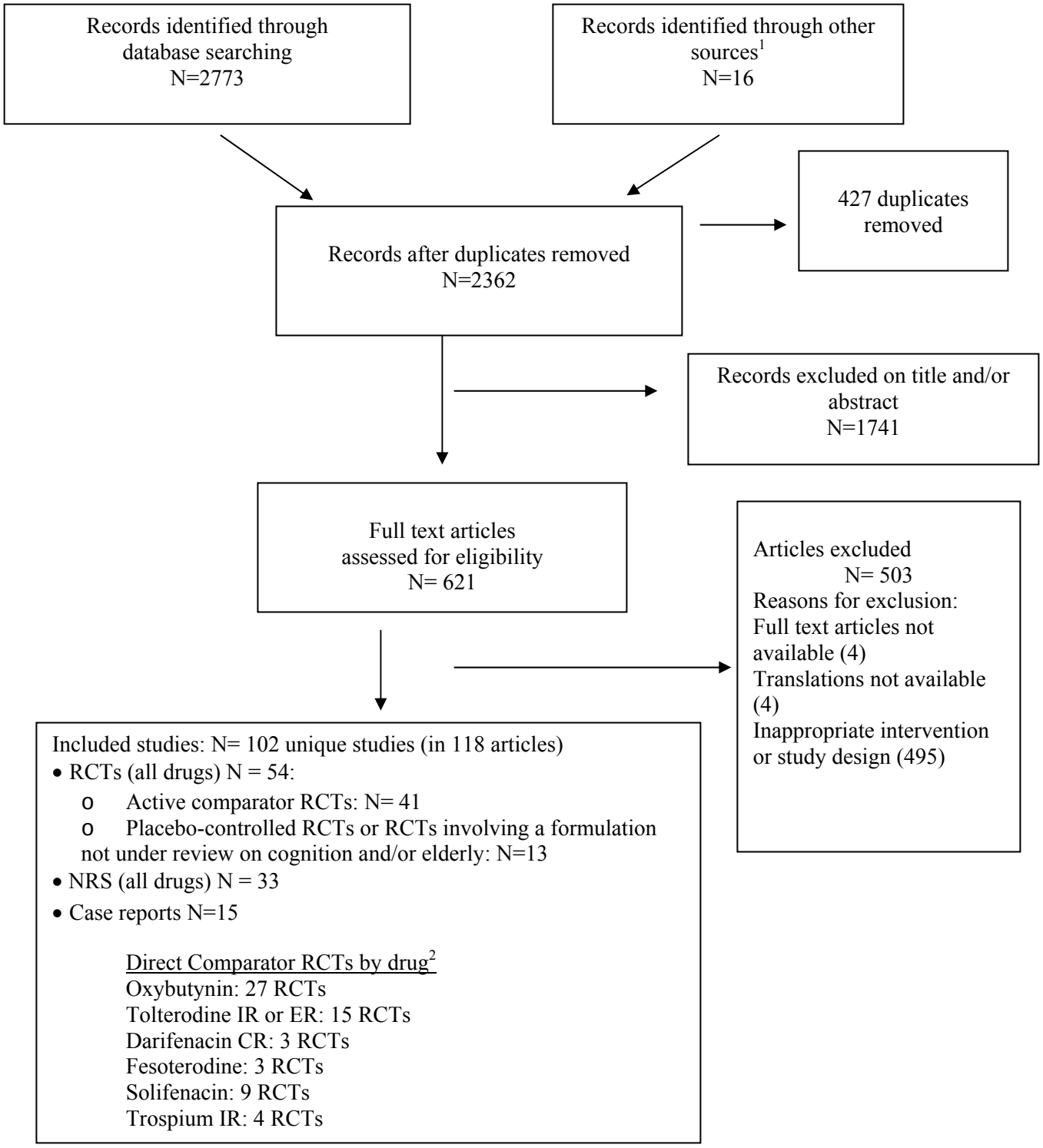
Non-English Language Reports: 54 non-English articles were identified for full text screening. Due to resource and time constraints, we prioritized articles for translation by applying eligibility criteria to available English titles, abstracts and data tables. Twenty-four articles of low potential relevance were excluded on this basis. Also excluded were a total of 14 non-randomized, non-comparative studies of drugs of interest because of small sample size (13 studies $\leq$ 100 patients, and one study < 500 patients). One placebo-controlled RCT was excluded. Of the remaining 15 articles targeted for translation, translators were available for nine articles. Of these, three RCTs (Herbert 1997, Qiu 2002, Xia 2001), an uncontrolled cohort analysis (Amarenco 1998), and two case series (t'Veld 1998, Jonvelle 1992) were included. One comparator RCT with > 20% of participants with neurogenic bladder (Osca-Garcia 1997) , and a pooled RCT study (two studies, one of which was included) (Herbert 1999) were excluded, the latter on the basis that it did not use appropriate meta-analytic techniques. Another article, a case report, was identified for inclusion but was not translated (Bilici 2010). The remaining four non-English articles could not be assessed for eligibility.

Additional documentation provided by the Pharmaceuticals Service Division, as noted below, was also considered. Articles submitted by third parties were first checked to determine if they were already in our database, then screened for eligibility. Regulatory material from Canada, the U.S., the European Medicines Agency, Australia/New Zealand, and clinical trial registry material was used as noted in each drug comparison section.

Drug	CDR Review	PSUR	Other submission
Oxy ER (Ditropan)	No CDR review avail.	Y	--
Oxy Transdermal Patch (Oxytrol)	No CDR review avail.	Y	--
Oxy Gel (Gelnique)	Y	Y	--
Darifenacin (Enablex)	Y	N	--
Solifenacin (Vesicare)	Y	Y	Vesicare clinical update
Tolterodine (Detrol)	No CDR review avail.	Y	--
Trospium IR	Y	Y	Unpublished full study report
Fesoterodine (Toviaz)	Y	Y	02.02 Toviaz_disease prevalence; 03.01 Toviaz PE Evaluation

Table 2. Documentation provided by Pharmaceuticals Service Division

PRISMA Flowchart Detailing Flow of Studies



[1]Other sources include: reviewer-nominated articles and submissions through Pharmaceuticals Service Division.
[2] Numbers include the listed drug vs. any other comparator. The total adds up to more than the total number of direct comparator RCTs as each study is included in the sum for each drug in the pairwise comparison.
NRS= nonrandomized studies; RCTs= randomized, controlled trials.

Existing Systematic Reviews

We identified six potentially relevant systematic reviews that analyzed direct comparisons of drugs of the antimuscarinic class for incontinence, in a search strategy designed to identify higher quality reviews from high-yield databases rather than comprehensively search for all reviews (Shamliyan 2012; Madhuvrata 2012; Semla 2011; McDonagh 2009; Hartmann 2009; Chapple 2008) (Appendix C). AHRQ 2009 (Hartmann 2009) is a review on OAB in community dwelling women, which was updated in the larger 2012 AHRQ review on incontinence in women (Shamliyan 2012). One relevant network meta-analysis, based on indirect comparisons, was also identified (Buser 2012).

The reviews varied in search strategy, study eligibility criteria and methods, with overlapping relevance to this review. Other differences in methods were noted. For example, Chapple 2008 reported pairwise comparisons of each drug or dose and formulation but did not adjust for multiple comparisons (Chapple 2008).

We chose three reviews to assess in-depth for their possible inclusion in this review (Madhuvrata 2012, Shamliyan 2012, Mcdonagh 2009). All met quality criteria for systematic reviews according to AMSTAR (Shea 2007). Because of the differences between our eligibility criteria and the existing reviews, we chose to conduct our own meta-analyses (see Table 3 below). We cross-checked reference lists and compare the results of these previous reviews to this review's results in the discussion section of the report.

Table 3. Existing Systematic Reviews

	AHRQ 2012	Cochrane 2012	DERP 2009
Research Question	What is the efficacy, safety, comparative effectiveness of drugs for urinary incontinence in women?	Which anticholinergic drug for overactive bladder syndrome in adults? Does this differ by dose?	For adults with overactive bladder syndrome do anticholinergic drugs… differ in effectiveness, safety or AE? Differ by demographic subgroups? Age?
Inclusion criteria	≥75% women in RCTs or SRs for effectiveness; RCTs, observational studies for AE	RCTs only including abstracts	RCT or SR for effectiveness; RCT, observational studies of at least 6 months for AE
Search end dates and major	Dec 2011 Medline; Cochrane	March 2011 Cochrane Incontinence	Dec 2008 Medline; Cochrane Library;

databases searched	Library; SCIRUS; Google Scholar; Regulatory documents; Clinical Trial Registries;	Group Specialised Register of controlled trials (incudes CENTRAL, MEDLINE, CINAHL + handsearching)	July 2005 EMBASE
Comments/ limitations	Women only; EMBASE not searched	Harms inadequately covered by RCTs; published RCT reports only (not FDA reports);	Fesoterodine not included; Requires updating – end date Dec 2008
AE=adverse events; SR=systematic review; AHRQ 2012: Shamliyan 2012; Cochrane 2012:Madhuvrata 2012; DERP 2009: McDonagh 2009			

We also identified three systematic reviews (Paquette 2011; Tannebaum 2012; Meek 2011) and one limited literature search (Boudreau 2009) that reported on specific adverse events. Paquette 2011 and Tannenbaum 2012, reported on central nervous system adverse events or cognition. Because the most recent literature search data was 2011 we did not include these reviews but cross-checked reference lists. Meek 2011, a review on constipation, included placebo-controlled trials only and was therefore excluded.

Appendix A lists included clinical trials, non-randomized studies, and relevant systematic reviews (see Appendices page 1).

Other References – Chapter 3

Shea B, Grimshaw JM, Wells GA, Boers M, Andersson N, et al. (2007) Development of AMSTAR: A Measurement Tool to Assess Systematic Reviews. BMC Medical Research Methodology 7:10, doi:10.1186/1471-2288-7-10.

Chapter 4. Tolterodine vs. Oxybutynin Systematic Review

Tolterodine versus Oxybutynin for Overactive Bladder Syndrome

Executive Summary

Tolterodine, like oxybutynin, is a nonselective muscarinic receptor antagonist. Although tolterodine has been marketed with claims of tissue selectivity for the bladder, the evidence for this is weak and may not be clinically significant. Tolterodine is available in both immediate and extended-release formulations. The immediate-release formulation (Detrol™) has been available in Canada since 1998; the extended-release formulation (Detrol LA™) since 2002.

Research Questions:
Q1. In adults, including the frail elderly, does tolterodine (Detrol™, Detrol LA™) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) or other formulations of oxybutynin, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that tolterodine (Detrol™, Detrol LA™) improves clinically relevant outcomes or has a better safety profile compared to oxybutynin IR or other formulations of oxybutynin?

Q3. In adults, particularly the elderly, does tolterodine (Detrol™, Detrol LA™) have less effect on cognition when compared to oxybutynin IR or to other formulations of oxybutynin?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Non-randomized studies, case reports, and pharmacovigilance data were included to supplement the RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all-cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

Results: 14 RCTs met inclusion criteria:

- 10 compared tolterodine IR vs. oxybutynin IR (Abrams 1998; Altan-Yaycioglu 2005; Appell 1997; Drutz 1999; Giannitsas 2004; Lee 2002; Leung 2002; Malone-Lee 2001; Qiu 2002; Xia 2001);
- 1 compared tolterodine ER vs. oxybutynin IR (Homma 2004);
- 1 compared tolterodine IR vs. oxybutynin ER (Appell 2001);
- 1 compared tolterodine ER vs. oxybutynin ER (Diokno 2003);
- 1 compared tolterodine ER vs. transdermal (TDS) oxybutynin (Dmochowski 2003).

An additional 12 non-randomized studies were included to assess harms. Adverse event data were further supplemented by available pharmacovigilance data and case reports.

Tolterodine IR vs. Oxybutynin IR randomized controlled trials (RCTs)
All 10 RCTs meeting inclusion criteria were short, ranging from 3 to 12 weeks, with a total of 1986 participants, 1853 on active drug and 133 on placebo. Most trials compared tolterodine IR 2 mg twice a day with oxybutynin IR 5 mg twice or three times a day. Nine were parallel-arm trials and one was a crossover trial (Giannitsas 2004). The latter did not provide any data that contributed to meta-analyses.

Overview of results for tolterodine IR vs. oxybutynin IR RCTs:

- **All cause mortality:** Seven trials (1459 patients) reported that there were no deaths in either treatment arm. The trials were under-powered and too short in duration to assess comparative effects of tolterodine and oxybutynin on survival.
- **Non-fatal serious adverse events (SAE):** Four trials (1061 patients) indicate no difference between drugs, RR= 0.92 (95% CI 0.41 to 2.07)**.** However, the trials were under-powered and too short in duration to assess SAE.
- **Cognitive adverse events:** No information is available from the included RCTs.
  Quality of life (QoL): One trial (277 patients) measured overall health-related quality of life (SF-36), and reported no difference between tolterodine and oxybutynin. No condition-specific QoL measures were reported. Insufficient data are available to compare effects on quality of life.
- **Withdrawals due to adverse events (WDAE):** Based on six trials (1409 patients), there were 7% fewer WDAE (95% CI 4% to 10%) on tolterodine than on oxybutynin; RR= 0.57 (95% CI 0.43 to 0.76).
- **Patient-reported improvement or cure:** Based on four trials (898 patients), there was no difference between drugs: RR = 1.03 (95% CI 0.90-1.19). Of note, the largest placebo-controlled trial (Abrams 1998, N=236) reported no significant difference between active drug and placebo in the percentage of patients reporting improvement, with 47% to 50% improving per group.
- **Mean reduction in incontinence episodes per 24 hours:** The mean number of incontinence episodes at baseline ranged from 2.4 to 4.8 per day in these studies. In six trials (912 patients), oxybutynin and tolterodine reduced daily incontinence by 1.3 to 2.2 episodes per day, with no significant difference between the drugs: mean difference 0.09 (95% CI -0.35 to 0.52) (Abrams 1999; Drutz 1999; Lee 2002; Malone-Lee 2002; Study A015; Xia 2001). A sensitivity analysis excluding two clinically dissimilar studies in younger, Asian populations (Lee 2002, Xia 2002) indicates an advantage for oxybutynin, of an average 0.40 fewer incontinence episodes (95% CI 0.02 to 0.78).

- **Urgency:** One trial (106 patients) reported on this outcome (Leung 2002). Neither drug led to a reduction in urgency episodes (data not provided). There is insufficient evidence to assess effects on urgency, but available data fail to support an effect on this outcome.
- **Nocturia:** No trials assessed this outcome.
- **Total adverse events (AE):** Seven trials (1613 patients) reported on this outcome. Fewer patients experienced adverse events on tolterodine than oxybutynin: relative risk 0.78 (95% CI 0.69 to 0.89). The absolute difference was 17% fewer patients experiencing one or more adverse events during the trials (95% CI 10% to 24%).
- **Dry mouth:** Seven trials (1410 patients) reported on this outcome**.** Fewer patients on tolterodine vs. oxybutynin experienced dry mouth: relative risk 0.54 (95% CI 0.49 to 0.60); absolute difference 32% (95% CI 27% to 37%).
- **Blurred vision:** Two trials, including 614 patients in total (Abrams 1999, Malone-Lee 2002) report on the frequency of blurred vision. There was no statistically significant difference between tolterodine IR and oxybutynin IR: 4% vs. 6%, RR 0.72 (95% CI 0.36 to 1.44), p=0.35.
- **Dry eye:** In one RCT that actively sought eye symptoms (52 patients, Altan-Yaycioglu 2005), the proportion of patients experiencing dry eye did not differ significantly between tolterodine and oxybutynin: 14-17%; 43% on tolterodine vs. 58% on oxybutynin reported a burning sensation in the eye (difference not significant).

Tolterodine ER vs. Oxybutynin ER RCTs

One short-term trial was identified that enrolled women only and compared the maximum recommended dose of tolterodine ER (4mg/day) with 10mg/day of oxybutynin ER, which is at the lower end of recommended doses (Diokno 2003). The trial was under-powered and too short to assess mortality and serious non-fatal SAE. There was no difference in WDAE. Fewer patients on tolterodine ER experienced resolution of incontinence (defined as 7 days without incontinence), at week 12 than on oxybutynin ER: 16.8% vs. 23.0%; RR = 0.73 (95% CI 0.55 to 0.97), p=0.03. Fewer patients on tolterodine ER experienced dry mouth: RR 0.75 (95% CI 0.59 to 0.95), p= 0.02. However, as noted above, doses were non-equivalent.

Tolterodine ER vs. Oxybutynin TDS RCTs

One short-term trial compared oxybutynin TDS 3.9 mg/day with tolterodine ER 4mg (Dmochowski 2003). Mortality and non-fatal serious adverse events could not be assessed, due to inadequate power. The tolterodine ER group had fewer WDAE than patients on oxybutynin TDS (Dmochowski 2003). Most differences were due to application site reactions: RR 0.15 (95% CI 0.03 to 0.66), absolute difference 6.6%. There was no difference between drugs in condition-specific quality of life, and no difference in reduction from baseline in incontinence episodes. Dry mouth did not differ significantly between tolterodine ER and oxybutynin TDS although was numerically increased with tolterodine: RR 1.77 (95% CI 0.61 to 5.13), p=0.29 (Dmochowski 2003).

RCTs comparing extended release vs. immediate-release formulations

Two trials compared an ER with an IR formulation, one assessing tolterodine ER vs. oxybutynin IR (Homma 2003), and the other, oxybutynin ER vs. tolterodine IR (Appell 2001). These trials are less informative as long-acting formulations mitigate fluctuations in drug plasma levels experienced with IR formulations, leading to differences in clinical response. These comparisons do not allow differentiation of drug effects from effects of the ER formulation. Dry mouth was greater in the IR arm of each of the trials (oxybutynin in one trial; tolterodine in the other), which is suggestive of lower frequency of this adverse event with extended-release formulation.

Pooling of RCTs for all formulations of oxybutynin vs. tolterodine
We pooled all tolterodine-oxybutynin comparator trials to determine whether findings were consistent across formulations. The main findings did not differ: inadequate data were available to assess mortality and SAE, and no data are available on cognition. Quality of life did not differ. In total, 6% more patients on oxybutynin than tolterodine withdrew due to adverse events (95% CI 1% to 13%), 17% more patients experienced one or more adverse event (95% CI 10% to 24%) and 19% more patients experienced dry mouth (95% CI 8% to 30%). There was no difference in headache, constipation or dyspepsia between the two drugs.

Critical appraisal of RCTs: None of the trials were rated as low risk of bias (i.e., high quality) across all assessed features. The trials did not describe their randomization process and most did not describe method of allocation concealment. Few trials adequately reported blinding and none tested for maintenance of blinding. One published trial had evidence of selective outcome reporting (Drutz 1999); to circumvent this, we used data from the FDA medical and statistical reviews for an intention-to-treat analysis.

A number of the trials were designed as 'equivalence' trials, using inappropriately wide margins of confidence intervals to determine equivalence for incontinence episodes (Abrams 1999, Drutz 1999, Study A015, Malone-Lee 2001, Lee 2002). Such trials are inadequately powered to determine whether one drug was superior.

Most trials selectively and inconsistently reported adverse events and were underpowered to detect differences in serious or uncommon events. Active surveillance was not conducted in most trials, with adverse events collected by spontaneous reporting. However, in one RCT that actively solicited eye symptoms, the incidence of symptoms such as dry eye was higher than in other trials. Although direct comparisons cannot be made as trial populations differed, this suggests that method of ascertainment is important, and that spontaneous reporting underestimates events.

Non-randomized studies assessing serious and infrequent adverse events
Twelve non-randomized studies met inclusion criteria including three controlled cohort analyses (Gomes 2011; Jumadilova 2006; Sink 2008), seven uncontrolled cohort analyses (Layton 2001, Kreder 2002; Abrams 2001; Appell 2001; Michel 2005: Elinoff 2006; Michel 2002), one uncontrolled before-after study (Monnot 2012) and one case series (Alzayer 2010).

Controlled cohort analyses
Outcomes that were assessed in controlled cohort analyses included falls and fractures; depression; urinary tract infections, and cognitive and functional decline.

Two population-based comparative cohort analyses, one in Ontario (Gomes 2011; N=81,126) and the other in the U.S. (Jumadilova 2006; N=26,386), evaluated the rate of falls and fractures among patients taking oxybutynin and tolterodine. Both studies used propensity score matching to adjust for confounding. Neither found a difference in the rate of fractures. The Ontario study evaluated an older population, mean age 78, over a 90-day period, and also assessed the rate of serious falls and delirium; neither differed between users of oxybutynin and tolterodine. (Gomes 2011). This is despite likely differences in overall health status, as reflected in 0.6% higher all-cause hospitalization and 0.3% higher mortality on oxybutynin over this 90-day period. The authors used propensity score matching but residual confounding is likely. Alternatively, oxybutynin may be

leading to serious harm; these were secondary exploratory outcomes that are inconsistent with the primary outcome of no difference in falls, fractures and delirium. Additional research is needed to confirm or refute these results.

Jumadilova 2006 found that 1.5% fewer patients on tolterodine ER than oxybutynin IR experienced depression (95% CI 0% to 3%). There was no difference between users of ER formulations of each drug. Urinary tract infections also occurred more often on oxybutynin (ER and IR formulations) than on tolterodine ER. This study assessed three unrelated outcomes: fractures, depression and urinary tract infections. Selective reporting is likely, as there is no published protocol, only positive or neutral outcomes for tolterodine are reported, and tolterodine's manufacturer sponsored the study. Neither Jumadilova 2006 nor Gomes 2011 reports discontinuation rates. Jumadilova followed patients for one year; in other observational studies of oxybutynin and tolterodine, most patients discontinued use by one year. (Sexton 2011).

A third controlled cohort analysis compared rates of cognitive and functional decline among patients in long-term care in Indiana who were taking a cholinesterase inhibitor alone versus a cholinesterase inhibitor with oxybutynin or tolterodine (Sink 2008). The authors found no difference in cognitive decline. Activities of daily living (ADL) did not differ for patients with moderate, severe or nearly complete dependence. The least impaired had 0.53 points less decline per quarter on a 28-point ADL scale. No comparisons between oxybutynin and tolterodine are reported, as neither differed significantly compared with users of a cholinesterase inhibitor alone.

Uncontrolled observational studies

There are three uncontrolled observational studies of patients in usual care (N=6966) (Michel 2002; Michel 2005, Elinoff 2006), and three uncontrolled RCT extension studies, (N=2645; Abrams 2001; Appell 2001; Kreder 2002) with durations from 3-12 months. Rates of adverse events varied from 4% to 51% in 3-month studies, and 51% to 76% in one-year studies. Given the lack of controls, these studies provide little interpretable evidence on drug effects.

A UK prescription event monitoring study surveyed physicians about experiences of patients prescribed tolterodine (n=14,526; 53% response rate; Layton 2001). Hallucinations were noted as an adverse event in an indirect comparison with 10 cohorts of users of unrelated new drugs. The rate was 4.46/1000 patient years on tolterodine; women and patients ≥ 75 were at greatest risk.

A before-after study of 10 adults aged 60-85 (N=9 on oxybutynin; N=1 on tolterodine) reports on neurological test results pre and post discontinuation. Test results did not differ overall, but some subtest scores improved after withdrawal. These results are exploratory and non-comparative.

Spontaneous adverse event (AE) reports and published case reports

In an analysis of US spontaneous AE reports (oxybutynin N=1565; tolterodine N=11,670), Alzayer 2010 found that the most frequently reported AE were cardiovascular both with oxybutynin (8.4%) and tolterodine (4.9%). The higher reporting rate for tolterodine most likely reflects a growth in AE reporting over time, making comparisons between drugs unreliable.

Published case reports are mainly about CNS effects (N=8), including delirium, delusions, disorientation, confusion, memory loss and acute change in mental status (Edwards 2002; Salvatore 2007; Tsao 2003; Womack 2003; Juss 2005). There were also 3 published case reports of hyponatremia (Juss 2005; Madewell 2008; Bryan 2010), 3 warfarin interactions (Colucci 1999;

Taylor 2006) and one mixed liver injury with features of a hypersensitivity reaction (Schlienger 2002).

Regulatory documents
Available periodic safety update reports (PSURs) covered the period from 2004 to April 2011, with some additional information on earlier post-market safety experience.

From 2004 to 2011, global exposure to tolterodine was estimated at 9.8 million patient-years, with 83% of exposure to tolterodine ER. Over one third of patients were ≥75 years old. The PSUR lists 15,047 AE, including 2,789 serious adverse events. There were 106 deaths reported, 42 from Canada (also listed in the Canada Vigilance Adverse Reaction Online Database). The most frequent types of SAE were nervous system disorders, followed by renal and urinary disorders, including urinary retention. Cardiac disorders were reported in 133 cases, and the PSUR includes 18 cases of events potentially related to QT prolongation (e.g., ventricular tachycardia, cardiac arrest), including 3 deaths. There were 134 cases of falls and fractures, mainly in the elderly. In the elderly, there was a three-fold higher rate of reporting of five events compared to the non-elderly: thirst; confusional states; nocturia; drug interactions; and falls.

Canada's adverse reaction database includes 264 AE reports, 179 identified as SAE, including 69 deaths. Limited information is available on causes of death.

Discussion and conclusions

Q1: Does tolterodine provide a therapeutic advantage over oxybutynin?
The available short-term RCTs do not provide evidence of an efficacy advantage for tolterodine. Qualitatively, the adverse event profiles for tolterodine IR and oxybutynin IR were similar. Treatment with Tolterodine IR resulted in fewer WDAE (absolute risk difference 7%), fewer total AE (absolute risk difference 17%) and less risk of dry mouth than oxybutynin IR (absolute risk difference 32%). It is unclear whether this represents a therapeutic advantage for tolterodine as the higher incidence of dry mouth observed with oxybutynin may be attributable to a relatively greater anticholinergic dose (Center for Drug Evaluation and Research NDA 20-771). It is questionable whether the dose of oxybutynin most commonly used in the trials (5 mg t.i.d.) is comparable to the dose used for tolterodine (2 mg b.i.d.) Although not regarded as a SAE, dry mouth can lead to a range of oral health problems in older people, including mucosal candidiasis, bacterial infections, dental caries, gum recession, denture sores and difficulty with retention of prostheses, and eating and speech difficulties (Turner 2007).

Our findings from RCTs comparing tolterodine IR with oxybutynin IR are consistent with prior systematic reviews (Shamliyan 2012, Madhuvrata 2012). Compared with a review published by the Cochrane Collaboration (Madhuvrata 2012), we included one additional study (Study A015, as reported in the FDA review), ensured intention-to-treat analyses were included in the meta-analyses for study A010/Drutz 1999, corrected the number of evaluable patients for incontinence analyses, corrected the findings for one study, and included additional data for several meta-analyses. A systematic review conducted for the Agency for Healthcare Research and Quality (Shamliyan 2012) is restricted to women only. A third comparative systematic review (McDonagh 2009) only covers studies published to 2008.

Only two trials compared ER formulations of oxybutynin and tolterodine, one of which used doses that were most likely non-equivalent (Diokno 2003). Trial outcomes support this interpretation as tolterodine was associated both with less resolution of incontinence and less dry mouth. The other trial compared an extended release with a transdermal preparation. Greater tolerability for tolterodine, as reflected in fewer withdrawals due to adverse events, was mainly linked to application site reactions with oxybutynin TDS. The RCT evidence comparing ER formulations is too limited for any conclusions to be drawn.

Several additional gaps in evidence are noted. There are no available RCT data on longer-term outcomes such as mortality or other potential adverse events associated with chronic use. The duration of treatment in all available RCTs ($\leq$ 12 weeks) was too short to draw any conclusion about long-term consequences, and the trials were not statistically powered to detect potential differences in short-term harms. Most included trials were sponsored by manufacturers. Independently conducted trials are also needed to answer questions about which dose and formulation provides the greatest net benefit, particularly in the frail elderly and patients with co-morbidities.

The observational research evidence provides limited additional evidence on infrequent harms. Two population-based observational studies failed to find a difference in the rate of falls or fractures between oxybutynin and tolterodine (Gomes 2011; Jumadilova 2006). A higher than expected hallucination rate was found in an indirect comparison of an uncontrolled cohort of new users of tolterodine (Layton 2001). The existing observational evidence cannot answer the question as to whether rare, serious harms are more frequently associated with oxybutynin or tolterodine. There are reports for both drugs of serious cardiovascular and cognitive adverse events.

There is no evidence of an efficacy advantage for either drug. However, patients taking placebo in OAB trials show a marked improvement. This has been shown for commonly measured outcomes: number of incontinence episodes per day, micturition frequency per day, and mean volume voided. The response is likely multifactorial and in part attributable to a bladder training effect (facilitated by filling out a "bladder diary" in studies). The magnitude of placebo effect as a percentage of total benefit for this drug class, as well as the frequency of troublesome adverse events, suggests that non-drug approaches should be tried as first line treatment.

Q2. New Evidence since CDR Review

The approval of tolterodine IR and ER pre-dates the CDR review process. No CDR reviews have been conducted on tolterodine and no available CDR reviews address comparative data on tolterodine and any formulation of oxybutynin. Q2 is therefore not applicable to this comparison.

Q3. Comparative Cognitive Effects

We did not identify any published RCTs comparing oxybutynin with tolterodine that assessed cognition. It is not appropriate to rely solely on voluntary reporting for cognitive changes as patients may be unaware of such changes or may not attribute them to drug treatment, and none of the identified short-term trials specifically measured cognitive effects. The available trials were under-powered for CNS effects and information on these effects was not systematically collected.

One unpublished, short-term RCT assessing cognitive effects of tolterodine ER vs. oxybutynin ER in the elderly (clinicaltrials.gov NCT00411437) was identified. A brief summary of the placebo-controlled trial is in the PSUR documentation but dosages of the drugs are not provided, and

without further information on the methods and a full study report, the trial cannot be critically appraised. Results are therefore not presented. The final study report has been requested.

No non-randomized studies are available that provide direct comparative data on the cognitive effects of oxybutynin and tolterodine.

In conclusion, there is insufficient evidence publicly available to assess the magnitude of tolterodine's effects on cognition, versus oxybutynin. One short unpublished trial has directly addressed relative effects on cognition and may help to shed additional light on this issue. Based on case reports and data submitted to regulators, there is evidence of adverse cognitive effects associated with tolterodine, but insufficient research to assess the frequency of effects or how this compares to oxybutynin.

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Background

Tolterodine L-tartrate Immediate-Release Product Data

Tolterodine was first introduced onto the global market in 1997, and was first approved for market entry in Canada in 1998. The information in Box 1, below, is derived from the Canadian Product Monograph.

Box 1: Tolterodine IR Product Information

Categorization: anticholinergic-antispasmodic agent

Indication: the symptomatic management of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Recommended Usual Dose: initial dose 2 mg twice daily; may be reduced to 1 mg twice daily depending on individual response and tolerability. Maximum recommended daily dose 4 mg.

Mechanism of Action: competitive, nonselective muscarinic receptor antagonist

Source: Tolterodine L-Tartrate Immediate Release. Canadian Product Monograph. Feb 10, 2010

Tolterodine L-tartrate Extended-Release Product Data

Tolterodine ER was approved for market entry in Canada in 2002.

Box 2: Tolterodine ER Product Information

Categorization: anticholinergic-antispasmodic agent

Indication: the symptomatic management of patients with an overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms.

Recommended Usual Dose: initial dose: 4 mg once daily; may be reduced to 2 mg once daily based on individual response and tolerability. Maximum recommended daily dose 4 mg.

Mechanism of Action: competitive, nonselective muscarinic receptor antagonist

Source: Tolterodine L-Tartrate Extended Release. Canadian Product Monograph. June 20, 2011

Q1. Comparative Harms and Benefits

Results

Search Findings

Fourteen RCTs (all formulations and comparisons) and 12 non-randomized studies (not including case reports) were identified for this comparison.

Direct Comparator RCTs

Fourteen active comparator RCTs (in 20 publications) met inclusion criteria and compared tolterodine (ER or IR) with oxybutynin (all formulations):

Tolterodine IR vs. Oxybutynin IR: 10 RCTs
Tolterodine ER vs. Oxybutynin IR: 1 RCT
Tolterodine ER vs. Oxybutynin ER: 1 RCT
Tolterodine ER vs. Oxybutynin TDS: 1 RCT
Tolterodine IR vs. Oxybutynin ER: 1 RCT

Six companion papers were identified that were secondary analyses of RCTs or pooled RCTs. We did not include pooled analyses of two RCTs (Armstrong 2007) and four RCTs (Appell 1997) because pooling was not conducted as a standard meta-analysis. Appropriate meta-analytic techniques include stratification on the basis of study to retain the advantage of randomization in included RCTs and the validity of within-study comparisons. Pooling in its simplest form (adding up events for each combined group) is considered inadequate for efficacy outcomes and increasingly so for safety data because it can introduce a bias or systematic error (Altman and Deeks 2002, Leivre 2002). The relevant pooled RCTs are available as separate full study reports (Abrams 1998, Drutz 1999, Appell 2001, Diokno 2003) or as part of the FDA Detrol New Drug Approval (NDA) review (Study A015, NDA 20-771).

We also considered six recent high- or fair-quality antimuscarinic drug class reviews for inclusion (Shamliyan 2012, Madhuvrata 2012, Semla 2011, McDonagh 2009, Hartmann 2009, Chapple 2008). Based on an in-depth evaluation of eligibility criteria and methods for three of the reviews (Table 3 in Chapter 3), we elected to conduct our own meta-analyses for tolterodine vs oxybutynin comparisons. We compare our findings to prior reviews in the discussion section.

Analyses of RCT findings are divided into two main sections:

1. tolterodine IR vs. oxybutynin IR
2. tolterodine vs. oxybutynin comparisons that include ER or transdermal formulations in either or both treatment arms.

1. Tolterodine IR vs Oxybutynin IR

Ten studies compared tolterodine IR with oxybutynin IR. Of these, nine were a parallel-group design and contributed data to one or more meta-analyses (Abrams 1998, Altan-Yaycioglu 2005, Drutz 1999, Lee 2002, Leung 2002, Malone-Lee 2001, Qiu 2002, Xia 2001, Study A015). The tenth trial (Giannitsas 2004), a crossover trial that reported predominantly urodynamic findings along with adverse events, was not included in any meta-analysis. Observations in crossover trials are not independent as the same patient contributes data for each treatment arm. Because the available data were not reported as within-individual comparisons, we chose not to combine them with the parallel group data (Higgins and Green 2011, Elbourne 2002).

All RCTs were short, ranging from three to twelve weeks long, with a total of 1986 participants, 1853 who received active drug and 133 who received placebo. Most trials compared tolterodine IR 2 mg b.i.d with oxybutynin IR 5 mg b.i.d or t.i.d, with the exception of Qiu 2002 (oxybutynin 5 mg once daily vs. tolterodine 2 mg once daily). Study characteristics are presented in Table 1 in Appendix D.

Results are presented according to our hierarchy of outcomes. For the meta-analyses, if a relative risk (RR) is < 1, it means fewer people experienced events (beneficial or harmful) in the tolterodine group. Data for outcomes in individual trials are presented in Table 2 in Appendix D.

1. All-cause mortality

No deaths were reported to occur during the short-term RCTs. Seven trials either explicitly reported no deaths or this could be inferred from an accounting of all serious adverse events. Reporting was incomplete for three trials. The FDA review reported that one study participant with a history of cardiovascular disease and syncope died two months after completing study treatment (tolterodine) in Abrams 1999 (Study A010) (NDA 20-771). Syncope was reported as a SAE during the trial.

2. Serious Adverse Events (SAE)

The proportions of patients who had ≥1 (non-fatal) SAE were similar for tolterodine IR and oxybutynin IR.

Data were incompletely reported and available for six of the ten trials (Abrams 1999, Drutz 1999/Study A010, Malone-Lee 2001, Altan-Yaycioglu 2005, Lee 2002, Leung 2001). In two trials, there were zero events in both treatment arms (Lee 2002, Leung 2001); these trials did not contribute to the meta-analysis for relative risk. When the remaining four trials (N=1061) were combined, 2% of patients per treatment arm experienced SAE: RR 0.92 (95% CI 0.41 to 2.07), P=0.84. The wide confidence intervals reflect the uncertainty in this treatment effect estimate. Studies were not statistically powered to detect differences in this outcome.

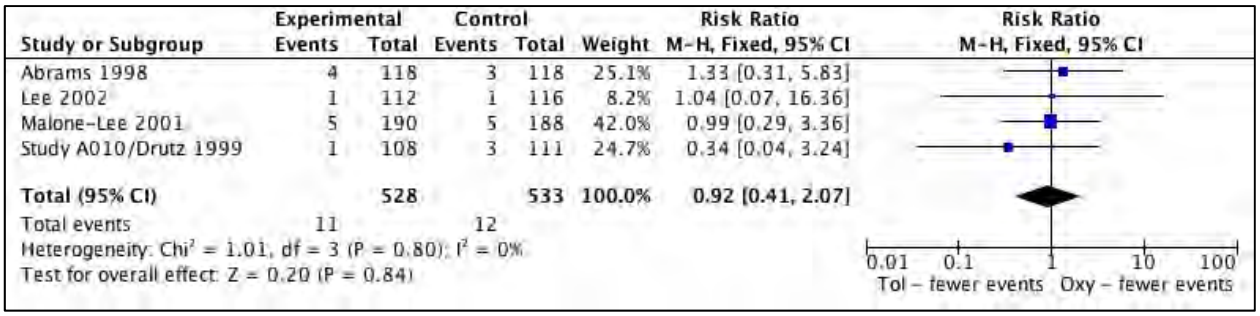

Figure 1. SAE (non-fatal)

Details on individual SAE are presented in Table 3 in Appendix D. These included one case each of syncope, gastrointestinal bleeding (hematemesis and esophagitis), abdominal pain +/- vomiting and urinary retention in patients treated with tolterodine IR.

None of the identified SAE involved the central nervous system. However, no RCTs were specifically designed to assess cognitive impairment.

3. Withdrawals due to Adverse Events (WDAE)/Tolerability
Six trials reported WDAE and were combined for meta-analysis (N=1409). Tolterodine IR was associated with fewer WDAE (9%) than oxybutynin IR (16%): RR 0.57 (95% CI 0.43 to 0.76), P=0.0001; absolute risk difference: -7% (95% CI -10% to -4%).

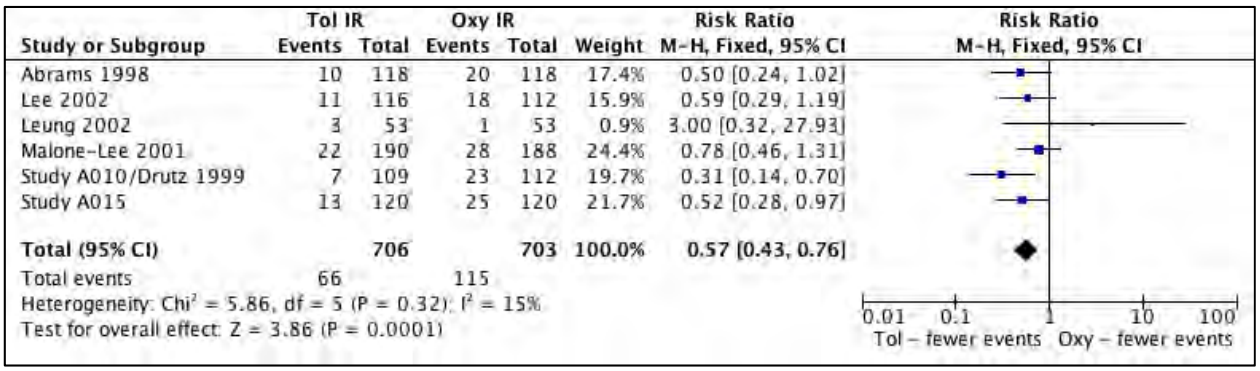

Figure 2. WDAE

4. Quality of life (QoL)
One RCT (N=221) included measurements of the QoL SF-36 instrument (Drutz 1999/Study A010). The SF-36 results did not show clinically meaningful differences between treatment arms according to the FDA review (data were not provided) (Center for Drug Research and Evaluation NDA 20-771). It is unclear whether additional trials measured QoL but did not report the outcomes.

5. Patient-Reported Perception of Improvement
Seven studies measured patients' perception of improvement in symptom severity or treatment benefit (Table 4 in Appendix D) (Abrams 1998, Drutz 1999, Lee 2002, Leung 2002, Malone-Lee 2001, Qiu 2002, Study A015).

Measurements were mainly based on non-validated questions or scales and varied across studies. Patient perception of bladder condition (PPBC), a single-item global measure used in several trials (Abrams 1998; Drutz 1999; Study A015), has since undergone validation predominantly in females and has been shown to have construct validity and responsiveness to treatment (Coyne 2006). However, it has weak test-retest reliability compared with multi-item scales, and only 54% of clinically stable respondents reported the same level of bladder problems between visits two weeks apart (Matza 2005). A lower score corresponds to improvement.

Four studies, including one trial that used patient perception of bladder condition (PPBC), provided data for meta-analysis (Abrams 1998; Lee 2002; Malone-Lee 2001; Qiu 2002). Four studies, including one trial that used PPBC, provided data for meta-analysis (Abrams 1998; Lee 2002; Malone-Lee 2001; Qiu 2002). Across the four trials, the proportion of patients who reported subjective improvement with either drug ranged from 41% (largest trial) to 74% (smallest trial). When data were combined (N=898), 48% of patients receiving tolterodine IR and 47% receiving oxybutynin IR reported improvement. There was no statistically significant difference between tolterodine IR and oxybutynin IR: RR 1.03 (95% CI 0.90 to 1.19), P=0.63.

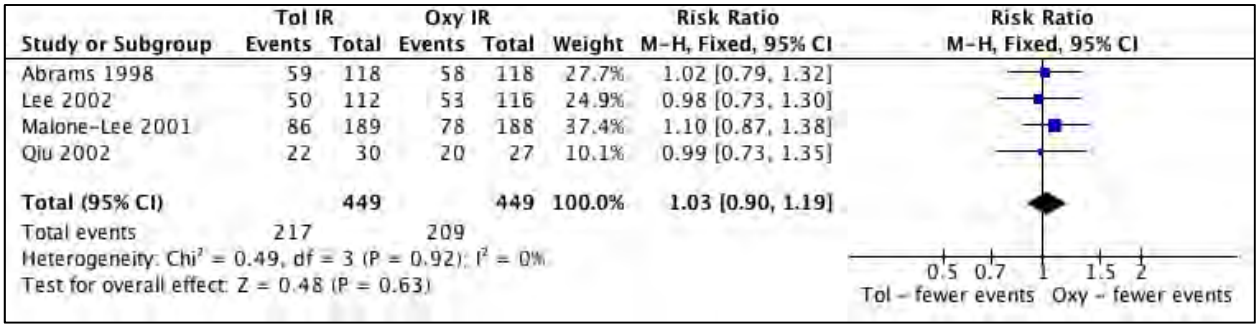

Figure 3. Patient Perception of Improvement

A sensitivity analysis excluding Qiu 2002, which used lower doses of both drugs and a shorter duration of treatment (three weeks), did not reveal a significant difference: tolterodine IR vs. oxybutynin IR (N=670), RR 1.04 (95% CI 0.90, 1.20), P=0.61.

Two trials also included a placebo arm. In the largest placebo-controlled trial (Abrams 1998, N=236), there was no difference between placebo (47%) and active drug (tolterodine IR 50% and oxybutynin IR 49%).

Two studies (Study A015 and Drutz 1999/Study A010) had no available published data although patient perception of bladder condition (PPBC) was measured. Another reported no statistical difference between tolterodine IR and oxybutynin IR in the scoring for two visual analogue scales, one on perceived change with treatment and the other on overall severity of symptoms (Leung 2002).

6. Quantification of Incontinence Episodes

Cure or Dryness Rate: No trials reported resolution of incontinence or 'cure' as an outcome (defined as zero incontinence episodes over a specified time period, usually 3 or 7 days).

Reduction in incontinence episodes: End of treatment data and mean differences from baseline were combined for six trials (Abrams 1999, Drutz 1999, Lee 2002, Malone-Lee 2001, Study A015, Xia 2001). Additional data for Drutz 1999 was obtained from the FDA review (NDA 20-771) so that an intention-to-treat analysis could be included rather than the per protocol data provided in the publication.

Incontinence was not required for enrolment in any trial so numbers of evaluable patients (N=912) were less than the total numbers enrolled. The mean number of episodes of incontinence at baseline ranged from 2.4 to 4.8 episodes per day, depending on the study. Active drug treatment reduced daily incontinence by 1.3 to 2.2 episodes. Oxybutynin IR was slightly numerically better at reducing incontinence, but this was not statistically significant and is too small a difference to be clinically meaningful: Mean Difference (MD) 0.09 episodes /day (95% CI -0.35 to 0.52), P=0.69.

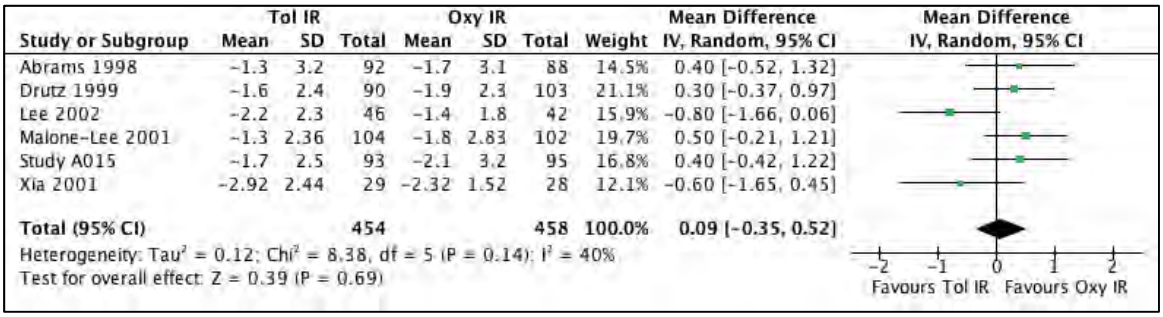

Figure 4. Incontinence episodes per 24 hours. Change from baseline or end of treatment.

Heterogeneity across studies (I^2=40%) was attributable to Lee 2002. This was one of two studies that reported a numerical result favoring tolterodine. The result was not statistically significant for either study when the appropriate numbers of evaluable participants were included. Lee 2002 (N=88) included a relatively young population of Korean patients (mean age 52 years) who were treated for eight weeks, in contrast to four longer and larger studies that enrolled older and predominantly Caucasian participants (mean age varied from 56 to 65 years). The second, smaller study (N=57) was also conducted in a younger Asian population (mean age 49 years) and was of shorter duration (Xia 2001).

In a sensitivity analysis, removal of Lee 2002 and Xia 2002 resulted in a statistically significant difference in favor of oxybutynin IR, which reduced incontinence episodes by an additional 0.4 episodes/day: MD 0.40 (95% CI 0.02 to 0.78), P=0.04. This difference may not exceed the threshold for a minimal clinically important change (see discussion).

7. Nocturia
No trials report on this outcome.

8. Urgency episodes
One trial (N=106) reported on urgency episodes (Leung 2002). There was no significant improvement from baseline with tolterodine IR or oxybutynin IR, and no difference between groups, using repeated-measures analysis of variance.

9. Total AE: Total AE were reported in seven of the ten trials. Combining seven trials (N=1613), 65% of patients taking tolterodine IR and 82% of patients taking oxybutynin IR reported one or more AE: RR 0.79 (95% CI 0.74 to 0.84), P= 0.0002; absolute risk difference 17% (95% CI -24% to -10%). Substantial heterogeneity was present (I^2=81%) and attributable to three studies, Lee 2002, Xia 2001 and Study A015. These studies report a larger advantage for tolterodine IR than the other four studies. However, clinical or methodological reason(s) for the heterogeneity could not be ascertained.

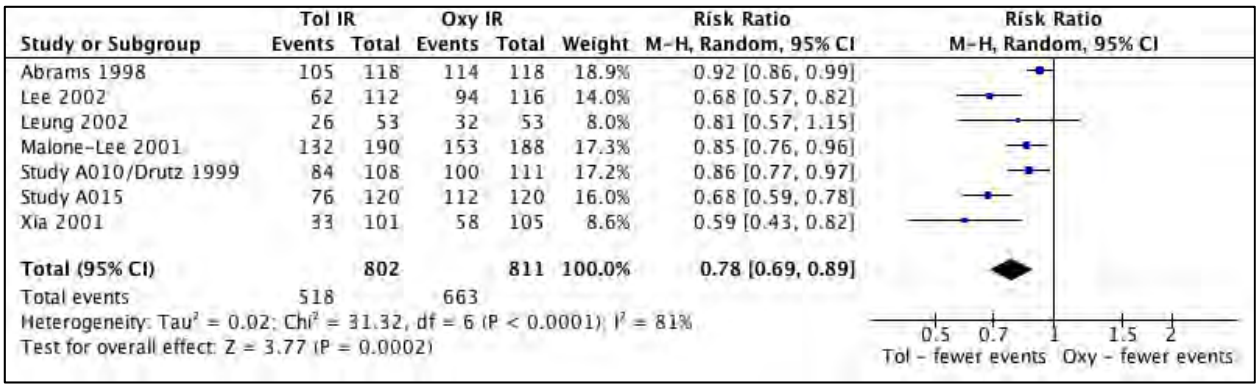

Figure 5. Total AE

10. Specific AE

Dry mouth:

The most commonly reported and the most frequent AE in the trials was dry mouth. Six trials (N=1353) contributed data for meta-analysis. Fewer patients treated with tolterodine IR experienced dry mouth compared with oxybutynin IR: RR 0.54 (95% CI 0.49 to 0.61), P< 0.00001; tolterodine IR 38% vs. oxybutynin IR 70%; absolute risk difference: 32 % (95% CI -37% to -27%). The severity of dry mouth was categorized in some studies; however, scoring of severity was inadequately defined so is not reported here.

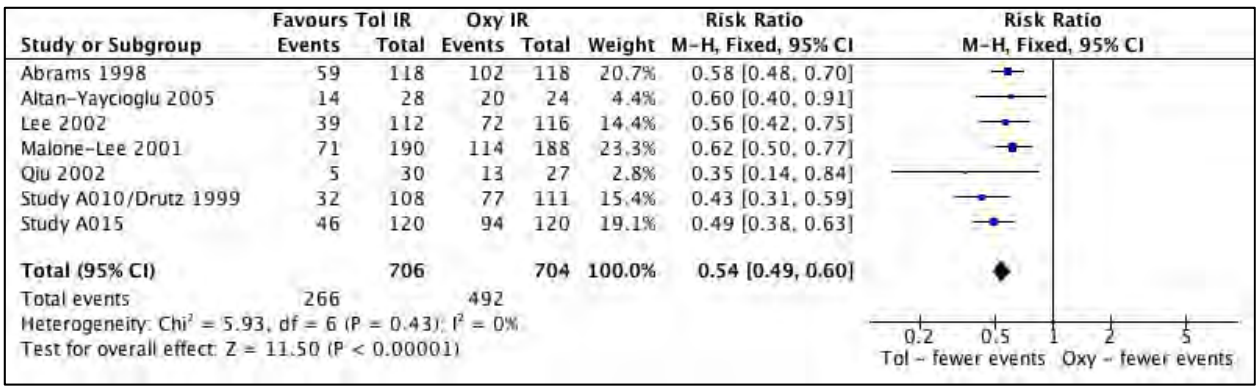

Figure 6. Dry Mouth

It is questionable whether oxybutynin IR 5 mg t.i.d is an anticholinergic dose comparable to tolterodine IR 2 mg b.i.d (Center for Drug Research and Evaluation NDA 20-771). It is therefore unclear whether this finding represents a therapeutic advantage for tolterodine or merely reflects the greater anticholinergic dose of oxybutynin. There were two trials that used a lower dose of oxybutynin, Lee 2002 (oxybutynin 5 mg b.i.d vs. tolterodine 2 mg b.i.d) and Qiu 2002 (oxybutynin 5 mg once daily vs. tolterodine 1 mg once daily). We did not perform a subgroup analysis because there was only one trial that compared a lower dose of oxybutynin vs. tolterodine 2 mg b.i.d. Excluding Lee 2002 from the meta-analysis had minimal effect on the relative risk, as similar percentages of patients experienced dry mouth in this trial as in the studies using higher doses: tolterodine IR 35% vs. oxybutynin IR 62%. Excluding Qiu 2002 alone or in combination with Lee 2002 also had minimal effect on the relative risk.

Three additional meta-analyses were conducted on adverse events that were reported in two or more trials. Forest plots for these are located in Appendix D.

Headache:
More headache occurred in the tolterodine IR group but the difference was not statistically significant: tolterodine IR vs. oxybutynin IR (3 trials, N=825), RR 1.29 (95% CI 0.83 to 2.01), P=0.25.

Dyspepsia:
More dyspepsia occurred in the oxybutynin IR group but was not statistically significantly different from tolterodine IR (3 trials, N=842): RR 0.70 (95% CI 0.38 to 1.30), P=0.26. Moderate heterogeneity in this meta-analysis was attributable to Abrams 1999 although the reason was not ascertained.

Blurred vision:
Two trials (Abrams 1999, Malone-Lee 2002) reported the percentage of patients experiencing blurred vision. When combined, 4% of patients receiving tolterodine IR and 6% of patients receiving oxybutynin IR reported blurred vision. There was no statistically significant difference between tolterodine IR and oxybutynin IR (2 trials, N=614): RR 0.72 (95% CI 0.36 to 1.44), P=0.35.

Other Ocular AE:
One assessor-blinded RCT (N=52) specifically evaluated short-term tolterodine IR and oxybutynin IR effects on the eye, with symptoms actively sought by specific questions (Table 1 in Appendix D) (Altan-Yaycioglu 2005). Dry eye was reported by 14 to 17% of participants in both treatment arms, and a burning sensation in the eye was reported by 43% in the tolterodine IR group and 58% in the oxybutynin IR group (difference not statistically significant). The high incidence of such symptoms raises the possibility that eye symptoms are under-reported in clinical trials because patients are not specifically asked about them.

Both drugs decreased accommodation amplitude, which results in an inability to focus on near objects and blurred vision. Measurement of pupillary diameter suggested there might be an (unanticipated) problem with night vision with tolterodine (due to an increase in pupillary diameter in dim light) but the measurement was not significantly different from oxybutynin IR, and the finding needs to be confirmed with more accurate measurement techniques.

Neither drug had an effect on Schirmer's test, which measures the aqueous tear layer, and is affected in dry eye. However, another layer of the precorneal tear film, the mucin layer (Leung 2005), was less stable following treatment with either drug, as measured by a shorter mean tear-break-up time compared to baseline. This may have implications for the development of dry eye, and requires confirmation and further evaluation.

11. Volume voided per micturition
Five trials reported on this outcome, including the one crossover trial (Table 2 in Appendix D). Volume voided per micturition is commonly used as a physiological and objective measure of the anticholinergic effect on the bladder (Center for Drug Evaluation and Research NDA review 20-771; Common Drug Review Fesoterodine Clinical and Pharmacoeconomic Report 2012). Of the four parallel group trials, one trial reported no statistically significant difference between drugs and did not provide a measure of variation to enable pooling (Malone-Lee 2001). The remaining three parallel group trials were combined (Abrams 1998/Study A008, Drutz 1999/Study A010, Study

A015) (Appendix D). Oxybutynin IR increased the mean volume voided per micturition by an additional 14 mls (95% CI -22 to -6), P=0.0003, compared with tolterodine. The crossover trial reported a smaller, 3 ml difference in the change from baseline between drugs in favor of oxybutynin (Giannitsas 2004).

12. Urodynamics/clinician measures
No useable data were available for meta-analysis of the three urodynamic/clinician measures, maximum cystometric capacity, volume at first contraction, and residual volume.

In a two-way crossover trial, (Giannitsas 2004), neither drug was consistently superior to the other in modifying urodynamic parameters in the overall group (Table 2 in Appendix D). For the two most severely affected subgroups, there were differences in the two drugs' actions on specific urodynamic parameters, with one drug being superior in changing some urodynamic parameters and the other superior in others (not all reaching statistical significance).

Critical Appraisal: Tolterodine IR vs Oxybutynin IR RCTs

As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity. For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results) (Table 5 in Appendix D). None of the trials were rated as low risk of bias (i.e., high quality) across all assessed features. The trials did not describe their randomization process and most did not describe method of allocation concealment.

Drutz 1999 had evidence of selective outcome reporting, including the reporting of per protocol analyses only, which excluded many patients particularly those who had a dose reduction of oxybutynin. The publication was thus rated at high risk of bias. The per protocol analyses favored the sponsor's drug tolterodine and contrasted with intention-to-treat (ITT) analyses available for the same study in the FDA medical and statistical reviews (Center for Drug Research and Evaluation NDA 20-771), where the study is listed as Study A010. We reported results based on the full dataset from the FDA review because ITT analyses reduce risk of bias. The study is referred to as Study A010 from hereon.

Study A010 included a placebo arm, and an ITT analysis indicated no statistically significant difference between placebo and tolterodine for change in mean incontinence episodes per 24 hours although a statistically significant difference between oxybutynin and placebo was observed. A second study that contained a placebo arm, Abrams 1998 (Study A008), also failed to show a statistically significant difference between tolterodine and placebo (Center for Drug Evaluation and Research NDA 20-771). In spite of these findings, equivalence between tolterodine and oxybutynin was claimed, as described below.

The clinical development Phase III (Abrams 1999/A008, Drutz 1999/Study A010, Study A015) and other trials (Malone-Lee 2001, Lee 2002) were designed as 'equivalence' trials and were not powered to determine whether one drug was superior to the other in terms of efficacy. The predefined confidence interval margins chosen to demonstrate equivalence were inappropriately wide for the outcome of incontinence episodes (95% CI +/- 1.5). Because the mean baseline number of incontinence episodes was about three, these margins allowed variations of +/- 50% to be considered equivalent (Center for Drug Evaluation and Research NDA 20-771). The mean

difference of -0.51 (95% CI – 0.66 to -0.37) between drug and placebo reported in the Cochrane systematic review on anti-muscarinic drugs for OAB (Nabi 2009) is well within these margins.

Few trials adequately described blinding and none tested for maintenance of blinding. The differential incidence of adverse events (dry mouth) can lead to loss of blinding, which may influence outcomes that are subjective such as patient satisfaction or perception of improvement. Additional uncertainty about the robustness of patient-reported perceptions arises from the use of unvalidated measures or measures with poor test-retest reliability such as PPBC.

Incomplete reporting of harms:
The majority of trials selectively and inconsistently reported adverse events. Trials were statistically underpowered to detect differences in serious but relatively uncommon events.

Active surveillance of harms was not conducted in most trials, with most adverse events collected by spontaneous reporting. However, in one RCT that actively solicited eye symptoms, the incidence was higher than in other trials. Although direct comparisons cannot be made as trial populations differed, this suggests method of ascertainment is important, and that spontaneous reporting underestimates events.

No trials specifically measured effects on cognition, and active surveillance methods were not used to detect CNS effects in RCTs.

The short-term trials provide no information on the consequences of taking either drug on a chronic basis and no evidence with which to assess a therapeutic advantage for either drug in the long-term.

Applicability:
Participants in the trials were highly selected with screening out of patients at higher risk for adverse events (e.g., patients with comorbidities who may have an increased anticholinergic load). No trials specifically enrolled patients in long-term care, who are more likely to be frail elderly and susceptible to AE. The age of trial participants ranged from 19 to 91 years. Trial publications did not, however, report the proportion of participants who were 65 years or older, and no trial reported data separately for the elderly. We were therefore unable to conduct a subgroup analysis by age.

The FDA carried out an analysis for patients aged 65 or older, but this includes a placebo vs. tolterodine IR trial that is not included in this review, and data were pooled inappropriately rather than being combined through meta-analysis. Therefore the results should be considered exploratory only. There were 117 patients aged 65 or older who received tolterodine IR 2 mg b.i.d and 105 patients who received oxybutynin IR 5 mg t.i.d. Neither group differed significantly versus placebo for reduction in incontinence episodes from baseline (Center for Drug Evaluation and Research NDA 20-771).

The populations in initial trials had a high incidence of prior lower urinary tract surgery (approximately a third); it is unclear how representative these population are without further details on the types of surgery (e.g., whether the procedures were for pelvic prolapse, stress urinary incontinence or prostatic conditions).

Findings may not be generalizable to some racial/ethnic groups as most participants were Caucasian. This is important because populations vary in the proportions of people who have

phenotypes with a reduced capacity to metabolize tolterodine (Bernard 2006). Two of the trials conducted in predominantly Caucasian populations assessed metabolizer phenotype in patients receiving tolterodine and identified 5% or 6% as poor metabolizers (Abrams 1998/Study A008, Drutz 1999/Study A010).

A third of participants overall were Asian. Intermediate metabolizer phenotypes are relatively common in Asian populations (up to 50%) although not tested for in the trials conducted in Asia (Bernard 2006). This is important because intermediate metabolizers may have the highest blood concentrations of active drug (active parent component plus active metabolite). Other populations vary in the proportion of intermediate and poor metabolizers and this must be considered in generalizing results to different populations (although other reasons for inter-individual variability also exist).

It is not clear how generalizable findings are to both sexes. Men represented about a third of participants and were not reported on separately. Men with benign prostatic hypertrophy (BPH) can have symptoms that overlap with OAB syndrome. If the etiology of symptoms in men is not adequately investigated, there is a risk of misdiagnosis, with implications for effectiveness of treatment because oxybutynin and tolterodine have not been shown to be effective against BPH.

The RCT on eye effects measured an effect on visual accommodation within a range associated with normal ageing and correctable by glasses (Leung 2005). However, the population was relatively young (mean age 40-42 years, range 22 to 60 years), and is not representative of the older population encountered in clinical practice.

Populations were not stratified on the basis of prior response to therapy: Even though treatment history was frequently documented as a baseline characteristic in 30 to 50% of participants, trial participants were not stratified on the basis of prior response to treatment. Conclusions could not therefore be drawn on ‘refractory’ populations or responses to “second-line” treatment.

Choice of comparator dose: Usual doses for oxybutynin IR and tolterodine IR may not be equivalent. A 5 mg dose of oxybutynin IR is higher in terms of its anticholinergic effect on the bladder than a 2 mg dose of tolterodine IR and therefore would be anticipated to have more anticholinergic-related adverse events such as dry mouth. This does not necessarily reflect a therapeutic advantage for tolterodine. A lower dose of oxybutynin may offer similar efficacy with fewer adverse events.

Industry sponsorship: Most trials were industry-sponsored. There is a lack of independently conducted head-to-head trials. In addition to selective outcome reporting, a bias associated with favorable results and conclusions for the sponsor’s drug may be mediated by factors other than traditional measures of risk of bias and sample size (Lundh 2012). This includes choice of dose for comparators as described above.

Table 1. Summary: RCTs Tolterodine IR vs Oxybutynin IR

Outcome	No. of studies (No. of Participants)	Tol vs Oxy RR or Mean Difference	Tol vs Oxy Absolute Risk difference	Summary
All-cause mortality	7 trials (1459) reported no deaths or inferred from SAE accounting	--	--	- No data on long-term mortality -Trials under-powered for short-term mortality (zero events)
SAE (non-fatal)	4 trials (1061)	RR 0.92 [95% CI 0.41 to 2.07]	--	- No difference between drugs - Trials under-powered for SAE
Cognitive AE	0 trials	--	--	- No data on cognition
QoL - Overall	1 trial (277)	SF-36 reported as no differences between drugs		- Insufficient evidence on overall QoL
QoL – Condition-Specific	0 trials	--	--	- No data on condition-specific QoL
WDAE	6 trials (1409)	RR 0.57 [95% CI 0.43 to 0.76]	RD -7% [95% CI -10% to -4%]	- 7% fewer WDAE with Tol IR - Insufficient studies to assess dose by subgroup analysis
Patient-reported improvement	4 trials (898)	RR 1.03 [95% CI 0.90 to 1.19]	--	- No difference between drugs
Incontinence episodes Mean reduction from baseline or end of Tx	6 trials (912) 4 trials* (767)	MD 0.09 [95% CI -0..35 to 0.20] MD 0.40* [95% CI 0.02 to 0.78]	--	- No difference between drugs
Urgency	1 trial (106)	No improvement with either drug (data not provided)		- Insufficient evidence on urgency
Nocturia	0 trials	--	--	- No data on nocturia
Total AE	7 trials (1613)	RR 0.78 [95% CI 0.69 to 0.89]	RD -17% [95% -24% to -10%]	- 17% fewer patients in Tol group had one or more AE
Dry mouth	7 trials (1410)	RR 0.54 [95% CI 0.49 to 0.60]	RD -32% [95% CI -37% to -27%]	- 32% fewer patients had dry mouth in Tol group

AE, adverse events; MD, (weighted) mean difference; NR, not reported; Oxy, oxybutynin; QoL, quality of life; RD, risk difference; RR, relative risk; Tol, tolterodine; WDAE, withdrawals due to AE; *Sensitivity analysis with exclusion of two studies (Lee 2001, Xia 2002) that were clinically and methodologically dissimilar to other trials

2. Other Tolterodine vs. Oxybutynin Comparisons

Four additional trials (in eight publications) were identified that involved comparisons of other formulations of tolterodine and oxybutynin. A total of 2147 participants were enrolled in the trials, 1898 who took active drug and 239 who received placebo.

Table 2. Other Tolterodine-Oxybutynin Comparisons

No. of RCTs	Tolterodine	Oxybutynin	Study
1	Tol ER 4 mg/d	Oxy ER 10 mg/d	Diokno 2003
1	Tol ER 4 mg/d	Oxy TDS 3.9 mg/d	Dmochowski 2003
1	Tol ER 4 mg/d	Oxy IR 3 mg tid	Homma 2003
1	Tol IR 2 mg bid	Oxy ER 10 mg/d	Appell 2001

a. Extended Release Comparisons of Tolterodine and Oxybutynin

Two trials compared tolterodine ER with an extended release formulation of oxybutynin (Diokno 2003, Dmochowski 2003).

Diokno 2003 (N=790 females) compared the *maximum* recommended dosage of tolterodine ER 4 mg/day with 10 mg/day oxybutynin ER, a dose at the *lower* end of the available range of oxybutynin ER. The trial enrolled women with urgency predominant mixed urinary incontinence as well as urgency incontinence. The proportion of women with mixed incontinence was not stated. Forty-seven percent of participants had previously received anticholinergic drugs.

Dmochowski 2003 (N=238 receiving active drug) compared tolterodine ER 4 mg with oxybutynin TDS 3.9 mg/day and placebo, in a predominantly female population. Eligibility for the trial included a prior beneficial response to anticholinergic therapy.

Baseline severity of incontinence episodes in both trials was approximately five episodes per day. Trial characteristics are presented in Table 6 in Appendix D. Results are presented in Table 7 in Appendix D.

1. Mortality
Diokno 2003 reported one death in the oxybutynin IR group during treatment and a second death in the same group after completion of study treatment. No details of the deaths are provided. Dmochowski 2003 did not report on this outcome.

2. Withdrawals due to adverse events/tolerability
In Diokno 2003, there was no difference in total WDAE for tolterodine ER and oxybutynin ER (5% each): RR 0.93 (95% CI 0.51 to 2.07), P=0.82.

Dmochowski 2003 reported significantly fewer WDAE in the tolterodine ER group (4.1%) than the oxybutynin TDS group (10.7%): RR 0.15 (95% CI 0.03 to 0.66), P=0.01. The increased WDAE in the oxybutynin TDS group were largely attributable to application site reactions to the transdermal system.

When the two trials were combined (N=1034), there were numerically fewer WDAE in the tolterodine ER group but the difference was not statistically significant: RR 0.43 (95% CI 0.07 to 2.48), P=0.34. Heterogeneity was high (I^2=80%) consistent with the clinical and methodological diversity of the studies.

3. SAE (non-fatal)
There were no non-fatal SAE in Diokno 2003. Dmochowski 2003 did not report on total SAE.

4. QoL
One trial (Dmochowski 2003) reported on condition-specific QoL using two validated instruments, the Incontinence Impact Questionnaire (IIQ) and the Urogenital Distress Inventory Questionnaire. There was improvement from baseline with both tolterodine ER and oxybutynin TDS in IIQ-travel and UDI irritative symptoms, with no difference between drugs. The changes approximate the threshold of minimal clinically important differences (Shumaker 1994, Shamliyan 2012)

5. Patient-Reported Perception of Improvement
Neither trial reported on this outcome.

6. Quantification of Incontinence Episodes
Diokno 2003 reported no statistically significant difference between drugs in mean number of weekly urgency incontinence episodes at study end: tolterodine ER 11.2 vs. oxybutynin ER 10.8

episodes/week (corresponding to 1.6 and 1.5 episodes per 24 hours, respectively). Similar findings were reported for total incontinence episodes (urgency plus stress UI episodes): tolterodine ER 13.8 vs. oxybutynin ER 12.3 per week (corresponding to 2.0 and 1.8 episodes per 24 hours, respectively). Measures of variation (standard deviation) are not reported so the data are not included in meta-analyses.

In the Diokno 2003 trial, more participants taking oxybutynin ER (23.0%) reported total dryness in week 12 compared with tolterodine ER (16.8%), based on a 7-day bladder diary: RR 0.73 (95% CI 0.55 to 0.97), P=0.03; absolute risk difference - 6% (95% CI -12% to -1%).

Dmochowski 2003 reported no statistically significant difference in the reduction in daily incontinence episodes when tolterodine ER was compared with oxybutynin TDS: MD 0.30 (05% CI -1.03 to 0.43), P=0.42. Both drugs reduced incontinence by approximately three episodes from a mean baseline of approximately five episodes per day. Placebo reduced incontinence by two episodes per day.

7. Nocturia
Neither trial reported on this outcome.

8. Urgency Episodes
Neither trial reported on this outcome.

9. Total AE
The total numbers of participants experiencing one or more AE are not reported in either trial.

10. Specific AE
Dry mouth:
In Diokno 2003, dry mouth was less common with tolterodine ER (22.3%) than oxybutynin ER (29.7%): RR 0.75 (95% CI 0.59, 0.95), P=0.02; absolute risk difference -7% (95% CI -13% to -1%). Using numbers reported in a post hoc analysis that excluded participants who experienced dry mouth only at baseline, the results did not change substantively: RR 0.77 (95% CI 0.59 to 0.95), P=0.02 (Armstrong 2005).

In Dmochowski 2003, dry mouth was more common with tolterodine ER (7.3%) than oxybutynin TDS (4.1%), but the difference was not statistically significant: RR 1.77 (95% CI 0.61 to 5.13), P=0.29.

CNS AE:
A post hoc analysis of Diokno 2003 lists CNS adverse effects, which were similar for each drug (Table 6 in Appendix D) (Chu 2005). No cognitive AE were reported, and there was no active surveillance for CNS effects in the trial. The trial was under-powered to detect differences in infrequent events.

Dmochowski 2003 did not report on CNS effects other than one withdrawal due to dizziness in the tolterodine ER group.

Application site reactions (Oxybutynin TDS):
Dmochowski 2003 reported that fewer people experienced application site reactions with

tolterodine ER (and the placebo transdermal patch) than with oxybutynin TDS: RR 0.26 (95% CI 0.12 to 0.54), P=0.0003; absolute risk difference -20% (95% CI -29% to -11%).

11. Volume voided per micturition: Dmochowski 2003 reported on this outcome. Both drugs increased the mean volume voided by 29-32 mls, with no statistically significant difference between drugs. Diokno 2003 did not report on this outcome.

12. Urodynamics/clinician measures
Neither trial measured maximum cystometric capacity, volume at first contraction and residual volume.

Critical Appraisal: RCTs comparing extended release formulations of oxybutynin and tolterodine
See Table 6 in Appendix D for risk of bias assessment of the two trials. Both trials were judged to be at high risk for bias due to incomplete outcome reporting. Both trials had differential drop-out rates between groups, which can introduce bias. Harms reporting was selective and incomplete in both trials. Other study features assessed for internal validity or risk of bias were predominantly evaluated as unclear, which may reflect poor reporting or methodological limitations. It is unlikely that blinding was maintained in Dmowchowski 2003 due to the frequent application site reactions with oxybutynin TDS.

Applicability:
Dmochowski 2003 only enrolled patients who had a prior beneficial response to anticholinergic treatment. The results from this highly selected population have limited applicability to clinical practice.

Diokno 2003 enrolled patients regardless of prior treatment. A post hoc, exploratory subgroup analysis reported that both treatment-naïve and treatment-experienced subgroups were responsive (Anderson 2006). However, trial participants were not stratified on the basis of prior therapy at the time of randomization so the analysis is exploratory only and cannot be used to draw conclusions. Subjects were also not stratified on the basis of prior treatment success so no information is provided on refractory populations.

Diokno 2003 included only females, and few males were enrolled in Dmochowski 2003 (7% of those receiving active treatment). This limits the applicability to men. In addition, both trial populations were predominantly Caucasian, which may limit generalizability of the findings to diverse racial/ethnic groups.

Dmochowski 2003 was included in an amendment to the FDA Oxybutynin TDS NDA 21-351 review. It is described as an equivalence trial but had no pre-specified equivalence margin with which to objectively judge evidence of statistical equivalence (NDA 21-351). The sponsor claimed that oxybutynin TDS and tolterodine ER were comparably effective in reducing incontinence with 95% CI of -1.0 to 0.0 for median change from baseline. Although urinary frequency is not included as an outcome in this review, the FDA noted that oxybutynin TDS was not superior to placebo in reducing urinary frequency. An equivalence trial requires evidence that each treatment is superior to placebo for all efficacy endpoints.

b. Extended Release vs. Immediate Release Comparisons

Two trials compared an ER formulation with an IR formulation of the comparator (Appell 2001, Homma 2003). Study characteristics, outcomes and risk of bias assessments are presented in Tables 5 to 7 in Appendix D. These trials are less informative than comparisons of the same type of formulation. Different formulations have disparate pharmacokinetics that can contribute to differences in clinical response. For example, long-acting forms of oxybutynin and tolterodine mitigate the magnitude of fluctuations in drug plasma levels that occur with IR forms.

Conclusions cannot be drawn about the comparative effectiveness (harms and benefits) of the two drugs with comparisons of different formulations. The two RCTs are included in meta-analyses pooling all formulations (see below) but sensitivity analyses conducted without them.

3. Meta-analyses Pooling All Formulations of Oxybutynin and Tolterodine

We pooled all tolterodine-oxybutynin comparator trials to determine if findings were consistent across formulations. Sensitivity analyses were performed by eliminating the comparisons that compared an IR to an ER formulation. The meta-analyses pooling all formulations are summarized in Table 3, on the following page. The Forest plots are located in Appendix D. Results of the meta-analyses are consistent with the findings for tolterodine IR vs. oxybutynin IR.

In addition to the outcomes meta-analyzed for tolterodine IR vs. oxybutynin IR, two additional meta-analyses could be performed, as noted below.

Quality of life (QoL)
Two RCTs of different formulations, Homma 2002 (Tol ER vs. Oxy IR) and Dmochowski 2003 (Tol ER vs. Oxy TDS), measured QoL but provided partial reporting only. The incontinence impact domain of the King's Health Questionnaire (KHQ) (Homma 2003) and UDI irritative symptoms (Dmochowski 2003) were combined in a meta-analysis, and did not show a difference between treatment arms: MD -0.08 (95% CI -5.87 to 5.70), P=0.98.

Specific AE
Constipation
Five trials, including one that compared tolterodine IR vs. oxybutynin IR, were combined and did not show a statistically significant difference, although numerically more patients taking tolterodine experienced constipation: RR 1.21 (0.88 to 1.64), P=0.24 (Appell 2001, Diokno 2003, Dmochowski 2003, Homma 2003, Malone-Lee 2001). Homma 2003 and Appell 2001 compared an IR formulation to an ER formulation. When these studies were removed in a sensitivity analysis, there was still no statistically significant difference between treatments.

Table 3. Summary: RCTs Tolterodine vs. Oxybutynin - Pooling All Formulations

Outcome	No. of studies (No. of Participants)	Tol vs. Oxy RR or mean difference	Tol vs. Oxy Absolute Risk difference	Summary
All-cause mortality	9 trials (2735) 1 death in Oxy group and 1 additional death post treatment	too few events to compare	--	- No data on long-term mortality -Trials under-powered for short-term mortality (1 event during treatment in oxybutynin group)

	in Oxy group			
SAE (non-fatal)	5 trials (1547)	RR 1.03 [95% CI 0.55 to 1.95]	--	- No difference between Tol and Oxy - Trials under-powered for SAE
Cognitive AE	0 trials	--	--	- No data on cognition
Overall QoL	2 trials (480)	MD -0.08 [95% CI -5.87 to 5.70]	--	- No difference between Tol and Oxy
Condition-Specific QoL	0 trials	--	--	- No data on condition-specific QoL
WDAE	10 trials (3307)	RR 0.59 [95% CI 0.44 to 0.79]	RD -6% (95% CI -9% to -2%)	- 6% fewer WDAE with Tol IR
Patient-reported improvement	5 trials (1381)	RR 0.96 [95% CI 0.88 to 1.05]	--	- No difference between Tol and Oxy
Incontinence episodes Mean reduction from baseline or end of Tx	8 trials (1534)	MD 0.16 [95% CI -0.07 to 0.39]	--	- Difference in favor of Oxy IR (0.2 episodes/day) is not statistically significant.
Urgency	1 trial (106)	No improvement with either drug (data not provided)		Insufficient data available
Nocturia	0 trials	--	--	No data available
Total AE	7 trials (1613)	RR 0.78 [95% CI 0.69 to 0.89]	RD -17% [95% CI -24% to -10%]	- 17% fewer patients with one or more total AE with Tol IR
Dry mouth	10 trials (3251)	RR 0.64 [95% CI 0.54 to 0.75]	RD -19% [95% CI -30% to -8%]	- 19% fewer patients experienced dry mouth with Tol IR
Headache	6 trials (2479)	RR 1.15 [95% CI 0.86 to 1.53]	RD	- No difference between Tol and Oxy
Constipation	5 trials (2276)	RR 1.21 [95% CI 0.88 to 1.64]	--	- No difference between Tol and Oxy
Dyspepsia	5 trials (1706)	RR 0.64 [95% CI 0.47 to 0.89]	RD -4 % [95% CI -6% to -1%]	- No difference between Tol and Oxy

AE, adverse events; NR, not reported; Oxy, oxybutynin; MD, (weighted) mean difference; QoL, quality of life; RD, risk difference; RR, relative risk; Tol, tolterodine; WDAE, withdrawals due to AE;

3. Non Randomized Studies

The aim in including non-randomized studies is to gain information on serious, infrequent adverse events, longer-term harms, and adverse effects in populations not adequately represented in the RCTs.

Published Non-Randomized Studies

Our literature search identified a total of 12 non-randomized studies that met eligibility criteria: three controlled cohort analyses (Gomes 2011, Jumadilova 2006, Sink 2008), seven uncontrolled cohort analyses (Layton 2001; Kreder 2002; Abrams 2001; Appell 2001; Michel 2005; Elinoff 2006; Michel 2002), one uncontrolled before-after study (Monnot 2012), and one case series (Alzayer 2010). The characteristics of these studies and their populations are presented in Table 4. An additional ten case reports (13 cases total) are presented briefly on page 120.

Table 4. Non-randomized studies to evaluate tolterodine vs. oxybutynin

Study	Design	Data source	Duration	OXY	TOL	Assessed outcomes
Gomes	Controlled	Ontario –	90 days	N=40,563	N=40,563	Falls

2011	cohort; propensity score match	population; age > 65; admin data		Mean age: 77 ± 7	Mean age: 77 ± 7	Fractures Delirium Hospitalization Deaths
Jumadilova 2006	Controlled cohort; propensity score match	US PharMetrics insurance database	1 year	OXY IR N=5936 OXY ER N=7257 Mean age 54 ± 14-17	TOL ER§ N=5936 TOL ER§ N=7257 Mean age 54 ± 14-18	Fractures Depression UTI
Sink 2008	Controlled cohort	Long-term care Indiana Medicaid; on Chol Inhibitors + OXY or TOL	≤ 2 years	N=196	N=231	Cognition ADL – Function
				Median age 80-84; 18% ≥ 90		
Layton 2001	Uncontrolled cohort ; indirect comparison (Rx event monitoring)	UK NHS prescribing data + physician survey (54% response)	6 months	*None* 10 other new drug cohorts; n=135,492	TOL IR N=14,526 Mean age 63 ± 16	Total AE WDAE Hospitalizations Deaths AE frequency
Kreder 2002	Uncontrolled cohort	Extension phase post 12-week RCT (70% of RCT participants)	1 year	*None*	TOL ER N=1077 Mean age 60 (range 20-93)	SAE WDAE Withdrawals Total AE
Abrams 2001	Uncontrolled cohort	Extension phase post 4, 4-week RCTs (% enrolled not available)	1 year	*None*	TOL IR N=714 Mean age 60 (range 18-92)	SAE WDAE Withdrawals Total AE
Appell 2001	Uncontrolled cohort	Extension phase post 4, 12-week RCTs (76% enrolled)	9 months	*None*	TOL IR N=854 Mean age 60 (range 19-89)	SAE WDAE Withdrawals Total AE
Michel 2002	Uncontrolled cohort	462 urologists in Germany .	12 weeks	*None*	TOL IR N=2250 Mean age 61 ± 14	WDAE Withdrawals Lack of efficacy AE
Michel 2005	Uncontrolled cohort	492 urologist offices + 498 GP/ other MD in Germany	9 months	*None*	TOL ER N=3824 Mean age 65 ± 13	SAE WDAE Withdrawals Total AE
Elinoff 2006	Uncontrolled cohort	82 primary care and 16 U.S. OB/GYN offices	12 weeks	*None*	TOL ER N=892 Mean age 56 ± 15	SAE WDAE Withdrawals Total AE
Alzayer 2010	Case series; indirect comparison	US FDA spontaneous ADR reports	No set duration; Reports 1988-2009	N=1565 with reported AE	N=11,670 with reported AE	Percent of AEs: Neurovascular Cardiovascular
Monnot 2012	Before-after study	Oklahoma:VA Alzheimer's centre clinics	4 weeks on drug; 4 week washout	N=9	N=1	Cognition pre- and post drug withdrawal
				Range 67-85 (all subjects)		

ADL=activities of daily living; admin=administrative; AE=adverse events; OXY=oxybutynin; Rx=prescription; SAE=serious adverse events; TOL=tolterodine; UTI=urinary tract infection; WDAE=withdrawals due to AE; §Jumadilova 2006 includes two propensity score matched comparison groups; one comparing OXY IR to TOL ER; the other OXY ER to TOL ER.

Three controlled cohort studies compared users of oxybutynin with tolterodine (Gomes 2011, Sink 2008, Jumadilova 2006). Gomes 2011 used Ontario Health Insurance Plan data to follow new users over the age of 65 for a 90-day period. With a mean age of 77, this study provides additional data on older patients; the main outcomes of interest were falls, fractures and delirium. Jumadilova 2006, a study conducted by the manufacturer of tolterodine, used a U.S. insurance database, PharMetrics, to examine fractures, urinary tract infections, and depression among users of tolterodine ER and oxybutynin IR or ER. This study is in younger patients (mean age 54). Both studies have used propensity scores to adjust for confounding by factors such as age and co-morbidities. However, neither study reports on the proportion of patients who withdrew early from treatment, or whether this differs by treatment arm.

Table 5 presents the findings of Gomes 2011 and Jumadilova 2006. Gomes 2011 found a statistically significant difference in all cause mortality and hospitalization favouring tolterodine: all cause mortality hazard ratio (HR) oxybutynin vs. tolterodine 1.20 (95% CI 1.07 to 1.35) and hospitalization HR 1.12 (95% CI 1.07 to 1.17). The authors consider these findings exploratory as they could not rule out the possibility that residual differences in health status, despite propensity score matching, may have been the cause rather than drug effects. We requested information on causes of death and hospitalization but none was available. [T. Gomes, personal communication, April 2013]

Jumadilova 2006 report an increase in depression diagnoses with oxybutynin IR vs. tolterodine ER but not oxybutynin ER vs. tolterodine ER. There was an increase in urinary tract infection with both oxybutynin IR and ER vs. tolterodine ER.

Both studies reported no difference in fracture rates (Gomes 2011, Jumadilova 2006). Gomes 2011 did not find a difference in the rate of serious falls leading to emergency room visit or hospitalization, delirium or pneumonia between tolterodine and oxybutynin users. Pneumonia was included as a control for comparability of patient populations and anticipated to be similar between groups.

Table 5. Population-based matched controlled cohort analyses

Outcome	Study	Unadjusted Rate: OXY	Unadjusted Rate: TOL	OXY vs. TOL Absolute Risk difference (95% CI)*	OXY vs. TOL Hazard Ratio (95% CI)
All cause mortality*	Gomes 2011	675 /40,563 (1.7%)	567/40,563 (1.4%)	0.3% (0.1% to 0.4%)	1.20 (1.07 to 1.35)
All cause hospitalization*	Gomes 2011	3841/40,563 (9.5%)	3608 /40,563 (8.9%)	0.6% (0.2% to 1.0%)	1.12 (1.07 to 1.17)
Serious Falls	Gomes 2011	1027 /40,563 (2.5%)	998 /40,563 (2.5%)	--	1.04 (0.95 to 1.14)
Fractures	Gomes 2011	326/40,563 (0.8%)	332/40,563 (0.8%)	--	0.96 (0.82–1.13)

	Jumadilova 2006§	IR: 291/5936 (4.9%) ER: 341/7257 (4.7%)	ER: 255/5936 (4.3%) ER: 298/7257 (4.1%)	-- --	1.15 (0.97 to 1.36) 1.13 (0.97 to 1.32)
Delirium	Gomes 2011	80/40,563 (0. 2%)	86 /40,563 (0. 2%)	--	0.90 (0.66 to 1.23)
Depression	Jumadilova 2006§	IR: 843/5936 (14.2%) ER: 885/7257 (12.2%)	ER: 754/5936 (12.7%) ER: 856/7257 (11.8%)	1.5% (0% to 3%) --	1.16 (1.05 to 1.28) 1.03 (0.94 to 1.13)
Pneumonia	Gomes 2011	424/40,563 (1.0%)	381/40,563 (0.9%)	--	1.11 (0.96-1.28)
Urinary Tract Infection	Jumadilova 2006§	IR: 1300/5936 (21.9%) ER: 1466/7257 (20.2%)	ER: 1140/5936 (19.2%) ER: 1299/7257 (17.9%)	2.7% (1.2% to 4.2%) 2.3% (1.0% to 3.6%)	1.18 (1.09 to 1.28) 1.13 (1.05 to 1.22)

ER=extended release; IR=immediate release; OXY=oxybutynin; TOL=tolterodine
*Unadjusted absolute risk differences for outcomes that differed significantly.
§ Jumadilova 2006 includes two propensity score matched comparison groups; one comparing OXY IR to TOL ER; the other OXY ER to TOL ER.

Cognitively impaired elderly population– controlled cohort analysis
Sink 2008 examined the rate of functional and cognitive decline in nursing home residents aged ≥ 65 who were co-prescribed a cholinesterase inhibitor and oxybutynin (N=231) or tolterodine (N=196) compared with 3141 residents on cholinesterase inhibitors alone. Dual therapy is pharmacologically irrational because cholinesterase inhibitors aim to increase acetylcholine levels in the brain whereas antimuscarinic drugs block the action of acetylcholine.

In analyses adjusted for demographics and comorbidities, only the least cognitively impaired and highest-functioning patients on dual anti-muscarinic and cholinesterase inhibitor therapy showed greater decline in activities of daily living (ADL) than those on a cholinesterase inhibitor alone (N=3141); rates did not differ for those with moderate, severe, or near complete dependence. The least cognitively impaired group declined a mean of 0.53 ADL points per quarter more than those on cholinesterase inhibitors alone, on a 28-point ADL scale, which was statistically significant. The clinical significance of this magnitude of change remains open to question, however.

The authors present results separately for patients taking oxybutynin and tolterodine. There were no significant differences in cognition or ADL for either drug, compared with users of a cholinesterase inhibitor alone. Oxybutynin and tolterodine were not directly compared, and inadequate data were provided to carry out such a comparison, but based on reported means, the two cohorts are unlikely to differ significantly. Whether this is due to inadequate power to detect a difference or lack of difference remains an open question. The authors report that cognitive decline did not differ between users of IR and ER formulations (data not shown).

Uncontrolled cohort analyses
In a U.K. study, Layton 2001 indirectly compares rates of serious adverse events among new users of tolterodine with an historical cohort of new users of ten unrelated drugs. The aim of the prescription event monitoring pharmacosurveillance approach used in the U.K. is to monitor the safety of new drugs in the early post market period. Physicians who have prescribed a new drug are

identified from a prescription database and sent forms requesting patient follow-up information about AEs over a six-month period (N=14,526 patient forms received; 54% response rate).

There was an unexpected increased signal for hallucinations (predominantly visual) with tolterodine. Women and individuals ≥75 years of age were more likely to experience an event. The observed rate was 4.46/1000 patient years and the age- and sex-adjusted relative risk, as compared to ten drugs in other therapeutic classes, was 4.85 (95% CI 2.72 to 8.66) . Although this is an indirect comparison to a combined cohort of users of unrelated new drugs, the much higher than expected hallucination rate on tolterodine is a strong signal. It was not possible to compare tolterodine with another, currently available, antimuscarinic drug as the only other antimuscarinic drug in the prescription database had been withdrawn from the market due to safety concerns. Hallucinations are now a listed post market adverse event in both the tolterodine IR and ER product monographs.

Palpitations/tachycardia were also identified as potentially associated with tolterodine use, but the rate did not differ from the combined data for the ten unrelated drugs.

As described in Table 4, there are six additional uncontrolled cohort analyses, three of which used tolterodine IR (Michel 2002; Abrams 2001; Appell 2001) and three used tolterodine ER (Michel 2005; Elinoff 2006; Keller 2002). Three studies were conducted as convenience samples in usual care settings (Michel 2002; Michel 2005; Elinoff 2006) involving large numbers of physicians reporting on a few patients per practice. Of these, two were of three months duration (Michel 2002; Elinoff 2006) and one was nine months long (Michel 2005). Michel 2002 and 2005 were based in Germany; Elinoff 2006 in the U.S. There were also three RCT extension studies (Keller 2002; Abrams 2001; Appell 2001) of 9 to 12 months. Extension phases are limited to patients who met RCT inclusion criteria and completed the trials. Participants unable to tolerate medications or who withdrew due to lack of efficacy are therefore excluded. AE rates varied considerably in these cohorts, likely reflecting whether data collection was active or passive as well as patient experiences and characteristics.

Table 6 summarizes the rates of observed AE according to our hierarchy of outcomes for the two sets of uncontrolled cohort studies and the UK active surveillance study described above.

Table 6. Adverse events reported in uncontrolled cohorts using tolterodine

Adverse events and Total Withdrawals	Convenience Sample, Usual Care AE (%)			Extension studies (post-RCT) AE (%)			Active surveillance AE (%)
	Michel 2002 (N=2250) 3 months	Michel 2005 (N=3824) 9 months	Elinoff 2006 (N=892) 3 months	Abrams 2001 (N=714) 12 months	Appell 2001 (N=854) 9 months	Kreder 2002 (N=1077) 12 months	Layton 2001 (N=14,526) 6 months
All cause mortality	NR	NR	NR	8 (1%)	4 (0.4%)	NR	379 (0.3%)

SAE	NR	NR	18 (2%)	58 (8%)	72 (8%)	79 (7%)	NR
Total Withdrawals	271 (12%)	408 (11%)	134 (15%)	273 (38%)	260 (30%)	316 (29%)	NR
WDAE	61 (2.7%)	NR	59 (7%)	105 (15%)	73 (9%)	107 (10%)	NR
Total AE§	93 (4.1%)	496 (13%)	455 (51%)	340 (48%)	652 (76%)	NR	NR

AE= adverse events; SAE= serious adverse events; WDAE= withdrawals due to adverse events; NR= not reported; §The total number of participants who experienced one or more AE.

Analysis of spontaneous AE reports

Alzayer 2010 report a case series of neurovascular and cardiovascular effects of oxybutynin and tolterodine in an FDA safety dataset of all spontaneously reported adverse events (oxybutynin N=1565; tolterodine N=11,670). Among the oxybutynin reports, 8.4% were cardiovascular AE and 2.8% reports of stroke. Among the tolterodine reports, 4.9% were cardiovascular AE and 1.0% reports of stroke. Any comparison of proportions is likely to be spurious, however, given the much larger number of tolterodine than oxybutynin reports. This likely reflects an increase in spontaneous adverse drug reaction reporting rate in the U.S. over time. Lower proportions of specific AE can reflect a higher reporting rate for other types of AE. For both drugs, arrhythmias were the most commonly reported cardiovascular AE.

Before-after study

Monnot 2012 conducted a before-and-after study with neuropsychological testing in 10 adults between age 60 and 85 taking either oxybutynin or tolterodine (1 patient only) before stopping and after a 4 week drug washout period. This study could not compare outcomes between oxybutynin and tolterodine. No difference was reported in overall cognitive scores. However, specific cognition and behavioural index subtest scores improved after oxybutynin or tolterodine were withdrawn. Although exploratory and based on a small set of patients, this study suggests that both drugs can affect cognition, with effects reversible on discontinuation.

Study quality /risk of bias

The strength of study design features used to protect the non-randomized study findings from bias was variable. Amongst the controlled cohort studies, Gomes 2011 and Jumadilova 2006 used population-based datasets that are not as prone to researcher driven selection bias and are more representative of routine practice settings. However, selective reporting of outcomes is a major potential problem. Neither study has a published protocol and Jumadilova 2006 was carried out by Pfizer, the manufacturer of tolterodine. Without a published protocol, it is not possible to know whether reported outcomes consist of a subset of analyses carried out or whether all analyses were reported. In the former case, substantial bias is possible, for example, if only outcomes favourable or neutral towards tolterodine were reported. Jumadilova 2006 reports on a diverse subset of AE associated with anti-muscarinic therapy, adding to the possibility of selective reporting.

Neither Gomes 2011 or Jumadilova 2006 report on the proportion of patients who discontinued therapy during the observation period or use censoring of patients to account for discontinuation in the analysis. As discussed in the introduction, persistence is generally low in observational studies of antimuscarinic therapy (Sexton 2011). Differences in persistence may also have affected observed outcomes.

Studies that use data collected for pharmacosurveillance purposes include Layton 2001 and Alzayer 2010. These have the advantage of being independent of manufacturers. Alzayer 2010 relied on spontaneous adverse reaction reports in the U.S. Reporting rates are known to be low and denominators unknown. Layton 2001 reports on active U.K. surveillance in which physicians identified as having prescribed tolterodine when it was first marketed were mailed reporting forms. Patients' medical records were used to report on all observed events. This has the advantage of complete adverse event reporting regardless of assumed causality; disadvantages are the uncontrolled nature of the cohort and the 54% response rate.

The uncontrolled clinical cohorts Michel 2002, Michel 2005 and Elinoff 2006 collected data from physicians in their routine practice settings. These studies had large numbers of physicians participating, each of whom reported on few patients. AE reporting is likely incomplete. The RCT extension studies were also uncontrolled, and the patient population is highly selected, as patients met RCT inclusion criteria (elderly patients with many comorbidities excluded) and any RCT participant who had withdrawn early due to adverse events, lack of efficacy or for other reasons was excluded.

Case reports

Case reports may provide signals of previously unrecognized or rare adverse events. However, the decision to publish a case report is multifactorial and numbers cannot be used to draw inferences about incidence rates. Ten case reports (1-3 cases each) involving tolterodine use were identified in the literature (Salvatore 2007, Tsao 2003, Womack 2003, Juss 2005, Madewell 2008, Bryan 2010, Schlienger 2002, Taylor 2006, Colucci 1999, Edwards 2002) (Table 7). Six cases involved central nervous system effects including delirium, confusion, short term memory loss and hallucination (Edwards 2002, Salvarore 2007, Tsao 2003, Womack 2003). There were three cases of hyponatremia, three cases of a drug-drug interaction of tolterodine with warfarin, and one case of reversible, mixed liver injury associated with other features that are consistent with a hypersensitivity reaction. All cases improved or resolved with discontinuation of the medication.

Table 7. Case Reports of Tolterodine AE

Study	Exposure (drug and dose)	Patient	Adverse event	Outcome/Comment
Edwards 2002 U.S. **Case 1**	TOL dose NR x 1 wk + donepezil 5mg x 2mo	82 year old male with Alzheimer's dementia	Delirium	Resolution in all three cases after stopping TOL TOL hypothesized to precipitate a state of cholinergic neurogenic hypersensitivity similar to that often seen with withdrawal of acetylcholinesterase inhibitors
Case 2	TOL dose NR x 1 week +rivastigmine 6mg bid	65 year old female with Alzheimer's dementia	Anxiety, confusion, delusions	
Case 3	TOL dose 2mg bid x 2 wks + donepezil 10mg x 2yrs	82 year old male with Parkinson's disease and dementia	Disorientation, confusion, combativeness	
Salvatore 2007 Italy	TOL 2mg bid	65 year old healthy female; neurologist referral for confusion	De novo confusion 8 days after TOL initiated	Resolution with dose reduction to 1mg bid
Tsao 2003 U.S.	TOL 2mg bid Donepezil	73 year old female with no prior history of cognitive impairment	Short term memory loss and hallucination	Improvement with discontinuation of TOL Association with TOL

			Prescribing cascade; donepezil prescribed for AE	confirmed with TOL dechallenge and rechallenge
Womack 2003 U.S.	TOL 4mg/d x 3 mo Polypharmacy	46 year old female with a 2 year history of memory problems	Increase in memory loss	Memory improved substantially on stopping TOL
Juss 2005 U.K.	TOL 2mg tid Polypharmacy	78 year old female with extensive medical history including recent admission for diarrhea-induced hypovolemia	Confusion and hyponatremia	Plasma sodium levels correlated with TOL challenges Inprovement with TOL discontinuation
Madewell 2008 U.S.	TOL 2mg bid x 4 wks Polypharmacy incl. hydrochlorothiazide	86 year old female with dementia and a four minute episode of unresponsiveness	Acute change in mental status and hyponatremia	Resolution within 24 hrs of stopping TOL
Bryan 2010 U.S.	TOL 2mg ER Polypharmacy	99 year old female with gastrointestinal bleed secondary to duodenal ulcer	Hyponatremia	Resolution to usual baseline values after stopping TOL
Schlienger 2002 Switzerland	TOL 2m bid x 18 days Polypharmacy	81 year old female	Acute mixed liver injury (raised liver enzymes) associated with malaise, fever and eosinophilia	Resolution within 4 wks of TOL discontinuation Features consistent with hypersensitivity syndrome
Taylor 2006 U.S.	TOL ER 4mg OD Warfarin goal INR 2-3 Polypharmacy	53 year old female with extensive medical history	Warfarin-TOL interaction	INR increased despite warfarin dose reduction with TOL start
Colucci 1999 U.S. **Case 1**	TOL 2 mg/d Warfarin 5mg/day x1 yr (INR 2-3) Polypharmacy	72 year old male with extensive medical history		Stable INR before TOL initiated, after discontinuation; other causes excluded
Case 2	TOL 2mg every night; (INR goal 1.5-2)	83 year old male with chronic atrial fibrillation		

INR, international normalized ratio; TOL=tolterodine

4. Other Adverse Event Data

Regulatory Data

Data on adverse events was sought from government and regulatory resources including periodic safety update reports (PSURs), the Canada Vigilance Adverse Reaction Online Database, and the US Food and Drug Agency new drug approval reviews (Center for Drug Evaluation and Research NDA 20-771).

Periodic Safety Update Reports (PSUR)

Tolterodine periodic safety update reports (PSURs) obtained for this review include an overview or bridging report and three consecutive reports spanning a total of seven years between 6 March 2004 to 7 April 2011:

- Period 1: PSUR#11 (6 Mar 2004 to 30 Sept 2007)
- Period 2: PSUR#12 (1 Oct 2007 to 4 Sept 2010)
- Period 3: PSUR Addendum (Sept 2010 to 27 Apr 2011)

Also included in PSUR#11 is a European clinical review of PSUR reports from Sept 2001to Mar 2005 plus a bridging report Sept 1999 to Oct 2005.

Cumulative experience since initial market date is not provided in a comprehensive manner in the available PSURs.

Estimated global exposure for tolterodine from 2004 to 2011 was 9,833,497 patient years, with 83% of exposure due to tolterodine ER. Global marketing data from 2008 to 2011, provided in the Summary Bridging Report, highlights the frequency with which elderly patients are prescribed tolterodine: 58% of all women and 72% of all men prescribed tolterodine were over the age of 65. Over a third of women and men prescribed tolterodine were 75 years or older (36% of women and 42% of men). This underscores the need to include the 'oldest old' in clinical studies and active pharmacosurveillance. Approximately 3% of prescriptions were for prostate hyperplasia and 2% for cystitis, unapproved indications for which tolterodine has not been shown to be effective. Another estimated 5% of prescriptions were for polyuria, which should be ruled out prior to prescribing for OAB syndrome.

The purpose of the database maintained by the market authorization holder (MAH) is to identify new signals for AE. AE are classified on the basis of whether they are listed (i.e., already identified in the reference safety information) or unlisted, and whether they are serious or non-serious.

A total of 4,134 medically confirmed cases of one or more AE are reported for the seven-year period 2004 to 2011. This includes 1) SAE (both listed and unlisted) and 2) non-serious events that were not listed in the reference safety information at the time of reporting. There are several sources of cases, including spontaneous reports from health professionals of SAE (both listed and unlisted) and unlisted non-serious events. Also included are SAE from clinical studies or marketing programs that have been *judged related* to tolterodine. These are a subset of the total number of reports of SAE. From this number and the number of non-serious unlisted events, we calculated there were 2,789 cases involving at least one SAE (PSUR Summary Bridging Report).

An additional 10,913 cases in total, reported by consumers and non-health professionals are classified as non-medically confirmed and maintained in a separate dataset. Cases include both serious and non-serious adverse events regardless of listing status. The MAH states that no new signals were generated in the latter dataset.

Deaths

In total, 106 deaths are reported in the PSUR case reports (line-listings) plus one intrauterine death for the seven year period, the majority of which are classifed as non-medically confirmed because

they are reported by non-health professionals and consumers. All 42 deaths reported in the Canada Online Vigilance Database for that time period are included.[2]

Although 42/106 deaths reported in the PSURs are from Canada, Canada contributed only 2% to 3% of total cases of medically-confirmed AE (as defined above by the MAH) in the two longest time periods covered by the PSURs. It is possible that the disproportionate reporting of deaths from Canada is due to incomplete reporting of deaths from larger jurisdictions. We have not been able to search other jurisdictional databases to determine whether this is the explanation.

The available PSURs provide further details on the 33 'medically confirmed' deaths. These are deaths reported by health professionals, published in the medical literature, occurring in a study or otherwise confirmed by the manufacturer. Combining the available information from the three PSUR time periods, 70% of cases with known age (or reported as elderly) were individuals > age 65 (total age range 17 to 97 years). Eighteen (56%) were women and fourteen (44%) were men; the sex of one individual was not reported. Specific causes of death were listed in less than half the cases. Four (12%) of the 33 deaths were intentional suicides/overdoses (age 22, age 51, age 73 and age 89), and a fifth case was termed an accidental overdose (age 17). Six deaths were listed as secondary to cancer (metastatic renal carcinoma (1); metastatic ovarian carcinoma (1); metastatic gall bladder cancer (2); non-small cell lung carcinoma (1); bladder cancer (1)). Other causes of death were: mesenteric thrombosis/sepsis (1); aspiration of food (1); cardiopulmonary arrest (1); ruptured brain aneurysms (2) and Stevens-Johnson Syndrome (1).

Stevens-Johnson syndrome is a severe immune complex-mediated cutaneous drug reaction that can also be associated with mycoplasma. Although the MAH states there were several suspect drugs and positive mycoplasma serology, the role of tolterodine cannot be ruled out.

Some medical history is provided on cases with unspecified cause of death. One patient was on concurrent warfarin for an unspecified reason and had hypertension. Others had: neuropathy (1); cardiopulmonary problems (1); a history of multiple myeloma (1); adhesive ileus with long-term persistent diarrhea along with dementia, stroke and other conditions (1); hypothyroidism (1); a fall preceding death by an unspecified time period (1).

Serious Adverse Events (SAE)

Total SAEs are not provided in a cumulative manner extending to the latest date of the available PSURs (April 27 2011). The only identified cumulative summary is a summary of medically confirmed cases covering a 13-year period from Sept 5, 1997 to Sept 4 2010 (Appendix 6 in PSUR#12). This represents a subset of the reported events as noted in the above sections.

In the 1,421 'serious cases' that are reported in the summary, there were 2,014 SAE. Of the total number of SAE, 23% (466) of the events correspond to events 'listed' in reference safety data as recognized adverse events associated with tolterodine. The other 1,487 (74%) were unlisted or not recognized to be associated with tolterodine.

In this table, the method of summarizing by body system subdivides some adverse events of interest between two categories. For example, the nervous system was coded as having the most

[2] A discrepancy in a case number for one case with matching details is assumed to be a clerical error.

'adverse events in serious cases' at 272 events. However this category does not include psychiatric disorders (156), a category that includes hallucinations and confusional states that are central nervous system adverse events of interest. Renal and urinary disorder categories (259), gastrointestinal (155) and cardiac disorders (133) were categories of interest without comprehensive reporting and analyses.

Cumulative reviews: the PSUR documents contain two cumulative reviews, one on QT prolongation and related events (Period 1) and another one on falls, fractures, and surgery cases secondary to fall (Period 2). This information covers medically confirmed cases only.

QT prolongation: The review of terms potentially related to QT prolongation (including ventricular tachycardia and cardiac arrest) covers the time period from 1997 to the end of Period 1 (2007). There are 18 cases, including three fatalities. One of the deaths was in a patient with serious concomitant illnesses and renal impairment. Torsade de pointes, ventricular tachycardia, cardiac arrest, or syncope were documented in 12 of the other 15 cases. The MAH concluded causality could not be determined in the majority of cases due to concomitant medications. There were an additional seven cases reported in Periods 2 and 3 up to April 2011.

Falls and Fractures: from 1997 to 2010 (end of Period 2), 134 cases were identified by terms related to falls and fractures. Seventy reported falls and three reported a fall preceding a fracture or head injury. The majority of cases (80%) were in the elderly. The MAH claims there were concomitant risks for fall in the majority of cases including dizziness (a listed event) in 34% of the cases in the elderly.

Other topic-specific reviews

Cognition: There is no cumulative review of cognition-related terms that covers the entire time period since tolterodine has been on the market. Topic-specific reviews included cognition-related events in Period 1. Of 37 cases, 21 were poorly documented and lacked, for example, information on drug dechallenge/rechallenge. In 12 of the remaining 16 cases (75%), an association between tolterodine use and cognitive impairment could not be ruled out. In six cases, there was a temporal association between onset and tolterodine use, and a positive dechallenge. An additional 30 cases were identified in Period 2; however the MAH did not include in this number, cases that included the term 'memory impairment'. The reason given for this is that the event had been listed in the reference safety information in 2007. In Period 3 (a 7 month period in 2010-2011), there were 7 cases with cognitive-related terms: 3 cognitive disorder, 3 amnesia and 1 disturbance in attention.

Approximately 2% of reported cases over the entire time period of the PSUR documents are for confusion.

Other topics reviewed in Period 1 included: cardiac disorders 115 cases (5.8%); hypoesthesia, paresthesia oral (sensory) 25 cases (1.3%); insomnia 52 cases (2.6%) (unlisted); feeling abnormal 41 cases (2.1%) (unlisted); immune disorder 26 cases (1.3%) (unlisted).

Other listed events: urinary retention over the 3 periods comprised 6.0% of cases; dizziness was reported in 3.3% of cases.

Elderly: based on an analysis in Period 2, five adverse events were reported in people aged 65 or older at over a 3-fold greater rate compared to the non-elderly: thirst; confusional states; nocturia; drug interactions; falls.

Unlisted events
Unlisted events are not contained in information to physicians and patients and therefore may be overlooked. In Period 1, 2.1% of cases were reports on 'feeling abnormal'. 51% of such cases had a positive de-challenge, resolving when tolterodine was discontinued. Nausea was reported in 2.6% of cases, and insomnia also in 2.6%. In Periods 1 and 2, rash comprised 2.1% of cases.

For the entire time covered by the PSUR documents, 'drug ineffective' was one of the most common unlisted events.

Changes to Reference Safety Information

In the post-market period, a number of changes have been made to tolterodine's reference safety information. The following changes were made during the time period of the PSUR documents.

Changes pertain to:

Driving and heavy machinery precaution

Specific populations

- Patients vulnerable to the effect of tolterodine on the QT interval
- Patients with myasthenia gravis

Specific adverse events

- QT prolongation
- disorientation and hallucinations
- memory impairment
- aggravated symptoms of dementia
- diarrhea

Prior changes to references safety information (based on included review of PSURs from 2001 to 2005):

- Contraindications: known hypersensitivity
- Interactions: ketoconazole and other CYP 3A4 inhibitors
- Pregnancy and lactation: recommendation not to use during pregnancy, on the basis of findings from a study in mice
- Special warnings and precautions: patients at risk of urinary retention and of decreased gastrointestinal motility; dose reduction when impaired renal function
- Safety information: dizziness/vertigo, bronchitis, increased weight, sinusitis, gastroesophageal reflux, flushed skin, anaphylactoid reactions, tachycardia, peripheral edema, hallucination.

Canada Vigilance Adverse Reaction Online Database

A total of 264 adverse reaction reports related to tolterodine use are in the Vigilance Adverse Reaction Online Database, to its most recent data entry point, Dec 31, 2012. Of these, 179 reports

are identified as serious adverse events, including 69 deaths.[3] Many reports lack detail. As with other voluntary reporting systems, it is not possible to confirm causality in most cases. There is no denominator data and known under-reporting so these data are not suitable for estimating incidence rates. The database overlaps with the available PSUR documents.

Of the 69 deaths in the database, covering approximately a 14-year period of market availability, 27 were spontaneously reported, 3 by physicians and 24 by consumers, and 42 occurred in clinical studies. The Canadian database reports an additional 26 deaths outside the seven-year time period covered by the PSUR (two deaths from 1998 to 2004, and 24 deaths from May 2011 to Dec. 31 2012). The increasing number of deaths reported over time in the Canadian database could reflect increased awareness of potential adverse effects, increased reporting, increased use of the drug, a greater number of studies or other factors.

Cause of death is not provided in the database. Only seven reports provide additional details: 1 sepsis/thrombocytopenia; 1 colonic obstruction/sepsis; 1 hydrocephalus/brain stem syndrome/intraventricular hemorrhage/myocardial infarction; 1 prostate cancer; 1 autoimmume disorder; 2 completed suicide/overdose using tolterodine, as reported in the PSUR documents.

There were 110 non-fatal SAE (Appendix E). Many cases involved more than one adverse event. Nine cases involved hypersensitivity reactions, including at least one life-threatening event; 11 cases reported urinary retention; 2 cases reported QT prolongation or arrhythmia.

Cognition: There were 27 adverse events related to central nervous system disorders. These included four reports of amnesia or memory impairment, two reports of confusion, and five reports of hallucination.

5. Discussion and Conclusions Tolterodine vs. Oxybutynin

Q1: Does tolterodine provide a therapeutic advantage over oxybutynin?

The available short-term RCTs do not provide evidence of an efficacy advantage for tolterodine. Qualitatively, the adverse event profiles for tolterodine IR and oxybutynin IR were similar. Treatment with Tolterodine IR resulted in fewer WDAE (absolute risk difference 7%), fewer total AE (absolute risk difference 17%) and less risk of dry mouth than oxybutynin IR (absolute risk difference 32%). It is unclear whether this represents a therapeutic advantage for tolterodine as the higher incidence of dry mouth observed with oxybutynin may be attributable to a relatively greater anticholinergic dose (Center for Drug Evaluation and Research NDA 20-771). It is questionable whether the dose of oxybutynin most commonly used in the trials (5 mg t.i.d.) is comparable to the dose used for tolterodine (2 mg b.i.d.) Although not regarded as a SAE, dry mouth can lead to a range of oral health problems in older people, including mucosal candidiasis, bacterial infections, dental caries, gum recession, denture sores and difficulty with retention of prostheses, and eating and speech difficulties (Turner 2007).

[3] Excluding three duplicate reports of non-fatal SAE and one duplicate report of a death.

Our findings from RCTs comparing tolterodine IR with oxybutynin IR are consistent with prior systematic reviews (Shamliyan 2012, Madhuvrata 2012). Compared with the Cochrane review (Madhuvrata 2012), we included one additional study (Study A015, as reported in the FDA review), ensured intention-to-treat analyses were included in the meta-analyses for study A010/Drutz 1999, corrected the number of evaluable patients for incontinence analyses, corrected the findings for one study, and included additional data for several meta-analyses. The AHRQ systematic review (Shamliyan 2012) is restricted to women only. A third comparative systematic review (McDonagh 2009) only covers studies published to 2008.

Only two trials compared ER formulations of oxybutynin and tolterodine, one of which used doses that were most likely non-equivalent (Diokno 2003). Trial outcomes support this interpretation as tolterodine was associated both with less resolution of incontinence and less dry mouth. The other trial compared an extended release with a transdermal preparation. Greater tolerability for tolterodine, as reflected in fewer withdrawals due to adverse events, was mainly linked to application site reactions with oxybutynin TDS. The RCT evidence comparing ER formulations is too limited for any conclusions to be drawn.

Several additional gaps in evidence are noted. There are no available RCT data on longer-term outcomes such as mortality or other potential adverse events associated with chronic use. The duration of treatment in all available RCTs ($\leq$ 12 weeks) was too short to draw any conclusion about long-term consequences, and the trials were not statistically powered to detect potential differences in short-term harms. Most included trials were sponsored by manufacturers. Independently conducted trials are also needed to answer questions about which dose and formulation provides the greatest net benefit, particularly in the frail elderly and patients with co-morbidities.

The observational research evidence provides limited additional evidence on infrequent harms. Two population-based observational studies failed to find a difference in the rate of falls or fractures between oxybutynin and tolterodine (Gomes 2011; Jumadilova 2006). A higher than expected hallucination rate was found in an indirect comparison of an uncontrolled cohort of new users of tolterodine (Layton 2001). The existing observational evidence cannot answer the question as to whether rare, serious harms are more frequently associated with oxybutynin or tolterodine. There are reports for both drugs of serious cardiovascular and cognitive adverse events.

There is no evidence of an efficacy advantage for either drug. However, patients taking placebo in OAB trials show a marked improvement. This has been shown for commonly measured outcomes: number of incontinence episodes per day, micturition frequency per day, and mean volume voided. The response is likely multifactorial and in part attributable to a bladder training effect (facilitated by filling out a “bladder diary” in studies). The magnitude of placebo effect as a percentage of total benefit for this drug class, as well as the frequency of troublesome adverse events, suggests that non-drug approaches should be tried as first line treatment.

Q2. New Evidence since CDR Review

The approval of tolterodine IR and ER pre-dates the CDR review process. No CDR reviews have been conducted on tolterodine and no available CDR reviews address comparative data on tolterodine and any formulation of oxybutynin. Q2 is therefore not applicable to this comparison.

Q3. Cognition

We did not identify any published RCTs comparing oxybutynin with tolterodine that assessed cognition. It is not appropriate to rely solely on voluntary reporting for cognitive changes as patients may be unaware of such changes or may not attribute them to drug treatment, and none of the identified short-term trials specifically measured cognitive effects. The available trials were under-powered for CNS effects and information on these effects was not systematically collected.

One unpublished, short-term RCT (clinicaltrials.gov NCT00411437) was identified. This trial was completed approximately seven years ago yet appears to be unpublished. There is a brief summary of the trial in the PSUR documentation (Protocol number A6121154). The study (N=255) was designed as a non-inferiority trial vs. placebo and also compared tolterodine ER with oxybutynin ER. Participants were men and women aged 65 to 75 years. Cognitive tests included delayed and immediate recall. Dosages of the active drugs are not provided and without further information on the methods and a full study report, the trial cannot be critically appraised. Results are therefore not presented. A request for the final study report has been made.

In addition to a lack of short-term trials, there are no long-term trials that assess cognition.

No non-randomized studies are available that provide direct comparative data on the cognitive effects of oxybutynin and tolterodine.

There is one controlled cohort analysis in nursing home residents 65 years of age or older. The study compared residents who were co-prescribed a cholinesterase inhibitor and either oxybutynin or tolterodine (N=366) with residents on cholinesterase inhibitors alone (N=3141). There was a greater adjusted rate of decline in activities of daily living for the most highly functioning residents, i.e. in the top quartile of activity of daily living (ADL) ability at baseline, with dual therapy compared to cholinesterase inhibitors alone. The authors report an average decline in 0.5 points on a 28-point ADL scale. The measured change on an ADL scale would represent, if a constant rate of decline over the course of a year, a change from requiring only limited assistance to being completely dependent in a particular ADL, or a change from supervision only to requiring extensive assistance for a specific ADL. However, with analyses limited to the magnitude of change per quarter, effects over a one-year period cannot be estimated. Moreover, the effect of the change may be overstated as it assumes change in one of the seven ADL domains whereas smaller declines may be spread over several domains. No differences in the rate of cognitive decline were detected on dual therapy compared with cholinesterase inhibitors alone.

The authors present results separately for patients taking oxybutynin and tolterodine. There were no significant differences in cognition or ADL for either drug, compared with users of a cholinesterase inhibitor alone. Although the authors stated their intent to compare oxybutynin and tolterodine directly in the methods section, this comparison was not reported, no doubt because of the lack of significant difference among users of either drug versus a cholinesterase inhibitor alone. Inadequate data were provided to carry out such a comparison, but based on reported means, the two cohorts are unlikely to differ significantly. Whether this is due to inadequate power to detect a difference or lack of difference remains an open question.

One additional exploratory before-after study was conducted in 10 adults aged 60 to 85 (Monnot 2012). Half of the participants had mild cognitive impairment. Cognitive scores were first assessed while taking oxybutynin or tolterodine (one patient) and then after a four-week drug washout period. There were insufficient numbers of patients to compare drugs. No difference was reported in overall cognitive scores. However, specific cognition and behavioural index subtest scores improved after oxybutynin or tolterodine withdrawal. There was one exception, a patient with non-amnestic mild cognitive impairment (early frontotemporal dementia), who had a consistent decline on all tests. The authors suggest that total scores from multidimensional instruments may not be sensitive enough to reveal subtle cognitive problems that arise with use of anticholinergic medication. Although exploratory and requiring confirmation, the overall results suggest the drugs can affect cognition in a subtle and reversible manner. The study also highlights some of the methodological issues in cognitive assessment.

Although cognitive-related events were reviewed in the PSUR documentation, there is no available cumulative review of memory impairment.

In conclusion, there is insufficient evidence publicly available to assess the magnitude of tolterodine's effects on cognition, versus oxybutynin. One short unpublished trial has directly addressed relative effects on cognition and may help to shed additional light on this issue. Based on case reports and data submitted to regulators, there is evidence of adverse cognitive effects associated with tolterodine, but insufficient research to assess the frequency of effects or how this compares to oxybutynin.

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Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part II

Fesoterodine versus Oxybutynin and Other Anti-Muscarinic Drugs for Overactive Bladder Syndrome

Table of Contents – Part II

Fesoterodine versus Oxybutynin and Other Anti-Muscarinic Drugs for Overactive Bladder Syndrome

Executive Summary

Fesoterodine is the most recent antimuscarinic drug for overactive bladder syndrome (OAB) to be approved in Canada. It was approved in February 2012, with the Canadian Drug Expert Committee (CDEC) recommendation dated October 18, 2012. Fesoterodine is produced by the same manufacturer as tolterodine, Pfizer, and is closely related to tolterodine. Fesoterodine is the ester analogue of 5-hydroxymethyl tolterodine (5-HMT), the major metabolite of tolterodine. The activity of fesoterodine is solely attributable to 5-HMT, with the parent drug undetectable in the bloodstream. In contrast, tolterodine's antimuscarinic activity is due both to the parent drug (tolterodine) and 5-HMT. Fesoterodine has a long half life as it was developed in a sustained-release formulation.

Research Questions:

Q1. In adults, including the frail elderly, does fesoterodine (Toviaz™) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR), other formulations of oxybutynin or other antimuscarinic drugs included in this review, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that fesoterodine (Toviaz ™) improves clinically relevant outcomes or has a better safety profile compared to oxybutynin IR or other antimuscarinic drugs?

Q3. In adults, particularly the elderly, does fesoterodine (Toviaz™) have less effect on cognition when compared to oxybutynin IR, other formulations of oxybutynin or other antimuscarinic drugs?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included as supplemental information on harms if they exclusively enrolled elderly populations or assessed cognitive function. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement the RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included

determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

A submission from the manufacturer (Pfizer Toviaz (Fesoterodine Fumarate) Confidential Clinical Summary, Undated) was also obtained for this review. All studies listed in the submission were included in the literature database and screened for eligibility.

Q1. Comparative Harms and Benefits

Results

Search Findings

Three RCTs meeting inclusion criteria compared fesoterodine with tolterodine extended release (ER):

- Chapple 2007, corresponding to trial SP583;
- Herschorn 2010 corresponding to trial A1008;
- Kaplan 2010, corresponding to trial A1046.

No published or unpublished trials compared fesoterodine with oxybutynin or other drugs included in this review.

Two placebo-controlled RCTs are included as they address effects in the elderly:

- Protocol A0221049 [unpublished 12-week RCT, with full study report in the Periodic Safety Update Report (PSUR)];
- Wagg 2013a ; Protocol A012245.

Two uncontrolled cohort analyses met inclusion criteria to assess infrequent harms:

- Sand 2012 (also described in Scarpero 2011 and Kelleher 2011)
- Wagg 2013b.

We also considered five recent high- or moderate-quality antimuscarinic drug class reviews for inclusion (Shamliyan 2012; Madhuvrata 2012; Semla 2011; Hartmann 2009; Chapple 2008). For several continuous outcomes, as noted below, we used unadjusted data or meta-analyses reported in a systematic review for the Cochrane Collaboration (Madhuvrata 2012).

Regulatory documents provided additional information on infrequent adverse events, labeling changes and safety advisories.

Direct Comparator RCTs

Fesoterodine vs. Tolterodine ER randomized controlled trials (RCTs)

The three trials meeting inclusion criteria were all 12 weeks in duration (Chapple 2007; Herschorn 2010; Kaplan 2010). In total, in the three trials, 1927 patients were randomized to fesoterodine 8mg/day; 271 to fesoterodine 4mg/day; 1947 to tolterodine ER 4mg/day and 1090 to placebo (N=5235). Fesoterodine doses were not combined in meta-analysis as there is evidence of non-equivalency from placebo-controlled trials. Tolterodine ER, 4mg/day, the maximum daily dose, was the comparator in all 3 trials.

Most comparisons were between fesoterodine 8mg/day and tolterodine ER 4mg/day. In the trial with a fesoterodine 4mg/day (N=271) treatment arm, there were no significant differences in benefit or harm at that dose as compared with tolterodine (Chapple 2007).

Fesoterodine 8mg/day vs. tolterodine ER 4mg/day (meta-analyses, 3 trials):
More patients experienced serious adverse events (SAE) on fesoterodine than tolterodine. The relative risk (RR) is 1.84 (95% CI 1.1 to 3.1), with an absolute risk difference of 1% (95% CI 0% to 2%). There were also more withdrawals due to adverse events on fesoterodine: RR=1.60 (95% CI 1.2 to 2.2), with an absolute risk difference of 2% (95% CI 1% to 3%).

The rate of total adverse events (AE) was higher on fesoterodine than tolterodine: (RR = 1.24 (95% CI 1.2 to 1.3). This translates to 10% more patients experiencing an AE (95% CI 7% to 13%) on fesoterodine. More patients had dry mouth: RR=1.91 (95% CI 1.7 to 2.2; absolute risk increase 14% (95% CI 11% to 18%); constipation: RR=1.41 (95% CI 1.0 to 1.9); absolute risk increase 1% (95% CI 0 to 3%); and dyspepsia (95% CI 0 to 2%); RR=1.85 (95% CI 1.1 to 3.1). No information is available on cognition.

None of the trials measured general health-related quality of life. On OAB-specific quality of life scales, fesoterodine improved symptom bother more than tolterodine, with a standardized mean difference of 0.20 points (scale 0 to 1) on condition-specific quality of life scores. This is equivalent to around a 4.6-point difference on a 100-point symptom bother scale, below a minimal clinically important difference.

More patients reported improvement or cure with fesoterodine, based on 3-day bladder diaries at end of trial: RR=1.11 (95% CI 1.1 to 1.2). The absolute difference was 7% (95% CI 4% to 10%). Fesoterodine use led to a reduction of an additional 0.11 to 0.48 urinary incontinence episodes per day in each trial. When data were pooled, a mean difference of 0.20 episodes (95% CI -0.04 to -0.36), or 1 per 5 days, was observed. Fesoterodine also reduced urgency by an additional 0.29 episodes per day compared with tolterodine (95% CI 0.30 to 0.87). A marginally significant difference of a mean of 0.09 fewer episodes per night of nocturia (95% CI 0 to -0.18) was also seen. This may be a chance finding and the magnitude of difference is unlikely to be clinically meaningful.

The three RCTs were under-powered to detect differences in serious but infrequent events. All were sponsored by the manufacturer, and risk of bias was unclear to high for most criteria on the Cochrane Risk of Bias tool, measuring internal validity. In general, results suggest a stronger antimuscarinic effect for fesoterodine 8mg/day vs. tolterodine 4mg/day, reflected both in effectiveness and harm outcomes.

Approximately one third of participants were aged ≥65. A post hoc analysis of pooled results for Herschorn 2010 and Kaplan 2010 in older patients (Dubeau 2012) found no difference for efficacy outcomes, but an increase with age in rates of constipation with both drugs, and in dry mouth and withdrawals due to adverse events with fesoterodine. Results are exploratory only as this is a post hoc subgroup analysis that failed to use appropriate meta-analysis techniques to pool data.

Placebo-controlled trials in the elderly

The two placebo-controlled trials in the elderly were 12-weeks in duration (N=1347; 673 receiving fesoterodine) and enrolled community-dwelling high functioning individuals (Pfizer Protocol A0221049; Wagg 2013a). Dosing was flexible and around half each were on fesoterodine 4 mg and 8 mg/day.

The trials were not adequately powered to assess mortality or SAE. There were more AE on fesoterodine than placebo in both trials; risk difference 14.2% in A0221049 and 26.1% in Wagg 2013a. There were also more withdrawals due to adverse events, dry mouth and constipation in both trials, and more dizziness in Wagg 2013a. Wagg 2013a was stratified by age ≤75 and 75+. No difference was observed for AE by age but 4mg and 8mg doses were pooled, which limits interpretation. Mini-Mental Status Examination (MMSE) scores did not differ in general, but in A0221049, there were two cases of memory impairment with dose escalation to 8mg and one WDAE due to confusional state on 4mg. A signal was noted for urinary retention, with 9 cases on fesoterodine (3.2%) and 0 on placebo.

Non-randomized studies

There were two open-label extension studies following 12-week RCTs, one lasting a mean of 21 months (Sand 2012) and the other 12 weeks (Wagg 2013b). Dosing was flexible: 4mg or 8mg. Both studies report results stratified by age (≤ 75 and 75+). Both also relied on passive adverse event reporting, rather than active questioning. Wagg 2013b reports results separately for patients previously randomized to placebo. Withdrawals due to adverse events, total adverse events, dry mouth and constipation occurred more frequently in patients who had previously taken placebo. These differences were most pronounced among patients over 75. The longer-term trial (Sand 2012) indicates a high rate of early withdrawal, 94% overall and 96% in patients aged >75.

Post-market surveillance safety data

The WHO Monitoring Centre in Uppsala published a signal of gastrointestinal (GI) hemorrhage with fesoterodine (Hill 2012) based on 7 reports in their international database. GI hemorrhage had previously been reported with tolterodine.

Post marketing events targeted for ongoing assessment in the manufacturer's periodic safety updates include: QT prolongation, cardiac arrhythmias, elevated liver enzymes, cognitive impairment, urinary retention, angioedema, anaphylaxis and severe skin events. Recent events added to safety reference material are: angioedema, dizziness, rash, urticaria and pruritus.

Q1 Discussion and Conclusions

There is no evidence available for comparisons of fesoterodine with oxybutynin (IR, ER or transdermal), solifenacin, darifenacin or trospium. No conclusions can be drawn on comparative effectiveness or safety.

Based on 3 RCTs comparing fesoterodine 4mg and 8mg with tolterodine ER 4mg (N=5235 in total), there is no evidence of a therapeutic advantage for fesoterodine.

There were no differences in beneficial or harmful outcomes between fesoterodine 4mg/day and tolterodine ER 4mg/day.

At 8mg/day, 7% more patients on fesoterodine reported improvement or cure. In total, patients experienced one fewer urgency episode per 3.4 days, one fewer urgency incontinence episode per 5 days, and one fewer nocturia episode per 11 days.

On the other hand, 14% more patients experienced dry mouth, 10% more experienced an adverse event of any sort, 2% withdrew due to adverse events, 1% more experienced constipation, 1% more experienced dyspepsia, and 1% more experienced serious adverse events.

These modest differences in benefit fail to outweigh increased harm. In general, these differences are consistent with a stronger antimuscarinic effect from fesoterodine 8mg/day vs. tolterodine ER 4mg/day.

There are no comparative RCT data in the frail elderly, and the maximum duration of RCTs was 12 weeks, too brief to assess longer-term effects. There are no long-term comparative observational studies; one uncontrolled cohort analysis provides limited data, as only 98 patients over the age of 75 were included, 96% of whom withdrew early.

Q2. New Clinical Evidence since CDR Review

No new direct comparator RCTs have been published since the CDR review and the CDEC Final Recommendation, dated October 18, 2012 (Common Drug Review 2012). The CDEC recommendation was to list fesoterodine in the same manner as extended-release tolterodine.

One new placebo-controlled RCT was identified that assessed steady-state cognitive effects of fesoterodine, as described below.

Two uncontrolled cohort analyses were identified in this review that were not part of the CDR review as the latter is restricted to RCTs only (Sand 2012; Wagg 2013b). Both were post-RCT extension studies and are described above. Withdrawals due to adverse events, total adverse events, dry mouth and constipation occurred more frequently in patients who had previously taken placebo. These differences were most pronounced among patients aged 75+, suggesting that the strongest selection effects in patients previously randomized to fesoterodine occurred in this population group. These studies cannot be used to draw conclusions about any therapeutic advantage of fesoterodine and do not modify the conclusions of the CDR review.

Similarly, the available PSUR (April 2011 to April 2012) reveals a similar adverse event profile as other antimuscarinic drugs and also cannot be used to draw conclusions about the relative rate of adverse events for fesoterodine versus comparator drugs.

Since completion of the CDR review in October 2012, there is no substantive evidence available that would lead to a difference in recommendation as compared with the CDR review, either with respect to comparative effectiveness or safety of fesoterodine versus other anti-muscarinic drugs. For most of the drugs in this class, no comparative evidence exists. The additional non-randomized studies included in this review were uncontrolled cohort analyses, a weak methodology that limits interpretability of results.

Q3. Cognition

No direct comparator RCTs were identified that compared the short- or long-term cognitive effects of fesoterodine with oxybutynin or any other antimuscarinic drug. The available 12-week RCTs on patients with OAB syndrome were under-powered to detect differences in central nervous system effects and none actively assessed cognition.

One six-day placebo-controlled RCT enrolled 20 healthy volunteers aged 65 years or older (mean age 72, range 65 to 85) and tested the cognitive effects of steady state fesoterodine 4mg/day or 8mg/day. All volunteers had normal cognition on a Mini-Mental Status Examination at baseline. (Kay 2012) A battery of computerized tests was used to assess cognitive ability, including reaction time, following fesoterodine or an acutely sedating high dose of alprazolam (1mg, 4 x the usual starting dose in the elderly). The latter was used as a positive control. There were no differences in change from baseline between placebo and either dose of fesoterodine. The high dose of alprazolam showed deterioration in scores.

A per protocol analysis on 18 patients was conducted. Reported AE for fesoterodine were dry mouth in 10% of patients on 4mg and 32% of patients on 8mg. After the single dose of alprazolam, 63% of patients complained of sedation or somnolence. Although the study was blinded, the acutely sedating effects of alprazolam, and the incidence of dry mouth associated with 8mg fesoterodine would have affected blinding. No information is provided in the paper about the sensitivity or validity of the administered cognitive tests, or how the minimal clinically meaningful difference was derived for the primary outcome,

a reaction time test. The only conclusion from this study is that fesoterodine, in the short-term, does not impair the ability to carry out cognitive tasks to the same extent as a high dose of a benzodiazepine.

The study provides no information on potential effects on cognition from chronic use of fesoterodine.

The available evidence is insufficient to draw conclusions about the cognitive effects of fesoterodine compared with other antimuscarinic drugs.

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Chapter 5. Fesoterodine vs. Other Antimuscarinic Drugs Systematic Review

Background

Fesoterodine Fumarate Extended-Release Product Data

Box 1: Fesoterodine Fumarate Product Information

Categorization: anticholinergic-antispasmodic agent

Indication: the treatment of patients with overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms

Recommended Usual Dose: 4 mg once daily starting dose; may be increased to 8 mg once daily depending on individual response and tolerability.

Mechanism of Action: the active metabolite (5-HMT) of fesoterodine is a competitive, nonselective muscarinic receptor antagonist

Above is derived from Fesoterodine Fumarate Extended-Release Tablets (Toviaz™) Product Monograph dated October 23, 2012.

Fesoterodine is the most recent antimuscarinic drug for OAB to be approved in Canada. It was approved in February 2012, with the Canadian Drug Expert Committee (CDEC) recommendation dated October 18 2012. The drug was first introduced worldwide in 2007.

Manufactured by Pfizer, the same company that produces tolterodine, fesoterodine is the ester analogue of 5-hydroxymethyl tolterodine (5-HMT) and is rapidly converted to 5-HMT by nonspecific esterases. 5-HMT is the same chemical entity that is the major metabolite of tolterodine. These two drugs are thus closely related. In contrast to tolterodine, however, the CYP 2D6 enzyme is not involved in the production of 5-HMT from fesoterodine. This feature of fesoterodine has been suggested to reduce the variability of 5-HMT plasma levels (Malhotra 2011). However, 5-HMT is subsequently metabolized by CYP 2D6 and CYP 3A4 enzymes; genetic variants of CYP 2D6 and potent CYP 3A4 inhibitors can thus affect active drug levels.

The activity of fesoterodine is solely attributable to 5-HMT, and the parent drug is undetectable in the bloodstream. This also contrasts with tolterodine as both tolterodine and 5-HMT have antimuscarinic activity. 5-HMT has different physicochemical properties from tolterodine. For example, 5-HMT is less lipid soluble and less easily crosses biological membranes such as the blood brain barrier. This has led to marketing claims that the adverse effect profile of fesoterodine might be more favorable that tolterodine. Clinically, this has not been proven.

Fesoterodine has a long half life as it was developed in a sustained-release formulation. See Appendix B and Chapter 1, Table 7, for further information on fesoterodine pharmacokinetics and selected characteristics.

Q1. Comparative Harms and Benefits

Methods – see Chapter 2, p. 77

Results

Search Findings

Our literature search did not identify any RCTs that compared fesoterodine with oxybutynin IR. Three RCTs that compared fesoterodine with tolterodine extended release (ER) met eligibility criteria. No RCTs were identified that compared fesoterodine with any other antimuscarinic drug under review (other formulations of oxybutynin, solifenacin, darifenacin and trospium). In addition to the three RCTs, two uncontrolled cohort analyses were included, and three placebo-controlled trials addressing effects in the elderly.

We also considered five recent high- or fair-quality antimuscarinic drug class reviews for inclusion (Shamliyan 2012; Madhuvrata 2012; Semla 2011; Hartmann 2009; Chapple 2008), as they include an analysis of fesoterodine trials. For several continuous outcomes, as noted below, we used unadjusted data or meta-analyses reported in a systematic review for the Cochrane Collaboration (Madhuvrata 2012).

A submission from the manufacturer (Pfizer Toviaz (Fesoterodine Fumarate) Confidential Clinical Summary, Undated) was also obtained for this review. All studies listed in the submission were included in the literature database and screened for eligibility.

Direct Comparator RCTs

Three twelve-week parallel-group RCTs compared fesoterodine to tolterodine ER:

- Chapple 2007, corresponding to trial SP583;
- Herschorn 2010 corresponding to trial A1008;
- Kaplan 2010, corresponding to trial A1046.

Each trial also included a placebo control arm. All three trials were sponsored by the manufacturer. Sample size calculation for Herschorn 2010 and Kaplan 2010 were based on the results of Chapple 2007.

The RCTs were twelve weeks long, with a total of 5264 participants randomized. Of participants who received one or more doses of medication, 4145 received active drug (1927 fesoterodine 8mg, 271 fesoterodine 4mg, 1947 tolterodine ER), and 1090 received placebo. One trial was designed as a superiority trial for the comparison of fesoterodine vs. placebo (Chapple 2007) and included two dosages of fesoterodine, 4mg and 8mg once daily. The other two trials were designed as superiority trials for the comparison of fesoterodine vs. tolterodine, and included a single fesoterodine treatment arm with a starting dose of 4mg that was increased to 8mg after one week. All three trials used tolterodine 4mg once daily, the maximum recommended dosage of tolterodine ER. Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix F.

We chose not to combine doses of fesoterodine in the meta-analyses conducted for this comparison, given the existence of evidence from placebo-controlled trials that fesoterodine 4mg per day is not equivalent to fesoterodine 8mg per day. We therefore present available results for fesoterodine 4mg vs. tolterodine separately for the one trial that included this dosage (Chapple 2007).

If data for continuous outcomes met normality assumptions, the outcomes were reported by trial investigators as an analysis of covariance model with the terms treatment and country and baseline value

as covariates. These data could not be used in meta-analyses as unadjusted means and standard deviations were required.

One or two trials reported a non-parametric distribution for two continuous outcomes of interest. These were incontinence episodes in two trials (Herschorn 2010; Kaplan 2010), as discussed on page 149, and mean volume voided in one trial (Kaplan 2010).

When necessary and possible, data in trial publications were supplemented by data in regulatory reviews including the Fesoterodine CDR Review, and by the systematic review conducted by Madhuvrata et al. for the Cochrane Collaboration (Madhuvrata 2012).

Results are presented according to our hierarchy of outcomes. For meta-analyses of dichotomous outcomes, if a relative risk (RR) is < 1, it means fewer people experienced events (beneficial or harmful) in the fesoterodine group.

1. All-cause mortality

The RCTs were too short for an assessment of long-term mortality, and were under-powered to detect any differences in mortality between active comparator drugs (or placebo) in the short-term.

There were seven deaths in the three trials. Of these, three were in the fesoterodine group and none were in the tolterodine ER group. Four deaths were reported for the placebo group.

Five deaths are reported in trial publications (Herschorn 2010; Kaplan 2010) as Chapple 2007 did not report on this outcome. The Common Drug Review reports two deaths in the Chapple 2007 study, including one patient in the fesoterodine 8mg/day group (Common Drug Review 2012). The patient was hospitalized for bronchitis two weeks after discontinuation of fesoterodine, and then died one day post-discharge of a myocardial infarction (26 days post discontinuation). The other death occurred in the placebo group, and no details are available.

One death was reported in the placebo group in Kaplan 2010, and four deaths were reported in Herschorn 2010, two in the placebo and two in the fesoterodine group. The two deaths in the fesoterodine group were reported as a traumatic brain injury secondary to a car accident, and a death due to (non-verified) cardiac failure.

2. Serious Adverse Events (SAE)

The published report for Chapple 2007 did not report SAE. The numbers of SAE used for meta-analysis were therefore obtained from the CDR review. In the three trials (N=3873), more people on fesoterodine (2.1%) had SAE than tolterodine ER (1.1%): RR 1.84 (95% CI 1.10 to 3.08), P=0.02. The absolute risk difference was 1% (95% CI 0% to 2%).

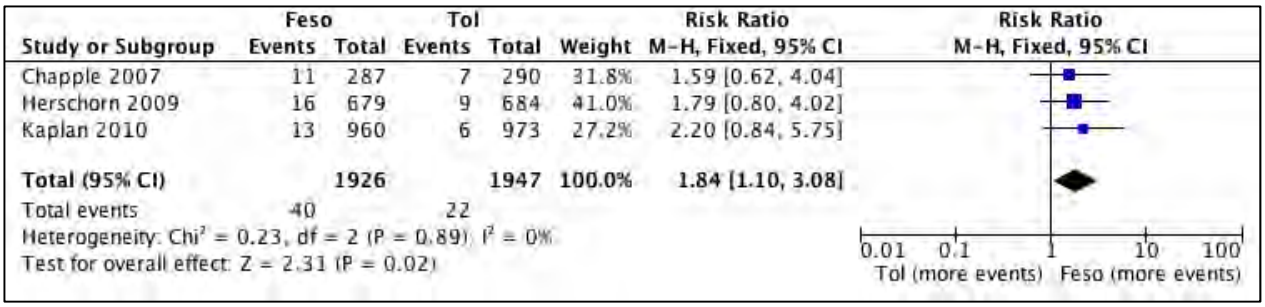

Figure 1. SAE

There was no statistically significant difference in SAE for the comparison of fesoterodine 4mg vs. tolterodine ER in the one available study testing this dosage, Chapple 2007 (Table 2 in Appendix F).

No details of the type of SAE are available for Chapple 2007. The only SAE described in Herschorn 2010 was a case of urinary retention in a 70 year old who had a history of benign prostatic hypertrophy and developed urinary retention six days after initiation of treatment with fesoterodine 4mg. In Kaplan 2010, two of the 13 SAE in the fesoterodine (8mg) group were described: acute pyelonephritis in a 49 year old female, and acute urinary retention in a 72 year old male, both occurring within two weeks of initiation of treatment. Other SAE in Kaplan 2010 and Herschorn 2010 are listed in Table 3 of Appendix F, as obtained from study results posted on clinicaltrials.gov.

3. Withdrawals due to Adverse Events (WDAE)/ Tolerability

There were more WDAE with fesoterodine 8mg than with tolterodine ER (N=3873, 3 trials): RR 1.60 (95% CI 1.18 to 2.17), P=0.002; absolute risk difference 2% (95% CI 1% to 3%).

In one trial (N=562) that tested fesoterodine 4mg, there was no difference in WDAE between fesoterodine 4mg and tolterodine ER: RR 0.83 (95% CI 0.31 to 2.20), P=0.71.

Details of WDAE were selectively reported. In Chapple 2007, one patient in the fesoterodine 4mg group and two in the fesoterodine 8mg groups withdrew due to urinary retention. Three patients taking fesoterodine also withdrew due to QT prolongation, one in the 4mg and two in the 8mg group. One case of acute urinary retention in Kaplan 2010 study led to withdrawal. Other events leading to discontinuation in the three trials were not adequately described.

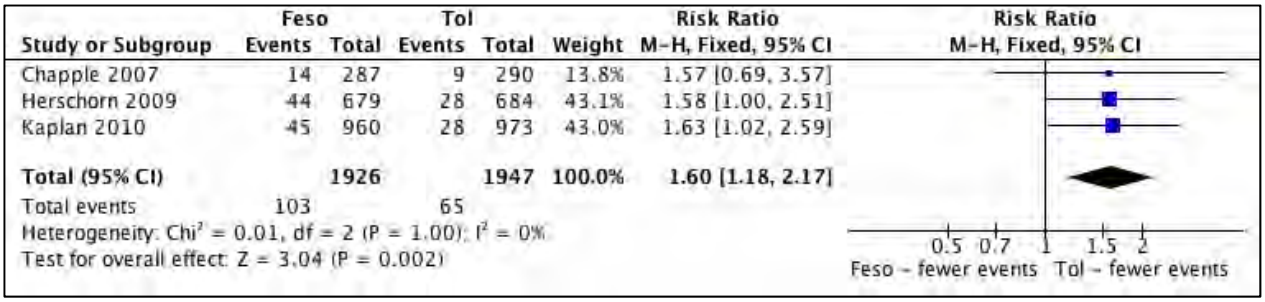

Figure 2. WDAE

There was no statistically significant difference in WDAE when fesoterodine 4mg was compared to tolterodine ER 4mg in Chapple 2007 (Table 4 in Appendix F).

4. Quality of life (QoL)

All three trials reported on quality of life using condition-specific, validated instruments. Chapple 2007 used the King's Health Questionnaire (KHQ) and the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF). The other two trials used the OAB-questionnaire (OAB-q).

We report first the individual trial results and then a meta-analysis of the three trials in a Cochrane review (Madhuvrata 2012), which used standardized mean differences to combine results of different scales.

The KHQ is comprised of nine domains, each of which has a score of 0 (best outcome) to 100 (worst outcome). A negative score from baseline is an improvement; minimal clinically important differences are in the range of 5-10 points (Kelleher 2004).

For Chapple 2007, there were no statistically significant differences between fesoterodine 8mg and tolterodine for any of the nine KHQ domains. Additionally, numerical differences between drugs were below a threshold for minimal clinically important differences (Table 2 in Appendix F). These analyses were obtained from the Cochrane systematic review (Madhuvrata 2012, Table 1, page 236-7) because the Chapple 2007 publication only reports comparisons versus placebo.

Kaplan 2010 and Herschorn 2010 reported QoL data based on the OAB-questionnaire (OAB-q), a 33-item validated questionnaire, with 8 items on symptom bother and 25 items that assess the impact of OAB on four domains (coping, concern/worry, sleep and social interaction). Scoring for each domain subscale is 0 to 100 points, and the recommended threshold for minimal clinically important differences is 10 points (Coyne 2006b; Shamliyan 2012).

Kaplan 2010 reported statistically significantly greater improvements for fesoterodine compared with tolterodine at week 12 on the OAB-q symptom bother scale, total health-related quality of life (HRQL) scale and three of the four domains (coping, sleep, social interaction). The difference between drugs on the symptom bother subscale is – 4.6 in favor of fesoterodine (least squares mean) (Table 2 in Appendix F) (Common Drug Review 2012, p. 54). This is well below the minimal clinically important difference of ten points.

Herschorn 2009, in a post hoc analysis, reported that fesoterodine 8mg improved symptom bother, total HRQL and the concern, coping and social interaction domains to a greater extent than tolterodine. The difference between drugs on the symptom bother subscale was also -4.6 in favor of fesoterodine (least squares mean) (Common Drug Review 2012, p. 54).

Madhuvrata et al. obtained unadjusted data from study investigators to conduct a meta-analysis on QoL data from the three trials, using the symptom bother score of OAB-q for Herschorn 2010 and Kaplan 2010 and the KHQ severity-coping domain for Chapple 2007. The combined data (3 trials, N=3492) showed slightly greater improvement with fesoterodine 8mg vs. tolterodine: standardized mean difference -0.20 (95% CI -0.26 to -0.14) (Madhuvrata 2012). This difference is equivalent to ~4.6 points on the symptom bother score for OAB-q, which is below the threshold for a minimal clinically important difference.

To put this 4.6 point difference into perspective, Kaplan 2010 reports a mean difference of 21.8 points from baseline in the placebo group on the symptom bother scale.

There was no statistically significant difference in the KHQ domains when fesoterodine 4mg was compared with tolterodine in the one trial that included this dose (Table 5 in Appendix F).

5. Patient-Reported Improvement/Cure

All three trials reported the proportion of participants with self-reported improvement or cure. For two trials, the Patient Perception of Bladder Condition (PPBC) was reported (Herschorn 2010; Kaplan 2010).

The PPBC is a 6-point categorical single-item scale that measures perceptions of patients regarding the severity of problems related to their bladder condition. This global single-item measure has been shown to have construct validity and responsiveness to treatment (Coyne 2006). However, it has weak test-retest reliability compared with multi-item scales, and only 54% of clinically stable respondents reported the same level of bladder problems between visits two weeks apart (Matza 2005). Chapple 2007 reported treatment response on a global single-item four-point scale termed the Treatment Benefit Scale: 1=greatly improved; 2=improved; 3=not changed; 4=worsened. The first two categories were combined and categorized as improvement. The Treatment Benefit Scale has construct validity but has not been tested for test-retest reliability (Colman 2008).

When the trials were pooled (N=3691), more patients on fesoterodine 8mg reported improvement than on tolterodine: RR 1.11 (95% CI 1.06 to 1.16), absolute risk difference 7% (95% CI 4% to 10%).

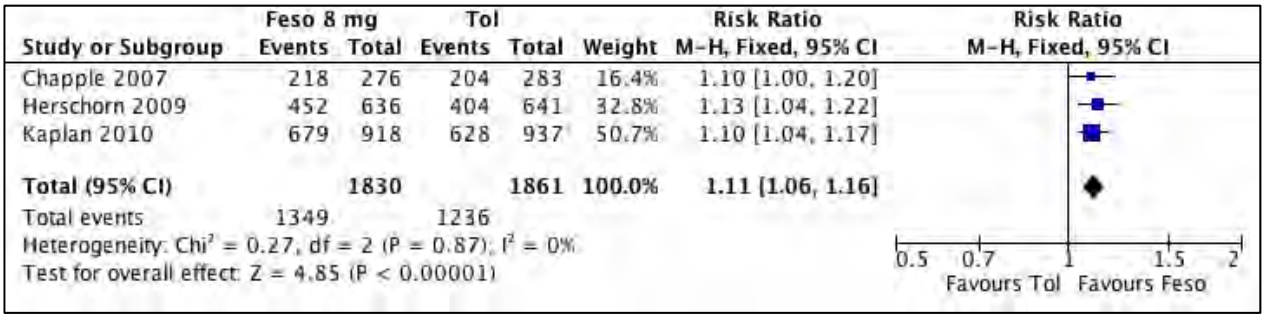

Figure 3. Patient-Reported Perception of Improvement/Cure

When the lower dose of fesoterodine 4mg daily was compared with tolterodine ER 4mg in one trial (N=548), there was no statistically significant difference between active drugs: RR 1.04 (95% CI 0.94 to 1.15).

6. Quantification of Incontinence Episodes

Cure or total dryness: Two trials reported on patients achieving continence for a specified time period, based on 3-day bladder diaries (Kaplan 2010; Chapple 2007).

Kaplan 2010 reported the proportion of evaluable participants who recorded no incontinence episodes at study end. More patients treated with fesoterodine were dry for 3 days when compared with tolterodine (P=0.0169, ~60% vs. ~55%, values estimated from graph only).

Chapple 2007 estimated the mean number of continent days per week. These results were extrapolated from a 3-day bladder diary, and the statistical significance of the 3-day data are not provided. At baseline, the range of continent days was estimated to be 0.6 to 0.8 continent days per week. At study end, the placebo group had an estimated 2.9 continent days per week, fesoterodine 8mg 3.4 days, and tolterodine ER 3.1 days (Common Drug Review 2012). For the comparison fesoterodine 8mg vs. tolterodine ER, the least squares mean difference in the change from baseline was 0.85 days (95% CI 0.29 to 1.41) per week, the difference statistically significant in favor of fesoterodine (Common Drug Review 2012, p.49). The difference in the change from baseline for the comparison fesoterodine 4mg vs. tolterodine was not statistically significant.

Incontinence Episodes: Fesoterodine 8mg reduced mean incontinence episodes from baseline by an additional 0.11 to 0.48 episodes per day compared with tolterodine in the individual trials (using adjusted means). The statistical technique for reported means depended on the trial and whether the data fit a normal distribution.

Chapple 2007 conducted an analysis of covariance and reported least squares means and standard errors. This is an appropriate analysis for continuous data when the underlying distribution of the measurement is a normal distribution. Fesoterodine 8mg reduced incontinence episodes from baseline by an additional 0.48 episodes per day compared with tolterodine ER (95% CI -0.9 to -0.1) (Table 1) (Common Drug Review 2012). Fesoterodine 4mg was not significantly better than tolterodine: MD 0.23 episodes (95% CI -0.71 to -0.25).

The data for incontinence episodes in Herschorn 2010 and Kaplan 2010 were skewed. Although analyses similar to those used in Chapple 2007 were planned, one of the assumptions for the model (normal distribution of residuals) failed when testing whether the data fit a normal (parametric) distribution (Herschorn 2010; Kaplan 2010; Common Drug Review 2012, p. 41). A possible reason for lack of a normal distribution is deterioration (i.e., increased incontinence episodes from baseline) in some subjects or high baseline values of incontinence episodes (Common Drug Review 2012).

In both trials, two steps were employed to overcome non-normality. First, a 5% Winsorized mean was used. This adjustment involves calculating the mean for each treatment group after replacing the high and low end of the probability distribution with the 5th and 95th percentile. This eliminates outliers in the sample distribution tails. Second, a non-parametric test, the Van Elteren's test, was used to calculate p-values for the treatment effect of change from baseline. This is a modified Wilcoxon-Mann-Whitney test, a widely used method for comparing two treatments when the underlying distribution of the outcome variable does not fit a normal distribution. The Van Elteren's test adjusted for baseline incontinence by using baseline quartiles as strata.

The reason for using both of these techniques is unclear as either one would be sufficient on its own. The CDR review points out that both techniques are regarded as more liberal than the conservative parametric modeling (Common Drug Review 2012). Because of this, the CDR review conducted a sensitivity analysis of the statistical significance of the results, and compared the statistical significance of the mean difference using the Winsorized means of change alone with the p-value calculated from the Van Elteren's test (Table 1). For one of the two trials (Kaplan 2010), there was a statistically significant difference only when both techniques were combined (non-parametric testing and Winsorized adjustment of the mean) (Common Drug Review 2012).

Table 1. Incontinence Episodes per Day. Modified from CDR Review

Trial/Test	Tol 4mg	Feso 8mg	Placebo
Chapple 2007			
N	223	223	211
Baseline Mean (SD)	3.8 (3.07)	3.7 (2.97)	3.7 (3.13)
End of treatment Mean (SD), LOCF	2.0 (3.04)	1.4 (2.46)	2.5 (3.54)
Feso vs. Tol LSM difference	MD = -0.48 [95% CI -0.92 to -0.05] (statistically significant)		
Herschorn 2010			
N	684	679	
Baseline Mean (SD)	2.5 (2.2)	2.4 (2.0)	2.6 (2.3)
End of treatment Mean (SD), LOCF	NR	NR	NR
Change from baseline Winsorized mean (SE)	-1.61 (0.06)	-1.72 (0.06)	-1.46 (0.1)
Feso vs. Tol Winsorized Mean Difference p-value, Van Elteren's Test	MD = -0.11, p=0.0172 (statistically significant)		--
Feso vs. Tol Winsorized Mean Difference	MD = -0.11 [95% CI -0.28 to 0.06]		--

[95% CI calculated]	(*not* statistically significant)		
Kaplan 2010			
N	973	960	478
Baseline Mean (SD)	2.6 (2.1)	2.6 (2.2)	2.4 (1.9)
End of treatment Mean (SD), LOCF	NR	NR	NR
Change from baseline Winsorized mean (SE)	-1.74 (0.06)	-1.95 (0.05)	-1.62 (0.07)
Feso vs. Tol Winsorized Mean Difference p-value, Van Elteren's Test	MD = -0.21, p=0.0072 (statistically significant)		--
Feso vs. Tol Winsorized mean [95% CI calculated]	MD = -0.21 [95% CI -0.36 to -0.06] (statistically significant)		--

CI=confidence intervals; **feso**=fesoterodine; **LOCF**, last observation carried forward; **LSM**=least squares mean; **MD**=mean difference; **SE**=standard error; **SD**=standard deviation; **tol**=tolterodine;
Numbers and calculated confidence intervals are as reported in the CDR review.

There was no statistically significant difference when fesoterodine 4mg was compared with tolterodine ER in Chapple 2007 (Table 4 in Appendix F).

For large samples, standard inferences on the means of skewed data are valid because of the central limit theorem, which determines that the distribution of a population of means approaches a normal distribution. Since standard meta-analysis methods assume normality in the distribution of the means (but not the raw data), they are valid when sample sizes are large (Higgins 2008). Madhuvrata 2012 obtained the unpublished, unadjusted means and standard deviations from trial investigators for all three trials, and conducted a standard (fixed effects) meta-analysis, using numbers of evaluable patients as reported in the publications. The pooled treatment effect estimate (3 trials, N=3525) showed an additional reduction of 0.19 episodes per day in the fesoterodine group: MD -0.19 (95% CI -0.30 to -0.09). A similar result was obtained when we conducted a random effects model using the data provided in the Cochrane review for Herschorn 2010 and Kaplan 2010: MD -0.20 (95% CI -0.36 to -0.04).

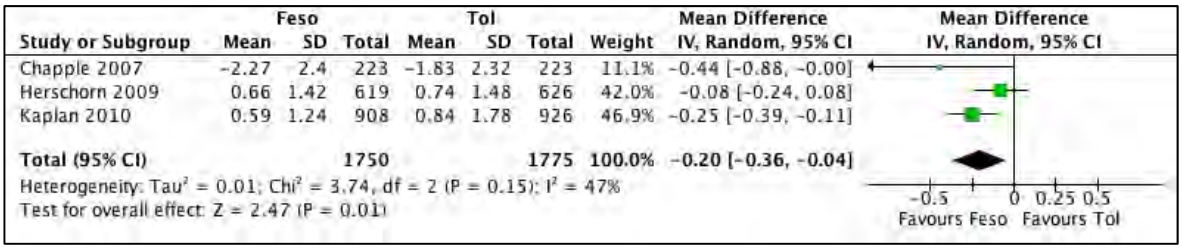

Figure 4. Incontinence Episodes (end of treatment or change from baseline)

None of the trials addressed the clinical meaningfulness of the small differences observed. Overall, the difference is one-fifth of an episode a day, or a difference of one episode every five days.

In the meta-analysis above, there is considerable heterogeneity. In a sensitivity analysis, we found that the heterogeneity between trial effect estimates is due to Herschorn 2010. However, removal of this trial has very limited effect on the estimate (mean difference -0.27; 95% CI -0.13 to -0.40), or a difference of one episode every four rather than five days.

7. Nocturia

End of treatment means and standard deviations were used for pooling the three trials (N=3593). Values were obtained from the CDR Review and assumed to be unadjusted means (Common Drug Review 2012). We were unable to verify this using another source. Fesoterodine on average reduced waking up at night

to void by an additional 0.09 episodes (95% CI -0.18 to 0.00), P=0.05. This marginally significant difference is not large enough to be clinically meaningful.

Figure 5. Nocturia

8. Urgency

Data in useable form for meta-analysis (unadjusted means and standard deviations) were not available in the trial publications for this outcome. Madhuvrata et al. had obtained end-of-treatment unadjusted data from the trial investigators and conducted a fixed effects meta-analysis on the three trials (N=3666) (Madhuvrata 2012). Fesoterodine 8mg reduced urgency episodes by an additional 0.44 episodes per day compared with tolterodine: MD -0.44 (95% CI -0.72 to -0.16) (Madhuvrata 2012). Because our protocol had stipulated using a random-effects model in the presence of heterogeneity, we conducted a random-effects meta-analysis, which weights smaller studies to a greater extent, using the data published in Madhuvrata 2012: MD -0.29 (95% CI -0.87 to 0.30). A random effects model results in wider CI and the difference was not statistically significant. In a sensitivity analysis, the statistical heterogeneity was attributable to Chapple 2007 although the cause was not identified.

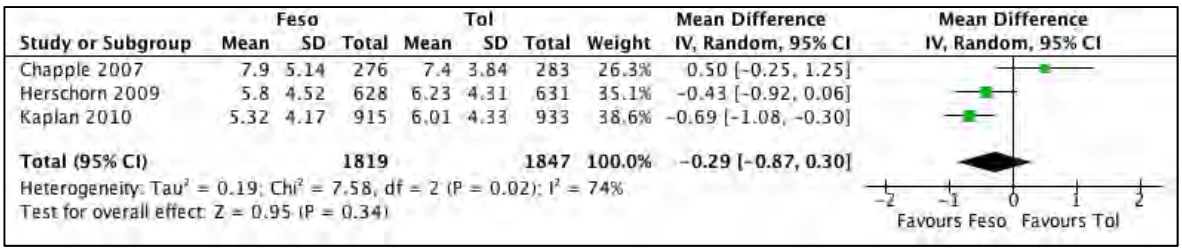

Figure 6. Urgency Episodes

9. Total AE

In the three trials combined (N= 3873), more participants on fesoterodine 8mg experienced one or more AE than on tolterodine: RR 1.24 (95% CI 1.16 to 1.33), P<0.00001; absolute risk difference 10% (95% CI 7% to 13%).

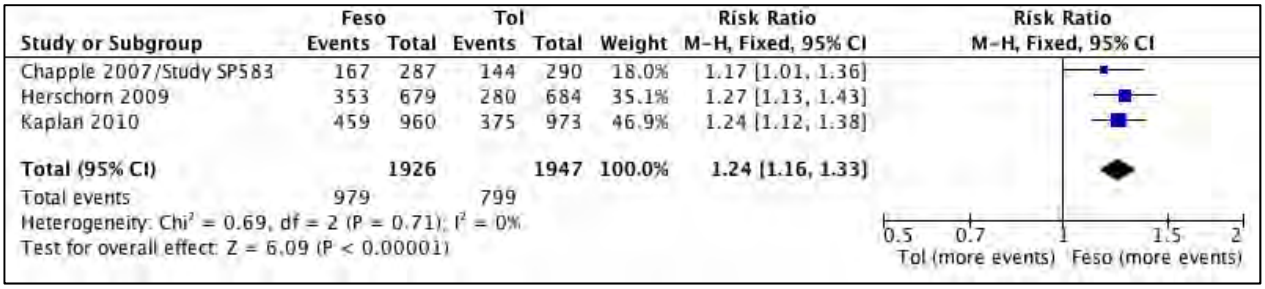

Figure 7. Proportion of patients experiencing ≥ 1 AE.

There was no difference between fesoterodine 4mg and tolterodine ER in the number of patients experiencing one or more AE (Table 4 in Appendix F).

10. Specific AE

Dry mouth: In the three trials combined (N=3873), fesoterodine 8mg was associated with more dry mouth than tolterodine ER: RR 1.91 (95% CI 1.69 to 2.17), P=0.38; absolute risk difference 14% (95% CI 11% to 16%).

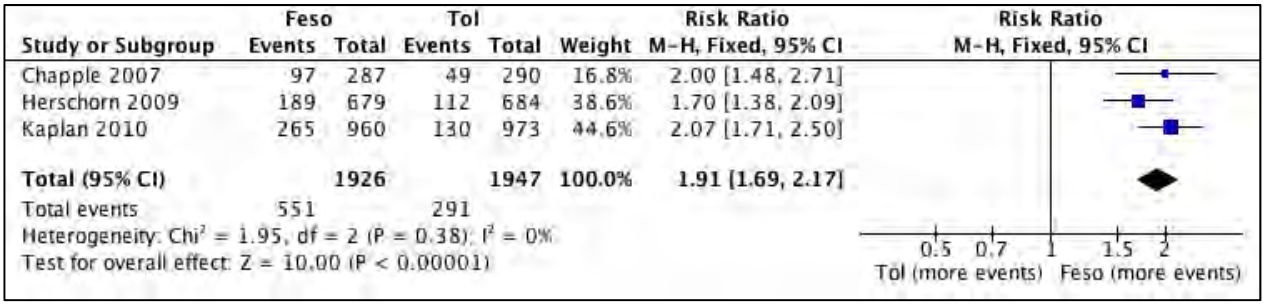

Figure 8. Dry mouth

Constipation: In the three trials combined (N=3863), participants taking fesoterodine 8mg experienced more constipation than participants taking tolterodine ER: RR 1.41 (95% CI 1.03 to 1.92), P=0.03; absolute risk difference 1% (95% CI 0% to 3%).

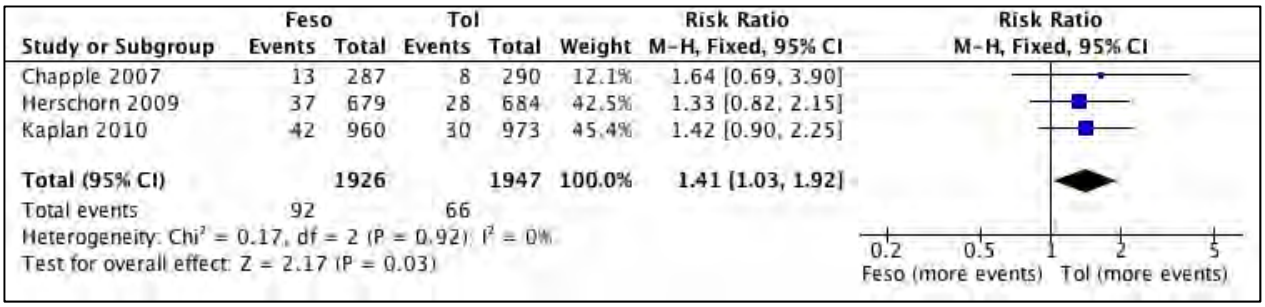

Figure 9. Constipation

Dyspepsia: In the three trials combined (N=3873), more participants on fesoterodine 8mg experienced dyspepsia than on tolterodine: RR 1.85 (95% CI 1.11 to 3.06), P=0.02; absolute risk difference 1% (95% CI 0% to 2%).

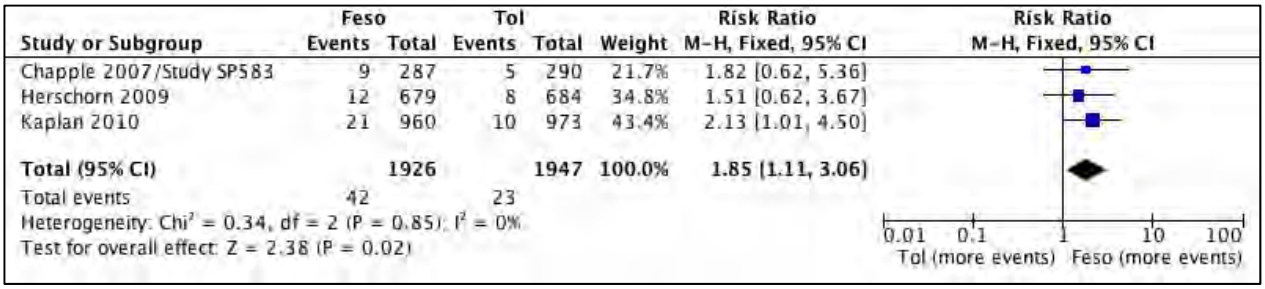

Figure 10. Dyspepsia

Other AE: there was no statistically significant differences between fesoterodine 8mg and tolterodine ER in the incidence of headache; dizziness; or urinary tract infection.

There were no statistically significant differences between fesoterodine 4mg and tolterodine ER in incidence rates of dry mouth, constipation, dyspepsia, headache, dizziness or other AE in Chapple 2007 (tables 2 and 4, Appendix F).

11. Urodynamics/clinician measures
None of the trials reported on maximum cystometric capacity, volume at first contraction, or residual volume.

12. Mean volume voided
For two trials (Chapple 2007; Herschorn 2010), this continuous outcome met normality assumptions and could be combined in a standard meta-analysis. The pooled treatment effect estimate (N=1816), showed that tolterodine increased mean volume voided more than fesoterodine: MD 15.6 mls (95% CI 5.3 to 25.8 mls), P=0.03. The third trial (Kaplan 2010) reported a Winsorized mean for each treatment group, with a mean difference of 6.0 mls numerically in favor of tolterodine but not statistically significant, p = 0.0525 with the Van Elteren's test (see incontinence for a discussion of use of this test).

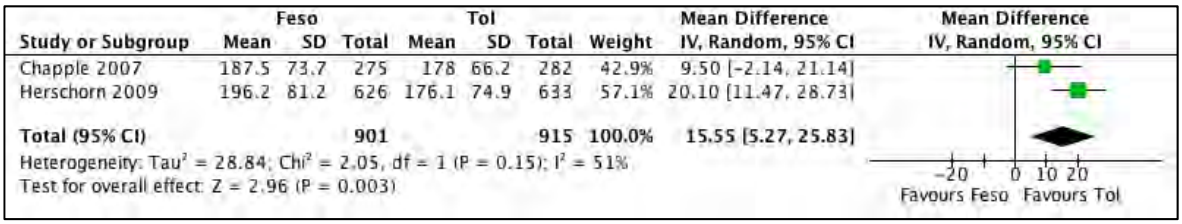

Figure 10. Average volume voided

RCT data on the Elderly
A post hoc analysis (DuBeau 2012) pooled two of the direct comparator RCTs of similar design (Herschorn 2009; Kaplan 2010) and presented results by age (< 65; 65-74; ≥ 75 years) (Table 2). Neither trial was stratified by age at randomization so baseline characteristics within each age subgroup may differ across treatment groups. The pooled data for dichotomous outcomes was not a standard meta-analysis that retains within-trial randomization; instead patient groups were simply added together as though they were part of the same trial. Due to these limitations, this pooled analysis should be considered exploratory only. We have therefore not carried out any statistical analyses.

The data include a total of 448 participants who were 75 years of age or older. Fesoterodine 8mg/day had higher rates of antimuscarinic AE, including dry mouth and constipation compared with tolterodine ER (4mg/day). There was a trend to increased SAE, WDAE, total AE, dry mouth and constipation with age across active treatment groups. This is especially striking for constipation in comparison with placebo. On placebo, constipation rates did not increase with age (rates 2% to 3% per age category). On tolterodine they increased from 2% among patients <65 to 7% on patients >75. On fesoterodine, the increase was from 4% at age <65 to 10% of those >75. Four patients on fesoterodine experienced urinary retention; proportionally, more patients ≥65 versus younger patients experienced this adverse event.

Although investigators state rates of self-reported cognitive AE were low and similar across age and treatment groups, a passive method of collecting cognitive AE is an inadequate assessment of cognitive function.

Table 2. Select AE in age subgroups (pooled analysis of Herschorn 2010 and Kaplan 2010)

Treatment	Placebo			Tolterodine ER			Fesoterodine		
Age group	< 65 years N=506	65-74 years N=199	≥ 75 years N=107	< 65 years N=1071	65-74 years N=412	≥ 75 years N=174	< 65 years N=1093	65-74 years N=379	≥ 75 years N=167
SAE	0	7 (4%)	3 (3%)	0	6 (2%)	1 (1%)	1 (1%)	14 (4%)	4 (2%)
WDAE	5 (1%)	5 (3%)	6 (6%)	30 (3%)	17 (4%)	9 (5%)	39 (4%)	30 (8%)	17 (10%)
Total AE	169 (33%)	63 (32%)	38 (36%)	421 (39%)	155 (38%)	79 (45%)	513 (47%)	217 (57%)	82 (49%)
Dry mouth	28 (6%)	12 (6%)	6 (6%)	156 (15%)	55 (13%)	31 (18%)	283 (26%)	121 (32%)	50 (30%)
Constipation	10 (2%)	5 (3%)	2 (2%)	25 (2%)	21 (5%)	12 (7%)	41 (4%)	22 (6%)	16 (10%)
Headache	12 (2%)	1 (1%)	1 (1%)	33 (3%)	8 (2%)	2 (1%)	48 (4%)	15 (4%)	2 (1%)
Diarrhea	7 (1%)	0	0	14 (1%)	4 (1%)	8 (5%)	14 (1%)	8 (2%)	3 (2%)
Urinary retention[1]	1 (0.2%)	0	0	0	0	0	1 (0.1%)	2 (0.5%)	1 (0.6%)

[1]requiring catheterization

Critical Appraisal: Fesoterodine vs. Tolterodine ER

As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity. For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results).

None of the trials were rated as low risk of bias (i.e., high quality) across all assessed features (Table 6 in Appendix F). A number of domains were rated unclear, which could reflect either poor reporting in trial publications or poor methodological quality, as not enough information was provided to assess this. One of the three trials was rated 'unclear' for randomization sequence and allocation concealment (Chapple 2007) as these were not described. All three trials were rated unclear for blinding of outcome assessors as this was not explicitly stated in any of the trials. Chapple 2007 did not adequately account for discontinuations in the trial publication. However, as this information was available in the confidential CDR review, the trial was assessed on that basis.

For efficacy outcomes, 107 patients and 77 patients were removed from the efficacy analyses of Herschorn 2010 and Kaplan 2010, respectively, due to violation of good clinical practice guidelines. In addition, although these two trials had an eligibility criterion for an average of one or more urgency incontinence episodes per day, Kaplan 2010 included 10% to 20% of participants per group and Herschorn 2010 included 1% to 2% of participants who did not meet this criterion.

In two trials (Herschorn 2010; Kaplan 2010), data for incontinence episodes did not meet normality assumptions for a parametric analysis (analysis of covariance model). (The outcome of such testing is not reported in Chapple 2007 although a nonparametric sensitivity analysis was conducted.) At issue is why two steps were undertaken to address the non-normal distribution of incontinence episodes in Herschorn 2010 and Kaplan 2010 when one procedure would have been sufficient. A Winsorized mean was first

calculated, which eliminates outliers. This technique replaces 5% of the sample distribution tails with values at the 5th and 95th percentile. The investigators then compared Winsorized means by calculating p values with the nonparametric Van Elteren's test for change from baseline. The latter test introduces stratification (by quartile for incontinence severity at baseline). Both procedures are considered more liberal than parametric modeling (Common Drug Review 2012). In a sensitivity analysis, for one trial (Kaplan 2010), CDR reviewers found that the difference between fesoterodine 8mg and tolterodine was only significant when both tests were used, and not if Winsorized means alone were compared. The results should therefore not be considered significant for Kaplan 2010, one of the two trials using non-parametric analyses.

Adjusted means were reported selectively in the publications. As noted in the CDR review, the reported mean difference (least square mean difference based on ANOVA model) in Chapple 2007 was -0.48 (95% CI -0.92 to -0.05) for incontinence episodes change from baseline per 24 hours, but the statistical plan for both Herschorn 2010 and Kaplan 2010 (for a sample size calculation based on the Chapple 2007 study) used an unadjusted mean difference of 0.44 (SD 2.36). The CDR review points out that the manufacturer selectively reported the adjusted, and marginally statistically significant value when reporting the results of this trial rather than the smaller unadjusted value (Common Drug Review 2012).

A number of analyses on fesoterodine vs. tolterodine (e.g., QoL for two trials) were post hoc and exploratory only.

All three trials used last observation carried forward (LOCF) for missing bladder diary outcome (except in the case where only baseline data were available). This was appropriate in that missing bladder diary data was in the range 3% to 8% and there was no specific pattern for missing data. Sensitivity analyses with per protocol datasets yielded similar results (Center for Drug Evaluation and Research NDA 22-030).

Each trial had a run-in placebo phase. Antimuscarinic drug trials for OAB are known to have a substantive placebo response. Although the focus of this review is active drug comparisons, screening out placebo-responsive individuals may have resulted in more favorable results for active drug versus placebo comparisons.

Harms: Trials were statistically under-powered to detect differences in serious but relatively uncommon events. Active surveillance of harms was not conducted in any of the trials. No trials specifically measured effects on cognition.

The short-term trials provide no information on the consequences of taking either drug on a chronic basis and no evidence with which to assess a therapeutic advantage for either drug in the long-term.

Applicability

Participants in the trials were highly selected with screening out of patients at higher risk for adverse events (e.g., patients with co-morbidities who may have an increased anticholinergic load; subjects with a post residual void volume of > 100 mls who are at increased risk of urinary retention). It is also noted that a higher percentage of patients were screened with each successive trial (up to 40% of those screened for Kaplan 2010). The selection process limits the generalizability of findings to patients routinely encountered in clinical practice who are likely at more risk of adverse events. Placebo responders were also screened out, as noted above, which would be expected to lead to an overestimate of drug versus placebo differences as compared with an unselected clinical sample.

No trials specifically enrolled patients in long-term care, who are more likely to be frail elderly and susceptible to AE. For the two largest trials, approximately a third of participants were 65 years or older.

No trial reported data separately for the elderly. We were therefore unable to conduct a subgroup analysis by age.

The majority of participants in the three trials were women. It is not clear how generalizable findings are to both sexes. Men represented about 20% of participants and were not reported on separately. Men with benign prostatic hypertrophy (BPH) can have lower urinary tract symptoms that overlap with OAB syndrome. If the etiology of symptoms in men is not adequately investigated, there is a risk of misdiagnosis, with implications for effectiveness of treatment because fesoterodine and tolterodine have not been shown to be effective against BPH.

Most participants were Caucasian in the three trials, and findings may not be generalizable to diverse racial/ethnic groups. Different populations may have different proportions of individuals with poor or intermediate CYP 2D6 rates of metabolism of 5-HMT due to genetic variants.

Only one trial included a fesoterodine 4mg arm, and a fixed dosage regimen was used in all three trials. Results obtained with fesoterodine 8mg cannot be extrapolated to the lower dosage of fesoterodine (as confirmed by Madhuvrata 2012). This may affect the generalizability of the results as flexible dosing may be frequent in clinical practice. The lower dosage of fesoterodine, used in one trial in this review, was not superior to tolterodine ER in any efficacy outcomes.

Populations were not stratified on the basis of prior response to therapy: Even though treatment history was frequently documented as a baseline characteristic, trial participants were not stratified on the basis of prior response to treatment. Conclusions could not therefore be drawn on refractory populations and responses to second-line treatment.

Dose/comparator choice: Fesoterodine 8mg showed a slight increase in efficacy as well as an increase in anticholinergic-associated adverse effects compared with tolterodine 4mg/day. This may reflect a greater anticholinergic dose as supported by pharmacokinetics data.

The sum of active drug exposure (i.e., the active moiety), in terms of peak plasma concentration, C_{max}, and area under the concentration curve over time (AUC), a measure of drug exposure, consists of two entities for tolterodine (parent drug + 5-HMT) and only 5-HMT for fesoterodine (Malhotra 2011). Taking this into account, at identical doses, average exposure to active drug is somewhat higher for tolterodine ER compared to fesoterodine because of a narrower range of exposure (less variability) with fesoterodine (Malhotra 2011). In the one trial that compared fesoterodine 4mg with tolterodine ER 4mg, there was no advantage for fesoterodine in efficacy outcomes nor AE, consistent with the pharmacokinetics findings (Malhotra 2011).

When fesoterodine 8mg is compared with tolterodine ER 4mg, there is modestly higher active drug exposure with fesoterodine (Malhotra 2011). The findings in the trials that compared 8mg fesoterodine with 4mg tolterodine ER may thus reflect a greater anticholinergic dose of fesoterodine

Industry sponsorship
All three trials were sponsored by the manufacturer of fesoterodine, the same company that sells tolterodine ER, a drug soon to come off patent. There are no independently conducted head-to-head trials for this comparison. Industry sponsorship can be a source of what has been termed ‘meta-bias’ (Lundh 2012).

RCT outcomes are summarized in Table 3, below, for the comparison fesoterodine 8mg vs. tolterodine ER, and in Table 4 in Appendix F for fesoterodine 4mg vs. tolterodine ER.

Table 3. Fesoterodine 8mg vs. Tolterodine ER Summary of RCTs

Outcome	No. of studies (No. of Participants)	Feso vs. Tol RR or mean difference	Feso vs. Tol Absolute Risk difference	Summary
All-cause mortality	3 trials (4145) 3 deaths in fesoterodine group; 0 in tolterodine group	too few events to compare	--	No data on long-term mortality Trials under-powered for short-term mortality
SAE (non-fatal)	3 trials (3873)	RR 1.84 [95% CI 1.10 to 3.08]	RD 1% [95% CI 0% to 2%]	1% more SAE with fesoterodine
Cognitive AE	0 trials	--	--	No data on cognition
Condition-Specific QoL	3 trials (3492)	SMD -0.20 [95% CI -0.26 to -0.14] (Madhuvrata 2012); equivalent to -4.6 points on a 100-point scale	--	Fesoterodine improved symptom bother more than tolterodine, but the difference is below the threshold for clinical relevance. Changes in other domains also failed to exceed the threshold for clinically important difference.
WDAE	3 trials (3873)	RR 1.60 [95% CI 1.18 to 2.17]	RD 2% [95% CI 1% to 3%]	2% more WDAE with fesoterodine
Patient-reported improvement	3 trials (3691)	RR 1.11 [95% CI 1.06 to 1.16]	7% [95% CI 4% to 10%]	7% more patients reported improvement/cure with fesoterodine
Incontinence episodes Mean reduction from baseline	3 trials (3525)	See text for discussion on parametric analysis MD -0.20 [95% CI -0.36 to -0.04]	--	On pooled analysis, fesoterodine reduced incontinence by an additional 0.2 episodes per day (range per trial 0.11 to 0.48); difference unlikely to be clinically meaningful.
Urgency	3 trials (3666)	MD -0.29 [95% CI -0.87 to -0.30]	--	Fesoterodine reduced urgency episodes by and additional 0.29 episodes per day; unlikely to be clinically meaningful
Nocturia	3 trials (3593)	-0.09 [95% CI -0.18 to -0.00]	--	Marginal difference in favor of fesoterodine is unlikely to be clinically meaningful
Total AE	3 trials (3873)	RR 1.24 [95% CI 1.16 to 1.33]	RD 10% [95% CI 7% to 13%]	10% more patients experienced one or more AE with fesoterodine
Dry mouth	3 trials (3873)	RR 1.91 [95% CI 1.69 to 2.17]	RD 14% [95% CI 11% to 16%]	14% more patients had dry mouth with fesoterodine
Headache	3 trials (3873)	RR 1.28 [95% CI 0.91 to 1.80]	--	No difference between fesoterodine and tolterodine
Constipation	3 trials (3873)	RR 1.41 [95% CI 1.03 to 1.92]	RD 1% [95% CI 0% to 3%]	1% more patients had constipation with fesoterodine
Dyspepsia	3 trials (3873)	RR 1.85 [95% CI 1.11 to 3.06]	RD 1% [95% CI 0% to 2%]	1% more patients had dyspepsia with fesoterodine

AE=adverse events; **CI**=confidence intervals; **Feso**=fesoterodine; **QoL**=quality of life; **RD**=risk difference; **RR**=relative risk; **SMD**= standardized mean difference; **Tol**=tolterodine; **WDAE**=withdrawals due to adverse events;

Supplemental data for AE

Fesoterodine vs. Placebo RCTs
We did not identify any RCTs comparing fesoterodine with oxybutynin, or any of the other drugs included in this review, that assessed cognition or exclusively enrolled an elderly population.

Placebo-controlled RCTs were therefore sought as supplemental information on AE, including cognition, in elderly populations. We report only AE data because assessment of efficacy in placebo-controlled RCTs is beyond the scope of this review.

An unpublished placebo-controlled RCT (Pfizer Protocol A0221049) is available as a full study report in the PSUR documentation.

1. Protocol: A0221049
Study Title: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Trial to Evaluate the Efficacy and Safety of Fesoterodine Flexible Dose Regimen in Vulnerable Elderly Patients with Overactive Bladder

Participants (N=566) were community-dwelling men and women who scored $\geq$ 3 on a Vulnerable Elderly Survey (VES)-13. This screening tool uses age, self-reported health, limitation in physical function, and functional abilities to identify those at increased risk for functional decline or death in the next two years (Saliba 2001). Scores $\geq$ 3 identify individuals as vulnerable (range 0-10). Note that any individual older than age 85 would score at least 3 on the basis of age alone. The study population had an average VES-13 score of 5, and an average age of 75 years.

Study exclusion criteria included a resting heart rate > 90; liver enzyme elevation; a creatinine clearance (CrCl) of 45 mls/min (later lowered to 30 mls/min) and known renal, cardiovascular or other medical history at the discretion of the investigator. People with a Mini-Mental Status Examination (MMSE) score of < 20 were excluded. The MMSE screens for cognitive impairment and has a maximum score of 30 (highest-functioning). A score of 23 or 24 would warrant investigation for cognitive impairment, and a score of < 20 corresponds to moderate or more severe impairment. The average MMSE score of participants at baseline was 28.

The majority of participants were on at least one other medication (most commonly prescribed medications were antidiabetic agents, lipid-lowering agents and antihypertensive agents), and 41% had previously taken antimuscarinic drugs for OAB.

Fesoterodine was initiated at 4mg and could be increased to 8mg at week 4 (and decreased at any time thereafter). 53% of the fesoterodine group and 64% of the placebo group increased the dose at week 4; of these, 5% and 1%, respectively, later decreased their dose.

MMSE was assessed at baseline and week 12. There was no statistically significant difference between the placebo and fesoterodine groups at week 12 although scores were slightly lower for the fesoterodine group: least squares mean difference -0.18 (standard error (SE) 0.17) (95% CI -0.51 to 0.15).

Table 4 below summarizes the AE experience of trial participants. There was no statistically significant difference in the proportion of participants with SAE. SAE in the fesoterodine group included one case each of: fall (hip fracture); femur fracture; osteoarthritis; muscular weakness; hemarthrosis; influenza; bladder cancer; coronary occlusion; urosepsis.

More WDAE occurred in the fesoterodine group. Among AE that had a higher incidence in the

fesoterodine group, the most frequent were dry mouth, constipation and urinary retention (Table 4). There were nine cases of urinary retention (3.2%) in the fesoterodine group and none in the placebo group.

There were three cases of memory impairment or confusion. Two cases of memory impairment occurred after escalation to the 8mg dose. One male had worsening of an existing memory problem; his MMSE score was 25 at baseline and at week 12, but this screening tool can miss mild or subtle changes. A female with memory impairment had a deterioration in MMSE score from 27 at baseline to 23 at week 12. One case of confusional state on 4mg fesoterodine led to withdrawal of drug. No details were provided on 3 of the 6 reported cases of psychiatric disorders and 7 of the 17 cases of central nervous disorders in the fesoterodine group.

Table 4. Selected AE in Protocol A0221049

Treatment	Placebo N=281	Fesoterodine N=281	RR or MD Feso vs. Placebo [95% CI]
Mortality	0	0	--
Total AE	120 (42.7)	158 (56.2)	RR 1.33 (1.11 to 1.56)
SAE	6 (2.1)	8 (2.8)	NS
Total withdrawals	61 (21.7%)	55 (19.6%)	NS
WDAE	14 (5.0)	26 (9.3)	RR 1.32 (1.11 to 1.56)
Temporary discontinuation or dose reduction due to AE	10 (3.6)	21 (7.4%)	RR 2.10 (1.01 to 4.38)
MMSE score Change from baseline	0.4 ± 1.98	0.09 ± 1.84	NS
Dry mouth	17 (6.0)	66 (23.5)	RR 3.88 (2.34 to 6.44)
Constipation	12 (4.3)	31 (11.0)	RR 2.78 (1.40 to 5.53)
Diarrhea	7 (2.5)	8 (2.8)	NS
Total nervous system disorders	12 (4.3%)	17 (6.0%)	NS
Dizziness	2 (0.7)	3 (1.1)	NS
Headache	5 (1.8)	7 (2.5)	NS
Psychiatric disorders	3 (1.1) (3 insomnia)	6 (2.1) (3 insomnia; 3?)	NS
Fatigue	3 (1.1)	8 (2.8)	NS
Urinary retention	0	9 (3.2%)	RD 3.2% (-0.6% to 8.1%)* RR 19 (1.1. to 324.88), P=0.04§
Falls	8 (2.8%)	8 (2.8%)	--

*Data as reported by the manufacturer in the study report; §RevMan calculation – different statistical programs may adjust differently for a zero cell.

2. Wagg 2013a (Protocol A012245)

A second 12-week, placebo-controlled, parallel group RCT enrolled men and women 65 or older (N=785) The study was stratified by age (≤ 75, > 75 years). About a third of participants were > age 75, and 47% were men. Of the men, 39-44% had benign prostatic hypertrophy. One of the eligibility criteria was a MMSE score ≥ 20. The mean MMSE at baseline was ~28 in both groups and only 5-6% had a baseline score < 25.

Fesoterodine was initiated at 4mg with options to increase to 8mg at weeks 4 and 8; 52% on fesoterodine and 66% on placebo opted for dose escalation at week 4 and similar proportions subsequently decreased

the dose at week 8 (4% fesoterodine; 3% placebo).

AE profiles were similar to previous studies when compared indirectly.

About twice as many fesoterodine-treated participants discontinued prematurely because of adverse events compared with placebo SAE were not statistically significantly different between groups although there were more in the fesoterodine group. More participants on fesoterodine experienced one or more AE compared with placebo. Dry mouth, constipation and dizziness were significantly more frequent in the fesoterodine group vs. placebo (Table 5).

Participants older than age 75 had slightly more WDAE than those younger in both treatment groups. Analysis by age group revealed similar AE profiles and incidence rates.

The published article provides incomplete information on CNS events. In the full study report (Protocol A012245 in the PSUR), a total of 7 cognitive function-related adverse events are reported in the fesoterodine group (2.0%): amnesia (1); cognitive disorders (2); confusional state (3); hallucination (1). Three participants in the fesoterodine group (0.8%) withdrew due to cognition function-related adverse events: cognitive disorder (1); amnesia (1); confusional state (1). There was one cognitive function-related AE in the placebo group: thinking abnormal (1).

MMSE score did not change from baseline to a clinically meaningful extent, and there was no difference between drug and placebo in the average magnitude of change at week 12: fesoterodine 0.24 ± 1.82 vs. placebo 0.23 ± 1.76 (reported for the total group).

Table 5. Selected Adverse Events Reported by Age Group in Wagg 2013a

AE/age	Placebo			Fesoterodine			RR Feso vs. Placebo (Total group) [95% CI]
Age	65-75 yrs n=267	>65 yrs n=126	Total n=393	65-75 yrs n=264	> 75 yrs n=128	Total n=392	
Mortality			1 metastatic colon cancer			1 abscess, appendicitis perforated	--
Total AE	91 (34.1%)	51 (40.5%)	142 (36.1%)	171 (64.8%)	73 (57.0%)	244 (62.2%)	1.72 [1.48 to 2.01]
SAE[1]	5 (1.9%)	4 (3.2%)	9 (2.3%)	10 (3.8%)	4 (3.1)	14 (3.6%)	NS
Total withdrawals	34 (12.7%)	18 (14.3%)	52 (13.2%)	50 (18.9%)	28 (21.9%)	78 (19.9%)	1.50 [1.09 to 2.07]
WDAE	15 (5.6%)	7 (5.6%)	22 (5.6%)	29 (11.0%)	17 (13.3%)	46 (11.7%)	2.10 [1.29 to 3.42]
MMSE score Change from baseline	0.23 ± SD 1.76			0.24 ± SD 1.82			--
Dry mouth	12 (4.5%)	9 (7.1%)	21 (5.3%)	101 (38.3%)	32 (25.0%)	133 (33.9%)	6.35 [4.10 to 9.84]
Constipation	5 (1.9%)	5 (4.0%)	10 (2.5%)	25 (9.5%)	10 (7.8%)	35 (8.9%)	3.51 [1.76 to 6.99]
Dizziness	3 (1.1%)	1 (0.8%)	4 (1.0%)	8 (3.0%)	6 (4.7%)	14 (3.6%)	3.51 [1.17 to 10.57]
Headache	4 (1.5%)	1 (0.8%)	5 (1.3%)	10 (3.8%)	1 (0.8%)	11 (2.8%)	NS
UTI	5 (1.9%)	2 (1.6%)	7 (1.8%)	5 (1.9%)	5 (3.9%)	10 (2.6%)	NS

Urinary retention			1 (0.3%)			5 (1.3%)	NS

Feso=fesoterodine; **MMSE**=mini-mental status examination; **NS**=difference not statistically significant; **RR**= relative risk; **SAE**=serious adverse events; **SD**=standard deviation; **UTI**=urinary tract infection; **WDAE**=withdrawals due to adverse events; **yrs**=years

[1]In the full study report safety database, 17 SAE are listed for fesoterodine, including 2 that started pre-treatment, and others that occurred within 7 days of the end of the DB RCT and continued into an open label phase.

In both these trials, the dose of fesoterodine group was flexible, resulting in about half taking the lower 4mg dose. Outcomes were reported together for the two doses, making it impossible to distinguish dose-related AE rates.

Both studies enrolled community-dwelling, high functioning individuals who had the ability to fill in bladder diaries and study-related questionnaires, and had an average MMSE score of about 28 at baseline. This limits the generalizability of the results to populations with cognitive impairment.

Non Randomized Studies

There were no non-randomized studies that compared fesoterodine to oxybutynin or to other active comparators. Our search identified two uncontrolled cohort analyses. We do not report on efficacy outcomes as RCTs provide more reliable efficacy estimates than open-label uncontrolled cohort studies.

Uncontrolled cohort analyses (2):

- Sand 2012 (secondary publications: Kelleher 2011; Scarpero 2011);
- Wagg 2013b.

Findings from published non-randomized studies

Table 6 describes study design, data source, duration, numbers and age of subjects and assessed outcomes.

Table 6. Non-randomized studies to evaluate fesoterodine

Study	Design	Data source	Duration	Fesoterodine	Assessed outcomes
Sand 2012	Uncontrolled cohort	Open-label extension study of 2 pooled RCTs (53% enrolled)*	2-3 years; mean 21 ± 12 months	N=890 Mean age: 58 ± 14 4mg or 8mg; >80% on 8mg	Total AE WDAE Age-stratified results
Wagg 2013b	Uncontrolled cohort	Open-label extension study post-RCT (82% enrolled)*	12 weeks	N=654 Mean age 72 (all >65) 4mg or 8mg; ~50% on each	Total AE SAE WDAE Age-stratified results

*% enrolled refers to numbers of RCT completers that were enrolled in the extension phase

These are both open-label extension studies following 12-week placebo-controlled RCTs (including Chapple 2007, discussed above), in which all patients were offered fesoterodine treatment. In both studies, generalizability is limited as the patient population not only met initial RCT inclusion criteria but also consists of the subset of patients who tolerated treatment initially (with either fesoterodine, tolterodine ER or placebo) and agreed to continue during an open-label extension period.

Table 7, below, summarizes results for both cohort studies, with outcomes reported separately for patients aged 65-74 and aged 75 +. There was a trend towards all adverse outcomes occurring more frequently in patients aged 75+ in Sand 2012.

Wagg 2013b also reports separately on those who had initially been randomized to placebo; this provides extra information concerning tolerability in the elderly, as this subgroup is not pre-selected for tolerance to fesoterodine during the initial RCT. Withdrawals due to adverse events, total adverse events, dry mouth and constipation occurred more frequently in patients who had previously taken placebo. These differences were most pronounced among patients aged 75+, suggesting that the strongest selection effects in patients previously randomized to fesoterodine occurred in this population group. Less frequent AE, such as SAE and urinary tract infections, occurred equally among patients previously randomized to drug and placebo.

Table 7. Adverse events reported in uncontrolled cohorts

Outcome	Sand 2012§			Wagg 2013b				
	Age 65-74 n=208 (23%)	Age 75+ N=98 (11%)	Total n=890 Mean age 58± 13	Age 65-74 prevPL* N=233	Age 65-74 prevFES* N=213	Age 75+ PrevPL* N=108	Age 75+ prevFES* N=100	Total n=654
All cause mortality	NR	NR	NR	NR	NR	NR	NR	NR
SAE	NR	NR	NR	3 (1%)	7 (3%)	4 (4%)	4 (4%)	18 (3%)
Total withdrawals *Sand, Table 3*	116 (56%)	70 (71%)	509 (57%)	24 (10%)	19 (9%)	18 (17%)	12 (12%)	73 (11%)
Total withdrawals *Sand, Fig 1*	194 (93%)	94 (96%)	839 (94%)					
WDAE	35 (17%)	26 (27%)	119 (13%)	18 (8%)	9 (4%)	15 (14%)	2 (2%)	44 (7%)
Total AE	164 (79%)	82 (84%)	679 (76%)	105 (45%)	70 (33%)	59 (55%)	26 (26%)	260 (40%)
Hyper-tension	12 (6%)	8 (8%)	36 (4%)	5 (2%)	2 (1%)	2 (2%)	0	9 (1%)
UTI	31 (15%)	19 (19%)	134 (15%)	4 (2%)	8 (4%)	0	6 (6%)	18 (3%)
Dry mouth	67 (32%)	25 (26%)	271 (30%)	63 (27%)	16 (8%)	32 (30%)	5 (5%)	116 (18%)
Constipation	17 (17%)	16 (8%)	66 (7%)	15 (6%)	4 (2%)	6 (6%)	1 (1%)	26 (4%)

AE=adverse event; **SAE**=serious adverse event; **WDAE**= withdrawals due to adverse events; **NR**=not reported; **UTI**=urinary tract infection;

***prevPL**= patients who had been randomized to placebo in the RCT before open-label extension; **prevFES** = randomized to fesoterodine

§ Breakdown of patient experience by age from Sand 2012; results are from Table 3, p126, Sand 2012, unless otherwise stated; results reporting inconsistent between and within reports of the same trial.

Study quality /risk of bias

These RCT extension studies were uncontrolled, and the patient population is highly selected, as patients met RCT inclusion criteria and any RCT participant who had withdrawn early due to adverse events, lack of efficacy or for other reasons was excluded. In Sand 2012 additional exclusion criteria were introduced at the open-label extension stage, including an absolute corrected QT interval > 500ms or individual increase >60ms compared to baseline values, and patients who completed the RCT but had AE that investigators judged to be of concern were also excluded. Wagg et al. invited all RCT completers to enroll. However, 12 weeks' duration is too short to assess long-term outcomes (despite a title referring to 'long-term safety, tolerability and efficacy').

There is no indication of active data collection on adverse events in any of the study reports for Sand 2012 (e.g. also Scarpero 2011; Kelleher 2011), or in Wagg 2013b. Studies that rely on passive reporting collect less complete data on adverse events. Both of these studies were sponsored by the manufacturer. Neither reports on mortality or addresses cognition.

Other Adverse Event Data

Case reports
No published case reports were identified.

Regulatory Data

Periodic Safety Update Reports (PSUR)

One periodic safety update report (PSUR) for fesoterodine was obtained for this review:
PSUR #8 April 20, 2011 to April 19, 2012

The time periods reported in the PSUR are:

- One year (April 20, 2011 to April 19, 2012) (all AE) – referred to as the current time period.
- Five years, dating from April 20, 2007, the international birthdate (date of first regulatory approval in any country), to April 19, 2012 (select AE only) – this is referred to as the cumulative time period.

Whenever possible, in this section we provide cumulative data or identify where it is missing.

During 2011-2012, global exposure was estimated at 241,780 patient-months, based on sales data in 25 countries. IMS marketing data from five countries, including the U.S., indicated that 37% of prescriptions for women and 68% for men are for patients aged 65 or older, and 17% of prescriptions for women and 39% for men are for patients aged 75 or older. Canadian data were not included in estimates of patient exposure or sex/age distribution.

Almost 6% of prescriptions were for the unapproved indication benign prostatic hypertrophy, an indication for which fesoterodine is ineffective (Fesoterodine Product Monograph).

There are 852 case reports identified for the one-year period, including 358 that were medically confirmed. Medically confirmed reports are defined in PSURs as those provided by health professionals, reports to regulators, events occurring in clinical trials, or reports listed in the medical literature. More detail was available for this subset of reports. Of the medically confirmed cases, 66 were for non-serious events already listed in reference safety material. The emphasis in the PSUR is on the remaining 292 cases. Over fesoterodine's five years of marketing, 1397 medically confirmed cases were reported

Deaths
Two deaths were reported in the current time period: an 84 year old male who died of esophageal cancer; and a 63 year old female with completed suicide (inquest pending at time of documentation). Two deaths had also been reported in the previous PSUR. No details are provided. The cumulative number of deaths is not provided.

Total Serious Adverse Events (Non-fatal)

155 of the 292 medically confirmed cases (as described above) for 2011-2012 were SAE. These 155 patients experienced 280 SAE, 71% of which were unlisted in product monographs or reference safety information (Appendix 7, p. 299).

In the five-year cumulative period, there were a total of 529 medically confirmed cases. These 529 patients had experienced 866 SAE, 76% of which (656) were unlisted.

In the 494 non-medically confirmed cases reported over the current one year time period, 170 cases reported one or more SAE. In the previous PSUR #7, also over a one year time period, 446 non-medically confirmed reports were identified, with 225 cases reporting $\geq$ 1 SAE. Cumulative numbers of cases with SAE are not provided for non-medically confirmed cases.

Specific AE
For some specific AE, detailed cumulative reviews are provided: amnesia/memory impairment; loss of consciousness; hallucination; hypertension; nausea. For a subset of additional AE, cumulative numbers can be calculated from the information provided although a detailed full review is not available.

Selected AE are presented below. Totals usually refer to medically confirmed cases, as these were most frequently the only cases for which cumulative information on specific AE was available.

Central nervous system and psychiatric disorders
Cognitive impairment: Cognitive-related effects are classified as either nervous system or psychiatric disorders. For example, amnesia/memory impairment is reported as a nervous system disorder, but confusion and bradyphrenia (slow thought processing) are classified as psychiatric disorders. All of these events are unlisted.

Memory impairment: A cumulative review identified 11 cases of amnesia (3) or memory impairment (8) (0.8% of total cases reported). Nine were identified as SAE.

In the pooled clinical trial database (double-blind and open-label), 3/5928 (0.05%) participants in the fesoterodine group and 0/3995 subjects in the placebo group had memory impairment. Clinical trial participants represent a highly selected patient population and are unlikely to reflect usual clinical practice. The number of participants over the age of 65 in this database is not provided.

One additional case was reported as a ‘cognitive disorder’ AE temporally related to fesoterodine.

Confusion and bradyphrenia: In a category of psychiatric disorders described as agitation, bradyphrenia, confusion and disorientation, 27 cases were identified cumulatively (1.9% of total case reports), including five in the current PSUR. These included: bradyphrenia (2); confusion (22); disorientation (2); agitation (1). 18/27 cases were regarded as SAE. The mean age of the patients in these cases (67 years) was older than the mean age of patients in the overall dataset. Of the 20 cases providing age, 17 (85%) were elderly.

Dizziness: A cumulative review identified 77 cases (5.4% of total case reports) over 5 years; 11 cases were categorized as SAE. In approximately a third of cases, dizziness resolved or was resolving following discontinuation or dose reduction. In most other cases, there was insufficient information to refute or confirm probable causality. Five cases were associated with falls, 2 of which were serious. One of the latter may have been syncopal episodes in a patient with a first degree atrioventricular heart block. Review of the database resulted in a decision to list the event in reference safety material.

Somnolence: A cumulative review identified 18 cases of somnolence, 5 of which were judged SAE. Of the 13 patients with reported age, 11 were elderly.

Hallucination: A cumulative review identified 10 cases (0.7% of total case reports) in the five-year dataset (4 female, 3 male, 3 sex not reported). Five cases with reported age were elderly. Most had potential confounding features in their medical history or concomitant medications. However, in spite of potential confounders, the three patients with follow-up information recovered following discontinuation of fesoterodine.

Loss of consciousness: A cumulative review identified a total of 6 cases (0.4% of total case reports). Patient age ranged from 59 to 91 years (mean 69) in the five cases reporting age. Details were often lacking and hampered assessment of causality or etiology. One patient was diagnosed with dysrhythmia that resolved after fesoterodine discontinuation. Another patient with multiple sclerosis was diagnosed with vasovagal syncope after respiratory arrest.
Note: although loss of consciousness is a CNS event, most of these cases were associated with cardiac disease (syncope) rather than an underlying neurological etiology.

Gastrointestinal hemorrhage: This was described in an information bulletin article analyzing spontaneously reported adverse events; see page 167.

Cardiac disorders
QT prolongation
Regulators have previously requested continued monitoring of fesoterodine for this event. Over the cumulative time period, 3 cases of QT prolongation were identified in a search for terms related to torsade de pointes/QT prolongation: EKG QT prolongation (2); heart rate irregular and QT prolonged (1).

Arrhythmias: Eleven cases related to cardiac arrhythmia were identified, including the three cases listed for QT prolongation. The additional eight cases are: arrhythmia (6); atrial fibrillation (1); supraventricular tachycardia (1).

Hypertension: there were 27 cumulative cases, and in 6 cases, there was recovery post discontinuation of fesoterodine (with 2 cases receiving anti-hypertensive medication). In the majority of other cases (15) not enough detail was provided to determine probable causality although 4 of these reported a temporal association. In 2 other cases, an association was judged unlikely; 2 did not recover post discontinuation, and in 2 other cases, fesoterodine was not temporally related.

Urinary retention: over the cumulative five year period, there were 240 cases (17% of total case reports). Of the 69 cases requiring catheterization, 41% were in men. Of the men who required catheterization, most (69%) had a history of benign prostatic hypertrophy or concomitant alpha blocker of 5-alpha reductase inhibitor.

The incidence of urinary retention in elderly in Study A0221049, the unpublished placebo-controlled RCT that was reported in the PSUR, was 3.2% (9 cases) in the fesoterodine (4-8 mg) group vs. 0% in the placebo group.

Elderly
There were 128 medically confirmed case reports in elderly patients during the one-year period, which represented the majority (65%) of medically confirmed cases with known age. However, age was unknown in 162 (45% of total) cases. Of the 128 case reports, 69 were serious (including 1 death) and 59 were non-serious unlisted AE. Age ranged from 65 to 98 (mean 75.6) years. There were more females (59%) than males (38%) in the cases that identified sex.

The most commonly reported (≥10 cases each) in the elderly were: dry mouth (21); urinary retention (20); constipation (12), drug ineffective (11), and dizziness (10). Of the 20 cases with urinary retention, 16 were in males.

Constipation was the only event reported in the one year period that had a ≥ 3-fold difference in reporting rates in the elderly (≥ age 65 years) compared with non-elderly. There were no events reported by a particular organ class system (SOC) that had a greater than 3-fold difference between age groups.

A separate review in elderly males was conducted, with no new safety information identified.

Long term use: Limited data were available to assess longer duration use. Almost 90% of case reports did not report duration of use, with insufficient data to draw conclusions about longer-term AE profiles. Only one medically confirmed case report is highlighted as having duration longer than 9 months prior to the event. The patient had a history of scleroderma and the event (dry throat, dysphagia, throat tightness and choking) resolved following drug discontinuation. One SAE also lists one-year duration of use (vomiting, neutropenia, abdominal pain and diarrhea); this case was more likely related to cetuximab toxicity.

Based on this PSUR, the following events were listed in the reference safety material:

- Dizziness
- Rash

The following AE are to be reviewed and discussed in future PSURs: QT prolongation; rhythm disorders; elevated liver enzymes; cognitive function impairment; urinary retention; angioedema; anaphylactic reactions; severe cutaneous adverse events; other relevant skin events. The following AE are to be reviewed but not discussed unless new information is identified: blurred vision; nausea; vomiting; stomatitis; gastroesophageal reflux; edema; loss of consciousness; hallucination; depression/depressed mood; renal failure; hypertension/blood pressure increased.

Changes to Reference Safety Information

In addition to decisions to list dizziness and rash as AE, two changes were made to fesoterodine's reference safety information during the one-year time period covered by the PSUR (see below for 'US FDA - post-market labeling changes' for changes prior to and after PSUR 8#). The additions represent harms not identified by the initial RCTs.

Changes made:

Special warnings and precautions

- Angioedema added. Angioedema has been reported with fesoterodine and has occurred after the first dose in some cases. If angioedema occurs, fesoterodine should be discontinued and appropriate therapy should be promptly provided.

Undesirable effects

- urticaria and pruritus added

Canada Vigilance Adverse Reaction Online Database

Six adverse reaction reports related to fesoterodine are in the Health Canada Vigilance database, as of Dec 31, 2012, the most recent date of entry of the database. None overlap with the available PSUR.
The low number in comparison to other antimuscarinic drugs likely reflects the short time fesoterodine has been available in Canada.

Deaths: No fatal SAE have been reported.

Non-fatal SAE: Five reports are described as serious. They were: life-threatening anaphylactic shock (1); urinary retention (1); asthma (1); dizziness/somnolence/gait disturbance (1); depression/ activities of daily living impaired/pain (1).

Other (non-serious) AE: The sixth report was anxiety/discomfort/dysuria in an 88 year old male.

World Health Organization VigiBase – Gastrointestinal Hemorrhage

The World Health Organization (WHO) International Monitoring Centre for drug safety in Uppsala, Sweden, reported a signal of gastrointestinal haemorrhage associated with fesoterodine in 2012, based on 7 reports (Hill 2012) Time to onset was less than one week following treatment initiation in 4 of the 7 cases and patients recovered following drug dechallenge in 5 cases. A signal of gastrointestinal bleeding had initially been detected in an analysis of electronic health records in the U.K. and was confirmed through mining of data in the Uppsala Monitoring Centre's international database (VigiBase), which contains over 7 million reports. All of the patients were women. Age was reported for 5 patients (range 62 to 69). The reports were from Germany (2), the U.S. (2), Netherlands, Switzerland and the U.K.

Two plausible mechanisms are proposed. The first is reduced gastric motility leading to increased exposure to concomitant drugs and other gastric irritants. Five of the patients were taking drugs identified as leading to gastric irritation: aspirin, diclofenac, oxycodone, tramadol and bendroflumethiazide. The second potential mechanism is chronic constipation and increased sequelae such as hemorrhoids, which may result in bleeding. The report cites a doubling of risk of constipation with fesoterodine in a meta-analysis of placebo-controlled trials: Odds ratio (OR) =2.1 (95% CI 1.3 to 3.4); 4 trials (n=2614) (Meek 2011). The report also notes gastrointestinal hemorrhage has previously been reported in association with tolterodine (Garely 2004).

In response to detection of the signal in the WHO database, the manufacturer conducted a cumulative review in fesoterodine's safety database up to May 28 2012. Of a total of 3446 case reports, 17 (0.5%) were gastrointestinal hemorrhage-related events. Events included: diarrhea hemorrhagic (1); gastric hemorrhage (1); gastrointestinal hemorrhage (3); hematemesis (2); hematochezia (5); rectal hemorrhage (2); ulcer hemorrhage (3). The clinical database of all completed double-blind and open label Phase 2-4 trials was also searched. Of 9762 subjected exposed to fesoterodine, 16 (0.2%) reported relevant events. In double blind trials, 7/6132 (0.11%) of subjects exposed to fesoterodine and 7/3993 (0.18%) subjects exposed to placebo reported events. The events in subjects exposed to fesoterodine were: anal hemorrhage (1); gastrointestinal hemorrhage (1) hematemesis (1), hematochezia (4), hemorrhoidal hemorrhage (1), occult blood positive (1), rectal hemorrhage (7). In subjects for whom patient profiles were available, constipation was reported in a minority of cases, 2/15 subjects exposed to fesoterodine and 2/6 subjects exposed to placebo.

U.S. FDA - post-market labeling changes

The U.S. FDA provides a record of all changes made to the U.S. label in the post market time period. These changes include (but are not limited to) the following:

- Warnings and precautions: CNS effects including headache, dizziness and somnolence (08/2012)
- Contraindications: hypersensitivity to tolterodine (02/2011)
- Warnings and precautions: angioedema (10/2011)
- Warnings and precautions: concomitant administration of CYP 3A4 potent inhibitors – doses greater than 4mg are not recommended (10/2011)

- Post market adverse events (added at various times)
    - Blurred vision;
    - Palpitations;
    - Hypersensitivity reactions, including angioedema with airway obstruction, face edema;
    - Dizziness, headache, somnolence (08/2012)
    - Urticaria, pruritus

Of the changes listed above, the Canadian product monograph (last accessed June 9, 2013) does not include the warnings and precautions related to CNS effects nor does it list the CNS adverse events dizziness, headache and somnolence in post market experience.

Discussion and Conclusions

Q1: Does fesoterodine provide a therapeutic advantage over oxybutynin IR or other comparators included in this review?

There is no evidence available for comparisons of fesoterodine with oxybutynin (IR, ER or transdermal), solifenacin, darifenacin or trospium. No conclusions can be drawn on comparative effectiveness or safety.

Three randomized controlled trials compared fesoterodine 4mg/d and 8mg/day with tolterodine ER 4mg/day, including 5235 patients in total.

There were no differences in beneficial or harmful outcomes between fesoterodine 4mg/day and tolterodine ER 4mg/day.

On average, 7% more patients on fesoterodine 8mg/day reported improvement or cure. Patients on fesoterodine 8mg experienced one fewer urgency episode per 3.4 days, one fewer urgency incontinence episode per 5 days, and one fewer nocturia episode per 11 days than patients on tolterodine ER. Patients on fesoterodine also did better on symptom bother, based on validated condition-specific quality of life measures, although the difference was below a threshold for minimal clinically important differences (standardized mean difference of 0.20 points, equivalent to 4.6 points on a 100-point scale).

On the other hand, 14% more patients on fesoterodine 8mg experienced dry mouth, 10% more experienced an adverse event of any sort, 2% more withdrew due to adverse events, 1% more experienced constipation, 1% more experienced dyspepsia, and 1% more experienced serious adverse events, as compared with patients on tolterodine ER.

In summary, there is no documented therapeutic advantage from use of fesoterodine 4mg/day or 8mg/day as compared with tolterodine ER 4mg/day. These modest differences in benefit for fesoterodine 8mg/day fail to outweigh increased harm. In general, differences are consistent with a stronger antimuscarinic effect from fesoterodine 8mg/day vs. tolterodine ER 4mg/day.

There are no comparative RCT data in the frail elderly, and the maximum duration of RCTs was 12 weeks, too short to draw any conclusions about longer-term consequences. The trials were not statistically powered to detect potential differences in mortality or serious morbidity. The finding of a 1% increase in serious adverse events with fesoterodine 8mg/day on meta-analysis of the 12-week trials is especially of concern because of the short-term duration of these trials, and the relatively healthy and younger patient populations included, as compared with usual clinical care.

There are no long-term comparative observational studies. One uncontrolled cohort analysis of up to 2 years' duration provides limited data, as only 98 patients over the age of 75 were included, 96% of whom withdrew early.

Independently conducted trials are needed to answer questions about use in elderly including the frail elderly, patients with co-morbidities, and patients who are refractory to oxybutynin. Such trials must include a placebo treatment arm because of the placebo effect in OAB.

Comparison with existing systematic reviews: We incorporated some of the data provided in Madhuvrata 2012 in this review (condition-specific QoL; urgency; incontinence). Other results are consistent with Madhuvrata 2012 and Shamliyan 2012, an AHRQ systematic review focused on community-dwelling women. The current review extends the Cochrane review (Madhuvrata 2012) by addressing what a minimal clinically important difference is for the included outcomes, and adding the outcome nocturia.

We did not compare dosages of fesoterodine. However, a prior systematic review assessed dosages of fesoterodine and included four trials that compared 8mg with 4mg fesoterodine. That review concluded clinical efficacy (patient-reported improvement/cure, incontinence episodes and frequency) was better with 8mg than 4mg but was associated with a higher risk of dry mouth (Madhuvrata 2012). There was no difference in QoL between the two dosages.

Q2. New Clinical Evidence since CDR Review

There has been one CDR Review on fesoterodine, dated September 2012. The CDEC Final Recommendation, dated October 18, 2012, was to list fesoterodine in a similar manner as tolterodine.

The CDR Review included three direct comparator RCTs, all comparing fesoterodine to tolterodine ER:

- SP583, corresponding to Chapple 2007;
- Trial A0221008, corresponding to Herschorn 2010;
- Trial A0221046, corresponding to Kaplan 2010.

Placebo-controlled trials in elderly patients included:

- Wagg 2013a (in conference abstract form, now published; fesoterodine vs. placebo)
- DuBeau 2012 (in conference abstract form, now published; pooled studies, fesoterodine vs. tolterodine ER)
- Kraus 2010 (pooled studies, fesoterodine vs. placebo; did not meet this review's inclusion criteria)

We identified one new placebo-controlled crossover trial that evaluated cognitive function in 18 healthy elderly volunteers after 6 days of fesoterodine (Kay 2012). Based on a battery of cognitive tests, the study did not detect an effect of fesoterodine 4mg or 8mg on cognition vs. placebo, in contrast to an acutely sedating dose of 1mg of alprazolam, a benzodiazepine. The findings of this study cannot be used to draw conclusions about a therapeutic advantage of fesoterodine over other antimuscarinic drugs. The study provides insufficient evidence to conclude fesoterodine does not affect cognition.

Two uncontrolled cohort analyses were also identified in the current review that were not part of the CDR review as the latter is restricted to RCTs only (Sand 2012; Wagg 2013b). These cohorts reported separately on elderly populations. Both were extension phases of RCTs, one of which was included in this review (Chappell 2007). The participants of the uncontrolled cohorts were highly selected, having first been screened for RCT enrolment and then for tolerating treatment for the duration of the RCT prior to the

open label uncontrolled phase. Withdrawals due to adverse events, total adverse events, dry mouth and constipation occurred more frequently in patients who had previously taken placebo. These differences were most pronounced among patients aged 75+, suggesting that the strongest selection effects in patients previously randomized to fesoterodine occurred in this population group. The selection process limits the generalizability of the research findings to elderly people in community or nursing home settings.

The available PSUR (April 2011 to April 2012) reveals a similar adverse event profile as other antimuscarinic drugs and also cannot be used to draw conclusions about whether fesoterodine has fewer or more adverse events than comparator drugs. Available pharmacovigilance databases are predominantly voluntary reporting systems. These data cannot be used to calculate AE incidence rates due to the large extent of under-reporting of AE, and the wide variation in reporting rates over time and in different health care settings, depending on a range of factors such as national pharmacovigilance systems, health professional and consumer education, and media coverage of harmful drug effects. This supplemental AE information does not modify the conclusions of the CDR Review.

Conclusion: Since completion of the CDR review in October 2012, there is no substantive evidence available that would lead to a difference in recommendation as compared with the CDR review, with respect to either comparative effectiveness or safety of fesoterodine versus other antimuscarinic drugs. For most of the drugs in this class, no comparative evidence exists. The additional non-randomized studies included in this review were uncontrolled cohort analyses, a weak methodology that limits interpretability of results.

Q3. Cognition

We did not identify any RCTs that compared the short- or long-term cognitive effects of fesoterodine with another antimuscarinic drug.

One placebo-controlled RCT was identified in 20 healthy volunteers (efficacy analysis on 18 of the 20) (Kay 2012). This was a double-blind, double-dummy four-way crossover trial that compared fesoterodine 4 mg and fesoterodine 8mg (3 days of 4 mg, then 3 days of 8mg fesoterodine) with placebo after 6 days of treatment. All participants were elderly (mean age 72, range 65 to 85) with normal cognition on a Mini-Mental Status Examination (mean score 29). A battery of proprietary computer-based cognitive tests and the Rey Auditory-Verbal Learning Test, a test of global cognitive function (Callahan 1994), were conducted on day 6. The primary endpoint was the Detection task, a simple reaction time test during which subjects must respond as quickly as they can to a series of visual stimuli in the middle of a computer screen, and press an appropriate key. The primary outcome for this test is the number of correct responses expressed as a percentage of the total trials. Measures of effect size express the difference between the test group mean and a control group mean as a function of their pooled standard deviations (Maruff 2009).

The positive control in this trial (the fourth treatment arm) was a 1mg dose of alprazolam (Xanax) on day 6. This dose of alprazolam is much higher than the recommended starting dose for the elderly (0.125mg) (Alprazolam (Xanax) Product Monograph), and 63% of patients complained of sedation or somnolence. Not surprisingly, participants on the acutely sedating dose of alprazolam had deterioration in cognitive task scores compared with placebo.

There were no statistically significant differences in change from baseline between placebo and either dose of fesoterodine across the battery of cognitive tests. Reported AE for fesoterodine were dry mouth in 10% of patients on 4mg and 32% of patients on 8mg. Dizziness was experienced by 5-10% of patients on

fesoterodine and 21% of patients on alprazolam. No patients on fesoterodine complained of sedation or somnolence.

A per protocol analysis was carried out, including results from the 18 patients (90%) who completed the trial. Although the study was blinded, the acutely sedating effects of alprazolam were likely to break blinding. Additionally, one-third of patients at the 8mg dose of fesoterodine experienced dry mouth, which would also have affected blinding. There is no information provided in the paper about the sensitivity or validity of the administered cognitive tests, or how the minimal clinically meaningful difference was derived, limiting the interpretability of the study. The only conclusion from this study is that fesoterodine, in the short-term, does not impair the ability to carry out cognitive tasks to the same extent as a high dose of alprazolam. This was a healthy volunteer study, and results may not be directly applicable to elderly with overactive bladder syndrome and to elderly who have cognitive impairment.

The study provides no information on potential effects on cognition from chronic use.

Conclusion: There is insufficient evidence to draw conclusions about fesoterodine's effects on cognition, as compared with oxybutynin or any of the other comparators in this review. There is no evidence of any therapeutic advantage for fesoterodine in terms of effects on cognition.

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Fesoterodine vs. Placebo RCTs (focus on elderly or cognition only)

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Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part III

Solifenacin versus Oxybutynin and Other Antimuscarinic Drugs for Overactive Bladder Syndrome

Part III - Table of Contents

Solifenacin versus Oxybutynin and Other Anti-Muscarinic Drugs for Overactive Bladder Syndrome

Executive Summary

Solifenacin (Vesicare®) is a competitive antimuscarinic antagonist that binds to all five muscarinic receptor subtypes, but has more affinity for binding to M3 receptors (the receptor subtype predominantly involved in bladder contraction) than M1 and M2 receptors. Solifenacin was approved in Canada in 2006, with the most recent Canadian Drug Expert Committee Recommendation dated June 17, 2009. It is a long-acting drug (half-life 45-60 hours). Solifenacin is extensively metabolized in the liver by CYP 3A4 enzyme, and predominantly excreted by the kidneys. The majority of the drug's clinical activity is due to the parent drug.

Research Questions:

Q1. In adults, including the frail elderly, does solifenacin (Vesicare®) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) or other antimuscarinic drugs, for the treatment of overactive bladder syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that solifenacin improves clinically relevant outcomes or has a better safety profile compared to oxybutynin IR, other formulations of oxybutynin, or other antimuscarinic drugs under review?

Q3. In adults, particularly the elderly, does solifenacin have less effect on cognition when compared to oxybutynin IR, other formulations of oxybutynin or other antimuscarinic drugs under review?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included direct comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and (short-term) harms.

Placebo-controlled trials exclusively enrolling elderly patients or assessing cognition were also included as supplemental information on harms in the absence of direct comparator RCTs. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement the RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the

patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

Results: Nine RCTs met inclusion criteria:

- 3 compared solifenacin vs. oxybutynin IR (Herschorn 2010; Wagg 2013; Wesnes 2009);
- 5 compared solifenacin vs. tolterodine extended release (ER) or IR: 5 RCTs (Ho 2010; Choo 2008; Chapple 2005; Chapple 2004a; Chapple 2004b);
- 1 compared solifenacin vs. darifenacin (But 2012).

All trials were short-term (4-12 weeks). Of the three trials identified for the comparison of solifenacin with oxybutynin, only one trial enrolled patients with OAB syndrome. The other two tested cognitive effects in healthy volunteers and are included in Q3 only.

An additional three non-randomized studies were included to assess harms. Adverse event data were further supplemented by available case reports, regulatory data and pharmacovigilance data.

Q1: Does solifenacin provide a therapeutic advantage over oxybutynin IR or other comparators?

Solifenacin vs. Oxybutynin IR

A fixed dose of solifenacin, 5mg once daily, was compared with oxybutynin IR 5mg t.i.d. (15mg total/day) in the one trial that enrolled patients with OAB syndrome (Herschorn 2010) and was considered for Q1. The trial was small (132 patients), eight weeks in duration, and had a primary outcome of dry mouth. The study was at high risk of bias on the basis of the different rates of early withdrawals between groups, and the use of per protocol analyses.

Solifenacin-treated patients (5mg/day) had fewer withdrawals due to adverse events (WDAE) (absolute risk difference 15%), fewer adverse events (AE) overall (absolute risk difference 20%), and less dry mouth (absolute risk difference 48%) than patients on oxybutynin IR (total 15mg/day). In this trial, a higher proportion of patients in the oxybutynin group reported dry mouth (83%) than in other studies included in this review. This may have reflected sensitization of patients to the outcome and over-reporting. On the other hand, trials that passively collect data may under-report. Patients on solifenacin experienced more constipation than those on oxybutynin IR but the difference was not statistically significant.

Solifenacin showed a trend for less efficacy than oxybutynin for most efficacy outcomes including patient-reported outcomes (quality of life (QoL), patient perception of bladder condition (PPBC), reduction in incontinence episodes, and nocturia). The difference in efficacy was statistically significant for only one outcome (PPBC), in favour of oxybutynin IR, with the small difference of uncertain clinical meaningfulness (on average, 0.5 points on a 6-point scale).

A post hoc subgroup analysis on age ($\leq$ age 65 and > age 65) did not detect a significant treatment-age interaction for dry mouth (Herschorn 2011). The trial was not stratified at the time of randomization by age and the trial was not statistically powered to detect differences between subgroups. This analysis is therefore observational and exploratory only. AE profiles and discontinuations due to AE appeared similar in both age subgroups but numbers were small, with only 27 patients $\geq$ 65 on solifenacin and 30 patients $\geq$ 65 on oxybutynin in this trial.

As the comparison was based on a single trial of low quality, evidence is insufficient to conclude whether solifenacin has a therapeutic advantage (incorporating benefit and harm) over

oxybutynin IR. The high rates of dry mouth and total AE on oxybutynin in this trial raises concerns about the profile of harmful effects with this dose and formulation of oxybutynin.

There are no available trials that compare an extended release formulation of oxybutynin with solifenacin. An extended release formulation is a more appropriate comparison, given solifenacin's long half-life. Extended release formulations have less fluctuation of drug plasma concentrations and oxybutynin ER has been shown to have a lower incidence of dry mouth compared with the immediate release formulation.

Solifenacin vs. Tolterodine ER or IR

For the comparisons of solifenacin vs. tolterodine, there were five trials, two comparing solifenacin with tolterodine ER (Ho 2010; Chapple 2005), and three comparing solifenacin with tolterodine IR (Choo 2008; Chapple 2004a; Chapple 2004b).

Four trials included separate treatment arms for 5 and 10mg (Ho 2010; Choo 2008; Chapple 2004a; Chapple 2004b), and one trial used a flexible-dose regimen of 5-10mg (Chapple 2005). We did not consider doses lower or higher than the standard doses (range 5-10mg).

Solifenacin 5mg or 5/10mg flexible dose led to more dry mouth than tolterodine ER but less than tolterodine IR. There was more constipation with solifenacin (5mg or 5/10 flexible dose) compared with either formulation of tolterodine. For urgency incontinence episodes, when both formulations of tolterodine were pooled, solifenacin (5mg or 5/10 flexible dose) reduced incontinence by an additional half episode per day: MD -0.54 (95% CI -0.82 to -0.26) compared with tolterodine. Solifenacin also reduced urgency by an additional half episode per day compared with either formulation of tolterodine.

The quality of evidence for this comparison is moderate. In general, analysis of solifenacin vs. tolterodine was hampered by outcome under-reporting (e.g., measures of variability and denominators for evaluable patients were not consistently reported) as well as the non-parametric nature of some of the data. Because of this, data for meta-analysis were not available for several outcomes.

Comparison with each tolterodine formulation

Solifenacin vs. tolterodine ER: Solifenacin 5/10mg and tolterodine ER (4mg/day) had similar WDAE and total AE, but 6% more patients on solifenacin experienced dry mouth, and 4% more patients had constipation compared with tolterodine ER. In the largest trial, Chapple 2005, solifenacin 5/10 reduced incontinence episodes to an additional 0.6 episodes per day compared with tolterodine ER, and 9% more patients achieved continence (3-day time period). Differences for both benefit and harm are modest. There was no difference in nocturia. The use of a flexible dosing regimen for solifenacin obscures the extent of dose-response and may underestimate the differential AE profile of the two drugs. The overall strength of evidence is moderate.

Solifenacin vs. Tolterodine IR: Both drugs had similar WDAE and total AE, but solifenacin 5mg was associated with less incidence of dry mouth than tolterodine IR (total 4mg/day) (absolute risk difference 7%). However, the occurrence of dry mouth with solifenacin 10mg was similar to tolterodine IR, reflecting the known dose-response with solifenacin (Madhuvrata 2012). Both doses of solifenacin increased the rate of constipation (absolute risk difference 5% for 5mg and 7% for 10mg) compared with tolterodine IR.

Solifenacin 10mg reduced incontinence episodes by an estimated additional half an episode a day, compared with tolterodine IR, but the difference was not statistically significant. There was no

difference in nocturia. One trial provided adequate data to estimate absolute differences in rates of urgency; both drugs reduced urgency by 2-3 episodes per day from a baseline of 5-6. However, solifenacin reduced average urgency episodes by an additional 0.8 (5mg) or 1.0 (10mg) episodes compared with tolterodine IR.

Overall, there is more dry mouth with tolterodine IR vs. solifenacin but less constipation, with a similar magnitude of effect for each adverse event. The magnitude of differences in efficacy outcomes is small. The overall strength of evidence is moderate.

Solifenacin vs. Darifenacin CR
One non-blinded trial compared solifenacin 5mg vs. 7.5mg darifenacin CR in women with urgency (But 2012). Efficacy outcomes included urgency and nocturia but not incontinence (But 2012). The quality of the trial is poor.

The trial was small (77 patients), termed 'exploratory' by its investigators, without sample size or power calculation (recruitment goal =100). It was open-label and therefore at high risk of performance and detection bias, particularly for subjective outcomes. It is unclear if all outcomes are reported and none are identified as pre-defined. The withdrawal rate was 21% and did not differ per study arm. A per protocol rather than intention-to-treat analysis is reported and it is likely that patients who withdrew differed from completers. AE are incompletely reported.

Conclusions cannot be drawn from this trial due to its methodological limitations. There is insufficient evidence to determine whether solifenacin has a therapeutic advantage over darifenacin.

Comparison with other systematic reviews: Our findings from RCTs are consistent with prior reviews (Madhuvrata 2012; Shamliyan 2012). Compared with the recent Cochrane review (Madhuvrata 2012), we had additional information for at least one trial (Herschorn 2010), adjusted evaluable patient denominators for at least one trial, and identified an additional trial for the comparison solifenacin vs. darifenacin. Although we did not assess dose comparisons, the RCT data included in this review are consistent with evidence of an anticholinergic AE dose response for solifenacin, as evaluated in Madhuvrata 2012.

Supplemental AE data: No comparative non-randomized studies were identified. Three uncontrolled cohort analyses were identified (Michel 2008; Garely 2006; Haab 2005). Two were short-term (12 weeks) (Michel 2008; Garely 2006) and the other was a 40-month post RCT extension trial that confirmed a dose response for anticholinergic effects such as dry mouth and constipation (Haab 2005).

Signals highlighted in the available Periodic Safety Update included a signal for muscle weakness and a possible signal for Parkinson's disease. Events targeted for further monitoring by the manufacturer also include cardiac events such as arrhythmias, and interstitial lung disease. Because of the limitations of voluntary reporting systems, such data can be used for signal detection only and not incidence rates.

Of particular concern with solifenacin is that it has the longest half life of available antimuscarinic drugs, and there is a need to adjust the dose for patients with kidney or hepatic impairment. This concern exists for all extended-release forms but particularly so for this drug. Because the drug is used in the elderly, the long half-life may increase the risks of drug-drug interactions and adverse events, and lead to longer duration of AE following discontinuation of the drug.

Gaps in Evidence: There is no available evidence to assess the long-term benefits and harms of solifenacin as compared with other drugs in this review.

None of the trials assessed patients who are refractory to, or intolerant of, oxybutynin IR.

There continues to be insufficient evidence on comparative, cognitive effects in both the short- and long-term in OAB patients.

There is need for well-conducted, independent direct comparator trials. All available trials for comparing solifenacin to other drugs were industry-sponsored. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007).

Because of the substantive placebo response in OAB, trials should include a placebo arm. While some of the available trials did so, they also had placebo run-in phases that would have screened out placebo responders, leading to an overestimate of the effect of active drug in any comparison of active drug vs. placebo, and limiting generalizability to usual practice.

Q1 conclusions
In summary, evidence is sparse for the comparison of solifenacin with oxybutynin IR, of low quality, and insufficient to conclude whether solifenacin has a therapeutic advantage over oxybutynin IR, incorporating both benefit and harm. However, the evidence is suggestive of a potential therapeutic advantage and needs to be verified in larger better quality studies.

There is no evidence of an advantage for solifenacin versus tolterodine IR or ER, insufficient evidence to judge effects versus darifenacin, and no comparisons with trospium or fesoterodine.

Q2. New Evidence since CDR Review

There have been two submissions to CDR, a 2009 resubmission and the original submission considered January 24, 2007. The CDEC resubmission recommendation (dated May 20, 2009) was to list solifencin for patients who cannot tolerate or have an insufficient response to an adequate trial of immediate-release oxybutynin, and to list in a similar manner as drug plans list tolterodine.

A total of six active comparator RCTs are identified in the 2009 CDR review:

- Herschorn 2010 (VECTOR clinical study report) (solifenacin vs. oxybutynin IR)
- Choo 2008 (solifenacin vs. tolterodine IR)
- Chapple 2004a = Study A005 (solifenacin vs. tolterodine IR)
- Chapple 2004b = Study A015 (solifenacin vs. tolterodine IR)
- Chapple 2005 = STAR trial (solifenacin vs. tolterodine ER)
- Wesnes 2009 = SCOPE trial – included as supplemental information on cognition as it is a healthy volunteer RCT.

In the current review, we identified three additional direct comparator RCTs plus one additional subanalysis:

- Wagg 2013 (solifenacin vs. oxybutynin IR), N = 26 – assessing cognition in the elderly;
- Ho 2010 (solifenacin vs. tolterodine ER), N = 75
- Chapple 2007 (solifenacin vs. tolterodine ER, predefined subanalysis of the STAR trial at 4 weeks, a time point when all participants in the solifenacin group were taking 5 mg/day)
- But 2012 (solifenacin vs. darifenacin), N = 77

The additional RCTs do not provide evidence that would modify the conclusions of the CDR 2009 review substantively. However, we note that the CDEC recommendation for listing for patients who are refractory or intolerant of oxybutynin IR is not based on evidence in the CDR review, and there continue to be no RCTs specifically assess populations refractory or intolerant of oxybutynin IR.

Q3. Comparative Cognitive Effects

Two placebo-controlled crossover trials were identified that compared the effect of solifenacin and oxybutynin IR on cognitive function in elderly volunteers (Wagg 2013; Wesnes 2009).

A three-way crossover pilot study, tested cognitive function before and after single doses of solifenacin 10 mg, oxybutynin IR 10 mg and placebo in 12 healthy, elderly volunteers (Wesnes 2009). The dose of oxybutynin IR is twice the recommended maximum single dose and is therefore an inappropriate dose for comparative analysis.

In the second study, Wagg 2013 compared the cognitive effects of solifenacin 5 mg daily with oxybutynin 5 mg b.i.d (10 mg total/day) and placebo in 26 men and women, aged 75 years or older, who had mild cognitive impairment, at steady state (21 days of treatment). At estimated peak dose level (6 hours for solifenacin and 2 hours for oxybutynin), there were no statistically significant changes from baseline when each drug was compared with placebo. The authors did not carry out any statistical analyses directly comparing the two active drugs. Post hoc analyses were performed pooling time points but are exploratory only. Drug levels were not measured. This trial provides insufficient evidence upon which to draw conclusions about the relative short-term cognitive effects of solifenacin vs. oxybutynin IR.

There are no available studies of solifenacin in OAB patients that were adequately powered for central nervous system effects or actively assessed cognition. In particular, there are no studies that compare the longer-term effects of solifenacin with oxybutynin, or any other antimuscarinic drug.

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Chapter 6. Solifenacin vs. Other Anti-Muscarinic Drugs Systematic Review

Background

Solifenacin was first introduced onto the market globally in 2004, and was first approved for market entry in Canada in 2006. The information in Box 1, below, is derived from the Canadian Product Monograph.

Box 1: Solifenacin Succinate Product Information

Categorization: urinary antispasmodic agent

Indication: treatment of overactive bladder in adults with symptoms of urge urinary incontinence, urinary urgency and urinary frequency

Recommended Usual Dose: 5mg once daily; if 5mg is well tolerated, the dose may be increased to 10mg once daily

Mechanism of Action: competitive muscarinic receptor antagonist

Source: Solifenacin Succinate Canadian Product Monograph, dated September 10, 2012

Solifenacin is a muscarinic receptor antagonist with a half-life of 45 to 68 hours, and is predominantly excreted by the kidneys. Solifenacin has greater affinity for binding to M3 receptors (the receptor subtype predominantly involved in bladder contraction) than M1 and M2 receptors in experiments. However it binds to all five muscarinic receptor subtypes and is not as selective for the M3 receptor as darifenacin is (see Chapter 1, Table 7 on p. 59 for ratios of M3:M1 binding for each drug). The clinical significance of this minimal selectivity for the M3 receptor has not been established. In preclinical studies, solifenacin is reported to have more tissue selectivity for the bladder rather than salivary glands although the basis for this and the clinical meaningfulness of these findings have not been established. Solifenacin is extensively metabolized in the liver by CYP 3A4 enzyme although alternate metabolic pathways exist. The majority of clinical activity is due to the parent drug. Renal insufficiency prolongs its apparent half-life and increases exposure to solifenacin (Health Canada Summary of Basis for Decision). See Chapter 1 and Appendix B for more details on the characteristics and pharmacokinetics of solifenacin.

According to the manufacturer's clinical update submission, IMS prescription data in Canada in 2008 indicated the 5mg dose is used in approximately 80% of patients, and about 20% use the 10mg dose (Solifenacin Clinical Update). We provide 5mg solifenacin data wherever possible.

Q1. Comparative Harms and Benefits

Methods – see Chapter 2.

Results

Search findings

In total, nine direct comparator RCTs were identified for this comparison. Three uncontrolled cohort analyses were included for additional information on harms. Case reports (N=3) and regulatory documents were also included as supplemental information on adverse events.

Direct Comparator RCTs

Nine trials (in 12 publications) compared solifenacin with other antimuscarinic drugs.

Solifenacin vs. Oxybutynin immediate release (IR): 3 RCTs
Solifenacin vs. Tolterodine extended release (ER) or IR: 5 RCTs
Solifenacin vs. Darifenacin: 1 RCT

A fixed dose of solifenacin, 5mg once daily, was used in the three trials comparing solifenacin with oxybutynin IR.

For the comparisons with tolterodine, four trials included separate treatment arms for 5 and 10mg, and one trial used a flexible-dose regimen of 5-10mg. We did not consider doses lower or higher than the standard doses (range 5-10mg). The trial comparing solifenacin with darifenacin used a 5mg fixed dose of solifenacin.

We considered recent systematic reviews for data comparisons (Shamliyan 2012; Madhuvrata 2012; Semla 2011; McDonagh 2009; Hartmann 2009; Chapple 2008). There were some differences in approach, as compared with the question addressed in the current review. Shamliyan 2012 focused on community-dwelling women whereas this review includes both men and women. Madhuvrata 2012 is a recent Cochrane systematic review. Due to additional data made available for at least two trials (Herschorn 2010; But 2012), discrepancies in evaluable patient numbers for at least one study, and omission of the outcome of nocturia from the Cochrane review, we elected to do our own meta-analyses wherever possible. We compare our results to existing systematic reviews in the discussion section.

Each trial is identified by the first author/year of the primary publication. However, additional data sources were used, as noted, if data were missing in the primary publications.

1. Solifenacin vs. Oxybutynin IR

One eight-week parallel group trial compared solifenacin 5mg with oxybutynin IR 5mg t.i.d. (15mg total/day) in patients with OAB (Herschorn 2010; Herschorn 2011). This trial is identified as the VECTOR trial in the Common Drug Review (CDR) and Clinical Update. The trial was relatively small (N=132) with a primary outcome of dry mouth. Study characteristics and outcome data are presented in Tables 1 and 2 in Appendix G.

Two other trials assessed cognition in elderly volunteers and are considered in Q3 only.

Results for Herschorn 2010 are presented according to this review's hierarchy of outcomes. For dichotomous outcomes, if a relative risk is < 1, fewer patients taking solifenacin experienced the event (benefit or harm).

1. All-cause mortality
No deaths are reported.

2. Serious Adverse Events (SAE)
Three SAE (4%) are reported in the solifenacin 5mg group (worsening depression, fractured foot secondary to motorcycle accident, and cervical adenocarcinoma in situ) and none (0%) in the oxybutynin IR group. The difference was not statistically significant. One event, worsening depression, was judged by investigators as possibly related to solifenacin.

3. Withdrawals due to Adverse Events (WDAE)
Fewer people treated with solifenacin withdrew due to adverse events: solifenacin 11/68 (16%) vs. oxybutynin IR 20/64 (31%%); RR 0.52 (95% CI 0.27 to 0.99), P=0.05; absolute risk difference 15% (95% CI -29% to -1%), P=0.04 (Solifenacin Clinical Update, p.25) .

4. Quality of life (QoL)
The OAB-questionnaire (OAB-q), a validated, 33-item questionnaire was used to assess condition-specific QoL. Both drugs improved QoL based on this questionnaire, without significant between-treatment differences.

The OAB-q consists of an 8-item symptom bother scale, and 25 items related to QoL that form 4 subscales (coping, concern, sleep, social interaction) and a total QoL score (Coyne 2002). Each item is rated on a 6-point Likert scale, items are summed and the sum transformed into scores ranging from 0 to 100. Improvement is indicated by a decrease in the symptom bother score and an increase in QoL domain scores. A change of 10 points is considered the minimal clinically important difference (MCID) for each questionnaire scale (Coyne 2006).

In all domains, solifenacin improved scores less than oxybutynin although there were no statistically significant differences and the between-treatment differences did not meet or exceed the MCID (Solifenacin Clinical Update, p. 26). Improvement from baseline in the various subscales for each drug was greater than the 10-point minimal important difference (MCID).

5. Patient-Reported Perception of Improvement
The trial reported Patient Perception of Bladder Condition (PPBC) scores. The PPBC is a 6-point categorical single-item scale that measures perceptions of patients regarding the severity of problems related to their bladder condition. Scores are from 1 (no problems) to 6 (many severe problems). It has been validated predominantly in females, and shown to have construct validity and responsiveness to treatment (Coyne 2006). However, it has weak test-retest reliability compared with multi-item scales, and only 54% of clinically stable respondents reported the same level of bladder problems between visits two weeks apart (Matza 2005).

Mean change from baseline in the single-item global assessment of Patient Perception of Bladder Condition (PPBC) was solifenacin -0.9 (standard deviation (SD) 1.3) vs. oxybutynin IR -1.4 (SD 1.3) (Solifenacin Clinical Update, p. 26). The mean difference was statistically significant and in favor of oxybutynin: MD 0.50 (95% CI 0.05 to 0.95), P=0.03. However, this magnitude of difference (half a point on a 6-point scale) is unlikely to be clinically meaningful.

6. Quantification of Incontinence Episodes
Cure or total dryness: The trial does not report on this outcome.

Reduction in incontinence episodes: Baseline severity of incontinence was 1.5-1.6 episodes per 24 hours (Solifenacin Clinical Update). The average reduction from baseline in incontinence episodes per day was -0.6 (SD 1.5) for solifenacin vs. -1.0 (SD 1.9) for oxybutynin IR. The mean difference, numerically in favor of oxybutynin, was not statistically significant: MD 0.40 episodes/day (95% CI -0.25 to 1.05), P=0.23 (Solifenacin Clinical Update, p. 23).

Numbers of evaluable patients for this outcome are those who completed bladder diaries at study end (Solifenacin Clinical Update). This comprised 93% of the solifenacin group (63/68) and 75% (48/64) of participants in the oxybutynin IR group. Incontinence was not a criterion for enrolment, and we were unable to confirm in other documentation that all completers were evaluable patients for this outcome.

7. Nocturia
The average number of nocturia episodes was about 2 per 24 hours. The mean change from baseline in nocturia was -0.4 (SD 1.0) episodes for solifenacin vs. -0.7 (SD 1.5) for oxybutynin (Solifenacin Clinical Update, p. 24). Oxybutynin IR reduced nocturia episodes by an additional 0.3 episodes/night, but this was not statistically significant: MD 0.3 episodes/night (95% CI -0.19 to 0.79), P=0.23.

8. Urgency
The mean baseline number of urgency episodes was 6-7 episodes per 24 hours. Solifenacin reduced urgency, on average, by 2.5 (SD 4.4) episodes per day vs. 3.5 (SD 4.4) episodes per day for oxybutynin, corresponding to a 40% and 53% reduction, respectively. The mean difference was numerically in favor of oxybutynin IR but was not statistically significant and confidence intervals were wide: MD 1.00 episodes/day (95% CI -0.65 to 2.65), P=0.24 (Solifenacin Clinical Update, p.23).

9. Total AE:
Fewer patients on solifenacin experienced one or more AE compared with oxybutynin IR: 72% vs. 92%; RR 0.78 (95% CI 0.66, 0.92), P=0.003; absolute risk difference 20% (95% CI -33% to -8%).

10. Specific AE
Dry mouth: Fewer patients treated with solifenacin experienced dry mouth compared with oxybutynin IR: 35% vs. 83%, RR 0.43 (95% CI 0.30, 0.60), P<0.00001; absolute risk difference 48% (95% CI -62%, -33%).

Constipation: Numerically more patients on solifenacin had constipation compared with oxybutynin IR but the difference was not statistically significant: 9/68 (13%) vs. 4/64 (6%); RR 2.12 (95% CI 0.69 to 6.54), P=0.19. The trial was not powered to detect differences in this adverse event.

Other AE that occurred in > 2% of participants in at least one group are listed in Table 2 in Appendix G (Solifenacin Clinical Update, p. 25). These included (listed as solifenacin vs. oxybutynin IR): nasal dryness 0% vs. 14%; headache 3% vs. 6%; dizziness 2% vs. 8%; somnolence 2% vs. 3% and fatigue 6% vs. 9% among others. There were two cases of urinary retention in the oxybutynin group and none in the solifenacin group. Because of the small sample size and small numbers of events, the trial was under-powered to assess these events.

11. Urodynamics/clinician measures
The study did not report on these outcomes.

12. Mean volume voided: Solifenacin increased the mean volume voided by approximately 38 mls (SD 48) vs. oxybutynin IR by 31 mls (SD 52). The mean difference was approximately 7 mls, in favor of solifenacin: MD 6.95 (95% CI 1.26 to 12.64), P=0.02.

The Elderly
A post hoc subgroup analysis on age (≤ age 65 and 65+) did not detect a significant treatment-age interaction for dry mouth (Herschorn 2011). The trial was not stratified at the time of randomization by age, and was not statistically powered to detect differences between subgroups. This analysis is therefore observational and exploratory only. AE profiles and discontinuations due to AE appeared similar in both age subgroups but numbers were small, with only 27 patients ≥ age 65 on solifenacin and 30 patients ≥ age 65 on oxybutynin in this trial.

Critical Appraisal: Solifenacin vs. Oxybutynin IR

Risk of bias
As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity. For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results).

The trial publication was at high risk of bias for selective outcome reporting because it did not provide data on all outcomes measured (e.g., efficacy outcomes). However, we obtained further information from the Clinical Update provided by the manufacturer, the CDR Reviews and results posted on clinicaltrials.gov, and based our assessment of risk of bias or internal validity on all available data.

Randomization was appropriate but there is no information on the adequacy of allocation concealment. It is unclear whether data assessors were blinded. A large proportion of patients withdrew (30%) from this small study. Fewer participants in the oxybutynin group completed bladder diaries at study end and because of the difference in rates of attrition between the study arms, the study was judged at high risk of attrition bias. The large proportion of missing data limits the conclusions that can be drawn on the basis of this trial.

In the publication, investigators indicate intent-to-treat analysis was used for efficacy outcomes (without data imputation). However, most of the efficacy outcomes are not published and the efficacy outcomes reported in the Clinical Update appear to be a completer (i.e., per protocol) analysis.

Applicability of trial results (external validity)
The majority of participants were female and Caucasian, potentially limiting applicability to other populations. About 40% were elderly.

Dose/Comparator choice: The recommended doses of solifenacin are 5mg and 10mg once daily, and the usual dose for oxybutynin IR is 5mg b.i.d. to t.i.d. This trial compared the lower dose of solifenacin to the higher usual dose of oxybutynin. The differences observed may reflect differences in total anticholinergic dose. For both efficacy and AE outcomes, the direction of effect in this trial is consistent with this hypothesis.

Because solifenacin has a long half life and differences in pharmacokinetics can modify clinical response, an extended release formulation of oxybutynin is a more suitable comparator. Immediate release formulations may be associated with increased AE, as noted in a comparison of extended release versus immediate release formulations (see Chapter 9; also Madhuvrata 2012). The choice of an immediate release formulation as the comparator potentially biases results in favor of solifenacin.

There are no trials available that compare any extended release formulation of oxybutynin with solifenacin.

Harms: The primary outcome for Herschorn 2010 was dry mouth, which was ascertained by direct questioning. Patients were informed that the purpose of the study was to assess the incidence and severity of dry mouth. This could have influenced the results and contributed to the relatively high incidence of dry mouth overall. On the other hand, in studies that rely on passive AE reporting, dry mouth may be under-reported.

Industry sponsorship: The trial was sponsored by the manufacturer of solifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007).

Overall results – comparisons between solifenacin and oxybutynin IR

As summarized in Table 1, below, there were fewer WDAE, total AE and less dry mouth with solifenacin 5mg. For efficacy outcomes, oxybutynin IR appeared slightly better but most of the differences were not statistically significant.

Table 1. Summary of RCTs Solifenacin vs. Oxybutynin IR

Outcome	No. of studies (No. of Participants)	RR or MD (95% CI) SOL vs.OXY IR	Absolute Risk Difference (95% CI) SOL vs. OXY IR	Summary
All-cause mortality	1 (132) No events reported	--	--	- The one trial was under-powered to assess this outcome in the short-term (no events) - No long-term data are available.
Non-fatal SAE	1 (132) 3 events	--	--	- 3 SAE in the SOL 5 group, none in the OXY IR group; difference NS - The trial was under-powered for this outcome. No long-term data available
QoL	1 trial (125)**	Symptom Bother: MD 4.0 [95% CI -3.6 to 11.6] HRQL: MD 3.0 [95% CI -10.5 to 4.5]	--	- OXY IR improved scores to a greater extent but the difference was not statistically significant and did not

				reach MID
Patient-reported improvement (PPBC Scores)	1 (111)**	MD 0.50 [95% CI 0.05 to 0.95]	--	- OXY IR improved mean PPBC score more than SOL 5. Clinical meaningfulness of the difference (0.5 on a 6 point scale) is not known.
WDAE	1 (132)	RR 0.52 [95% CI 0.27 to 0.99]	RD -15% [95% CI -29% to -1%]	- 15% fewer WDAE with SOL 5
Incontinence Episodes Mean Change from Baseline	1 (111)**	MD 0.40 [95% CI -0.25 to 1.05]	--	OXY IR numerically reduced incontinence episodes by an additional 0.4 episodes but the difference is not statistically significant.
Urgency Episodes Mean Change from Baseline	1 (111)**	MD 1.00 [95% CI -0.65 to 2.65]	--	OXY IR numerically reduced urgency episodes by 1 additional episode but the difference is not statistically significant.
Nocturia Episodes Mean Change from Baseline	1 (111)**	MD 0.30 [95% CI -0.19 to 0.79]	--	OXY IR numerically reduced nocturia episodes by an additional 0.3 episodes but the difference is not statistically significant.
Total AE*	1 (132)	RR 0.78 [95 % CI 0.66 to 0.92]	RD -20% [95% CI -33% to -8%]	- 20% fewer patients on solifenacin experienced AE
Dry mouth	1 (132)	RR 0.43 [95% CI 0.30 to 0.60]	RD -48% [95% CI -62% to -33%]	- 48% fewer patients had dry mouth in the solifenacin group

* Proportion of participants who experienced one or more AE. For specific AE, proportion of participants experiencing the AE are reported. ** patient numbers as reported in Solifenacin Clinical Update, p. 23-26.
AE=adverse events; **CI**=confidence intervals; **HRQL**=health-related quality of life; **No.**=number;; **MD**=mean difference; **MID**=minimal important difference; **NS**=not significant; **RD**=absolute risk difference; **RR**=relative risk; **SAE**=serious adverse events; **SOL**=solifenacin; **OXY**=oxybutynin; **WDAE**=withdrawals due to adverse events; **QoL**=quality of life;

2. Solifenacin vs. Other Comparator Drugs

(1) Solifenacin vs. Tolterodine

Five parallel group trials compared solifenacin vs. tolterodine, two comparing solifenacin with tolterodine ER (Chapple 2005; Ho 2010) and three comparing solifenacin with tolterodine IR (Chapple 2004a; Chapple 2004b; Choo 2008). These involved a total of 2633 participants who received active drug in approved dosages, and 305 who received placebo. Two of the solifenacin vs. tolterodine IR trials included a placebo control (Chapple 2004a; Chapple 2004b). All trials were short-term (4-12 weeks). Study characteristics are presented in Table 6 in Appendix G.

In four trials, the approved dosages of solifenacin, 5mg and 10mg, were fixed and included in separate treatment arms (Chapple 2004a; Chapple 2004b; Choo 2008; Ho 2010). One trial (Chapple 2005) used a flexible dosing regimen of 5-10mg in a single arm.

a. Solifenacin vs. Tolterodine ER

Two trials compared solifenacin with tolterodine ER (Chapple 2005; Ho 2010). Both were 12 weeks in duration, involving a total of 1275 subjects.

The largest trial, Chapple 2005 (the STAR trial) is a two-arm double-blind RCT that randomized 1200 patients in 17 European countries. The trial was designed as a non-inferiority trial for the primary outcome of numbers of micturitions per day. The population was predominantly female, and included an unspecified number of participants who had urgency predominant mixed incontinence. Solifenacin was initiated at 5mg/day with the option to increase to 10mg/day after four weeks if desired. A similar proportion of participants requested an increase in dose for each drug, suggesting similar efficacy: solifenacin 48% vs. tolterodine 52%. Those who were on tolterodine continued to receive the same dose in a sham dose escalation.

Results at study end in Chapple 2005 are presented with both solifenacin doses mixed as this represents the randomized population (designated solifenacin 5/10). However, this limits the ability of this particular trial to detect dose-response relationships for adverse event rates or efficacy. A prespecified analysis was conducted at the four-week time point, when all participants in the solifenacin group were receiving 5mg (Chapple 2007).

Ho 2010 is a small open label trial on 75 patients, conducted in Taiwan, and compared a fixed dose of solifenacin 5mg/day with tolterodine ER 4mg/day.

Both trials included patients with and without urgency incontinence, as incontinence was not an eligibility criterion for either trial.

Results are presented according to this review's hierarchy of outcomes. For dichotomous outcomes, if a relative risk is < 1, fewer patients taking solifenacin experienced the event (beneficial or harmful).

1. All-cause mortality

There were no deaths in either trial.

2. Non-fatal Serious Adverse Events

In Chapple 2005, there were 3 SAE (0.5%) in the solifenacin group and 7 (1.2%) SAE in the tolterodine group: RR 0.44 (95% CI 0.11, 1.69), P=0.23.

The SAE in Chapple 2005 are incompletely described with no details for five cases: solifenacin – angioneurotic edema (1), 2 not described; tolterodine – myocardial infarction (2), cerebrovascular accident (1), laryngeal edema (1), 2 not described (Common Drug Review 2009, p. 81).

Ho 2010 reported no 'severe' AE in the trial but the relation of severe AE to SAE is not defined.

3. Withdrawals due to Adverse Events

WDAE were similar in both treatment groups in Chapple 2005, and there was one event in each treatment group in Ho 2010. Combined (N=1275), there was no statistically significant difference between treatment groups: RR 1.18, 95% CI 0.64 to 2.16, P=0.59.

Figure 1. WDAE – SOL 5/10 vs. TOL ER

4. Quality of life (QoL)

Neither trial reported QoL using a generic or condition-specific instrument.

5. Patient-Reported Perception of Improvement /Cure

Both trials reported Patient Perception of Bladder Condition (PPBC) scores. The improvement (reduction) in scores from baseline was in the range 1.3 to 1.5 points. In Chapple 2005, patients treated with solifenacin had a statistically significant improvement in mean PPBC of -0.18 points (95% CI -0.35 to -0.01) compared with tolterodine. There was no difference in scores for the smaller trial. When the two trials are combined (N=1252), solifenacin improved PPBC compared with tolterodine: mean difference - 0.17 points (95% CI -0.33 to -0.01), P = 0.04. A difference of this magnitude, on a 6-point scale, is unlikely to be clinically meaningful.

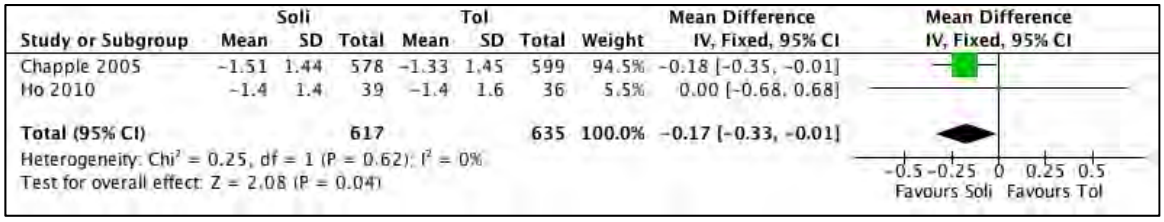

Figure 2. Patient-Reported Improvement – SOL 5/10 vs. TOL ER

6. Quantification of Incontinence Episodes

Cure or dryness rate (3-day): One trial reported on this outcome (Chapple 2005). The number of evaluable patients is less than the total number enrolled because incontinence was not an eligibility criterion. Chapple 2005 did not report the number of patients with incontinence at baseline. We therefore used the denominator numbers of evaluable patients reported in the Public Summary Document of the Pharmaceuticals Benefits Advisory Committee (PBAC) of Australia (Pharmaceuticals Benefits Advisory Committee Public Summary Document July 2007, p. 4). Evaluable patients were ~63% of the total groups.

More participants on solifenacin achieved continence, based on a 3-day bladder diary, at week 12 compared with tolterodine: 218/364 (60%) vs. 191/378 (51%); RR 1.19 (95% CI 1.04 to 1.35), P=0.01; absolute risk difference 9% (95% CI 2% to 16%).

At four weeks when all participants in the solifenacin group were on a 5mg dose, similar proportions of patients on solifenacin and tolterodine achieved continence (39% vs. 34%, difference not statistically significant), as reported by study investigators) (Chapple 2007).

Mean reduction in incontinence episodes: Both trials reported this outcome (Table 2). Chapple 2005 enrolled patients who had mixed incontinence (urgency predominant) as well as urgency incontinence, and reported both total incontinence (including stress incontinence) and urgency incontinence episodes. For calculations, we used the number of evaluable patients for incontinence as reported by PBAC. Solifenacin reduced urgency incontinence episodes, on average, by an additional 0.59 episodes per 24 hours (95% CI -0.93 to -0.25), P=0.0007. The difference between active drugs was slightly less for total incontinence episodes in this study: mean difference in episodes per day -0.49 (95% CI -0.83 to -0.15)

Table 2. Incontinence Episodes per 24 hours - mean change from baseline

Parameter	SOL 5-10mg	TOL ER 4 mg	Mean Difference (95% CI) from baseline between drugs§
Chapple 2005			
Baseline Urgency Incontinence Episodes	2.31 ± 2.35	2.12 ± 2.14	--
Urgency incontinence episodes per 24 h Change from baseline mean ± SD	-1.42 ± 2.26** N=364*	-0.83 ± 2.36** N=379*	-0.59 (95% CI -0.93 to -0.25) P=0.0007
Baseline Total Incontinence Episodes	2.77 ± 2.65	2.55 ± 2.37	--
Total incontinence episodes per 24 h change from baseline mean (SD)	-1.60 ± 2.26 N=364***	-1.11 ± 2.49 N=379***	-0.49 (95% CI -0.83 to -0.15) P=0.005
Ho 2010	**SOL 5 mg**	**TOL ER 4 mg**	
Baseline Incontinence Episodes	3.21 ± 3.05	6.19 ± 5.83	--
Incontinence episodes change from baseline mean ± SD	-2.79 ± 2.82 N=35*	-4.67 ± 9.29 N=33*	1.88 [95% CI -1.42 to 5.18], P=0.26^

§calculated in RevMan 5.2. *Numbers of evaluable patients for incontinence as reported in the Pharmaceuticals Benefit Advisory Committee, Australia July 2007; ** Standard deviation as reported in Chapple 2006; *** Per protocol analysis numbers for efficacy outcomes as stated in Ho 2010, p. 704; ^ p value reported in publication for this outcome is 0.28. **CI**=confidence intervals; **ER**=extended release; **h**=hours; **N**=number of patients; **SD**=standard deviation; **SOL**=solifenacin; **TOL**=tolterodine

At four weeks, when all participants in the solifenacin group were taking 5mg, a mean difference from baseline of 0.31 episodes for urgency incontinence episodes, favoring solifenacin, was not statistically significant. The mean change from baseline in total incontinence episodes per 24 hours was greater for solifenacin: MD 0.4 episodes (P=0.0181) (Chapple 2007, p values as reported in publication). Measures of variability (e.g., standard deviations) are not reported, limiting interpretation of these findings.

In Ho 2010, the tolterodine group had a higher mean number of incontinence episodes at baseline (6.2 vs. 3.2). This may reflect the small sample size and chance variation or represent true differences in severity. Ho 2010 reported a greater numerical reduction in urgency incontinence episodes for tolterodine that was not statistically significant: MD 1.88 (95% CI -1.42 to 5.18), P=0.26.

Because there were only two studies, with heterogeneity between studies, we chose not to combine the studies in a meta-analysis. Use of a random effects model raises concerns about

exaggeration of small study effects, as the smaller study obtains greater weight than with a fixed effects model (Cochrane Handbook). The larger study represents more usual circumstances and although both studies contain methodological flaws, Chapple 2005 is likely to be more methodologically rigorous of the two, based on the fact that the smaller study, Ho 2010, was unblinded.

7. Nocturia

One trial, Chapple 2005, reported on this outcome. At baseline, participants had an average of about two episodes of waking up at night to void, which was reduced by 0.6-0.7 episodes with treatment. There was no difference between solifenacin 5/10 and tolterodine ER in average reduction from baseline: mean difference -0.08 (95% CI -0.22 to 0.06), P=0.25.

The numbers of evaluable patients used for this calculation are the denominator numbers reported by the Pharmaceuticals Benefit Advisory Committee for Australia for nocturia (PBAC Public Summary Document July 2007, p. 5).

The PBAC documentation also reported numbers of patients with no nocturia at study end. There was no difference between solifenacin and tolterodine ER: 100/479 (21%) vs. 111/496 (22%), RR 0.93 (95% CI 0.73 to 1.19), P=0.57 (PBAC Public Summary Document July 2007, p. 5).

8. Urgency

Baseline urgency episodes per 24 hours were about 6 for the Chapple 2005 trial, and 3-6 for Ho 2010. When combined (N=1190), solifenacin reduced urgency episodes by an additional 0.44 episodes per 24 hours vs. tolterodine: mean difference -0.44 (95% CI -0.84 to -0.04), P=0.03.

The evaluable patient numbers for Chapple 2005 are the numbers reported by the Pharmaceuticals Benefit Advisory Committee for Australia for this outcome (PBAC Public Summary Document July 2007, p. 4).

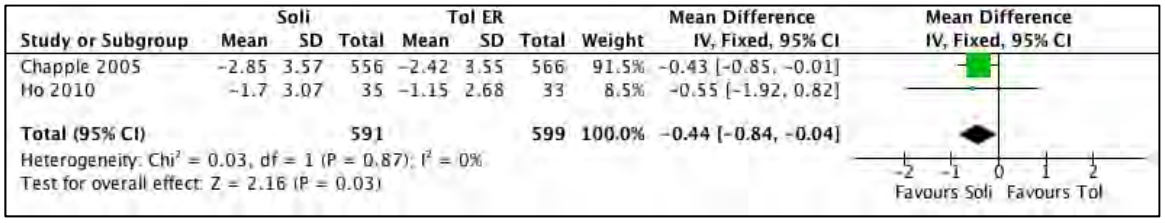

Figure 3. Urgency Episodes – SOL 5/10 vs. TOL ER

9. Total Adverse Events (AE)

In both trials, more participants experienced adverse events in the solifenacin 5/10 group compared with tolterodine ER but the difference was not statistically significant. Chapple 2005 results are mixed doses for solifenacin as a flexible dosing regimen was used. This may have obscured a dose response for AE.

Combined (N=1275), there was no statistically significant difference: RR 1.10 (95% CI 0.98 to 1.25), P=0.11.

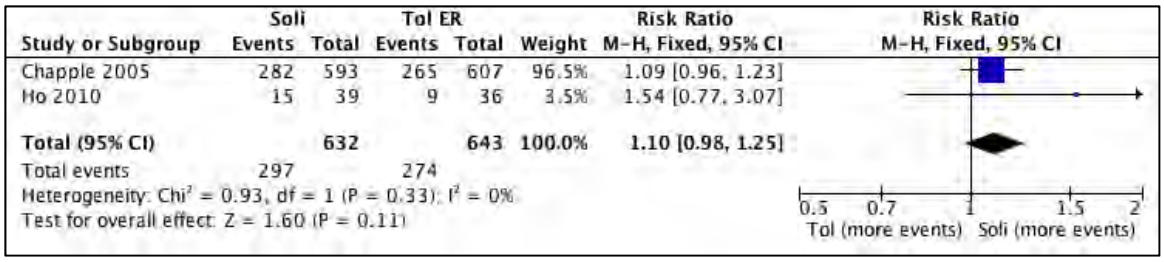

Figure 4. Proportion of Participants with ≥ 1 AE – SOL 5/10 vs. TOL ER

10. Specific AE

Dry mouth:

Solifenacin 5/10 was associated with a higher incidence of dry mouth than tolterodine ER (2 trials, N=1275): RR 1.27 (95% CI 1.05 to 1.53), P=0.30; absolute risk difference 6% (1% to 11%).

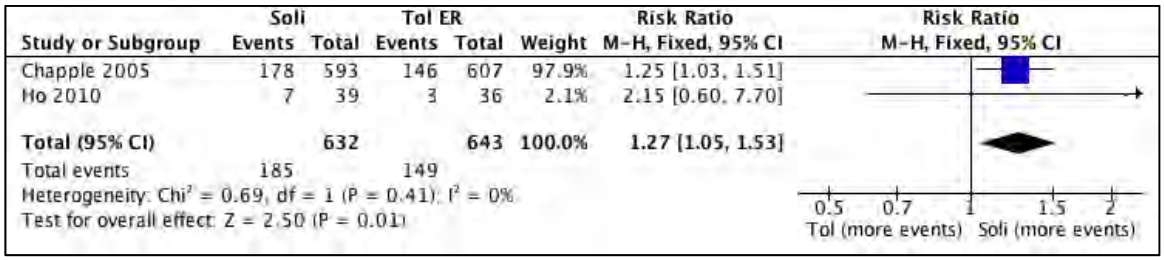

Figure 5. Dry Mouth – SOL 5/10 vs. TOL ER

Constipation:

More patients on solifenacin 5/10 experienced constipation than on tolterodine ER (2 trials, N=1275): RR 2.60 (95% CI 1.47 to 4.58), P=0.001; absolute risk difference 4% (95% CI 2% to 6%).

Figure 6. Constipation – SOL 5/10 vs. TOL ER

Nervous system AE: The CDR Review reports similar rates of nervous system disorders for solifenacin 5/10 and tolterodine ER in the Chapple 2005 trial: 6.2% vs. 6.3% (Common Drug Review 2009, p. 83).

11. Urodynamics/clinician measures

Ho 2010 reported change in post void residual volume was small in both groups (on average < 1 ml for solifenacin and 3.5 mls for tolterodine) and not clinically or statistically significant. Urodynamic parameters were reported not to differ between drugs among women patients, but were not reported for the entire group (Hsaio 2010).

12. Mean volume voided:
Combining the two trials (N=1245), solifenacin increased the mean volume voided by an additional 7.5 mls compared with tolterodine ER: MD 7.5 (95% CI 1.9 to 13.0), P=0.008.

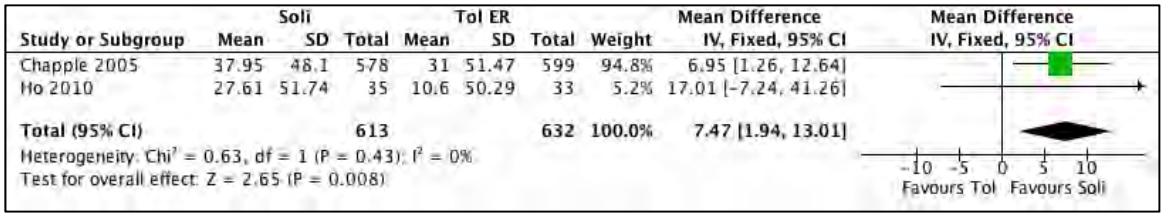

Figure 7. Mean volume voided – SOL 5/10 vs. TOL ER

Critical Appraisal: Solifenacin vs. Tolterodine ER

Risk of bias
The primary publication of Chapple 2005 selectively reported outcomes, did not report evaluable patient numbers for incontinence and nocturia, and did not report measures of variability although these were subsequently published (Chapple 2006). We sought missing data from other sources and assessed the internal validity of the trial (risk of bias) based on all available data rather than those data in the publication only.

For Chapple 2005, random sequence generation was incompletely described but allocation concealment was adequate. Blinding was appropriate (double-dummy and identical for the dose increase) but maintenance of blinding was not tested. It is possible that the occurrence of dry mouth following dose escalation of solifenacin might have broken blinding. The study was assessed to be at high risk of bias for selective outcome reporting on the basis that two outcomes identified in the trial registration on clinicaltrials.gov (physician and patient assessment of treatment benefit) were not published and results could not be found elsewhere. The trial was assessed as 'unclear' for attrition bias as a full accounting of patients who were excluded from the modified intent-to-treat analysis was not found.

Small differences were observed for efficacy outcomes, generally in favor of tolterodine although most were not statistically significant. Study investigators did not discuss the clinical relevance of the observed differences.

Ho 2010 was a small trial and did not report a sample size calculation. As it was open label, the trial was at high risk for performance and detection bias It also did not explicitly report evaluable patient numbers for incontinence. Patients in the tolterodine group reported a higher number of incontinence episodes per day at baseline, suggesting the possibility that this group may have had more severe incontinence. This could also have reflected chance variation and the small numbers in each group. A per protocol analysis was used for efficacy outcomes in this trial (10% overall excluded).

Applicability of trial results (external validity)
Chapple 2005 had a placebo run-in phase that would have screened out placebo responders. A substantive and varied placebo response is observed in OAB trials and may contribute to variability in response in the community setting. Ho 2010 did not utilize a placebo run-in phase.

The majority of participants were women. The findings may have limited applicability to men who often have lower urinary tract symptoms due to benign prostatic hypertrophy, a condition for which neither drug is approved or effective. In Chapple 2005, 6-7% were > age 75 and about a third were > age 65.

Neither trial conducted subgroup analyses on patients who were intolerant of, or refractory to, oxybutynin. Chapple 2005 did not report the proportion of patients who had previously received treatment. In Ho 2010, about 50% had received prior therapy, but the trial was small and there was no stratification on the basis of prior response to therapy or subgroup analysis.

Dose/comparator choice: The most appropriate comparator for solifenacin is another long-acting or sustained-release form such as tolterodine ER because of solifenacin's long half-life. Treatment in Chapple 2005 was initiated with the recommended starting dose for each drug. However, only the dose of solifenacin was permitted modification at four weeks. A similar proportion of patients in each group requested a dose increase, suggesting similar efficacy. Because the recommended starting dose of tolterodine ER is the maximum dose, an increase would not have been possible for tolterodine.

Use of a flexible dose mix obscures a dose response for AE (or efficacy). In a prior systematic review, doses of solifenacin were compared (Madhuvrata 2012). Patients receiving 5mg were between 50% and 78% less likely to experience dry mouth compared to 10mg solifenacin. There was no difference in WDAE between the doses. A 10mg dose was slightly more effective than 5mg for some efficacy outcomes (micturition and urgency per 24 hours) (Madhuvrata 2012).

For tolterodine, the dose could not be escalated. However, a lower dosage is recommended depending on tolerability (Tolterodine ER Product Monograph). If a truly pragmatic trial in a 'real world' setting was intended, then dosage adjustment should have been allowed for tolterodine (albeit a dose decrease for AE). This might have altered (further increased) the differences observed in AE.

Harms: Neither trial had an active surveillance framework for harms. Neither trial actively assessed cognitive adverse events.

Industry sponsorship: Both trials were sponsored by the manufacturer of solifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). There is also evidence that in active comparator trials within a drug class, the sponsor is highly predictive of which drug does better (Bero 2007).

Overall results – comparisons between solifenacin and tolterodine ER

Solifenacin 5/10 and tolterodine ER had similar WDAE but 6% more patients on solifenacin experienced dry mouth, and 4% more patients had constipation compared with tolterodine ER. In the largest trial, Chapple 2005, solifenacin 5/10 reduced incontinence episodes to a greater extent by 0.6 episodes per day, and 9% more patients achieved continence (3-day time period).

Results for the two RCTs are summarized, below, in Table 3.

Table 3. Solifenacin vs. Tolterodine ER – Summary of RCTs

Outcome	No. of studies (No. of Participants)	RR or MD (95% CI) SOL 5/10mg vs. TOL ER 4 mg	Absolute Risk Difference SOL 5/10mg vs. TOL ER 4mg	Summary
All-cause mortality	2 trials (1275) 0 events	--	--	- Short-term trials were under-powered to assess any effect on mortality (no events) - No long-term data are available.
Non-fatal SAE	1 trial (1200)	RR 0.44 [95% CI 0.11 to 1.69]		- Short-term trials are under-powered (few events) - No long-term data are available
Cognitive AE	0 trials	--	--	- No data are available; available trials did not specifically assess cognitive AE
QoL generic	0 trials	--	--	- No data
QoL condition-specific (change in PPBC scores)	2 trials (1252)	MD -0.17 [95% CI -0.33 to -0.01]	--	- Slight difference in favor of SOL 5/10 (0.17 on 6-point scale) unlikely to be clinically significant
WDAE	2 trials (1275)	RR 1.18 [95% CI 0.64 to 2.16]	--	- Similar WDAE for both drugs
Dry rate (3-day bladder study end)	1 trial (742)	RR 1.19 [95% CI 1.04 to 1.35)	RD 9% [95% CI 2% to 16%]	9% more patients on SOL 5/10 achieved continence
Incontinence episodes	2 trials, no meta-analysis Chapple 2005 (743) Ho 2010 (68)	Chapple 2005 MD =0.59 [95% CI -0.93 to -0.25] Ho 2010 MD 1.88 [95% CI -1.42 to 5.18]	Chapple 2005	Chapple 2005 SOL 5/10 reduced incontinence by an additional 0.6 episodes per day Ho 2010: difference was not significant
Urgency Episodes Mean Change from Baseline	2 trials (1190)	MD -0.44 [95% CI -0.84 to -0.04]	--	- slightly greater reduction with SOL 5/10 (0.4 episode per day)
Nocturia Episodes Mean Change from Baseline	1 trial (975)	MD -0.08 [95% CI -0.22 to 0.06]	--	- No difference between drugs
Total AE*	2 trials (1275)	RR 1.10 [95% CI 0.98 to 1.25]	--	- No difference between drugs
Dry mouth	2 trials (1275)	RR 1.27 [95% CI 1.05 to 1.53]	RD 6% [95% CI 1% to 11%]	- 6% more participants had dry mouth with SOL 5/10mg
Constipation	2 trials (1275)	RR 2.60 [95% CI 1.47 to 4.58]	RD 4% [95% CI 2% to 6%]	- 4% more participants had constipation with SOL 5/10mg

* Proportion of participants who experienced one or more AE; for specific AE, proportion of participants experiencing that AE are reported.
AE=adverse events; **CI=**confidence intervals; **No**.=number;; **MD**=mean difference; **PPBC**, patient perception of bladder condition; **QoL**=quality of life; **RD**=absolute risk difference; **RR**=relative risk; **SAE**=serious adverse events; **SOL**=solifenacin; **TOL**=tolterodine; **WDAE**=withdrawals due to adverse

events;

b. Solifenacin vs. Tolterodine IR

Three parallel group trials compared solifenacin (fixed doses of 5 or 10mg once daily) with tolterodine IR 2mg b.i.d (4mg/day). The trials involved a total of 1280 participants who were randomized to active drug (doses of interest) and 305 randomized to placebo (Chapple 2004a; Chapple 2004b; Choo 2008). Two were 12 weeks in duration and one, a dose-finding Phase II trial, was four weeks (Chapple 2004a). Two trials included a placebo arm (Chapple 2004a; Chapple 2004b), and all three had a two-week placebo run-in phase, screening out placebo responders. None of the trials had urgency incontinence as a criterion, and two included patients with mixed incontinence if it was urgency predominant (Chapple 2004b; Choo 2008).

1. All-cause mortality

No deaths occurred during the Chapple 2004a (Study 005) study. In Chapple 2004b (Study A015), there were two deaths, one in the solifenacin10mg arm (acute heart failure), and one in the tolterodine arm (cerebral atherosclerosis). No deaths are inferred in Choo 2008 by the reporting of only one SAE, which was non-fatal (see below).

2. Non-fatal Serious Adverse Events

There were no SAE in Chapple 2004a. The other two trials did not report total SAE. Chapple 2004b reported only a subset of SAE judged by investigators to be 'treatment-related', with details on three SAE. Two patients in the solifenacin group developed tachyarrhythmia and syncope, and one patient in the solifenacin 10mg group had a myocardial infarction (Common Drug Review 2009). In Choo 2008, there was one SAE reported in the solifenacin 5mg group, a gastric ulcer perforation, and no events in the 10mg solifenacin or tolterodine IR groups (Common Drug Review 2009).

3. Withdrawals due to Adverse Events

In the three trials (N=852), although there were numerically more WDAE in the solifenacin 5mg group, the difference was not statistically significant: RR 1.81 (95% CI 0.78 to 4.23), P=0.17.

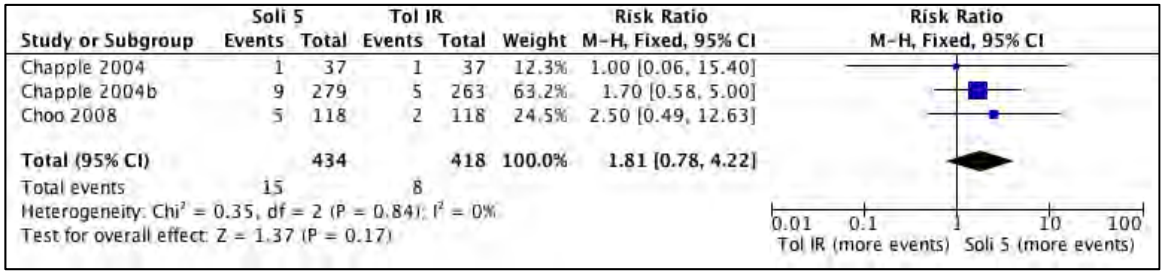

Figure 8. WDAE – SOL 5mg vs. TOL IR

In the solifenacin 10mg vs. tolterodine IR comparison, the difference was also not statistically significant although there were more WDAE in the solifenacin 10mg group (3 trials, N=843, same tolterodine arm): RR 2.14 (95% CI 0.94 to 4.89), P=0.07.

4. Quality of life (QoL)

Condition-specific QoL was measured in all three trials, using three different validated instruments: the Contilife scale (Quality of Life Assessment Concerning Urinary Incontinence

Questionnaire); Urge Urinary Distress Inventory (U-UDI); and the King's Health Questionnaire (KHQ).

Contilife is a 28-item instrument, which covers six domains: daily activities, effort, self-image, emotional consequences, sexuality and well-being (Amarenco 2003). The 28th item is a patient assessment of overall QoL, and a sum score is also tallied across domains (0 to 100). The higher the score, the better the QoL. Contilife was developed for any type of incontinence and validated predominantly in women and for stress incontinence, with a minimal clinically important difference identified as -7 to -20 depending on the domain (Shumaker 1994; Shamliyan 2012; Amarenco 2003). Chapple 2004a reported the average Contilife sum score and statistical tests for each drug/dose compared with placebo only. The difference in change from baseline was significant for both doses of solifenacin vs. placebo but not for tolterodine. There was a slight numerical improvement for solifenacin 5mg and 10mg over tolterodine but the difference does not exceed the available minimal clinically important difference. Patients did better on both solifenacin 10mg and tolterodine IR than placebo on Contilife overall (patient-rated) QoL (data not provided).

Chapple 2004a also reported the Urge-Urinary Distress Inventory (U-UDI). U-UDI is a 9-item questionnaire with a single summary score that measures the extent to which urinary incontinence symptoms (mixed or urgency incontinence) bother patients. The overall score is from 0 (no symptoms) to 8 (greatest degree of bother). It has been validated, predominantly in women. U-UDI scores were similar with 21-31% improvement in scores from baseline for active treatment arms (placebo results not reported) (Common Drug Review 2009, p. 76).

Two trials reported KHQ (Choo 2008; Chapple 2004b). KHQ is comprised of three sections: 1) 2 items on general health perception; 2) 21 items on the following domains: incontinence impact; role limitations; physical limitations; social limitations; personal relationships; emotions; sleep/energy; severity coping measures, and symptom severity, and 3) 11 items on symptom bother. The score for each health-related quality of life domain is from 0 (best) to 100 (worst). A minimal clinically important difference is 5-10 points for each domain (Kelleher 2004). Although the KHQ was initially used in women, it has been validated in both men and women.

Choo 2008 found no statistically significant difference between either solifenacin dose and tolterodine. Changes from baseline did not meet the minimal important difference of 5-6 points for general health perception and symptom severity. Chapple 2004b reported differences from baseline but did not provide statistical tests for active drug comparisons (Common Drug Review 2009). All three active treatment arms did better than placebo, exceeding the minimal clinically important difference, except for scores for general health perception and symptom severity. Interpretation of differences between active drug and placebo must take into account the use of a placebo run-in phase in which placebo responders were screened out.

5. Patient-Reported Perception of Improvement /Cure
No trial reported on this outcome.

6. Quantification of Incontinence Episodes
Cure or total dryness: No trial reported on this outcome.

Reduction in incontinence episodes: Two trials did not provide a measure of variability for this outcome (Chapple 2004a; Choo 2008) and therefore results could not be combined in meta-analysis. The number of evaluable patients for Chapple 2004a was 100% of those enrolled. For Choo 2008, the number of evaluable patients may have been fewer than the total because

enrolment was not restricted to people who had incontinence. However, the numbers are not provided. Chapple 2004b provides evaluable patient numbers but it is unclear how these were ascertained. This study reports urgency incontinence and total incontinence episodes, with different numbers of patients for each. A total of 93% of participants had incontinence (63% urgency incontinence and 30% urgency predominant mixed UI). All patients should have been included for the outcome urgency incontinence because all must have had urgency incontinence at baseline in order to be eligible. However, fewer patients are reported for this outcome than for total incontinence, and the numbers do not correspond to the majority of participants.

Table 4. Urgency Incontinence Episodes per 24 hours: Change from baseline

Study		Mean change from baseline ± SD (% reduction from baseline)			
Drug	Placebo	Solifenacin 5mg/d	Solifenacin 10mg/d	Tolterodine 4 mg/d	Mean Difference [95% CI] p value
Baseline	2.02 ± 2.50	2.33 ± 2.42	2.14 ± 2.44	1.86 ± 1.5	--
Chapple 2004b	-0.62 ± 1.96 (-40%) N=127*	-1.41 ± 1.74 (-65%) N=113*	-1.36 ± 2.13 (-63%) N=127*	-0.91 ± 2.01 (-58%) N=119*	SOL 5 vs. TOL -0.50** [95% CI -0.98 to -0.20], P=0.04 SOL 10 vs. TOL: -0.45** [95% CI -0.97 to 0.07] P=0.09

* Numbers of evaluable patients as reported in Chapple 2004b, Table 2. ** Calculated in RevMan v5.2.
CI=confidence intervals; **d**=day; **N**=number of evaluable patients; **NR**=not reported; **SD**=standard deviation; **SOL**=solifenacin; **TOL**=tolterodine IR

7. Nocturia

Two trials reported on nocturia (Chapple 2004b; Choo 2008). Study investigators did not provide a measure of variability so meta-analysis was not conducted. Solifenacin 5mg or 10mg reduced nocturia numerically slightly more than tolterodine in each of the two trials (Table 6). The slight difference is unlikely to be clinically meaningful.

Table 5. Nocturia Episodes per 24 hours: change from baseline

Study		Change from baseline Mean ± SD (% reduction from baseline); N			
Drug	Placebo	Solifenacin 5mg/d	Solifenacin 10mg/d	Tolterodine IR 4 mg/d	Mean Difference [95% CI] p value
Chapple 2004b	NR	-0.57*, SD NR (NR) N=240	-0.51*, SD NR (NR) N=235	-0.48*, SD NR (NR) N=232	NR
Choo 2008	--	-0.7**, SD NR (-31%) N=NR	-0.6*, SD NR (-29%) N=NR	-0.5*, SD NR (-25%) N=NR	NR

* From CDR Review 2009, Appendix IV, p.81; ** From CDR Review 2009, p. 32;
CI=confidence intervals; **d**=day; **N**=number of evaluable patients; **NR**=not reported; **SD**=standard deviation; **SOL**=solifenacin; **TOL**=tolterodine IR

8. Urgency

Solifenacin 5mg and 10mg reduced urgency episodes to a slightly greater extent than tolterodine IR in all three studies. A meta-analysis was not conducted because two trials did not report a measure of variability (Chapple 2004a; Choo 2008). In the largest trial (Chapple 2004b), there were ~5-6 episodes of urgency at baseline. Even though a placebo run-in phase had screened out

placebo responders, placebo alone reduced urgency episodes from baseline by 40%. In this trial, the differences in the average change from baseline between solifenacin 5mg or 10mg and tolterodine were statistically significant (Table 6).

Table 6. Urgency Episodes per 24 hours: change from baseline

Study		Change from baseline Mean ± SD (% reduction from baseline)			
Drug	Placebo	Solifenacin 5mg/d	Solifenacin 10mg/d	Tolterodine IR 4 mg/d	Mean Difference [95% CI] P-value
Chapple 2004a	-1.03 (-20%) N=36	-2.35 (42%) N=37	-2.46 (-46%) N=33	-1.62 (-28%) N=37	Study was not adequately powered to compare SOL and TOL arms; p NR
Chapple 2004b	-1.41 ± 3.67 (-40%) N=248	-2.85 ± 3.74 (-65%) N=264	-3.07 ± 3.90 (-63%) N=261	-2.05 ± 3.58 (-58%) N=250	SOL 5 vs TOL IR: -0.80* [95%CI -1.43 to -0.17], P=0.01 SOL 10 vs TOL IR: -1.04 [95% CI -1.69 to -0.39], P=.002
Choo 2008	--	-2.50, SD NR (-58%) N=107	-2.35, SD NR (-60%) N=111	-2.20, SD NR (-54%) N=111	--

*Calculated in RevMan 5.2. **CI**=confidence intervals; **d**=day; **N**=number of evaluable patients; **NR**=not reported; **SD**=standard deviation; **SOL**=solifenacin; **TOL**=tolterodine IR

9. Total Adverse Events (AE)

When pooled (3 trials, N=852), there was no significant difference in the proportion of patients who experienced one or more AE when solifenacin 5mg was compared with tolterodine IR: RR 0.95 (95% CI 0.82 to 1.09), P=0.46.

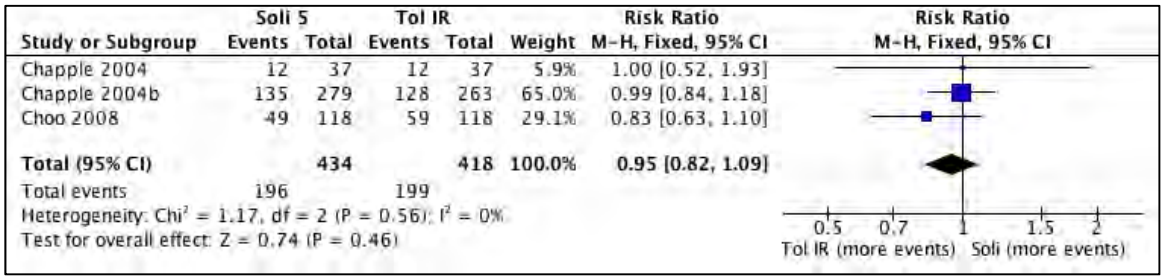

Figure 9. Total AE - SOL 5 vs. TOL IR

Solifenacin 10mg was associated with more AE than tolterodine IR but this was not statistically significant (3 trials, N=837, same tolterodine arm): RR 1.12 (95% CI 0.98 to 1.28), P=0.10.

10. Specific AE

Dry mouth: All three trials reported on dry mouth, the most common adverse event. When the three trials were pooled (N=852), there was less dry mouth associated with solifenacin 5mg compared with tolterodine IR: RR 0.64 (95% CI 0.46 to 0.88), P=0.006; absolute risk difference 7% (95% CI -12% to -2%).

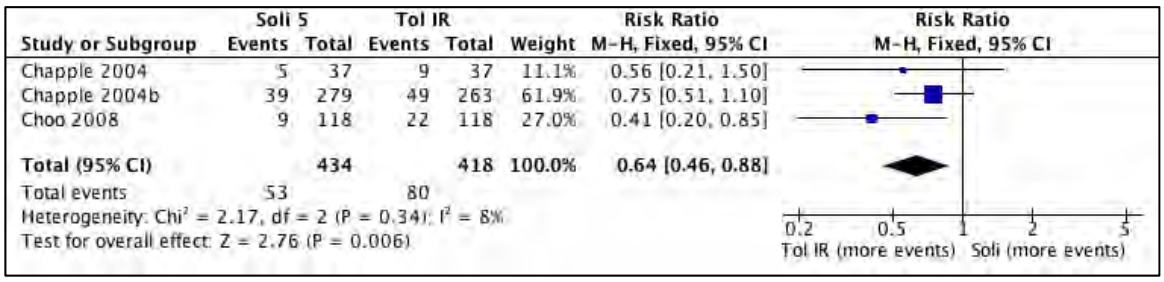

Figure 10. Dry mouth – SOL 5 vs. TOL IR

The higher dose of solifenacin, 10mg, was numerically associated with slightly more dry mouth than tolterodine IR (3 trials, N=837, same tolterodine arm) but the difference was not statistically significant: RR 1.06 (95% CI 0.80 to 1.40), P=0.66.

Constipation:
More patients experienced constipation on solifenacin 5mg than tolterodine IR: RR 2.89 (95% CI 1.48 to 5.64), P=0.002; absolute risk difference 5% (95% CI 2% to 8%).

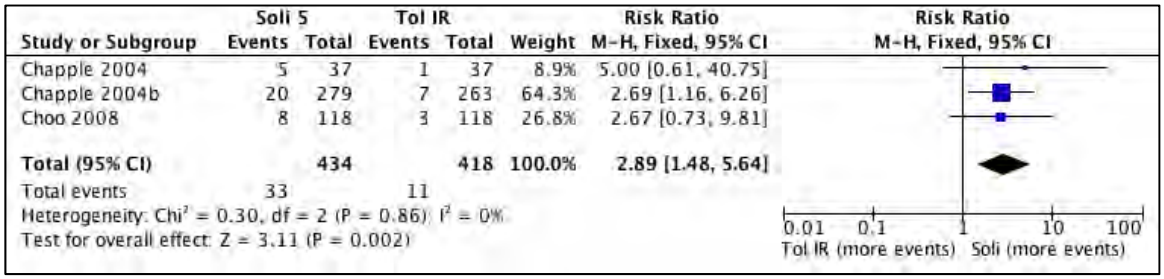

Figure 11. Constipation – SOL 5 vs. TOL IR

There was also more constipation with solifenacin 10mg vs. tolterodine IR: RR 3.63 (95% CI 1.89 to 6.97), P=0.0001; absolute risk difference 7% (95% CI 4% to 10%).

11. Urodynamics/clinician measures
All three trials measured post residual volume, with data provided for one study. Post residual void volume was reported by Choo 2008 for men and women separately, with average increases ranging from 6 to 10 mls (Table 7 in Appendix G), and no statistically significant differences between drugs. Chapple 2004a and Chapple 2004 b reported no clinically relevant differences in post void residual volume. No trial reported volume at first contraction or maximum cystometric capacity.

12. Mean volume voided:
All three trials reported mean volume voided (Table 7 in Appendix G), but two trials did not provide a measure of variability so a meta-analysis was not performed. In the largest trial (Chapple 2004b), the estimated differences in the average increase in volume voided for the 5 or 10mg doses of solifenacin vs. tolterodine were 8 mls and 15 mls, respectively, both reported as statistically significant.

Critical Appraisal: Solifenacin vs. Tolterodine IR

Risk of bias

Analysis of these trials was hampered by incomplete reporting in the trial publications (e.g., a lack of reporting of measures of variability and evaluable patient numbers). Because of this, useable data for meta-analysis were not available for several outcomes of interest.

For the risk of bias assessment, we used all available data, including data from regulatory sources to provide a measure of the internal validity. Each trial was assessed to be at low risk of bias for selective outcome reporting when all available sources of data were considered. Most of the other methodological domains were assessed as 'unclear' as insufficient detail was provided. None were rated at low risk of bias for blinding of participants and personnel because it wasn't clear whether the placebos were identical in appearance to the test medications, although two indicated a double-dummy technique was used (Chapple 2004b; Choo 2008). No trial adequately described their randomization process or sequence allocation concealment.

In Chapple 2004a and Chapple 2004b, comparisons of active drug were viewed as exploratory as the primary comparison was between solifenacin and. placebo (Chapple 2004b), and between different doses of solifenacin (Chapple 2004a).

Applicability of trial results (external validity)
Dose/comparator choice: These trials compared solifenacin, a long-acting drug, to an immediate release, short-acting formulation of tolterodine. Immediate release formulations have different pharmacokinetics and wider fluctuations in drug levels that can modify clinical effects, including adverse events. For example, tolterodine IR has been associated with more dry mouth than tolterodine ER (see clinical review on different formulations, Chapter 9). A more suitable comparison for solifenacin is an extended release formulation.

The recommended starting dose of solifenacin is 5mg. Comparisons with a fixed dose of 10mg may be less applicable than treatment arms with a 5mg dose, based on IMS data that the majority of prescriptions in Canada are for 5mg (Solifenacin Clinical Update).

All three trials had a placebo run-in phase. Screening out placebo responders modifies the comparisons between placebo and active drug in the two trials that had a placebo control arm (Chapple 2004a; Chapple 2004b), leading to an overestimate of active drug vs. placebo comparisons. A substantive and varied placebo response is observed in OAB trials and may contribute to variability in response in the community setting.

The majority of trial participants were women so generalizability to men may be limited. The QoL instruments used for two of the trials (Contilife; U-UDI) have been validated predominantly in women so these findings, in particular, may not be applicable to men.

Most participants were Caucasian. One of the studies was in an Asian population, representing 23% of the overall participants. This may limit generalizability to diverse racial/ethnic groups.

Harms: None of the trials reported an active, systematic method of assessing and collecting harms data, and no trials actively assessed cognitive effects.

Industry sponsorship: The three trials were sponsored by the manufacturer of solifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

Overall results – comparisons between solifenacin and tolterodine IR

In summary, solifenacin 5mg and tolterodine IR had similar efficacy for the outcome incontinence. In the one trial that provided a measure of variability for the outcome of urgency, both drugs reduced urgency by 2-3 episodes per day from a baseline of 5-6. However, solifenacin reduced average urgency episodes by an additional 0.8 (5mg) or 1.0 (10mg) episodes compared with tolterodine IR. Although solifenacin 5mg was associated with less incidence of dry mouth than tolterodine IR (absolute risk difference 7%), solifenacin 10mg was not. Both doses of solifenacin increased risk of constipation (absolute risk difference 5% for 5mg and 7% for 10mg) compared with tolterodine IR.

RCT outcomes for the comparison solifenacin vs. tolterodine IR are summarized in Table 7.

Table 7. Solifenacin vs. Tolterodine IR. Summary of RCT Outcomes

Outcome	No. of studies (No. of Participants)	RR or MD (95% CI) SOL 5 or 10mg vs. TOL IR 2mg bid (4 mg/d)	Absolute Risk Difference SOL 5 or 10mg vs. TOL IR 2mg bid (4 mg/d)	Summary
All-cause mortality	3 trials (1585) 2 events reported	--	--	- Short-term trials were under-powered to assess any effect on short-term mortality (no events) - No long-term data are available.
Non-fatal SAE	3 trials (1585), 4 events	--	--	- Short-term trials are under-powered (few events) and reporting is incomplete - No long-term data are available
Cognitive AE	0 trials	--	--	- No data available
QoL KHQ	0 trials for meta-analysis	--	--	- KHQ similar between drugs; both drugs improved vs. placebo
Patient-reported improvement	0 trials	--	--	- No data available
WDAE	3 trials (SOL 5: 857) (SOL 10: 843)	SOL 5: RR 1.81 [95% CI 0.78 to 4.23] Soli10: RR 2.13 [95% CI 0.93 to 4.88]	--	- No significant difference between drugs
Incontinence Episodes Mean change from baseline	1 trial (SOL 5: 298) (SOL 10: 315)	SOL 5 vs. TOL -0.50 [95% CI -0.98 to -0.20] SOL 10 vs. TOL: -0.45 [95% CI -0.97 to 0.07]	--	- SOL 5 reduced incontinence episodes by a further 0.5 episode per day vs. TOL. However, the difference between SOL 10 and TOL was not statistically significant.
Urgency Episodes Mean change from baseline	1 trial (SOL 5: 514) (SOL 10: 511)	SOL 5: MD -0.80 [95% CI -1.43 to -0.17] SOL 10: MD -1.04 [95% CI -1.69 to -0.39]	--	- SOL 5 reduced urgency by an additional 0.8 episodes per day -SOL10 reduced urgency by an additional 1.0 episodes per day
Nocturia Episodes Mean change from	0 trials available for meta-analysis; 2 trials report	--	--	- Data not in useable form for meta-analysis and statistical tests NR for comparisons; similar reduction for each

baseline	mean without SD			drug (<1/5th episode difference)
Total AE	3 trials (SOL 5: 852) (SOL 10: 839*)	SOL 5: RR 0.95 [95% CI 0.82 to 1.09] SOL 10: RR 1.12 [95% CI 0.98 to 1.28]	--	- No difference between drugs
Dry mouth	3 trials (SOL 5: 852) (SOL 10: 839*)	SOL 5: RR 0.64 [95% CI 0.46 to 0.88] SOL 10: RR 1.06 [95% CI 0.80 to 1.39]	SOL 5: RD -7% [95% CI -12 to -2%]	- 7% fewer patients on SOL 5 experienced dry mouth vs. TOL IR - No significant difference between SOL 10 and TOL IR
Constipation	3 trials (SOL 5: 852) (SOL 10: 839)	SOL 5: RR 2.91 [95% CI 1.49 to 5.68] SOL10: RR 3.63 [95% CI 1.89 to 6.97]	SOL 5: RD 5% [95% CI 2% to 8%] SOL 10: RD 7% [95% CI 4% to 10%]	- 5% more patients on SOL 5 had constipation vs. TOL IR -7% more patients on SOL 10 had constipation vs. TOL IR
AE=adverse events; **CI**=confidence intervals; **No**.=number;; **MD**=mean difference; **PPBC**, patient perception of bladder condition; **RD**=absolute risk difference; **RR**=relative risk; **SAE**=serious adverse events; **SOL**=solifenacin; **TOL**=tolterodine; **QoL**=quality of life; **WDAE**=withdrawals due to adverse events;				

c. Meta-analyses of solifenacin vs. pooled formulations of tolterodine

We pooled tolterodine IR and ER and conducted subgroup analyses to determine if findings were consistent across formulations for selected outcomes. Below are forest plots for dry mouth, constipation, and urgency incontinence. Solifenacin (5mg or 5/10 flexible dose) was associated with more dry mouth than tolterodine ER but less than tolterodine IR. A summary total is not provided due to the substantive statistical heterogeneity. More constipation was associated with solifenacin (5mg or 5/10 flexible dose) compared with either formulation of tolterodine. For urgency incontinence episodes, when both formulations of tolterodine were pooled, solifenacin (5mg or 5/10 flexible dose) reduced episodes by an additional half episode per day.

Dry mouth

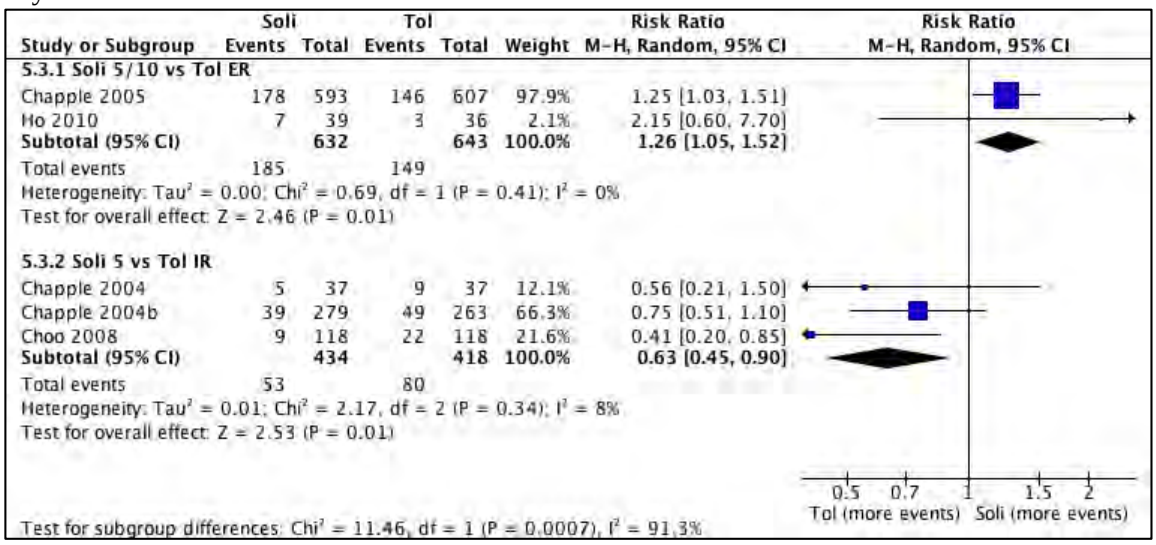

Figure 12. SOL vs. TOL ER and TOL IR

Constipation

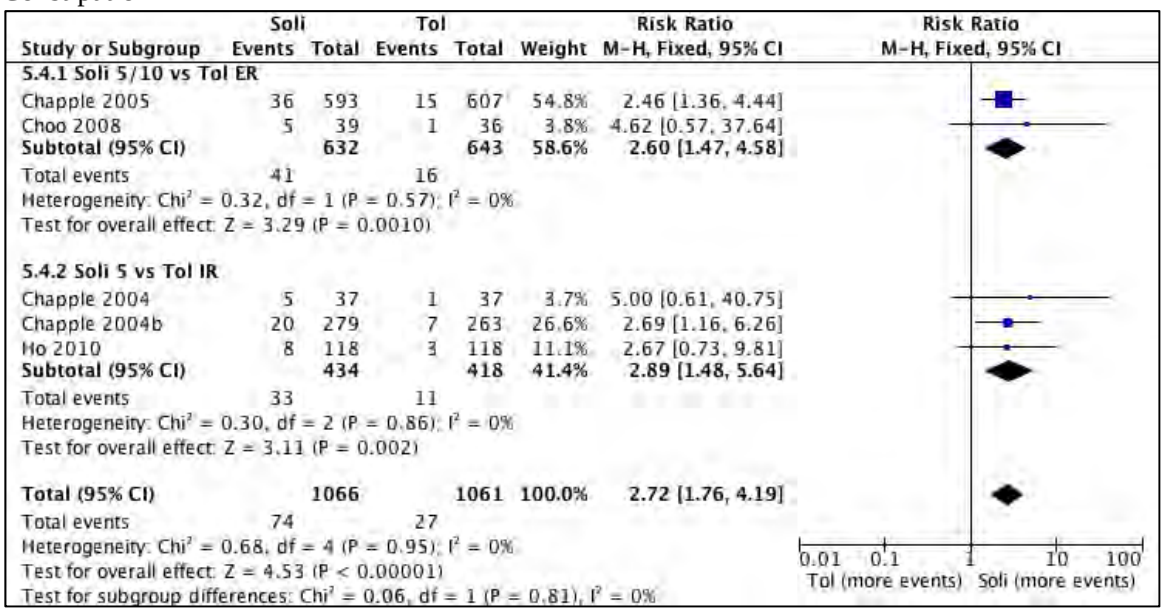

Figure 13. SOL vs. TOL ER and TOL IR

Urgency Incontinence Episodes

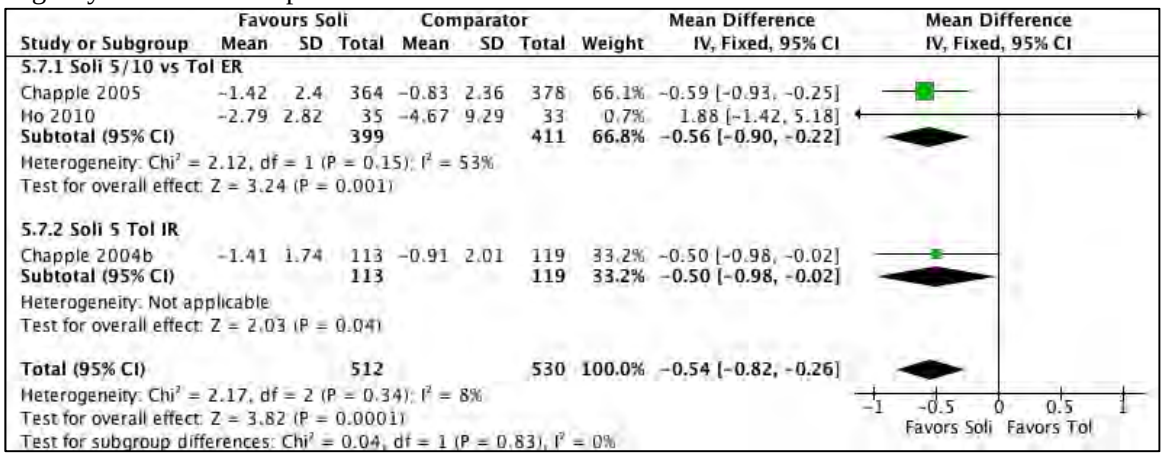

Figure 14 . SOL vs. TOL ER and TOL IR

(2) Solifenacin vs. Darifenacin

One open-label parallel group RCT compared solifenacin 5mg with darifenacin 7.5mg (But 2012). This is a small 12-week trial (N=77) that enrolled ambulatory women (median age 54 years) with urgency intensity and urgency incontinence described as $\geq$ 3 on the Urgency Perception Scale and $\geq$ 1 urgency episode per day. Study characteristics and outcomes are presented in Table 9 in Appendix G. The primary outcome of the study is the number and intensity of urgency episodes using the Urgency Perception Scale, a scale that rates subjective sensation. It is not clear which scale was used as the enrollment criteria suggest this was the Patient Perception of Intensity of Urgency Scale (PPIUS) with a rating from 0 to 4 whereas the Urgency Perception Scale (UPS) has only 3 items/responses (1-3). Although these scales have

been validated in some populations, their use is debated by some investigators as they may confuse normal filling sensations ('urge') with urgency, which is an 'all-or-nothing' phenomenon (Abrams 2012).

1. All-cause mortality – no deaths are reported.

2. Serious Adverse Events (SAE) – no SAE are reported.

3. Withdrawals due to Adverse Events (WDAE) – a similar proportion of patients withdrew due to AE in each group: solifenacin 4/40 (10%) vs. darifenacin 4/37 (11%).

4. Quality of life (QoL) – Two validated questionnaires, the Urogenital Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) were used to assess impact on QoL and effect of treatment. Both questionnaires have acceptable reliability and validity (Hagen 2002; Shumaker 1994). A total of 29 patients were used to calculate treatment differences from baseline to week 12.

The IIQ is a 30-item questionnaire developed to measure psychosocial impact of incontinence in women and has four subscales; physical activity, travel, social relationship and emotional health. Responses of an individual are transformed into subscores from 0 to 100 and the total score is also summed (0 to 400).

The total score of the IIQ and the subscore social relationship domain were significantly improved in the solifenacin group compared to darifenacin: total IIQ: median -35, p=0.018. The 35 point difference in the total score for IIQ is in the range of values for the minimal important difference (Shamliyan 2012).

The UDI measures the degree of bother with obstructive, irritative and stress symptoms and consists of 19 questions. The range of minimal important differences for the UDI (0-300) is -35 to -45 points and for the irritative subscale -15 to -25 points (Dyer 2011). The differences in UDI scores between drugs were not statistically significant nor did they exceed the minimal important difference.

5. Patient-Reported Perception of Improvement /Cure – Patients reported their assessment of treatment improvement on a visual analogue scale (VAS). Improvement or 'success' was not further defined, validation of the VAS was not discussed and the clinical meaningfulness of the difference was not discussed. The VAS score was significantly higher with solifenacin: median 22.5, p = 0.010.

6. Incontinence Episodes –the trial did not report the proportion of patients who were incontinent at enrollment and does not report number of incontinence episodes or change from baseline. There was no significant difference between drugs in incontinence pad usage/day. The difference in median reduction from baseline was 0.6, P=0.19.

7. Nocturia – there was no statistically significant difference in change from baseline between solifenacin and darifenacin at 12 weeks.

8. Urgency – there was no statistically significant difference in change from baseline between solifenacin and darifenacin at 12 weeks.

9. Total AE – the trial did not report on this outcome.

10. Specific AE – the study used a checklist of adverse effects (dry mouth, constipation, blurred vision, headache, dizziness, lack of concentration, memory problems and insomnia) at baseline, 4 weeks, and 12 weeks. However, the proportion of participants who experienced a particular AE at any time throughout the study period is not presented, and cannot be summed from the 4 and 12 week data. A high proportion of participants experienced AE at baseline, and for most AE, incidence decreased during the treatment period. The exceptions were dry mouth and constipation at 4 weeks. The incidence of these events was not significantly different between active drugs. Although the authors state there was a decreased incidence of dry mouth after 12 weeks in the solifenacin group compared with darifenacin, the numerical difference was not statistically significant: RR 0.65 (95% CI 0.39 to 1.09), P=0.10.

11. Urodynamics/clinician measures – the trial did not measure these outcomes.

12. Mean volume voided – the trial did not measure these outcomes.

Critical Appraisal: Solifenacin vs. Darifenacin

Risk of bias

But 2012 is a small study termed ‘exploratory’ by its investigators, without sample size or power calculation, and failed to meet its stated recruitment goal of 100 patients. Randomization was adequate but allocation concealment is not described. The study was open-label and therefore at high risk of performance and detection bias, particularly for subjective outcomes such as patient reported treatment success, quality of life or symptom bother. It is unclear if all outcomes are reported and none are identified as pre-defined. The withdrawal rate was 21%, with similar proportions and reasons for withdrawal from each arm. The study reports a per protocol analysis, rather than intention-to-treat and it is likely that patients who withdrew differed from completers.

The data did not meet normality assumptions so medians are reported and a non-parametric test was used to test treatment differences. No adjustments were made for multiple significance testing, with the reason given that the study was exploratory.

The study actively collected harms data by using a checklist. However, the high proportion of AE at baseline and the reduction in AE frequency during the study confounds interpretation of AE data. It is surprising, for example, that nearly half of patients randomized to darifenacin (47%) report dry mouth at baseline, although one of the study inclusion criteria was no anticholinergic drug use for 6 months pre-enrollment. In addition, the study does not report the cumulative numbers of patients experiencing a particular AE throughout the entire course of the study.

Applicability

Because the trial was conducted solely in women, and used QoL instruments predominantly validated in women, generalizability to men is limited. Additionally, subjective outcomes in an open-label trial may strongly reflect expectation bias.

Comparator choice: both drugs are long-acting so this is a reasonable comparison. The recommended starting dose of both drugs was chosen as a fixed dose.

The study does not report whether it was industry-sponsored. However, it is likely to be industry sponsored as statistical analysis was carried out by a contract research organization (CRO) that carries out clinical trials, statistical analysis and medical writing for the pharmaceutical industry, Wilkinson Associates. See for example: http://www.wilkinson-associates.co.uk/clients.shtml.

In summary, this small exploratory study does not provide evidence that solifenacin has a therapeutic advantage over darifenacin in the treatment of women with urgency.

Non-Randomized Studies

The aim in including non-randomized studies is to gain information on serious, infrequent adverse events, longer term harms, and adverse effects in populations not adequately represented in the RCTs.

There were no non-randomized observational studies comparing solifenacin to oxybutynin. Our literature search identified three uncontrolled cohort studies that met study inclusion criteria + 3 case reports. We do not report on efficacy outcomes as uncontrolled cohort studies provide unreliable estimates.

- Uncontrolled cohort analyses (3)
  - Michel 2008;
  - Garely 2006 (also described in Capo 2008; Garely 2007; Lucente 2010; Mallet 2007; Sand 2009; Chancellor 2008; Swift 2009; Capo 2011);
  - Haab 2005
- Case reports (3)
  - Asajima 2008; Pemmaraju 2008; Shalders 2007

Findings from published non-randomized studies

Table 8 describes study design, data source, duration, numbers and age of subjects and assessed outcomes.

Table 8. Non-randomized studies to evaluate solifenacin vs. oxybutynin

Study	Design	Data source	Duration	SOL Sample size Age	Assessed outcomes
Garely 2006	Uncontrolled cohort	US, clinical population; VOLT Primary publication	12 weeks	N=2225 Mean age 60 ±14	Total withdrawal Total AE
Haab 2005	Uncontrolled cohort	Extension study, two 12-week RCTs (82% enrolled)	40 weeks	N=1633 Mean age 56 ±14	WDAE
Michel 2008	Uncontrolled cohort	Germany, clinical population, urologists	12 weeks	N=4450 Mean age 64 ± 13	Deaths, SAE Total withdrawal WDAE Total AE

The VESIcare Open-Label Trial (VOLT), primary publication by Garely 2006, reports on 2225 patients (n=82.2% female) over a 12-week period in 207 clinical centres in the US. Patients were started on 5mg/day for 4 weeks, which could be titrated to 10mg if desired (51.8% of patients). Six companion papers present post hoc analyses of subgroups or report on specific outcomes: Hispanics (Capo 2008), blacks (Mallett 2007); patients ≥ 65 (Capo 2011), duration of symptoms

(Lucente 2010), incontinence as most bothersome symptom (Garely 2007) and most bothersome symptom (Sand 2009).

Haab 2005 reports on a 40-week open-label extension trial involving participants in two placebo-controlled RCTs. Dosing could be adjusted at weeks 4, 16 and 28 of the open-label extension period, and AE are reported separately for patients on solifenacin 5mg or 10mg.

Michel 2008 reports on 4450 patients (83.5% female) of 1316 German urologists. The only inclusion criteria was age ≥ 18 years and solifenacin prescription for OAB. The study actively sought data on heart rate and blood pressure. Comorbid cardiovascular conditions were also reported. Adverse event reporting was passive. Most patients (72%) received 5mg/day solifenacin to the final visit but 19% were titrated to 10mg.

Table 9 summarizes the rates of observed AE for the three uncontrolled cohort studies. Michel 2008 reports a 0.3% rate of SAEs (fatal and non-fatal). No difference was seen in blood pressure or heart rate at 12 weeks versus baseline. In regression analysis, the odds ratio for experiencing an AE was 3.9 (95% CI 1.3-11.5) in patients > 80, as compared to those ≤ 40. Co-medication use was associated with higher risks of AE: OR =1.8 (95% CI 1.2-2.6). Without controls, however, attribution to solifenacin use is not possible.

In Garely 2006, a 3% rate of SAE was reported in patients ≥ 65 and 1% in those <65; estimated 1.8% in all included patients (Capo 2011). Few differences were reported in AE rates for patients <65 and ≥65, but the cohort's mean age was 60. More patients ≥ 65 than <65 withdrew due to adverse events: 219 (25%) vs. 249 (19%), chi square analysis, p<.01.

Table 9. Adverse events reported in uncontrolled cohorts

Adverse events	Haab 2005 40 weeks (n=1633)		Michel 2008 (n=4450) 12 weeks	Garely 2006 12 weeks (n=2225 total)	
	SOL 5mg (n=1633)	SOL 10mg (N=1114)§		Entire cohort (n=2225) Mean age 60 ±14	Patients ≥65 (n=892)* Capo 2011 Mean age 74 ±6
All-cause mortality	NR		4 (0.09%)	1 (0.04%)	1 (0.1%)
Non-fatal SAE	NR		9 (0.2%)	1.8%**	3%**
Total Withdrawals	304 (18.6%)		304 (6.8%)	482 (21.7%)	219 (24.9%)
WDAE	4.7%		62 (1.4%)	216 (9.7%)	104 (11.7%)
Total AE	NR		215 (4.8%)	1321 (59.4%)	529 (59.3%)
Dry mouth	167 (10.2%)	194 (17.4%)	NR	477 (21.4%)	205 (23.0%)
Constipation	80 (4.9%)	88 (7.9%)	NR	295 (13.3%)	140 (15.7%)
Nausea	NR		NR	39 (1.8%)	15 (1.7%)
Dyspepsia	NR		NR	34 (1.5%)	NR
Blurred vision	67 (4.1%)	49 (4.4%)	NR	57 (2.6%)	24 (2.7%)

Dry eye	NR	NR	29 (1.3%)	15 (1.7%)

AE=adverse events; **SAE**=serious adverse events; **SOL**=solifenacin **WDAE**=withdrawals due to adverse events; **NR**=not reported;
§ denominator = patients on solifenacin 10mg at any time; numerator = dose at time of AE;
*reported as 892 in AE analyses; 880 elsewhere in paper – no explanation.
**estimates based on a reported 1% rate in patients <65; 3% in those ≥65.

Study quality /risk of bias
Haab 2005 is an open-label extension study post RCT, which includes only patients who completed the trial and agreed to further medication (82% of total). There is limited reporting of harm outcomes, for example mortality, SAE, and total AE are not reported. The study provides very limited outcome data; it confirms a dose-response for anti-muscarinic AE such as dry mouth and constipation. AE reported during the 12-week RCTs were combined with those in the 40-week open-label extension phase and it was unclear how the authors dealt with patients who had been on placebo or tolterodine in the initial RCTs, or how denominators were adjusted to reflect this. The open-label phase included very few assessments (3 in 40 weeks).

With a follow-up period of 12 weeks, Michel 2008 and Garely 2006 do not provide information on longer-term safety. The low AE rate in Michel 2008 is striking, especially as 68% of patients had coronary heart disease, congestive heart failure or diabetes. The <5% total AE rate contrasts with the 22% rate in Garely 2006, and suggests under-reporting. Both studies relied on passive AE reporting. The large number of urologists enrolled in Michel 2008 and very few patients per physician (mean of 3.4) is suggestive of a market seeding trial. US FDA officials described seeding trials as studies with a primary aim of enticing physicians to prescribe a new medication (Kessler 1994). Both studies would be rated as very weak methodology and high risk of bias, given the lack of control group, blinding or active AE reporting. Results of the VOLT study (Garely 2006) are reported in a total of 7 articles, a high rate of duplicate publication.

All three uncontrolled cohort analyses were industry-sponsored.

Other Adverse Event Data

Case reports
Case reports may provide signals of previously unrecognized or rare adverse events. Table 10, on the following page, presents the details of the 2 published case reports of solifenacin SAE and a 3rd case of an unexpected AE. The report of QT prolongation and torsade de pointes is of particular concern as torsades de pointes is a life-threatening AE. This was the first case reported for solifenacin although additional cases are now identified in the PSUR. (*Note: the US FDA added this AE to labeling in 2008 and Canada has done so more recently)*. Terodiline, another antimuscarinic drug for OAB, was withdrawn from market for this serious cardiac AE. The second report is of small bowel pseudo-obstruction, acute renal failure and urinary retention. The third is of a photodistributed lichenoid drug eruption (LDE), a rash on skin exposed to sun, and the first LDE report with an antimuscarinic drug. The patient had been taking other medications for ≥ 3 years; resolution following solifenacin withdrawal is suggestive of causation.

Table 10. Case reports of solifenacin AE

Study	Exposure (drug and dose)	Patient (sex and age)	Adverse event	Outcome
Asajima 2008, Japan	SOL 5mg qd x 9 days + amlodipine + antibiotics	81 year old female with history of sick sinus syndrome admitted to hospital with hip/joint dislocation/infection one year post hip arthroplasty	QT prolongation, recurrent loss of consciousness and torsade de pointes	Resuscitated with DC shock. ECG abnormalities resolved a few days after stopping SOL
Pemmaraju 2008, USA	SOL 5mg qd x 10 days + multiple other	89 year old female with hemicolectomy and colostomy	Small bowel pseudo-obstruction, acute renal failure and urinary retention	Resolution after stopping SOL
Shalders 2007, UK	SOL dose NR x 4 months; polypharmacy for ischemic heart disease; including other drugs implicated in LDE	55 year old male with history of ischemic heart disease	photodistributed lichenoid drug eruption starting one month after initiation of solifenacin	Gradual resolution w/ topical corticosteroid 5 months after stopping SOL; post inflammatory hypopigmentation and hyperpigmentation

LDE=lichenoid drug eruption; NR=not reported; SOL=solifenacin; qd=every day

Regulatory Data

Data on adverse events was sought from government and regulatory resources including periodic safety update reports (PSURs), the Health Canada Vigilance Database records and the U.S. Food and Drug Agency new drug application reviews and safety updates. Pharmacosurveillance databases have major limitations including under reporting and lack of denominator data which precludes rate calculations.

Periodic Safety Update Reports (PSUR)

One recent periodic safety update report (PSUR) for solifenacin – the 13th – was obtained for this review. It covers the one year period from June 9th, 2011 to June 8th 2012 during which approximately 2 million patient years of exposure occurred in the 72 countries in which solifenacin in available. The international birthdate for solifenacin succinate is June 8th, 2004. Cumulative exposure for 8 years of post-market data represents approximately 8.2 million patient years.

The PSUR provides detail only for "medically-confirmed" cases during the entire exposure period. These are cases that were reported by health professionals, published case reports, AE during clinical trials or were noted in registries or special programs. They exclude consumer reports and non health professional reports. In total there were 6017 medically confirmed reports during 8 years of marketing; 720 patients experienced serious and unlisted events (936 events).

Table 11, below, provides an overview of medically confirmed CNS and psychiatric disorders listed in the PSUR for the 8-year period, in order of frequency.

Table 11. Cumulative Summary – medically confirmed psychiatric and CNS disorders

Event	Total AE #	SAE #
Insomnia	47	2
Amnesia	28	5
Memory impairment	27	3
Dementia	26	17
Cognitive disorder	20	6
Nightmare	16	0
Agitation	14	7
Restlessness	8	2
Abnormal behaviour	7	2
Abnormal dreams	4	1
Mental status change	4	2
Mental impairment	3	1
Speech disorder	3	2
Mental impairment	3	1
Aggression	3	1
Dementia – Alzheimer's type	2	2
Dementia – with Lewy bodies	2	1
Terminal insomnia	1	0

Source: Tables 50 and 51, Vesicare (Solifenacin) PSUR

Highlighted concerns – Parkinson's Disease and muscle weaknesses

There were 29 medically confirmed cases of Parkinson's disease over this 8-year period, and 40 cases of muscle weakness in the cumulative spontaneous reports described in the PSURs. Both were highlighted by regulators as signals of concern, requiring further investigation by the manufacturer. As noted below, muscle weakness has been highlighted in labeling as a safety concern.

Interstitial lung disease was also highlighted, with a cumulative total of nine cases and will continue to be monitored by the manufacturer, as will cardiac arrhythmias, other cardiac events and hypertension.

Non-fatal Serious Adverse Events – June 2011 to 2012

There were 202 medically confirmed SAE amongst the 1467 medically confirmed case reports for the year long period. There were 1486 consumer cases reported involving 3124 AEs of which 184 were serious.

The one-year SAE data provided was not comprehensive. The following information in Table 12 is on select SAEs of interest reported by medical professionals.

Table 12. Unlisted Select SAEs presented in 1 year PSUR June 2011/12

Adverse Event Preferred Term	Medically Confirmed* reports	Consumer/ non-health professional reports	Total
Cardiac disorders	22	7	29
Chest discomfort/ chest pain	6	3	9
Hypertension	2	2	4
Dementia / Cognitive disorders	12	1	13
Psychiatric disorders	6	1	7
Glaucoma/ Intraocular pressure	7	3	10
Drug interactions	4	2	6

Gastro-oesophageal reflux disease/ dyspepsia	4	0	4
Muscular weakness	2	1	3
Renal failure acute	2	1	3
Ileus/ Intestinal obstruction	2	1	3

*reported by a health professional, in a clinical trial, published case report, or registry.
Source: Appendix-3-1-1: All Medically Confirmed Serious Cases, Summary Tabulation: p.166-184 and Appendix 3-2: Medically Unconfirmed Cases, Summary Tabulation p. 1228-1247.

Deaths – June 2011 to 2012

Data on deaths were available only for the one-year period June 2011/12. There were 26 cases with fatal outcome amongst the 1467 "medically-confirmed" and 1486 non "medically-confirmed". Six deaths were medically confirmed: 1 cardio-respiratory arrest (following sequelae of a fall); 1 cardiac disorder (no additional information), 1 ileus (follow-up report indicated that patient had not taken solifenacin), 1 death (no additional information), 1 accidental overdose (assessed as morphine related) and 1 large intestine perforation (tumour)/ septic shock (assessed as unrelated). Of fatal SAE that were consumer-reported 13 were described only as death, 1 as death /intra-abdominal hematoma, 3 pneumonia, 1 dementia/pneumonia and 2 neoplasms**.**

The Elderly

The 13th PSUR provided a presentation of the anticholinergic AEs with the highest reporting rate in elderly and non-elderly users of solifenacin. This analysis was carried out at the request of the European Medicines Agency. This comparison is suggestive only as it suffers from two limitations: 1) lack of denominators for the exposed elderly and non-elderly groups; 2) unknown and likely variable extent of under-reporting in spontaneous AE reports.

Table 13. Medically Confirmed Anticholinergic AEs; Elderly vs Non-Elderly June 2011-12

AE	Elderly Age ≥ 65 # (% of reports)	Non-elderly Age < 65 # (% of reports)	Total (includes those w/ age unknown)
Urinary retention	34 (4.6%)	14 (2.7%)	57 (3.4%)
Constipation	81 (11.0%)	43 (8.2%)	152 (9.2%)
Dry mouth	141 (19.2%)	92 (17.6%)	313 (18.9%)
Vision blurred	23 (3.1%)	26 (5.0%)	60 (3.6%)

Adapted from: Table 45, page 102, June 2011-2012 PSUR

A recently completed placebo-controlled, three-way crossover study investigating the cognitive effects of solifenacin and oxybutynin ER in subjects ≥ 75 with mild cognitive impairment (the SENIOR study) was also summarized and is now published (Wagg 2013) – see cognition Q3.

Changes to Reference Safety Information

A number of changes were made to solifenacin's reference safety information during the time period covered by this PSUR dated June 2011-12 (see Appendix G 'US FDA - post-market labeling changes' for changes prior to PSUR 13). All these additions represent harms not identified by the initial RCTs.

Changes pertain to:

- Driving and heavy machinery precaution (identifies somnolence as well as blurred vision as potentially affecting ability to drive or use machinery)
- A new safety signal – muscle weakness
- Specific adverse events added:

- Dysphonia
- gastroesophageal reflux disease
- glaucoma
- ileus

Changes made in Canada during the PSUR period include the following:

- Angiooedema, Anaphylactic reaction, QT prolongation and Torsade de Pointes were added to the Warnings and precautions
- The following events were added to the Post-Marketing adverse drug reactions: - Torsade de Pointes - Glaucoma - Gastro-oesophageal reflux disease - Ileus - Liver disorders - Anaphylactic reaction - Somnolence - Confusional state - Delirium - Disorientation - Renal impairment - Dysphonia- Angiooedema - Exfoliative dermatitis, Erythema multiforme

Canada Vigilance Adverse Reaction Online Database

There were 31 adverse reaction reports related to solifenacin use identified by searching the Canadian Vigilance Dataset to December 31, 2012.

Fatal SAE: No deaths were reported.

Non-fatal SAE: Twelve of the 14 SAE reports were in females. Age ranged from 40 to 92 (mean 64) with age unknown in 6 cases. Cases included: diplopia/migraine with aura (1); headache (1); Amnesia/anxiety (1); major depression (1); affective disorder/BP increase/other (1); pyelonephritis/urinary tract infection (1); urinary retention (1): blood pressure increased (2) (1+fluid retention); macular degeneration (2); eye/neck pain (1); myasthenia gravis/thymic neoplasm/pneumothorax/respiratory failure (1); pulmonary edema/fluid retention (1). Of these, 7 were categorized as nervous system and/or psychiatric disorders.

Discussion and Conclusions

Q1: Does solifenacin provide a therapeutic advantage over oxybutynin IR or other comparators?

Short-term RCT data (4-12 weeks) are available comparing solifenacin with the following three comparator drugs: oxybutynin IR, tolterodine and darifenacin. There were no trials comparing solifenacin with trospium, fesoterodine, or other formulations of oxybutynin.

Solifenacin vs. oxybutynin IR

One trial was included for this comparison (Herschorn 2010). The one available trial is small (132 patients) and had a primary outcome of dry mouth. The study was at high risk of bias on the basis of the different rates of early withdrawals between groups, and use of per protocol analyses.

Solifenacin-treated patients (5mg/day) had fewer WDAE (absolute risk difference 15%), fewer AE overall (absolute risk difference 20%), and less dry mouth (absolute risk difference 48%) than patients on oxybutynin IR (total 15mg/day). In this trial, a higher proportion of patients in the oxybutynin group reported dry mouth (83%) than in other studies included in this review. This may have reflected sensitization of patients to the outcome and over-reporting. On the other hand,

trials that passively collect data may under-report. Patients on solifenacin experienced more constipation than those on oxybutynin IR but the difference was not statistically significant.

Solifenacin showed a trend for less efficacy than oxybutynin for most efficacy outcomes including patient-reported outcomes (QoL, patient perception of bladder condition (PPBC), reduction in incontinence episodes, and nocturia). The difference in efficacy was statistically significant for only one outcome (PPBC), in favour of oxybutynin IR, with the small difference of uncertain clinical m subgroup analysis by age indicated the AE profile was qualitatively similar in younger and older populations but was exploratory only and did not preserve randomization as the trial was not stratified by age.

As the comparison was based on a single trial of low quality, evidence is insufficient to conclude whether solifenacin has a therapeutic advantage (incorporating benefit and harm) over oxybutynin IR. The high rates of dry mouth and total AE on oxybutynin in this trial raises concerns about the profile of harmful effects with this dose and formulation of oxybutynin.

There are no available trials that compare an extended release formulation of oxybutynin with solifenacin. An extended release formulation is a more appropriate comparison. Extended release formulations have less fluctuation of drug plasma concentrations and oxybutynin ER has been shown to have a lower incidence of dry mouth compared with the immediate release formulation (see Chapter 9; also Madhuvrata 2012).

Solifenacin vs. Tolterodine ER or IR

For the comparison of solifenacin vs. tolterodine, solifenacin 5mg or 5/10mg flexible dose was associated with more dry mouth than tolterodine ER but less than tolterodine IR. Patients on solifenacin experienced more constipation (5mg or 5/10 flexible dose) compared with either formulation of tolterodine. For urgency incontinence episodes, when both formulations of tolterodine were pooled, solifenacin (5mg or 5/10 flexible dose) reduced episodes by an additional half episode per day: mean difference -0.54 (95% CI -0.82 to -0.26). Solifenacin also reduced urgency episodes by an additional half episode per day compared with either formulation of tolterodine.

The quality of evidence for this comparison is moderate. In general, analysis of solifenacin vs. tolterodine was hampered by outcome under-reporting (e.g., measures of variability and denominators for evaluable patients were not consistently reported) as well as the non-parametric nature of some of the data. Because of this, data for meta-analysis were not available for several outcomes. The comparison of solifenacin with each tolterodine formulation is summarized separately below, starting with the most relevant comparison, tolterodine ER.

Solifenacin vs. tolterodine ER: Solifenacin 5/10mg and tolterodine ER (4mg/day) had similar WDAE and total AE, but 6% more patients on solifenacin experienced dry mouth, and 4% more patients had constipation compared with tolterodine ER. In the largest trial, Chapple 2005, solifenacin 5/10 reduced incontinence episodes by an additional 0.6 episodes per day, and 9% more patients achieved continence (3-day time period). The differences for both efficacy and AE are modest. There was no difference in nocturia. The use of a flexible dosing regimen for solifenacin obscures the extent of dose-response for solifenacin, and may underestimate the differential AE profile of the two drugs. The overall strength of evidence is moderate.

Solifenacin vs. tolterodine IR: Both drugs had similar WDAE and total AE, but solifenacin 5mg was associated with less incidence of dry mouth than tolterodine IR (total 4mg/day) (absolute risk

difference 7%). However, patients taking solifenacin 10mg had similar a frequency of dry mouth to tolterodine IR, reflecting the known dose-response with solifenacin (Madhuvrata 2012). There was more constipation with both doses of solifenacin (absolute risk difference 5% for 5mg and 7% for 10mg) compared with tolterodine IR.

Both drugs reduced incontinence from a baseline of about 2 episodes but solifenacin 5mg was modestly better by an estimated additional half an episode per day. However, the difference between solifenacin 10mg and tolterodine IR was not statistically significant. There was no difference in nocturia. One trial provided adequate data to estimate absolute differences in rates of urgency; both drugs reduced urgency by 2-3 episodes per day from a baseline of 5-6. However, solifenacin reduced average urgency episodes by an additional 0.8 (5mg) or 1.0 (10mg) episodes compared with tolterodine IR.

Overall, there is more dry mouth with tolterodine IR vs. solifenacin but less constipation, with a similar magnitude of effect for each adverse event. The magnitude of differences in efficacy outcomes is small. The overall strength of evidence is moderate.

Solifenacin vs. darifenacin
There is insufficient evidence to determine whether solifenacin has a therapeutic advantage over darifenacin. One small, non-blinded trial compared solifenacin with darifenacin in women for the outcome urgency and nocturia but not incontinence (But 2012). The quality of the trial is poor.

But 2012 is a small study (77 patients) termed ‘exploratory’ by its investigators, without sample size or power calculation, and failed to meet its stated recruitment goal of 100 patients. The study was open-label and therefore at high risk of performance and detection bias, particularly for subjective outcomes such as patient reported treatment success, quality of life or symptom bother. It is unclear if all outcomes are reported and none are identified as pre-defined. The withdrawal rate was 21%, with similar proportions and reasons for withdrawal from each arm. The study reports a per protocol analysis, rather than intention-to-treat and it is likely that patients who withdrew differed from completers. There was no adjustment for multiple comparisons. AE are incompletely reported.

Conclusions cannot be drawn from this trial due to its methodological limitations.

Cognitive effects: No long-term data are available, and the one short-term steady-state trial that compared solifenacin 5mg once daily with oxybutynin IR (10mg total/day) in healthy volunteers aged 75 years or older provides insufficient evidence upon which to draw conclusions about the relative short-term cognitive effects of each drug. There are no available studies in OAB patients that were adequately powered for CNS effects or actively assessed cognition.

Comparison with other systematic reviews: Our findings are consistent with prior reviews (Madhuvrata 2012; Shamliyan 2012). In comparison with Madhuvrata 2012, we had additional information for at least one trial (Herschorn 2010), adjusted patient denominators for at least one trial, and identified one small trial for the comparison solifenacin vs. darifenacin.

Supplemental AE data: No comparative non-randomized studies were identified. Three uncontrolled cohort analyses were identified. Two were short-term (12 weeks) and the other was a 40 month extension phase that confirmed a dose response for anticholinergic AE for solifenacin, with more dry mouth at higher doses.

Signals highlighted in the available Periodic Safety Update included a signal for muscle weakness and a possible signal for Parkinson's disease. Events targeted for further monitoring by the manufacturer also include cardiac events such as arrhythmias, and interstitial lung disease. Because of the limitations of voluntary reporting systems, such data can be used for signal detection only and not incidence rates.

Of particular concern with solifenacin is its long half life and the need to adjust dose for kidney impairment. Because the drug is used in the elderly, this may increase drug-drug interactions or increase risk of adverse events, including their duration following discontinuation of the drug. The increased rate of constipation and cases of intestinal obstruction or ileus are also of concern. Effects on gastrointestinal motility are a well-known anticholinergic effect. However, solifenacin increased the risk of constipation in RCTs over the comparator tolterodine ER or IR.

Gaps in evidence
There is no evidence available to assess long-term comparative benefits and harms of solifenacin, as compared with oxybutynin or any of the other drugs included in this review.

None of the trials assessed patients who are refractory to, or intolerant of, oxybutynin IR.

There continues to be insufficient evidence on comparative, cognitive effects in both the short- and long-term in OAB patients.

There is need for well-conducted, independent direct comparator trials. All available trials comparing solifenacin to other drugs were industry-sponsored. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007).

Because of the substantive placebo response, trials should include a placebo arm. While some of the available trials did so, they also had placebo run-in phases that would have screened out placebo responders, leading to an overestimate of the effect of active drug in any comparison of active drug vs. placebo, and limiting generalizability to usual practice.

In summary, evidence is sparse for the comparison of solifenacin with oxybutynin IR, of low quality, and insufficient to conclude whether solifenacin has a therapeutic advantage (incorporating benefit and harm) over oxybutynin IR. However, the evidence is suggestive that solifenacin may have a therapeutic advantage and needs to be verified in larger studies.

There is no evidence of an advantage for solifenacin versus tolterodine IR or ER, insufficient evidence to judge effects versus darifenacin, and no comparisons with trospium or fesoterodine.

Q2. New Evidence since the CDR Review

There have been two submissions to CDR, a 2009 resubmission and the original submission considered January 24, 2007. The CDEC resubmission recommendation (dated May 20, 2009) was to list the drug for patients who cannot tolerate or have an insufficient response to an adequate trial of immediate-release oxybutynin, and to list in a similar manner as drug plans list tolterodine.

A total of six active comparator RCTs are identified in the 2009 CDR review:

- Herschorn 2010 (VECTOR clinical study report) (solifenacin vs. oxybutynin IR)
- Choo 2008 (solifenacin vs. tolterodine IR)
- Chapple 2004a = Study A005 (solifenacin vs. tolterodine IR)
- Chapple 2004b = Study A015 (solifenacin vs. tolterodine IR)
- Chapple 2005 = STAR trial (solifenacin vs. tolterodine ER)
- Wesnes 2009 = SCOPE trial – included as supplemental information on cognition as it is a healthy volunteer RCT.

A clinical update submission has also been provided by the manufacturer for the current review. All identified studies in the clinical update were included in the literature database and screened for Q1. The majority were placebo-controlled trials and not eligible for this review as they are not direct comparator RCTs.

In the current review, we identified three additional direct comparator RCTs plus one additional subanalysis:

- Wagg 2013 (solifenacin vs. oxybutynin IR), N = 26 – assessing cognition in the elderly;
- Ho 2010 (solifenacin vs. tolterodine ER), N = 75
- Chapple 2007 (solifenacin vs. tolterodine ER, predefined subanalysis of the STAR trial at 4 weeks, a time point when all participants in the solifenacin group were taking 5mg/day)
- But 2012 (solifenacin vs. darifenacin), N = 77

The current review found no evidence to support the CDEC recommendation in populations who were refractory to or intolerant of oxybutynin. Furthermore, a refractory population or an insufficient response to oxybutynin was not defined in any of the trials or observational studies.

The additional RCTs do not provide evidence that would modify the conclusions of the CDR 2009 review substantively. However, we note that the CEDAC recommendation for listing for patients who are refractory or intolerant of oxybutynin IR was not based on evidence in the CDR review, and there have been no RCTs conducted specifically in these populations since the CDR assessment.

Q3. Cognition

Two active comparator and placebo-controlled crossover trials, sponsored by the manufacturer of solifenacin, assessed cognition in elderly volunteers, one a pilot study on healthy volunteers (Wesnes 2009), and the other, a study on 26 volunteers who had mild cognitive impairment (etiology not determined) (Wagg 2013).

Wesnes 2009 was a three-way crossover pilot study that conducted a battery of computerized cognitive tests in 12 elderly healthy volunteers, before and after a single dose of solifenacin 10mg, oxybutynin IR 10mg or placebo. The results are not presented here because the dose of oxybutynin IR was twice the maximum recommended single dose. This dose choice limits the utility and applicability of the findings, which cannot be used as the basis of conclusions about the comparative cognitive effects of recommended doses.

Wagg 2013 compared solifenacin 5mg daily with oxybutynin 5mg b.i.d and placebo in 26 men and women, aged 75 years or older (mean age ~79), who had mild cognitive impairment. Cognitive ability was tested at baseline and, at steady state after 21 days of treatment. The trial

used the same cognition testing system as Wesnes 2009, a battery of proprietary computerized tests on attention, reaction time and memory that involved a total of 17 different measures, and five composite outcomes, each with results from 2-5 separate tests, and a sensitivity index for recognition. Testing was conducted at multiple times pre- and post dose (1 to 6 hours). Five composite outcomes at estimated peak blood concentrations of each drug are identified as the primary outcome for the study. There is little information provided about the sensitivity of scores or minimal clinically meaningful differences, and statistical testing is reported for the comparison vs. placebo only. There were no differences in any of the composite outcomes when each drug compared to placebo. Outcomes are described below according to the review hierarchy.

1. All-cause mortality – no deaths are reported.

2. SAE - 2 SAE are reported but not the treatment or details of the events, which were judged not related to treatment.

3. WDAE – there were two WDAE, one for dry mouth and one for oral candidiasis. The treatment period for the withdrawals is not stated.

4. Cognition

At estimated peak dose level (6 hours for solifenacin and 2 hours for oxybutynin), there were no statistically significant changes from baseline when each drug was compared with placebo. No statistical testing was conducted for a direct comparison of the active drugs. Post hoc analyses were performed pooling different time points but are exploratory only and are not presented here.

Table 14. Results of Cognitive Tests Solifenacin or Oxybutynin IR vs. Placebo Wagg 2013

Study	**Treatment**	
Treatment	Solifenacin 5mg once daily for 21 days	Oxybutynin IR 5mg bid for 21 days
N	N=26 randomized N=23 (completed cognitive function tests for 2 or more treatment periods)	
Cognitive function assessment	Change from baseline vs. placebo* LSM (95% CI)	
Time of measurement	Solifenacin 6 hours post dose in steady state	Oxybutynin 2 hours post dose in steady state
Power of attention, ms *- low score reflects a fast reaction time and a high intensity of concentration.*	-20.99 (95% CI -68.58 to 26.61)	17.51 (95% CI -28.85 to 63.87)
Continuity of attention, no. *high score = ability to keep mind on a single task for a prolonged period.*	-0.51 (95% CI -2.29 to 1.28)	-0.79 (95% CI -2.12 to 0.54)
Quality of Working Memory Sensitivity Index *high score reflects a good working memory*	-0.04 (95% CI -0.21 to 0.13)	-0.05 (95% CI -0.19 to 0.10)
Quality of Episodic Memory, % *- a high score reflects a good ability to store, hold and retrieve information of an episodic nature (e.g., an event or name)*	4.66 (95% CI-14.86 to 24.17)	-1.46 95% CI -18.98 to 16.06)
Speed of Memory (milliseconds) **(95% CI)** *- low score reflects the ability to quickly recall of a name, face or any other item.*	-77.92 (95% CI -372.81 to 216.98)	157.78 (95% CI -182.02 to 497.58)

*Active drug was compared to placebo only; the difference was not significant vs. placebo for any comparison.

5. **Total AE** – rates of total AE did not differ significantly between solifenacin and oxybutynin although numerically more participants experienced AE in the oxybutynin group: solifenacin 61% vs. oxybutynin 84%.

6. **Specific AE**
Dry mouth: solifenacin was associated with less dry mouth than oxybutynin: 17% vs. 52%; RR 0.33 (95% CI 0.12 to 0.87), P=0.03; absolute risk difference 3% (95% CI 1% to 6%).

Reported CNS effects did not differ between active drugs. For additional information on specific AE, refer to Table 10 in Appendix G.

Critical appraisal
Risk of bias/quality assessment
Participants were randomized to different sequences of treatment, as appropriate for a crossover trial, but the process used for generation of the randomization sequence is not described. The washout period between treatments was appropriate. Although matching placebos were used in the trial, the increased rate of dry mouth in the oxybutynin group is likely to have broken blinding. The primary analysis was conducted on 23/26 participants who completed cognitive function tests for at least two treatment periods. There were six withdrawals, two for AE and the other four are not accounted for.

There are multiplicity concerns with use of so many outcomes and time points. A repeated measurements model was not used based on the results of the pilot study, which suggested nonparallel treatment slopes over time.

Applicability of trial results (external validity)
No information is provided about minimal clinically important differences in composite outcomes, or the sensitivity of tests, limiting interpretability. The participants had mild cognitive impairment but were relatively high-functioning as participants with a Mini-Mental Status Examination (MMSE) score of $\leq$ 23 were excluded. The results may therefore not be applicable to patients with more extensive cognitive impairment.

Dose choice: both drugs were used in recommended doses and doses are comparable. However, drug levels were not measured to ensure that measurements were taken at the peak steady state blood concentrations of drug. The choice of time point based on the estimated peak blood concentrations also may not represent the timing of peak effects on the central nervous system.

The trial was sponsored by the manufacturer of solifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

In summary, this trial provides insufficient evidence with which to conclude an advantage for either drug in terms of short-term (3 weeks) cognitive effects. There are no comparative studies on the effects of solifenacin and oxybutynin when taken on a chronic basis, and none of the available studies in OAB patients were adequately powered for CNS effects or actively assessed cognition.

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Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part IV
Darifenacin vs. Oxybutynin or Other Antimuscarinic Drugs
Systematic Review

Part IV - Table of Contents

Darifenacin versus Oxybutynin and Other Anti-Muscarinic Drugs for Overactive Bladder Syndrome

Executive Summary

Introduction

Darifenacin hydrobromide extended-release (ER) was approved in Canada in 2006. A review by the Common Drug Review was conducted in 2006, with a resubmission report in 2009. The most recent CDEC recommendation is dated April 16, 2009**.**

Darifenacin is a selective, competitive muscarinic receptor antagonist with greater affinity for the M3 muscarinic receptor subtype than other muscarinic receptor subtypes such as M1. However, it does bind to all five muscarinic receptor subtypes. The drug is lipophilic and crosses the blood brain barrier. It is also a substrate for the p-glycoprotein transport system that transports the drug out of the brain. Based on selectivity and active transport out of the brain, darifenacin has been hypothesized to impair cognition to a lesser extent than non-selective antimuscarinic drugs that cross the blood brain barrier. This has not been proven clinically. Darifenacin is metabolized by CYP 2D6 and CYP 3A4 enzymes, predominantly in the liver. The drug is therefore affected by genetic polymorphisms affecting CYP 2D6 activity or metabolizer phenotype. There is substantive inter-individual variability unrelated to CYP 2D6 as well. Most of the drug's activity is due to the parent drug although it has one active metabolite.

Research Questions:

Q1. In adults, including the frail elderly, does darifenacin extended-release (Enablex™) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR), other formulations of oxybutynin, or other antimuscarinic drugs included in this review, for the treatment of overactive bladder (OAB) syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that darifenacin extended-release (Enablex™) improves clinically relevant outcomes or has a better safety profile compared to oxybutynin IR, other oxybutynin formulations or other antimuscarinic drugs included in this review?

Q3. In adults, particularly the elderly, does darifenacin extended-release (Enablex™) have less effect on cognition when compared to oxybutynin IR, other oxybutynin formulations or other antimuscarinic drugs included in this review?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included as supplemental information on harms if they exclusively enrolled elderly populations or assessed cognitive function. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all-cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

Q1. Comparative Harms and Benefits

Results

Search Findings

In total, four direct comparator RCTs met inclusion criteria for Q1. These compared darifenacin ER with oxybutynin IR, tolterodine IR or solifenacin. No available RCTs compared darifenacin with an extended-release formulation of oxybutynin (oral or transdermal), fesoterodine or trospium.

Two published RCTs compared darifenacin ER with oxybutynin IR:

- Zinner 2005, corresponding to study 137-666;
- Chapple 2005, corresponding to study 137-307.

One unpublished RCT compared darifenacin ER with tolterodine IR:

- Study 137-1001

One published RCT compared darifenacin ER with solifenacin:

- But 2012

Three additional studies are included to further assess harms. Of these, one is a placebo-controlled RCT to assess effects in the elderly:

- Chapple 2007

The other two studies are uncontrolled cohort analyses that met inclusion criteria to assess infrequent harms:

- Haab 2006 (also described in Hill 2007 and Dwyer 2008);
- Schneider 2010.

We also considered recent high-quality antimuscarinic drug class reviews for inclusion (Shamliyan 2012; Madhuvrata 2012). Because of additional data available for two studies (But 2012; Study A137-1001), we elected to conduct our own review.

Regulatory documents provided additional information on infrequent adverse events, labelling changes and safety advisories.

Direct Comparator Randomized Controlled Trials (RCTs)

All comparator RCTs compared fixed doses of darifenacin ER with a fixed dose of the comparator drug.

Darifenacin ER vs. Oxybutynin IR

Two double-blind, placebo-controlled crossover RCTs compared darifenacin ER 15mg, the highest recommended dose of darifenacin, with oxybutynin IR 5mg t.i.d. (15mg total/day) (Zinner 2005; Chapple 2005). The trials were very short (1-2 weeks) and included a total of 100 patients for comparisons/ doses of interest.

Observations in crossover trials are not independent as the same patient contributes data for each treatment arm. Because the available data were not reported as within-individual paired comparisons, no meta-analyses were conducted (Higgins and Green 2011, Elbourne 2002).

There were similar rates of serious adverse events and withdrawals due to adverse events for darifenacin ER and oxybutynin IR in both trials. The studies, however, were likely under-powered to detect differences. Cognitive impairment was not assessed.

The rates of total adverse events (AE) were similar for darifenacin ER and oxybutynin IR in both trials. There was less dry mouth with darifenacin ER, with the difference statistically significant in the larger trial (13% vs. 36%, $p < 0.05$) (Zinner 2005). In the second smaller trial (N=24), there was also less dry mouth associated with darifenacin ER (54% vs. 71%), but no statistical tests for significance are reported. An exploratory unpaired analysis in RevMan failed to find a statistically significant difference. In both trials, numerically more patients experienced constipation on darifenacin but again the differences were not statistically significant on exploratory analysis. [Note: these tests are exploratory because we had no access to the paired crossover data or first period data needed for testing.]

Only one trial (N=76) reported clinical efficacy outcomes (Zinner 2005). A per protocol analysis on 58 patients eliminated those who dropped out early and were likely to be less tolerant of treatment. Quality of life and patient-reported subjective improvement were not measured. There was no difference between drugs in adjusted mean reduction from baseline in incontinence episodes per week or urgency episodes per day. This trial may have been under-powered to detect such differences.

Based on these two RCTs, darifenacin ER (15mg) is associated with less dry mouth than oxybutynin IR (15mg/day total) and showed a trend for increased incidence of constipation. The strength of evidence is low for these adverse outcomes. For efficacy outcomes, based on one trial (N=58 in a per protocol analysis), similar efficacy was observed for each drug. However, this trial is not sufficient evidence to draw conclusions on efficacy for this comparison. Overall, the available evidence is insufficient to conclude a therapeutic advantage (incorporating beneficial and harmful effects) for darifenacin ER.

A more suitable comparator would have been an extended-release formulation of oxybutynin. Differences in pharmacokinetics between extended-release and immediate-release formulations modify clinical response. For oxybutynin, extended-release formulations are associated with lower rates of dry mouth than the immediate-release formulation (see Chapter 9; also Madhuvrata 2012).

There is no available evidence with which to conclude a therapeutic advantage for longer-term use of either darifenacin ER or oxybutynin (any formulation).

Darifenacin ER vs. Tolterodine IR

Study 137-1001 is a 12-week placebo-controlled, parallel group Phase III trial that compared darifenacin ER 15mg with tolterodine IR 2mg b.i.d. (4mg total/day). A total of 335 patients received darifenacin 15mg or tolterodine and another 115 received placebo (1:2:1 randomization). An additional treatment arm of darifenacin 30mg is not considered as it is not an approved dose.

A full study report remains unpublished even though the trial was completed by 2004 (Novartis Pharmaceuticals Canada 2006). This report has been requested and is pending. For an interim analysis, trial data were obtained from the FDA medical and statistical reviews and the Common Drug Review reports (Center for Drug Evaluation and Research NDA 21-513; Common Drug Review 2009).

For the statistical analyses of this trial, two separate step down procedures were used for hypothesis testing, one for efficacy of all darifenacin doses (15mg and 30mg) versus placebo, and the other for all darifenacin doses versus tolterodine (Center for Drug Evaluation and Research NDA 21-513 Statistical Review). Because of this, the significance level for the study was 2.5% ($p<0.025$) rather than 5% ($p<0.05$).

There was no difference in rates of serious adverse events or withdrawals due to adverse events between darifenacin 15mg and tolterodine IR. The trial was under-powered for serious adverse events. Cognitive impairment was not assessed. Total AE rates were not significantly different between drugs. Darifenacin ER was associated with a higher incidence of constipation compared with tolterodine IR (absolute risk difference 12%). Darifenacin ER 15mg was associated with more dry mouth than tolterodine IR (25.0% vs. 12.6%), but the difference was not statistically significant.

Darifenacin ER and tolterodine IR showed similar improvement in condition-specific quality of life, median incontinence episodes per week and median urgency episodes per day, based on 2-week bladder diaries. However, darifenacin ER 15mg did not show a statistically significant improvement over placebo for either incontinence or urgency episodes at the pre-set 2.5% significance level (Center for Drug Evaluation and Research NDA 21-513).

In the absence of a complete study report (pending), a full critical appraisal of the study, including assessment of the study's internal validity, could not be conducted. Failure to publish a full study report, if the decision is based on the magnitude and direction of results, is a form of publication bias (Hopewell 2009).

A more suitable comparator would have been the extended-release formulation of tolterodine. Differences in pharmacokinetics between extended-release and immediate-release formulations may modify clinical response. For tolterodine, the extended-release formulation is associated with lower rates of dry mouth than the immediate-release formulation (see Chapter 9; also Madhuvrata 2012).

Darifenacin ER vs. Solifenacin

One open-label parallel group RCT compared darifenacin 7.5mg with solifenacin 5mg once daily (But 2012). This is an appropriate comparison because solifenacin is long-acting, and also has some selectivity for the M3 muscarinic receptor subtype although less than darifenacin.

But 2012 is a small study (N=77) termed ‘exploratory’ by its investigators, without sample size or power calculation and failed to meet its stated recruitment goal of 100 patients. The trial was 12 weeks long and enrolled women only.

There were no serious adverse events in the trial, and no significant difference between drugs in withdrawals due to adverse events. The study actively collected specific harms data by using a checklist. However, the high proportion of adverse events at baseline and the reduction of most during the study confounds interpretation of the AE data. It is surprising, for example, that nearly half of patients randomized to darifenacin (47%) report dry mouth at baseline, although one of the study inclusion criteria was no anticholinergic drug use for 6 months pre-enrollment. In addition, the study does not report the cumulative numbers of patients experiencing a particular AE throughout the entire course of the study.

The Incontinence Impact Questionnaire (IIQ) was used to measure condition-specific quality of life (QoL). The total IIQ score showed significantly less improvement with darifenacin, with the difference within the range of values for a minimal clinically significant difference. There was no difference between drugs in incontinence pad usage, urgency or nocturia. Incontinence episodes were not reported.

This trial is of low quality and at high risk of bias. In open-label trials, subjective outcomes such as quality of life, patient-reported treatment success and symptom bother may strongly reflect expectation bias. The study reports a per protocol analysis rather than intention-to-treat and it is likely that patients who withdrew differed from completers.

The trial provides insufficient evidence to conclude if either darifenacin or solifenacin has a therapeutic advantage.

All of the available comparator RCTs for darifenacin were industry-sponsored. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For comparator trials within a drug class, industry sponsorship has also been reported to predict benefit (Bero 2007).

Supplemental Adverse Event Data

Placebo-controlled trials in the elderly

There were no direct comparator trials that exclusively enrolled adults aged 65 years or more. We therefore identified placebo-controlled trials that enrolled elderly populations as supplemental information for tolerability and adverse events.

One 12-week parallel group, placebo-controlled trial that exclusively enrolled patients 65 years of age or older (N=400) was identified and provides information on short-term harms (Chapple 2007). The mean age of participants was 72 years, with a third of participants > 75 years of age.

The trial used a flexible dosing regimen, with about half (47%) of darifenacin-treated patients on 15mg and the other half on 7.5mg. The mixture of doses obscures a dose-response for harms. There was no statistically significant difference between darifenacin and placebo in serious adverse events, but the trial was under-powered for this outcome. There was also no difference in withdrawals due to adverse events. More patients on darifenacin experienced any adverse event (absolute risk difference 11%). Darifenacin was associated with more dry mouth (absolute risk difference 18%) and constipation (absolute risk difference 7%) than placebo. The trial included

93 men, about 40% of whom had benign prostatic hypertrophy. There were no cases of acute urinary retention.

The reported adverse event profile was consistent with studies in younger populations. However, adverse events occurring in less than 5% of participants in each group were not reported in the publication, and the trial provides no information on cognitive effects. Cardiac events were reported to occur in 3.4% of participants on darifenacin ER and 0% on placebo (Common Drug Review 2009). Because cognitive impairment and other clinically significant medical conditions were exclusion criteria, the findings are not generalizable to the frail elderly.

This trial failed to find a significant efficacy advantage for darifenacin over placebo. Given the inclusion of one-third of patients > age 75, this raises a signal of concern of potential lack of efficacy in this population. If a drug has not been shown to be effective, no degree of harm is worth risking, and therefore this is also relevant to application of evidence on harm.

Available comparator and placebo-controlled trials were too brief to assess long-term safety and effectiveness when darifenacin and its comparators are used on a chronic basis.

Non-randomized studies

No comparative non-randomized observational studies were identified. There were two uncontrolled cohort analyses, one a two-year open-label extension study following two RCTs (Haab 2007), and the other a post hoc analysis of an open-label cohort of a clinic population (Schneider 2010). Both were industry-sponsored.

Haab 2006 selectively enrolled patients who had met RCT inclusion criteria and excludes those patients randomized to darifenacin who failed to tolerate the drug. There was a higher rate of withdrawal due to AE in patients ≥65 than in younger patients (risk difference 10%). Few of the very elderly were enrolled in Haab 2006. Harms data were passively collected.

Schneider 2010 is a post hoc evaluation of the influence of age, gender and lifestyle on response to treatment. It provides little information as it was an uncontrolled open-label study, and this design does not allow differentiation of drug effects from expectation biases, co-interventions, other morbidities and trends over time. The design, with a large number of physicians enrolling few patients is highly suggestive of a market seeding trial (Kessler 1994).

The two uncontrolled cohort analyses fail to provide adequate information to assist in the assessment of darifenacin's adverse effects, either in the elderly or in patients in general with overactive bladder syndrome. It is impossible to know whether or not darifenacin has a more favourable AE profile than alternatives based on these data.

Post-market surveillance and regulatory safety data

Periodic safety updates from the manufacturer were not available for this review. Safety updates based on the clinical development program and conducted during the FDA approval process (2004 or earlier) included a review on bone fractures. This was prompted by the reporting of fractures as serious adverse events in darifenacin-treated but not placebo-treated subjects. The review concluded there was no increased risk of bone fractures attributable to darifenacin. Other safety reviews conducted on the database of the clinical development program included cardiovascular events, urinary retention and constipation. Based on the FDA documentation and the Canadian Online Vigilance Database, the adverse event profile is qualitatively similar to those

identified for other antimuscarinic drugs. However, these data do not allow conclusions on comparative safety or effectiveness.

Additions to the U.S. labelling information based on post market experience include warnings on central nervous system effects (headache, confusion, hallucinations and somnolence) and angioedema. The following adverse events were added: anaphylactic reaction; hypersensitivity reactions including angioedema with airway obstruction; erythema multiforme; interstitial granuloma annulare; confusion; hallucinations; and palpitations.

Q1 Discussion and Conclusions

There is no evidence available for comparisons of darifenacin with any extended-release formulation of oxybutynin (oral or transdermal), fesoterodine or trospium. No conclusions can be drawn on comparative effectiveness or safety.

Sparse evidence is available for the comparisons of darifenacin with oxybutynin IR, tolterodine IR and solifenacin.

Based on two short (1-2 week) crossover RCTs (N=100), darifenacin ER is associated with less dry mouth than oxybutynin IR, and a trend to increased constipation. The strength of evidence for these outcomes is low. One crossover RCT reported similar efficacy for darifenacin and oxybutynin IR (N=58 in a per protocol analysis). However, this trial alone provides insufficient evidence on which to draw conclusions about efficacy. In total, there is insufficient evidence to conclude a therapeutic advantage (incorporating beneficial and harmful effects) for darifenacin.

Based on one trial (N=355), darifenacin ER is associated with increased constipation compared with tolterodine IR (absolute risk difference 12%). Both drugs had similar efficacy. Critical appraisal could not be conducted on this trial pending receipt of a full study report.

Based on one low-quality trial (N=77), there is insufficient evidence to conclude a therapeutic advantage for darifenacin versus solifenacin.

There are no comparative data in the frail elderly, and the maximum duration of RCTs was 12 weeks, too brief to assess longer-term safety and effectiveness. No RCTs have been conducted to assess cognitive effects in patients with OAB.

The two uncontrolled cohort analyses fail to provide adequate information to assist in the assessment of darifenacin’s adverse effects, either in the elderly or in patients in general with overactive bladder syndrome.

No RCTs have been conducted in patients who are refractory to, or intolerant of, oxybutynin IR.

Q2. New Clinical Evidence since CDR Review

There have been two Common Drug Review reports, one based on the original submission, dated September 2006 and a resubmission report in 2009. The CDEC recommendation dated April 16, 2009 was to list darifenacin for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and to list in a similar manner as drug plans list tolterodine.

Conclusions of the 2006 review were that darifenacin improves measures of quality of life and various OAB symptoms (incontinence, urgency, frequency) versus placebo, and that darifenacin is similar to tolterodine or oxybutynin for these measures (Common Drug Review 2009, Appendix IV). Based on the one additional study in the resubmission, Chapple 2007, the adverse event profiles were noted to be consistent for younger and older adults. Of note, for one key efficacy outcome (incontinence), darifenacin was not better than placebo in the Chapple 2007 study.

In the current review, one additional direct comparator RCT (77 patients) compared darifenacin ER with solifenacin (But 2012). This trial is the only identified RCT that compares darifenacin ER with another long-acting drug in OAB patients. The trial is of low quality and provides insufficient evidence for a therapeutic advantage for either drug.

Our review did not identify new comparator RCTs that assess cognitive effects. We also did not identify new placebo-controlled RCTs on the elderly or on cognition. The identification of all new placebo-controlled RCTs, regardless of outcome or population, was beyond the scope of this review.

The available new RCT evidence, and the non-randomized studies included in this review, do not change the conclusions of the CDR Review substantively.

We note there continue to be no direct comparator trials that compare darifenacin with another antimuscarinic drug in a population that is refractory to or intolerant of oxybutynin IR, in spite of the CDEC Final Recommendation in 2009.

Q3. Cognition

No comparative RCTs in patients with OAB were identified. Data on cognition were obtained from two RCTs in healthy volunteers, one comparative RCT and the other, a placebo-controlled trial. A third trial assessing cognition is excluded as the active comparator, dicyclomine, is not included in this review, and the study included only healthy volunteers with a mean age of 28; results are therefore irrelevant to older patients (Kay 2005).

Darifenacin ER vs. Oxybutynin ER

One three-week parallel group, placebo-controlled trial assessed effects of darifenacin ER and oxybutynin ER on cognition (Kay 2006). 150 healthy volunteers ≥ age 60 were enrolled (mean age 66-68 years) and given a battery of computerized cognitive tests at baseline and weeks 1, 2 and 3. Participants on oxybutynin ER received 10mg/day week 1, 15 mg/day week 2 and 20mg/day week 3 whereas participants on darifenacin received 7.5mg/day for 2 weeks, than 15 mg/day for week 3.

In total, 144 different comparisons in cognition scores are reported on, without adjustment for multiple comparisons, and with 48 comparisons each for weeks 1-3. Little published data exist on test parameters.

The identified primary outcome measure was delayed recall on the name-face association test. In week 2, participants on darifenacin ER 7.5mg/day did significantly better than those on oxybutynin ER 15mg/day. In week 3, participants on darifenacin 15mg did significantly better than participants on oxybutynin ER 20 mg/day: mean difference 1.23 points (95% CI 0.4 to 2.1).

These differences were adjusted for baseline score, age and sex. The clinical meaning of a 1.23 point difference is unknown.

Although the name-face association test at week 3 is identified as the primary outcome measure in the published report, this primary outcome was first reported in a protocol amendment on www.clinicaltrials.gov on May 24, 2006, one year after trial completion. Thus it is unlikely to have been identified *a priori* as the primary outcome measure.

In total, participants on oxybutynin ER did worse than those on darifenacin in 2 (4.2%) comparisons and did worse than placebo in 4 (8.3%). Participants on darifenacin did worse than those on oxybutynin ER on one comparison (2.1%) and did worse than placebo on one comparison (2.1%). Thus there was a trend towards participants on oxybutynin ER experiencing more effects on cognition than those on darifenacin.

The study was at high risk of bias for incomplete outcome data as it had differential withdrawal rates in treatment arms, and reported a per protocol analysis. It was also at high risk of bias for selective outcome reporting because of the amendment to disclose the primary outcome one year after trial completion.

The lack of information provided on maximum test scores or on established minimal clinically important differences in scores limits interpretability. The emphasis on the name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008).

This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome, or to patients with any degree of underlying cognitive impairment.

Placebo-controlled RCTs

One placebo-controlled RCT on cognition was identified. Lipton 2005 is a three-period crossover trial, in which healthy volunteers were randomized to 2-week periods of drug treatment, with 1 week in between. Volunteers received 3 of 5 treatments: 3.75mg, 7.5mg, or 15mg of darifenacin ER; darifenacin IR 15mg; and placebo.

The authors identify three domains as primary cognition function variables: memory scanning sensitivity; choice reaction speed; and delayed word recognition sensitivity. There were no significant differences at $p<0.05$ in any of these measures versus placebo. A trend was seen in reduced speed in choice reaction time for the two higher dose groups (darifenacin 15mg/ day – either extended-release or immediate-release), with the lower doses (3.75mg/day and 7.5 mg/day ER) and placebo exhibiting improvements in speed over time, as would be expected with a practice effect.

The authors identified an additional five domains as secondary cognitive function variables: simple reaction time; digit vigilance task – speed; digit vigilance task – accuracy; memory scanning speed; and word recognition scanning speed. For recommended doses of darifenacin, there were no significant differences versus placebo.

It is not clear whether the differences between primary and secondary outcomes were established *a priori*, as the rationale for the sample size calculation is not provided.

The study is at high risk of bias for incomplete outcome reporting because the analyses were per protocol. There was also high risk of bias for selective outcome reporting.

This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome. It is also unclear whether primary outcome measures on cognition tests were determined *a priori*, or whether a minimal clinically important difference was identified for cognition scores.

Additionally, because patients with serious comorbidities and with dementia, depression, or other psychological disorders were excluded, the trial results are unlikely to be applicable to the frail elderly with multiple morbidities.

Both trials on cognition were sponsored by the manufacturer of darifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

There is no evidence with which to conclude darifenacin has less effect on cognition than oxybutynin IR. Based on one short-term (3-week) RCT in healthy volunteers, there is insufficient evidence to conclude darifenacin ER has less effect than oxybutynin ER.

There are no short-term RCTs that compared darifenacin to other drugs included in this review.

No RCTs in any population have assessed the cognitive effects of chronic use of darifenacin. No observational studies were identified that assessed long-term cognitive effects.

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Chapter 7. Darifenacin ER vs. Comparator Drugs Clinical Review

Background

Darifenacin Hydrobromide Extended-Release Product Data

Box 1: Darifenacin Hydrobromide Extended-Release Product Information

Categorization: anticholinergic-antispasmodic agent

Indication: treatment of overactive bladder. Overactive bladder is used to describe a collection of urinary symptoms composed of urgency, with or without incontinence, usually with frequency and nocturia, in the absence of proven infection or other obvious pathology.

Recommended Usual Dose: 7.5 mg once daily; may be increased to 15 mg daily as early as two weeks after starting therapy, based on individual response.

Mechanism of Action: competitive, M3-selective muscarinic receptor antagonist

Above is derived from Darifenacin Hydrobromide Extended-Release Tablets (Enablex™) Product Monograph dated April 9, 2013.

Darifenacin extended-release (ER) was approved in Canada in 2006. A review by the Common Drug Review (CDR) was conducted in 2006, followed by a resubmission report in 2009. The most recent CDEC recommendation is dated April 16, 2009**.**

Darifenacin has greater affinity for the M3 muscarinic receptor subtype than other receptor subtypes such as M1. However, it does bind to all five muscarinic receptor subtypes. The drug is lipophilic and crosses the blood brain barrier. It is also a substrate for the p-glycoprotein transport system that transports the drug out of the brain and back into the bloodstream. Based on selectivity and active transport out of the brain, darifenacin has been hypothesized to impair cognition to a lesser extent than non-selective antimuscarinic drugs that cross the blood brain barrier. This has not been proven clinically. Darifenacin is metabolized by CYP 2D6 and CYP 3A4 enzymes, predominantly in the liver. The drug is therefore affected by genetic polymorphisms affecting CYP 2D6 enzyme activity and metabolizer phenotype. The main pathway of metabolism in 'poor metabolizers' is via the CYP 3A4 enzyme. There is substantive inter-individual variability as well. Most of the drug's activity is due to the parent drug although it has one active metabolite. Further information on the pharmacokinetics and other properties of darifenacin is available in Chapter 1, Table 7, and Appendix B.

Q1. Comparative Harms and Benefits

Methods – see Chapter 2.

Results

Search findings

We identified five active comparator RCTs, four published and one unpublished, that compared darifenacin ER to the other antimuscarinic drugs under review. One of the comparator RCTs was in healthy volunteers and is considered in Q3 only. Supplemental data on adverse events (AE)

were obtained from two placebo-controlled RCTs, one in the elderly and one on cognition (see Q3), and two uncontrolled cohort studies. Additional information on harms was obtained from one case report, the U.S. FDA regulatory medical review (Center for Drug Evaluation and Research NDA 21-513), and pharmacovigilance databases.

We also considered recent high-quality systematic reviews for inclusion (Shamliyan 2012; Madhuvrata 2012). We conducted our own systematic review due to the availability of additional data for two RCTs that had been reported in abstract form only in Madhuvrata 2012 (Novartis Pharmaceuticals Canada 2006 Study A137-1001; But 2012).

Direct Comparator RCTs

Five direct comparator trials compared darifenacin with other antimuscarinic drugs.

- 2 compared darifenacin ER vs. oxybutynin IR (Zinner 2005; Chapple 2005);
- 1 compared darifenacin ER vs. oxybutynin ER (Kay 2006) (Q3);
- 1 compared darifenacin ER vs. tolterodine IR (Study A137-100);
- 1 compared darifenacin ER vs. solifenacin (But 2012).

Only recommended doses of darifenacin ER (7.5mg and 15mg once daily) are considered in this review. All included direct comparator RCTs used fixed doses of darifenacin. Missing data were supplemented by data from the CDR Review(s) and other regulatory data, where possible, and as indicated.

Results are presented according to this review's hierarchy of outcomes, with those outcomes of greatest important to the patient highest in the hierarchy.

For dichotomous outcomes, if a relative risk is < 1, fewer patients taking darifenacin experienced the event (beneficial or harmful).

1. Darifenacin ER vs. Oxybutynin

Three trials compared darifenacin ER with oxybutynin. All were short-term trials (1-3 weeks) (Zinner 2005; Chapple 2005; Kay 2006).

One parallel group trial compared darifenacin ER with oxybutynin ER, and assessed cognitive function in healthy volunteers only (Kay 2006). This trial is discussed in Q3 only.

The other two trials compared darifenacin ER with the immediate-release form of oxybutynin.

Darifenacin ER vs. Oxybutynin IR

Both trials are crossover trials, involving a total of 100 patients for comparisons of interest. Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix H.

Zinner 2005 (N=76) (Study 137-666) is a four-way crossover trial that compared darifenacin ER 15mg once daily with oxybutynin IR 5mg t.i.d. (15mg total/day), placebo, and darifenacin 30mg once daily. The latter is not a recommended dose and therefore that treatment arm is not of relevance to this review. This trial included efficacy outcomes and AE of interest. Each treatment period was 2 weeks long with a 10-day wash-out period between treatments.

Chapple 2005 (Study 137-307) included three separate cohorts, each reported as a separate two-way crossover comparison. Each of the cohorts was randomized to a different dose or formulation

of darifenacin versus oxybutynin. One cohort/comparison (N=24) is of interest to this review as darifenacin ER 15mg once daily was compared with oxybutynin IR 5mg t.i.d. The other two cohorts are not relevant to this review, as they compared a non-approved dose (darifenacin ER 30mg) or the IR formulation of darifenacin, which is not included in this review. Most of the efficacy outcomes in Chapple 2005 were pharmacodynamic e.g., salivary flow and visual nearpoint, and are not eligible efficacy outcomes. Each treatment period was 7 days followed by a wash-out period of $\geq$ 14 days.

For both efficacy and specific AE, Zinner 2005 reported 'complete cases'. Complete cases were defined for safety analysis as participants who were exposed to all four treatments for at least 7 days (or less if antimuscarinic AE were observed earlier). For efficacy, a per protocol analysis was conducted on participants who had at least one recorded efficacy variable at week 2 for each of the four treatment periods. Such an analysis excluded the 21% of participants who did not complete all four treatments.

Observations in crossover trials are not independent as the same patient contributes data for each treatment arm. Because the available data were not reported as within-individual paired comparisons or first period data, no meta-analyses were conducted (Higgins and Green 2011; Elbourne 2002).

1. All-cause mortality
No deaths are reported in either trial.

2. Non-fatal Serious Adverse Events (SAE)
Both trials reported on SAE. In Zinner 2005, in the three relevant treatment periods, there were a total of 2 SAE, one in the placebo group (menometrorrhagia and elective hysterectomy) and one in the oxybutynin IR group (fever and poorly differentiated adenocarcinoma), neither of which were judged treatment-related.

In Chapple 2005, there was only1 SAE in the cohort of interest, which occurred in the darifenacin ER group in the 2nd treatment period (no details provided) (CDR Review 2009, Appendix IV, p. 72).

3. Withdrawals due to Adverse Events (WDAE)
Zinner 2005 reported an overall 21% withdrawal rate (including the darifenacin ER 30mg arm), with 11/16 withdrawals described as 'unrelated to treatment', without further detail. There were a total of 12 withdrawals in the relevant treatment arms: 6 during treatment with oxybutynin IR, 4 with placebo, and 2 with darifenacin ER 15mg q.d. Reasons for 8 of the 12 withdrawals in these treatment arms are not provided. Only the subset of WDAE judged 'treatment related' by investigators are reported. These included 4 'treatment-related' WDAE in the oxybutynin IR group due to dry mouth (with rhinitis N=2, dysphagia and dyspepsia N=1) and none in the 15mg darifenacin ER group (a 5th WDAE, dry mouth and constipation, was in the 30mg darifenacin group). Withdrawals are not reported by treatment period.

Chapple 2005 reported one WDAE in the second treatment period for darifenacin ER (dry mouth) and none in either treatment period for oxybutynin IR.

Table 1. WDAE

Study	Zinner 2005 (Study 137-666)			Chapple 2005 (Study 137-307)	
Treatment arm	Placebo	DARI ER 15 mg qd	OXY IR 5 mg tid	DARI ER 15 mg qd	Oxy IR 5 mg tid

Total withdrawals (%)	4/68 (5.9%)*	2/69 (3.1%)*	6/64 (8.7%)*	1	0
Total WDAE	NR	NR	NR	1	0
'Treatment-related' WDAE	0	0	4	--	--

* Common Drug Review 2009, p. 74.
DARI= darifenacin; **ER**= extended-release; **IR**= immediate-release; **NR**= not reported; **OXY**= oxybutynin; **qd**= every day; **tid**= three times daily

4. Quality of life (QoL)
No trial reported on this outcome.

5. Patient-Reported Perception of Improvement
Neither trial reported on this outcome.

6. Quantification of Incontinence Episodes
Cure or total dryness rate: Neither trial reported on this outcome.

Mean reduction in incontinence episodes: One trial, Zinner 2005, reported on urgency incontinence episodes. The average baseline number of incontinence episodes was 20 episodes per week, corresponding to 2.9 episodes per day. Darifenacin ER 15mg and oxybutynin IR reduced incontinence episodes from baseline on average by 10.1 and 11.6 episodes per week, respectively. The between-treatment difference was 1.5 episodes per week and was not statistically significant. This corresponds to a difference of 0.2 episodes per day, or 1 episode every 5 days, in favour of oxybutynin ER. Both darifenacin ER 15mg and oxybutynin IR significantly improved incontinence episodes per week vs. placebo.

Table 2. Incontinence Episodes per week – mean change from baseline (Zinner 2005)

Measure	Placebo	DARI ER 15 mg qd	OXY IR 5 mg tid
Baseline episodes per week	20.4 ± 17.7 [=2.9/day] (N=76)		
Mean change* from baseline per week (N=58 completers)	-6.38	-10.09/week [= 1.4/day]**	-11.57/week [= 1.7/day]**

* Means are adjusted for sequence and period from a crossover analysis of variance.
** P values < 0.05 vs. placebo, accounting for multiplicity by the least significant difference method
DARI= darifenacin; **ER**= extended-release; **IR**= immediate-release; **OXY**= oxybutynin; **qd**= every day; **tid**= three times daily

7. Nocturia
Neither trial reported on this outcome.

8. Urgency
Zinner 2005 reported on urgency episodes. The improvement in urgency episodes was similar for darifenacin ER 15mg and oxybutynin IR, a reduction of about one episode per day.

Table 3. Urgency Episodes per day – mean change from baseline (Zinner 2005)

Treatment arm	Placebo	DARI ER 15 mg qd	OXY IR 5 mg tid
Baseline episodes per day	9.3 ± 3.4 (N=76)		
Mean change* from baseline per day (N=58 completers)	-0.51	-1.27**	-1.10**

* Means are adjusted for sequence and period from a crossover analysis of variance.
** P<0.05 vs. placebo, accounting for multiplicity by the least significant difference method

DARI= darifenacin; **ER**= extended-release; **IR**= immediate-release; **OXY**= oxybutynin; **qd**= every day; **tid**= three times daily

9. Total AE

Both trials reported on participants who experienced one or more AE on each treatment. There were no statistically significant differences between darifenacin ER and oxybutynin IR in either trial (Table 4). For Zinner 2005, numbers were obtained from the CDR Review (Common Drug Review 2009).

Table 4. Proportion of patients with one or more AE

Study	Zinner 2005			Chapple 2005	
Treatment arm	Placebo	DARI ER 15 mg qd	OXY IR 5 mg tid	DARI ER 15 mg qd	OXY IR 5 mg tid
Total AE	32/68* (47%)	36/64* (56%)	47/69* (68%)	16/24 (67%)	19/24 (79%)
DARI vs. OXY RR (95% CI)		RR 0.83 [95% CI 0.63 to 1.08] P=0.16§		RR 0.84 [95% CI 0.59 to 1.19] p =0.34§	

* Common Drug Review 2009, Appendix IV, p. 73;

§ It is unclear whether this analysis took into account the lack of independence of observations in each arm of the crossover trial.

CI= confidence intervals; **DARI**= darifenacin; **ER**= extended-release; **IR**= immediate-release; **OXY**= oxybutynin; **qd**= once daily; **RR**= relative risk; **tid**= three times a day.

10. Specific AE

Dry mouth: The most commonly reported AE in the darifenacin ER 15mg and oxybutynin IR treatment periods of the two trials was dry mouth. The between-treatment difference was reported as statistically significant in Zinner 2005, with less dry mouth associated with darifenacin ER 15mg (13%) vs. oxybutynin (36%), $P<0.05$. In Chapple 2005, there was also less dry mouth experienced by participants on darifenacin ER 15mg vs. oxybutynin IR: 13/24 (54%) vs. 17/24 (71%). No statistical analyses are provided for Chapple 2005 and data were not presented in a useable form for pairwise comparisons. An exploratory unpaired analysis in RevMan failed to find a statistically significant difference. The incidence rate of dry mouth is relatively high in Chapple 2005 although a direct comparison with other studies cannot be made as populations may differ. It is possible that the measurement of salivary flow, a pharmacodynamic outcome in this study, may have sensitized participants to this particular event. On the other hand, other studies may under-estimate the incidence of dry mouth.

Constipation: In Zinner 2005, more patients reported constipation on darifenacin ER 15mg (9.8%) than on oxybutynin IR (8.2%), but the difference was not statistically significant. There were also more participants experiencing constipation with darifenacin ER 15mg vs. oxybutynin IR in the relevant cohort in Chapple 2005 (Table 5).

Blurred vision: In Zinner 2005, no patients on darifenacin ER 15mg and 2 patients on oxybutynin IR (3.3%) experienced blurred vision. In Chapple 2005, blurred vision was experienced by 1 participant on darifenacin ER 15mg (4%) and 3 participants on oxybutynin IR (13%).

Dizziness: In Zinner 2005, no patients on darifenacin ER 15mg and 1 patient on oxybutynin IR (1.6%) experienced dizziness.

Table 5. Adverse events

Study	Zinner 2005 (N=61)			Chapple 2005 (N=24)	
Adverse Event	Placebo	DARI ER	OXY IR	DARI ER	OXY IR

		15 mg qd	5 mg tid	15 mg qd	5 mg tid
Dry mouth	4.9%	13.1%*	36.1%	13 (54.2%)	17 (70.8%)
Constipation	3.3%	9.8%	8.2%	8 (33.3%)	6 (25.0%)
Dyspepsia	NR	NR	NR	3 (12.5%)	5 (20.8%)
Dysphagia	NR	NR	NR	1 (4.2%)	3 (12.5%)
Dizziness	0%	0%	1.6%	NR	NR
Headache	NR	NR	NR	1 (4.2%)	3 (12.5%)
Abnormal vision or Blurred vision	0%	0%	3.3%	1 (4.2%)	3 (12.5%)
UTI	NR	NR	NR	2 (8.3%)	1 (4.2%)

* P < 0.05 vs. oxybutynin IR, as reported in Zinner 2005
DARI= darifenacin; **ER**=extended-release; **IR**=immediate-release; **NR**=not reported; **OXY**= oxybutynin; **qd**=every day; **tid**=three times a day; **UTI**=urinary tract infection;

Chapple 2005 conducted ambulatory Holter heart rate monitoring and reported no meaningful difference between treatments in average heart rate. The trial also reports measures of heart rate variability, which suggest a greater heart-rate variability with oxybutynin. However, the clinical meaningfulness of this surrogate or intermediate marker is not addressed.

There were no identified laboratory-measured AE in either trial.

11. Urodynamics/clinician measures
Chapple 2005 reports ambulatory urodynamic pressure measurements over a 6-hour period and found no difference between darifenacin and oxybutynin in number or duration of phasic contractions or a detrusor activity index (Table 2 in Appendix H). Both drugs demonstrated a significant decrease from baseline in these parameters. Neither trial reported on conventional cystometric measures - maximum cystometric capacity, pressure at first contraction, and post residual volume.

12. Mean volume voided: Neither trial reported on this outcome.

Critical Appraisal: Darifenacin ER vs. Oxybutynin IR

Risk of bias/other quality assessment
See table 3 in Appendix H. As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity. For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results). Zinner 2005 incompletely reported some outcomes and published trial data were supplemented by data in the CDR reports. An assessment of the trial's internal validity was based on all available data.

Both trials were short (1-2 week) crossover trials with an appropriate wash-out period between treatments. OAB syndrome is considered an appropriate condition for crossover trials. Analyses were reported as appropriately adjusted with respect to sequence, subject and period. Both trials conducted paired analyses. For efficacy outcomes, Zinner 2005 conducted an analysis of variance (ANOVA) for a four-way crossover design, and made pairwise treatment comparisons using the least significant difference method. Both trials randomized the order of receiving treatment. Zinner 2005 did not adequately describe the trial's randomization process. Neither trial described allocation concealment.

Zinner 2005 was of 'unclear' risk of attrition bias because the reasons for all drop-outs (21% of participants) were not provided. For the analysis of specific AE in Zinner 2005, a 'completer'

analysis was conducted on participants who received all four treatments for at least 7 days (or less if an AE was observed) (80% of those randomized). This type of analysis would have eliminated participants who withdrew early and who are likely to have been less tolerant of treatment. For efficacy outcomes, a per protocol analysis was reported on participants who completed all 4 treatments and had at least one efficacy outcome measured for each treatment (76% of those enrolled). This is likely to have eliminated participants who dropped out due to lack of efficacy before the end of the 2-week treatment period. Reasons for 11/16 withdrawals were not disclosed. Without full disclosure, the possible impact of withdrawals on the analyses cannot be assessed.

Chapple 2005 was rated at low risk for attrition bias specifically for the cohort of interest as there was only 1 withdrawal, which occurred in the 2nd treatment period.

The sample size calculation for Zinner 2005 was based on ability to detect differences in antimuscarinic AE rates. The trial may have been under-powered to detect differences in efficacy outcomes. Chapple 2005 was powered on the basis of anticipated differences in the inhibition of salivary flow, an intermediate outcome, and may not have been adequately powered for AE rates (efficacy outcomes were not measured in this trial).

Applicability of trial results (external validity)
The majority of participants in Zinner 2005 were women. Chapple 2005 enrolled more men than women and all participants had cystometric evidence of detrusor activity. Chapple 2005 did not include efficacy outcomes related to symptoms of OAB so has limited applicabilty.

Neither trial reported the number of elderly participants. No clinical outcome data are available on poor metabolizers (low CYP 2D6 enzyme activity) in either trial.

Comparator/dose choice: The trials used oxybutynin 5mg t.i.d. and the highest recommended dose of darifenacin, 15mg, both of which are reasonable dose choices.

Harms: Zinner 2005 reported only the subset of WDAE that were judged by the investigator to be treatment-related. Collection of adverse events was passive in both trials other than routine laborary parameters and heart rate variability in Chapple 2005. The latter is a pharmacodynamic parameter and an intermediate or surrogate marker. The incidence rate of dry mouth is relatively high in Chapple 2005 although a direct comparison with other studies cannot be made. It is possible that the measurement of salivary flow, a pharmacodynamic measure, in this study may have sensitized participants to this particular event. On the other hand, other studies may under-estimate the incidence of dry mouth.

Industry sponsorship: Both trials were sponsored by the manufacturer of darifenacin. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007).

Overall results – Darifenacin ER vs. Oxybutynin IR
Results are summarized, below, in Table 6. One crossover trial (76 patients) (Zinner 2005) found no difference between darifenacin ER 15mg and oxybutynin IR 5mg t.i.d. (15mg total/day) in reduction in incontinence episodes per week or urgency episodes per day, based on a per protocol analysis. Darifenacin ER 15mg was associated with significantly less dry mouth than oxybutynin IR (13% vs. 36%, $P < 0.05$). More patients were constipated on darifenacin ER compared with oxybutynin IR, but the difference was not statistically significant. A second smaller crossover

trial (24 patients) (Chapple 2005) also reported less dry mouth and more constipation with darifenacin ER 15mg compared with oxybutynin IR 15mg total/day but did not report whether differences were statistically significant. The second trial did not report efficacy outcomes of interest.

No trials compared darifenacin ER 7.5mg, the recommended starting dose, with oxybutynin.

The available evidence is insufficient to conclude a therapeutic advantage for either drug.

Table 6. Summary of Darifenacin ER 15mg vs. Oxybutynin IR RCTs

Outcome	No. of studies (No. of Participants)	DARI ER 15 mg vs. OXY IR	Summary
All-cause mortality	2 trials Chapple 2005: N=24 Zinner 2005: n=76 No events	--	0 events with 1-2 week of treatment. RCTs are too short and under-powered to draw conclusions.
SAE (non-fatal)	2 trials Chapple 2005: N=24 1 event Zinner 2005: N=76 2 events	--	RCTs are too short and under-powered to draw conclusions (3 events).
QoL	0 trials	--	No available evidence
WDAE	1 trial Chapple 2005: N=24 1 event Zinner 2005 – did not report total WDAE	--	Insufficient evidence: too few events to draw conclusions
Patient-reported improvement	0 trials	--	No available evidence
Incontinence episodes per week Mean reduction from baseline*	1 trial Zinner 2005: N=58 completers	DARI ER: -10.09/week OXY IR: -11.57/week MD: -1.5 per week or 0.2 episodes/day	Similar reduction in incontinence episodes for DARI ER and OXY IR in 1 trial
Urgency per day Mean reduction from baseline*	1 trial Zinner 2005 N=58 completers	DARI ER -1.27 Oxy IR – 1.10 MD -.17	Similar reduction in urgency episodes per day for DARI ER and OXY IR in 1 trial
Nocturia	0 trials	--	No available evidence
Total AE	2 trials, meta-analysis ND Zinner 2005: N=69 Chapple 2005: N=24	Zinner 2005: DARI 56% vs. OXY 68% Chapple 2005: DARI 67% vs. OXY 79%	Similar total AE for each drug
Dry mouth	2 trials, meta-analysis ND Zinner 2005: N=61 Chapple 2005: N=24	 Zinner 2005: DARI 13% vs. OXY 36% Chapple 2005: DARI 54% vs. OXY 71%	Less dry mouth with DARI ER, with the difference statistically significant in the largest available trial but not the smaller trial
Constipation	2 trials, meta-analysis ND Zinner 2005: N=61	 Zinner 2005: DARI 9.8% vs. OXY 8.2%	No significant difference

	Chapple 2005: N=24	Chapple 2005: DARI 33% vs. OXY 25%	
* Means are adjusted for sequence and period from a crossover analysis of variance. **AE**=adverse events; **DARI**=darifenacin; **ER**=extended-release; **IR**=immediate-release **MD**=mean difference; **ND**=not done; **OXY**=oxybutynin; **QoL**=quality of life; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events			

2. Darifenacin ER vs. Other Comparator Drugs

a. Darifenacin ER vs. Tolterodine IR

One parallel group, placebo-controlled Phase III trial (Study A137-1001) compared darifenacin 15mg once daily with tolterodine IR 2mg b.i.d. (4mg total/day) (Common Drug Review 2009). A treatment arm of darifenacin 30mg once daily is not considered in this review as it is not a recommended dose. A total of 335 patients received active drugs of interest and 115 received placebo. The trial was 12 weeks long.

This trial, described as the major comparator trial in the CDR review, is not published as a full study report. Conference proceedings were identified (Romanzi 2005; Foote 2004), as were pooled analyses with two placebo-controlled RCTs (Tack 2012; Khullar 2011; Abrams 2008; Chapple 2005; Foote 2005). Most of the latter analyses, with the exception of Tack 2012, include darifenacin vs. placebo comparisons only. Tack 2012 reports only the AE constipation for all three treatment arms.

A full study report has been requested from the manufacturer and is pending. In the interim, data were obtained from the CDR Review(s) (Common Drug Review 2009) and the FDA medical and statistical reviews (Center for Drug Evaluation and Research NDA 21-513).

The primary outcome of the study was incontinence episodes per week, and the results were based on 14-day (electronic) bladder diaries.

For the statistical analyses of this trial, two separate step down procedures were used for hypothesis testing, one for efficacy of all darifenacin doses (15mg and 30mg) vs. placebo, and the other for all darifenacin doses vs. tolterodine (Center for Drug Evaluation and Research NDA 21-513 Statistical Review). Because of this, the significance level for the study was 2.5% ($p<0.025$) rather than 5% ($p<0.05$). Additionally, the step down process restricted statistical testing for the darifenacin 15mg dose vs. tolterodine IR, with outcomes not tested for significance unless they had been found first to be significant for darifenacin versus placebo.

1. All-cause mortality

There were no deaths in the trial (Center for Drug Evaluation and Research NDA Review 21-513).

2. Non-fatal Serious Adverse Events (SAE)

There was no statistically significant difference in SAE between darifenacin ER (1 event) and tolterodine IR (4 events). One atrial fibrillation/congestive heart failure event was judged treatment-related for tolterodine but the details of the other SAE are not provided (Common Drug Review 2009, Appendix IV, p. 73).

Table 7. SAE

Event	Placebo	DARI ER 15 mg qd	TOL IR 2 mg bid	DARI vs. TOL RR [95% CI]

SAE	1/115* (0.9%)	1/112* (0.9%)	4/223* (1.8%)	RR 0.5 [95% CI 0.06 to 4.40], P=0.53§

*Common Drug Review 2009, Appendix IV, p. 72; §calculated in RevMan v5.2
bid=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ER**=extended-release; **IR**=immediate-release; **PL**= placebo; **qd**=every day; **RR**=relative risk; **TOL**=tolterodine;

3. Withdrawals due to Adverse Events (WDAE)
For WDAE, there was no statistically significant difference between darifenacin ER 15mg and tolterodine IR: RR 0.94 (95% CI 0.4 to 2.1), P=0.87. Details of the WDAE are not available.

Table 8. WDAE

Event	Placebo	DARI ER 15 mg qd	TOL IR 2 mg bid	DARI ER vs. TOL IR RR [95% CI]
Total withdrawals*	11/115	20/112	NR**	--
WDAE*	4 /115 (4%)	8/112 (7%)	17/223 (8%)	RR 0.94 [95% CI 0.4 to 2.1] P=0.87§

*Common Drug Review 2009, Appendix IV, p. 75; **Not available in the CDR Review or in FDA Review 21-513; §calculated in RevMan v5.2
bid=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ER**=extended-release; **IR**=immediate-release; **qd**=every day; **RR**=relative risk; **TOL**=tolterodine;

In a pooled analysis with two other Phase III trials that did not include an active comparator, the leading cause of AE-related study discontinuation in darifenacin-treated patients was constipation (Center for Drug Evaluation and Research NDA Review 21-513).

4. Quality of life (QoL)
Condition-specific QoL was reported using the King's Health Questionnaire (KHQ).
KHQ is comprised of three sections: 1) 2 items on general health perception; 2) 21 items on the following nine domains: incontinence impact; role limitations; physical limitations; social limitations; personal relationships; emotions; sleep/energy; severity (coping) measures; and symptom severity, and 3) 11 items on symptom bother. The score for each QoL domain is from 0 (best) to 100 (worst). Improvement is reflected by a reduction in score. Minimal clinically important differences (MCID) are in the range of 5-10 points (Kelleher 2004). Although the King's Health Questionnaire was initially used in women, it has been validated in both men and women.

There were no statistically significant differences between darifenacin ER and tolterodine IR in KHQ scores (Common Drug Review 2009, p. 68). Of the subset of domains that were reported (incontinence impact, role limitations and severity (coping) measures), the between-treatment differences did not reach the threshold for MCID (Table 9). Data are, however, incompletely reported and provided only for those domains showing a significant difference in the change from baseline for darifenacin vs. placebo.

Table 9. Selected Scores from King's Health Questionnaire

Domain/Score	Measure	Placebo	DARI ER 15 mg qd	TOL IR 2 mg bid
KHQ – Total Score		NR	NR	NR
Incontinence impact domain	Baseline	77.0	74.9	78.4
	Mean change	-6.1	-18.0**	-16.9
Role limitations	Baseline	64.4	58.2	61.5

domain	Mean change	-20.6	-22.0**	-20.6
Severity (coping) measures domain	Baseline	52.0	47.5	48.4
	Mean change	-5.6	-11.9**	-9.5

* Data from Common Drug Review 2009, Appendix IV, p. 68
** P<0.05 for treatment difference vs. placebo, using Wilcoxon Rank Sum test, as per CDR Review
bid=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ER**=extended-release; **IR**=immediate-release; **KHQ**=King's Health Questionnaire: **NR**=not reported; **qd**=every day; **TOL**=tolterodine;

5. Patient-Reported Perception of Improvement: not available.

6. Quantification of Incontinence Episodes
Cure or total dryness rate: not available.

Median reduction in incontinence episodes:
Data for incontinence episodes were not normally distributed and are presented as medians rather than means. The median reduction from baseline in incontinence episodes per week was similar for darifenacin ER 15mg and tolterodine IR (Table 10).

Table 10. Incontinence Episodes per week – median change from baseline

Measure	Placebo	DARI ER 15 mg qd	TOL IR 2 mg bid	Difference (97.5% CI)
Median baseline episodes per week*	15.5	16.2	NR	--
Median change (%) from baseline to week 12**	-9.0/week (-71%)	-11.4/week (-83%)	-10.3/week (-74%)	DARI ER vs. PL -2.4 [97.5% CI -5.2 to -0.3] P=0.049 (not significant)§ DARI ER vs. TOL IR -0.9 [97.5% CI -3.4 to 1.4], ND

* Data from FDA Review, Table VI-C-6.1; ** Data are as reported in the Common Drug Review 2009 report, Appendix IV, p. 69. It is unclear whether CI and p-values were calculated by the manufacturer or CDR pending receipt of the full report.
§ p-value statistically significant at the 0.025 significance level for this study
bid=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ER**= extended-release; **IR**= immediate-release; **ND**=not done due to restrictions of step down testing procedure; **qd**=every day; **TOL**=tolterodine;

7. Nocturia
Study 137-1001 did not report on this outcome.

8. Urgency
Data for this outcome were not normally distributed and are presented as medians. The median reduction from baseline in urgency episodes (a reduction of 25 to 33%) was similar for darifenacin ER and tolterodine IR.

Table 11. Urgency Episodes per day – median change (%) from baseline per day

Measure	Placebo	DARI ER 15 mg qd	TOL IR 2 mg bid	Difference (97.5% CI)
Median Baseline*	8.5	8.6	NR	--
Median change from baseline**	-2.3 (-26%)	-2.6 (-33%)	-1.9 (-25%)	DARI ER vs. TOL IR: -0.3 [97.5% CI -1.1 to 0.6], ND

				DARI ER vs. PL: -0.7 [97.5%% CI -1.6 to 0.1], p=0.61§

*Data from FDA Review, Table VI-C-7.2; **Data in this table are as reported in the Common Drug Review Report 2009, Appendix IV, p. 70. It is unclear whether CI and p-values were calculated by the manufacturer or CDR pending receipt of the full report.
§ p-value statistically significant at the 0.025 significance level for this study (FDA Review 21-513); **bid**=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ND**=not done due to step down testing procedure; **PL**=placebo; **qd**=every day; **TOL**=tolterodine;

9. Total AE:
More participants on darifenacin ER experienced AE than on tolterodine IR, but the difference is not statistically significant: 76% vs. 66%; RR 1.14 (95% CI 0.99 to 1.32), P=0.06.

10. Specific AE
Dry mouth: Dry mouth occurred numerically more frequently in patients on darifenacin ER than tolterodine IR, but the difference is not statistically significant: RR 1.29 (95% CI 0.93 to 1.81), P=0.13.

Constipation: Constipation occurred more often in the darifenacin ER group than in the tolterodine IR group: RR 1.99 (95% CI 1.24 to 3.19), P=0.004; absolute risk difference 12% (95% CI 3% to 22%).

Dyspepsia: Incidence of dyspepsia was similar for darifenacin ER and tolterodine IR (Table 12).

Nervous system AE: Dizziness and depression were identified as examples of nervous system AE but details of all events were not provided (Foote 2004). Incidence of AE were similar for the darifenacin ER and tolterodine IR: RR 0.66 (95% CI 0.14 to 3.24), P=0.061.

Table 12. Specific AE

AE	Placebo N=115	DARI ER 15 mg qd N=112	TOL IR 2 mg bid N=223	DARI ER vs. TOL IR RR (95% CI)
Total AE	69 (60%)	85 (76%)	148 (66%)	RR 1.14 (95% CI 0.99 to 1.32)
Dry mouth	11 (9.6%)	39 (34.8%)	60 (26.9%)	RR 1.29 (95% CI 0.93 to 1.81)
Constipation	7 (6.1%)	28 (25.0%)	28 (12.6%)	**RR 1.99 (95% CI 1.24 to 3.19)**
Dyspepsia	4 (3.5%)	10 (8.9%)	17 (7.6%)	RR 1.17 (95% CI 0.55 to 2.47)
UTI**	5 (4.3%)	7 (6.3%)	NR	--
Nervous system§	5 (4.3%)	2 (1.8%)	6 (2.7%)	RR 0.66 (95% CI 0.14 to 3.24)

Data are from Common Drug Review 2009, Appendix IV, p. 74, unless otherwise specified.
** FDA Review, Table VII –C.5.1.4
§ Foote 2004; Identified nervous system AE were dizziness and depression but full details not provided.
AE=adverse events; **bid**=twice a day; **CI**=confidence intervals; **DARI**=darifenacin; **ER**= extended-release; **IR**= immediate-release; **ND**=not done due to step down testing procedure; **NR**=not reported; **qd**=every day; **RR**=relative risk; **TOL**=tolterodine; Note: statistically significant differences bolded.

11. Urodynamics/clinician measures – not reported.

12. Mean volume voided: Both active drugs increased the median volume voided. The difference between medians was 15 mls, in favour of darifenacin. Statistical testing was not conducted on this comparison.

Table 13. Mean volume voided

Measure	PL N=115	DARI ER 15 mg qd N=112	TOL IR 2 mg bid N=223	Difference (97.5% CI)
Median at week 12	11 (9.6%)	39 (34.8%)	60 (26.9%)	DARI ER vs. PL 20 mls [97.5% CI 6 to 34], P=0.002 DARI ER vs. TOL IR 15 mls [97.5% CI 4 to 26 mls], ND

From Common Drug Review 2009 report, Appendix IV, p. 76
bid=twice daily; **CI**=confidence intervals; **DARI**=darifenacin; **ER**= extended-release; **IR**= immediate-release; **mls**=millimeters; **ND**=not done due to step down testing procedure; **PL**=placebo; **qd**=every day; **TOL**=tolterodine

Critical Appraisal: Darifenacin ER vs. Tolterodine IR

Assessment of risk of bias (internal validity) and other aspects of the methodological quality of a study requires access to a full study report (requested and pending). In the absence of a full study report it is not possible to critically appraise the study. This study was completed prior to drug approval in the U.S. (2004). Failure to publish a full study report is a form of publication bias if the decision is based on the magnitude and direction of results (Hopewell 2009).

To summarize the trial findings, darifenacin ER 15mg and tolterodine were similar in terms of median reduction in incontinence episodes per week and urgency episodes per day. Because of the restrictions of a step down procedure for hypothesis testing for all doses of darifenacin ER (including an additional treatment arm of 30mg,) vs. tolterodine, a statistical analysis for darifenacin ER 15mg vs. tolterodine was not reported for these outcomes. More participants on darifenacin experienced constipation compared with tolterodine, absolute risk difference 12% (95% CI 3% to 22%). In the absence of a full study report (pending), a full critical appraisal of this study could not be conducted.

Of note, darifenacin did not show a statistically significant improvement over placebo for either incontinence or urgency episodes at the 2.5% significance level.

Table 14. Summary of Darifenacin ER 15mg vs. Tolterodine IR Outcomes

Outcome	No. of studies (No. of Participants)	DARI ER vs.TOL IR Median difference (97.5% CI) or RR (95% CI)	DARI ER vs. TOL IR Absolute Risk difference (95% CI)	Summary
All-cause mortality	1 trial (355)* 0 events	--	--	Trial under-powered for events in the short-term No available longer-term evidence
SAE (non-fatal)	1 trial (355)	RR 0.5 [95% CI 0.06 to 4.40]	--	No difference between drugs Trial under-powered for events No available longer-term evidence
WDAE	1 trial (355)	--	--	No difference between drugs
QoL	1 trial (355)	--	--	Similar improvement between drugs

Incontinence episodes/week Median change from baseline	1 trial (355)	Median - 0.9 [97.5% CI -3.4 to 1.4]**	--	Similar improvement between drugs
Urgency episodes/day Median change from baseline	1 trial (355)	Median – 0.3 [97.5% CI -1.1 to 0.6]§		Similar improvement between drugs
Nocturia	0 trials	--	--	No available evidence
Total AE	1 trial (355)	RR 1.14 [95% CI 0.99 to 1.32]	--	No significant difference more participants
Dry mouth	1 trial (355)	RR 1.29 [95% CI 0.93 to 1.81]	--	No significant difference
Constipation		RR 1.99 [95% CI 1.24 to 3.19]	RD 12% [95% CI 3% to 22%]	12% more participants experienced constipation on DARI ER

AE=adverse events; **CI**=confidence intervals; **DARI**=darifenacin; **ER**=extended-release; **IR**= immediate-release; **QoL**=quality of life; **RD**=absolute risk difference; **RR**=relative risk; **WDAE**=withdrawals due to adverse events; **TOL**= tolterodine;
* active drug in doses of interest
§ Common Drug Review 2009 report , Appendix IV, p. 69-70

b. Darifenacin ER vs. Solifenacin

One open-label parallel group RCT compared solifenacin 5mg with darifenacin 7.5mg (But 2012). This is a small twelve-week trial (N=77) that enrolled ambulatory women (median age 54 years) with urgency intensity and urgency incontinence described as $\geq$ 3 on the Urgency Perception Scale and $\geq$ 1 urgency episode per day. Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix H. The primary outcome of the study is the number and intensity of urgency episodes using the Urgency Perception Scale, a scale that rates subjective sensation. It is not clear which scale was used as the enrollment criteria suggest this was the Patient Perception of Intensity of Urgency Scale (PPIUS) with a rating from 0 to 4 whereas the Urgency Perception Scale (UPS) has only 3 items/responses (1-3). Although these scales have been validated in some populations, their use is debated by some investigators as they may confuse normal filling sensations ('urge') with urgency, which is an 'all-or-nothing' phenomenon (Abrams 2012).

1. All-cause mortality – no deaths are reported.

2. Serious Adverse Events (SAE)– no SAE are reported.

3. Withdrawals due to Adverse Events (WDAE) – a similar proportion of patients withdrew due to AE in each group: darifenacin 4/37 (11%) vs. solifenacin 4/40 (10%).

4. Quality of life (QoL) – Two validated questionnaires, the Urogenital Distress Inventory (UDI) and the Incontinence Impact Questionnaire (IIQ) were used to assess impact on QoL and effect of treatment. Both questionnaires have acceptable reliability and validity (Hagen 2002; Shumaker 1994). A total of 29 patients were included in analysis of treatment differences from baseline to week 12.

The IIQ is a 30-item questionnaire developed to measure psychosocial impact of incontinence in women and has four subscales; physical activity, travel, social relationship and emotional health. Responses of an individual are transformed into subscores from 0 to 100 and the total score is also summed (0 to 400).

The total score of the IIQ and the subscore social relationship domain showed significantly less improvement in the darifenacin group compared to solifenacin, with a 35 point between-treatment difference in medians for total IIQ score, in favour of solifenacin, p=0.018 (based on Wilcoxon Rank Sum test). The 35 point difference is within the range of values for the minimal clinically important difference (MCID) (Shamliyan 2012).

The UDI measures the degree of bother with obstructive, irritative and stress symptoms and consists of 19 questions. The range of minimal clinically important differences for the UDI (0-300) is -35 to -45 points and for the irritative subscale -15 to -25 points (Dyer 2011). The differences in UDI scores between drugs were not statistically significant nor did they exceed the MCID.

5. Patient-Reported Perception of Improvement – Patients reported their subjective assessment of treatment improvement on a visual analogue scale (VAS). Improvement or 'success' was not further defined and validation of the VAS was not discussed. The higher the score, the greater the improvement. There was significantly less improvement with darifenacin, with a 22.5 point between-treatment difference in medians, P = 0.010. The clinical meaningfulness of the difference was not discussed.

6. Incontinence Episodes – the trial did not report the proportion of patients who were incontinent at enrollment and does not report number of incontinence episodes or change from baseline. There was no significant difference between drugs in incontinence pad usage/day. The difference in median reduction from baseline was 0.6, P=0.19.

7. Nocturia – there was no statistically significant difference in change from baseline between darifenacin and solifenacin at 12 weeks. The difference in median reduction from baseline was 0.3, P=0.43.

8. Urgency – there was no statistically significant difference in change from baseline between darifenacin and solifenacin at 12 weeks.

9. Total AE – the trial did not report on this outcome.

10. Specific AE – the study used a checklist of adverse effects (dry mouth, constipation, blurred vision, headache, dizziness, lack of concentration, memory problems and insomnia) at baseline, 4 weeks, and 12 weeks. However, the proportion of participants who experienced a particular AE at any time throughout the study period is not presented, and cannot be summed from the 4 and 12 week data. A high proportion of participants experienced AE at baseline, and for most AE, incidence decreased during the treatment period. The exceptions were dry mouth and constipation at 4 weeks. The incidence of these events was not significantly different between active drugs. Although the authors state there was more dry mouth at 12 weeks in the darifenacin-treated group, the difference was not statistically significant: RR 1.53 (95% CI 0.92 to 2.54), P=0.10.

11. Urodynamics/clinician measures – the trial did not measure these outcomes.

12. Mean volume voided – the trial did not measure this outcome.

Critical Appraisal: Darifenacin ER vs. Solifenacin

Risk of bias/quality assessment:
See Table 3 in Appendix H. But 2012 is a small study termed 'exploratory' by its investigators, without sample size or power calculation, and failed to meet its stated recruitment goal of 100 patients. Randomization was adequate but allocation concealment is not described. Failure to conceal allocation can lead to selection bias or systematic differences between groups. In open-label studies, allocation concealment can be particularly challenging. Because the study was open-label, it was at high risk of performance and detection bias, particularly for subjective outcomes such as patient-reported treatment success, quality of life or symptom bother. It is unclear if all outcomes are reported and none are identified as pre-defined. The withdrawal rate was 21%, with similar proportions and reasons for withdrawal from each arm. The study reports a per protocol analysis, rather than intention-to-treat and it is likely that patients who withdrew differed from completers.

Efficacy data did not meet normality assumptions so medians are reported and a non-parametric test was used to test treatment differences. No adjustments were made for multiple significance testing, the reason given that the study was exploratory.

The study actively collected harms data by using a checklist. However, the high proportion of AE at baseline and the reduction of most during the study confounds interpretation of AE data. It is surprising, for example, that nearly half of patients randomized to darifenacin (47%) report dry mouth at baseline, although one of the study inclusion criteria was no anticholinergic drug use for 6 months pre-enrollment. In addition, the study does not report the cumulative numbers of patients experiencing a particular AE throughout the entire course of the study.

Applicability (external validity of trial results)
Because the trial was conducted solely in women, and used QoL instruments predominantly validated in women, generalizability to men is limited. Additionally, subjective outcomes in an open-label trial may strongly reflect expectation bias.

Comparator/dose choice: both drugs are long-acting so this is a reasonable comparison. The recommended starting dose of both drugs was chosen as a fixed dose.

Industry sponsorship: The full study report does not declare sponsorship. However, industry sponsorship by the manufacturer of solifenacin is reported in conference proceedings (But 2010). Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

In summary, this small exploratory study does not provide evidence that darifenacin has a therapeutic advantage over solifenacin in the treatment of women with urgency or urgency incontinence.

3. Trials in Elderly Populations

Direct Comparator Trials: There were no direct comparator trials that exclusively enrolled adults aged 65 years or more. We therefore identified placebo-controlled trials that enrolled elderly populations as supplemental information for tolerability and adverse events.

Placebo-controlled trials: One 12-week, parallel group, placebo-controlled RCT was identified that exclusively enrolled patients 65 years of age or older (N=400) (Chapple 2007). See Table 6 in Appendix H for study characteristics. A flexible dose regimen of darifenacin ER was used, starting with 7.5mg once daily and increasing to 15mg if desired. After 2 weeks, 47% of the darifenacin group increased their dose to 15mg, and 66% of the placebo group requested an increase (subjected to a sham increase). Mean age of participants was 72 years (range 64 to 89), and 139 (35%) were > 75 years of age. The majority were female (77%).

Harms data were passively collected. The trial publication incompletely reported harms and data were supplemented by data obtained from the Common Drug Review (Common Drug Review 2009). We report harms outcomes in order of the hierarchy of outcomes for this review.

1. All-cause Mortality – there were no deaths in either group.

2. Non-fatal Serious Adverse Events (SAE)
Four patients (1.5%) were reported as having SAE in the darifenacin group, and four in the placebo group (3.0%) (Common Drug Review 2009). The difference was not statistically significant: RR 0.5 (95% CI 0.13 to 1.97), P=0.32. Two of the events in the darifenacin-treated group were gastrointestinal hemorrhage.

Table 15. Serious Adverse Events

Treatment	DARI ER N=266	Placebo N=133
N (%)	4 (1.5%)	4 (3.0%)
# of events	6	4
Specific SAE	GI hemorrhage (2) Mallory-Weiss syndrome Atrial fibrillation Urosepsis Renal colic	Osteoarthritis Breast cancer Cerebrovascular accident Transient ischemic attack

From Common Drug Review 2009, p. 30; **ER**=extended-release; **GI**=gastrointestinal hemorrhage; **DARI**=darifenacin; **N**=number of patients; **SAE**=serious adverse events;

Cognition: the trial did not actively assess cognitive outcomes.

CNS events: are not reported separately for this trial. A pooled analysis with two other placebo-controlled trials reports somnolence and dizziness for tolterodine ER (1.3%) (Common Drug Review 2009, p. 75) and darifenacin 15mg ER (0.9%). However, the method of pooling, numbers of patients and age of patients are not provided.

Cardiac: 9 patients (3.4%) on darifenacin ER and 0% on placebo experienced cardiac events (Common Drug Review 2009). The events were: atrial fibrillation; cardiac failure; palpitations (2); and angina pectoris. ECG findings that were asymptomatic included extrasystoles, supraventricular extrasystoles, left bundle branch block and sinus arrhythmia. One event, atrial fibrillation was reported as a SAE.

Falls/fractures: 1 fracture was reported in the placebo group only (Common Drug Review 2009).

Acute urinary retention: no cases occurred in the trial.

3. Withdrawals due to adverse events (WDAE)
There was no statistically significant difference in WDAE between groups: darifenacin 12/266 (5%) vs. placebo 9/133 (7%): RR 0.67 (95% CI 0.29 to 1.54), P=0.34 (Common Drug Review 2009, p. 9).

4. Total AE: More participants in the darifenacin group experienced one or more AE: darifenacin 149/266 (56.0%) vs. placebo 60/133 (45.1%): RR 1.24 (95% CI 1.00 to 1.54), P=0.05; absolute risk difference 11% (95% CI 1% to 21%).

5. Specific AE:
Dry mouth: Darifenacin was associated with more dry mouth than placebo: darifenacin 59/266 (22.2%) vs. placebo 5/133 (3.8%): RR 5.90 (95% CI 2.43 to 14.35), P<0.0001; absolute risk difference 18% (95% CI 12% to 24%).

Constipation: Darifenacin was associated with more constipation than placebo: DARI 41/266 (15.4%) vs. PL 11/133 (8.3%): RR 1.86 (95% CI 0.99 to 3.51), P=0.03; absolute risk difference 7% (95% CI 1% to 14%).

ECG: "No trends were seen in ECG evaluations conducted at baseline and week 12". No further details are provided.

Post void residual volume: This was measured in men only. No significant difference was detected between darifenacin and placebo. Mean changes from baseline: darifenacin +12 (95% CI 2 to 22) vs. placebo +17 (95% CI 18 to 53). Median change in both: 0 mls.

Laboratory tests: not specified but measured at baseline and week 12. "No important changes in laboratory variables or vital signs" were identified.

This trial did not report any unanticipated adverse events.

The primary outcome for the trial was the change from baseline in incontinence episodes per week. There was no significant difference between placebo and darifenacin in improvement in incontinence. There was also no significant difference between placebo and darifenacin for the outcomes nocturia and urgency.

Critical appraisal: Darifenacin vs. Placebo in Elderly

Risk of bias
An assessment of risk of bias was based on all available data (Table 7 in Appendix H). The study did not describe the process of randomization or method of allocation concealment so was rated to be at 'unclear' risk of bias for these methodological features. Blinding was appropriate for participants, health care personnel and outcomes assessors (low risk of bias). An intent-to-treat analysis with last-observation-carried-forward was used, and withdrawals were comparable. Only commonly reported harms (> 5% of patients in either group) were reported in the trial publication. There was no other evidence of selective outcome reporting.

Sample size calculation was based on an efficacy outcome and the trial was likely to have been under-powered to detect differences in serious adverse events.

Applicability (external validity) of trial results
The study was included in this review for harms data only. Because of the flexible dosing regimen (mixed doses 7.5mg and 15mg), this may have obscured a dose-response for harms. Almost half of the participants in the darifenacin group (47%) were on the higher 15mg dose of darifenacin.

A third of participants were 75 years of age or older. Exclusion criteria included cognitive impairment (and other significant medical conditions) so the findings are not generalizable to cognitively impaired individuals or the frail elderly. The most common comorbidities in participants were hypertension and hypercholesterolemia, both surrogate markers that are not necessarily associated with clinically apparent disease. The most common co-medications were aspirin (26-32%), multivitamins (14-15%), a statin (10-15%) and thyroid hormone (11-12%).

Most of the trial participants were women. The study did include 93 men (23% of total population), 39 (41% of men) of whom had benign prostatic hypertrophy. Stable doses of alpha-blockers or 5-alpha-reductase inhibitors were permitted, but the percentage of men on these medications is not reported.

As noted above, this trial failed to find a significant efficacy advantage for darifenacin over placebo. Given the inclusion of one-third of patients ≥75 years of age, this raises a signal of concern of potential lack of efficacy in this population. If a drug has not been shown to be effective, no degree of harm is worth risking, and therefore this is also relevant to application of evidence on harm.

Harms: Harms data were passively collected other than for vital signs, ECGs, and laboratory variables. The trial provides no information on cognitive effects. Passive collection of harms is inadequate for the assessment of cognitive impairment.

The trial was under-powered for mortality and serious adverse events in the short-term, and provides no information on harms with chronic use of darifenacin.

Summary –Darifenacin vs. Placebo in Elderly
This trial provides short-term (12 week) information on harms in a relatively young older population (mean age 72) without cognitive impairment. More patients on darifenacin experienced any AE (absolute risk difference 11%), dry mouth (absolute risk difference 18%) and constipation (7%) compared with placebo. The reported adverse event profile is consistent with other studies in younger populations. However, adverse events occurring in less than 5% of participants in each group were not reported in the publication, and the trial provides no information on cognitive effects. Cardiac events were reported to occur in 3.4% of participants on darifenacin ER and 0% of the placebo group (Common Drug Review 2009).

Non-Randomized Studies

The aim in including non-randomized studies is to gain information on serious, infrequent adverse events, longer-term harms, and adverse effects in populations not adequately represented in the RCTs.

There were no comparative non-randomized observational studies that compared darifenacin with oxybutynin or any of the other drugs in this review.

Two uncontrolled cohort analyses met study inclusion criteria:

- Haab 2006 (also reported in Hill 2007, Dwyer 2008);
- Schneider 2010.

Haab 2006 is a two-year year open-label extension trial following participation in two 12-week placebo-controlled RCTs. Patients were from 15 countries, mainly in Europe and Latin America. Additional data were extracted from secondary publications (Dwyer 2008; Hill 2007). Hill 2007 is a post hoc subgroup analysis of patients aged ≥65.

Schneider 2010 is a post hoc analysis of an open-label cohort study involving 3766 patients of 1155 physicians in Germany, mainly urologists. Table 15 presents an overview of study design, data source, duration, numbers and age of subjects and assessed outcomes.

Table 16. Non-randomized studies to evaluate darifenacin

Study	Design	Data source	Duration	DARI ER Sample size Age	Assessed AE outcomes
Haab 2006	Uncontrolled cohort	Open-label uncontrolled extension trial post 2 placebo-controlled RCTs in 15 countries; participation 75%	2 years	N=716 Mean age 57 30% ≥ 65 Flexible dose DARI; started at 7.5mg/d;	WDAE Total AE Withdrawals
Schneider 2010	Uncontrolled cohort; post hoc analysis	Clinic population; Germany; 1155 physicians (81% urologists; 14% general practitioners)	12 weeks	N=3766; Mean age 63 ± 13 DARI 7.5mg/d (97% of patients); 15mg/d (3%)	AE

AE= adverse events; **d**= day; **DARI**= darifenacin; **ER**= extended release; **WDAE**= withdrawals due to adverse events;

Table 17 describes the main safety outcomes in these two studies. As is noted below, very limited data were available. For Haab 2006, results from the post hoc subgroup analysis in the elderly (Hill 2007) are also presented: 78% of patients were aged 65-74; few of the very elderly were enrolled. In both studies, most patients were women: 85% in Haab 2006; 78% in Schneider 2010.

In Haab 2006, patients ≥65 were significantly more likely to withdraw from the study due to AE than patients <65. There were 64 WDAE in total, 34 in patients ≥ 65: 34/214 (15.9%) of older patients vs. 30/502 (6.0%) of patients <65 withdrew due to AE; RR=2.7 (95% CI 1.7 to 4.2), p<.001; risk difference 9.9% (95% CI 4.6% - 15.2%) [RevMan v5.2]. Schneider 2010 provides very limited information on patient experiences of harm.

Table 17. Adverse events reported in uncontrolled cohorts

	Haab 2006 ≤ 2 years		Schneider 2010 N=3766 12 weeks
Adverse events	**Entire sample N=716**	**Patients ≥65 N=214§**	
All-cause mortality	1*	NR	NR

SAE	84 (11.7%)	NR	NR
Total Withdrawals	241 (33.7%)	77 (36.0%)	NR
WDAE	64 (8.9%)	34 (15.9%)	102 (2.7%)
Total AE	572 (79.9%)	NR	NR
Dry mouth	167 (23.3%)	50 (23.4%)	NR
Constipation	150 (20.9%)	48 (22.4%)	NR
Urinary tract infection	82 (11.5%)	NR	NR
Dyspepsia	65 (9.1%)	NR	NR

§Results for this subgroup reported in Hill 2007 *due to metastatic melanoma with haemorrhage; **AE**= adverse events; **SAE**= serious adverse events; **WDAE**= withdrawals due to adverse events; **NR** = not reported;

Study quality /risk of bias

As uncontrolled cohort analyses, both included studies are of poor quality, with a high risk of bias. As an open-label extension study following RCT participation, Haab 2006 selectively includes patients who met RCT inclusion criteria and excludes those patients randomized to darifenacin who failed to tolerate the drug. Reporting of harm was passive.

Schneider 2010 is a post hoc evaluation of the influence of age, gender, and lifestyle on response to treatment. The latter provides little information of value as this was an uncontrolled open-label study, and this design does not allow differentiation of drug effects from expectation biases, co-interventions, other morbidities and trends over time.

Schneider 2010 enrolled 1155 physicians, mainly board-certified urologists (81%), with the rest comprising mainly of general practitioners. On average each physician enrolled around 3 patients. This design is highly suggestive of a market seeding trial. US FDA officials described seeding trials as studies with a primary aim of enticing physicians to prescribe a new medication (Kessler 1994).

Both studies were industry-sponsored. Schneider 2010 states that the manuscript was drafted by two academic authors but was funded by Bayer Vital. Haab 2006 and companion papers acknowledge commercial ‘editorial and project management’ by the company ACUMED as well as Novartis funding.

Summary – non-randomized studies

The two uncontrolled cohort analyses available fail to provide adequate information to assist in the assessment of darifenacin’s adverse effects, either in the elderly or in patients in general with overactive bladder syndrome. It is impossible to know whether or not darifenacin has a more favourable AE profile than alternatives based on the available published data. In Haab 2006, there was a higher rate of withdrawal due to AE in patients ≥65 than in younger patients.

Other Adverse Event Data

Case reports

There is one published case report of a previously unlisted AE following darifenacin exposure (Mason 2008). This was a biopsy-confirmed case of interstitial granulomatous dermatitis (IGD) in a 54-year old woman who was on multiple other medications for rheumatoid arthritis, depression, anxiety and fibromyalgia. IGD can occur with autoimmune diseases as well as with medications. The rash appeared soon after initiation of darifenacin, resolved on discontinuation, re-appeared on re-initiation and resolved again on discontinuation.

Regulatory Data

Data on adverse events were sought from government and regulatory resources including periodic safety update reports (PSURs), the Health Canada Vigilance Database records and the U.S. Food and Drug Agency reviews. Pharmacosurveillance databases have major limitations including under-reporting and lack of denominator data which precludes rate calculations.

Periodic Safety Update Reports (PSUR)

Periodic safety updates for darifenacin were not made available for this review.

Canada Vigilance Adverse Reaction Online Database

There are a total of 27 adverse reactions associated with darifenacin use in the Health Canada Vigilance Database, up to December 31, 2012, the most recent date of entry for the database. The age range of reported cases is 37 to 90 years.

Fatal SAE: No deaths are reported.

Non-fatal SAE: 9 case reports are identified as serious. Of the 7 serious cases that specified age (range 57 to 90), 5 involved people who were > age 65. Three serious cases were identified as central nervous system or psychiatric disorders. The events were: confusional state/dementia/disturbance in attention (1); abnormal behaviour/somnolence (1); feeling abnormal/tremor (plus other events) (1).

The other serious cases are: blindness/eye pain/vision blurred (1); blood pressure increased (1); chest pain (1); muscle spasms (1); arthralgia/herpes zoster/weight increased/blood pressure increased (1); bladder disorder/drug ineffective (1).

Central Nervous System Effects: In total, seven unique case reports were identified with terms for nervous system or psychiatric disorders (isolated or in association with other events). The three cases identified as serious are described in the above section.

The four other case reports are: balance disorder/dizziness (plus nausea/abdominal pain) (1); confusional state/balance disorder/asthenia/dizziness/somnolence/drug interaction – the patient was on fluconazole, a moderate CYP 3A4 inhibitor (1); dizziness/ headache (plus dry mouth/lip swelling/groin pain) (1); emotional distress (plus cystitis/malaise/peripheral edema/micturition urgency/urinary incontinence) (1).

Cardiac: No cases of torsade de pointes, ventricular tachycardia or cardiac arrest were reported. Three of the case reports identified as serious included blood pressure increased, two with multiple other events. Another serious case was chest pain in a female with no further details. None of the cases in the database were identified in a search for cardiac or vascular disorders.

Fourteen other (non-serious) case reports are in the database. These include: asthma/cough (1); dsypnea/productive cough/feeling hot (1); muscle spasms (plus drug ineffective) (1); constipation/dysuria (1); abdominal pain/distension/flatulence/dysuria (1). Nine other reports are drug ineffective, with pollakiuria (abnormally frequent urination) or incontinence in 3.

FDA Regulatory Data

As part of the drug approval process, the following safety updates were reviewed by the FDA: bone fractures; cardiovascular events; constipation; and urinary retention (Center for Drug Evaluation and Research NDA 21-513 Medical Review, 2004). No periodic safety updates are available for more recent data.

Deaths: a total of four deaths occurred during the clinical program, 3 in darifenacin-treated subjects and 1 in placebo-treated subjects. None were attributed to darifenacin.

Bone fractures: 18 fractures were reported as SAE in 7528 darifenacin-treated subjects (0.25% incidence) across all studies and doses (3.75mg-30mg) in the darifenacin clinical program, and none in 2343 placebo-treated patients. The fractures occurred in both males and females across all ages and doses. Eight of the 18 cases were in patients over the age of 65. Upon review of case narratives, the FDA reviewer concluded all could be attributed to causes other than darifenacin.

Cardiovascular events:
The following are cardiovascular events that occurred in all Phase II/III studies in the darifenacin clinical program (Table 18).

Table 18. Cardiovascular AE in all Phase II/III OAB/Irritable Bowel Syndrome studies

Adverse event	Darifenacin N=2101 N (%)	Active comparator N=450 N (%)	Placebo N=830 N (%)
Palpitation	9 (0.4%)	5 (1.1)	5 (0.6%)
Tachycardia	5 (0.2%)	4 (0.9)	1 (0.1%)
Syncope	3 (0.1%)	1 (0.2)	2 (0.2%)
Angina pectoris	4 (0.2%)	1 (0.2)	0
Arrhythmia	4 (0.2%)	0	2 (0.2%)
Hypotension	4 (0.2%)	0	0
Bradycardia	3 (0.1%)	0	0
ECG abnormal	2 (0.1%)	0	1 (0.1%)
Myocardial infarct	1 (0.04%)	0	0
Myocardial ischemia	2 (0.1%)	3 (0.7%)	0
Atrial fibrillation	2 (0.1%)	0	1 (0.1%)
AV block	1 (0.04%)	0	0
Coronary artery disease	1 (0.04%)	0	1 (0.1%)
Bundle Branch Block	1 (0.04%)	0	0
Ventricular arrhythmia	0	0	1 (0.1%)

From FDA Review 21-513, Table 16. AV= atrioventricular;

In an update, a total of 31 cardiovascular SAE were reported in darifenacin-treated subjects (1.8 cases per 100 subject-years of exposure), in all Phase I, II and III studies, compared with 9 cases in placebo-treated subjects (2.5 cases per 100 subject-years of exposure). Of the 31 SAE in darifenacin-treated subjects, 9 were in the heart rate/rhythm category whereas none of the SAEs in placebo-treated subjects were in this category. Four arrhythmia cases were considered to be clinically significant. Each had a complicated medical history and comorbidity making it challenging to ascertain cause. Incorporating eight additional cases from a long-term open-label

safety study, including two arrhythmias (atrial fibrillation in two subjects with prior atrial fibrillation), the updated incidence rate remained at 1.8 per 100 subject years of exposure. The FDA review concluded the clinical program showed no increased risk of cardiovascular disorders.

A 'thorough QT' study (Study DAR328A2302) was conducted on 179 subjects (age 44 to 65) who received either darifenacin 15mg once daily, darifenacin 75mg once daily, a positive control moxifloxacin or placebo for 6 days (Serra 2005). The higher dose was chosen to achieve plasma concentrations that would occur in poor CYP 2D6 metabolizers in the presence of a CYP 3A4 inhibitor, thereby affecting both routes of metabolism of the drug. Darifenacin was not associated with clinical or statistically significant QT/QTc prolongation or cardiac conduction abnormalities. In this study, approximately 20% of subjects were poor metabolizers.

Urinary retention: In the NDA safety database, 53 darifenacin-treated subjects (0.7%), 2 placebo-treated subjects (0.1%) and 4 subjects treated with an active comparator (0.5%) were reported to have urinary retention. Of the 53 cases associated with darifenacin, 16 were classified as acute urinary retention, 7 as a SAE. Of the 7 SAE, 3 were taking recommended doses, and 4 were taking a higher-than-recommended dose (30mg). The three cases that involved approved doses were in males, two of whom had benign prostatic hypertrophy. Of the 9 'non-serious' cases of acute urinary retention, 3 were taking recommended doses.

Table 19. Adverse Events – Urinary Retention

Urinary retention	Darifenacin N=7258 N (%)	Placebo N=2343 N (%)	Active comparator N=887 N (%)
AE	53 (0.73%)	2 (0.09%)	4 (0.45%)
SAE	7 (0.10%)	0	0

Constipation: In 7528 subjects treated with darifenacin in all Phase I, II and III trials, there have been 6 cases of constipation as a SAE, 4 of which occurred at recommended doses.

Elderly – no overall differences were observed in safety between subjects $\geq$ 65 years of age and younger populations. There were 75 patients over the age of 75 in four pivotal Phase III studies on OAB with a comparable safety profile (Darifenacin (Enablex) Product Monograph).

US FDA - post-market labelling changes

The U.S. FDA provides a record of revisions to product labelling since approval. The following additions have been required by the U.S. Food and Drug Administration since market entry in 2004, reflecting post market experience.

Warnings and precautions

- Angioedema (2010)
- Central nervous system effects (2012) - headache, confusion, hallucinations and somnolence

Adverse reactions – postmarketing experience

- Confusion and hallucinations (2008)
- Palpitations (2008)
- Hypersensitivity reactions, including angioedema (2008);
- "With airway obstruction" added to angioedema (2010)

- Anaphylactic reaction (2011)
- Erythema multiforme and interstitial granuloma annulare (2011)

Discussion and Conclusions

Q1: Does darifenacin provide a therapeutic advantage over oxybutynin IR or other comparators?

Direct Comparator RCTs

Darifenacin ER vs. Oxybutynin IR

Two crossover RCTs compared darifenacin ER 15mg with oxybutynin IR 5mg t.i.d. (15mg total/day) (Zinner 2005; Chapple 2005). The trials were very short (1-2 weeks) and included a total of 100 patients for comparisons/ doses of interest. A meta-analysis was not conducted because useable data were not provided in the publications. In crossover trials, observations may not be independent, and for dichotomous outcomes, the trial publications did not indicate whether observations for each treatment period occurred in the same or different individuals. Useable data for meta-analysis were also not provided for continuous outcomes.

SAE and WDAE were similar for both drugs but the studies were likely to have been under-powered to detect differences. Similar proportions of patients experienced one or more AE on each drug. There was less dry mouth associated with darifenacin ER compared with oxybutynin IR, with the difference statistically significant in the larger trial (13% vs. 36%, $p< 0.05$) (Zinner 2005). In the second smaller trial (N=24), there was less dry mouth on darifenacin (54% vs. 71%). No statistical tests for significance are reported, but an exploratory unpaired analysis in RevMan failed to find a statistically significant difference. Numerically more patients on darifenacin ER 15mg experienced constipation in both trials, but again the differences were not statistically significant on exploratory analysis. [Note: these tests are exploratory because we had no access to the paired crossover data, or first period data, needed for testing.]

Only one trial (N=76) reported clinical efficacy outcomes and in this trial, a per protocol analysis eliminated those who dropped out early (Zinner 2005). This was likely to have excluded patients less tolerant of treatment. There was no difference between drugs in reduction from baseline in incontinence episodes per week or urgency episodes per day. The trial may have been under-powered to detect such differences.

No trials compared darifenacin ER 7.5mg, the recommended starting dose, with oxybutynin.

Based on these two RCTs (N=100), darifenacin ER is associated with less dry mouth, and showed a trend for increased incidence of constipation. The strength of evidence is low. For efficacy outcomes, based on one trial (N=58 in a per protocol analysis), there is insufficient evidence to conclude if either darifenacin ER or oxybutynin IR is superior.

A more suitable comparator would have been an extended-release formulation of oxybutynin. Extended-release formulations have less fluctuation in drug plasma levels, which can modify clinical response. Extended-release formulations of oxybutynin (oral or transdermal) are associated with less dry mouth than oxybutynin IR (see Chapter 9; also Madhuvrata 2012).

There is no available evidence with which to conclude a therapeutic advantage for either darifenacin ER or oxybutynin (any formulation) when used on a chronic basis.

Darifenacin ER vs. Other Comparators
Two trials were identified, one comparing darifenacin ER with tolterodine IR (Study A137-1001) and the other comparing darifenacin ER with solifenacin (But 2012). No trials were identified that compared darifenacin with fesoterodine or trospium.

Darifenacin ER vs. Tolterodine IR: Study A137-1001 is a 12-week, placebo-controlled, parallel group Phase III trial. It compared darifenacin ER 15mg with tolterodine IR 2mg b.i.d. (4mg total/day). This trial has not been published as a full study report, even though it was completed by 2004. A full study report has been requested from the manufacturer and is pending (Novartis Pharmaceuticals Canada 2006).

For an interim analysis, available sources of trial data were the FDA medical and statistical reviews and the Common Drug Review reports. There was no difference in SAE between drugs, but the trial was under-powered for this outcome. There was also no difference in WDAE. Darifenacin ER and tolterodine IR showed similar improvement in condition-specific quality of life, incontinence episodes per week and urgency episodes per day. Darifenacin ER was associated with a higher incidence of constipation (absolute risk difference 12%) compared with tolterodine IR. Darifenacin ER 15mg was also associated with more dry mouth than tolterodine IR, but the difference was not statistically significant.

It is noteworthy that darifenacin ER 15mg did not show a statistically significant improvement over placebo for either incontinence or urgency episodes at the pre-set 2.5% significance level (Center for Drug Evaluation and Research NDA 21-513).

A full study report is needed to critically appraise this study and its findings.

Darifenacin vs. Solifenacin: One open-label parallel group RCT compared darifenacin 7.5mg with solifenacin 5mg once daily (But 2012). This is an appropriate comparison because solifenacin is long-acting, and also has some selectivity for the M3 muscarinic receptor subtype although less than darifenacin. The trial was 12 weeks long and enrolled women only. It is a low quality trial and at high risk of bias due to its lack of blinding, and per protocol analysis. It provides insufficient evidence to conclude if either drug has a therapeutic advantage over the other.

All of the available comparator RCTs for darifenacin were industry-sponsored. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). Industry sponsorship has also been reported to predict benefit for comparator trials within a drug class (Bero 2007).

Publication bias is a form of reporting bias that occurs when a decision to publish a trial depends on the magnitude or direction of results (Hopewell 2009). Lack of publication of a full study report of a relatively large comparative trial (Study A137-1001, completed by 2004) likely represents publication bias.

Comparison with other systematic reviews
This review's RCT findings are consistent with the main conclusions of a recent systematic review published by the Cochrane Collaboration (Madhuvrata 2012) and Shamliyan 2012, a review conducted for the Agency for Healthcare Research and Quality (AHRQ). Compared with

Madhuvrata 2012, we included additional data on Study A137-1001 and But 2012. Shamliyan 2012 did not include Study A137-1001 except for some placebo-controlled data that had been pooled with other RCTs.

Some minor differences were noted compared with the AHRQ review. Shamliyan 2012 reported there was a differential in dose increases for darifenacin and solifenacin in But 2012. According to the full publication, this was a fixed dose trial. Dose increases were reported for post study treatment only. In addition, the AHRQ review combined data for the two crossover trials comparing darifenacin vs. oxybutynin for WDAE. We chose not to do a meta-analysis as we did not have access to paired data, or first period data, for both trials. Observations may not have been independent, given the crossover design. We also did not include non-approved doses of darifenacin ER or results for the immediate-release formulation of darifenacin as this was not a drug formulation under review for the current report. In contrast, the AHRQ review did not distinguish between formulations in its conclusions.

Supplemental Adverse Event data

Placebo-controlled trials in the elderly: One 12-week trial provided additional information on harms in patients who were ≥ age 65 and without cognitive impairment (Chapple 2007). The mean age was 72 years, and about a third of participants were >75 years of age. The trial used a flexible dosing regimen, with about half (47%) of darifenacin-treated patients on 15mg and the other half on 7.5mg. The mixture of doses obscures a dose-response for harms. There was no statistically significant difference in serious adverse events or withdrawals due to adverse events compared with placebo. More patients on darifenacin experienced any AE (absolute risk difference 11%), dry mouth (absolute risk difference 18%) and constipation (absolute risk difference 7%) compared with placebo.

The reported adverse event profile was consistent with studies in younger populations. However, adverse events occurring in less than 5% of participants in each group were not reported in the publication, and the trial provides no information on cognitive effects. Cardiac events were reported to occur in 3.4% of participants on darifenacin ER and none in the placebo group (Common Drug Review 2009). Because cognitive impairment and other clinically significant medical conditions were exclusion criteria, the findings may not be generalizable to the frail elderly.

This trial failed to find a significant efficacy advantage for darifenacin over placebo. Given the inclusion of one-third of patients > age 75, this raises a signal of concern of potential lack of efficacy in this population. If a drug has not been shown to be effective, no degree of harm is worth risking, and therefore this is also relevant to application of evidence on harm.

Non-randomized studies: No comparative non-randomized observational studies were identified. There were two uncontrolled cohort analyses, one a two year open-label extension study following two RCTs (Haab 2006), and the other a post hoc analysis of an open-label cohort of a clinic population (Schneider 2010). Both were industry-sponsored.

Haab 2006 selectively enrolled patients who had met RCT inclusion criteria and excludes those patients randomized to darifenacin who failed to tolerate the drug. Few of the very elderly were enrolled. There was a higher rate of withdrawal due to AE in patients ≥65 than in younger patients (risk difference 10%). Harms data were passively collected.

Schneider 2010 is a post hoc evaluation of the influence of age, gender and lifestyle on response to treatment. It provides little information as it was an uncontrolled open-label study, and this design does not allow differentiation of drug effects from expectation biases, co-interventions, other morbidities and trends over time. The design, with a large number of physicians enrolling few patients is highly suggestive of a market seeding trial (Kessler 1994).

The two uncontrolled cohort analyses fail to provide adequate information to assist in the assessment of darifenacin's adverse effects, either in the elderly or in patients in general with overactive bladder syndrome. It is impossible to know whether or not darifenacin has a more favourable AE profile than alternatives based on these data.

Post-market surveillance and regulatory safety data: Periodic safety updates from the manufacturer were not available for this review. Safety concerns during the FDA approval process (2004 or earlier) included a possible signal for bone fractures. Upon review of 18 SAE involving bone fractures in darifenacin-treated subjects (0.85% incidence), and none in placebo-treated subjects, the FDA reviewer concluded there was no increased risk attributable to darifenacin. Other safety reviews conducted on the database of the clinical development program included cardiovascular events, urinary retention and constipation. Based on the FDA documentation and reports in the Canadian Vigilance Database, the adverse event profile is qualitatively similar to those identified for other antimuscarinic drugs. However, these data do not allow conclusions of comparative safety or effectiveness.

Additions to the U.S. labelling information based on post market experience include warnings on central nervous system effects (headache, confusion, hallucinations and somnolence) and angioedema. The following adverse events were added: anaphylactic reaction; hypersensitivity reactions; erythema multiforme; interstitial granuloma annulare; confusion; hallucination; and palpitations.

Gaps in evidence

There is a lack of well-designed, independently conducted active comparator trials for this drug.

No active comparator trials were identified that exclusively assessed elderly populations. Because older individuals are frequently prescribed antimuscarinic drugs, and often have comorbidities or increased anticholinergic loads due to polypharmacy, it is imperative to collect data in this population, including those $\geq$ age 75, and the frail elderly.

Available trials were too brief to assess long-term safety and effectiveness when darifenacin and its comparators are used on a chronic basis.

No RCTs have been conducted to assess cognitive effects in patients with OAB.

No RCTs have been conducted in patients who are refractory to, or intolerant of, oxybutynin IR.

In summary, sparse evidence is available for the comparisons of darifenacin with oxybutynin IR, tolterodine IR and solifenacin.

Based on 2 short (1-2 week) crossover RCTs (N=100), darifenacin is associated with less dry mouth than oxybutynin IR. The strength of evidence is low. Based on 1 crossover RCT (N=58 in a per protocol analysis), there is insufficient evidence on efficacy outcomes to conclude if darifenacin ER or oxybutynin IR is superior. In total, there is insufficient evidence to conclude a therapeutic advantage for either drug.

Based on one trial (N=77), there is insufficient evidence to conclude a therapeutic advantage for darifenacin versus solifenacin.

Based on one trial (N=355), darifenacin ER was associated with increased constipation compared with tolterodine IR (absolute risk difference 12%) and similar efficacy. A full study report for this study has been requested from the manufacturer and is pending.

There is no available evidence for the comparison of darifenacin vs. fesoterodine or trospium.

Q2. New Evidence since the CDR Review

There have been two CDR Reviews, the original submission dated September 2006 and a resubmission report dated March 2009. The CDEC recommendation dated April 16, 2009 was to list darifenacin for patients who cannot tolerate or have insufficient response to an adequate trial of immediate-release oxybutynin, and to list in a similar manner as drug plans list tolterodine.

For the original review, eight RCTs of one to 12 weeks were included. Of these, three RCTs were active comparator trials. The rest were placebo-controlled trials, none of which were exclusively in an elderly population. For the resubmission, one additional placebo-controlled RCT, enrolling patients $\geq$ age 65 was included, bringing the total to six placebo-controlled RCTs.

The direct comparator trials in the CDR Review(s) are:

Zinner 2005 (darifenacin ER vs. oxybutynin IR)
Chapple 2005 (darifenacin ER vs. oxybutynin IR)
Study 137-1001 (darifenacin ER vs. tolterodine IR)

Supplemental information in the CDR Review on the elderly and on cognition included:

Chapple 2007 (darifenacin vs. placebo; RCT on elderly)
Kay 2006 (darifenacin ER vs. oxybutynin ER, cognition in healthy volunteers)
Lipton 2005 (darifenacin ER or IR vs. placebo, cognition in healthy volunteers)

Conclusions of the 2006 review were that darifenacin improves measures of quality of life and various OAB symptoms (incontinence, urgency, frequency) versus placebo, and that darifenacin is similar to tolterodine or oxybutynin for these measures (Common Drug Review 2009, Appendix IV). Based on the one additional study in the resubmission, Chapple 2007, the adverse event profiles were noted to be consistent for younger and older adults. Of note, for one key efficacy outcome (incontinence), darifenacin was not better than placebo in the Chapple 2007 study.

In the current review, one additional 12-week, direct comparator, parallel-group RCT (77 patients) compared darifenacin ER with solifenacin (But 2012). This trial is the only identified RCT that compares darifenacin ER with another long-acting drug in OAB patients. Solifenacin shows some selectivity for the M3 receptor subtype although not to the same extent as darifenacin. The trial provides insufficient evidence for a therapeutic advantage for either drug. Therefore, the available new evidence does not change the conclusions of the CDR Review substantively.

Our review did not identify new comparator RCTs that assess cognitive effects. We also did not

identify new placebo-controlled RCTs on the elderly or on cognition. The identification of all new placebo-controlled RCTs, regardless of outcome or population, was beyond the scope of this review.

We note there are no direct comparator trials that compare darifenacin with another antimuscarinic drug in a population that is refractory to or intolerant of oxybutynin IR, in spite of the CDEC Final Recommendation in 2009.

Q3. Cognition

Data on cognition were obtained from two RCTs, one comparative RCT and the other, a placebo-controlled trial, both in healthy volunteers. A third trial assessing cognition is excluded as the active comparator, dicyclomine, is not included in this review, and the study included only healthy volunteers with a mean age of 28; results are therefore irrelevant to older patients (Kay 2005). For this question, the same hierarchy of AE outcomes developed for Q1 is used, with omission of the efficacy outcomes.

Direct Comparator RCTs

Darifenacin ER vs. Oxybutynin ER

One three-week parallel group trial assessed effects of darifenacin ER and oxybutynin ER on cognition (Table 8 in Appendix H) (Kay 2006). 150 healthy volunteers ≥ 60 were enrolled, 62% female and 94% Caucasian. Participants were given a battery of computerized cognitive tests at baseline, week 1, 2 and 3.

Participants on oxybutynin ER (OXY) were started at 10mg/day on week 1; increasing to 15mg/day on week 2 and 20 mg/day on week 3 (N=50 randomized).

Participants on darifenacin (DARI) received 7.5mg/day on weeks 1 and 2 (with sham dose increase on week 2); 15mg/ day on week 3 (N=49 randomized).

Participants on placebo (PL) received sham dose increases on week 2 and 3 (N=51 randomized).

1. All-cause mortality
No deaths are reported.

2. Serious Adverse Events (SAE)
One serious adverse event occurred in a patient on oxybutynin ER, a hip fracture.

3. Withdrawals due to Adverse Events (WDAE)
Numerically, more patients on darifenacin ER withdrew due to adverse events than on oxybutynin ER: DARI 9 (18.4%) vs. OXY ER 4 (8.0%), but the difference is not significant (p=0.14; Mantel-Haenszel RR, RevMan). There were no WDAE on placebo.

4. Cognition
In total, 144 different comparisons in cognition scores are reported on, with 48 comparisons each for week 1, week 2 and week 3. No adjustment was made for multiple comparisons. The battery of tests used are proprietary (CogScreen, Psychologix, Inc.) and the lead author of the article is the president of the company. Little published data exist on test parameters.

The identified primary outcome measure was delayed recall on the name-face association test, described in Table 20. In week 2, participants on darifenacin ER 7.5mg/day did significantly better than those on oxybutynin 15mg/day. In week 3, participants on darifenacin 15mg did significantly better than participants on oxybutynin ER: mean difference 1.23 points (95% CI 0.4 to 2.1). These differences were adjusted for baseline score, age and sex.

The clinical meaning of a mean 1.23-point difference is unknown. The maximum total score is unstated but likely to be 14 on this test, for recall of names for 14 faces (2 recall tests). Mean scores at week 3 ranged from 4.9 to 6.1 (Figure 3, Kay 2006). A previous assessment of name recall performance with age in which 1205 participants aged 18-90 were recruited, found an age-related gradient in recall at the second try ranging from 10.1 ± 3.2 for those aged 18-39 to 4.8 ± 3.2 for participants aged 70-90, with no significant difference in mean score between participants aged 40-60 (Crook 1990).

Although the name-face association test at week 3 is identified as the primary outcome measure in the published report, this primary outcome was first identified in a protocol amendment on www.clinicaltrials.gov on May 24, 2006, one year after trial completion. Thus it is unlikely to have been identified *a priori* as the primary outcome measure.

Table 20. Delayed recall on the name-face association test

Comparisons	Least Square Mean difference*		
	Week 1	Week 2	Week 3
DARI vs. OXY ER	0.61 (-0.3 to 1.5)	1.23 (0.4 to 2.1)**	1.24 (0.2 to 2.3)**
DARI vs. PL	0.32 (-0.5 to 1.2)	0.25 (-0.6 to 1.1)	-0.06 (-1.1 to 1.0)
OXY ER vs. PL	-0.29 (-1.1 to 0.6)	-0.99 (-1.8 to -0.2)**	-1.30 (-2.3 to -0.3)**

*adjusted for age, sex, and baseline score; negative differences indicate worse scores;
DARI= darifenacin; **OXY ER**= oxybutynin ER; **PL**= placebo
**p<0.05

Additional significant differences between test scores at p<0.05:

- Darifenacin ER vs. oxybutynin ER – darifenacin worse
  - Divided attention (single task premature hits): DAR + 0.56 vs. OXY ER, week 2
- Darifenacin ER vs. placebo – darifenacin worse
  - Divided attention, information processing speed: 0.3 seconds slower than placebo, p=0.012
- Oxybutynin ER vs. placebo – oxybutynin ER worse
  - First-last name association (immediate recall): OXY ER -0.55 vs. PL, week 2
  - First-last name association (delayed recall): OXY ER -0.53 vs. PL (weeks 1 & 2)
  - Misplaced objects (delayed recall): OXY ER -1.51 vs. PL (p< 0.01)

In total, participants on oxybutynin ER did worse than those on darifenacin in 2 (4.2%) comparisons and did worse than placebo in 4 (8.3%). Participants on darifenacin did worse than those on oxybutynin ER on one comparison (2.1%) and did worse than placebo on one comparison (2.1%). Thus there was a trend towards participants on oxybutynin ER experiencing more effects on cognition than those on darifenacin.

With limited information available on total test scores or on minimally clinically important differences, interpretation of this signal remains limited. The emphasis on the name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008).

5. Self-Reported Perception of Memory loss
Participants used the Memory Assessment Clinics Self-Rating Scale. Mean scores did not differ significantly between groups at any time point.

6. Total AE:
Rates of total AE did not differ between darifenacin ER and oxybutynin ER: DARI ER 27 (55%) on darifenacin and OXY ER 26 (52%).

7. Specific AE
Dry mouth: Numerically fewer participants on darifenacin ER experienced dry mouth: 13 (26.5%) vs. 20 (40.8%), but the difference was not significant (p= 0.16)

Constipation: More patients experienced constipation on darifenacin: DARI ER 10 (20.4%) vs. OXY ER 2 (4.0%), RR=5.1 (95% CI 1.2-22.1), p=0.03 [Mantel Haenszel analysis; RevMan]. The absolute risk difference was 16.4% (95% CI 4% to 29%).

The rate of dyspepsia did not differ: darifenacin ER 3 (6.1%) vs. oxybutynin ER 2 (4.0%).

All-cause CNS AE also did not differ: darifenacin ER 5 (10.2%) vs. oxybutynin ER 4 (8.0%).

Critical Appraisal: Darifenacin ER vs. Oxybutynin ER

Risk of bias
See Table 7 in Appendix H. The study did not describe how the randomization sequence was generated or how allocation was concealed. Failure to conceal allocation can lead to selection bias or systematic differences between groups. Although the study used a double-dummy technique for blinding, the placebos were not further described so it is not known if they were identical in appearance to active drug. It is also not known if outcome assessors were blinded. These methodological features were all rated as 'unclear' for risk of bias. The study was at high risk of bias for incomplete outcome data as it had differential withdrawal rates in treatment arms, and reported a per protocol analysis. It was also at high risk of bias for selective outcome reporting because of an amendment to disclose primary outcome one year after trial completion.

Applicability of trial results (external validity)
The lack of information provided on maximum test scores or on established minimal clinically important difference in scores limits interpretability. This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome.

Dose/Comparator choice: Both treatment arms used increasing doses that are within the approved treatment range. A gradual increase in dose for darifenacin (e.g. 7.5mg, 11mg, 15mg), mimicking the schedule of dose increase used for oxybutynin ER, would have created a more comparative titration schedule than the use of 7.5mg for 2 weeks, and 15mg for only the 3rd week.

Harms: Numerically more patients on darifenacin withdrew due to adverse events than patients on oxybutynin ER, suggesting a signal towards less tolerability. There was significantly more constipation on darifenacin than oxybutynin ER, number needed to harm = 6.1. Reported CNS AE did not differ. Effects on cognition scores were mixed, but there is a trend towards more significantly negative effects on oxybutynin ER than darifenacin.

Industry sponsorship: The trial was sponsored by the manufacturer of darifenacin, Novartis, with editorial and project management contracted to a second company, ACUMED. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

Darifenacin vs. Placebo RCTs

One placebo-controlled RCT on cognition was identified. Lipton 2005 is a three-period crossover trial, in which healthy volunteers were randomized to 2-week periods of drug treatment, with 1 week in between. In total, 129 patients were randomized. The mean age of participants was 71.2 years (range 65-84) and 58% were female. See Table 8 in Appendix H for study characteristics.

Five treatment arms were compared:

- Darifenacin ER 3.75mg once daily
- Darifenacin ER 7.5mg once daily
- Darifenacin ER 15mg once daily
- Darifenacin IR 5mg 3x/day (15mg total)
- Placebo

Intervention:

- 2 screening visits, including 2 training runs on function tests, with the aim of eliminating practice effects during the study; those with a maximum score were excluded.
- Baseline evaluation at visit 3
- No smoking or coffee in 90 minutes pre-test
- Treatment period for 14 days; testing at end of period; then 7 day period with no treatment (other medication allowed).
- Bond-Lader questionnaire administered at baseline and at end of treatment; 16 visual analog scales on subjective alertness, contentment and calmness.

Analysis: an analysis of variance (ANOVA) model was used, fitted with terms for crossover sequence, subject, period, treatment and carryover effects. Analysis was per protocol.

Cognition test results:
The authors identify three domains as primary cognition function variables:

- Memory scanning sensitivity
- Choice reaction speed
- Delayed word recognition sensitivity.

There were no significant differences at $p<0.05$ in any of these measures versus placebo. A trend was seen in reduced speed in choice reaction time for the two higher dose groups (DARI 15mg/ day – either ER or IR), with the lower doses (3.75mg/day and 7.5 mg/day ER) and placebo exhibiting improvements in speed over time, as would be expected with a practice effect.

The authors identified an additional five domains as secondary cognitive function variables:

- Simple reaction time
- Digit vigilance task – speed
- Digit vigilance task – accuracy
- Memory scanning speed
- Word recognition scanning speed.

Only one comparison vs. placebo is significant: memory scanning speed, in milliseconds, for darifenacin 3.75mg/day CR -11.7 milliseconds ±14.0 vs. -53.9 milliseconds ± 13.9: mean difference 42.3 milliseconds (95% CI 2.9-81.7), p=0.04.

This degree of difference in speed is unlikely to be clinically significant. Additionally, there were 52 comparisons in total and this may have been a chance difference (1.9% of comparisons; 5% expected by chance at p= 0.05).

It is not clear whether the differences between primary and secondary outcomes were established *a priori*, as the rationale for the sample size calculation is not provided.

Self-assessment:
The Bond-Lader questionnaire was used to assess subjective alertness, calmness and contentment. Darifenacin did not differ from placebo in alertness or contentment at any dose level.

Mean self-rated calmness decreased from baseline by -1.72 mm vs. placebo for darifenacin ER 15mg, p=0.007. There was a marginally significant increase in calmness vs. placebo for darifenacin 3.75mg but the magnitude was only 0.27mm and the p-value 0.046. Additionally, a statistically significant period effect on calmness was noted, p<0.001. The authors suggest a "learning effect" but the Bond-Lader questionnaire does not test skills. Repeat testing may have led to a shift in overall responses over time.

Adverse events:
Very limited information was provided on AE experienced during the trial, with no reporting on mortality, withdrawals due to AE, total AE or total numbers of specific AE. Only the subset of AE judged by investigators to be treatment-related and to have been reported by 2.0% or more of volunteers were reported. Similarly, withdrawals due to "treatment-related adverse events" are reported, but not all WDAE. As this is a selected subset that may differ by group, particularly if blinding is compromised, it is not reported here. Table 21 provides an overview of total withdrawals. Ten of the 22 early withdrawals are described as treatment related (study arm not stated).

SAE:
Three participants experienced SAE during the study: skin carcinoma, cerebral hemorrhage and angina pectoris. Treatment group is not reported.

Table 21. Total early withdrawals – all reasons

	DARI ER 3.75mg (n=72)	DARI ER 7.5mg (n=74)	DARI ER 15mg (n=65)	DARI IR 5mg (3x/d) (n=71)	Placebo (n=69)
Total withdrawals	6 (8.3%)	7 (9.5%)	2 (3.1%)	4 (5.6%)	3 (4.4%)

Critical Appraisal: Darifenacin vs. Placebo

Risk of bias
Overall, there was a high risk of bias (see Table 7 in Appendix H). The study used a balanced incomplete block design (two participants) to receive 3 of 5 oral treatments, namely darifenacin extended release (ER) tablets (3.75, 7.5 or 15mg once daily), darifenacin immediate-release (IR) tablets (5mg 3 times daily) or matching placebo (20 possible treatment sequences). However, the

process of selecting the blocks is not specified, and allocation concealment is also not described. These features were rated as 'unclear'. Features of blinding were also rated as 'unclear'. A double-dummy technique was used for blinding but the appearance of the placebos is not described so it is not known whether they were identical in appearance to active drug. The study is at high risk of bias for incomplete outcome reporting because the analyses were per protocol. There was high risk of bias for selective outcome reporting. Total AE, WDAE, specific AE are not reported. The extent to which a period, subject or sequence effect was noted, or other influences from covariates that were included in the analysis, is not reported, nor is the proportion of participants who stayed in the trial for 1, 2 or 3 crossover periods.

This was a negative trial. The authors had hypothesized that darifenacin would have a beneficial effect on cognition and this did not happen. Although the initial hypothesis is stated in the trial report, the abstract and conclusions fail to clearly state that this was a negative trial, or describe the identified primary outcome measure and estimated difference on which the sample size calculation was based.

Applicability of trial results (external validity)
This was a healthy volunteer study, and results may not be directly applicable to patients with overactive bladder syndrome. It is also unclear whether primary outcome measures on cognition tests were determined *a priori*, or whether a minimal clinically important difference was identified for cognition scores or self-assessment scores for alertness, calmness, and mood.

Additionally, because patients with serious co-morbidities and with dementia, depression, or other psychological disorders were excluded, the trial results are unlikely to be applicable to the frail elderly with multiple morbidities.

Dose/Comparator choice: This was a single product (darifenacin) dose ranging study versus placebo. The single arm IR formulation (5mg/ 3x daily) vs. three arms of darifenacin ER does not allow for an assessment of the difference in effect between an IR and ER dose. All comparisons are made with the placebo arm, and not between doses or formulations.

Harms: Limited information on harm is provided.

Industry sponsorship: The trial was sponsored by the manufacturer of darifenacin, Novartis, with editorial and project management contracted to a second company, ACUMED. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012).

Summary - Cognition
In summary, there is no evidence with which to conclude darifenacin has less effect on cognition than oxybutynin IR.

Based on one short-term (3-week) RCT in healthy volunteers, there is insufficient evidence to conclude darifenacin ER has less effect than oxybutynin ER.

There are no short-term RCTs that compared darifenacin to other drugs included in this review.

No RCTs in any population have assessed the cognitive effects of chronic use of darifenacin. No observational studies were identified that assessed long-term cognitive effects.

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Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part V
Trospium vs. Oxybutynin or Other Antimuscarinic Drugs
Clinical Review

Part V - Table of Contents

Chapter 8. Trospium versus Oxybutynin and Other Anti-Muscarinic Drugs for Overactive Bladder Syndrome

Executive Summary

Introduction

Trospium immediate-release (IR) (Trosec®) was approved as a treatment for overactive bladder syndrome (OAB) in Canada in 2006. A Common Drug Review was conducted with final CDEC recommendation dated July 26, 2006.

Trospium is a nonselective muscarinic receptor antagonist and binds to all five muscarinic receptor subtypes. The physicochemical properties of trospium suggest the drug has reduced capacity to cross an intact blood-brain barrier relative to other antimuscarinic drugs. It is also a substrate for the drug efflux transporter P-glycoprotein and other transporter proteins that limit penetration of the blood-brain barrier (Chancellor 2012; Wenge 2011). In spite of these features, trospium has not been proven, in the elderly population most likely to be prescribed the drug, to have less of an effect on the central nervous system than other anti-muscarinic treatments for OAB. The blood-brain barrier can be compromised in the elderly and by a wide range of medical conditions. The activity of transporter proteins also varies, in part because of genetic variations or drug-drug interactions. Most importantly, trospium, like other drugs in this class, has been reported to be associated with central nervous system effects in post market experience.

Research Questions:

Q1. In adults, including the frail elderly, does trospium immediate-release (Trosec®) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR), other formulations of oxybutynin, or other antimuscarinic drugs included in this review, for the treatment of overactive bladder syndrome (OAB) or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that trospium immediate-release (Trosec®) improves clinically relevant outcomes or has a better safety profile compared to oxybutynin IR, other oxybutynin formulations or other antimuscarinic drugs included in this review?

Q3. In adults, particularly the elderly, does trospium immediate-release (Trosec®) have less effect on cognition when compared to oxybutynin IR, other oxybutynin formulations or other antimuscarinic drugs included in this review?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included as supplemental information on harms if they exclusively enrolled elderly populations or assessed cognitive function. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all cause mortality and serious adverse events including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

Q1. Comparative Harms and Benefits

Results

Search Findings

Five direct comparator RCTs compared trospium IR with other antimuscarinic drugs.

- 4 compared trospium IR versus oxybutynin IR, only 2 of which enrolled OAB patients:
    - Zellner 2009 (related paper: Bodecker 2010);
    - Halaska 2003;
    - Herberg 1997 (Q3 only – multiple-dose healthy volunteer RCT);
    - Diefenbach 2005 (Q3 only – single-dose healthy volunteer RCT)
- 1 compared trospium IR versus tolterodine IR (Study MP94D2.15, unpublished full study report)

No RCTs were identified that compared trospium with darifenacin, fesoterodine or solifenacin.

Placebo-controlled RCTs on trospium IR, and direct comparator or placebo-controlled RCTs on trospium ER, a drug formulation that is not included in this review, were included for additional information on harms in the elderly or on cognition. Two trials on OAB patients were identified for supplemental information:

- NCT01178827, a comparative RCT on trospium ER versus oxybutynin IR that is relevant to cognition (Q3) only
- Sand 2010 (a subgroup analysis on patients aged 75+ from two pooled RCTs that compared trospium ER with placebo).

Non-randomized, observational studies were also identified for supplemental harms information. No observational studies were identified on trospium IR. Four non-randomized studies on trospium ER were considered:

- Isik 2009
- Staskin 2010
- Geller 2012
- Zinner 2011

Regulatory documents provided additional information on infrequent adverse events, labeling changes and safety advisories.

Additionally, we considered two recent high-quality systematic reviews for inclusion (Shamliyan 2012; Madhuvrata 2012). Because of the availability of additional data for a study that is published in abstract form only (Study MP94D2.15), we elected to do our own systematic review.

The reference list of a systematic review on cognitive effects of anticholinergic drugs was also cross-checked for included studies (Tannenbaum 2012). This review was not included because its search date was in 2011.

Direct Comparator Randomized Controlled Trials (RCTs)

Trospium vs. Oxybutynin

Two parallel-group trials (Zellner 2009; Halaska 2003) compared trospium IR versus oxybutynin IR. In total, in the two trials, 267 patients were randomized to recommended doses of trospium IR (40mg total/day), 830 patients to higher-than-recommended doses of trospium IR (45-90mg total/day) and 920 patients to recommended doses of oxybutynin IR (7.5-15mg total/day).

Halaska 2003 was a 52-week trial and used fixed doses of trospium 20mg b.i.d. (40mg total/day) (N=267) and oxybutynin IR 5mg b.i.d. (10mg total/day) (N=90). This trial was designed as a non-inferiority trial, with a non-inferiority margin for the lower 95% confidence interval limit of 3.5 urgency incontinence episodes per week.

Zellner 2009 (N=1659) used flexible dosing regimens, starting with trospium IR 15mg t.i.d. (45 mg/day total) and oxybutynin IR 2.5mg t.i.d. (7.5mg/day total), with an option to double the dose after four weeks. The trial was 12 weeks long and conducted in Europe where at least one jurisdiction has a maximum approved dosage of 90mg for trospium. The majority of participants remained on the 45mg dose of trospium (71%) and the 7.5mg dose of oxybutynin (77%). Because so few direct comparator trials were available, we have included this trial even though the trospium starting dose was slightly above the recommended usual dose of 40mg total/day in Canada. Outcomes were reported at four weeks when all participants were on the starting doses of the drugs as well as at study end.

Based on two trials (N=2015), rates of serious adverse events (SAE) were similar for each drug: trospium IR vs. oxybutynin IR RR=1.26 (95% CI 0.68 to 2.31), P=0.46. The trials were under-powered for infrequent serious events. There were lower rates of withdrawals due to adverse events (WDAE) with trospium IR: RR=0.69 (95% CI 0.50 to 0.95), P=0.02, risk difference -3% (95% CI -5% to 0%), and fewer patients with one or more AE: RR 0.85 (95% CI 0.75 to 0.97), P=0.01; risk difference -5% (-9% to -1%). Specific adverse events such as dry mouth and constipation could not be evaluated as only a subset of adverse events believed to be treatment-related were reported; the results are unlikely to reflect full patient experience. The level of evidence is low for WDAE and total AE, and insufficient for specific AE such as dry mouth.

In general, efficacy outcomes did not differ between the two drugs, based on limited evidence. There was no difference in patient-reported improvement or cure (low level of evidence). There was also no difference in the reduction of incontinence in the two individual trials; results could not be pooled for this outcome because useable data were not provided (low level of evidence). There was insufficient evidence to draw conclusions on quality of life, with one trial (Zellner 2009) reporting no between-treatment differences. However, in this trial, about 30% of participants in the trial were on higher-than-recommended doses of trospium.

The largest trial, Zellner 2009, was designed as a non-inferiority trial based on incontinence episodes and was not powered to determine superiority of either drug. Halaska 2003 did not report a sample size calculation so it is not possible to determine whether the trial was adequately powered to detect differences in efficacy outcomes of interest.

Overall, incorporating benefit and harm, trospium IR had a therapeutic advantage over oxybutynin IR, based on similar reductions in incontinence episodes and better tolerability (a 3% lower rate of WDAE and 5% fewer patients in total with adverse events). The strength of evidence is low. The studies may not have been adequately powered to detect differences in efficacy. Comparisons were for doses at or exceeding the maximum recommended dose for trospium IR versus mid-low range doses for oxybutynin IR. Given the direction of dose-nonequivalence, however, the findings of higher rates of AE with oxybutynin IR are likely to be robust.

Trospium IR vs. Tolterodine IR: One 3-week, placebo-controlled, parallel group Phase III trial (N=232, with 153 patients receiving active drug) compared trospium IR 20 mg b.i.d. (40mg total/day) with tolterodine IR 2mg b.i.d. (4mg total/day) (Madaus AG 2001 Study MP94D2.15).

The trial was under-powered to assess short-term mortality (0 events), SAE (0 events) or WDAE (1 event in the trospium group and none in the tolterodine group). There was no difference between trospium IR and tolterodine IR in the proportion of patients experiencing one or more AE: trospium IR 34% vs. tolterodine IR 33%, RR=1.05 (95% CI 0.67 to 1.65), P=0.82. There was also no difference in the rate of dry mouth: trospium IR 29% vs. tolterodine IR 27%, RR=1.06 (95% CI 0.64 to 1.76), P=0.82. Other AE were also similar between drugs.

There was no difference between the drugs in reduction of incontinence episodes or patient-reported perception of improvement or cure. As a quality of life measure, visual analogue scales (VAS) were used to measure restriction in activities in 4 domains (work/everyday activities, recreational activities, eating/drinking habits, social gatherings). Trospium IR was slightly better in lessening restriction of work/every day activities, recreational activities, and eating/drinking habits but not social gatherings (with differences of 14-19 mm on a 100 mm scale). It is unclear whether these VAS scales have been validated, and the clinical meaningfulness of reported differences is unclear. There is insufficient evidence to conclude trospium IR has an efficacy advantage.

This trial was designed as a superiority trial of trospium versus placebo and a non-inferiority trial for trospium versus tolterodine, based on sequential testing of results for the trial's primary outcome, micturition frequency. There was no difference in micturition frequency between trospium and placebo (intention-to-treat analysis). Although micturition frequency was not an outcome of interest for this review, this finding highlights the need to include a placebo treatment arm in comparator trials as the placebo effect can be large and varies across populations.

Based on the one trial and incorporating benefit and harm, there is insufficient evidence to conclude a therapeutic advantage for trospium IR over tolterodine IR or placebo. The trial's unpublished status, with study report dated 2001, likely represents a publication bias or failure to publish because of the negative results (e.g., lack of effectiveness advantage for trospium IR versus placebo).

Supplemental Adverse Event Data

Placebo-controlled trials in the elderly: No RCTs were identified that compared trospium IR to placebo in populations that were exclusively ≥ age 65.

The only available RCT data in the elderly was a post hoc subgroup analysis that pooled the subgroup of patients ≥ age 75 from two placebo-controlled RCTs on trospium ER (Sand 2010). The two pooled RCTs compared 60mg extended-release (ER) trospium versus placebo. Although this drug formulation is not included in this review, we chose to review this study for supplemental data on harms.

In the two RCTs, there were a total of 143 patients who were ≥ age 75 (mean age 79 years), 85 of whom received trospium ER 60mg and 58 who received placebo. There were no SAE. Similar proportions of patients in the trospium ER and placebo arms experienced one or more AE (49% vs. 50%). Specific harms (e.g., dry mouth) are incompletely reported, with details provided only for the subset of AE considered related to study medication. These numbers may be influenced by physician and patient expectation and are not presented here. Harms data were passively collected, which is inadequate for the assessment of cognitive impairment. A mean increase in heart rate of 4.8 beats per minutes was noted with trospium ER.

This study was limited by pooling without usual meta-analytic technique (merely summing up those for each treatment), inadequate power to detect a difference, and its post hoc nature. The results should be considered exploratory only. Compared to trospium ER, the IR formulation results in greater fluctuations of drug with higher maximum plasma concentrations, resulting in higher overall drug exposure at the same (or lower) dose (Silver 2010). This limits the applicability of findings on trospium ER to use of trospium IR in clinical practice. Higher drug exposure, including higher peak drug levels in the bloodstream, is likely to result in greater numbers of AE, particularly in frail, vulnerable populations.

Non-randomized studies

No observational studies on trospium IR were identified.

Four non-randomized studies evaluated trospium ER. These are not directly applicable to use of trospium IR because drug exposure with the extended-release formulation is lower.

One 36-week extension phase of two placebo-controlled RCTs provides limited information on patient experiences and reports only on specific AE believed to be treatment-related (Zinner 2011). It is unclear whether reporting of AE was active or passive, or how often these data were collected. This study reported a subgroup analysis on patients aged 75+ (112 patients enrolled), with a trend towards higher WDAE and total AE compared with the entire group. Three patients had urinary retention (2.7%) and 2 had central nervous system AE (dizziness and vertigo) (1.8%).

One 6-month study reported no change from baseline in mini-mental status examination (MMSE) scores in three groups of patients: 1) patients with late onset Alzheimer's dementia who were treated with trospium ER in combination with galantamine; 2) patients who did not have dementia and were treated with trospium alone; and 3) patients with dementia and without urge incontinence were treated with galantamine alone (Isik 2009). The study fails to provide information of value on trospium's effects on cognition or on safety in the elderly due to the use of groups which differed widely at baseline, a per protocol analysis (22% drop-outs in the group receiving trospium + galantamine) and incomplete AE reporting.

Two other observational studies reported neuropsychological tests for cognition in patients but provide limited information only. One 12-week study enrolled 50 women aged 55+ but reports only per protocol results for the 70% who stayed in the study to week 4. Only 15/50 (30%) were assessed at week 12, making these results highly unreliable. A statistically significant decrease in Hopkins Verbal Learning Test-Revised (HVLT-R) total score was noted at day 1, but the degree of difference is likely to be below the threshold for minimal clinically important difference. There were no differences from baseline in this and other cognitive tests at week 4.

The other study was a pilot study (Staskin 2010) for a direct comparator RCT that is discussed below, for Q3. It reported HVLT-R total recall and delayed recall scores below the level of reliable change indices for trospium ER.

Post-market surveillance and regulatory safety data: Based on the one available Periodic Safety Update (both IR and ER formulations), adverse events included disorientation (with a positive dechallenge), hallucination, confusion and cognitive disorder; these suggest trospium is able to penetrate the blood-brain barrier. There was also one case report of aggravation of Parkinson's disease. AE appeared qualitatively similar to other anticholinergic drugs. These data cannot be used to draw conclusions on comparative safety because of their limitations including the lack of denominator data.

Additions to the U.S. labelling information based on post market experience have included a warning for CNS effects (dizziness, confusion, hallucinations, somnolence and operating heavy machinery or driving).

Q1 Discussion and Conclusions

There is no direct comparator evidence available for comparisons of trospium with fesoterodine, darifenacin or solifenacin. No conclusions can be drawn on comparative effectiveness or safety.

Two RCTs were available for the comparison of trospium IR versus oxybutynin IR, one a 52-week trial and the other, a 12-week trial. Trospium IR demonstrated a therapeutic advantage based on similar efficacy in terms of reduction in incontinence episodes and better tolerability (3% fewer WDAE and 5% fewer adverse events in total). The quality of evidence is low and the differences in tolerability are modest. The two trials may not have been adequately powered to detect differences in efficacy. Additionally, comparisons were for doses at or exceeding the maximum recommended dose for trospium IR versus doses in the mid-low range for oxybutynin IR. Given the direction of dose-nonequivalence, however, the findings of higher rates of AE with oxybutynin are likely to be robust.

Based on one unpublished trial for the comparison of trospium IR versus tolterodine IR, there is insufficient evidence to conclude a therapeutic advantage (incorporating benefit and harm) for trospium IR over tolterodine IR. The trial's unpublished status, with study report dated 2001, likely represents a publication bias or failure to publish because of the negative results (e.g., lack of effectiveness advantage for trospium IR versus placebo).

There are no comparative RCT data that evaluate trospium IR in the frail elderly or in populations refractory to oxybutynin IR.

Q2. New Clinical Evidence since CDR Review

One CDR review has been conducted on trospium IR. The CDEC recommendation dated July 26, 2006 was to list trospium for patients who cannot tolerate immediate-release oxybutynin and in a similar manner as drug plans list tolterodine.

Twelve double-blind RCTs were included in the CDR review, 8 of which were placebo-controlled. The majority of studies were short (2-4 weeks) and described as focusing on urodynamics. Four were direct comparator RCTs (Madaus AG Study MP94D2.15; Madersbacher 1995; Conejero-Sugranes 2006; Halaska 2003), three comparing trospium IR to oxybutynin IR, and one comparing trospium IR to tolterodine IR. Two of the direct comparator RCTs were in neurogenic populations and are not included in the current review.

The CDR review based its conclusions on efficacy predominantly on 3 RCTs that were $\geq$ 12 weeks long, two placebo-controlled and one active comparator trial (Halaska 2003). Trospium improved quality of life over placebo in two trials but this was not assessed relative to an active control. Several frequency and incontinence outcomes were significantly improved versus placebo. In the 52-week trial, efficacy was not significantly different than oxybutynin (Halaska 2003). For conclusions on harms, all available trials were assessed. Trospium was not significantly different from oxybutynin or tolterodine although more AE occurred with trospium versus placebo. In the 52-week study, fewer patients on trospium were noted to experience dry mouth than oxybutynin.

In the current review, the following additional RCT was identified:

- Zellner 2009 (a 12-week trial on trospium IR vs. oxybutynin IR – note this trial used a trospium dose range [45-90mg total/day] above the recommended dose range in Canada [40mg total/day])

For the comparison of trospium IR versus oxybutynin IR, the current review's conclusions are based on two trials, Zellner 2009 and Halaska 2003. Trospium IR was similar to oxybutynin IR for efficacy but had lower rates of WDAE and total AE. Because only a subset of specific AE judged by investigators to be treatment-related were reported, rather than all specific AE, we did not base conclusions on specific AE data.

Zellner 2009 provided quality of life outcomes, which were similar for both drugs. The strength of evidence for this outcome is insufficient in part because about 30% of participants were on more than double the recommended dose of trospium IR.

There were no new data for the comparison of trospium IR versus tolterodine IR (Study MP94D2.15, unpublished). This trial provides insufficient evidence to conclude a therapeutic advantage (incorporating benefit and harm) for trospium IR over tolterodine IR or placebo. We note that the full study report of the 3-week trial comparing trospium IR vs. tolterodine IR reported impact of each drug on aspects of quality of life using visual analogue scales but not a validated quality of life scale, and the clinical meaningfulness of the differences between trospium IR and tolterodine IR was not addressed. These results do not change the CDR review conclusions substantively.

There continue to be no direct comparator trials that compare trospium with another antimuscarinic drug in a population that is refractory to or intolerant of oxybutynin IR.

In the CDR review, supplemental information on cognition included two short-term studies on

young healthy volunteers that reported rapid eye movement (REM) sleep patterns and EEG data (Diefenbach 2003; Todorova 2001). Both studies used trospium IR – one study used 3 doses of trospium IR (15mg t.i.d, total 45mg), oxybutynin IR (5mg t.i.d, total 15mg) and tolterodine (2 mg b.i.d, total 4mg) and the other study used high single doses of trospium IR (45mg), oxybutynin IR (15mg) and tolterodine (4mg). Although these studies were thought to represent some limited evidence to support the claim that trospium does not cross the blood-brain barrier to the same extent as oxybutynin (e.g., a 2% difference in REM sleep), they were identified as having significant limitations. The review points out that the theory that trospium should be less likely to cross the blood-brain barrier compared to oxybutynin (or tolterodine), resulting in fewer central nervous system effects, has not been critically evaluated in the population that will be using the drug. No RCTs were identified specifically in the elderly.

In the current review, supplemental information on cognition included additional studies on trospium IR:

- Herberg 1997 (a 7-day multiple-dose RCT on trospium IR vs. oxybutynin IR in healthy volunteers aged 35 to 70; translated from German)
- Diefenbach 2005 (a single-dose crossover RCT on trospium IR vs. oxybutynin IR, tolterodine IR or placebo in healthy volunteers aged ≥ 50 years)

Diefenbach 2005 is a similar study as Diefenbach 2003 but did not reproduce a difference observed in REM latency for oxybutynin although a larger difference in REM sleep was detected (about 15%) in the older population (mean age 60 years).

Studies that compared trospium ER versus oxybutynin IR were also considered for cognition in the current review:

- Allergan NCT 01178827 Study (unpublished direct comparator RCT, multiple doses, trospium ER (10 days) vs. oxybutynin IR (2 days) in OAB patients ≥ age 60, mean age 72 years)
- Staskin 2010 (non-randomized uncontrolled study, trospium ER)
- Geller 2012 (non-randomized uncontrolled study, trospium ER)

The extended-release formulation results in lower drug exposure and narrower fluctuations of drug levels in the bloodstream than trospium IR so that these findings cannot be directly extrapolated to use of trospium IR.

NCT 01178827 results are posted on clinicaltrials.gov but a full study report is not available. The primary outcome was cerebrospinal fluid levels of drug with secondary outcomes of cognitive tests. No statistical analyses were reported for the cognitive tests but in an exploratory analysis for this review, the Hopkins Verbal Learning Test-Revised Total Recall Score and other test scores (see below), did not show a statistically significant difference between drugs or versus placebo. Trospium was not detected in CSF but it is questionable whether this may in part be due to dose non-equivalence (see Q3).

Although there have been additional studies in an older age group since the CDR review with one study suggestive that trospium ER crosses the blood-brain barrier to a lesser extent than usual doses of oxybutynin IR, the available evidence is insufficient to conclude trospium IR is safer than oxybutynin IR for cognition in the short-term (see Q3). These results therefore do not modify the CDR conclusions substantively.

Q3. Cognition

No RCTs were identified that compared the cognitive effects of trospium IR to oxybutynin IR or other antimuscarinic drugs in patients with OAB.

Two RCTs on healthy volunteers were identified that compared trospium IR versus oxybutynin IR (Herberg 1997; Diefenbach 2005) and tolterodine IR (Diefenbach 2005).

One multiple-dose, double-blind parallel-group RCT on 36 healthy volunteers, aged 35 to 70 years, evaluated psychomotor function, including reaction time, after 7 days of treatment with trospium IR 20mg b.i.d. (40 mg/day total) or oxybutynin IR 5mg t.i.d. (15 mg/day total) (Herberg 1997, translated). Outcomes included precision of visual orientation, concentration, vigilance, motor co-ordination, reaction in stress situations and word match list using computerized tests. Few data are presented in the study with all outcomes described as showing no differences between trospium IR and oxybutynin IR.

A single-dose RCT in healthy volunteers ≥ age 50 (N=24, mean age 60) also provides insufficient evidence that trospium IR is safer than oxybutynin IR or tolterodine IR in terms of cognitive effects. The single doses used were an entire daily dose for each drug: 45mg trospium IR (slightly higher than the recommended Canadian dose of 40mg total/day) 15mg oxybutynin IR, and 4mg tolterodine IR. The study primarily analyzed sleep architecture by polysomnography but included two cognitive tests, a number-combination test that evaluated information-processing capacity and working velocity (expressed as a reaction time), and the d2 test of attention for assessing individual sustained attention and concentration. The d2 test measures processing speed, rule compliance and quality of performance. Results are expressed as number of items completed and mistakes/missed target items; the latter need to be interpreted with caution as they could be due to accommodation disturbances (Diefenbach 2003).

The timing of cognitive testing, 1 hour after administration, does not coincide with the peak plasma concentration for trospium IR (~5 hours for a single dose of trospium 20mg). The timing of peak drug exposure with the single dose was not verified by plasma levels; these were not measured beyond 1 hour because this was primarily a sleep study and the dose was given at night. No differences were detected in the two cognitive tests between active drugs or placebo. The study provides no information on steady state conditions and has limited generalizability. Sleep structure is an insufficient proxy for cognition and the clinical meaningfulness of a ~15% reduction in REM sleep with a higher-than recommended single dose of oxybutynin IR or tolterodine IR was not discussed.

Trospium ER vs. Oxybutynin IR: One comparative single-blinded, parallel group RCT was identified (NCT01178827). The trial evaluated cognitive effects of trospium ER versus oxybutynin IR in OAB patients who had age-related cognitive impairment (not further specified). The trial could not be critically appraised because a full study report was not available. Results are presented as posted on clinicaltrials.gov.

Twenty patients 60 years or older (mean age 72 ± 8 years) were randomized to trospium ER 60mg once daily x 10 days (N=6), oxybutynin IR 5mg t.i.d. x 2 days (N=10) or oxybutynin IR placebo x 2 days (N=4). Drug levels were measured in both cerebrospinal fluid (CSF) and plasma after the last dose. Trospium ER was undetectable in CSF at a time point when the plasma concentration was 1470 pg/ml. In contrast, oxybutynin (OXY) and its major metabolite N-

desethyl-oxybutynin (DEO) were detected in CSF (OXY=59.7 ± 30.9 pg/ml; DEO=386 ± 235 pg/ml) when the plasma concentrations of OXY and DEO were 8800 pg/ml ± 2840 pg/ml and 47,000 pg/ml ± 11,200 pg/ml, respectively.

The plasma levels of oxybutynin were much higher than trospium ER, and although penetration into the brain is complex and multifactorial, depending in part on the physicochemical properties of each drug (with increased propensity of oxybutynin to cross the blood-brain barrier), the use of non-equivalent doses may have contributed to the disparity seen. Furthermore, extended-release formulations are known to result in lower plasma drug levels and overall drug exposure so the results for trospium ER cannot be extrapolated to trospium IR.

Cognitive tests were HVLT-R (recognition and recall), and the Brief Visuospatial Memory Test-Revised (BMVT-R), a test that measures the ability to learn. Statistical analyses are not provided by the investigators for cognitive tests. Oxybutynin IR had greater negative changes on HVLT-R and BMVT-R scores, but the differences were not statistically significant based on our exploratory calculations (paired t-test). Changes did not meet the minimal threshold for reliable change indices that had previously been identified for each score (Staskin 2010).

This study's findings cannot be directly extrapolated to trospium IR because drug exposure is higher with the immediate-release formulation (Silver 2010) and this may affect blood-brain barrier crossing as well as clinical effects. In addition, information is needed on time points.

An additional non-randomized, uncontrolled 10-day study in cognitively intact healthy volunteers did not detect trospium ER in CSF (Staskin 2010). HVLT-R scores were also below reliable change indices but the BVMT-R results were invalid as they showed a practice or training effect. A second 12-week observational study on trospium ER in women only (Geller 2012) is unreliable due to use of per protocol analyses and the high withdrawal rate (30%).

Conclusion: There is insufficient evidence to conclude trospium IR is safer, in the short-term, than oxybutynin IR for cognition. In healthy volunteers, a multiple-dose study (7 days of treatment) reported no differences between trospium IR (40mg total/day) and oxybutynin IR (15mg total/day). A single-dose healthy volunteer study (mean age 60) also reported no difference between trospium IR and oxybutynin IR, when a total daily amount was given in a single dose (45mg trospium IR and 15mg oxybutynin IR), with cognitive testing one hour later. This time point is unlikely to have coincided with the peak plasma concentration for trospium (about 5 hours).

Available evidence on 16 patients with OAB, and an unspecified degree of age-related cognitive impairment (mild cognitive impairment), suggests that usual doses of extended-release formulation of trospium penetrate the blood-brain barrier less than oxybutynin IR. Cognitive testing did not reveal statistically significant between-treatment differences in the change from baseline between active drugs or placebo. This result cannot be applied to trospium IR because the IR formulation results in higher overall drug exposure compared to the extended-release formulation (Silver 2010).

No RCTs in any population have assessed the cognitive effects of chronic use of trospium IR (or ER). There are also no observational studies on trospium IR that have assessed long-term cognitive effects.

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Chapter 8. Trospium vs. Comparator Drugs Clinical Review

Background

Trospium Chloride Immediate-Release (IR) Product Data

Box 1: Trospium Chloride Immediate-Release Product Information

Categorization: anticholinergic-antispasmodic agent

Indication: the treatment of overactive bladder with symptoms of urge or mixed urinary incontinence, urgency, and urinary frequency

Recommended Usual Dose: 20 mg twice daily; for ≥age 75, may be titrated down to 20 mg once daily depending on tolerability.

Mechanism of Action: competitive, nonselective muscarinic receptor antagonist

The information above is derived from the Canadian Product Monograph for Trospium Chloride (Trosec®) Coated tablet 20 mg dated May 8, 2012.

Trospium immediate-release (IR) was approved in Canada in 2006. A Common Drug Review was conducted with final CDEC recommendation dated July 26, 2006. Worldwide, trospium was first launched in 1978.

Trospium is a nonselective muscarinic receptor antagonist and binds to all five muscarinic receptor subtypes. Trospium's physicochemical properties suggest it has reduced capacity to cross an intact blood-brain barrier. The drug is a positively charged, quaternary amine and water-soluble (hydrophilic), in contrast to other antimuscarinic drugs that are tertiary amines and lipid-soluble. Lipid-soluble (lipophilic) compounds cross biological membranes more readily than do hydrophilic agents. Trospium is a substrate for the drug efflux transporter P-glycoprotein and other transporter proteins that limit penetration of the blood-brain barrier (Chancellor 2012; Wenge 2011). Only a subset of antimuscarinics are known substrates for one or more transporter proteins (e.g., darifenacin, fesoterodine, oxybutynin).

In spite of these features, trospium has not been proven to have less of an effect on the central nervous system than other antimuscarinics in the elderly population most likely to be prescribed the drug. The blood-brain barrier can be compromised in the elderly and by a wide range of medical conditions. The activity of transporter proteins also varies, in part because of genetic variations or drug-drug interactions. Most importantly, trospium, like other drugs in this class, has been reported to be associated with central nervous system effects in post market experience.

Trospium is only minimally metabolized by CYP enzymes, in contrast to other antimuscarinic drugs, reducing the potential for drug-drug interactions. Its major metabolic pathway is ester hydrolysis to two inactive metabolites. These undergo conjugation and excretion by the kidney. About 60% of trospium is excreted by the kidneys unchanged.

Further information on the characteristics of trospium and its pharmacokinetic and other properties is available in Chapter 1, Table 7, and in Appendix B.

Q1. Comparative Harms and Benefits

Methods – see Chapter 2.

Results

Search findings

Five direct comparator RCTs were identified that compared trospium IR with other antimuscarinic drugs, either oxybutynin IR or tolterodine IR. Two of these were cognition studies in healthy volunteers and are considered in Q3 only.

No RCTs were identified that compared trospium with darifenacin. This comparison is of potential interest because of marketing claims related to reduced CNS effects for both drugs, based on different theoretical considerations. There were also no RCTs that compared the safety and effectiveness of trospium to fesoterodine, the drug most closely related to tolterodine, or to solifenacin.

Supplemental harms data were sought for information on serious, infrequent adverse events, longer-term harms, and adverse effects in populations not adequately represented in direct comparator RCTs. We considered placebo-controlled RCTs and comparative RCT data on trospium ER, a drug formulation that is not included in this review, for supplemental information on harms in the elderly and information on cognitive effects. We therefore briefly summarized 1) a comparative RCT on trospium ER that is relevant to cognition (Q3) only, based on clinicaltrials.gov posted results, and 2) a subgroup analysis on patients aged 75+ from two pooled RCTs that compared trospium ER with placebo. Four non-randomized observational studies were also considered, as were available pharmacosurveillance data.

Additionally, we considered two recent high-quality systematic reviews for inclusion (Shamliyan 2012; Madhuvrata 2012). Because of the availability of additional data for a study that is published in abstract form only (Study MP94D2.15), we elected to do our own systematic review. The reference list of a systematic review on cognitive effects of anticholinergic drugs was also cross-checked for included studies (Tannenbaum 2012). This review was not included based on its search date in 2011.

Direct Comparator RCTs

Five direct comparator trials compared trospium IR with other antimuscarinic drugs.

- 4 compared trospium IR vs. oxybutynin IR:
    - Zellner 2009 (related paper: Bodecker 2010);
    - Halaska 2003;
    - Herberg 1997 (Q3 only – multiple-dose healthy volunteer RCT);
    - Diefenbach 2005 (Q3 only – single-dose healthy volunteer RCT)
- 1 compared trospium IR vs. tolterodine IR (Study MP94D2.15, unpublished full study report; abstract Junemann 2000)

For this comparison, we excluded trials that enrolled patients with spinal cord injury and neurogenic bladder dysfunction only (Madersbacher 1995; Osca 1997), and a single dose trial that compared intravesical administration of trospium and oxybutynin (Froehlich 1998).

We also excluded a pooled study of 2 RCTs (Herberg 1999) for Q3 (cognition) because appropriate meta-analytic techniques had not been used for pooling.

Missing data were supplemented by data from the CDR Review(s) and other regulatory data, where possible, and as indicated.

Results are presented according to this review's hierarchy of outcomes, with those outcomes of greatest importance to the patient's health highest in the hierarchy.

For dichotomous outcomes, a relative risk (RR) < 1 indicates that fewer events (beneficial or harmful) occurred in the trospium group.

1. Trospium vs. Oxybutynin

Trospium IR vs. Oxybutynin IR

Two parallel group trials (Zellner 2009; Halaska 2003) compared trospium IR with oxybutynin IR in OAB patients. These involved a total of 267 patients randomized to recommended doses of trospium IR (40mg total/day), 830 patients randomized to higher-than-recommended doses of trospium (45-90mg total/day) and 920 patients randomized to recommended doses of oxybutynin (7.5-15mg total/day).

Halaska 2003 was a 52-week trial (N=358) with 3:1 randomization to fixed recommended doses, trospium 20mg b.i.d. (40mg total/day) (N=267) and oxybutynin IR 5mg b.i.d. (10mg total/day) (N=90). The trial included patients with symptoms of OAB, mixed incontinence and an unspecified number of patients with neurogenic bladder. Because there were so few direct comparator trials, we have included this trial although the proportion of patients with neurogenic bladder was not provided. This trial was designed as a non-inferiority trial, with a non-inferiority margin for the lower 95% confidence interval limit of 3.5 urgency incontinence episodes per week.

Zellner 2009 (N=1659) used flexible dosing for both drugs, starting with trospium IR, 45mg/day (15 mg t.i.d.) and oxybutynin IR 7.5mg/day (2.5 mg t.i.d.), with an option to increase the dose of either drug after 4 weeks. The dose of trospium was increased to 90 mg/day (30mg t.i.d.) and oxybutynin IR to 15mg total/day (5mg t.i.d.). The trial was 12 weeks long and conducted in Europe where at least one jurisdiction has a maximum approved dosage of 90mg for trospium. The majority (71%) remained on the 45mg dose of trospium. Because so few direct comparator trials were available we have included this trial even though the starting dose was slightly above the recommended usual dose of 40mg total/day in Canada. Results for the trial were reported at 4 weeks when all were on the same dose as well as at study end, and a post hoc analysis also reported the lower dose separately at 12 weeks (Bodecker 2011) (see below).

Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix I.

1. All-cause mortality

Two deaths occurred in Halaska 2003, both in the trospium group: 2/267 (0.7%) vs. 0/90. The difference was not statistically significant. One death was secondary to recurrent brain infarct, and the other was secondary to metastatic carcinoma and acute pulmonary embolus. There were no deaths in Zellner 2009. The trials were under-powered for mortality in the short-term.

2. Serious Adverse Events (SAE)

SAE were incompletely reported in Halaska 2003 and obtained from the Common Drug Review (Common Drug Review 2006, p. 26). There was no statistically significant difference between trospium IR and oxybutynin IR in the individual trials or when the two trials were pooled

(N=2015): RR 1.26 (95% CI 0.68 to 2.31), P=0.76. The two deaths were included in the SAE calculation.

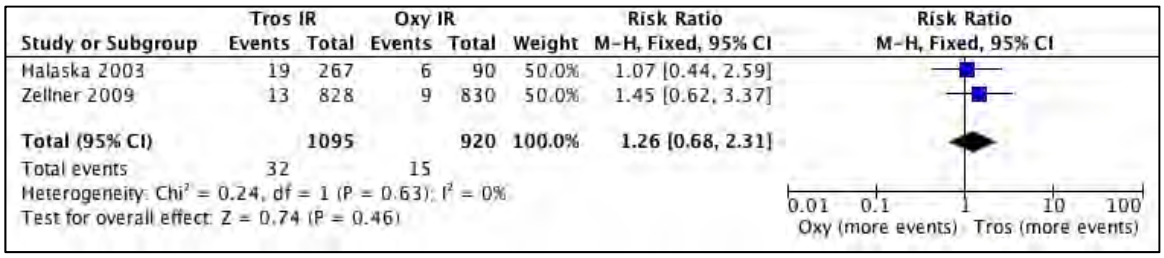

Figure 1. SAE

Available details of SAE are provided in the table, below.

Table 1. Serious Adverse Events

Study	TROS	OXY
Halaska 2003* (MP94D2.04)	o Recurrent brain infarct (death) o Acute PE secondary to adenocarcinoma of the bronchus (death) o Disseminated encephalitis o Angioedema o Renal calculus NOS o Abscess NOS o Ovarian cyst o Ataxia/hemiparesis/paresthesia o Back pain o UTI NOS o Operation NOS (N=4)	o Acute urinary retention due to BPH o Tachyarrhythmia o Generalized rash/diabetes o Operation NOS o Abscess NOS o Chest pain
Zellner 2009	o UTI o Visual disturbance and vertigo o Not specified N=11	o Not specified N=9

*Data for Halaska 2003 were obtained from Common Drug Review 2006, p. 26. Although 19 events were identified in the CDR report as having occurred in the trospium group, details are provided for 14.
BPH= benign prostatic hypertrophy; **NOS**= not otherwise specified; **PE**= pulmonary embolus; **UTI**= urinary tract infection;

There were no reported serious events of cognitive impairment or falls/fractures.

Acute urinary retention: in Halaska 2003, there was one episode of acute urinary retention in the oxybutynin IR group, in a male patient with benign prostatic hypertrophy. Urinary retention was not reported in Zellner 2009.

3. Withdrawals due to Adverse Events (WDAE)
When pooled (N=2015), significantly fewer patients on trospium IR discontinued treatment early due to AE: RR 0.69 (95% CI 0.50 to 0.95), P=0.02; risk difference 3% (95% CI -5% to -0%).

Figure 2. WDAE

4. Quality of life (QoL)

One trial (Zellner 2009) reported on quality of life. Zellner 2009 used the German version of the Medical Outcomes Study Short Form 36-item questionnaire (SF-36) and the condition-specific King's Health Questionnaire (KHQ).

SF-36 is a multipurpose general short-form health survey, with nine categories: a single-item health transition category and multi-item scales on physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental health. Scores range from 0 (worst) to 100 (best). The SF-36 has been validated in a number of languages and conditions (Aaronson 1992; Keller 1998) although has not been reported to be responsive to treatment with other antimuscarinic drugs for OAB.

In Zellner 2009, the proportion of patients reporting improvement (SF-36 health transition item) was similar for trospium IR and oxybutynin IR: 368/810 (45%) vs. 374/798 (47%). Values for the other domains of the SF-36 are not reported separately by treatment group.

The KHQ is a condition-specific instrument with items on general health perception, impact of incontinence, role limitation, physical limitations, social limitations, personal relationships, emotions, sleep/energy, severity coping measures, and symptom severity. The score for each domain is transformed from 0 (best) to 100 (worst) except for the Symptom Severity scale, which ranges from 0 (best) to 30 (worst). A negative score from baseline is an improvement; minimal clinically important differences are in the range of 3-4 points for general health and severity domains, and 5-10 points for other domains (Shamliyan 2012; Kelleher 2004).

In Zellner 2009, there was no significant difference between drugs in the median change from baseline in the KHQ domain total score: -0.23 (95% CI -2.11 to 1.72), based on Hodges-Lehmann estimate of the difference in median change from baseline. This type of estimate is used for non-parametric analysis when data are skewed and do not meet assumptions for a normal distribution. Median changes were > 5 points for 7 of the 10 individual domains but values are not reported separately by treatment group. Means were also reported and >5 points for all individual domains, with no differences between trospium IR and oxybutynin IR (graph only).

Zellner 2009 also reported the extent of problems caused by incontinence on a visual analogue score with similar improvement between treatment groups at study end. A Hodges-Lehmann estimate of the difference in median change from baseline was 0.00 (95% CI -2.00 to 3.00).

5. Patient-Reported Perception of Improvement or Cure

Halaska 2003 measured patients' perception of improvement or cure but did not report numbers. This study also reported physicians' appraisal of improvement and states that the patient estimates for cure were "practically identical" to those reported by physicians. A 'cure' was

reported after 52 weeks of treatment for numerically more patients on trospium IR: trospium IR 60/207 (29%) vs. oxybutynin IR 11/65 (17%) but the difference was not statistically significant. The denominators in the physicians' estimates do not match the number of patients who completed the study in either group.

In Zellner 2009, the SF-36 health transition item measures the proportion of patients reporting improvement. Improvement rates were similar for trospium IR and oxybutynin IR: trospium 368/810 (45%) vs. oxybutynin IR 374/798 (47%).

Combined (N=1880) in a random effects model, the difference in the proportion of patients reporting improvement or cure was not statistically significant: RR 1.20 (95% CI 0.70 to 2.06). Heterogeneity was substantive (I^2=73%) and possible reasons for this are the differences in study duration, dosage regimens, and populations including age (mean age in Zellner 2009 was 61-62 whereas the mean age in Halaska 2003 was 54 years), or the type of measurement (cure for Halaska 2003 and improvement for Zellner 2009).

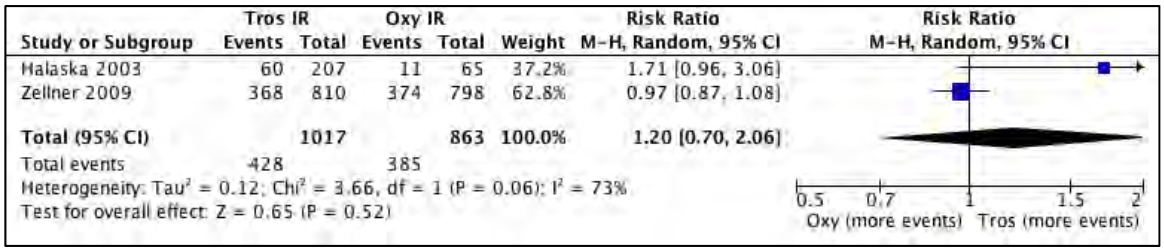

Figure 3. Patient (or physician)-reported improvement or cure

6. Quantification of Incontinence Episodes

Total dryness rate: This outcome was not specifically reported in either trial. The definition of 'cure', as identified above for Halaska 2003 was not explicitly defined and was based on subjective reporting rather than on data from bladder diaries. It is known whether this referred specifically to dryness rate as the proportion of participants who had incontinence at baseline was not provided so is not included here.

Reduction in incontinence episodes:

Data were not reported in a useable form for meta-analysis.

In Halaska 2003, there was no difference in the mean reduction in incontinence episodes between treatments. Baseline incontinence episodes were, on average, 1.5 episodes per day for trospium IR, and 2.1 episodes per day for oxybutynin IR. Treatment with either drug reduced incontinence by about one episode. A measure of variation was not reported.

In Zellner 2009, there was no difference between drugs in the median reduction in incontinence episodes. The median number of incontinence episodes at baseline was 14/week in both groups (full analysis set). Trospium reduced the median number of episodes by 10.42/week and oxybutynin, by 10.00/week. A Hodges-Lehmann estimate of the difference in the median change from baseline per week was 0.00 (95% CI -1.00 to 0.83). In an exploratory analysis, the mean difference per day was -0.10 (95% CI -0.32 to 0.12) (RevMan v5.2).

At week 4, when all participants were on the initial starting doses of 45mg/day trospium IR and 7.5mg/day oxybutynin IR, there was no difference in the median reduction in incontinence episodes: Hodges-Lehmann estimate for the difference was 0.00 (95% CI -1.00 to 1.00).

In Zellner 2009, trospium IR was found to be 'non-inferior' to oxybutynin IR as the lower limit of the confidence intervals was within the margin defined for noninferiority. Noninferiority trials are not adequately powered to determine which intervention is superior. Additionally, the use of a flexible dose regimen, including use of a higher-than-recommended dose for trospium in 29% of participants, limits interpretation of efficacy.

7. Nocturia
Neither trial reported on nocturia.

8. Urgency
One trial, Halaska 2003, reported on urgency episodes. The number of episodes was, on average, 10.2/day in the trospium group and 11.0/day in the oxybutynin group at baseline. There was no difference between drugs in the reduction in urgency episodes, with a mean reduction of 3.5 and 3.6 episodes per day on trospium IR and oxybutynin IR, respectively. A measure of variation was not provided.

Zellner 2009 reported the reduction in perceived intensity of urgency, as measured on a 5-point scale. Because of the potential overlap of urgency (episodic and maximal) with the normal sensation of urge when using such a scale (Abrams 2012), this was not included as an outcome of interest for this review.

9. Total AE
When the two trials were combined (N=2015), fewer patients on trospium IR experienced one or more AE than on oxybutynin IR: RR 0.85 (95% CI 0.75 to 0.97), P=0.01; absolute risk difference -5% (-9% to -1%).

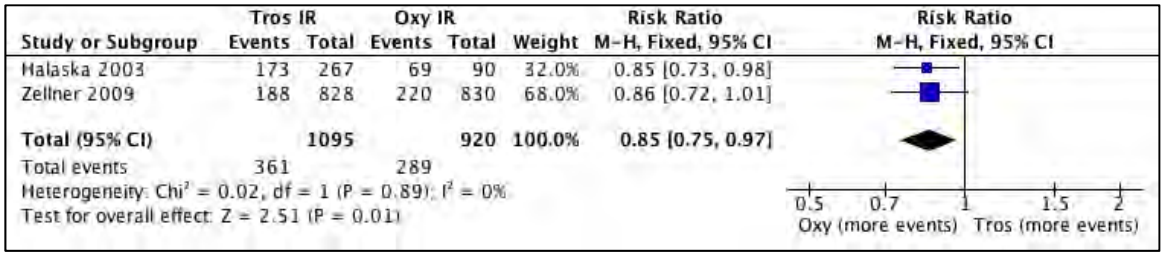

Figure 4. Proportion of patients with one or more AE

The flexible dose regimen in Zellner 2009 obscures a dose response and limits the interpretation of these data because the higher dose of trospium IR was more than double the recommended dose in Canada. An exploratory post hoc analysis indicated total AE rates were higher in the dose-increased subgroups for both trospium IR and oxybutynin IR but this did not lead to significantly greater numbers of early discontinuations (Bodeker 20120).

10. Specific 'non-serious' AE
Dry mouth: Full data on dry mouth were not available for either trial as only those AE believed to be treatment-related by investigators were reported. This may have introduced bias based on investigator and patient expectations.

Additionally, in Zellner 2009, intensity of mouth dryness was recorded at baseline and study end. A surprisingly high proportion, 52% and 54% of participants in the trospium and oxybutynin groups respectively, reported dry mouth at baseline, summed from different categories of intensity in Table IV, even though a washout period was included. At study end, 51% (trospium) and 64% (oxybutynin) had experienced worsening of dry mouth. These numbers are much higher than those reported for AE judged to be treatment-related. We therefore do not report the partial data on this outcome.

Constipation:
Both trials reported constipation rates judged to be potentially related to treatment (for Halaska 2003, events were 'probably or definitely related', and for Zellner 2009, events were 'probably' related). This represents only a subset of total AE and can be influenced by bias due to physician/patient expectations. Additionally, it is not known whether there were 'possibly' related events for either trial that are not included in the summary numbers. We did not have access to the full data so the numbers are not provided here.

Subsets of adverse events believed by investigators to be treatment-related were also reported for other specific events and are not reported here as full data were not available (Table 2 in Appendix I). Reported events for Halaska 2003 included dyspepsia, diarrhea, abdominal pain, nausea, headache, blurred vision and insomnia.

11. Urodynamics/clinician measures
One trial, Halaska 2003, measured and reported no difference in the median increase in maximum cystometric capacity, volume at first unstable contraction or volume at first sensation to void.

12. Mean or median volume voided:
One trial reported median volume voided (Zellner 2009). There was no significant difference between drugs in the median increase in volume voided. Hodges-Lehmann estimate of the difference in medians was – 4.00 (95% CI -9.90 to 1.90).

Critical Appraisal: Trospium IR vs. Oxybutynin IR

Risk of bias/other quality assessment
As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity (Table 3, Appendix I). For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results).

For Halaska 2003, the methods of randomization and allocation concealment were not described. Blinding of patients, physicians and assessors were also not described. The risk of bias was rated as 'unclear' for these features as it is not possible to distinguish poor reporting from poor methodology without further information. A similar proportion of participants withdrew early (25-27%) but reasons for withdrawals were not provided for 52% of the withdrawals in the trospium group and 29% in the oxybutynin group. Bias can be introduced if reasons are dissimilar. It is unclear whether an intention-to-treat analysis was carried out as the ITT population was described as 'all patients who had not shown any obvious deviations from protocol'. The study was judged at high risk of bias for selective outcome reporting on the basis it did not report all AE but only those believed by investigators to be treatment-related. No sample size calculation was provided so it is not possible to judge the adequacy of sample size for detecting a difference, and a primary outcome was not identified.

For Zellner 2009, there was low risk of bias for randomization, allocation concealment ,and blinding of patients and health care personnel. Blinding of outcome assessors was not described and so was rated 'unclear'. Overall, withdrawals were similar for each group, but the reasons for about a third of withdrawals in each group was not accounted for. The study was thus rated as 'unclear' for attrition bias as it is not known whether reasons of the unaccounted-for withdrawals differed. The study was also rated at high risk for incomplete outcome reporting as it reported only a subset of AE judged 'treatment related' by investigators.

Halaska 2003 did not report a sample size calculation or identify a primary outcome so it is not possible to determine the adequacy of sample size to detect differences in outcomes. Zellner 2009 was designed as a non-inferiority trial and not powered to determine superiority of either drug.

Applicability of trial results (external validity)
The majority of participants in both trials were women so it is unclear whether the findings are applicable to men. Zellner 2009 did conduct a subgroup analysis by sex (although the trial was not stratified by sex at randomization), with no differences between drugs for either sex. However, there were only 112 males included and the analysis may not have been adequately powered to detect differences. Men with benign prostatic hypertrophy (BPH) can have lower urinary tract symptoms that overlap with OAB syndrome. If the etiology of symptoms in men is not adequately investigated, there is a risk of misdiagnosis, with implications for effectiveness of treatment because trospium and oxybutynin have not been shown to be effective against BPH.

The mean age in Halaska 2003 was relatively young at 54 years whereas Zellner 2009 was 60-61 years. The number of participants $\geq$ age 75 in either trial is not reported (age range in Halaska 2003 18-89 years and in Zellner 2009, 20-91 years).

Dose/Comparator choice: Halaska et al compared trospium 40mg total/day (the usual recommended dose) to a dose of oxybutynin (10mg total/day), which is at the lower end of the range of doses (oxybutynin IR recommended up to 20 mg/day).

Zellner 2009 compared an initial dose of trospium which is slightly above the usual dose (45mg) to a relatively low dose of oxybutynin IR (2.5 mg t.i.d. initially, 7.5mg total/day). The higher dose of trospium (in a flexible dosing regimen), adjusted upwards in about a third to 90mg trospium IR, was more than double the usual recommended trospium dose whereas the higher dose of oxybutynin was still not maximum. The doses used limit the applicability of the findings to usual clinical practice in Canada

Harms: AE were incompletely reported in both trials, with both reporting 'treatment-related' dry mouth and other specific AE. This may depend on the investigators' interpretation and expectation. Halaska 2003 actively sought anticholinergic AE by using a specific checklist. The overall rates of dry mouth were much higher than in Zellner 2009 although comparisons cannot be made directly. In Zellner 2009, intensity of mouth dryness was recorded at baseline and study end. A surprisingly high proportion, 52% and 54% of participants in the trospium and oxybutynin groups respectively, reported dry mouth at baseline (summed from different categories of intensity in Table IV) even though a washout period was included. At study end, 51% and 64% had experienced worsening of dry mouth. This suggests numbers much higher than those reported for treatment-related AE.

Neither trial reported on cognitive impairment or actively assessed cognitive effects.

Industry sponsorship: Both studies were sponsored by the manufacturer of trospium. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

Overall results –Trospium IR vs. Oxybutynin IR

Results are summarized in table 2, below. Two trials, one a 52-week trial and the other, a 12-week trial using higher-than-recommended doses of trospium IR, were available. There was no difference between trospium IR and oxybutynin IR in patient-reported improvement or cure, or reduction in incontinence episodes. A meta-analysis could not be conducted on the outcome incontinence episodes because data were not provided in useable form. There was insufficient evidence to draw conclusions on quality of life, with one trial (Zellner 2009) reporting no between-treatment differences. There was also insufficient evidence on urgency, with one trial reporting no difference in reduction in urgency episodes (Halaska 2003). There were no data on nocturia.

The largest trial (Zellner 2009) was designed as a non-inferiority trial based on reduction in incontinence episodes, and was not powered to determine superiority of either drug. Halaska 2003 did not report a sample size calculation (or identify a primary outcome) so it is not possible to determine whether the trial was adequately powered for various outcomes.

There were fewer WDAE (risk difference 3%), fewer total AE (risk difference 5%) in spite of one trial using high doses of trospium in about 30% of patients. Numerically more patients experienced constipation on trospium IR but the difference was not significant.

Table 2. Summary of RCTs Trospium IR vs. Oxybutynin IR

Outcome	No. of studies (No. of Participants)	TROS IR vs. OXY IR RR or MD [95% CI]	TROS IR VS. OXY IR Absolute Risk difference [95% CI]	Summary
All-cause mortality	2 trials (2015) 2 events in trospium group in 52-week trial	--	--	Insufficient evidence Trials under-powered to detect differences.
SAE*	2 trials (2015)	RR 1.12 [95% CI 0.55 to 2.28]	--	No difference between TROS IR and OXY IR Trials under-powered to detect differences
QoL	1 trial (1659)	--	--	No difference between TROS IR and OXY IR. in general QoL (SF-36) or condition-specific QoL (KHQ); TROS IR flexible dose was higher-than-recommended and this is insufficient evidence.
WDAE	2 trials (2015)	RR 0.69 [95% CI 0.50 to 0.95]	RD 3% [-3% to 0%]	3% fewer WDAE on TROS IR
Patient-reported improvement or cure**	2 trials (1880)	RR 1.20 [95% CI 0.70 to 2.06]	--	No difference in the proportion of patients reporting improvement or cure

Incontinence episodes per week Reduction from baseline*	2 trials, meta-analysis ND Halaska 2003 (N=358) Zellner 2009 (N= 1658)	Halaska 2003: no difference in mean/week Zellner 2009: Week 12^: LH_{est} 0.00/week [95% CI -1.00 to 0.83] MD -0.10 (95% CI -0.32 to 0.12) episodes/day Week 4^: LH_{est} 0.00/week [95% CI -1.00 to 1.00]	--	No difference between TROS IR and OXY IR. Unable to do meta-analysis (no measure of variation in one trial, and median reported in other).
Urgency per day Mean reduction from baseline*	1 trial (358)	TROS IR -3.5 vs. OXY IR – 3.6	--	No difference between TROS IR and OXY IR
Nocturia	0 trials	--	--	No data available
Total AE	2 trials (2015)	RR 0.85 [95% CI 0.75 to 0.97]	RD-5% [95% CI -9% to -1%]	5% fewer patients on TROS IR experienced one or more AE
Dry mouth	0 trials	--	--	Insufficient evidence – only a subset reported believed by investigators to be 'treatment-related'
Constipation	0 trials	--	--	Insufficient evidence – only a subset reported believed by investigators to be 'treatment-related'

* includes 2 fatal SAE
** physician-reported values were used for Halaska 2003 as patient values were not reported but described were as 'practically identical' to physician-reported values;
^ week 4 was a comparison of 15mg t.i.d. (45mg total/day) TROS IR vs. OXY IR 2.5mg t.i.d. (7.5mg total/day); week 12 was a comparison of TROS IR 45-90mg total/day vs. OXY IR 7.5-15mg total/day
AE=adverse events; **OXY**=oxybutynin; **IR**=immediate-release; LHest= Hodges Lehmann estimate of differences in median; **MD**=mean difference; **ND**=not done; **QoL**=quality of life; **RR**= relative risk; **RD**= risk difference; **SAE**=serious adverse events; **TROS**= trospium; **WDAE**=withdrawals due to adverse events

2. Trospium IR vs. Other Comparator Drugs

a. Trospium IR vs. Tolterodine IR

One 3-week, placebo-controlled, parallel group Phase III trial (N=232, with 153 patients receiving active drug) compared trospium IR 20 mg b.i.d. (40mg total/day) with tolterodine IR 2mg b.i.d. (4mg total/day) and is available as an unpublished, full study report (Madaus 2001 Study MP94D2.15). Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix I.

Results for this trial for outcomes of interest are reported below in order of the hierarchy of outcomes for this review. We present intention-to-treat analyses wherever possible as per protocol analyses can introduce bias if drop-outs differ from completers.

1. All-cause mortality
There were no deaths in the trial.

2. Non-fatal Serious Adverse Events (SAE)
There were no SAE in the trial.

3. Withdrawals due to Adverse Events (WDAE)
There was one withdrawal due to AE in the trospium group (1.3%), 0 in the tolterodine group, and 1 in the placebo group (1.3%).

4. Quality of life (QoL)
Visual analogue scales (VAS) (0-100 mm scale) were used to assess patient-reported restrictions on activities related to quality of life: work and everyday activities, hobbies and recreational activities, social gathering and joint actions with other people, and adaptation of eating and drinking habits. A value of '0' indicates 'absolutely not restricted' and a value of 100 indicates 'very strong restricted [sic]'. No statistical analyses were provided in the study report as all outcomes other than the primary outcome of incontinence episodes were regarded as exploratory. In this review's exploratory analysis, the differences between the active treatment groups were statistically significant, in favour of trospium IR, for three of the four VAS scales: work and everyday activities; hobbies and recreational activities, and adaptation of eating and drinking habits (Table 3). The study report does not address the clinically meaningfulness of a 14-19 mm difference on a 100 mm scale or the validation of the scales, limiting interpretation.

Table 3. Quality of Life

Treatment	**TROS IR**	**TOL IR**	**Placebo**
N	N=76 (baseline); N=74 (study end)	N=77 (baseline); N=74 (study end)	N=79 (baseline); N=76 (study end)
Mean change from baseline in VAS			
Work and every day activities	-33.9 (31.9)	-15.0 (31.6)	-17.7 (30.1)
	MD= -18.9 [95% CI -29.1 to -8.7]*		
Hobbies and recreational activities	-32.6 (34.0)	-18.3 (31.3)	-15.5 (31.9)
	MD= -14.3 [95% CI -24.8 to -3.8]*		
Social gathering and joint actions with other people	-29.3 (34.9)	-19.2 (35.9)	-41.0 (-18.0)
	MD= -10.1 [95% CI -21.5 to 1.3]*		
Adaptation of eating and drinking habits	-30.0 (35.7)	-15.3 (30.6)	-16.9 (30.9)
	MD= -14.7 [95% CI -25.3 to -4.1]*		

* [RevMan v5.2] – significant results are bolded; Data from study report section 14.2, table 2.2, p. 260-261; **MD**= mean difference; **TROS**=trospium; **TOL**= tolterodine; **VAS**= visual analogue scale

5. Patient-Reported Perception of Improvement or Cure: A visual analogue scale was used to assess patient-reported improvement, which ranged from 'worsening of symptoms' (-1) via 'no improvement' (0) to 'patient is cured' (10). Mean improvement in scores for trospium IR and tolterodine IR were similar (5.5 and 5.0, respectively), corresponding to an improvement of about 50%. Both drugs were significantly better than placebo; improvement with placebo was about 35% and the difference between placebo and active drug was 15-20%.

Table 4. Patient-reported perception of improvement or cure

Treatment	TROS IR	TOL IR	Placebo
N	N=74	N=74	N=74
Mean VAS score (SD)	5.49 (3.51)	5.01 (3.60)	3.50 (3.25)
	MD=0.48 [95% CI -0.67 to 1.63]*		

* [RevMan v5.2] Data from study report section 14.2, Table 3.2, p. 263; **MD**= mean difference; **TROS**=trospium; **TOL**= tolterodine; **VAS**= visual analogue scale;

6. Quantification of Incontinence Episodes
Cure or total dryness rate – not reported.

Number of dry days: There was no difference between trospium IR and tolterodine IR in the mean number of dry days during the entire treatment period (day 1-20): 13.5 vs. 12.6 days, MD 0.9 (95% CI -1.40 to 3.20), P=0.44.

Reduction in incontinence episodes:
There was no difference in the reduction in incontinence episodes between trospium IR and tolterodine IR: MD -0.30 (95% CI -1.6 to 1.01), P=0.65. There was also no difference between either drug vs. placebo.

Table 5. Incontinence Episodes: change from baseline

Treatment	TROS IR	TOL IR	Placebo
	N=37	N=42	N=42
Baseline mean (SD)	3.7 (3.3)	3.4 (3.5)	2.8 (2.4)
Change in mean from baseline (SD)	-2.5 (3.1)	-2.2 (2.8)	-1.6 (2.3)
	MD= -0.30 [95% CI -1.6 to 1.01]*		

* [RevMan v5.2] Data from study report Table XIV, p. 70; **MD**= mean difference; **TROS**=trospium; **TOL**= tolterodine;

Pad or diaper usage:
There was no difference between trospium IR and tolterodine IR: MD -0.4 (95% CI -1.3 to 0.5), P=0.39.

Table 6. Diaper usage: change from baseline

Treatment	TROS IR	TOL IR	Placebo
	N=31	N=29	N=29
Baseline mean (SD)	2.8 (2.0)	2.4 (2.4)	2.7 (2.0)
Change in mean from baseline (SD)	-1.8 (1.8)	-1.4 (1.8)	-1.5 (2.1)
	MD= -0.4 [95% CI -1.3 to 0.5]*		

* [RevMan v5.2]; Data from study report Table XII, p. 68; **MD**= mean difference; **TROS**=trospium; **TOL**= tolterodine;

7. Nocturia – not assessed in the study.

8. Urgency – not assessed in the study.

9. Total Adverse Events:
Total AE rates were similar on trospium IR and tolterodine IR (Table 7): 34% vs. 33%; RR 1.05 (95% CI 0.67 to 1.65), P=0.82.

10. Specific AE

Dry mouth: The rate of dry mouth was similar for trospium IR and tolterodine IR: 29% vs. 27%, RR 1.06 (95% CI 0.64 to 1.76), P=0.82.

Other adverse events were infrequent with no significant differences between trospium IR and tolterodine IR (Table 7).

Table 7. Total and Specific AE

Event	TROS IR	TOL IR	Placebo
Total AE*	26/76 (34.2%)	25/77 (32.5%)	12/79 (15.2%)
Total gastrointestinal disorders	22 (28.9%)	22 (28.6%)	7 (8.9%)
Dry Mouth	22 (28.9%)	21 (27.3%)	5 (6%)
Central and peripheral system disorders	1 (1.3%)	1 (1.3%)	1 (1.3%)
Psychiatric disorders**	1 (1.3%)	1 (1.3%)	1 (1.3%)
Headache	0	0	3 (5.8%)
Abnormal accommodation	2 (2.6%)	0	2 (2.5%)
Vision abnormal	2 (2.6%)	0	0
Cardiovascular disorders, general	0	1 (1.3%)	0
Tachycardia, palpitation	2 (2.6%)	1 (1.3%)	0
Urinary Tract Infection	0	2 (2.6%)	2 (2.5%)

* Total AE = proportion of patients with one or more AE. ** Psychiatric AE - TROS: insomnia; TOL: aggressive reaction, somnolence; Placebo: anorexia; **TOL**= tolterodine; **TROS**= trospium;

Laboratory abnormalities: 1 patient in the tolterodine group had clinically significant thrombocytopenia but had a prior history of thrombocytopenia, and another, also in the tolterodine group, had an increase in liver enzymes that was not considered clinically relevant. No other clinically significant laboratory findings were noted.

Observed changes in blood pressure and heart rate (median increase of 2 beats per minute (bpm) for trospium, 1.5 bpm for tolterodine and 0 bpm for placebo) were not considered clinically significant.

11. Urodynamics/clinician measures – not reported in this study.

12. Mean volume voided: There was no significant difference between trospium IR and tolterodine IR in the increase in volume voided although this was numerically increased more for tolterodine.

Table 8. Mean volume voided

Treatment	TROS IR	TOL IR	Placebo
N	N=72	N=70	N=75
Mean volume voided at study end (SD) (% change)	36.0 (59.2) (30%)	45.0 (46.4) (39%)	18.6 (47.6) (15%)
	MD= -9.0 [95% CI -114.9 to 96.9]*		

* [RevMan v5.2]; Data from study report Table XIV, p. 70; **MD**= mean difference; **TOL**= tolterodine; **TROS**= trospium

Critical Appraisal: Trospium IR vs. Tolterodine IR

Risk of bias

As part of quality assessment, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity (Table 3, Appendix I). For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results).

Although block randomization was used, generation of the randomization sequence was not described and allocation concealment was also not described; both features were rated as 'unclear' risk of bias. There was low risk of bias for blinding of patients and healthcare personnel based on a double-blind, double-dummy technique but the report does not describe blinding of outcome assessors. There was also low risk of bias for incomplete outcome data (attrition bias) or selective outcome reporting, based on the information in the unpublished full study report.

This trial was designed to first establish superiority of trospium IR over placebo and then establish the non-inferiority of trospium IR with tolterodine IR for the outcome of micturition frequency.

Although frequency was not an outcome of interest for this review, it is noteworthy that the study failed to demonstrate superiority over placebo in an intention-to-treat analysis. The handling of multiplicity of comparisons was by the sequential statistical analysis and *a priori*, a statistical analysis was not permitted for the active drug comparison if trospium IR was not found to be superior to placebo. All of the secondary outcomes, including all outcomes of interest in this review, were exploratory. Because of this, inferential statistics were not reported for the active drug comparison in the study report. Although a per protocol analysis showed superiority of trospium but not tolterodine over placebo for reduction in frequency (as reported in a published narrative review sponsored by industry), this was exploratory only as the statistical analysis identified *a priori* was an intention-to-treat analysis. An intention-to-treat analysis is also generally considered a superior scientific approach to RCT outcome assessment, as it maintains the advantage of randomized allocation to treatment.

Publication bias: A form of publication bias, although not a source of internal validity, is the failure to publish, if the decision is based on the magnitude or direction of results (Hopewell 2009). This trial remains unpublished although the report date is 2001. It is highly likely the trial's unpublished status represents publication bias as the primary outcome did not show superiority of trospium over placebo. A placebo effect in OAB is substantial and varied, and this highlights the need to include placebo treatment arms in comparative studies.

Applicability (external validity) of study results
This was a short trial (3 weeks) and provides no information on comparative effectiveness or safety when the drugs are used on a chronic basis.

The majority of participants were women and the findings may have limited applicability to men. The age group was relatively young (mean age 51 years) and generalizability to the elderly, including the cognitively impaired, may also be limited. The numbers of participants 75+ years of age were not reported (age range was 18-78).

Dose/comparator choice: the usual maximum recommended doses of both drugs were used and were appropriate.

Industry sponsorship: the trial was industry-sponsored by the manufacturer of trospium. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug

comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

Refractory populations: The trial provides no information on populations refractory to, or intolerant of, oxybutynin IR.

Overall Results – Trospium IR vs. Tolterodine IR
Results are summarized in table 9, below. Based on 1 parallel group trial (N=153 receiving active drugs and 79 receiving placebo), there was no difference between trospium IR and tolterodine IR in reduction of incontinence episodes or patient-reported perception of improvement or cure. As a quality of life measure, visual analogue scales were used to measure restriction in activities in 4 domains (work/everyday activities, recreational activities, eating/drinking habits, social gatherings). Trospium IR was slightly better in lessening restriction of work/every day activities, recreational activities, and eating/drinking habits but not social gatherings (with differences of 14-19 mm on a 100 mm scale). The validation of the VAS scales, and the clinical meaningfulness of reported differences is unclear, and this is insufficient evidence to conclude trospium IR has an efficacy advantage.

This trial was designed as a superiority trial of trospium vs. placebo and a non-inferiority trial for trospium vs. tolterodine, based on sequential testing of results for the trial's primary outcome, micturition frequency. It failed to show a difference between trospium or tolterodine and placebo in an intention-to-treat analysis.

There was no difference between trospium IR and tolterodine IR in the proportion of patients experiencing one or more AE or dry mouth. Other AE were also similar between drugs. The trial was under-powered to assess short-term mortality, SAE or WDAE.

This trial provides insufficient evidence to conclude a therapeutic advantage (incorporating benefit and harm) for trospium IR over tolterodine IR. Its unpublished status, with study report dated 2001, likely represents publication bias, likely due to negative study results.

Table 9. Summary of Trospium IR vs. Tolterodine IR RCT Outcomes

Outcome	No. of studies (No. of Participants)	TROS IR vs. TOL IR RR or MD (95% CI)	Summary
All-cause mortality	1 trial (153)* 0 events	--	No events. The trial was under-powered for short-term mortality. No data are available on long-term mortality.
SAE (non-fatal)	1 trial (153) 0 events	--	No events. The trial was under-powered for SAE. No data are available on long-term SAE.
WDAE	1 trial (153) 1 event in TROS IR group	--	1 event only – the trial was under-powered for WDAE
QoL: VAS scales for restriction of: · Work/everyday activities	1 trial (153)	**MD -18.9** **[95% CI -29.1 to -8.7]**	TROS IR improved 3 of 4 VAS scales more than TOL IR by 14-19 mm on a 100 mm scale. The clinical meaningfulness of this difference is unclear.

· Hobbies/recreation · Social gathering · Adaptation of eating/drinking habits		**MD-14.3 [95% CI -24.8 to -3.8]** MD -10.1 [95% CI -21.5 to 1.3]* **MD -14.7 [95% CI -25.3 to -4.1]**	
Patient-reported perception of improvement or cure (VAS)	1 trial (153)	MD 0.48 [95% CI -0.67 to 1.63]	No difference between TROS IR and TOL IR
Incontinence episodes/week Median change from baseline	1 trial (153)	MD -0.30 [95% CI -1.6 to 1.01]	No difference between TROS IR and TOL IR
Urgency episodes/day Median change from baseline	0 trials	--	No data are available.
Nocturia	0 trials	--	No data are available
Total AE	1 trial (153)	RR 1.05 [95% CI 0.67 to 1.65]	No difference in the proportion of patients experiencing one or more AE
Dry mouth	1 trial (153)	RR 1.06 [95% CI -0.64 to 1.76]	No difference in dry mouth.

AE= adverse events; **IR**= immediate release; **MD**= mean difference; **QoL**= quality of life; **RR**= relative risk; SAE= serious adverse events; **VAS**= visual analogue scale; **WDAE**= withdrawals due to adverse events; * numbers of patients receiving active drug; bolded results are statistically significant.

3. Trials in Elderly Populations

Direct Comparator Trials: There were no direct comparator trials that evaluated trospium IR versus any comparator and that exclusively enrolled adults aged 65 years or more.

One direct comparator trial was identified that assessed the cognitive effects of the extended-release formulation of trospium versus oxybutynin IR in patients aged 60 or older. This was included in Q3 (cognition) as supplemental information on harms.

We also identified placebo-controlled trials that enrolled elderly populations as supplemental information on adverse events/tolerability.

Placebo-controlled trials: No RCTs were identified that compared trospium IR to placebo in populations that were exclusively ≥ age 65.

The only available RCT data in the elderly was a post hoc subgroup analysis that pooled the subgroup of patients ≥ age 75 from two placebo-controlled RCTs, The two pooled RCTs compared 60mg extended-release (ER) trospium vs. placebo (Sand 2010). Although the extended-release formulation is not included in this review, we chose to review this study for supplemental data on harms and briefly summarize it in this section. In the two RCTs, there were a total of 143 patients who were ≥ age 75 (mean age 79 years), 85 of whom received trospium ER 60mg and 58 who received placebo.

There were no SAE. Similar proportions of patients in the trospium ER and placebo arms experienced one or more AE (49.4% vs. 50.0%). For specific AE such as dry mouth or

constipation, details are only provided for the subset of AE considered at least possibly related to study medication. These numbers may be influenced by physician and patient expectation. Harms data were passively collected, which is inadequate for the assessment of cognitive impairment. A mean increase in HR of 4.8 beats per minutes (SE 1.23) was noted with trospium ER.

The study has a number of limitations. The pooled trials were not stratified by age at randomization and were pooled without usual meta-analytic techniques so within-trial randomization was not preserved. The post hoc nature of the subgroup analysis limits the credibility and interpretation of the findings. Results should be considered exploratory only. Additionally, the trials were not powered for this analysis and the reporting of harms was incomplete.

The study does not provide information on trospium IR. Trospium exposure is lower with the extended-release formulation of trospium 60mg compared with trospium IR 20mg bid (Silver 2010). The IR formulation results in greater fluctuations of drug with higher maximum plasma concentrations, resulting in higher overall drug exposure at the same (or lower) dose. This limits the applicability of findings on trospium ER to use of trospium IR in clinical practice. Higher drug exposure, including higher peak drug levels in the bloodstream, is likely to result in greater numbers of AE, particularly in frail, vulnerable populations.

Supplemental Adverse Event Data

Non-Randomized Studies

The aim in including non-randomized studies is to gain information on serious, infrequent adverse events, longer-term harms, and adverse effects in populations not adequately represented in the RCTs.

Findings from published non-randomized studies

There were no observational studies comparing trospium with oxybutynin or any of the other included antimuscarinic drugs.

One controlled cohort analysis (Isik 2009) compared patients on trospium alone with patients on trospium + galantamine or galantamine alone. Galantamine is a cholinesterase inhibitor used to treat Alzheimer's dementia. `

There were also three uncontrolled cohort analyses, two of which assess cognition in the elderly (Staskin 2010; Geller 2012; Zinner 2011). These studies are briefly described below.

Studies on cognition in the elderly were included regardless of sample size or duration.

Controlled cohort analyses – other drug therapy (non-antimuscarinic)

Isik 2009 (table 10, below) compared elderly patients with urge incontinence and dementia, who were treated with trospium + galantamine, with patients with dementia alone (treated with galantamine) and patients with urge incontinence alone. This study was carried out in Turkey and enrolled patients with late onset Alzheimer's dementia. Limited information is provided on the assessed sample and inclusion/ exclusion criteria. For example, patients with severe dementia or mild cognitive impairment were excluded but the limits to 'mild' or 'severe', or how 'late onset' was defined, are not specified. No information is provided on numbers of patients with prior anticholinergic or cholinesterase inhibitor use.

Table 10. Non-randomized studies to evaluate trospium - controlled cohort analysis

Study	Design Duration	Data source	TROS 45-60mg Sample size Mean age	GAL ≤ 24mg Sample size Mean age	TROS + GAL Sample size Mean age	Assessed outcomes
Isik 2009	Controlled cohort analysis 6 months	Turkey, geriatric patients; UI or dementia	N=106 Age 76.7±7	N=52 Age 78.4 ±7	N=46 Age 78.8 ± 7	ADL Subset of AE GDS MMSE

ADL= activities of daily living; **AE**= adverse events; **GAL**= galantamine; **GDS**= geriatric depression score; **MMSE**= mini mental state exam; **TROS**= trospium; **UI**= urge incontinence

Study outcomes:
Only per protocol results are reported, providing limited information on outcomes. Additionally, mortality, SAE, WDAE and total AE are not reported.

MMSE scores did not differ significantly from baseline in any of the groups. However, these are per protocol results that include only patients who remained in the trial until study completion, and the largest proportion of patients dropped out early from the trospium + galantamine group: 10/46 (22%), vs. 9/52 (17%) on galantamine alone and 7/106 (7%) on trospium alone.

Given the differences at baseline, incomplete reporting and lack of intention-to-treat analysis, this study fails to provide information of value on trospium's effects on cognition or on safety in the elderly, with or without concomitant use of a cholinesterase inhibitor.

Uncontrolled cohort analyses
There are three uncontrolled cohort analyses with patients exposed to trospium, all of which examine the effects of an extended-release formulation (Table 11). Two of the three studies specifically examine effects on cognition (Geller 2012; Staskin 2010); the third is an open label extension of two 12-week RCTs.

Table 11. Non-randomized non-comparative studies to evaluate trospium

Study	Design	Data source	Duration	TROS Sample size Age	Assessed outcomes
Geller 2012	Uncontrolled cohort	Clinic sample women 55+, USA	12 weeks (4 weeks for full sample)	TROS ER Dose NR N=35* Mean age 70.4 ±8	Cognition: HVLT-R OMC Mini-Cog
Staskin 2010	Uncontrolled cohort	Clinic sample; recruited via advertising, USA	10 days	TROS XR 60mg/day N=12 Mean age 69 [range 65-74]	Cognition: HVLT-R BVMT-R Cerebrospinal fluid drug levels
Zinner 2011	Uncontrolled cohort	Open label RCT extension following 2 – 12 week placebo controlled	36 week	TROS XR 60mg/day N=944 Mean age~60 (59.3 prior PL; 60.7 prior TRO-	Deaths SAE WDAE Total AE Withdrawals

		RCTs; 81% participation			

BVMT-R= Brief Visuospatial Memory Test-Revised; **HVLT-R**= Hopkins Verbal Learning Test-Revised Form; **OMC**= Orientation, Memory & Concentration; **Mini-Cog** - 3 minute drawing and learning test.
*50 were enrolled, but only 35 are reported on, including baseline characteristics

Uncontrolled cohorts assessing cognitive effects
Geller 2012 enrolled 50 women aged 55+, but reports only per protocol results for the 35 women (70%) who stayed in the study to week 4. The study duration was 12 weeks, but only 15 women (30%) were assessed at week 12, making these results highly unreliable.

Hopkins Verbal Learning Test-Revised Form (HVLT-R) was used to test cognition. This test has a maximum total score of 72 points. The mean baseline score was 60.3 ±6.0, which decreased to a mean of 56.1 ±12.2 at day 1, $p<0.05$, paired t-test. Test scores then reverted to normal at week 1 and week 4. Although this 4-point difference was statistically significant, it may be well below the threshold for a minimal clinically important difference. Staskin identified ≥6.43 points as a 'reliable change index' for one of the subscales of HVLT-R, total recall. (Staskin 2010). This subscale has a maximum of 36 points and in Geller 2012, mean score decreased from 26.7 ± at baseline to 25.4 ± 4.9 at day 1 for total recall', a difference that is not significant and is far below the 'reliable change index' identified by Staskin et al. The 'reliable change index' is a measure of the degree of difference for a single individual that reliably indicates a change in cognitive status. Although Geller 2012 report mean differences only, a 4-point difference on a 72-point total score is unlikely to be clinically meaningful, given the magnitude of the threshold for reliable change on this subscore.

Delayed recognition also decreased significantly at day 1 from a mean of 23.5 ± 0.8 points to a mean of 22.8 ±1.4 (max score = 24).

By week 4, there were no significant differences as compared with baseline. No significant differences were found for the other two cognition tests: OMC – orientation, concentration and memory test; and Mini-Cog.

A note of caution in the interpretation of these results: with a 30% early withdrawal rate, per protocol reporting is unlikely to be representative of the full patient experience.

Staskin 2010 enrolled 12 adults aged 65-75 with OAB and tested their cerebrospinal fluid for presence of trospium as well as testing cognition with HVLT-R and BVMT-R, a brief visuospatial memory test. All changes in total HVLT-R total scores and delayed recall scores were below thresholds for a 'reliable change index' except for one patient with significant improvement. BVMT-R results indicated marked improvement in recall, likely due to re-administration of the same test, which invalidates the test results. Concentrations of trospium in cerebrospinal fluid were all below the limit of detection, <40 pg/ml, including sampling at peak plasma concentration. This was a 10-day study.

Open-label RCT extension
Zinner 2011 reports on 944 patients who were enrolled in an open-label extension study for 36 weeks following participation in two 12-week placebo controlled RCTs. Efficacy outcomes were only collected once, at week 36 of the open-label extension. No information is provided on frequency of assessment of AEs. The authors note that an increase in pulse rate was seen by week

36, which was higher for patients who had been on trospium for 12 weeks in the RCT phase (median increase of 3 beats per minute) than those on placebo initially (median increase of 2 beats per minute), indicating a possible effect related to duration of treatment. Table 12 provides key safety results.

A post hoc subgroup analysis of Zinner 2011 reported separately on patients who were 75+ years of age (N=112) (Sand 2011). AE experienced during the open-label study included 3 cases of urinary retention (2.7%) and 2 CNS effects (dizziness and vertigo) (1.8%). Compared to the overall group, there was a trend to higher total AE and withdrawals among older patients.

Table 12. Adverse events reported in uncontrolled cohorts

Outcomes	Geller 2012 N=35 (to week 4)* N=50 in total 12 weeks*	Staskin 2010 N=12 10 days	Zinner 2011 36 weeks	
			Total N=944	≥ age 75 N=112
All-cause mortality	NR	0	3 (0.3%)	NR
SAE	NR	0	51 (5.4%)**	NR
Total Withdrawals	20/35 (57.1%)* 35/50 (70%) total	0	277 (29.3%)	48/112 (42.9%)
WDAE	NR §	0	105 (11.1%)	21/112 (18.8%)
Total AE	NR	10 (83%)	552 (58.5%)	73/112 (65.2%)

AE= adverse events; **SAE**= serious adverse events; **WDAE**= withdrawals due to adverse events; **NR**= not reported; *duration = 12 weeks, but most results only reported to 4 weeks; total n=50, but most outcomes reported for the 35 women who remained in the study to week 4. ** includes one small intestinal obstruction.
§ 6 (17%) discontinued medication due to AE, out of the 35 who continued to week 4; totals out of the 50 enrolled are not provided; no subjects "were withdrawn" due to AE.

Study quality /risk of bias
In Isik 2009, comparison groups differed at baseline. Only per protocol results are reported and rates of early withdrawal differed by study arm, compromising comparability. Both the study methods and reporting were weak.

Geller 2010 only reports on 35 of the 50 women enrolled who stayed in the study at least to week 4, with baseline characteristics also only provided for this subset of study participants. The per protocol reporting, with a 30% early withdrawal rate (by week 4), and a 70% total withdrawal rate (by week 12) during the study period, seriously limits interpretability of results. Assessment of effects on cognition should take into account test-retest reliability thresholds. Reporting of AE was also inadequate in this study.

Staskin 2010 also provides limited data on cognitive performance, as this is a very small study (N=12) carried out over only a 10-day period.

Zinner 2011 also provides limited information on patient experiences and reports only individual AE believed by investigators to be treatment-related. It is unclear whether reporting of AE was active or passive, or how often these data were collected.

Staskin 2010 and Zinner 2011 were sponsored by Allergan; Geller 2012 was not manufacturer-sponsored (funding provided by an IBM fund award) and declare no conflicts of interest.

All of the included studies except Isik 2009 assessed effects of extended-release trospium and thus fail to provide information on the effects of trospium IR, the formulation under consideration in this review. As is noted above, patients on trospium ER 60mg/day have lower exposure levels than patients on trospium IR 20mg b.i.d.

Other Adverse Event Data

Case reports

There is one case report on a manic episode in a 33 year old following ingestion of a high dose of trospium, 300 mg (Bilici 2010). The report, in Turkish, was not translated for this review.

Regulatory Data

Data on adverse events were sought from government and regulatory sources including periodic safety update reports (PSURs), the Health Canada Vigilance Online Database records and the U.S. Food and Drug Agency reviews or safety updates. Pharmacosurveillance databases have major limitations including under-reporting and lack of denominator data which precludes rate calculations.

Periodic Safety Update Reports (PSUR)

One recent periodic safety update report (PSUR) for trospium chloride was obtained for this review. It covers the one-year period from Oct 1st, 2011 to September 30th 2012 during which approximately 2,692,000 patient-months of exposure were estimated to have occurred worldwide based on sales data. Of this, 1,601,343 patient-months of exposure were due to the IR formulation. Canada's exposure was approximately 19,000 patient-months. No cumulative data are provided since trospium was first launched worldwide in 1978. Cumulative data are important for providing identifying infrequent serious adverse events.

Conditions discussed or analyzed by regulatory authorities and/or under monitoring were: confusional state, hallucination, agitation, hepatobiliary disorders, alteration of blood glucose level and visual disorders. These did not provide new safety signals according to the manufacturer.

Deaths: One 84 year-old male with an aortic ulcer experienced respiratory arrest following constipation and abdominal distension.

Serious Adverse Events (non-fatal): During the one year period, 76 case reports were received including 17 spontaneously reported SAE. Of the serious case reports, 16 were unlisted events and 1was a listed event. Listed events appear in product monographs that inform health care professionals and patients.

The SAE included 7 nervous system or psychiatric disorders and 10 other serious cases including 4 cardiorespiratory cases. No cases of torsades de pointes or ventricular arrhythmias were identified in the one-year period.

SAE, other than those related to nervous system or psychiatric disorders, were:

- Cardiovascular or respiratory disorders
    - Respiratory arrest/constipation/abdominal distension resulting in death (1)

  - Cardiac failure/arrhythmia/atrial fibrillation/peripheral edema (1);
  - Pulmonary embolism/atrial fibrillation (1)
  - Hypotension/dizziness with positive de-challenge (1)
- Renal and urinary disorders:
  - Acute urinary retention/confusion in male with history of kidney failure, stroke and rhabdomyolysis post fall (1)
  - Acute urinary retention/abdominal pain/acute fecal incontinence (female) (1)
- Skin disorders:
  - Follicular acne (1);
  - Skin haemorrhage (1)
- Eye: Glaucoma (1)
- General: Constipation/micturition disorder with hematuria in patient with tetraparesis (1)

Central nervous system or psychiatric disorders: 10 cases (including 7 serious listed or unlisted and 3 non-serious unlisted) were identified by the manufacturer, often in combination with other AE. These were:

  - Disorientiation with positive dechallenge (1) (serious unlisted)
  - Hallucination/condition aggravated (1) (serious unlisted)
  - Confusional state/feeling abnormal/visual hallucination/fall/road traffic accident, constipation/tachycardia/tremor/sleep disorder (1) (serious unlisted)
  - Confusional state/acute urinary retention in patient with history of kidney failure, stroke and rhabdomyolysis post fall (serious unlisted)
  - Cognitive disorder/somnolence/irritability/fatigue (1) (serious unlisted)
  - Disorientation/asthenia (serious unlisted)
  - Disorientation in a patient with history of dementia (non-serious unlisted)
  - Emotional disorder/depression (non-serious, unlisted)
  - Agitation/somnolence/tremor/tachycardia/abdominal discomfort after first dose (non-serious unlisted))
  - Parkinson's, drug interaction (serious unlisted)–*Note: This report is for aggravation of Parkinson's disease. The manufacturer dismissed potential causality on the basis that trospium is known to potentiate anticholinergic effects of amantadine. Without further follow-up information (e.g., a positive dechallenge/re-challenge), the dismissal of causality is premature, particularly when taking into account the different receptor targets of the two drugs, and the complexity of signalling pathways including cross-talk between receptors. We also note that a potential signal for Parkinson's disease was reported in the PSUR documentation for another antimuscarinic drug, solifenacin.*

In the reference safety documentation, listed AE for nervous system disorders are: headache; dizziness; hallucination; confusion; agitation. Hallucination, confusion and agitation were noted to have occurred mostly in elderly patients.

No changes were made to tolterodine's reference safety information during the one year time period covered by this PSUR.

Health Canada Vigilance Database

There are 12 adverse reaction reports pertaining to trospium use in the Canadian Vigilance Online Database up to March 31, 2013, the most recent date of entry for the database (Table 4, Appendix I). Ten of the 12 reports involved patients $\geq$ age 65.

The low number of adverse reaction reports cannot be used to draw conclusions about comparative safety due to under-reporting in voluntary databases, different durations of exposure of Canadian populations to various antimuscarinic drugs, and other factors that influence reporting rates.

Deaths: no deaths were reported.

Non-fatal SAE: There were 2 serious adverse reaction reports:

- A 90 year old female was hospitalized with atrial fibrillation/ hypertension/ dizziness/ dyspnea/ headache/ palpitations/ tachycardia/ ventricular extrasystoles, which resolved.
- An 88 year old male was hospitalized with dysuria.

Other reports included one case of urinary retention (Table 4, Appendix I).

US FDA - post-market labeling changes since approval in 2004
Changes include:

Warnings and Precautions

- Central Nervous System Effects: dizziness, confusion, hallucinations and somnolence; operating heavy machinery or driving (2012)
- Hepatic Impairment: the term "moderate" was added to the following:
    - Caution should be used when administering [Trospium] in patients with moderate or severe hepatic dysfunction.
    - Hepatic Insufficiency: There is no information regarding the effect of moderate to severe hepatic impairment

Adverse Reactions:

- dizziness; confusion (2012)
- angioedema (2011)

Post-Market Adverse Drug Reactions listed in Canadian Product Monograph (dated Jan 2012)

gastritis; palpitations; supraventricular tachycardia; chest pain; syncope; hypertensive crisis; Stevens-Johnson syndrome; anaphylactic reaction; angioedema; vision abnormal; hallucinations; delirium; rhabdomyolysis; rash.

Discussion and Conclusions

Q1: Does trospium IR provide a therapeutic advantage over oxybutynin IR or other comparators?

Direct Comparator RCTs

RCT data were available for comparisons with oxybutynin IR and tolterodine IR. There is no evidence available for comparisons of trospium IR with fesoterodine, darifenacin or solifenacin.

Trospium IR vs. oxybutynin IR: Two trials were identified, a 52-week trial using recommended doses of trospium IR and oxybutynin IR (Halaska 2003) and a 12-week trial that used a flexible dosing regimen up to ~2X the usual dose of trospium IR versus 7.5-15mg/day oxybutynin IR (Zellner 2009). Based on these two trials (N=2015), there is insufficient evidence to conclude trospium IR has an advantage over oxybutynin IR for efficacy outcomes. There was no difference

in patient-reported improvement or cure (low level of evidence). There was also no difference in the reduction of incontinence in the two individual trials; results could not be pooled for this outcome because useable data were not provided (low level of evidence). There was insufficient evidence to draw conclusions on quality of life with evidence from one trial (Zellner 2009) that reported no between-treatment differences.

Evidence was limited by the design of the largest trial, Zellner 2009, which was a non-inferiority trial based on incontinence episodes and not powered to determine superiority of either drug. Halaska 2003 did not report a sample size calculation so it is not possible to determine whether the trial was adequately powered to detect differences in efficacy outcomes of interest.

Trospium IR was associated with lower rates of WDAE (risk difference 3%) and total AE (risk difference 5%). Specific adverse events such as dry mouth and constipation could not be evaluated as only a subset of AE believed to be related to treatment were reported; the results are unlikely to reflect full patient experience in the trials. The level of evidence was low for WDAE and total AE, and insufficient for specific AE such as dry mouth.

Based on similar efficacy for reduction in incontinence episodes, and better tolerability (lower WDAE and total adverse events), there is a therapeutic advantage for trospium IR. However, the quality of evidence is low. Comparisons were for doses at or exceeding the maximum recommended dose for trospium IR versus doses in the mid-low range for oxybutynin IR. However, given the direction of dose-nonequivalence, the findings of higher rates of AE with oxybutynin are likely to be robust.

Trospium IR vs. Tolterodine IR: Based on one parallel group, placebo-controlled trial (N=153 receiving active drugs and 79 receiving placebo), there was no difference between trospium IR and tolterodine IR in reduction of incontinence episodes or patient-reported perception of improvement or cure. As a quality of life measure, visual analogue scales were used to measure restriction in activities in 4 domains (work/everyday activities, recreational activities, eating/drinking habits, social gatherings). Trospium IR was slightly better in lessening restriction of work/every day activities, recreational activities, and eating/drinking habits but not social gatherings (with differences of 14-19 mm on a 100 mm scale). It is unclear whether these VAS scales have been validated, and the clinical meaningfulness of reported differences is unclear. This is insufficient evidence to conclude trospium IR has an efficacy advantage.

This trial was designed as a superiority trial of trospium versus placebo and a non-inferiority trial for trospium vs. tolterodine, based on sequential testing of results for the trial's primary outcome, micturition frequency. It failed to show a difference between trospium and placebo in an intention-to-treat analysis. Although micturition frequency was not an outcome of interest for this review, this finding highlights the need to include a placebo treatment arm in comparator trials as the placebo effect can be large and varies across populations.

There was no difference between trospium IR and tolterodine IR in the proportion of patients experiencing one or more AE or dry mouth. Other AE were also similar between drugs. The trial was under-powered to assess short-term mortality, SAE or WDAE.

This trial provides insufficient evidence to conclude a therapeutic advantage (incorporating benefit and harm) for trospium IR over tolterodine IR or placebo. Its unpublished status, with study report dated 2001, likely represents a publication bias or failure to publish because of the negative results (e.g., lack of effectiveness advantage for trospium IR versus placebo).

Comparison with other systematic reviews: Conclusions of the current review are generally consistent with a Cochrane review (Madhuvrata 2012) for the comparison trospium IR vs. oxybutynin IR, and consistent with both Madhuvrata 2012 and a review for AHRQ, Shamliyan 2012, for the comparison trospium IR vs. tolterodine IR. For the comparison with tolterodine, we had more data available for the unpublished study NCT 01178827 (abstract Junemann 2000) than the prior reviews.

Our review, in contrast to Madhuvrata et al., included nocturia but did not include frequency. No data were available for nocturia so this did not alter conclusions. Madhuvrata 2012 also included populations with neurogenic bladder but this also did not alter conclusions substantively.

Shamliyan et al. used a lower number for WDAE in the oxybutynin group in Zellner 2009, which resulted in the difference between trospium IR and oxybutynin IR not reaching statistical significance for this outcome. We have reported the correct number, based on information provided in the published study report. Shamliyan 2012 also stated there was insufficient evidence from which to conclude comparative effectiveness between trospium and oxybutynin. This was largely attributable to the availability of evidence from one trial for each of the efficacy outcomes considered. While we also viewed evidence from one trial as insufficient, we combined the subjective reporting of ‘cure’ with ‘improvement’ and rated the strength of the available evidence as ‘low’ rather than insufficient. Shamliyan et al. interpreted the reporting of ‘cure’ in Halaska 2003 as a dryness rate whereas we considered it as a subjective outcome not specifically related to quantification of incontinence episodes because it was not explicitly defined in the study report, was not based on bladder diary data and we could not verify that all participants were incontinent at enrollment.

In contrast to Madhuvrata 2012 and Shamliyan 2012, we do not report AE in the direct comparator RCTs if only those subsets judged to be treatment-related are reported, as these may be influenced by physician and patient expectations, and these expectations can differ between treatment arms even in a double-blind RCT if blinding is imperfect and/or if patients or physicians are able to accurately guess their treatment allocation. Additionally, there was indication in Zellner 2009 that the total number of patients with dry mouth was much higher than the subset judged by investigators to be treatment-related.

Supplemental Adverse Event Data

Placebo-controlled trials in the elderly: No RCTs were identified that exclusively enrolled the elderly and compared trospium IR to any other antimuscarinic drug.

A post hoc subgroup analysis of two pooled placebo-controlled RCTs on trospium ER included 143 patients age 75+. There were no SAE or CNS adverse events reported and total AE were similar in the placebo and trospium ER group. Only those AE believed to be possibly related to treatment were reported, and this may be influenced by physician and patient expectation. Reported AE were consistent with anticholinergic effects. An increase in heart rate of 4.8 bpm was detected with trospium ER. This study was limited by pooling without usual meta-analytic technique (merely summing up those for each treatment), and its post hoc nature and inadequate power to detect a difference. The results should be regarded as exploratory only. Because trospium exposure is lower with the ER formulation, applicability of the findings to trospium IR is limited.

Non-randomized studies: No non-randomized observational studies on trospium IR were identified.

Four non-randomized studies evaluated trospium ER. These are not directly applicable to use of trospium IR because drug exposure with the extended-release formulation is lower.

One 36-week extension phase of two placebo-controlled RCTs provides limited information on patient experiences and reports only individual AE believed by investigators to be treatment-related (Zinner 2011). It is unclear whether reporting of AE was active or passive, or how often these data were collected. This study reported a subgroup analysis on patients aged 75+ (112 patients enrolled), with a trend towards higher WDAE and total AE compared with the overall group. There were 3 cases of urinary retention (2.7%) and 2 CNS AE (dizziness and vertigo) (1.8%).

One 6-month study reported no change from baseline in mini-mental status examination (MMSE) scores in three groups of patients: 1) patients with late onset Alzheimer's dementia who were treated with trospium ER in combination with galantamine; 2) patients who did not have dementia and were treated with trospium alone; and 3) patients with dementia and without urge incontinence were treated with galantamine alone (Isik 2009). The study fails to provide information of value on trospium's effects on cognition or on safety in the elderly due to the use of groups which differed widely at baseline, a per protocol analysis (22% drop-outs in the group receiving trospium + galantamine) and incomplete AE reporting.

Two other observational studies reported neuropsychological tests for cognition in patients but provide limited information only. One 12-week study enrolled 50 women aged 55+ but reports only per protocol results for the 70% who stayed in the study to week 4. Only 15/50 (30%) were assessed at week 12, making these results highly unreliable. A statistically significant decrease in Hopkins Verbal Learning Test-Revised (HVLT-R) total score was noted at day 1, but the degree of difference is likely to be below the threshold for minimal clinically important difference. There were no differences in this and other cognitive tests at week 4.

The other study was a pilot study (Staskin 2010) for a direct comparator RCT that is discussed below, for Q3. It reported HVLT-R total recall scores and delayed recall scores below the level of reliable change indices for trospium ER.

Post-market surveillance and regulatory safety data: Based on the one available PSUR (both IR and ER formulations), adverse events included disorientation (with a positive dechallenge), hallucination, confusion and cognitive disorder; these suggest trospium is able to penetrate the blood-brain barrier. There was also one case report of aggravation of Parkinson's disease. AE appeared qualitatively similar to other anticholinergic drugs. These data cannot be used to draw conclusions on comparative safety because of their limitations including the lack of denominator data.

Gaps in evidence

There is a lack of well-designed, independently conducted active comparator trials for this drug. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For active drug comparator trials within a drug class, there is evidence that sponsorship predicts which drug does better (Bero 2007) .

No active comparator trials were identified that exclusively enrolled elderly populations or actively assessed the cognitive effects of trospium IR.

There are also no studies on populations refractory to, or intolerant of, oxybutynin IR.

Although one longer-term trial was available, the trial was under-powered for serious adverse events, including all-cause mortality and cognitive impairment.

Q2. New Evidence since the CDR Review

One CDR review has been conducted on trospium IR. The CDEC recommendation dated July 26, 2006 was to list trospium for patients who cannot tolerate immediate-release oxybutynin and in a similar manner as drug plans list tolterodine.

Twelve double-blind RCTs were included in the CDR review, 8 of which were placebo-controlled. The majority of studies were short (2-4 weeks) and described as focusing on urodynamics.

Four direct comparator RCTs were identified, three comparing trospium IR to oxybutynin IR, and one comparing trospium IR to tolterodine IR (Study MP94D2.15; Madersbacher 1995; Conejero-Sugranes 2006 Internal Report; Halaska 2003). Two were in neurogenic populations and not included in the current review.

The review based its conclusions on efficacy predominantly on 3 RCTs that were $\geq$ 12 weeks long, two placebo-controlled and one active comparator trial. These were:

- IP631-003 – placebo-controlled 12-week RCT
- IP631-005 – placebo controlled 12-week RCT
- Halaska 2003, corresponding to MP94.D2.04 (Trospium IR vs. Oxybutynin IR, 52-week trial)

Conclusions on efficacy were that trospium improved quality of life over placebo in two trials but this was not assessed relative to an active control. Several frequency and incontinence outcomes were significantly improved versus placebo. In the 52-week trial, efficacy was not significantly different than oxybutynin.

For conclusions on harms, all available trials were assessed. Trospium was not significantly different from oxybutynin or tolterodine although more AE occurred with trospium versus placebo. In the 52-week study, fewer patients on trospium were noted to experience dry mouth than oxybutynin.

In the current review, the following additional RCT was identified:

- Zellner 2009 (a 12-week trial on trospium IR vs. oxybutynin IR – note this trial used a trospium dose range [45-90mg total/day] above the recommended dose range in Canada [40mg total/day])

Based on Zellner 2009 and Halaska 2003, this review's conclusions for the comparison trospium IR versus oxybutynin IR were that efficacy was similar to oxybutynin IR but that there were lower rates of WDAE and total AE on trospium IR.

We also note that the full study report of the 3-week trial comparing trospium IR vs. tolterodine IR reported impact of each drug on aspects of quality of life using visual analogue scales but not a validated QoL scale and the clinical meaningfulness of the differences between trospium IR and

tolterodine IR was not addressed. The results do not change the CDR review conclusions substantively.

We note there continue to be no direct comparator trials that compare trospium with another antimuscarinic drug in a population that is refractory to or intolerant of oxybutynin IR.

In the CDR review, supplemental information on cognition included two short-term studies on young healthy volunteers that reported REM sleep patterns and EEG data (Diefenbach 2003; Todorova 2001). Both studies used trospium IR – one study used 3 doses of trospium IR (15mg t.i.d, total 45mg), oxybutynin IR (5mg t.i.d, total 15mg) and tolterodine (2 mg b.i.d, total 4mg) and the other study used high single doses of trospium IR (45mg), oxybutynin IR (15mg) and tolterodine (4mg). Although these studies were thought to represent some limited evidence to support the claim that trospium does not cross the blood-brain barrier to the same extent as oxybutynin (e.g., a 2% difference in REM sleep), they were identified as having significant limitations. The review points out that although trospium is theoretically less likely to cross the blood-brain barrier and cause CNS effects compared with oxybutynin (or tolterodine), this possibility has not been critically evaluated in the population that will be using the drug. No RCTs on cognitive effects were identified specifically in the elderly.

In the current review, supplemental information on cognition included additional studies:

- Herberg 1997 (a 7-day multiple-dose RCT on trospium IR vs. oxybutynin IR in healthy volunteers aged 35 to 70; translated from German)
- Diefenbach 2005 (a single-dose crossover RCT on trospium IR vs. oxybutynin IR, tolterodine IR or placebo in healthy volunteers aged ≥ 50 years)

Diefenbach 2005 is a similar study as Diefenbach 2003 but did not reproduce the difference in REM latency for oxybutynin in the older age group although a larger difference in REM sleep was detected (about 15%).

Studies that compared trospium ER versus oxybutynin IR were also considered for cognition in the current review. The extended-release formulation results in lower drug exposure and narrower fluctuations of drug levels in the bloodstream than trospium IR so that these findings cannot be directly extrapolated to use of trospium IR.

- NCT 01178827 Study (unpublished direct comparator RCT, multiple doses, trospium ER (10 days) vs. oxybutynin IR (2 days) in OAB patients ≥ age 60, mean age 72 years)
- Staskin 2010 (non-randomized uncontrolled study, trospium ER)
- Geller 2012 (non-randomized uncontrolled study, trospium ER)

NCT 01178827 results are posted on clinicaltrials.gov but a full study report is not available. The primary outcome was cerebrospinal fluid levels of drug with secondary outcomes of cognitive tests. No statistical analyses were reported for the cognitive tests but in an exploratory analysis for this review, the Hopkins Verbal Learning Test-Revised Total Recall Score (see below), did not show a statistically significant difference between drugs or versus placebo. Trospium was not detected in CSF but it is questionable whether this may in part be due to dose non-equivalence (see Q3).

Although there have been additional studies in an older age group since the CDR review with one study suggestive that trospium ER crosses the blood-brain barrier to a lesser extent than usual doses of oxybutynin IR, the available evidence is insufficient to conclude trospium IR is safer than oxybutynin IR for cognition in the short-term (see Q3).

Q3. Cognition

This question was informed by 1 direct comparator RCT on trospium ER in OAB patients; 2 healthy volunteer direct comparator RCTs on trospium IR; and 2 observational studies on trospium ER in OAB patients. Trospium ER is not a drug formulation under review but was included as supplemental information on harms. Because of differences in the pharmacokinetics of extended-release versus immediate-release formulations, the findings from trospium ER studies may not be directly applicable to trospium IR use.

Direct Comparator RCTs – OAB patients

Trospium IR vs. Oxybutynin IR: No RCTs were identified that compared the cognitive effects of trospium IR with oxybutynin IR in patients with OAB.

Trospium ER vs. Oxybutynin IR: One comparative RCT was identified that evaluated cognitive effects of trospium ER versus oxybutynin IR in OAB patients. This trial, NCT01178827, was identified on the clinicaltrials.gov website and has not been published. Although the extended-release formulation was not included in this review, we briefly summarize trial results, as reported on clinicaltrials.gov, for supplemental information as it is the only identified RCT on cognitive effects that enrolled patients with OAB. Study characteristics and outcomes are presented in Tables 5 and 6, Appendix I.

The trial was a single-center RCT that enrolled 20 patients 60 years or older (mean age 72 ± 8 years) with symptoms of overactive bladder syndrome and 'age-associated memory impairment' (also known as mild cognitive impairment). The details of criteria for memory impairment are not available. The trial was single-blinded, with blinding of outcome assessors.

Patients were randomized to trospium ER 60mg once daily x 10 days (N=6), oxybutynin IR 5mg t.i.d. x 2 days (N=10) or oxybutynin IR placebo x 2 days (N=4). Drug levels were measured in both cerebrospinal fluid (CSF) and plasma after the last dose. The primary outcome measure was the CSF level of trospium IR, and oxybutynin IR plus its active metabolite, N-desethyl-oxybutynin (DEO). Trospium would achieve steady state within the time period of administration. However, oxybutynin IR achieves steady state within 3 days and was only given for 2 days (Kennelly 2010).

Trospium ER was undetectable in CSF at a time point when the plasma concentration was 1470 pg/ml. The sensitivity of the trospium assay is not provided in the clinicaltrial.gov results but is likely that reported in a pilot study (Staskin 2010, 40 pg/ml). Oxybutynin (OXY) and its major metabolite DEO were detected in CSF (OXY=59.7 ± 30.9 pg/ml; DEO=386 ± 235 pg/ml) when the plasma concentrations were: OXY 8800 pg/ml ± 2840 pg/ml; DEO 47,000 pg/ml ± 11,200 pg/ml. It is important to confirm the sensitivity and variability of both drug assays and the timing of CSF samples in relation to peak plasma levels.

The plasma levels of oxybutynin were much higher than trospium ER, and although penetration into the brain is complex and multifactorial, depending in part on the physicochemical properties of each drug (with increased propensity of oxybutynin to cross the blood-brain barrier), the use of non-equivalent doses may have contributed to the disparity seen. Furthermore, extended-release

formulations are known to result in lower plasma drug levels so the results for trospium ER cannot be extrapolated to trospium IR.

Cognitive tests were the Hopkins Verbal Learning Test-Revised (HVLT-R), a test that measures verbal learning and memory (recognition and recall), and the Brief Visuospatial Memory Test-Revised (BMVT-R), a test that measures the ability to learn. These are the same tests used in a non-randomized observational pilot study, Staskin 2010. The HVLT-R total recall score ranges from 0 (no memory) to 36 (best memory). Negative scores for change from baseline indicate deterioration. Baseline scores were in the range 23-24 across groups. No statistical analyses were provided but an exploratory analysis on the HVLT-R total recall score does not indicate a statistically significant difference between trospium IR and oxybutynin IR (paired t test). The threshold for a 'reliable change index' for HVLT-R total scores is $\geq$ 6.43 points (Staskin 2010). A reliable change index is a measure of the degree of difference for a single individual that reliably indicates a change in cognitive status. The mean changes were below this threshold although individual scores are not provided. Changes in all other scores with either active drug were also below the threshold for reliable change indices (Staskin 2010).

Table 13. Study NCT01178827: Trospium ER vs. Oxybutynin IR

Treatment	TROS ER 60 mg x 10 days	OXY IR 5 mg tid x 2 days	Placebo for OXY IR tid x 2 days
N	6	10	4
Plasma levels post dose (10 days for TROS; 2 days for OXY) pg/ml	1470 ± 1030 pg/ml)	OXY: 8800 ± 2840 pg/ml DEO: 47,000 ± 11,200	--
CSF fluid levels post dose (10 days for TROS; 2 days for OXY)	Below level of detection	OXY: 59.7 ± 30.9 DEO: 386 ± 23.5	--
HVLT-R Total Recall Score up to 10 days Mean (SD) change from baseline	Baseline: 22.5 ± 2.9	Baseline 24.4 ± 3.3	Baseline 24.0 ± 3.7
	-0.3 ± 3.3	-3.3 ± 5.4	-2.0 ± 4.8
HVLT-R Delayed Recall Score up to 10 days Mean (SD) change from baseline	Baseline 8.2 ± 1.2	Baseline	Baseline
	-1.2 ± 1.5	-1.3 ± 1.6	-0.3 ± 3.7
BVMT-R Total Recall Score up to 10 days Mean (SD) change from baseline	Baseline 15.8 ± 6.6	Baseline 20.3 ± 9.9	Baseline 16.8 ± 11.3
	1.2 ± 7.4	-1.1 ± 5.3	0.0 ± 3.5
BVMT-Delayed Recall Score up to 10 days Mean (SD) change from baseline	Baseline 6.0 ± 4.2	Baseline 8.0 ± 3.6	Baseline 4.5 ± 5.3
	0.2 ± 3.4	-1.8 ± 3.5	2.3 ± 3.9

BVMT-R= Brief Visuospatial Memory Test-Revised; **DEO**= N-desethyl-oxybutynin; **ER**= extended-release; **HVLT-R**= Hopkins Verbal Learning Test-Revised; **IR=** immediate-release; **OXY**= oxybutynin; **SD**= standard deviation; **TROS**= trospium;
For both HVLT-R and HVLT-R, a negative change indicates deterioration.
Data are results posted on clinicaltrials.gov.

A critical appraisal of the NCT01178827 study could not be completed in the absence of a full study report.

Direct Comparator RCTs – healthy volunteers

Two comparator RCTs in healthy volunteers were identified, one a single-dose study (Diefenbach 2005) and the other a 7-day study (Herberg 1997) that was translated from German. Study characteristics and outcomes are presented in Tables 5 and 6, Appendix I.

Herberg 1997
One double-blind multiple-dose RCT on healthy volunteers, aged 35 to 70 years, examined cognitive effects using computerized tests, including reaction time, after 7 days of trospium IR 20 mg b.i.d. (40 mg/day total) or oxybutynin IR 5mg t.i.d. (15 mg/day total) (N=18 in each treatment arm). A third treatment arm was not of interest (propiverine). Because crossover and washout periods are not mentioned in the article, it is assumed to be a parallel-group trial. Outcomes included precision of visual orientation, concentration, vigilance, motor co-ordination, reaction in stress situations and word match list. Few data are presented in the study with all outcomes described as showing no differences between trospium IR and oxybutynin IR.

Diefenbach 2005
Diefenbach 2005 was a double-blind crossover RCT in 24 healthy volunteers $\geq$ age 50. The trial assessed cognitive effects following single doses of the IR formulations of trospium, oxybutynin and tolterodine or placebo, with a between-treatment washout period of 12 days in between test treatments. The study primarily analyzed sleep architecture by polysomnography but included two cognitive tests, a number-combination test that evaluated information-processing capacity and working velocity (expressed as a reaction time), and the d2 test of attention for assessing individual sustained attention and concentration. The d2 test measures processing speed, rule compliance and quality of performance. Results are expressed as number of items completed and mistakes/missed target items; the latter need to be interpreted with caution as they could be due to accommodation disturbances (Diefenbach 2003).

The mean age of the healthy volunteers was 60 years (range 51 to 65 years). Participants were randomly assigned to one of four treatment sequences, and medications were administered in a single dose of 45mg trospium IR, 15mg oxybutynin IR, 4mg tolterodine IR or placebo. Cognitive testing took place one hour after ingestion of each drug, which may not have coincided with peak plasma concentrations of trospium. No information is provided about a learning curve or training (practice runs) for the cognitive tests and the analysis is regarded as exploratory. There were no differences detected between treatments including placebo. A positive control was not used and the sensitivity of the tests was not discussed.

In terms of sleep structure, the percentage of rapid-eye movement (REM) sleep was the primary outcome, and oxybutynin and tolterodine, but not trospium, showed reductions of 14-15% in REM sleep compared to placebo. The clinical meaningfulness of this difference was not addressed. There was no significant difference in REM sleep latency, in contrast to an earlier study, on young healthy volunteers, that showed an increase in REM sleep latency with oxybutynin.

After a single dose, more participants experienced dry mouth with oxybutynin (placebo 3; trospium 5; tolterodine 4; oxybutynin 8).

Risk of Bias/Quality Assessment
For Herberg 1997, most methodological features were poorly described leading to ratings of ‘unclear’ for randomization, allocation concealment and blinding (Table 3, Appendix I). There were no withdrawals in the study. The study was rated as ‘unclear’ for selective outcome reporting as few data were provided for the cognitive tests and AE reporting was incomplete.

For Diefenbach 2005, most methodological features were assessed as 'unclear' risk of bias except method of randomization and incomplete outcome data, which were both assessed as having low risk of bias (Table 3, Appendix I).

Interpretation of trial findings in Diefenbach 2005 are limited by the high doses used (total daily IR dose in one single dose – the 45mg dose of trospium was also slightly higher than the usual 40mg total in Canada), the lack of steady-state analysis and the use of sleep as a proxy for cognitive effects. The population tested was not the elderly frail or the cognitively impaired who are more likely to experience adverse effects as well as to have disturbed sleep patterns.

Diefenbach 2005 was industry-sponsored and Herberg 1997 did not declare sponsorship.

Two additional RCTs assessed sleep patterns or quantitative EEG patterns in young healthy volunteers (Todorova 2001; Diefenbach 2003). These trials were excluded based on their limited clinical relevance to the elderly. One was a single-blinded study of EEG patterns in young males 18 to 25 years only (median age 26 years) (Todorova 2001). This study showed fewer EEG changes (1 of 6 frequency bands) with trospium and tolterodine compared with oxybutynin (4 of 6 bands). These findings cannot be extrapolated to the elderly, the population of interest in Q3. The other study was similar to Diefenbach 2005 except it was a parallel group trial instead of a crossover design and enrolled healthy young volunteers with a mean age of 28.5 years. It showed a 2% difference in percentage of REM sleep between trospium IR and oxybutynin IR, and REM latency was 25 minutes longer in oxybutynin; the latter findings were not detected in the older age group study.

Non-randomized studies

Two uncontrolled cohorts assessed the cognitive effects of trospium ER in patients with OAB (Geller 2012; Staskin 2010).

One single-dose observational study assessing EEG activity in young, healthy male volunteers (mean age 26) was excluded based on its lack of clinical relevance to the elderly (Pietzko 1994).

Table 14. Uncontrolled Cohorts

Study	Design	Data source	Duration	TROS Sample size Age	Assessed outcomes
Geller 2012	Uncontrolled cohort	Clinic sample women 55+, USA	12 weeks (4 weeks for full sample)	TROS ER Dose NR N=35* Mean age 70.4 ±8	Cognition: HVLT-R OMC Mini-Cog
Staskin 2010	Uncontrolled cohort	Clinic sample; recruited via advertising, USA	10 days	TROS XR 60mg/day N=12 Mean age 69 [range 65-74]	Cognition: HVLT-R BVMT-R Cerebrospinal fluid drug levels

BVMT-R= Brief Visuospatial Memory Test-Revised; **ER**=**XR**= extended-release; **HVLT-R**= Hopkins Verbal Learning Test-Revised; **NR**= not reported; **TROS**= trospium;

Geller 2012 enrolled 50 women aged 55+ who were treated with unspecified doses of trospium ER. The study reports only per protocol results for the 35 women (70%) who stayed in the study

to week 4. The study duration was 12 weeks, but only 15 women (30%) were assessed at week 12, making these results highly unreliable.

Hopkins Verbal Learning Test-Revised Form (HVLT-R) was used to test cognition. This test has a maximum total score of 72 in this study. The mean baseline score was 60.3 ±6.0, which decreased to a mean of 56.1 ±12.2 at day 1, $p<0.05$, paired t-test. Test scores then reverted to normal at week 1 and week 4. Although this 4-point difference was statistically significant, a 4-point difference may be below the level of clinically meaningful difference. A threshold of ≥6.43 points was identified as a 'reliable change index' for HVLT-R total recall scores, one of the subscales of HVLT-R (Staskin 2010). In Geller 2012, mean change in HVLT-R total recall was -0.7 points at day 1, and was non-significant and far below this threshold. However, the 'reliable change index' described in Staskin 2010 is a measure of the degree of difference for a single individual that reliably indicates a change in cognitive status.

Delayed recognition also decreased significantly at day 1 from a mean of 23.5 ± 0.8 points to a mean of 22.8 ±1.4 (max score = 24).

By week 4, there were no significant differences as compared with baseline. No significant differences were found for the other two cognition tests: OMC – orientation, concentration and memory test; and Mini-Cog.

A note of caution in the interpretation of these results: with a 30% early withdrawal rate, per protocol reporting is unlikely to be representative of the full patient experience.

Staskin 2010 enrolled 12 cognitively intact adults aged 65-75 with OAB and tested their cerebrospinal fluid for presence of trospium as well as testing cognition with HVLT-R and BVMT-R, a brief visuospatial memory test. The study was 10 days. All changes in total HVLT-R total scores and delayed recall scores were below thresholds for a 'reliable change index' except for one patient with significant improvement. BVMT-R results indicated marked improvement in recall, likely due to re-administration of the same test and a practice or training effect, which invalidates the test results. Steady-state concentrations of trospium in cerebrospinal fluid were all below the limit of detection, <40 pg/ml. CSF samples were taken at multiple time points (0, 2, 5, 7, 12 and 24 hours post dose at 10 days), including the time point corresponding with peak plasma concentration (5 hours post dose, 925 pg/mL).

Study quality/ risk of bias

Geller 2012 only reports on 35 of the 50 women enrolled who stayed in the study at least to week 4, with baseline characteristics also only provided for this subset of study participants. The per protocol reporting, with a 30% early withdrawal rate (by week 4), and a 70% total withdrawal rate (by week 12) during the study period, seriously limits interpretability of results. Assessment of effects on cognition should take into account test-retest reliability thresholds. Reporting of AE was inadequate in this study.

Staskin 2010 also provides limited data on cognitive performance, as this is a very small study (N=12) carried out over only a 10-day period.

Staskin 2010 was sponsored by Allergan; Geller 2012 was not manufacturer-sponsored (funding provided by an IBM fund award) and declare no conflicts of interest.

The two studies assessed effects of extended-release trospium and thus fail to provide information on the effects of trospium IR, the formulation under consideration in this review. Trospium ER 60mg, at steady state, results in significantly lower peak plasma concentrations and overall drug exposure than trospium IR 20mg b.i.d. (Silver 2010). Higher drug exposure with trospium IR could increase penetration of the blood-brain barrier and increase adverse events.

Summary - Cognition

Trospium IR vs. oxybutynin IR or other antimuscarinic drugs: No RCTs were identified that compared trospium IR to oxybutynin IR in OAB patients. There were also no RCTs for other drug comparisons (tolterodine, fesoterodine, darifenacin, solifenacin or other formulations of oxybutynin) in OAB patients.

One multiple-dose RCT in healthy volunteers aged 35 to 70 years (N=36 for treatment arms of interest) provides insufficient evidence that trospium IR is safer than oxybutynin IR for cognition. Few data are presented but reported as showing no difference between these two drugs. It is not known whether the study was adequately powered for the computerized tests that were used.

An additional single-dose RCT in healthy volunteers $\geq$ age 50 (N=24, mean age 60) also provides insufficient evidence that trospium IR is safer than oxybutynin IR or tolterodine IR in terms of cognitive effects. The single doses used were an entire daily dose for each drug: 45mg trospium IR, slightly higher than the recommended Canadian dose of 40mg total/day, 15mg oxybutynin IR, and 4mg tolterodine IR. The timing of cognitive testing, 1 hour after administration, does not coincide with peak plasma concentration for trospium IR (~5 hours for a single dose of trospium 20mg). The timing of peak drug exposure with the single dose was not verified by plasma levels; these were not measured beyond 1 hour because this was primarily a sleep study and the dose was given at night. No differences were detected in the two cognitive tests between active drugs or placebo. The study provides no information on steady state conditions and has limited generalizability. Sleep structure is an insufficient proxy for cognition and the clinical meaningfulness of a ~15% reduction in REM sleep with a higher-than recommended single dose of oxybutynin IR or tolterodine IR was not discussed.

Trospium ER vs. comparators: One RCT compared trospium ER 60mg x 10 days with oxybutynin IR 5mg t.i.d. (15mg total/day) x 2 days or placebo in 20 OAB patients with 'age-related cognitive impairment' not further specified. This study was identified on clinicaltrials.gov and could not be critically appraised as a full study report was not available. Results posted on clinicaltrials.gov indicate that trospium ER was not detected in cerebrospinal fluid (minimal level of detection not specified for this study but likely 40 pg/ml based on Staskin 2010) after 10 days of treatment when plasma concentrations were 1470 ± 1030 pg/ml (N=6). Oxybutynin IR was detected in CSF after 2 days of treatment at a time point post dose when plasma concentrations of oxybutynin and its active metabolite were: OXY 8800 ± 2840 pg/ml and DEO 47,000 ± 11,200 pg/ml (N=10). Statistical analyses are not provided by the investigators. HVLT-R and BMVT-R results indicate the greatest negative changes with oxybutynin IR but the differences in mean for HVLT-R total recall, HVLT-delayed recall, BVMT-R total recall and BVMT-delayed recall scores are not statistically significant based on our calculations, paired t-test, and were not greater than the reliable change indices identified for each score (Staskin 2010).

This study cannot be directly extrapolated to trospium IR because drug exposure is higher with the immediate-release formulation (Silver 2010) and this may affect blood-brain barrier crossing as well as clinical effects. In addition, other information on time points is required.

An additional non-randomized, uncontrolled 10-day study in cognitively intact healthy volunteers, the pilot study for NCT01178827 did not detect trospium ER in CSF (Staskin 2010). In that study HVLT-R scores were also below reliable change indices but the BVMT-R results were invalid as they showed a practice or training effect. A second 12-week observational study on trospium ER in women only (Geller 2012) is unreliable due to use of per protocol analyses and the high withdrawal rate (30%).

Conclusion: In summary, there is insufficient evidence to conclude trospium IR is safer, in the short-term, than oxybutynin IR for cognition. A multiple-dose study (7 days of treatment) reported no differences between trospium IR (40mg total/day) and oxybutynin IR (15mg total/day). A single-dose healthy volunteer study (mean age 60) also reported no difference between trospium IR and oxybutynin IR, when given in a single high dose (45mg trospium IR and 15mg oxybutynin IR), with cognitive testing one hour later. This time point is unlikely to have coincided with the peak plasma concentration for trospium (about 5 hours).

Available evidence on 16 patients with OAB, and an unspecified degree of age-related cognitive impairment (mild cognitive impairment), suggests that usual doses of extended-release formulation of trospium penetrate the blood-brain barrier (N=6) less than oxybutynin IR (N=10). Cognitive testing did not reveal statistically significant between-treatment differences in the change from baseline between active drugs or placebo. This result cannot be applied to trospium IR, which results in higher overall drug exposure compared to the extended-release formulation (Silver 2010).

Validated neuropsychological tests in the short-term can provide some information but it is important to collect clinical information on cognition in the elderly over the long-term when a drug is used on a chronic basis. No RCTs in any population have assessed the cognitive effects of chronic use of trospium IR (or ER). There are also no observational studies on trospium IR that have assessed long-term cognitive effects.

References for Included Studies

Direct Comparator RCTs

Trospium IR vs. Oxybutynin IR

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Madaus AG. Study MP94D2.15: placebo-controlled, randomized, double-blind, multi-centre clinical trial on the efficacy and tolerability of 2 x 20 mg trospium chloride and 2 x 2 mg tolterodine daily for 3 weeks in patients with urge syndrome. Integrated Clinical Trial Report of the Final Analysis 2001. [Confidential Internal Manufacturer's Report]

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Supplemental Information on AE

Direct Comparator RCTs

Trospium IR vs. oxybutynin IR, healthy volunteers

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Trospium ER vs. oxybutynin IR

Allergan NCT01178827: Sanctura muscarinic receptor antagonist resists transport (SMART-II) trial. http://www.clinicaltrials.gov/ct2/show/NCT01178827?term=NCT01178827&rank=1

Placebo-controlled RCTs

Trospium ER vs. placebo

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Antimuscarinic Drugs for Overactive Bladder Syndrome
Clinical Review Series

Part VII

Different Formulations of Oxybutynin or Other Antimuscarinic Drugs
Systematic Review

Table of Contents

Different Formulations of Antimuscarinic Drugs for Overactive Bladder Syndrome

Executive Summary

Introduction

Background

Comparisons included in this review are the immediate versus extended-release formulations of oxybutynin, both oral and transdermal, and the immediate versus extended-release oral formulations of tolterodine. Only one formulation of trospium (IR) and darifenacin (ER) were included in this review so formulation comparisons were not included for these drugs.

Oxybutynin

Oxybutynin chloride is a nonselective muscarinic receptor antagonist. It has slightly greater binding affinity for the M3 receptor (thought to be most important in bladder contraction) but binds all five muscarinic receptor subtypes. Oxybutynin also has a direct antispasmodic action on smooth muscle but this is much weaker than its anticholinergic properties and may not be clinically significant (Oxybutynin Chloride Immediate Release Product Monograph; Kennelly 2010). A local anesthetic and analgesic effect is claimed as well but is of unknown clinical significance.

Oxybutynin is available in one immediate-release and four extended-release formulations, two of which are transdermal (Gelnique™, Oxytrol™, Ditropan XL®; Uromax®) (Table 1). The immediate-release formulation has been available in Canada since 1978. The most recent formulation, oxybutynin gel (Gelnique™), was approved in Canada in 2012. Only the oxybutynin gel has undergone an assessment by the Common Drug Review.

Table 1. Oxybutynin Formulations

Formulation	Oxybutynin IR (Ditropan; Generic)	Oxybutynin ER (Ditropan XL®)	Oxybutynin CR (Uromax®)	Oxybutynin TDS (Oxytrol™)	Oxybutynin Gel (Gelnique™)
Indication	Symptoms associated with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)	Symptoms of urge incontinence, urgency and frequency in patients with OAB	Symptoms of an overactive bladder including urge incontinence, urinary frequency, urgency or any combination of these symptoms	Treatment of OAB with symptoms of urge urinary incontinence, urgency and frequency	Treatment of OAB with symptoms of urge urinary incontinence, urgency and frequency
Formulation/ delivery system	Tablet	OROS (Osmotic pump)/tablet	Enteric coated tablet (cellulose	Matrix layer adhesive patch	Alcohol-based gel

Formulation	Oxybutynin IR (Ditropan; Generic)	Oxybutynin ER (Ditropan XL®)	Oxybutynin CR (Uromax®)	Oxybutynin TDS (Oxytrol™)	Oxybutynin Gel (Gelnique™)
			matrix and sodium alginate)		
Administration	Best taken on an empty stomach	Must be swallowed whole	Must be swallowed whole	Apply to dry, intact skin on abdomen, hip or buttocks	Apply to abdomen, upper arms/shoulders, or thigh once daily. Rub into skin until dry.
Usual dose	5 mg bid-tid	5-10 mg once daily	Initial dose 10-15 mg once daily	3.9 mg/day patch applied every 3-4 days	1 gm 10% OTG applied daily
Maximum dose	20 mg/day	30 mg/day	20 mg/day	As above	As above
Metabolism	Bowel, liver 1st pass extraction CYP 3A4	Bowel, liver 1st pass extraction CYP 3A4	Bowel, liver 1st pass extraction CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4
DEO:OXY ratio	5.5:1	4.3:1	--	1.3:1	0.9:1

CYP= cytochrome P450; **DEO**= N-desethyloxybutynin; **OAB**= overactive bladder; **OXY**= oxybutynin;
Ratios of DEO:OXY are from Kennelly 2010 and vary slightly from other estimates; other information obtained from Canadian Product Monographs

Tolterodine

Tolterodine, like oxybutynin, is a nonselective muscarinic receptor antagonist. Although tolterodine has been marketed with claims of tissue selectivity for the bladder, the evidence for this is weak and may not be clinically significant. The immediate-release formulation (Detrol™) of tolterodine has been available in Canada since 1998, and the extended-release formulation (Detrol LA™) since 2002.

Research Questions:

Q1. In adults, including the frail elderly, do different formulations of oxybutynin (or another antimuscarinic drug) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) (or the IR form of another antimuscarinic drug) for the treatment of overactive bladder (OAB) syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that different formulations of oxybutynin (or another antimuscarinic drug) improve clinically relevant outcomes or have a better safety profile compared to oxybutynin IR (or the IR form of another antimuscarinic drug)?

Q3. In adults, particularly the elderly, do other formulations of oxybutynin (or another antimuscarinic drug) have less effect on cognition when compared to oxybutynin IR (or the IR form of another antimuscarinic drug)?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included for supplemental information on harms if they exclusively enrolled elderly populations or assessed cognitive function. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all-cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included study design, techniques used to reduce confounding, patient and control selection criteria, blinding of outcome assessment, and completeness of follow-up and reporting.

Q1. Comparative Harms and Benefits

Results

Search Findings

In total, eight RCTs meeting inclusion criteria compared different formulations of the same drug:

- Seven compared different oxybutynin formulations versus oxybutynin immediate-release (IR)
  - Anderson 1999;
  - Barkin 2004;
  - Birns 2000;
  - Davila 2001;
  - Kay 2012b;
  - Minassian 2007;
  - Versi 2000.

- One compared tolterodine extended-release (ER) versus tolterodine IR:
  - van Kerrebroeck 2001

Of the seven RCTs that compared oxybutynin formulations, one was a healthy volunteer study and is considered in Q3 only (Kay 2012b). This trial compared oxybutynin gel with oxybutynin IR.

Of the six parallel-group trials on oxybutynin use in patients with OAB syndrome, five compared oral extended-release formulations with oxybutynin IR (Minassian 2007, Barkin 2004, Davila 2001, Birns 2000, Versi 2000, Anderson 1999) and one compared the oxybutynin transdermal patch (TDS) with oxybutynin IR. There were no active comparator trials on the comparison of oxybutynin gel with oxybutynin IR in patients with OAB.

Two placebo-controlled RCTs on oxybutynin are included as they address effects in the elderly and on cognition:

- Lackner 2008;
- Katz 1998.

Ten observational studies met inclusion criteria to assess infrequent harms:

- Amarenco 1998;
- CONTROL 2012;
- Diokno 2002;
- Gish 2009;
- Hussain 1996;
- Jonville 1992;
- Moga 2013;
- Movig 2001;
- Newman 2008 (also reported in Pizzi 2009);
- 't Veld 1998.

Regulatory documents provided additional information on infrequent adverse events, labelling changes and safety advisories.

Direct Comparator Randomized, Controlled Trials (RCTs)

Oral oxybutynin ER versus oxybutynin IR (RCTs)

Five trials involved a total of 658 participants who were randomized to receive active drug. Four trials had a titration phase or flexible dose regimen with individual dose adjustment (Barkin 2004; Versi 2000; Anderson 1999; Minassian 2007) whereas the fifth used fixed doses (Birns 2000) (Table 2).

Table 2. Total doses/day in RCTs

Study	OXY ER Total dose/day	OXY IR Total dose/day	Comment
Anderson 1999	5-30 mg/day (Ditropan XL)	5-20 mg/day	Responders only enrolled
Barkin 2004	5-20 mg/day (Uromax) mean 12.4 mg ± 4.4 /day	5-20 mg/day mean 14.0 ± 5.3 mg/day	
Birns 2000	10 mg/day (fixed dose)	10 mg/day (fixed dose)	Responders only enrolled
Minassian 2007	5-10 mg/day	5-10 mg/day	All participants > age 65
Versi 2000	5-20 mg/day (Ditropan XL)	5-20 mg/day	Responders only enrolled

Treatment duration was 2 to 12 weeks, with a stable-dose phase in each ranging from one week (Versi 2000) to eight weeks (Minassian 2007). The longest trial, Minassian 2007, did not meet its enrollment goal and was terminated early.

Three of the trials (N=461) (Anderson 1999; Birns 2000; Versi 2000) enrolled responders only, employing a trial responder phase to determine if potential participants were responsive and tolerant of oral oxybutynin. Only those patients who demonstrated tolerability and responsiveness

were randomized. The population was thus highly selected.

Trials were under-powered for all-cause mortality and serious adverse events (insufficient evidence). Harms were incompletely reported. There was no difference in the rate of withdrawals due to adverse events (5 trials; N=658) Based on two trials (N=193), there was no statistically significant difference in the proportion of patients experiencing one or more AE (Birns 2000; Minassian 2007) (low strength of evidence). Fewer patients on oxybutynin ER experienced dry mouth (risk difference 8%), based on five trials (moderate strength of evidence).

Most of the trials used a similar range of doses for the IR and ER formulations. Based on clinical pharmacological considerations, an equivalent dose of an IR formulation is a slightly lower dose.

Quality of life (condition-specific), based on total Urogenital Distress Inventory (UDI) and Urge-UDI scores were reported in two trials (Barkin 2004; Minassian 2007) improved less on oxybutynin ER. There was no statistically significant difference in total Incontinence Impact Questionnaire (IIQ) scores in Barkin 2004, and the five domain scores of the Urge-IIQ reported by Minassian 2007.

Improvement in incontinence episodes was similar between drugs in the five trials (moderate strength of evidence). A meta-analysis could not be conducted on this outcome as some trials reported medians instead of means or did not report a measure of variation. Only one trial reported on the outcome urgency, which did not show a difference between formulations (insufficient evidence). No trials reported on nocturia.

Minassian 2007 was the only direct comparator RCT identified for oxybutynin formulations that exclusively enrolled an older population, women > age 65. This trial was open-label and had serious methodological limitations. It was under-powered and terminated early due to recruitment difficulties and an interim analysis that indicated a much larger sample size would be required to detect a significant difference between formulations.

Oxybutynin Transdermal Patch (TDS) vs. Oxybutynin IR (RCTs)

Davila 2001 was a 6-week dose-titration, parallel group trial (N=76) that compared oxybutynin IR with transdermal oxybutynin (TDS). The trial enrolled oxybutynin responders only. Drug doses were initiated based on prior stable doses of oral oxybutynin and titrated according to tolerability. The recommended dose for oxybutynin TDS is 3.9 mg/day. The dose range of oxybutynin TDS in this trial was ~1-8mg/day and for oral oxybutynin IR, 5 to 22.5 mg/day (Center for Drug Evaluation and Research NDA 21-351). At study end, the majority (68%) of participants were on a higher-than-approved dose of oxybutynin TDS, limiting the applicability of the findings to usual practice.

The trial was under-powered for serious adverse events and withdrawals due to adverse events. Harms were incompletely reported. The proportion of patients experiencing one or more adverse events, in total, was not reported. Fewer patients experienced dry mouth (absolute risk difference 59%) and constipation (risk difference 29%) on oxybutynin TDS. Rates of nausea (risk difference 18%) and somnolence (risk difference 45%) were also lower on oxybutynin TDS. Although 15% more patients experienced erythema at the patch application site with active drug compared to placebo, this was not statistically significant. Other application site reactions, however, were incompletely reported. Dose ranges for oxybutynin TDS and oxybutynin IR in this trial were not comparable, and the lower rates of anticholinergic adverse events with oxybutynin TDS could have been due to the lower anticholinergic dose.

This trial was designed as an equivalence trial and failed to show equivalence of oxybutynin TDS with oral oxybutynin for the *a priori* primary outcome, the percentage of patients who were responders. A response was defined as a ≥ 30% reduction from baseline in incontinence episodes. The trial was under-powered for the primary outcome. Other efficacy outcomes were similar but the doses used of each formulation were not comparable.

There is insufficient evidence, based on this trial, to conclude a therapeutic advantage of oxybutynin TDS over oxybutynin IR.

Tolterodine ER versus Tolterodine IR

One 12-week parallel group RCT (N=1021 receiving active drug) compared tolterodine ER 4mg once daily with tolterodine IR 2mg bid (4mg total/day), and also included a placebo arm (N=508) (van Kerrebroeck 2001).

There was no difference between tolterodine ER and tolterodine IR in serious adverse events or withdrawal rates due to adverse events. The proportion of patients experiencing one or more adverse events, in total, was not reported. There was less dry mouth with tolterodine ER (risk difference 7%).

Comparative outcome data on quality of life are not available although quality of life was measured in this trial by both a general health-related questionnaire and a condition-specific instrument. There was no difference between formulations in the reduction from baseline in incontinence episodes. No data are available on urgency or nocturia.

This trial provides insufficient evidence on harms and efficacy outcomes to conclude a therapeutic advantage for tolterodine ER.

Placebo-controlled trials in the Elderly (Oxybutynin)

Placebo-controlled trials on the elderly were included for supplemental information on harms including cognition. One 4-week trial on patients with OAB (N=50) was identified that compared oxybutynin ER 5mg daily to placebo (Lackner 2008). This trial exclusively enrolled cognitively-impaired, elderly females (mean age 89 ± 6.2 years) who were residents of nursing home facilities. Participants had baseline Mini-Mental Status Examination (MMSE) scores of 5 to 23.

The study was designed an equivalence trial using margins of equivalence of ± 2 points for the 95% confidence intervals of mean change in the Confusion Assessment Methods algorithm. This is a validated instrument for assessing the presence or absence of delirium and includes items on inattention, disorganized thinking, disorientation, memory impairment, and altered level of consciousness (Inouye 1990). The scoring system was not described nor was the basis on which the margins of equivalence were chosen.

No patient experienced delirium during the study, and no differences between oxybutynin ER and placebo were detected on change from baseline in MMSE scores, before and after adjustment for potential confounders (age, number of medications known to have serum anticholinergic activity, and serum anticholinergic activity at 7 days), or on a Brief Agitation Rating Scale or Severe Impairment Battery. MMSE is unlikely to detect mild differences in cognition, and the Confusion

Assessment Method, the primary outcome in Lackner 2008, was predominantly designed to detect acute changes of delirium.

Only treatment-related harms were reported, which represents a subset of total AE and may not reflect the overall experience of the patient. Reported events were infrequent e.g., two people experience 'treatment-related' constipation and one experienced 'treatment-related' dry mouth in the oxybutynin ER group versus no events in the placebo group, suggesting the trial was under-powered to detect differences in harms. One individual on oxybutynin ER (3.9%), and none on placebo, experienced urinary retention. Falls were assessed during the study period as well as pre- and post-treatment. There were few events, with one person on oxybutynin ER group and two on placebo experiencing falls during the 4-week period.

This study was predominantly designed to detect acute changes of delerium.

Non-randomized studies
No observational studies compared the effects of one of the included formulations of oxybutynin with another, or compared tolterodine IR with tolterodine ER.

The ten observational studies meeting review inclusion criteria were included two controlled cohort analyses (Moga 2013; Movig 2001); four uncontrolled cohort analyses (Diokno 2002; Amarenco 1998; CONTROL 2012 [unpublished; in FDA advisory committee report]; and Newman 2008 (also reported in Pizzi 2009). There was one on-treatment comparison to pre- or post-treatment ECG readings (Hussain 1996), and three case series, all of spontaneous adverse drug reaction (ADR) reports to regulators (Gish 2009; Jonville 1992, 't Veld 1998).

Controlled cohort analyses
Moga 2013 (N=1125) is a controlled cohort analysis among residents of U.S. Veterans Administration long-term care facilities. Initial users of bladder antimuscarinics were compared with non-users. Patients were 96% male and elderly (~21% over the age of 85). Around 75% were taking oxybutynin IR; most of the remainder took another IR product (proportion per drug not stated). Key outcomes were reported separately for oxybutynin IR users.

The study assessed fractures, cognition, improvements in urinary incontinence and quality of life. Patients on antimuscarinics were at higher risk of fractures: Hazard Ratio (HR) =3.67 (95% CI 1.46 to 9.34) as compared with non-users. Risks for any fracture were also elevated: HR=2.64 (95% CI 1.37 to 5.10). Oxybutynin users also had an increased hip fracture risk compared with non-users: HR=4.89 (95% CI 1.79 to 13.44), and of any fracture: HR = 2.78 (95% CI 1.31 to 5.89).

For all bladder antimuscarinic drug users, the number needed to harm was calculated to be 36 (95% CI 12-209) for hip fracture at 90 days.

This was very similar to the number needed to treat for at least partial improvement in urinary incontinence (from at least 'frequent' to 'occasional' or 'occasional' to 'none'): number needed to treat = 32 (95% CI 17 to 125).

No effect was observed on cognition, but the scale used is highly correlated with MMSE, and may not be sensitive to mild cognitive changes (see section below on cognition).

Moga 2013 provides an important addition to the current body of research on drugs for OAB, as it addresses a little researched patient population: elderly men in nursing homes, many of whom

had multiple morbidities. The results raise a strong note of caution about use of antimuscarinics by elderly male nursing home residents, given the observed increased in hip fracture risk.

The second controlled cohort study, Movig 2001, used community pharmacy records in Tilburg, the Netherlands, to compare new users of oxybutynin or flavoxate (N=742), using new prescriptions for benzodiazepines or antipsychotics over a 2-year period as indicators of neuropsychiatric adverse effects. Flavoxate was used as a comparator because of lack of evidence of central nervous system (CNS) effects. No differences were found, but this is an indirect measure of adverse events that was unlikely to have captured all events.

Uncontrolled cohort analyses and case series

Four uncontrolled cohort analyses met inclusion criteria: a one-year open-label study of oxybutynin (OXY) ER 5 to 20mg/day in urge or mixed incontinence (Diokno 2002); a 12-week open-label study of OXY TDS 3.9mg/day in women (CONTROL 2012; in FDA advisory committee report; Merck, unpublished) a six-month open-label study of OXY TDS 3.9 mg (Newman 2008; Pizzi 2009); and a 3-month open-label study of OXY IR 7.5mg to 15mg/day in women (Amarenco 1998).

Diokno 2002 (N=1067) was a flexible dose study of oxybutynin ER over a one-year period of use in a mainly female sample (85%) with a mean age of 64. There was a strong dose response for dry mouth: OXY ER 5mg (12%); OXY ER 10mg (17%), OXY ER 15mg (21%); OXY ER 20mg (28%). Improvement in patients' self-assessed bother by urinary symptoms failed to demonstrate a similar dose-response relationship, based on a single question on a 0-100 visual analogue scale.

CONTROL 2012 (N=785) is an unpublished open-label 12-week study simulating over-the-counter (OTC) use of OXY TDS 3.9mg in women with OAB, described in US FDA materials for an advisory committee meeting. (CONTROL 2012) The primary outcome measure was the proportion failing to respect labeled instructions. Of 727 women completing diaries, 141 (19.1%) had symptoms indicating they should discontinue use (new or worse symptoms), 74.5% of whom continued use regardless. Following a mitigation strategy by the sponsor, 25 (17.7%) continued use. Patients aged ≥ 65 with new or worse symptoms had high initial ongoing use (83%). Although this study raises concerns about inappropriate OTC use, and the advisory committee voted against an OTC switch, the U.S. FDA has agreed to an OTC switch for OXY TDS 3.9mg in women.

Newman 2008 describes a subgroup of older patients in a 6-month study (N=2878 in total, 90% female; 699 aged ≥75). One fourth had lack of efficacy to previous treatment, but results are not presented separately. In total, 14% had application site reactions and 16.5% withdrew due to adverse events. Amarenco 1998 describes a 3-month follow up of French women initiating treatment with OXY IR 7.5mg to 15mg/day (N=1701). Overall, 8% had dry mouth and 11% had AE in total. Only 49 (3%) withdrawals are noted, which suggests a per protocol analysis, rather than the population initially enrolled.

Three case series are published (Jonville 1992; Gish 2009; 't Veld 1998) describing spontaneous ADR reports in France, the U.S. and the Netherlands, respectively, for oxybutynin. Jonville 1992 mainly highlights a signal of higher rates of pediatric CNS ADR reports. The formulation is not specified but the 1992 and 1998 studies are likely oxybutynin IR. Gish 2009 combines all oxybutynin formulations but reports separately for patients ≥60: confusional state, hallucination and sedation were the most commonly reported CNS AE; in younger patients sedation was the most common CNS AE followed by anxiety. The lack of denominators for spontaneous ADR reports and under-reporting limits interpretation to exploratory signals.

Conclusions
None of the observational studies compare effects of different formulations of the same drug. Moga 2013 provides an important note of caution concerning falls with oxybutynin IR, especially in frail, elderly men. Diokno 2002 found a strong dose-response for dry mouth with oxybutynin ER over one year of use, and a lack of dose response for self-perceived symptom abatement.

Additional Regulatory data
Two Periodic Safety Update Reports (PSURs) were available, for February to July 2012 for oxybutynin ER and IR and an annual summary report (February 2011 to February 2012) for oxybutynin gel and oxybutynin TDS. For oxybutynin ER, serious unlisted CNS events included amnesia, cognitive disorder, mental impairment, dementia, confusional state, hallucinations and mental status change. [Unlisted events are not listed in product monographs or safety information.] For oxybutynin IR, cognitive impairment and depression were identified as events requiring ongoing monitoring. The most common serious unlisted cardiac events for oxybutynin ER and IR were arrhythmias. Intestinal obstruction and intestinal ischemia have been reported for oxybutynin ER, and a case of severe constipation (a serious adverse event) in an 84 year-old woman. Falls and fractures were reported for both the ER and IR formulations.

For oxybutynin gel and TDS, only a few months of use were covered per product. There were 3 SAE reported for oxybutynin TDS in elderly patients: cognitive disorder/hallucination/anxiety/ disorientation and Parkinson's in a 92 year-old man; impaired walking (abasia) in a 78 year-old woman, and anuria/painful vaginal mucosal blistering in an 84 year-old woman. For oxybutynin gel, CNS AE included dizziness, somnolence, blurred vision (listed); and hallucination, insomnia, nightmare, ageusia, dysgeusia, burning sensation and sensory disturbance (unlisted). There were many cases of application site reactions for both formulations.

Health Canada's vigilance database includes 250 reports for oxybutynin, 94 serious. Formulations identified in the serious reports were: ER (12), oxybutynin gel (4), oxybutynin TDS (5) and the rest were either oxybutynin IR or ER but it was not possible to distinguish which, based on the information in the reports. Four deaths are described: 2 suicides, 1 dysuria/neoplasm/increased prostate-specific antigen, and 1 severe constipation/intestinal obstruction (Canada Vigilance Adverse Reaction Online Database).

Q1 Discussion and conclusions

Q1a. Do extended-release formulations of oxybutynin provide a therapeutic advantage over oxybutynin IR?

Comparative trials were available for oral oxybutynin ER versus oxybutynin IR, and oxybutynin TDS vs. oxybutynin IR. There were no direct comparator trials for oxybutynin gel.

Oral ER formulations vs. oxybutynin IR: The available RCT data are all short-term. Trials were under-powered for all-cause mortality and serious adverse events. Harms were incompletely reported. There was no statistically significant difference in withdrawals due to adverse events (WDAE; 5 trials; N=658) or on total AE (2 trials; N=193). Fewer patients on oxybutynin ER experienced dry mouth: risk difference 8% (95% CI -1% to -17%), 5 trials; N=658.

Quality of life (condition-specific), improved less on oxybutynin ER based on total UDI and Urge-UDI scores were reported in two trials (Barkin 2004; Minassian 2007). The mean difference was 0.23 points (95% CI 0.03 to 0.44) and may be below a clinically relevant threshold; total IIQ

score in Barkin 2004 and five Urge-IIQ domain scores in Minassian 2007 did not differ between formulations.

Effect on incontinence episodes did not differ. Only one trial reported on urgency, which did not show a difference between formulations (insufficient evidence). No trials reported on nocturia.

Interpretation of data is limited by the enrolment of participants with proven tolerability to oral oxybutynin in three of the five trials (Birns 2000; Versi 2000; Anderson 1999), a mix of doses in most trials, and the question of dose equivalence. Most trials used a similar range of doses for IR and ER formulations. Based on pharmacokinetics, equivalent doses would be slightly lower for the IR formulation. The strength of evidence is assessed as moderate for dry mouth, low for other specific adverse events and insufficient for all-cause mortality and serious adverse events.

An advantage has not been established for oxybutynin ER versus oxybutynin IR based on the available clinical trial evidence. There was an increase in dry mouth with oxybutynin IR (number needed to harm = 13) but condition-specific quality of life improved less on oxybutynin ER.

Transdermal formulations of oxybutynin vs. oxybutynin IR:
One dose-titration trial, designed as an equivalence trial, failed to show equivalence of oxybutynin TDS with oral oxybutynin for the *a priori* primary outcome, percentage of patients who were responders. Responders were defined as subjects who had a $\geq$ 30% reduction from baseline in incontinence episodes. This trial was under-powered to conclusively establish non-equivalence, however. At study end, most participants were on a higher-than-approved dose of oxybutynin TDS, limiting applicability to clinical practice. This raises questions about patient perception of effectiveness and whether higher-than-approved doses of oxybutynin TDS may also be used in clinical care.

The dose range for oxybutynin TDS and oxybutynin IR was not comparable in this study, and lower rates of anticholinergic adverse events such as dry mouth with oxybutynin TDS could have been due to the lower anticholinergic dose (range TDS 1-8mg/day versus IR 5-22.5mg total/day).

Based on this trial, there is insufficient evidence to conclude a therapeutic advantage of oxybutynin TDS over oxybutynin IR.

Oxybutynin gel vs. oxybutynin IR: no data are available.

Comparison with other systematic reviews: The findings of this review are generally consistent with two recent systematic reviews, Madhuvrata 2012 and Shamliyan 2012, as the same trials were included. For the comparisons of oxybutynin ER versus oxybutynin IR, Madhuvrata et al. reported that one trial had provided data for ‘cure’ (Birns 2000). We reported that no trials presented this outcome because the results for Birns 2000 was a partial reporting only – a daytime continence rate and not a 24 hour continence rate. This did not meet our definition of ‘cure’. We addressed the issue of dose equivalence to a greater extent than either of the previous reviews.

Supplemental Adverse Event data

Placebo-controlled trials in the elderly:
Lackner 2008 compared oxybutynin IR to placebo in elderly women with OAB who were residents of nursing home facilities (mean age 89). There were no differences in the development of delirium, agitation or change in MMSE in the treatment groups. MMSE is unlikely to detect

mild differences in cognition, and the Confusion Assessment Method, the primary outcome in Lackner 2008, was designed to detect acute changes of delirium.

Non-randomized studies:
None of the observational studies included in this review compare effects of different formulations of oxybutynin. Moga 2013 raises a note of concern about the potential for increased rates of falls and fractures in frail elderly men in nursing homes, particularly with oxybutynin IR. For all antimuscarinic drugs in this study, there was one additional hip fracture for every 36 men treated for 90 days, as compared with non-users matched for comorbidities. Most of this cohort used oxybutynin IR or other IR formulations of antimuscarinic drugs. However, whether similar risks occur with other formulations remains unknown. In Diokno 2002, over longer-term use (one year) a dose-dependent increase in dry mouth was observed with oxybutynin ER. CONTROL 2012 found that users of oxybutynin TDS may continue use despite lack of effectiveness or worsening symptoms, despite clear instructions not to do so.

Post-market surveillance and regulatory safety data: These data were not sufficient to distinguish the safety profiles of different formulations because of their many limitations including under-reporting.

Gaps in evidence
There are no comparative RCT data in the frail elderly, and the maximum duration of RCTs was 12 weeks, too brief to asses longer-term effects. For oxybutynin gel, no comparisons exist to other formulations. For oxybutynin TDS, a single trial was unable to establish equivalent effectiveness as compared with oxybutynin IR. This trial was under-powered and included a non-equivalent dose range. Thus insufficient comparative evidence exists for transdermal formulations to judge whether they provide a therapeutic advantage. For all formulations, there is a need to ensure that comparative RCTs are based on equivalent doses in order to adequately assess comparative benefit and harm. The available trial evidence for oxybutynin ER versus IR also fails to answer the question of better tolerability in patients who cannot tolerate oxybutynin IR, as three of the five trials only enrolled oxybutynin responders.

Q1b. Does tolterodine ER provide a therapeutic advantage over tolterodine IR?

One 12-week trial was available on tolterodine ER versus tolterodine IR (van Kerrebroeck 2001). Based on this trial (N=1021), there was no difference in SAE or WDAE. The trial was under-powered for mortality. The proportion of patients experiencing one or more AE was not reported. Tolterodine ER led to less dry mouth (risk difference 7%). There was no difference in reported efficacy outcomes (incontinence episodes). There are no comparative outcome data available on quality of life even though this was measured in the trial, and no available data on urgency or nocturia. There is insufficient evidence for harms and efficacy outcomes to conclude a therapeutic advantage for tolterodine ER. No long-term data are available (beyond 12 weeks).

Q2. New Evidence since the CDR Review(s)

There are no CDR reviews for the transdermal patch or oral extended-release formulations of oxybutynin. The approval of these products pre-dated the CDR process so this question is not applicable to those formulations. There are also no CDR reviews for the extended-release formulation of tolterodine. Approval of tolterodine ER pre-dates the CDR process.

Oxybutynin chloride gel: A CDR review on the gel formulation of oxybutynin chloride (Gelnique) was conducted in 2012. The CDEC recommendation, dated May 24, 2012, was that

oxybutynin chloride gel not be listed. Reasons cited were 1) the uncertain comparative clinical benefit in the absence of any RCTs that directly compare it to other pharmacological treatment, and 2) the absence of RCTs comparing the incidence of anticholinergic adverse effects (such as cognitive and neurological) between oxybutynin chloride gel and other oxybutynin products, particularly in the elderly (Common Drug Review 2012).

One placebo-controlled 12-week RCT (corresponding to Study OG05009, Staskin 2009) was included in the CDR clinical review. The submission also included subgroup analyses from that trial that showed the results for patients > 65 years did not differ between oxybutynin gel *and placebo* in reducing incontinence frequency or micturition. This is in contrast to the product monograph that states there were no observed differences in safety or effectiveness between older and younger patients.

For the current review, no direct comparator RCTs were identified for oxybutynin gel in OAB patients. The only direct comparator RCT was a healthy volunteer study (N=153) that compared short-term cognitive effects of oxybutynin gel to oxybutynin IR and placebo in healthy volunteers aged 60 or older (Kay 2012b). This study provides insufficient evidence to conclude a therapeutic advantage for oxybutynin gel over oxybutynin IR in regards to cognitive effects (see below). Because of this, the conclusions of the 2012 CDR review are not changed substantively.

There is insufficient evidence available with which to assess whether oxybutynin gel has a therapeutic advantage over oxybutynin IR or other comparators. This is consistent with the CDR review results and the rationale behind the CDEC recommendation.

Q3. Cognition

Four RCTs actively measured at least one cognitive outcome, two trials in patients with OAB, and two in healthy volunteers. Two of these trials compared different formulations: Minassian 2007 compared oxybutynin IR vs. ER in OAB patients and Kay 2012b compared oxybutynin gel with oxybutynin IR in healthy volunteers. The other two trials were placebo-controlled (Lackner 2008; Katz 1998).

Trials in OAB patients

Minassian 2007 is discussed above in the section on question 1. This 12-week, parallel-group trial (N=72) compared oxybutynin ER (5-10mg/day) to oxybutynin IR (7.5-15mg/day). It was terminated early due to recruitment difficulties after an interim analysis indicated that a much larger sample size than initially planned would be needed to detect a significant difference between formulations. The only cognitive outcome was MMSE, which did not show statistically significant differences between formulations. However, this screening tool is not likely to be sensitive to mild differences in cognition.

Lackner 2008 was a 4-week trial comparing oxybutynin ER 5mg/day with placebo. Cognitively impaired women residing in nursing home, aged > 65 (mean age 89 ± 6.2 years), and with OAB were enrolled. Participants had MMSE scores of 5 to 23 and randomization was stratified on the basis of MMSE score (11-23 and 5-10). The study primary outcome was mean change in the Confusion Assessment Methods (CAM) algorithm, used to measure delirium. No patient experienced delirium during the study. No difference was detected in median changes in MMSE before or after adjustment for potential confounders such as age and other medication use, but MMSE has poor sensitivity for mild CNS effects.

Reporting on harms was incomplete, with only the subset judged to be treatment-related reported. One patient on oxybutynin ER (3.9%) experienced urinary retention. There was no difference in the rate of falls between treatment groups. This study used the lowest recommended dose of oxybutynin ER, 5mg/day, and the changes assessed predominantly pertain to delirium, not all potential CNS effects. Risk of bias was unclear or high for most domains.

Trials in healthy volunteers

One 8-day, parallel group, placebo-controlled RCT (N=152; mean age 67-68) assessed the effects of oxybutynin topical gel (100mgday) and oxybutynin IR (15mg/day) on cognition (Kay 2012b). Participants had normal MMSE scores (~30). The identified primary outcome was delayed recall on the name-face association test (NFAT). In a pairwise analysis versus placebo, there was no significant effect of either oxybutynin gel or oxybutynin IR. The Misplaced Objects Test, a secondary outcome, showed a decline from baseline with oxybutynin IR whereas other groups showed an improvement (consistent with a practice effect). More participants on oxybutynin IR met or exceeded the minimal difference for reliable change (decline in score > 6 points) on HVLT-R immediate recall. However, on exploratory analyses (paired t-test) there were no statistically significant differences between oxybutynin IR and placebo or oxybutynin gel. Conclusions cannot be drawn on these post hoc analyses, which are hypothesis-generating only.

More participants on oxybutynin IR withdrew due to an AE: 5.8% vs. 0 on gel or placebo. Dry mouth was also much more frequent on oxybutynin IR: 73% vs. 6% on oxybutynin gel, risk difference 67% (53% to 81%).

Katz 1998 enrolled 12 healthy volunteers aged >65 in a single-dose, double-blind, placebo-controlled crossover trial vs oxybutynin IR 5mg or 10mg and an antihistamine (diphenhydramine 50mg). The higher dose is greater than the maximum recommended single dose. Washout period was 7 days between treatments. Significant oxybutynin effects ($P < 0.05$) were identified on 3 of 15 cognitive measures, all indicating some degree of impairment, after correcting for multiple comparisons. Diphenhydramine had no significant effects. This trial had methodological drawbacks such as lack of adequate blinding (drugs given in orange juice; taste may have been affected).

An additional non-randomized study**,** Moga 2003, a controlled cohort analysis among residents of U.S. Veterans Administration long-term care facilities, compared initial users of antimuscarinic drugs with non-users. The majority of patients were elderly males, with 21-22% over the age of 85. 10% had moderate to severe cognitive impairment at baseline; 75% of users were on oxybutynin IR. A cognitive performance scale that is highly correlated with the mini-mental state exam (MMSE) was used to assess cognition; range in scores 0 (intact) to 6 (very severe impairment). No difference was observed between patients on antimuscarinics and non-users. However, the scale is not likely to be sensitive to mild differences in cognition.

Conclusions

Taken together, these studies do not provide sufficient evidence with which to conclude one formulation of oxybutynin has a therapeutic advantage in terms of cognitive effects in the elderly. No RCTs were identified that assessed long-term cognitive effects of any formulation of oxybutynin.

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Chapter 9. Different Formulations of Antimuscarinic Drugs

Introduction
Research Questions:

Q1. In adults, including the frail elderly, do different formulations of oxybutynin (or another antimuscarinic drug) provide a therapeutic advantage, in terms of serious morbidity and/or mortality, urge incontinence, urgency, and nocturia, compared to oxybutynin immediate-release (IR) (or the IR form of another antimuscarinic drug) for the treatment of overactive bladder (OAB) syndrome or urge predominant mixed urinary incontinence?

Q2. Is there new evidence since the Common Drug Review Clinical Evidence reports that different formulations of oxybutynin (or another antimuscarinic drug) improve clinically relevant outcomes or have a better safety profile compared to oxybutynin IR (or the IR form of another antimuscarinic drug included in this review)?

Q3. In adults, particularly the elderly, do other formulations of oxybutynin (or another antimuscarinic drug) have less effect on cognition when compared to oxybutynin IR (or the IR form of another antimuscarinic drug included in this review)?

Methods: We searched OVID Medline, Embase, the Cochrane Incontinence Group Specialized Register and Cochrane databases without restriction on language or date, and included active comparator, randomized controlled trials (RCTs) for efficacy/effectiveness and short-term harms.

Placebo-controlled RCTs were included as supplemental information on harms if they exclusively enrolled elderly populations or assessed cognitive function. Non-randomized studies, case reports, and pharmacovigilance data were also included to supplement RCT data for information on infrequent harms, longer-term harms and populations not adequately represented in RCTs such as the frail elderly or people with comorbidities.

Outcomes were analyzed in order of clinical importance, with the greatest weight placed on all-cause mortality and serious adverse events (SAE) including cognitive impairment, patient-reported outcomes such as quality of life or perception of improvement, withdrawals due to adverse events as a measure of tolerability, and reduction in incontinence. Nocturia and specific adverse events such as dry mouth were also assessed.

Meta-analysis was carried out whenever possible, with random effects models used if there was evidence of heterogeneity, and sensitivity analyses carried out to assess the effects of differing patient characteristics, clinical setting, or dosage on outcomes where relevant and feasible. Risk of bias for RCTs was assessed according to standardized criteria and helped to inform conclusions. RCT quality assessment also included determining the generalizability of research findings to the patients most often encountered in clinical practice. Criteria used to appraise non-randomized studies included the assessment of techniques used to reduce the potential for confounding.

Background

This chapter reviews head-to-head comparisons of different formulations of the same product. Comparisons included in this review are the immediate-release (IR) versus extended-release (ER) formulations of oxybutynin, both oral and transdermal, and the immediate versus extended-

release oral formulations of tolterodine. Only one formulation of trospium (IR) and darifenacin (ER) were included in this review so formulation comparisons were not included for these drugs.

Oxybutynin

Oxybutynin chloride is a nonselective muscarinic receptor antagonist. It has slightly greater binding affinity for the M3 receptor (thought to be most important in bladder contraction) but binds all five muscarinic receptor subtypes. Oxybutynin also has a direct antispasmodic action on smooth muscle but this is much weaker than its anticholinergic properties and may not be clinically significant (Oxybutynin Chloride Immediate Release Product Monograph; Kennelly 2010). An additional local anesthetic and analgesic effect is claimed but is of unknown clinical significance.

Oxybutynin is available in one immediate-release and four extended-release formulations, two of which are transdermal (Table 1). The immediate-release formulation has been available in Canada since 1978. The most recent formulation, oxybutynin gel (Gelnique), was approved in Canada in 2012. Only the oxybutynin gel has undergone an assessment by the Common Drug Review.

Table 1. Oxybutynin Formulations

Formulation	Oxybutynin IR (Ditropan; Generic)	Oxybutynin ER (Ditropan XL)	Oxybutynin CR (Uromax)	Oxybutynin TDS (Oxytrol™)	Oxybutynin Gel (Gelnique™)
Indication	Symptoms associated with voiding in patients with uninhibited neurogenic and reflex neurogenic bladder (i.e., urgency, frequency, urinary leakage, urge incontinence, dysuria)	Symptoms of urge incontinence, urgency and frequency in patients with OAB	Symptoms of an overactive bladder including urge incontinence, urinary frequency, urgency or any combination of these symptoms	Treatment of OAB with symptoms of urge urinary incontinence, urgency and frequency	Treatment of OAB with symptoms of urge urinary incontinence, urgency and frequency
Formulation/ delivery system	Tablet	OROS (Osmotic pump)/tablet	Enteric coated tablet (cellulose matrix and sodium alginate)	Matrix layer adhesive patch	Alcohol-based gel
Administration	Best taken on an empty stomach	Must be swallowed whole	Must be swallowed whole	Apply to dry, intact skin on abdomen, hip or buttocks	Apply to abdomen, upper arms/shoulders, or thigh once daily. Rub into skin until dry.
Usual dose	5 mg bid-tid	5-10 mg once daily	Initial dose 10-15 mg once daily	3.9 mg/day patch applied every 3-4 days	1 gm 10% OTG applied daily
Maximum dose	20 mg/day	30 mg/day	20 mg/day	As above	As above

Metabolism	Bowel, liver 1st pass extraction CYP 3A4	Bowel, liver 1st pass extraction CYP 3A4	Bowel, liver 1st pass extraction CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4
DEO:OXY ratio	5.5:1	4.3:1	--	1.3:1	0.9:1

bid= twice a day; **CYP**= cytochrome P450; **DEO**= N-desethyloxybutynin; **OAB**= overactive bladder; **OXY**= oxybutynin; **tid**= three times a day
Ratios of DEO:OXY are from Kennelly 2010 and vary slightly from other estimates; other information obtained from Canadian Product Monographs

Oral formulations of oxybutynin undergo extensive first pass (pre-systemic) metabolism in the bowel and liver (Oxybutynin Chloride IR Product Monograph). Metabolism is predominantly due to the enzyme CYP 3A41, which is part of the cytochrome P450 system. An active metabolite, N-desethyloxybutynin (DEO), is equipotent to the parent compound. DEO has been hypothesized to account for some of the more common adverse effects. This has led to marketing claims based on differences in the amount of DEO produced by different routes of administration. Less DEO is produced with transdermal formulations (Table 1, DEO:OXY ratios). However, the exposure-response relationship of DEO is not well-characterized and this hypothesis is not proven. Because it is an active metabolite, DEO may also contribute to efficacy. The implication of the differences in production of DEO on clinical efficacy is unknown, and exploratory exposure-response analyses did not identify a significant correlation between oxybutynin or DEO concentrations and key efficacy endpoints for the transdermal formulations (Center for Drug Evaluation and Research NDA 22-204).

The immediate-release formulation has greater fluctuations in peak and trough plasma concentrations than longer-acting formulations, and wide interindividual variation.

Oxybutynin ER (Ditropan XL) uses a nondeformable delivery system (OROS) and has increased relative bioavailability of oxybutynin and lower relative bioavailability of DEO than oxybutynin IR (Oxybutynin Chloride Extended Release (Ditropan XL®) Product Monograph). Nondeformable formulations of other drugs have rarely been associated with intestinal obstruction (Bass 2002). A second controlled-release formulation (Uromax®) is also available (Oxybutynin Chloride Controlled Release (Uromax®) Product Monograph). Both long-acting oral formulations show less fluctuation in peak and trough plasma levels of oxybutynin and DEO than oxybutynin IR. Oral extended-release formulations have greater bioavailability of oxybutynin and less of DEO than oxybutynin IR.

Two transdermal formulations bypass first-pass gastrointestinal and hepatic metabolism, reducing the formation of the active metabolite DEO. The pharmacokinetics of the transdermal formulations are similar (Center for Drug Evaluation and Research NDA 22-204). Transdermal oxybutynin is absorbed through the skin and into systemic circulation by passive diffusion. Interindividual variation in skin permeability is about 20% (Oxybutynin Transdermal (Oxytrol™) Product Monograph). Only small amounts of CYP 3A4 enzyme are present in the skin so pre-systemic metabolism is low with these formulations.

In Canada, all formulations of oxybutynin, including transdermal preparations, are prescription only. In the U.S., the F.D.A. approved over-the-counter (OTC) use of oxybutynin TDS (Oxytrol, 3.9mg/day; Merck) in January 2013 for women (U.S. FDA Nov. 9, 2011). This decision overrode the recommendations of the nonprescription drug advisory committee, which had voted 6-5 in November 2012 against this partial OTC switch. The main reasons for the negative vote were the mainly elderly patient population and concerns about the anticholinergic adverse effects and

potential for drug interactions, the potential for consumers to misdiagnose themselves with OAB when the symptoms represent another condition requiring medical treatment, such as diabetes, urinary infection, or carcinoma in situ of the bladder, with negative consequences for health. OTC was not sought for men, likely due to overlap of symptoms with benign prostatic hypertrophy.

Tolterodine

Tolterodine is available in two formulations, immediate-release and extended-release. Comparisons of either formulation with other antimuscarinic drugs were reviewed in Chapter 5.

Q1. Comparative Harms and Benefits

Methods – see Chapter 2.

Results

Search Findings

A total of eight direct comparator RCTs were identified that compared different formulations of the same drug:

- 7 compared different oxybutynin formulations versus oxybutynin IR (Minassian 2007; Barkin 2004; Birns 2000; Versi 2000; Anderson 1999; Davila 2001; Kay 2012b
- 1 compared tolterodine ER versus tolterodine IR (van Kerrebroeck 2001)

Of the seven RCTs that compared oxybutynin formulations, one was a healthy volunteer study and is considered in Q3 only (Kay 2012b).

Of the six parallel-group trials on oxybutynin use in patients with OAB syndrome, five compared oral extended-release formulations with oxybutynin IR (Anderson 1999; Barkin 2004; Birns 2000; Davila 2001; Minassian 2007; Versi 2000,) and one compared the oxybutynin transdermal patch (TDS) with oxybutynin IR. There were no active comparator trials on clinical efficacy that compared oxybutynin gel with oxybutynin IR, or different extended-release formulations of oxybutynin with each other.

Nilsson 1997, an oxybutynin trial that had been included in Madhuvrata 2012, was excluded on the basis that the study was not randomized.

11 additional studies are included to further assess harms, including effects in the elderly and on cognition:

- 2 placebo-controlled RCTs (Lackner 2008; Katz 1998).
- 10 observational studies (Amarenco 1998; CONTROL 2012; Diokno 2002; Gish 2009; Hussain 1996; Jonville 1992; Moga 2013; Movig 2001; Newman 2008 (also reported in Pizzi 2009); 't Veld 1998)

Regulatory documents provided additional information on infrequent adverse events, labelling changes and safety advisories.

Direct Comparator RCTs

a. Different Formulations of Oxybutynin

1) **Oral Extended-Release Formulations vs. Oxybutynin IR**

Two different types of oral extended-release formulations were used, an osmotic pump (OROS) formulation (ER, Ditropan XL®) (Minassian 2007) and a controlled-release (CR, Uromax®)

formulation (Barkin 2004; Birns 2000; Versi 2000; Anderson 1999). These are jointly referred to as ER. Because their pharmacokinetics are similar, they are considered together although we distinguish the type in evidence tables if sufficient information has been provided. However, use of terminology in publications was not always consistent.

The five trials involved a total of 658 participants who were randomized to receive active drug. Four trials had a titration phase or flexible dose regimen with individual dose adjustment (Barkin 2004; Versi 2000; Anderson 1999; Minassian 2007). The fifth trial used fixed doses (Birns 2000) (Table 1).

Table 1. Total doses/day

Study	OXY ER Total dose/day	OXY IR Total dose/day	Comment
Anderson 1999	5-30 mg/day (Ditropan XL)	5-20 mg/day	Responders only enrolled
Barkin 2004	5-20 mg/day (Uromax) mean 12.4 mg ± 4.4 /day	5-20 mg/day mean 14.0 ± 5.3 mg/day	
Birns 2000	10 mg/day (fixed dose)	10 mg/day (fixed dose)	Responders only enrolled
Minassian 2007	5-10 mg/day	5-10 mg/day	
Versi 2000	5-20 mg/day (Ditropan XL)	5-20 mg/day	Responders only enrolled

Treatment duration was 2 to 12 weeks, with a stable-dose phase in each ranging from 1 week (Versi 2000) to 8 weeks (Minassian 2007). The longest trial, Minassian 2007, did not meet its enrollment goal and was terminated early.

Three trials had a screening phase in which participants' tolerability and responsiveness to oxybutynin IR was determined prior to randomization (Birns 2000; Anderson 1999; Versi 2000). Only patients known to be oxybutynin responders, and tolerant of the drug, were enrolled in these trials.

RCT study characteristics and outcomes are presented in Tables 1 and 2 in Appendix J.

Results are presented in order of a hierarchy of health outcomes with those outcomes most important to the patient higher on the list.

For dichotomous outcomes, a relative risk (RR) < 1 indicates that fewer events (beneficial or harmful) occurred in the group treated with the extended-release formulation.

1. All-cause mortality

Three trials (Birns 2000; Barkin 2004; Versi 200) (N=481) reported 0 events in each treatment group (either explicitly reported or inferred from an accounting of SAE). The other 2 trials did not report on this outcome.

2. Serious Adverse Events (SAE)

SAE were incompletely reported, with data available by treatment group for 3 of the 5 trials. In Birns 2000, there were 0 events in the oxybutynin ER group and 1 event (chest pain) in the oxybutynin IR group (1/66 or 1.5%) (Birns 2000). There were 2 other SAE in the screening phase of this study, during which all potential participants were treated with oxybutynin IR. Both events in the screening phase were chest pain.

SAE were available in an FDA review for two trials: Anderson 1999 – 1 SAE in total, in the oxybutynin IR group (1/115 or 0.8%): a subdural hematoma secondary to a fall while on study medication; Versi 2000 – 1 SAE in total, also in the oxybutynin IR group (1/52 or 1.9%): a small bowel obstruction in a patient with a history of a left colon resection for diverticulitis (Center for Drug Evaluation and Research 1998 NDA 20-897, Medical Review).

Barkin 2004 reported a total of 3 SAE (angina; accidental injury; allergic reaction) but did not specify the treatment group.

Based on the three trials reporting events by treatment group, there was no statistically significant difference between formulations. The trials were under-powered to assess SAE.

None of the trials reported on acute urinary retention; falls/fractures or cognitive impairment.

There were no identified events of gastrointestinal obstruction in patients using the OROS formulation (Ditropan XL). The deformable shell of the OROS formulation, which is excreted, has been reported in other drugs to rarely cause obstruction.

3. Withdrawals due to Adverse Events (WDAE)/Tolerability
WDAE were reported in all five trials. When combined (N=658), there were numerically fewer WDAE with oxybutynin ER compared with oxybutynin IR, but the difference was not statistically significant: RR 0.73 (95% CI 0.48 to 1.11), P=0.14.

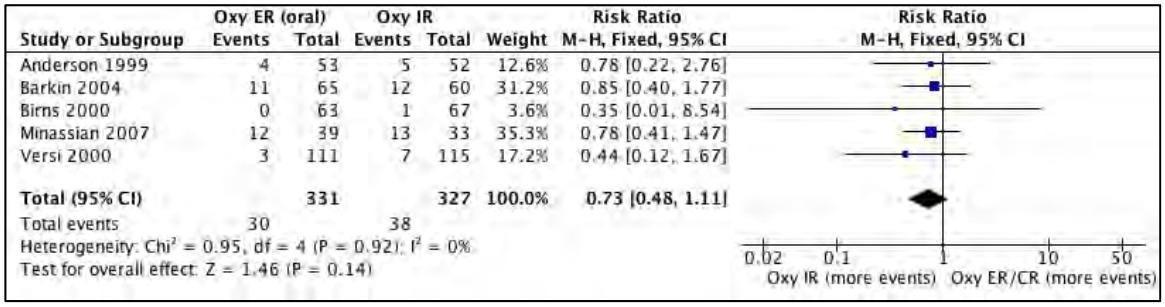

Figure 1. WDAE

4. Quality of life (QoL)
Two of the five trials (Minassian 2007, XL; Barkin 2004, Uromax or CR) reported on condition-specific quality of life. Minassian 2007 used two validated questionnaires, the Urge-Urogenital Distress Inventory (U-UDI) and the Urge-Incontinence Impact Questionnaire (U-IIQ) (Lubeck 1999).

The U-IIQ is a self-report condition-specific questionnaire, adapted from the IIQ, to assess the psychosocial impact of urgency incontinence or urgency predominant mixed incontinence on activities, travel, physical activities, feelings, relationships and sexual functioning (Lubeck 1999). Scales are scored 1-6 with higher scores reflecting greater impact or interference. The instrument may also include night bladder control items and satisfaction with treatment. Mean IIQ scores were reported for 5 domains (Table 2, Appendix J) (Minassian 2007). There was no difference between oxybutynin CR and oxybutynin IR.

The Urge-UDI, adapted from the Urogenital Distress Inventory, is a 9-item self-report questionnaire to assess the extent to which the patient is bothered by symptoms of urgency

urinary incontinence or urgency predominant mixed incontinence (Lubeck 1999). The items are averaged to form two scales, one summarizing urge symptoms and an overall score summarizing impact of mixed and urge symptoms, with both scales scored from 0 to 4. The higher the score, the more bothersome the symptom. Mean scores were reported, with improvement slightly less for oxybutynin ER.

Barkin 2004 used the original forms of the IIQ and UDI, which had predominantly been used in stress incontinence and also provided means on a 4-point scale (Hagen 2002; Shumaker 1994).

Combining the 2 trials for UDI total scores (N=159), there was a statistically significant difference between oxybutynin ER and oxybutynin IR, in favor of the IR formulation: MD 0.23 (95% CI 0.03 to 0.44), P=0.02. This is a modest difference in reduction of symptoms or bother, representing about 6% of the greatest possible change in score.

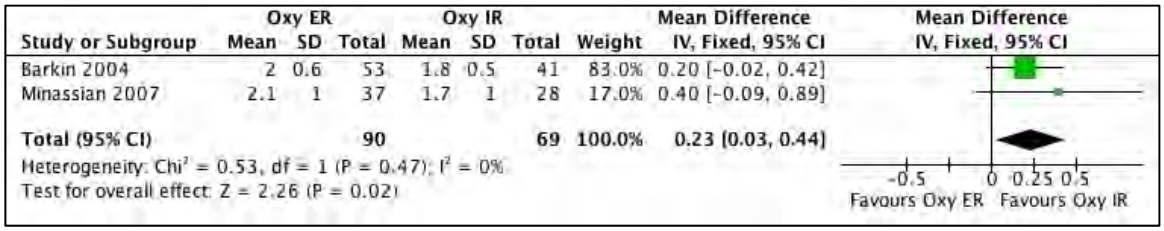

Figure 2. Condition-specific QoL (UDI and U-UDI)

5. Patient-Reported Perception of Improvement or Cure
None of the trials reported on this outcome.

6. Quantification of Incontinence Episodes
Cure or total dryness: No trials reported total dryness (lack of incontinence episodes over a specified period of time, usually assessed in a bladder-diary). Birns 2000 (N=125) reported the proportion of participants who had *daytime* dryness at study end. Oxybutynin ER and oxybutynin IR did not differ statistically: oxybutynin ER 33/ 61 (53%) vs. oxybutynin IR 38/64 (58%), RR 0.91 (95% CI 0.67, 1.24), P=0.55. For night-time dryness, there was no statistically significant difference between formulations (data were not provided). Continence over a 24 hour period was not reported.

Reduction in incontinence episodes: All 5 trials assessed the outcome of incontinence episodes, with 4 trials reporting either the number of episodes at study end or reduction from baseline (Minassian 2007; Versi 2000; Anderson 1999; Barkin 2004). Three of these did not provide useable data for a meta-analysis because medians were reported or a measure of variation was omitted (Minassian 2007; Versi 2000; Anderson 1999). The 5th trial (Birns 2000) failed to provide data. None of the trials reported a statistically significant difference in reduction in incontinence episodes between drugs (Table 3, below). The mean between-treatment difference (MD) for Barkin 2004 (N=94) was not statistically significant (per protocol analysis): MD 0.62 episodes per day (95% CI -0.20 to 1.44), P=0.14.

Anderson 1999 reported a per protocol analysis in the publication. This was an equivalence trial, and recalculated 95% confidence intervals for an intention-to-treat analysis, conducted by the FDA reviewer, were -2.93 and 6.35; the upper limit of the CI exceeded the predetermined margin of 4 episodes for equivalence, in both the ITT and per protocol analyses. This trial thus did not show equivalence between oxybutynin XL (ER) and oxybutynin IR (Center for Drug Evaluation and Research 1998 NDA 20-897).

Table 3. Incontinence Episodes Oxybutynin ER vs. Oxybutynin IR

Trial	Measure	Baseline		Study End		P-value for Difference between Formulations at Study End§
		OXY ER	OXY IR	OXY ER	OXY IR	
Minassian 2007	Median incontinence episodes/24 h (IQR)	2 (0-4)	1 (0-3)	1 (0-2) (N=34)	0 (0-1) (N=26)	P=0.6
Barkin 2004	Mean ± SD/week	24.3 ± 19.0 per week [=3.5 ± 2.7/ day]	23.0 ± 17.7 per week [=3.3 ± 2.5/ day]	10.4 ± 18.8 per week [=1.49 ± 2.69/ day] p<0.001 vs baseline	6.1 ± 8.8 per week [=0.87 ± 1.26/ day] p<0.001 vs baseline	P=0.404
Versi 2000	Mean /week (mean % change from baseline)	18.6 (SD NR)/ week	19.8 (SD NR)/ week	2.9/ week (-83%) p<0.001 vs. baseline	4.4/ week (-75%) p<0.001 vs. baseline	P=0.36
Anderson 1999	Mean/ week (% change from baseline)	Mean 27.4 ± SD 24.0 per week* [=3.9 ± 3.4 per day]	Mean 23.4 ± SD 16.3 per week* [=3.3 ± 2.3 per day]	-4.8 (-84%)	-3.1 (-88%)	P=0.7
Birns 2000	Median change in daytime episodes of incontinence	Data not provided. "No statistically significant difference between the treatments".				
	Median change in night-time episodes of incontinence	Data not provided. "No statistically significant difference between the treatments".				

* urge incontinence episodes reported (total incontinence episodes also reported in publication); § as reported by study investigators; **ER**= extended-release (either controlled-release or OROS formulation); **IR**= immediate-release; **IQR**= interquartile range; **NR**= not reported; **SD**= standard deviation.

7. Nocturia

No trials provided data on this outcome. One trial (Birns 2000) measured night-time incontinence episodes and night-time 'voluntary' voids (i.e., getting up to go to the toilet) and reported no statistically significant differences between oxybutynin ER and oxybutynin IR. However, no data were provided to support these conclusions.

8. Urgency episodes

One of the 5 trials (Barkin 2004, N=84) reported on urgency episodes in a per protocol analysis. There were no statistically significant difference between oxybutynin ER and oxybutynin IR: MD 0.40 (95% CI -0.02 to 0.82), P=0.06. Each formulation showed a statistically significant difference from baseline.

9. Total AE:
Only 2 of the 5 trials reported total AE (Birns 2000; Minassian 2004). When pooled (N=193), the difference in total AE rates between formulations was not statistically significantly different: RR 0.85 (95% CI 0.67 to 1.07), P=0.17.

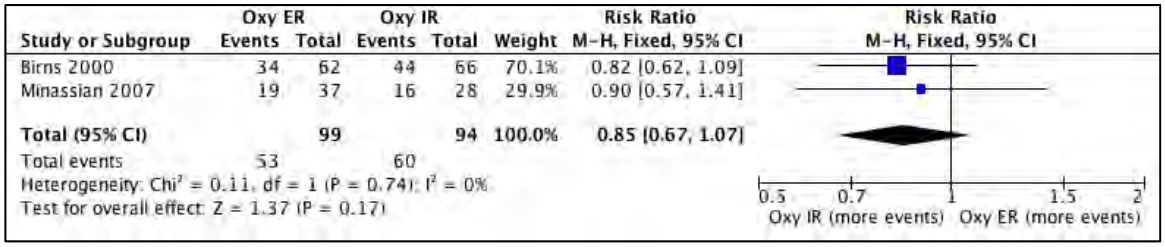

Figure 5. Total AE: proportion of patients experiencing one or more AE

10. Specific AE
Dry mouth:
All 5 trials reported the incidence of dry mouth. When combined (N=652), 48% of patients taking oxybutynin ER experienced dry mouth compared with 59% of patients taking oxybutynin IR: RR 0.86 (95% CI 0.75 to 0.98), P=0.02; absolute risk difference -8% (-17% to -1%).

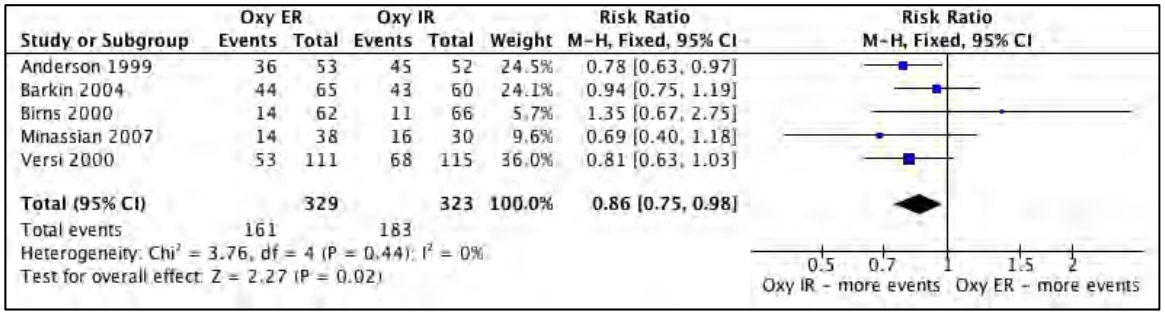

Figure 6. Dry Mouth

Nausea:
Two trials reported this adverse event (Anderson 1999; Barkin 2004). When combined (N=230), there was no difference between formulations: RR 0.66 (95% CI 0.34 to 1.26), P=0.21.

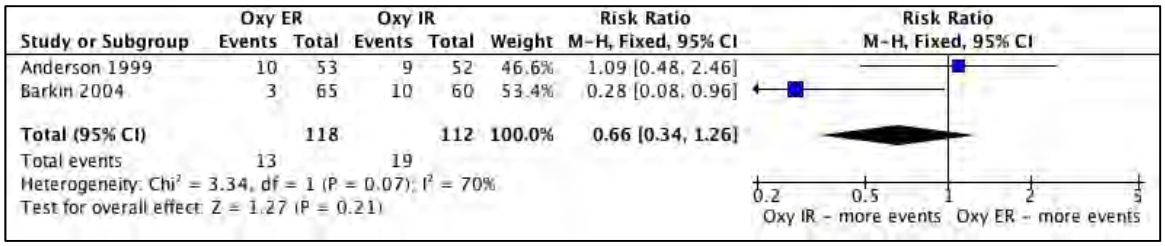

Figure 7. Nausea

Constipation:
Two trials (N=230) reported the incidence of constipation (Barkin 2004; Anderson 1999). There was no statistically significant difference between treatment groups: RR 0.93 (95% CI 0.56 to 1.56), P=0.79.

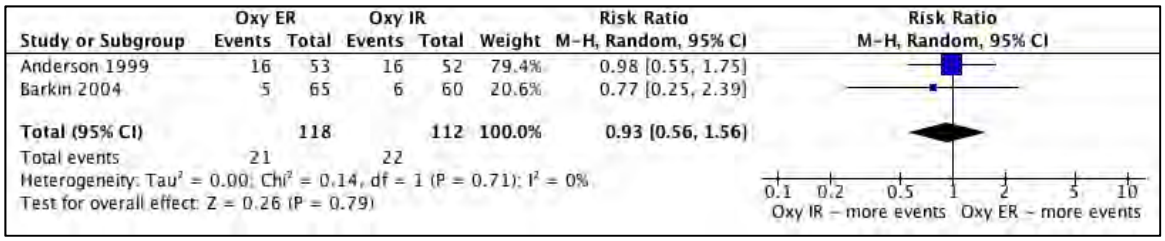

Figure 8. Constipation

Blurred vision:
Two trials (N=233) report blurred vision rates with no statistically significant difference between treatment groups: RR 1.58 (95% CI 0.82 to 3.05), P=0.17 (Anderson 1999; Birns 2000).

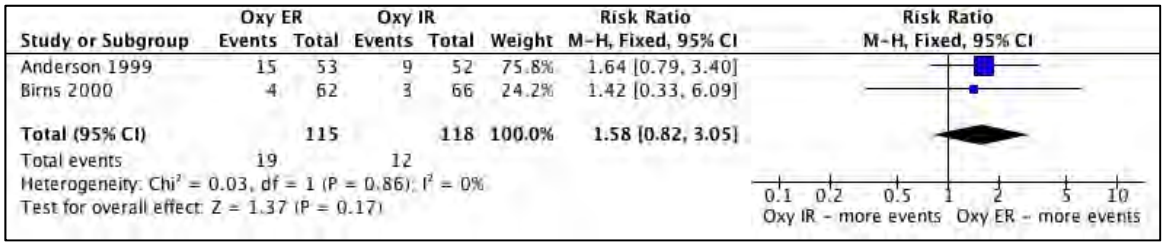

Figure 9. Blurred vision

Dizziness:
Three trials reported this adverse event (Barkin 2004, Birns 2000, Anderson 1999). When combined (N=358), there was no statistically significant difference although numerically fewer events with oxybutynin ER: RR 0.64 (95% CI 0.40 to 1.01), P=0.05.

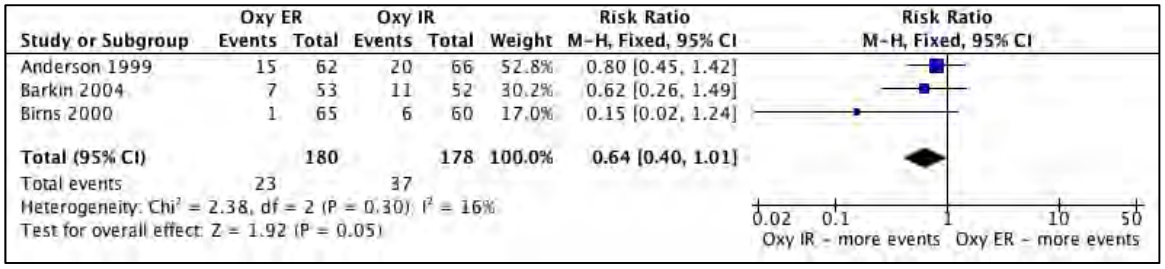

Figure 10. Dizziness

Headache:
Two trials (N=253) reported numerically fewer headaches in the oxybutynin ER group, but the difference was not statistically significant: RR 0.48 (95% CI 0.22 to 1.05), P=0.07.

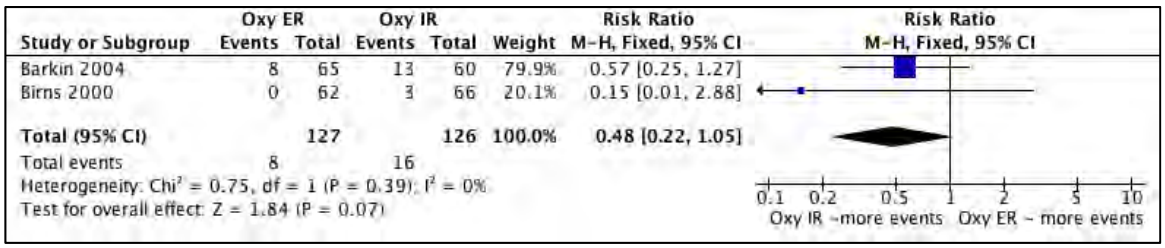

Figure 10. Headache

Central nervous system AE: CNS events were not reported other than dizziness, headache (see above) and taste perversion in one trial (Barkin 2004), with no significant difference between oxybutynin ER and oxybutynin IR.

ECG: Two trials (Anderson 1999; Versi 2000) assessed ECGs at baseline and study end, and had available results (Center for Drug Evaluation and Research NDA Review 20-897). For Anderson 1999, there were no statistically significant differences for PR, QRS or QT intervals within or between treatment groups from baseline to study end. 13/53 (25%) of patients on oxybutynin ER and 8/52 (15%) on oxybutynin IR had ECG changes at study end. This was not a statistically significant difference for the small sample size. Sinus bradycardia occurred in 5 patients (10%) on oxybutynin ER (Ditropan XL) and 1 patient (2%) on oxybutynin IR. 3 patients (6%) on oxybutynin IR developed first degree atrioventricular block compared to 1 (2%) in the oxybutynin IR. The differences were not statistically significant and the sample size was small. Sinus bradycardia and first degree heart block are not ECG changes expected with anticholinergic drugs. Other abnormalities occurred such as premature atrial contractions, atrial fibrillation, premature ventricular contractions but were not reported on in detail (Center for Drug Evaluation and Research NDA Review 20-897). None of these changes were reported to have resulted in clinical effects.

In Versi 2000, 3/111 (3%) patients on oxybutynin ER had ECG changes vs. 1/115 (1%) patients on oxybutynin IR (Center for Drug Evaluation and Research NDA Review 20-897).

When data from the two trials were combined for the total numbers of patients with ECG changes, there was no statistically significant difference between formulations.

11. Urodynamics/clinician measures

No trial reported on maximum cystometric volume or volume at first contraction. In the 2 studies reporting post-void residual volume (Anderson 1999; Minassian 2007), there was no difference between either the median (Minassian 2007) or the mean (Anderson 1999) post-void residual volume (Table 2, Appendix J). For Anderson 1999, the mean post-void residual volume was ~15-18 mls in each group.

12. Volume voided per micturition:

Two of the 5 trials reported on mean volume voided (Barkin 2004; Anderson 1999). There was no statistically significant difference between treatments in the individual trials. For Anderson 1999, the mean difference in favour of oxybutynin ER was 9 mls (95% CI -52 to 70). For Barkin 2004, the difference was in favor of oxybutynin IR (ER 25 mls vs. IR 40 mls, a mean difference of 15 mls). Because a measure of variation was not reported in Barkin 2004, a meta-analysis was not conducted for the difference in change from baseline. When the 2 trials (N=187) were combined for mean volume voided at study end, mean volume was higher for oxybutynin IR: oxybutynin ER vs IR, MD -45 mls (95% CI -79 to -11 mls).

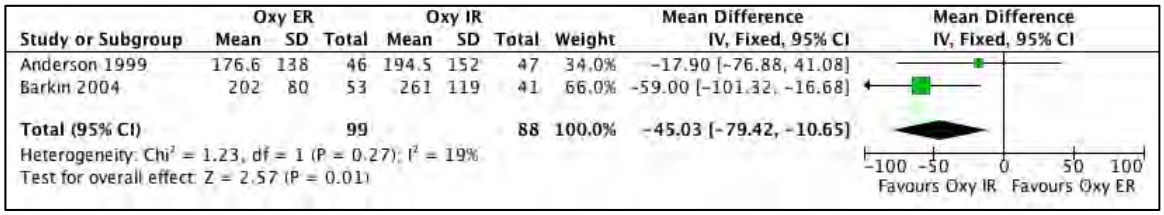

Figure 11. Mean volume voided at study end

Critical Appraisal: Oxybutynin ER vs. Oxybutynin IR

Risk of bias/other quality assessment

As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity (Table 3, Appendix J). For each included criterion, there is research evidence of a systematic effect on clinical trial outcomes (i.e., the ability to bias research results). Where feasible, we assessed the internal validity based on all available data and supplemented publication data with data available from regulatory sources, as indicated.

Minassian 2007 was open-label and at high risk of bias related to patient or physician behaviour (performance bias) or detection bias related to outcome assessment (Minassian 2007). This trial was also at high risk for incomplete outcome data due to a high drop-out rate. The trial failed to meet its enrolment goal and was under-powered for its primary outcome, incontinence. It was stopped early because of recruitment difficulties and also because an interim analysis revealed a much larger sample than had been estimated would be required to detect a significant difference between treatments. The trial did not describe its method of randomization but was at low risk of bias for allocation concealment (even though it was open-label) as it used a central telephone service.

None of the other four trials were rated at low risk of bias across all features. Only one trial (Birns 2000) had a low risk of bias for randomization. The other three provided insufficient information with which to assess the randomization process (Barkin 2004; Versi 2000; Anderson 1999). Versi 2000 adequately concealed allocation (low risk of bias), Barkin 2004 and Anderson 1999 provided insufficient information with which to assess allocation concealment, and Birns 2000 was at high risk of bias for this domain based on potential predictability of blocks of two. None of the blinded trials specifically described blinding of outcome assessors.

Anderson 1999 and Barkins 2004 were assessed to have high risk of bias for incomplete outcome data, based on per protocol analyses (Barkin 2004; Anderson 1999). Versi 2000 also conducted a per protocol analysis but had few drop-outs so was rated at unclear risk of bias. For selective outcome reporting, Barkin 2004 was rated as having high risk of bias. The publications of Anderson 1999 and Versi 2000 were also at high risk of bias for selective outcome reporting. However, based on the full reporting of data in the FDA review to supplement individual trial publications, there was low risk of bias (Center for Drug Evaluation and Research NDA 20-897).

Applicability of trial results (external validity)

Patients were highly selected for these trials, limiting applicability to populations encountered in clinical practice. Three of the five studies enrolled oxybutynin responders only and conducted a trial phase for responsiveness prior to randomization (Versi 2000; Anderson 1999; Birns 2000; Center for Drug Evaluation and Research Review NDA 20-897). Versi 2000 reported that only one patient was excluded because of non-responsiveness, of a total of 191 excluded during screening. In Birns 2000, 17 withdrew prior to randomization, 10 because of adverse events. In Anderson 1999, 158 were screened and 105 were enrolled; the number of non-responders, those experiencing AE, and the number who underwent a therapeutic responder screening trial are not reported.

One trial exclusively enrolled females > age 65 (Minassian 2007). However, this trial was under-powered and terminated early. The proportion of participants ≥ age 75 in this group of trials is not known.

The majority of participants were female, limiting applicability to men who can have symptoms that overlap with OAB but are due to benign prostatic hypertrophy, a condition for which oxybutynin is not efficacious.

Comparator/dose choice: The majority of trials (4/5) allowed individual dose adjustment, similar to that in clinical practice, with guidelines for titration that generally reflected the goal of maximizing efficacy while minimizing AE. However, mean doses are not reported for 3 of the 4 trials that used a range of doses, and the use of a mixture of doses obscures dose-responses for harms. The dose range was generally equivalent for IR and ER formulations, raising the issue of dose equivalence (see below).

One study used a fixed dose comparison of 10 mg oxybutynin CR (Uromax) versus oxybutynin 5 mg b.i.d. (10mg/day total). From a clinical pharmacologic perspective, evidence from a healthy volunteer pharmacokinetics study suggests that the most appropriate IR oxybutynin comparator for oxybutynin CR would be a slightly lower total daily dose of the IR formulation (for example, 5-7.5mg total/day for IR vs. 10mg/day for ER) (Reiz 2007). When equal total daily ingested doses are used, one might expect such trials to favour the CR drug in terms of (fewer) anticholinergic AE i.e., the IR treatment group is receiving a higher anticholinergic dose. On the other hand, this dose non-equivalence may favour the IR formulation in terms of efficacy. This also applies to the comparison of equal doses of the other extended-release formulation to oxybutynin IR (Center for Drug Evaluation and Research NDA 20-897 Clinical Pharmacology Review).

Harms: Because patients were highly selected, particularly in the three trials that enrolled oxybutynin responders who were known to tolerate the drug, harms data are unlikely to fully reflect the experience of patients in usual clinical practice settings. For Anderson et al, an anticholinergic effects questionnaire was used (Center for Drug Evaluation and Research FDA Medical Review 20-897) in addition to spontaneous reporting. While this might provide more accurate reporting, the participants had all demonstrated tolerability to oral oxybutynin IR previously. For Versi 2000, AE were also actively solicited although method was not described (Center for Drug Evaluation and Research FDA Medical Review 20-897).

Industry sponsorship: All five trials were sponsored by industry. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For comparator trials within a drug class, industry sponsorship has also been reported to predict benefit (Bero 2007).

Overall results – Oral Oxybutynin ER vs. Oxybutynin IR

Results are summarized, below, in Table 4. The available RCT data are all short-term. Trials were under-powered for all-cause mortality and serious adverse events. Harms were incompletely reported. Based on two trials (N=193), there was no statistically significant difference in the proportion of patients experiencing one or more AE (Birns 2000; Minassian 2007). Fewer patients on oxybutynin ER experienced dry mouth (risk difference 8%), based on five trials. Interpretation of harms data is limited by the enrolment of participants with proven tolerability to oral oxybutynin, in three of the five trials (Birns 2000; Versi 2000; Anderson 1999), a mixture of doses in most trials, and the question of dose equivalence. Most of the trials used a similar range of doses for the IR and ER formulations. Based on pharmacokinetic considerations, for IR and ER doses to be comparable, a slightly lower dose of the IR formulation should be used. The strength of evidence is assessed as moderate for dry mouth, low for other specific adverse events and insufficient for all-cause mortality and serious adverse events.

Quality of life (condition-specific), based on total UDI and Urge-UDI scores reported in two trials (Barkin 2004; Minassian 2007) improved less on oxybutynin ER than IR. This is a modest difference in reduction of symptoms or bother, representing about 6% of the greatest possible change in score. Using another quality of life condition-specific measure, in individual trials, there was no statistically significant difference in total IIQ score in Barkin 2004, and no difference in the five domain scores of IIQ reported by Minassian 2007. These could not be combined in a meta-analysis because the data were reported in different ways for the two trials.

Improvement in incontinence episodes was similar between drugs in the five trials. A meta-analysis could not be conducted on this outcome as some trials reported medians rather than means or did not report a measure of variation (moderate strength of evidence). Only one trial reported on the outcome urgency, which did not show a difference between formulations (insufficient evidence). No trials reported on nocturia.

Table 4. RCT Clinical Outcomes Oxybutynin ER vs. Oxybutynin IR

Outcome	No. of Studies (N)	OXY ER vs. OXY IR RR or MD [95% CI]	OXY ER vs. OXY IR Absolute Risk difference [95% CI]	Summary
All-cause mortality	3 trials (481), 0 events	--	--	Short-term trials under-powered (0 events); no long-term data
SAE	3 trials (460), 3 events in OXY IR group	RR 0.34 [95% CI 0.05 to 2.14]	--	Trials under-powered (3 events total); no statistically significant difference detected
QoL	2 trials (159)	MD 0.23 [95% CI 0.03 to 0.44]	--	Less improvement with OXY ER (on UDI total score)
WDAE	5 trials (658)	RR 0.73 [95% CI 0.48 to 1.11]	--	Numerically fewer WDAE with OXY ER but difference is not statistically significant
Patient-reported improvement	0 trials	--	--	No data available

Continence (Dryness Rate)	0 trials	--	--	No data available
Incontinence episodes per 24 h Mean reduction from baseline	5 trials, useable data for 1 (94)	Barkin 2004: MD 0.62 [95% CI -0.20 to 1.44]	--	No difference between OXY ER and OXY IR, based on 5 individual trials, no meta-analysis conducted
Urgency per 24h Mean reduction from baseline*	1 trial (94)	MD 0.40 [95% CI -0.02 to 0.82]	--	No difference between OXY ER and OXY IR
Nocturia	0 trials	--	--	No data available
Total AE	2 trials (193)	RR 0.85 [95% CI 0.67 to 1.07]	--	No difference between OXY ER and OXY IR
Dry mouth	5 trials (652)	RR 0.86 [95% CI 0.75 to 0.98]	RD -8% [95% CI -17% to -1%]	8% fewer patients on OXY ER experienced dry mouth
Nausea	2 trials (230)	RR 0.66 [95% CI 0.34 to 1.26]	--	No statistically significant difference
Constipation	2 trials (230)	RR 0.93 [95% CI 0.56 to 1.56]	--	No statistically significant difference between OXY ER and OXY IR
Blurred vision	2 trials (233)	RR 1.58 [95% CI 0.82 to 3.05]	--	No statistically significant difference
Dizziness	3 trials (358)	RR 0.64 [95% CI 0.40 to 1.01]	--	No statistically significant difference
Headache	2 trials (253)	RR 0.48 [95% CI 0.22 to 1.05]	--	No statistically significant difference

AE= adverse events; **CI=** confidence intervals; **ER**= extended-release; **IR**= immediate-release **MD**= mean difference; **ND**= not done; **OXY**= oxybutynin; **QoL**= quality of life; **RD**= (absolute) risk difference; **RR**= relative risk; **SAE**= serious adverse events; **WDAE**= withdrawals due to adverse events

2) Transdermal Formulations of Oxybutynin vs. Oxybutynin IR

Two trials evaluated a transdermal formulation of oxybutynin (Davila 2001; Kay 2012b). Kay 2012b evaluated cognitive effects and is considered in Q3 only.

i) Oxybutynin Transdermal Patch (TDS) vs. Oxybutynin IR

Davila 2001 (Study 96017) was a 6-week efficacy-equivalence study that compared oxybutynin IR with transdermal oxybutynin (TDS). The trial enrolled oxybutynin responders only (N=76). Study characteristics and outcomes are presented in Tables 1 and 2 in Appendix J. The dose of oxybutynin TDS was 1 to 4 13cm^2 patches of TDS. During the study, the dose range was ~1-8 mg/day for transdermal oxybutynin (Center for Drug Evaluation and Research NDA 21-351). The recommended dose is 3.9 mg/day. Of 38 patients treated with oxybutynin TDS, the majority at study end (26 or 68%) were on oxybutynin 52cm^2 TDS (=5.2mg/day), above the recommended dose. At weeks 4-6, 10 patients were on oxybutynin 39cm^2 (=the recommended dose, 3.9mg/day) and 2 on 26cm^2. Oral oxybutynin IR ranged from 5 to 22.5 mg/day (Center for Drug Evaluation and Research NDA 21-351). Dose initiation was one of three levels, corresponding to the

patient's prior stable daily oral dose of oxybutynin. Dose adjustment was at 2 weeks, on the basis of severity of anticholinergic adverse effects.

Results are presented according to our hierarchy of outcomes, with outcomes of greatest clinical importance higher up in the hierarchy. For dichotomous outcomes, if a relative risk (RR) is < 1, it means fewer people experienced events (beneficial or harmful) in the oxybutynin TDS group.

1. All-cause mortality
There were no deaths on study drug. An 86 year old female died of an apparent heart attack 3 ½ months after screening and during initial washout phase of oxybutynin (Center for Drug Evaluation and Research NDA Review 21-351).

2. Serious Adverse Events (SAE)
No data on SAE were available for this study.

3. Withdrawals due to Adverse Events (WDAE)
There were 2 withdrawals, in total, and 1 WDAE (Center for Drug Evaluation and Research NDA 21-351, Statistical Review). One patient in the oxybutynin IR group dropped out due to intolerable dry mouth, and one patient withdrew in the transdermal group for personal reasons unrelated to adverse events.

4. Quality of life (QoL)
Quality of life was not assessed or reported in this study (neither general nor condition-specific).

5. Patient-Reported Improvement/Cure
There was no outcome that assessed global improvement. A visual analogue scale on control of leakage episodes is discussed, below.

6. Quantification of Incontinence Episodes
Cure or total dryness:
The proportion of patients reporting continence (no incontinence episodes over 3 days, as recorded in a bladder diary) was similar in each group: oxybutynin TDS: RR 0.85 (95% CI 0.38 to 1.89), P=0.68.

Incontinence Episodes:
Based on data from 72 evaluable patients (of 76 enrolled) at study end, there was no statistically significant between-treatment difference. Both drugs reduced incontinence episodes from baseline (Table 5, below).

Table 5. Mean Change in Incontinence Episodes

Drug	Baseline	Study End	Mean difference from baseline	P-value
OXY TDS	7.2 (4.5)	2.4 (2.4)	4.8 (SD NR)	P=NS for differences between groups P< 0.0001 for change from baseline
OXY IR	7.2 (4.1)	2.6 (2.4)	4.6 (SD NR)	

IR= immediate-release; **NR**= not reported; **NS**= not significant; **OXY**= oxybutynin; **SD**= standard deviation; **TDS**= transdermal patch;

The *a priori* primary efficacy outcome, as reported in the FDA review, was the percentage of patients categorized as responders, defined as those with ≥ 30% reduction in incontinence episodes from washout (baseline). In the intention-to-treat analysis, 5% fewer patients on oxybutynin TDS (95% CI -20% to 10%) had ≥30% improvement in frequency of incontinence

episodes. The difference was -2% (95% CI -17% to 13%) for a per protocol (evaluable patient) analysis. Although neither comparison indicated a statistically significant difference between the formulations, they did not meet preset criteria for equivalence in this trial. This was because the lower limit of the 95% confidence interval was outside of the equivalence margin of 15% (Center for Drug Evaluation and Research NDA 21-351, Statistical Review).

Urinary leakage was also measured on a 13cm visual analogue scale (VAS) from 'none' to 'very bad'. There was no statistically significant between-treatment difference in mean scores: 5.8 ± SD 4.2 versus 6.0± SD 3.3 cm; MD 0.1cm; P=0.9.

7. Nocturia
Nocturia was not reported in this study.

8. Urgency
Urgency episodes were not reported on.

9. Total AE
The proportion of participants who experienced one or more AE in each group is not reported in this study.

10. Specific AE
An anticholinergic questionnaire was provided at each assessment visit with ten specific symptoms: palpitations; constipation; dry mouth; nausea; urinary hesitation; urinary retention; blurred vision; drowsiness; dizziness and for men only, impotence[1]

Dry mouth: the numbers reported in the FDA review are slightly different than numbers reported in a 'treatment-related' AE table in the published article. We report the FDA data (evaluable patients at study end; 1 oxybutynin IR patient missing): oxybutynin TDS 14/37 (38%) vs. oxybutynin IR 33/34 (94%): RR 0.39 (95% CI 0.26 to 0.59), P<0.00001; absolute risk difference -59% (95% CI -76% to -43%).

Constipation: Fewer patients on oxybutynin TDS experienced constipation: 8/38 (21%) vs. 19/38 (50%); RR 0.42 (95% CI -.21 to 0.84), P=0.01; risk difference -29% (95% CI -49% to -8%)

Nausea: Fewer patients on oxybutynin TDS experienced nausea: 3/38 (8%) vs. 10/38 (26%); RR 0.30 (0.09 to 1.01), P=0.05; risk difference -18% (95% CI -35% to -2%)

Urinary retention: Rates were similar on oxybutynin TDS and oxybutynin IR: 9/38 (24%) vs. 13/38 (34%), RR 0.69 (95% CI 0.34 to 1.42), P=0.32.

There were also 9/38 (24%) cases of impaired urination in each group – this is not further defined and it is not known if these overlap with the above.

Central nervous system effects

[1] The study report describes active data collection on these anticholinergic AE through a patient questionnaire. They are also described in the study report as 'treatment-related'. In this context, given the active data collection, the full patient experience of adverse events is likely to have been reported, rather than a subset judged by investigators to be related to treatment.

Somnolence: Fewer patients on oxybutynin TDS experienced somnolence: 7/38 (18%) vs. 14/38 (37%): RR 0.29 (95% CI 0.14 to 0.59), P=0.0007; risk difference -45% (95% CI -64% to -25%)

Dizziness: Fewer patients on oxybutynin TDS experienced dizziness: 6/38 (16%) vs. 10/38 (26%) but the difference was not statistically significant: RR 0.60 (95% CI 0.24 to 1.49), P=0.27.

Blurred vision: The difference in the proportion of patients experiencing blurred vision was not statistically significant: 7/38 (18%) vs. 9/38 (24%), RR 0.78 (95% CI 0.32 to 1.87), P=0.58.

Application site reactions: Based on inspection of the patch sites, numerically more patients in the oxybutynin TDS group experienced erythema at the site of application than the oxybutynin IR + placebo patch group, but the difference is not significant: 38% (14/38) vs. 23% (9/38), RR=1.56 (95% CI 0.77 to 3.15), P=0.22. Other application site reactions were not reported (e.g., pruritus).

Of note, one participant on oxybutynin TDS developed an allergic contact dermatitis to the patch, confirmed on rechallenge to be due to active drug (Center For Drug Evaluation and Research NDA 21-351).

11. Urodynamics/clinician measures
This study reported on volume at first contraction and maximum bladder capacity obtained only from patients who completed the study and agreed to cystometry procedures.

There was no statistically significant difference between treatments in the change from baseline in mean bladder volume at first contraction and maximum bladder capacity. These measures were statistically different from baseline for oxybutynin TDS and numerically increased in oxybutynin IR group but not reaching statistical significance.

No statistically significant change from baseline at study end in the post-void residual volume was observed in either group. 10 patients had a post-void residual volume > 100 mls, 3 in the TDS treatment group (Center for Drug Evaluation and Research NDA 21-351, Medical Review).

12. Mean volume voided
This outcome was not reported.

Critical Appraisal: Oxybutynin TDS vs oxybutynin IR

Risk of bias
As part of the quality assessment of included trials, the Cochrane Risk of Bias tool was used to assess various methodological features associated with internal validity. For a more complete assessment of risk of bias, we based the assessment on information available in the FDA review (Center for Drug Evaluation and Research NDA 21-351) as well as the publication Davila 2001. Although the study was described as a double-blind randomized trial, description of the randomization process as well as method of allocation concealment were not provided, and thus the risk of bias in these areas was rated as ‘unclear’. Maintenance of blinding was also not described or tested in the study. Application-site reactions (which were inspected at each visit) were relatively high for oxybutynin TDS and could have broken blinding. Although there were only 2 withdrawals in total, four patients are unaccounted for in analyses of evaluable patients, leading to a rating of ‘unclear’ for incomplete outcome data.

The publication was rated at high risk of bias for selective outcome reporting as it did not report the *a priori* primary efficacy outcome identified in the FDA review: number of responders, defined as those having a ≥ 30% decrease from baseline in daily incontinence episodes. This is likely to reflect that equivalence was not demonstrated for this outcome, and is clear evidence of selective reporting in the published article. However, because we used all sources of data, including the FDA review, for our assessment, the study was rated at low risk of bias for outcome reporting.

Equivalence between oxybutynin TDS and oxybutnin IR was not demonstrated because 5% fewer patients on oxybutynin TDS met the definition of responder, compared with oxybutynin IR, and the lower limit of the calculated 95% confidence interval exceeded what had been defined as an acceptable margin of difference. The lower limit of the 95% confidence interval was 20%. This means that the true difference could be as great as 20%, with 20% fewer patients responding to oxybutynin TDS. This exceeded the predefined acceptable difference of 15%. This study thus does not provide evidence that the two formulations are the same in terms of efficacy.

The FDA review notes a methodological irregularity in that an unplanned interim analysis was conducted by the manufacturer. The FDA statistical reviewer recalculated the confidence intervals for the primary outcome to take this interim analysis into account. The trial failed to demonstrate equivalence whether or not this extra statistical analysis was carried out. The FDA reviewer also notes that the trial was under-powered for its primary outcome (Center for Drug Evaluation and Research NDA 21-351, Statistical Review).

Applicability of results (external validity)
Only responders to oxybutynin were enrolled in this trial. The findings are thus unlikely to reflect clinical practice.

The majority of participants were women (92%) with only 6 male participants, 5 of whom were assigned to the oxybutynin TDS group.

Comparator/Dose comparability: Transdermal or oral oxybutynin were initiated in the study at one of three levels, according to prior stable daily doses of oral oxybutynin, for the first two weeks, as described in table 6, below. Over the course of the study, oxybutynin daily doses for the transdermal patch were in the range of 1-8mg/day, according to the FDA review, whereas for oral oxybutynin, the dose was in the range of 5-22.5mg/day. These dose ranges are not equivalent. Additionally, transdermal oxybutynin has decreased metabolite concentrations, and lower and less variable peak drug concentrations so it is unclear what dose of transdermal oxybutynin would be equivalent to a particular dose of oral oxybutynin from an efficacy perspective (Center for Drug Evaluation and Research NDA 31-351, Clinical Pharmacology Review). It is likely that the decreased incidence of dry mouth (or other anticholinergic effects) would reflect the lower anticholinergic dose for TDS.

Table 6. Dose Initiation in Davila 2001

Dose level Initiation	Prior stable oral OXY daily dose	OXY TDS	OXY IR
Level 1	≤ 10 mg	2 x 13cm^2 TDS patches twice a week = OXY 2-4 mg/day	10 mg total/day
Level 2	11-15 mg	3 x 13 cm^2 TDS patches twice a week = OXY 3-6	15 mg total/day

		mg/day	
Level 3	16-20 mg	4 x 13 cm^2 TDS patches twice a week = OXY 4-8 mg/day	22.5 mg total/day

Modified from FDA Review NDA 21-351; **IR**= immediate-release; **OXY**=oxybutynin; **TDS**= transdermal;

Harms: A questionnaire for anticholinergic AE was used. This active reporting adds more information than use of spontaneous reporting only. Reporting of harms was, however, incomplete as the total numbers of participants who experienced one or more AE were not provided.

Numerically more patients (15%) had erythema at patch application sites in the oxybutynin TDS group (P=0.22) compared to a placebo patch but the difference was not statistically significant. No patient withdrew from the study due to erythema. However, a patient did develop an allergic contact dermatitis (2%). Iinformation on other application site reactions such as pruritus is not provided.

This trial did not specifically measure effects on cognition.

This trial was of short duration (4 weeks on a stable dose) and provides no information on the consequences of using either formulation on a chronic basis.

Industry sponsorship
This trial was industry-sponsored by the manufacturer of the TDS patch. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For comparator trials within a drug class, industry sponsorship has also been reported to predict benefit (Bero 2007).

Summary Oxybutynin TDS vs. Oxybutynin IR
This dose-titration trial, designed as an equivalence trial, failed to show equivalence of oxybutynin TDS with oral oxybutynin for the *a priori* primary outcome, percentage of patients who were responders. A response was defined by a reduction from baseline of $\geq$ 30% in incontinence episodes. The trial was under-powered for the primary outcome. Other efficacy outcomes were similar but the doses used for each formulation were not comparable.

Dose-titration was based on tolerability of anticholinergic effects, as assessed by a patient questionnaire. At study end, the majority of participants were on a higher-than-approved dose of oxybutynin TDS, limiting the applicability of the findings. The dose range for oxybutynin TDS and oxybutynin IR was not comparable, and lower rates of anticholinergic adverse events with oxybutynin TDS (e.g., dry mouth) could have been due to the lower anticholinergic dose (range 1-8mg/day versus 5-22.5mg total/day).

There is insufficient evidence to conclude a therapeutic advantage of oxybutynin TDS over oxybutynin IR.

Table 7. Summary of RCT Clinical Outcomes: Oxybutynin TDS vs Oxybutynin IR

Outcome	No. of studies (No. of Participants)	OXY TDS vs. OXY IR RR or mean difference [95% CI]	OXY TDS vs. OXY IR Absolute Risk difference [95% CI]	Summary

All-cause mortality	1 trial (76), 0 deaths	--	--	No events, trial was under-powered for mortality in the short-term; no data on long-term mortality
SAE (non-fatal)	0 trials	--	--	No data on SAE
QoL	0 trials			No data on QoL
WDAE	1 trial (76), 1 event in OXY IR group (2.6%)	--	--	Insufficient data Trial is under-powered for WDAE
Patient-reported improvement or cure	0 trials	--	--	No data
Continence (3-day Dryness Rate)	1 trial (72)	RR 0.85 [95% CI 0.38 to 1.89]	--	No difference in continence
Incontinence episodes Mean reduction from baseline	1 trial (72)	MD 0.2 (unable to calculate 95% CI – measure of variation NR)		No difference between groups (P=NS as reported by authors)
Urgency	0 trials	--	--	No data on urgency
Nocturia	0 trials	--	--	No data on nocturia
Total AE	0 trials	--	--	No data on total AE
Dry mouth	1 trial (71)	RR 0.39 [95% CI 0.26 to 0.59]	RD -59% [95% CI -76% to -43%]	59% fewer patients had dry mouth in the OXY TDS group.
Application site reactions	1 trial (76)	RR 1.56 [95% CI 0.77 to 3.15]	--	15% more erythema at patch application sites in the OXY TDS group than placebo patch in OXY IR group but the difference was not statistically significant; other types of application site reactions NR
Constipation	1 trial (76)	0.42 [95% CI 0.21 to 0.84]	RD -29% [-49% to – 8%]	29% fewer patients experienced constipation on OXY TDS
Nausea	1 trial (76)	RR 0.30 [95% CI 0.09 to 1.01]	RD -18% [95% CI -35% to -2%]	18% fewer patients experienced nausea on OXY TDS (P=0.05)
Somnolence	1 trial (76)	RR 0.29 [95% CI 0.14 to 0.59]	RD -45% [95% CI -64% to -25%]	45% fewer patients experienced somnolence on OXY TDS
Dizziness	1 trial (76)	RR 0.60 [95% CI 0.24 to 1.49]	--	No statistically significant difference
Blurred vision	1 trial (76)	RR 0.78 [95% CI 0.32 to 1.87]	--	No statistically significant difference
Urinary Retention	1 trial (76)	RR 0.69 [95% CI 0.34 to 1.42]	--	No statistically significant difference

AE= adverse events; **CI**= confidence intervals; **IR**= immediate-release; **MD**= mean difference; **No.**= number; **NR**= not reported; **OXY**= oxybutynin; **QoL**= quality of life; **RD**= risk difference; **RR**= relative risk; **TDS**= transdermal; **WDAE**= withdrawals due to adverse events;
* As reported in FDA review; N=34 in Oxy IR, N=37 in Oxy TDS

ii) Oxybutynin Gel vs. Oxybutynin IR

No trials were identified that compared oxybutynin gel (Gelnique) with oxybutynin IR. The only available trial was a cognition trial in healthy volunteers and is discussed in Q3 only.

Pooling all extended-release formulations vs. Oxybutynin IR

We conducted meta-analyses combining the transdermal and oral extended-release formulations. Results were consistent with the results obtained for the oral extended-release formulations alone, which provided the majority of study data (see Appendix K for meta-analyses). One additional meta-analysis was possible, combining two studies for change from baseline or end of treatment incontinence episodes, as noted below.

Quantification of incontinence episodes:
Two studies were available for meta-analysis (N=170) (Barkin 2004; Davila 2001). Both trials used a dose-titration regimen. Barkin 2004 compared oral oxybutynin ER vs. oxybutynin IR; the mean dose following titration was 15.2mg/day oxybutynin ER and 14.0mg/day oxybutynin IR. A per protocol analysis was reported for Barkin 2004, with only 75% of participants (N=94) considered evaluable for efficacy even though all patients had incontinence at baseline. Davila 2001 compared oxybutynin TDS (dose range 1-8mg/day) vs. oxybutynin IR (dose range 5-22.5 mg/day). Neither Barkin 2004 nor Davila 2001found a statistically significant difference between oxybutynin formulations, and the difference remains non-significant when the two trials are combined: MD 0.39 (95% CI -0.31 to 1.08), P=0.28.

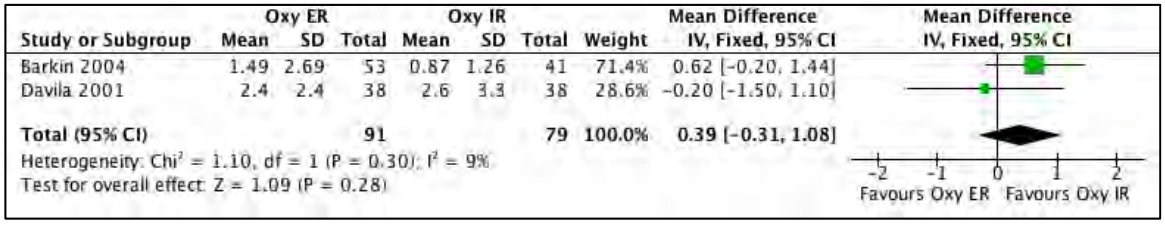

Figure 3. Incontinence episodes per 24 hours. Change from baseline or end of treatment.

3. Trials in Elderly Populations using different formulations of oxybutynin

Direct Comparator Trials: One trial enrolled elderly patients (Minassian 2007), which is discussed above. This trial was under-powered and terminated early due to recruitment difficulties. An interim analysis indicated that a much larger sample size would be required to detect a significant difference between formulations. Additionally, this study was open-label and had serious methodological limitations (see section on critical appraisal above).

Placebo-controlled trials: Placebo-controlled trials on the elderly were included for supplemental information on harms including cognition.

Oxybutynin ER vs. placebo: One 4-week, placebo-controlled trial on patients with OAB (N=50) was identified (Lackner 2008). The active treatment arm was 5mg oxybutynin ER once daily. This trial exclusively enrolled cognitively-impaired elderly females > age 65 (mean age 89 ± 6.2 years) who were residents of nursing home facilities. Participants had baseline MMSE scores of

5-23 and were stratified prior to randomization on the basis of MMSE scores in the range 11-23 and 5-10. See tables 5 in Appendix J for further study characteristics. The study was an equivalence trial using margins of equivalence of ± 2 points for the 95% confidence intervals of mean change in the Confusional Assessment Methods (CAM) algorithm. However, the scoring system is not described nor is the basis on which the margins of equivalence were chosen (referenced as a personal communication with the author of the algorithm). The CAM is a validated instrument for assessing the presence or absence of delirium (Inouye 1990) i.e., featueres of delirium that include an acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness. Items in the CAM include inattention, disorganized thinking, altered level of consciousness (e.g., includes drowsy), disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation and altered sleep-wake cycle.

No patient experienced delirium during the study. MMSE scores did not show differences between oxybutynin ER and placebo before and after adjustment for potential confounders (age, number of medications with anticholinergic effects, and measured serum anticholinergic activity at 7 days) (Table 6, Appendix J). Subgroup analysis for partcipants with baseline MMSE scores of 11-23 did not show a statistically significant difference at any time point between oxybutynin ER and placebo. There were too few patients in the MMSE 5-10 subgroup to draw conclusions. There were no differences between groups on a rating of agitation (Brief Agitation Rating Scale) or Severe Impairment Battery.

Harms: Only treatment-related harms were reported, which represents a subset of total AE and may not reflect the overall experience of the patient. Reported events were infrequent e.g., 2 people experience ‘treatment-related’ constipation and 1experienced ‘treatment-related’ dry mouth vs. 0 in the placebo group. This is likely to reflect both incomplete reporting and that the trial was under-powered to detect differences in harms. One individual on oxybutynin ER (3.9%), and none on placebo, experienced urinary retention. The incidence of falls was assessed before, during and after the study period, with no differences detected. During the 4-week study period, 1 person in the oxybutynin group and 2 people in the placebo group experienced falls.

Risk of bias/quality

Most of the methodological features were assessed as unclear risk of bias other than method of randomization (low risk of bias) and selective outcome reporting (high risk of bias based on the incomplete reporting of harms). An intention-to-treat analysis with last-observation-carried-forward was not used although the 3 individuals who withdrew had data collected for at least two weeks; because there were so few withdrawals, the effect of this on incomplete outcome data was rated as ‘unclear’ risk of bias rather than high.

b. Comparison of Different Formulations of Tolterodine

Tolterodine ER vs. Tolterodine IR

One published 12-week RCT (N=1021 receiving active drug) compared tolterodine ER 4mg once daily with tolterodine IR 2mg bid (4mg total/day), and also included a placebo arm (N=508) (van Kerrebroeck 2001).

A second completed Phase III trial (N=260), conducted in China, was identified on clinicaltrials.gov (NCT00139724) but has not been published and has no results posted.

Study characteristics and outcomes for van Kerrebroeck 2001 are presented in Tables 6 and 7, respectively, in Appendix J.

1. All-cause Mortality
One death (sudden death) occurred in the tolterodine ER group and another in the placebo group. There were no deaths in the tolterodine IR group. Sudden death is often associated with ventricular arrhythmias but no further details are provided.

2. Serious Adverse Events (SAE)
There were 7 SAE in the tolterodine ER group (1.4%), 12 in the tolterodine IR group (2.3%) and 18 (3.4%) in the placebo group. Details of the SAE are not provided in the publication. The FDA review provides details only for some of the AE for tolterodine ER; these included intestinal obstruction and palpitation. There was no statistically significant difference between tolterodine ER and tolterodine IR in SAE: RR 0.59 (5% CI 0.23 to 1.49), P=0.27.

3. Withdrawals due to Adverse Events/Tolerability
There was no difference between active drug treatments in WDAE: tolterodine ER vs. tolterodine IR RR 0.89 (95% CI 0.58 to 1.63), P=0.93. Five percent of each group withdrew due to adverse events.

4. Quality of Life
Patients were assessed in this trial using both the SF-36 (general measures of health-related quality of life) and the King's Health Questionnaire (a condition-specific instrument). Results were not reported in Kerrebroeck 2001, and not available for tolterodine IR in the available FDA Review, which focused on the tolterodine ER vs. placebo comparison (Center for Drug Evaluation and Research NDA 21-228).

In the absence of full data, we report the results for tolterodine ER versus placebo. For KHQ, only 2 of the 10 scores (domains on role limitations and severity (coping) measures) exceeded the minimal criteria considered to be a meaningful improvement when compared to placebo. The difference in mean change from baseline was -7.36 for the role limitations domain score and -5.58 for the severity (coping) measures domain score, small differences on a 100-point scale; these differences barely exceed the minimal criteria for a meaningful difference (-6.75 for role limitations and -4.49 for severity (coping) measure) (Center for Drug Evaluation and Research NDA 21-228). For the SF-36, there were no statistically significant differences between tolterodine ER and placebo on the physical component summary and the mental component summary measures.

5. Patient-reported Perception of Condition
The trial measured this outcome but did not report the active drug comparison in the publication.

In the absence of full data and the active drug comparison, we report the tolterodine ER and placebo results from the FDA Review. At study end, 61.8% of tolterodine ER subjects reported improvement as did 47.6% of placebo subjects.: RR 1.30 (95% CI 1.16 to 1.46), P <0.00001, absolute risk difference 14% (95% CI 8 to 20%). No data are available for tolterodine IR.

6. Quantification of Incontinence Episodes
At baseline, patients on tolterodine ER had, on average, 22 incontinence episodes per week (range 0-168) and patients on tolterodine IR, a mean of 23 (range 0-168). This corresponds to just over 3 episodes per day. There was no statistically significant difference in the reduction in incontinence episodes between tolterodine ER and tolterodine IR. Both reduced incontinence

episodes by 1.5 or 1.7 episodes per 24 hours: MD 0.18 episodes/day (95% CI -0.12 to 0.48), P=0.25. Both active drugs were better than placebo; placebo reduced daily incontinence by 1 episode. The difference between tolterodine ER vs. placebo was statistically significant.

7. Nocturia
The trial did not report on this outcome.

8. Urgency Episodes
The trial did not report on this outcome.

9. Total AE
The trial did not report on this outcome.

10. Specific AE

Dry mouth: Fewer patients in the tolterodine ER group reported dry mouth compared with tolterodine IR: RR 0.77 (95% CI 0.62 to 0.94), P=0.01; absolute risk difference -7% (95% CI -13% to -2%).

CNS effects: included headache, somnolence, dizziness, fatigue and insomnia in both groups, in the range of 1%-6% of participants (Table 7 in Appendix J). Headache was the most common CNS effect and was not statistically different between groups although numerically greater in the tolterodine ER group. There were no statistically significant differences between active treatment groups but events were few. No active assessment of cognition was conducted.

11. Mean volume voided
Volume voided per micturition was similar for the two formulations.

11. Urodynamic/clinician measures
The trial did not report on these outcomes.

Critical Appraisal
Risk of bias: Although randomization was appropriate, most of the other methodological features assessed for risk of bias were judged 'unclear' as they were not described. The study was assessed to be at high risk of bias for selective outcome reporting as QoL information was collected, according to FDA NDA 21-228 review, but not reported in the publication, and harms were incompletely reported. Although data for missing outcomes were available for the tolterodine ER and placebo treatment arms in the FDA review, we were unable to find published data for tolterodine IR.

Applicability of results (external validity)
The majority of participants were women, limiting applicability to men. About 50% had previously received treatment but no separate analysis was carried out for patients with previous treatment and/or who had failed to improve on treatment.

Comparator/Dose comparability: Doses were comparable, based on pharmacokinetics studies (Center for Drug Evaluation and Research NDA 21-228, Clinical Pharmacology Review). Upon administration of the ER formulation, peak plasma concentrations of tolterodine and its active metabolite are 50-75% of the peaks attained with the IR formulation, and trough (lowest) concentrations are 1.5 x higher. The ER formulation thus results in narrower fluctuations of

tolterodine. The AUC (area under the curve) for total drug exposure does not differ substantively, but the difference in peak and trough concentrations may have clinical consequences.

Harms: Harms were passively collected and incompletely reported.

Industry sponsorship
This trial was -sponsored by the manufacturer of tolterodine ER. Industry sponsorship has been reported to be a form of meta-bias (Lundh 2012). For comparator trials within a drug class, industry sponsorship has also been reported to predict benefit (Bero 2007).

Summary
Based on one 12-week trial (N=1021), there was no difference in SAE or WDAE between tolterodine ER and tolterodine IR. The trial was under-powered for mortality. The proportion of patients experiencing one or more AE, in total, was not reported. There was less dry mouth with tolterodine ER (risk difference 7%). There was no difference in reported efficacy outcomes (incontinence episodes). There are no comparative outcome data available on quality of life even though this was measured in the trial, and no available on urgency or nocturia. There is insufficient evidence based on both harms and efficacy outcomes to conclude a therapeutic advantage for tolterodine ER versus IR. No long-term data (beyond 12 weeks) are available.

Table 8. Summary of RCT Clinical Outcomes; Tolterodine ER vs Tolterodine IR

Outcome	No. of studies (No. of Participants)	TOL ER vs.TOL IR RR or mean difference [95% CI]	TOL ER vs. TOL IR Absolute Risk difference [95% CI]	Summary
All-cause mortality	1 trial (1021) 1 event in TOL ER group (0.2%)	--	--	Trial was under-powered for short-term mortality; no data on long-term mortality
SAE (non-fatal)	1 trial (1021)	RR 0.59 [95% CI 0.23 to 1.49]	--	No difference in SAE
QoL	0 trials	--	--	No available data on active treatment groups (although measured in trial)
WDAE	1 trial (1021)	RR 0.98 [95% CI 0.58 to 1.63]	--	No difference in WDAE
Patient-reported improvement or cure	0 trials	--	--	Outcome measured but not reported; no available data
Continence (Dryness Rate)	0 trials	--	--	No available data
Incontinence episodes Mean reduction from baseline	1 trial (1021)	MD 0.18 [95% CI -0.12 to 0.48]	--	No statistically significant difference between drug formulations
Urgency	0 trials	--	--	No available data
Nocturia	0 trials	--	--	No available data
Total AE	0 trials	--	--	No available data
Dry mouth	1 trial (1017)	RR 0.77 [95% CI 0.62 to 0.94]	RD 7% [95% CI -13% to -2%]	7% fewer patients experienced dry mouth on TOL ER

AE= adverse events; **CI**= confidence intervals; **MD**= mean difference; **QoL**= quality of life; **RD**= (absolute)

risk difference; **RR**= relative risk; **SAE**= serious adverse events; **TOL**= tolterodine; **WDAE**= withdrawals due to adverse events;

Non-Randomized Studies

Findings from published non-randomized studies

Non-randomized studies can provide additional information on longer-term or less frequent harmful drug effects, or on effects in populations excluded from RCTs. As they provide a less accurate and reliable evaluation of effectiveness than RCTs, only harms data are included below.

There were no observational studies comparing the effects of one formulation of oxybutynin with other formulations included in this review.

In total, ten observational studies are examined, including two controlled cohort analysis. The controls for these cohort analyses were non-users of antimuscarinic drugs for OAB in one study and in the other, a drug that is not included in this review (flavoxate). There were also four uncontrolled cohort analyses, one pre- or post-treatment comparison examining heart rhythm abnormalities in the elderly, and three case series of spontaneous adverse drug reaction reports in the U.S., France and the Netherlands.

Controlled cohort analysis (non anti-muscarinic users or non-included control)

- Moga 2013; fractures and effects on cognition vs. non-users; all antimuscarinic dugs for OAB included, most on IR formulations; most on oxybutynin (OXY) IR (specific results reported)
- Movig 2001: neuropsychiatric AE following oxybutynin or flavoxate use

Uncontrolled cohort analyses

- Diokno 2002: one-year open-label study of OXY ER (Ditropan XL); urge or mixed incontinence
- Amarenco 1998: 3-month open-label study of OXY IR 7.5mg to 15mg/day; women only
- CONTROL 2012 (in FDA advisory committee report; Merck, unpublished): 12-week open-label study of OXY TDS 3.9mg/day; women only
- Newman 2008: MATRIX; six-month open-label study of OXY TDS; also reported in Pizzi 2009

On-treatment comparison to pre- or post- treatment

- Hussain 1996: ≥4 weeks OXY IR (2.5-10mg/day); ECG comparison on drug to pre- or post-use

Case series

- Gish 2009: comparison of pediatric and adult ADR reports to the US FDA for oxybutynin
- Jonville 1992: pediatric and adult ADR reports, French regional pharmacovigilance centres
- 't Veld 1998: pediatric and adult neuropsychiatric ADR reports, Dutch pharmacovigilance centre (LAREB); includes 3 case reports on hallucinations.

Controlled cohort analysis

Moga 2013 is a controlled cohort analysis among residents of U.S. Veterans Administration long-term care facilities comparing initial users of bladder antimuscarinics with non-users.

The aim of the study was to assess fractures, cognition, improvements in urinary incontinence and quality of life. Patients were followed from first dispensing of a bladder antimuscarinic (with non-use for 1 year prior) until the first of the following events: 7 days past discontinuation of therapy; fracture; death; discharge from nursing home; or end of study period (Sept 30, 2009). Non-users were assigned a matched index date to initiation of use among users and followed up until fracture; death; discharge or end of study period.

Patients were 96% male and elderly (21-22% over the age of 85). Around 10% had moderate to severe cognitive impairment at baseline, and 28-29% had indwelling catheters. Around 75% took oxybutynin IR. Of the remainder, 21% took another IR product; 9% took ER formulations of oxybutynin, tolterodine, and hyoscyamine. The cohort included some users of drugs not included in this review (hyoscyamine, dicyclomine, flavoxate). The two additional included drugs were tolterodine and trospium. A separate analysis of oxybutynin IR users was planned *a priori* and is reported below. All comparisons were to non-users; there were no comparisons carried out between different antimuscarinic drug users.

Table 9. Controlled cohort analyses – antimuscarinics

Study	Design	Data source	Duration	Exposed Sample size Age	Nonusers	Assessed AE outcomes
Moga 2013	Controlled cohort	US Veterans Administration; long-term care residents, 2002-2009 Age ≥65; (n=27,930); Propensity score matched to non-users	< 8 years; median 49 days (drug); median 95 days (control)	N=1125 (181,669 person-days) 51% >80 96% male	N=5469 (1,280,2012 person-days) 52% >80 96% male	Fractures Cognition Urinary incontinence 2 QoL scales: -social engagement - overall QoL(MDS-HS1)

Results

In total 9.8% of nursing home residents took bladder antimuscarinics, 44% of whom were new users (n=1195), of whom 1125 (94%) could be matched to 5469 non-users through propensity scores.

Mortality and SAE: The authors do not report on mortality or total SAE, although there is likely to have been considerable mortality among this elderly nursing home population over the 7-year study period.

Fractures: Patients on antimuscarinics were at a higher risk both of hip fracture and of fractures at any site than non-users. The hazard ratio for hip fracture = 3.67 (95% CI 1.46-9.34) among users of all antimuscarinic drugs. When this was limited to oxybutynin IR users, the hazard ratio was 4.89 (95% CI 1.79-13.44).

Risks for any fracture were also elevated: HR= 2.64 (95% CI 1.37-5.10) among all users; HR=2.78 (95% CI 1.31-5.89) among oxybutynin IR users.

The authors report a number needed to harm at 90 days of 36 (95% CI 12-209) for hip fracture among all users.

Quality of Life: The two Quality of life (QoL) scales used have been previously validated in nursing home residents. The Health Status Index (MDS-HS1) measures overall quality of life. The score ranges between -0.02 and 1.0, where 0=dead and 1.0 is in the best possible health one can achieve. A difference of 0.03 or more is considered clinically important.

The Index of Social Engagement (MDS-ISE) has a 0-6 score, with a change in one point considered clinically significant, and 0 equivalent to complete withdrawal, 6 to high level of participation and initiative. A difference of 1 point is considered clinically significant.

There was no difference in overall quality of life (MDS-HS1): difference in mean score – 0.0005 (95% CI -0.0168 to 0.0158). Patients on anti-muscarinics did better on social engagement than non-users: Mean difference in score 0.2074 (95% CI 0.055-0.3598). However, both the point estimate of the difference and the upper confidence interval are far below the minimal clinically significant difference of one point.

Cognition: A cognitive performance scale that is highly correlated with the mini-mental state exam (MMSE) was used to assess cognition; range in scores 0 (intact) to 6 (very severe impairment). No difference was observed between patients on anti-muscarinics and non-users. However, the scale is not likely to be sensitive to mild differences in cognition.

Table 10. Key outcomes in nursing home residents

	Anti-muscarinic drug users N=1125 N=181,669 person-days	**Non-users N=5469 N=1,280,201 person-days**	**Comparisons (95% CI)**
Mortality	NR	NR	
Total non-fatal SAE	NR	NR	
Hip fracture –all users Hip - Oxybutynin IR	13 12	100 71	**HR= 3.67 (1.46-9.34)** NNH=36 at 90 days **HR=4.89 (1.79-13.44)**
All fractures –all users All – Oxybutynin IR	23 20	172 130	**HR=2.64 (1.37-5.10)** **HR=2.78 (1.31-5.89)**
Cognitive performance scale	Mean scores NR		MD=0.005 (-0.1 to 0.1)
Improvement in Urinary incontinence*	90 days: 16.35%	90 days: 13.02%	**OR=1.34 (1.13- 1.60)** NNT=32 (17-125) at 90 days
Overall QoL (MDS-HS1)	Mean scores NR		MD= -0.001 (-0.02 to 0.02)
Social engagement	Mean scores NR		**MD=0.21 (0.06-0.36)**

Bolded results are significant at p<0.05; **HR**= hazard ratio; **MD**=mean difference; **NNH**= numbers needed to harm; **NNT**=numbers needed to treat; **NR**=not reported; **OR**=odds ratio;
*defined as going from frequently incontinent to occasionally incontinent or from occasionally incontinent to usually continent

The second controlled cohort analysis, Movig 2001 (table 11, below), used community pharmacy records in Tilburg, the Netherlands, to identify all new patients aged >18 who were prescribed either oxybutynin or flavoxate (n=742). Flavoxate was used as a comparator because it is a non-centrally acting spasmolytic agent, therefore not expected to cause neuropsychiatric AE. The authors used new prescriptions of benzodiazepines or antipsychotics and benzodiazepine switching as indicators of occurrence of neuropsychiatric AE. Patients' drug exposure was assessed over a 2-year period, and Poisson regression was used, with adjustment for gender, age and concomitant drug use. The authors calculated incidence density ratios (IDR; a relative risk measure based on Poisson analysis, allowing for comparison of time on and off drug regardless of

time sequence) and found no difference in any of the outcomes between patients taking flavoxate or benzodiazepines.

Table 11. Controlled cohort analysis to assess oxybutynin – non-included comparator

Study	Design Duration	Data source	OXY	FLAV	Assessed outcomes
Movig 2001	Controlled cohort analysis 2 years	Pharmacy records, Tilburg region, NL	N=742 patients in total; n=70,539 exposure days OXY; n=33,470 exposure days FLAV* Mean age = 59 (52% were age 60-97)		BENZO Rx or switch; Antipsychotic Rx or switch

BENZO= benzodiazepine; OXY=oxybutynin (formulations not stated), all doses; FLAV= flavoxate, all doses; Rx= treatment

*number of patients / group not stated; exposure days for 'any endpoint' outcome; # days differ per outcome.

Study outcomes:

The authors found no difference in adjusted ADRs between oxybutynin and flavoxate for any of the assessed endpoints nor a combined outcome:

- New benzodiazepine Rx among previous non-users: adjusted IDR OXY vs. FLAV: 0.94 (95% CI 0.40-2.22), NS
- Benzodiazepine switch among previous users: OXY vs. FLAV adjusted IDR 1.90 (0.66-5.49), NS
- New antipsychotic Rx: OXY vs. FLAV crude IDR 0.30 (95% CI 0.05-1.78), NS; adjusted IDR not estimable;
- Any of above endpoints: adjusted IDR OXY vs. FLAV 1.08 (95% CI 0.60-1.92), NS

Non-randomized non-comparative studies

There are four uncontrolled open-label cohort analyses, one U.S. study of oxybutynin ER (Ditropan XL) (Diokno 2002), two U.S. cohort studies of oxybutynin TDS 3.9mg (Oxytrol), one unpublished (CONTROL 2012), and a second study, MATRIX, with published results on an elderly subgroup (Newman 2008), and a French study of oxybutynin IR (Amarenco 1998). A fifth study (Hussain 1996) evaluates effects of oxybutynin on heart rhythms in a small sample of elderly patients (n=21; mean age 77), most of whom had cardiovascular or cerebrovascular disease. Table 12 provides an overview of study characteristics.

Table 12. Non-randomized non-comparative studies to evaluate oxybutynin

Study	Design	Data source	Duration	Sample size Age	Assessed outcomes
Diokno 2002	Uncontrolled open-label cohort	Clinical sample (98 centres); community dwelling with OAB, USA; OXY ER 5mg-30mg/day	12 months	N=1,067 Mean age 64 ±14 85% female	Total withdrawals WDAE Total and specific AE
CONTROL 2012	Uncontrolled open-label cohort; unpublished	Pharmacy-based (26 in 10 cities); test of OTC OXY TDS 3.9 mg/day; self-diagnosed with OAB	12 weeks (median exposure 45 days)	N=785; Female Mean age NR; 33% ≥65	Misuse (inconsistent with label) SAE Total and specific AE
Newman 2008; Pizzi 2009	Uncontrolled open-label cohort	Clinical sample, USA; adults age ≥18; OXY TDS 3.9mg/day	6 months	N=2878 Mean age 63±15; n=699 ≥	WDAE Elderly subgroup; application site

Study	Design	Data source	Duration	Sample size Age	Assessed outcomes
				75; 90% female	reactions
Amarenco 1998	Uncontrolled open-label cohort	Clinical sample (GP practices); women with urgency with or without incontinence; France; OXY IR 7.5-15mg/day	3 months	N=1701 Mean age 47.6 (age 20-60)	Total AE
Hussain 1996	Pre- or post-treatment comparison with on-treatment*	Urology outpatients and hospitalized; patients with incontinence; most with cardiovascular disease: OXY IR 2.5-10mg/day	≥4 weeks (median duration 38 days (25-400)	N=21; Median age 77 (range 58-88) 57% male	ECG QT prolongation

*comparison ECG obtained either before treatment initiation or ≥ 7 days after discontinuation

Results: uncontrolled cohort analyses

Diokno 2002 followed 1067 patients ≥ 18 (mean age 64) on OXY ER for up to one year, allowing patients to adjust dosage to maximize effectiveness and tolerability within a range of 5 to 30mg/day. Doses were relatively evenly distributed: 15% of patients took OXY ER 5mg, 27% OXY ER 10mg, 17% OXY ER 15mg, 23% OXY ER 20mg (including 3 patients on 25mg), and 18% OXY ER 30mg. As is noted on Table 13, below, frequency of dry mouth was strongly dose-related. Interestingly, improvements in patients self-assessed 'bother' by urinary symptoms failed to demonstrate a similar dose relationship. A single question was used to assess 'general health and bother' on a 0-100 visual analogue scale, with patients asked to mark how bothersome their urinary leakage and/or bladder problem was, ranging from 'not bothersome at all'' to 'as bothersome as I can imagine'. Improvements from baseline were significant at all dose levels and were similar regardless of dose, with doses ranging from 5mg (N=160) to 30mg (N=180) per day. The lack of dose response is consistent with the strong placebo effect in RCTs and the lack of control group in this study.

CONTROL 2012 was an unpublished open-label 15-week uncontrolled cohort study carried out at 26 community pharmacies in 10 U.S. cities. The aim was to simulate over-the-counter (OTC) use, as part of a Merck application for a U.S. switch to partial OTC status for Oxybutynin TDS. Study duration was 12 weeks, with patient diaries, telephone interviews at week 3, 7 and 12, and a urine sample at end-of-study. The primary outcome measure was proportion failing to respect labeled instructions.

Of 1,218 screened, 1,069 agreed to participate (88%); 785 participated and 727 completed diaries ("verified users"). Of the 1,069 women agreeing to participate, 80% failed to meet labeled eligibility criteria for OXY TDS use, most often due to: incomplete bladder emptying, diabetes risk factors, possible UTI, stress incontinence, other OAB drug use, bladder cancer risk, diuretic use, or failing to meet OAB criteria. Patients were enrolled nevertheless unless they met exclusion criteria (N=214).

Of 727 users completing diaries, 141 (19.4%) had symptoms indicating they should discontinue (new or worsening symptoms); 105/141 (74.5%; 95% CI 66% to 85%) failed to stop use (14% of enrolled patients). Among patients ≥65 with new or worse symptoms, 48/58 (83%) continued use inappropriately. The sponsor employed a mitigation strategy if ongoing use was judged to be harmful; 25/105 inappropriate users continued use post-mitigation nevertheless.

For patients with no symptom improvement, median time to discontinuation was 36 days despite labeled instructions to discontinue use after 2 weeks. Nearly half (46%) of patients incorrectly used patches for >4 days and 11% used >1 patch simultaneously. Results raise concerns about frequent ongoing use among patients unlikely to benefit and frequency of incorrect use.

AE rates were reported separately for patients <65, ≥65 and ≥75. Total AE and SAE did not differ. There were more application site reactions and constipation among women <65, and more UTI, cystitis and dysuria among older patients.

Newman 2008 describes a subgroup analysis of older patients a 6-month uncontrolled open-label study of 2878 outpatients, 90% female (MATRIX). MATRIX was planned as an RCT comparing OXY-TDS plus an educational interview to OXY-TDS alone. Comparative RCT results remain unpublished; published report describe the joint experience of both treatment arms. 699 patients (24%) were aged ≥75 and over half of patients had discontinued previous OAB treatment, mainly due to lack of efficacy (~25% of total sample; age not specified). Few outcomes are reported, mainly quality of life, for which an uncontrolled open-label cohort study cannot provide accurate estimates. Adverse events are incompletely reported, only the subset believed to be treatment-related. In total, 475 patients (16.5%) discontinued due to AE. Deaths, SAE, total AE, and total withdrawals are not reported. Application site reactions were reported in 14% of patients overall (14.9% < 75; 11.6% ≥ 75).

Amarenco 1998 included women aged 20-60 with urgency with or without incontinence, who were followed for up to 3 months following treatment initiation with OXY IR 7.5 to 15mg/day. Patients were assessed 10 days, 30 days and 90 days following treatment initiation, and were asked to keep a bladder diary. The primary study outcome measure was quality of life. Given the uncontrolled open-label nature of the study, these data are unreliable. An identical number of total withdrawals and WDAE are reported, both of which are very low for a cohort of this size, raising questions about completeness of reporting; reported results are likely per protocol only (not stated). By 3 months, and with an ER formulation, 26% of patients enrolled by Diokno 2002 had withdrawn from the study, in contrast to results reported for Amarenco 1998. Only limited information on AE is reported and data collection was likely to have been passive.

Table 13. Adverse events reported in uncontrolled cohorts

Outcomes	Diokno 2002 (n=1067) OXY ER	CONTROL 2012 (n=785) OXY TDS	Newman 2008 (n=2878) OXY TDS	Amarenco 1998 (n=1701) OXY IR
All-cause mortality	1§	1¶	NR	NR
SAE	NR	41 (5.2%); 35 (4.5%) on-treatment	NR	NR
Total Withdrawals	574 (43.8%)	152 (19.4%)	NR	49 (3%)*
WDAE	256 (24.0%)	141 (18%)	475 (16.5%)	49 (3%)*
Total AE	NR	519 (66.1%)	NR	181 (11%)

Dry mouth	OXY ER 5mg= 12% Oxy ER 10mg = 17% OXY ER 15mg = 21% OXY ER 20mg = 28% OXY ER 30mg = 36%	32 (4.1%)	NR	133 (8%)
Application site irritation	--	142 (18.1%)	14% in total 225/2176 (10.3%) < age 75; 81/699 (11.6%) ≥ 75[§]	--
UTI	NR	50 (6.4%)	NR	NR
Constipation	NR	20 (2.5%)	NR	NR

AE= adverse events; SAE= serious adverse events; WDAE= withdrawals due to adverse events; NR = not reported;
§cause unspecified; authors judged to be unrelated to treatment;
¶ complications of viral pneumonia in a patient with HIV; judged unrelated
*The authors report that 97% of subjects remained on treatment, with only 49 early withdrawals, and also report later in the same paragraph that 49 women with AE discontinued treatment.
§reported numbers inconsistent; reported as 14% in total;14.9% aged less than 75; but 225/2176 = 10.3% (11% total)

The fifth study (Hussain 1996) compared ECG readings on or off therapy. Patients received a median dose of OXY IR 7.5mg (range 2.5-10mg). Median duration of therapy was 38 days (range 25-400). Some patients received baseline comparison ECG's pre-treatment; others post-treatment discontinuation (numbers per group not specified). Most participants had cardiovascular or cerebrovascular disease: ischaemic heart disease (n=4); heart failure (n=3); hypertension (n=3), cerebrovascular disease (n=7), and were taking a range of concurrent therapies, none of which were altered during the study period (e.g. during ECG readings with and without OXY IR exposure). There were no changes in heart rate, PR interval, QTc interval or QT dispersion following OXY therapy.

Mean readings off-treatment vs. during OXY IR therapy:

- heart rate 74 ± 11 vs. 69 ± 11 beats/minute
- PR interval: 168 ± 27 vs. 156 ± 27 milliseconds (ms)
- QTc 454 ± 27 vs. 447 ± 31 ms [1/2]
- QTc dispersion (QTc max-QTc min): 68 ± 24 vs. 63 ± 26 ms [1/2]

The authors conclude that oxybutynin is not associated with QTc interval prolongation to a similar extent to terodiline.

Case series

There were three case series, all of which describe spontaneous ADR reports collected by regulatory agencies. All three case series represent an incomplete overview of AE, due to under-reporting of AE, and none distinguish between different formulations of oxybutynin.

The primary aim of both Gish 2009, a U.S. analysis, and Jonville 1992, a French analysis, was to compare pediatric and AE reports. Gish 2009 also includes a breakdown of CNS events in patients aged 17-59 versus those aged over 60, which is of relevance to this review (Table 14). As the focus of this report is on use of oxybutynin in adults, the results for adults only are reported below.

In addition to the CNS events listed below in Table x, Jonville 1992 lists ocular AE in 11 adults (10% of AE reported in adults). These were mainly trouble with accommodation (6). There were 5 reports of tachycardia and 15 reports of cutaneous or allergic reactions.

Table 14. Overview of CNS events in case series of spontaneous AE

CNS events	Jonville 1992 Adults age 18-87 N=31 CNS cases (of 115 in total)**	Gish 2009, USA Ages 60 + N=97 (% CNS cases)	Gish 2009, USA Ages 17-59 N=46 (% CNS cases)
Confusional state	16 (52%)	29 (30%)	4 (9%)
Hallucination*	4 (13%)	25 (26%)	5 (11%)
Delirium	3 (10%)	-	-
Sedation	-	21 (22%)	13 (28%)
Agitation	4 (13%)	6 (6%)	3 (7%)
Anxiety	-	6 (6%)	6 (13%)
Amnesia	=	6 (6%)	3 (7%)
Disorientation	5 (16%)	6 (6%)	-
Abnormal dreams	-	3 (3%)	2 (4%)
Thinking abnormal	-	2 (2%)	2 (4%)
Psychotic disorder	-	2 (2%)	2 (4%)
Convulsion	-	1 (1%)	3 (7%)
Abnormal behavior	-	1 (1%)	-
Personality disorder	-	-	1 (2%)
ADHD	-	-	1 (2%)

*includes 'hallucination' and 'hallucination, visual' in Gish; and either auditory or visual in Jonville
** 15 additional unspecified CNS events in both children and adults (no breakdown)

The focus of 't Veld 1998, a Dutch case series, is on neuropsychiatric events in 17 patients, 11 of whom were adults, all over the age of 40. Two cases of hallucination, in a 72-year old man and an 85 year-old woman, are presented in greater detail. Other reported CNS AE in this series include drowsiness and sleepiness (5), apathy (1), listlessness (1) anxiety (1), disorientation (1), nervousness and psychosis (1), and agitation. The authors report that symptoms improved or disappeared in all patients after dose reduction or withdrawal of oxybutynin.

Case reports
No published case reports were identified for oxybutynin ER, TDS or gel.

Study quality /risk of bias

Controlled cohort analyses
Moga 2013: In general, this is a well-conducted observational study, both in terms of the use of intensive propensity score matching to adjust for confounders and the detailed description of the study population and follow-up procedures. The authors used a standardized tool for comprehensive assessment of nursing home residents, the 'Minimum Data Set" (MDS), both to obtain a detailed medical history and to assess outcomes during the study. This was combined with administrative pharmacy, inpatient and outpatient data.

Exposure assessment was unrelated to outcome assessment, as administrative data collected *a priori* were used to assess exposure, and outcome assessments used standardized measures. The decision to include only initial anti-muscarinic drug users (with one year of non-use preceding initial use) avoids the problem of survival bias.

Patients with other recognized risk factors for fracture (bone cancer, bone metastasis or previous pathological fracture) were excluded from the analysis.

Reporting on the pattern of exposure is very general (median length of exposure; proportion of patients on IR formulations and on oxybutynin IR) without detailed breakdown of patient numbers on specific drugs.

Outcome reporting: there was incomplete outcome reporting with no information provided on mortality or SAE. The definition *a priori* of a primary outcome is unclear, as no sample size calculation was included.

Outcome assessment for fractures was well documented via medical records (minimum data set) and hospital records. The scales used for quality of life had been previously validated in a nursing home population. However, the difference observed was well below the threshold for minimal clinical significance and the authors report this as a significant difference without commenting on the small magnitude of effect. Note: comparative quality of life measures are likely to be unreliable in an observational study, given the inherent biases in selection of patients for treatment and lack of blinding to treatment allocation.

For cognition, the scale used is unlikely to be able to detect mild differences in cognition. Therefore it is unclear whether the lack of detected difference reflects no effect on cognition or the scale's lack of ability to detect minor differences. Major short-term effects on cognition were excluded, over a median of 45 days, but a claim of no effect on cognition cannot be supported.

This study was not industry-sponsored.

Applicability: Most outcomes included both drugs that were and were not part of this review. Exact numbers of patients and period of follow-up on specific drugs are not stated, with the exception of oxybutynin IR, for which additional information is provided but not exact numbers of patients or patient-days of therapy. The oxybutynin sub-analysis is the part of this study most relevant to our review, but only hip fracture and total fracture results are included.

With a 96% male population included in the study, the results can only be applied to elderly men in long-term care, not to women. This is an otherwise understudied population and includes patients with multiple morbidities.

Movig 2001 is a research letter providing limited information on patient characteristics or study methods. For example, there is no baseline characteristics table, no information on drug formulation or dose, no reporting of numbers of patients exposed to each drug, no reporting of loss to follow-up. A study strength is that all patients newly prescribed oxybutynin within a community setting in the Netherlands were followed up for 2 years. A Poisson analysis was used to assess AE only during periods of drug exposure, presumably based on prescription duration (no details provided).

The main study weakness is the use of blunt instruments to measure neuropsychiatric effects: initial benzodiazepine or antipsychotic prescriptions, or a switch of benzodiazepines. These prescriptions are unlikely to have captured all neuropsychiatric AE. If patients discontinued oxybutynin use as a first step following experience of an AE, as would be considered best clinical practice if a psychiatric reaction is suspected to result from drug use, and the event resolved without the need for a psychiatric drug prescription, the information would not have been captured. Conversely, life events and co-morbidities could lead to prescriptions for benzodiazepines or antipsychotics in the absence of AE, reducing the study's ability to detect a difference between study arms. Additionally, no information is provided on median duration of

exposure and many patients may have been exposed to the drugs for a relatively short period, reducing the study's strength to assess longer-term effects. In general, outcome assessment is too limited to draw conclusions about a lack of neuropsychiatric effect.

Uncontrolled cohort analyses

Diokno 2002 and Amarenco 1998 both provide limited information because these are uncontrolled open-label cohort analyses. Both relied on passive AE reporting. In Amarenco 1998, reporting on patient characteristics, dose exposure, follow-up and AE is selective and incomplete. Diokno 2002 provides more complete reporting on follow-up, early withdrawals and WDAE, and dose-related dry mouth. Newman 2008, similarly, provides very incomplete reporting, with no information provided on mortality, SAE, total AE, or total withdrawals, and only selective reporting of specific AE. This was a planned RCT, comparing OXY TDS + an educational intervention to OXY TDS alone; only combined results for the entire cohort were published. Pizzi 2009 reports that productivity scores did not differ among those with and without the educational intervention; this likely reflects negative results and publication bias. The study was sponsored by Watson laboratories. No information is provided on funding for Diokno 2002 or Amarenco 1998.

CONTROL 2012 is an unpublished study carried out by the manufacturer, Merck, with Merck employees involved in outcome assessment, mitigation strategies and analysis, and no blinding of assessments. The FDA review report for an advisory committee meeting provides the only publicly available trial report, and in many cases the FDA reviewer's assessment differed from the sponsor's.

Hussain 1996 used blinded outcome assessment, a study strength, and provides details on how ECG results were analyzed. The sample size calculation was based on an ability to detect a change in QTc of 9 $ms^{1/2}$. If QTc prolongation is an infrequent or dose-related AE, this study would have been unable to detect an effect, as doses were generally low (median 7.5mg/day; range 2.5 mg- 10mg) and the sample size small (N=21). The authors provided little data on inclusion criteria or baseline characteristics and do not distinguish between those with control ECG readings pre-treatment or 7 days post- treatment. However, patients were elderly, and most had cardiovascular or cerebrovascular disease. The study provides reassurance that oxybutynin IR does not lead to the magnitude or frequency of QT prolongation as terodiline, an antimuscarinic drug for urinary incontinence that was withdrawn from the market due to cardiac effects in elderly patients with serious comorbidities. It was not designed to measure infrequent or longer-term cardiac or cardiovascular adverse events.

Conclusions: results of observational studies of oxybutynin AE

Moga 2013 provides an important addition to the current body of research on drugs for OAB, as it addresses a little researched patient population: elderly men in nursing homes, many of whom had multiple morbidities. The results raise a strong note of caution over use of these medicines, as one additional patient per 36 treated experienced a hip fracture.

The number needed to harm of 36 for hip fracture is very similar to the number needed to treat in the same patients, 32, for improvement in urinary incontinence (at least frequent to occasional or occasional to none). However, a hip fracture is a serious and often catastrophic event, with a high risk of death following hip fracture among elderly patients; the severity of the event greatly outweighs urinary incontinence results. It has been argued that nocturia leads to night-time falls and fractures and therefore OAB treatment could prevent fractures. Moga 2013 fails to support this hypothesis.

This study's results raise concerns that treatment of elderly male nursing home residents with oxybutynin IR is leading to greater harm than benefit. It cannot answer the question of whether this harm is shared by all drugs in the class or by both IR and ER formulations, or whether it occurs in women as well as men.

In general, none of the observational studies of oxybutynin allow an assessment of relative AE rate for different formulations of oxybutynin or provide specific signals of harm, for example, for an IR versus an ER or transdermal formulation. Thus in terms of the central question of this review, they provide little additional information of relevance.

Diokno 2002 highlights the existence of a dose response for dry mouth with oxybutynin ER, over a one-year period of use, in a mainly female population of patients with a mean age of 64. Amarenco 1998 highlights the lack of dose response for female patients' perception of improvement with oxybutynin IR.

CONTROL 2012 aims to simulate OTC use of OXY TDS, which has been approved in women in the US (January 2013). Although use in Canada is prescription-only, this study raises a red flag about the high proportion of ongoing use among patients with no improvement or worsening of symptoms, despite labeled instructions to discontinue use, and the many patients with symptoms of other conditions or who failed to meet OAB criteria but nevertheless chose treatment. Whether longer-term prescription-only users similarly continue use and fail to seek additional care in these types of situations is unknown.

Hussain 1996 provides reassurance of lack of evidence of QT prolongation in a small series of elderly patients with cardiovascular and cerebrovascular co-morbidities, at low to normal doses of oxybutynin IR. (Ventricular tachycardia and torsade de pointes has rarely been reported in pharmacosurveillance data – see below.)

The cases series of spontaneous AE reports (Gish 2009; Jonville 1992; 't Veld 1998) highlight the existence of CNS events but fail to distinguish between different formulations of oxybutynin.

Other Adverse Event Data

Regulatory Data

Data on adverse events was sought from government and regulatory sources including periodic safety update reports (PSURs), records in the Health Canada Vigilance Adverse Reaction Online Database and the U.S. Food and Drug Agency reviews. Pharmacosurveillance databases have major limitations including under-reporting and lack of denominator data, which precludes rate calculations.

Periodic Safety Update Reports (PSUR)

Two PSURs were available for oxybutynin. One PSUR covers a 6 month period only, from Feb-Jul 2012, for oxybutynin ER and oxybutynin IR. A second PSUR-type document, entitled an annual summary report, includes data for oxybutynin gel 10% and oxybutynin TDS over a one year period from Feb 2011 to Feb 2012. However, because of the timing of market entry of oxybutynin gel and a change in the market holder of oxybutynin TDS, < 4 months of case reports are included.

Oxybutynin ER (XL) and IR

The available PSUR covers the 6-month period from Feb 1st, 2012 to July 31th 2012 during which approximately 19,452,064 patient-days of exposure were estimated to have occurred worldwide for either oxybutynin IR or ER. The report concludes that no new signals were

identified and the data are consistent with reference safety information. Oxybutynin first entered the global market in 1975 and some cumulative data are provided.

Deaths: No deaths were reported during the 6-month PSUR period. Cumulative deaths to July 2012 were 23 for oxybutynin ER and 11 for oxybutynin IR. Details are not provided.

Serious Adverse Events (Non-fatal)
The total number of cases that involved one or more serious events are not clearly summarized.

During the 6-month period, there were 17 AE reports in total related to Oxybutynin ER (PSUR Tables 4-5); these included a total of 7 serious events (3 of which were listed and 4 unlisted). For oxybutynin IR, there were a total of 18 case reports, including a total of 12 serious events (4 listed and 12 unlisted) (PSUR Tables 6-7). Listed events are those that are included in product monographs to inform health care professionals and patients.

Cumulative data were provided to July 31st, 2012 with the caveat that not all historical manufacturer datasets coded seriousness. This may have resulted in an underestimate of the cases identified as serious AE. The proportion of the dataset without seriousness coding is not provided. Reported as cumulative were 456 serious unlisted AE in 278 patients using oxybutynin ER and 513 unlisted SAE in 265 patients using oxybutynin IR tabulated by ADR term and reporting source.

Central Nervous System Effects
Terms related to nervous system disorders or psychiatric disorders have relevance to central nervous system effects.

Oxybutynin ER: Cumulative to July 2012 (with the caveat above), for all terms related to nervous system disorders, there were a total of 54 serious unlisted events in 46 patients; these included 8 events of cognitive impairment, amnesia, cognitive disorder, mental impairment or dementia (Appendix 4.1, p.160-161). For psychiatric disorders (includes confusional state, hallucination, mental status changes and many other terms), there were 32 serious unlisted events in 20 patients. In the 6-month time period, 1 case report involved a SAE of cognitive impairment without details on age, sex, treatment duration or medical history.

Oxybutynin IR: For all terms related to nervous system disorders, there were 61 serious unlisted events in 50 patients in the cumulative dataset, including 1 event each of dementia, amnesia and incoherence (Appendix 4.2, p. 200-202). For psychiatric disorders, there were 47 events in 30 patients.

Cognitive impairment was identified as an event that will continue to be monitored. It is not listed in the reference safety material.

Depression is also an event undergoing continued monitoring. Cumulatively, there was 1 event of depression reported with oxybutynin ER and 4 events of depression reported with oxybutynin IR. The interim analyses from this PSUR did not result in new safety signals.

Cardiac:
Oxybutynin ER: There were 33 cumulative serious unlisted cardiac events (with the caveat above) in 32 patients (includes 16 events of arrhythmia; 4 cardiac arrests) for oxybutynin ER (Appendix 4.1, p.137-138).

Oxybutynin IR: There were 32 cumulative serious unlisted cardiac events in 27 patients (includes 18 events of arrhythmia; 4 cardiac arrests). There were 2 events of ventricular tachycardia and 2 events of torsade de pointes (Appendix 4.2, p. 177-178).

No cases of QT prolongation and one report of chest pain were reported during the 6 month period. Cumulatively, each had 1 case of ECG QT prolongation.

Gastrointestinal: Intestinal obstruction
Amongst gastrointestinal AE in the cumulative dataset, there were 3 cases of intestinal obstruction and 1 of intestinal ischemia associated with oxybutynin ER (Appendix 4.1, p. 144), and 3 events of intestinal obstruction and 2 events of intestinal ischemia (2 different categories) associated with oxybutynin IR (Appendix 4.1, p. 183).

Falls/fractures: For oxybutynin ER, in the cumulative dataset, there were 3 falls and 5 events of fractures (different categories). For oxybutynin IR, in the cumulative dataset, there were 2 falls and 7 events of fractures (different categories).

Elderly: During the time period covered, two cases were identified, one a SAE of severe constipation in an 84 year-old female, associated with oxybutynin ER, and the other, lack of efficacy with IR. These are medically confirmed cases only (e.g. clinician vs. patient reported), the majority of which had age unknown. More AE in elderly were reported in unconfirmed cases. No new signals were generated.

Changes to Reference Safety Information
No changes were made to oxybutynin's reference safety information during 6 months covered by the 16th PSUR.

Oxybutynin Gel 10% and Transdermal System 36 mg (3.9 mg/day)
An Annual Summary Report for oxybutynin TDS and oxybutynin gel covers the one-year period from Feb 26, 2011 to Feb 25th 2012. However, the reporting period for oxybutynin gel is only Nov 4, 2011 to Feb 25th 2012 as it came on market and for oxybutynin TDS, Jan 1, 2012 to Feb 25th, 2012, due to a change in manufacturer with market approval. The international birthdate of February 26th, 2003 was based on the U.S. granting of market approval for the TDS product. The report concludes that there were 'no unusual findings'.

Total case reports: Oxybutynin TDS was implicated in 30 adverse reaction case reports during the 56 day reporting period available, of which 3 were serious (see below).

Oxybutynin gel was implicated in 61 adverse reaction case reports received during the 113 day reporting period available to this report. None of the cases were coded as serious.

Two of the 91 case reports were from Canada, one for each product.

Deaths: No deaths were reported for either oxybutynin gel or oxybutynin TDS during the time period covered by the PSUR.

Serious Adverse Events (non-fatal)
There were 3 case reports of reactions described as 'serious, unexpected' (i.e., unlisted) cases received from European Union regulatory authorities.

- A 92 year old male with cognitive disorder/visual hallucination/anxiety/ disorientation/Parkinson's disease

- A 78 year old woman with reported abasia – impaired walking
- An 84 year old woman with reported anuria/painful vaginal mucosal blistering

There were no listed serious events reported.

Elderly: The three serious cases (above) for oxybutynin TDS were in elderly patients. Of 30 case reports related to oxybutynin TDS there were 13 (43%) in patients 65 or older, 11 (37%) with no age reported and 6 (20%) with reported age <65.

Of the 61 cases reported in patients using oxybutynin gel there were 37 (61%) in the elderly 65 or older versus 13 (21%) age <65 and 11 (18%) with no reported age.

Central nervous system effects
The majority of events classified as nervous system or psychiatric disorders may be considered central nervous system effects. These include cognitive impairment and events such as hallucination.

Oxybutynin TDS: 1 serious case report (reviewed above) contained 5 serious unlisted events: cognitive disorder, Parkinson's disease, anxiety, disorientation, and hallucination, visual. Abasia (impaired walking), a serious event categorized under general disorders, may also be related to a central nervous system effect. Non-serious reports were: headache; dizziness.

Oxybutynin Gel: 13 case reports included terms related to nervous system or psychiatric disorders. Listed adverse events were: dizziness, somnolence, blurred vision. The following unlisted events were also reported: hallucination, insomnia, nightmare, ageusia, dysgeusia, burning sensation and sensory disturbance.

Cardiac
There was 1 'cardiac disorder' event each for oxybutynin TDS (bradycardia) and oxybutynin gel (palpitations), both unlisted non-serious events.

Application site reactions
Oxybutynin TDS: Of the total of 30 case reports, 13 cases included a total of 32 events classified as either application site reactions or skin disorders. The following unlisted adverse events: scarring, discolouration; eczema; erosion; pain; dermatitis (contact); erythema; pruritus; and skin irritation (N=11 events). There were also 21 listed events (e.g., application site erythema, irritation, inflammation or pruritus).

Oxybutynin Gel: Of 61 case reports, there were 17 cases that included a total of 29 events classified as either application site reactions or skin disorders. These included the following unlisted events (N=17 events): exfoliation, papules, rash, swelling, urticaria, erythema, rash, pruritic rash and skin haemorrhage. There were also 12 listed events.

Health Canada Vigilance Database
A total of 250 unique adverse reaction reports (-4 duplicate reports) for oxybutynin are in the Canadian Vigilance Dataset, up to March 31st, 2013, the latest date of entry for the database. This number includes all age groups and products. The majority of reports were for oral oxybutynin IR or ER; 44 case reports were on oxybutynin TDS (oxytrol) and 11 on oxybutynin gel (gelnique), likely reflecting the duration each product has been on the market, as well as other factors that influence reporting rates over time. These numbers cannot be used to compare formulations.

There were a total of 94 case reports described as serious. Of these, the type of formulation was clearly specified in only a minority of reports: ER (12); oxybutynin gel (4); oxybutynin TDS (5). The majority were either ER or IR oral formulations identified as Ditropan or generic oxybuytnin.

Deaths: Four deaths were reported: 2 completed suicides (overdose); 1 dysuria/neoplasm malignant/PSA increased; 1 constipation/intestinal obstruction/faecaloma/faecal vomiting/gastrointestinal tube insertion/sepsis and other terms related to infection.

Serious Adverse Events in specific categories:
Central Nervous System Effects: A total of 34 case reports with terms related to nervous system disorders were identified as serious in adults 18 years of age (or age unspecified) (Appendix L). These included confusion and amnesia. An additional 12 unique cases in adults were identified as psychiatric disorders that included depression, aggression, psychotic disorder and other terms. Of nervous system or psychiatric case reports, 3 were associated with oxybutynin transdermal patch, 2 associated with oxybutynin gel, and the rest associated with oral ER or IR oral formulations. It was not possible to determine whether an oral formulation was immediate or extended-release in the majority of cases due to lack of details in the reports.

Cardiac: A total of 11 case reports were identified for 'cardiac disorders', including 8 case reports described as serious (Appendix L). These included 1 event of chest pain with oxybutynin gel and 7 cases associated with oral oxybutynin IR or ER, including events such as arrhythmia or tachycardia, palpitations, cyanosis and congestive heart failure.

Falls: 3 cases of falls were reported, all in patients> age 65.

Urinary retention: 4 cases were reported, 3 in men.

Discussion and Conclusions

Q1: Do extended-release formulations of oxybutynin provide a therapeutic advantage over oxybutynin IR?

One or more trials were available for the comparisons of oral oxybutynin ER versus oxybutynin IR, and oxybutynin TDS vs. oxybutynin IR. No direct comparator trials were identified for oxybutynin gel.

Oral ER formulations vs. oxybutynin IR: The available RCT data are all short-term. Trials were under-powered for all-cause mortality and serious adverse events. Harms were incompletely reported. There was no statistically significant difference in WDAE suggesting similar tolerability. Based on two trials (N=193), there was no statistically significant difference in the proportion of patients experiencing one or more AE (Birns 2000; Minassian 2007). Fewer patients on oxybutynin ER experienced dry mouth (risk difference 8%), based on five trials. Interpretation of harms data is limited by the enrolment of participants with proven tolerability to oral oxybutynin in three of the five trials (Birns 2000; Versi 2000; Anderson 1999), a mixture of doses in most trials, and the question of dose equivalence. Most of the trials used a similar range of doses for the IR and ER formulations. Based on pharmacokinetic considerations, equivalent doses would be a slightly lower dose for the IR formulation. The strength of evidence is assessed as moderate for dry mouth, low for other specific adverse events and insufficient for all-cause mortality and serious adverse events.

Quality of life (condition-specific), based on total UDI and Urge-UDI scores were reported in two trials (Barkin 2004; Minassian 2007) improved less on oxybutynin ER. There was no statistically significant difference in total IIQ score in Barkin 2004, and the five domain scores of IIQ reported by Minassian 2007.

Improvement in incontinence episodes was similar between drugs in the five trials. A meta-analysis could not be conducted on this outcome as some trials reported medians instead of means or did not report a measure of variation (moderate evidence). Only one trial reported on urgency, which did not show a difference between formulations (insufficient evidence). No trials reported on nocturia.

Transdermal formulations of oxybutynin vs. oxybutynin IR:
Oxybutynin TDS vs. Oxybutynin IR: One dose-titration trial, designed as an equivalence trial, failed to show equivalence of oxybutynin TDS with oral oxybutynin for the *a priori* primary outcome, percentage of patients who were responders. Responders were defined as those participatns who had a $\geq$ 30% reduction from baseline in incontinence episodes. This trial was under-powered for the primary outcome; the results therefore also fail to conclusively establish non-equivalence. Other efficacy outcomes were similar but the doses were not comparable.

Dose-titration was based on tolerability of anticholinergic effects, based on AE experience via regular reports on a patient questionnaire. At study end, the majority of participants were on a higher-than-approved dose of oxybutynin TDS, limiting the applicability of the findings to usual clinical practice. This also raises questions about patient perception of effectiveness at approved dose levels, and whether use of higher-than-approved doses of oxybutynin TDS may also occur in clinical care. The dose range for oxybutynin TDS and oxybutynin IR was not comparable, and lower rates of anticholinergic adverse events such as dry mouth with oxybutynin TDS could have been due to the lower anticholinergic dose (range 1-8mg/day versus 5-22.5mg total/day).

There is insufficient evidence to conclude a therapeutic advantage of oxybutynin TDS over oxybutynin IR.

Oxybutynin gel vs. oxybutynin IR: no data are available.

Comparison with other systematic reviews: The findings of this review are generally consistent with two recent systematic reviews, Madhuvrata 2012 and Shamliyan 2012, as the same trials were included. For the comparisons of oxybutynin ER versus oxybutynin IR, Madhuvrata et al. reported that one trial had provided data for ‘cure’ (Birns 2000). We reported that no trials presented this outcome because the results for Birns 2000 was a partial reporting only – a daytime continence rate and not a 24 hour continence rate. This did not meet our definition of ‘cure’. We addressed the issue of dose equivalence to a greater extent than either of the previous reviews.

Supplemental Adverse Event data

Placebo-controlled trials in the elderly:
Lackner 2008 compared oxybutynin IR to placebo in elderly women with OAB who were residents of nursing home facilities (mean age 89). There were no differences in the development of delirium, agitation or change in MMSE in the treatment groups. MMSE is unlikely to detect mild differences in cognition, and the Confusion Assessment Method, the primary outcome in Lackner 2008, was predominantly designed to detect acute changes of delirium.

Non-randomized studies:

None of the observational studies included in this review compare effects of different formulations of oxybutynin. Moga 2013 raises a note of concern about the potential for increased rates of falls and fractures in frail elderly men in nursing homes, particularly with oxybutynin IR. For all antimuscarinic drugs in this study, there was one additional hip fracture for every 36 men treated for 90 days, as compared with non-users matched for comorbidities. Most of this cohort used oxybutynin IR or other IR formulations of antimuscarinic drugs. However, whether similar risks occur with other formulations remains unknown. In Diokno 2002, over longer-term use (one year) a dose-dependent increase in dry mouth was observed with oxybutynin ER. CONTROL 2012 found that users of oxybutynin TDS may continue use despite lack of effectiveness or worsening symptoms, despite clear instructions not to do so.

Post-market surveillance and regulatory safety data: These data were not sufficient to distinguish the safety profiles of different formulations because of their many limitations including under-reporting.

Gaps in evidence

There are no comparative RCT data in the frail elderly, and the maximum duration of RCTs was 12 weeks, too brief to asses longer-term effects. For oxybutynin gel, no comparisons exist to other formulations. For oxybutynin TDS, a single trial was unable to establish equivalent effectiveness as compared with oxybutynin IR. This trial was under-powered and included a non-equivalent dose range. Thus insufficient comparative evidence exists for transdermal formulations to judge whether they provide a therapeutic advantage. For all formulations, there is a need to ensure that comparative RCTs are based on equivalent doses in order to adequately assess comparative benefit and harm. The available trial evidence for oxybutynin ER versus IR also fails to answer the question of better tolerability in patients who cannot tolerate oxybutynin IR, as three of the five trials only enrolled oxybutynin responders.

Q1b. Does tolterodine ER provide a therapeutic advantage over tolterodine IR?

One 12-week trial was available on tolterodine ER versus tolterodine IR (van Kerrebroeck 2001). Based on this trial (N=1021), there was no difference in SAE or WDAE (ven Kerrebroeck 2001). The trial was under-powered for mortality. The proportion of patients experiencing one or more AE was not reported. Tolterodine ER led to less dry mouth (risk difference 7%). There was no difference in reported efficacy outcomes (incontinence episodes). There are no comparative outcome data available on quality of life even though this was measured in the trial, and no available data on urgency or nocturia. There is insufficient evidence for harms and efficacy outcomes to conclude a therapeutic advantage for tolterodine ER. No long-term data are available (beyond 12 weeks).

Q2. New Evidence since the CDR Review(s)

There are no CDR reviews for the transdermal patch or oral extended-release formulations of oxybutynin. The approval of these products pre-dated the CDR process so this question is not applicable to those formulations.

There are also no CDR reviews for the extended-release formulation of tolterodine. Approval of tolterodine ER pre-dates the CDR process.

Oxybutynin chloride gel: A CDR review on the gel formulation of oxybutynin chloride (Gelnique) was conducted in 2012. The CDEC recommendation, dated May 24, 2012, was that

oxybutynin chloride gel not be listed. Reasons cited were 1) the uncertain comparative clinical benefit in the absence of any RCTs that directly compare it to other pharmacological treatment, and 2) the absence of RCTs comparing the incidence of anticholinergic adverse effects (such as cognitive and neurological) between oxybutynin chloride gel and other oxybutynin products, particularly in the elderly (Common Drug Review 2012).

One placebo-controlled 12-week RCT (Study OG05009, Staskin 2009) was included in the CDR clinical review. The submission also included subgroup analyses from that trial that showed the results for patients > 65 years did not differ between oxybutynin gel *and placebo* in reducing incontinence frequency or micturition. This is in contrast to the product monograph that states there were no observed differences in safety or effectiveness between older and younger patients.

For the current review, no direct comparator RCTs were identified in OAB patients.

No new comparative RCTs in OAB patients were identified for the current review i.e., there continue to be no direct comparator RCTs that compare oxybutynin chloride gel to any formulation of oxybutynin or other antimuscarinic drugs.

The only direct comparator RCT was a healthy volunteer study (Kay 2012b) that compared short-term cognitive effects of oxybutynin gel to oxybutynin IR and placebo in healthy volunteers aged 60 or older. This study provides insufficient evidence to conclude a therapeutic advantage for oxybutynin gel over oxybutynin IR in regards to cognitive effects (see below). Because of this, the conclusions of the 2012 CDR review are not changed substantively.

The conclusions of the current review is that there is insufficient evidence with which to assess whether oxybutynin gel has a therapeutic advantage over oxybutynin IR or other comparators. This is consistent with the CDR review results and the rationale behind the CDEC recommendation.

Q3. Cognition

A total of 4 RCTs were identified that actively measured at least one cognitive outcome, two trials in patients with OAB, and two in healthy volunteers (Table 15, below). Two were direct comparator trials (Minassian 2007; Kay 2012b) and the other two were placebo-controlled.

Table 15. RCTs on cognition

Study	Comparison	Population	Outcomes
Patients with OAB			
Minassian 2007	OXY ER vs. OXY IR	Females with OAB > age 65	MMSE only
Lackner 2008	OXY ER vs. Placebo	Female nursing home residents with OAB	Multiple cognitive tests
Healthy volunteers			
Kay 2012b	OXY Gel vs. OXY IR	Male and female healthy volunteers	Multiple cognitive tests
Katz 1998	OXY IR vs. Placebo and diphenhydramine	Male and female healthy volunteers	Multiple cognitive tests

ER= extended-release; **IR**= immediate-release; **OXY**= oxybutynin; **MMSE**= mini-mental status examination

a. RCTs in OAB patients:

Direct Comparator Trials: Minassian 2007 is discussed above. This parallel-group trial compared oxybutynin ER to oxybutynin IR. The trial was under-powered and terminated early due to recruitment difficulties and an interim analysis that indicated a much larger sample size than initially planned would be required to detect a significant difference between formulations. The only cognitive outcome was MMSE, which did not show statistically significant differences between formulations. However, this screening tool is not likely to be sensitive to mild differences in cognition.

Placebo-controlled trials: Lackner 2008 was a 4-week parallel-group trial that enrolled cognitively-impaired elderly females > age 65 (mean age 89 ± 6.2 years) with OAB. All participants were residents of nursing home facilities. Participants had MMSE scores of 5 to 23 and randomization was stratified on the basis of MMSE score (11-23 and 5-10). The study was an equivalence trial for the primary outcome, mean change in the Confusion Assessment Methods (CAM) algorithm. The CAM is a validated instrument for assessing the presence or absence of delirium (Inouye 1990) i.e., based on features of acute onset and fluctuating course, inattention, disorganized thinking and altered level of consciousness. Items in the CAM include inattention, disorganized thinking, altered level of consciousness (e.g., includes drowsy), disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation and altered sleep-wake cycle. The margins of equivalence for the 95% confidence intervals of the mean change were ± 2 points. The scoring system is not described nor is the basis on which the margins of equivalence were chosen (referenced as a personal communication with the author of the algorithm). Secondary outcomes included change in MMSE scores, Severe Impairment Battery and Brief Agitation Rating Scale.

No patient experienced delirium during the study. A subgroup analysis of patients with baseline MMSE scores of 11-23 did not show a statistically significant difference at any time point between oxybutynin ER and placebo. There were too few patients in the MMSE 5-10 subgroup to draw conclusions. No difference was detected in median changes in MMSE before or after adjustment for potential confounders (age, number of medications known to have serum anticholinergic activity, or measured serum anticholinergic activity at 7 days). There was also no difference in the Severe Impairment Battery or Brief Agitation Rating Scale between oxybutynin ER and placebo.

Harms: Only treatment-related harms were reported, which represents a subset of total AE and may not reflect the overall experience of the patient. Reported events were infrequent e.g., 2 people experience ‘treatment-related’ constipation and 1 patient experienced ‘treatment-related’ dry mouth vs. 0 in the placebo group, further suggesting incomplete reporting and lack of power to detect differences in harms. One individual on oxybutynin ER (3.9%), and none on placebo, experienced urinary retention. The incidence of falls was assessed during the study period and for the 3-month period before and after the study, with no differences detected in rates of falls during any time period. One person in the oxybutynin group and 2 people in the placebo group experiencing falls during the 4-week treatment period.

Risk of bias/quality

Most of the methodological features were assessed as unclear risk of bias other than method of randomization (low risk of bias) and selective outcome reporting (high risk of bias based on the incomplete reporting of harms). An intention-to-treat analysis with last-observation-carried-forward was not employed. However, as only 3 individuals withdrew early, use of a per protocol analysis is likely to have had minimal effect on results. Therefore this was rated as ‘unclear’ risk of bias.

Assessed outcomes in this trial predominantly pertain to severe acute changes (delirium), and not to all potential CNS effects. However, assessment of delirium is applicable to the frail elderly. The lowest recommended dosage of oxybutynin ER was used, 5mg/day. All participants were women so the results may not be applicable to elderly men.

The study was sponsored by the manufacturer of oxybutynin ER (Ditropan XL).

b. RCTs in healthy volunteers

Direct Comparator RCTs

One 8-day, parallel group, placebo-controlled RCT assessed the effects of oxybutynin topical gel and oxybutynin IR on cognition (Kay 2012b). One hundred and fifty-two healthy volunteers were enrolled (mean age 67-68; range 60 to 79 years). Volunteers received 8 days of treatment with oxybutynin gel (1 gram=100mg oxybutynin once daily), oxybutynin IR 5mg t.i.d. (15mg total/day) or placebo. Cognition was assessed on a battery of cognitive and psychomotor tests at screening, baseline (day 1) and study end (day 8). Participants had no cognitive impairment at enrollment based on mean MMSE scores (~30).

The identified primary outcome was delayed recall on the name-face association test (NFAT). Treatment effects were analyzed on the basis of an all-group analysis of covariance model (with variables included for baseline score, centre and treatment group). There was no significant difference among the three treatment groups after adjustment for baseline scores. In a pairwise analysis versus placebo, there was no significant effect of either oxybutynin gel or oxybutynin IR. This was described as unexpected because a prior study (comparing darifenacin vs. oxybutynin ER) had shown deterioration of this test with oxybutynin (Kay 2006).

The emphasis on the name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008).

A total of thirteen different cognitive outcomes were reported, divided into two categories: 1) learning and recent memory, and 2) visual attention, reaction time and information processing. Some post hoc, exploratory analyses were conducted: an analysis of the proportion of participants with reliable change scores on NFAT Delayed Recall, change from baseline in the Hopkins Verbal Learning Test-Revised (HVLT-R) scores, and the proportion of participants whose HVLT-R immediate recall scores met or exceeded the threshold for a reliable change (decline in score $\geq$ 6 points).

The Misplaced Objects Test, a secondary outcome, showed a decline from baseline with oxybutynin IR whereas other groups showed an improvement (consistent with a practice effect): oxybutynin gel mean 1.00 ± SD 2.25; oxybutynin IR -0.29 ± 2.97; placebo 0.67 ± 2.36. The clinical meaningfulness of this difference is not discussed in the publication.

In the post hoc analyses, a decrease from baseline in HVLT-R (immediate recall or delayed recall) scores was statistically significant only for oxybutynin IR. A statistical comparison of the mean change from baseline vs. placebo (or oxybutynin gel) was not reported. More participants on oxybutynin IR met or exceeded the minimal difference for reliable change (decline in score > 6 points) on HVLT-R immediate recall. However, our exploratory analyses (paired t-test) did not show statistically significant differences between oxybutynin IR and placebo or oxybutynin gel. Conclusions cannot be drawn on these post hoc analyses, which are hypothesis-generating only.

The authors suggest that a failure to detect a (negative) effect with oxybutynin IR, in contrast to their prior study, may have been because the total dose of oxybutynin in this study was lower (15mg/day total IR) compared with the prior study (20mg/day total ER). This explanation fails to take into account differences in pharmacokinetics and dose equivalence between ER and IR formulations; the doses used in the two studies were comparable.

Harms
SAE: there were no SAE during the trial.

WDAE: 3/52 (5.8%) of participants on oxybutynin IR withdrew due to AE and none in the oxybutynin gel or placebo groups. WDAE were due to nausea/sore throat/abdominal distension (1); nausea (1); and decrease in urine flow (1).

Total AE: were not reported.

Specific AE
Dry mouth: The most common specific AE was dry mouth: oxybutynin gel 3/49 (6%) vs. 38/52 (73%) of the oxybutynin IR group: RR 0.8 (95% CI 0.03 to 0.25), P <0.0001; risk difference: -67% (-81% to -53%).

Other AE are in the table 16, below.

Table 16. Adverse events reported in Kay 2012b

Treatment arm	OXY gel	OXY IR	Placebo
Total AE	NR	NR	NR
Dry Mouth	3 (6.1%)	38 (73.1%)	4 (7.8%)
Headache	0	4 (7.7%)	2 (3.9%)
Nausea	0	4 (7.7%)	0
Constipation	0	3 (5.8%)	0
Cough	0	3 (5.8%)	0
Dizziness	0	3 (5.8%)	0
Nasal dryness	0	3 (5.8%)	0
Urinary hesitation	0	3 (5.8%)	0
Dry eye	0	2 (3.8%)	0
Dry throat	0	2 (3.8%)	0
Urine flow decreased	0	2 (3.8%)	0

AE= adverse events; **IR**= immediate-release; **NR**= not reported; **OXY**= oxybutynin;

Vital signs and laboratory test results did not indicate any clinically significant changes.

Risk of bias/quality assessment: This study was appropriately randomized (low risk of bias) but did not describe allocation concealment, which was rated to be of 'unclear' risk of bias. Blinding of participants and personnel was rated at low risk of bias on the basis of identical appearance of placebo gels and capsules. The high incidence of dry mouth in the oxybutynin IR group, however, is likely to have led to a loss in blinding. Blinding for outcome assessment was not described ('unclear' risk of bias). There was low risk of bias related to incomplete outcome reporting and selective outcome reporting.

Comparator/dose choice: There is limited information on which to base a judgment about equivalence of the doses used (oxybutynin gel 1 gram 10% and oxybutynin IR 15mg total/day) because a direct comparative pharmacokinetic study is not available (Center for Drug Evaluation and Research NDA 22-204 Clinical Pharmacology Review). The pharmacokinetics and dose of 1

gram 10% oxybutynin gel is similar to oxybutynin TDS (3.9mg/day). One prior review suggests, based on estimates of available mean steady state concentrations, that a 3.9 mg/d dose of oxybutynin TDS is similar to an oral oxybutynin dose of 15-30 mg. However, an FDA clinical pharmacology review was unable to accept that a dose range of oxybutynin TDS 1-8mg per day was comparable to a dose range of 5-22.5mg for oxybutynin IR without further supporting evidence, which was not available (Center for Drug Evaluation NDA 20-351). This indirect evidence suggests the issue of dosage equivalence between oxybuytnin gel and oxybutynin IR remains an open question.

The RCT was sponsored by the manufacturer of oxybutynin gel, with medical writing assistance from the pharmaceutical company.

Placebo-controlled RCTs
A single-dose, double-blind, placebo-controlled crossover trial enrolled 12 healthy, cognitiviely intact volunteers > age 65 years (mean age 69 years) (Katz 1998). The trial was sponsored by a grant frm the U.S. National Institutes on Aging. Oxybutynin IR 5mg or 10mg was compared to placebo and an antihistamine (diphenhydramine 50mg) control. The highest dose of oxybutynin was greater than the maximum recommended single dose. Washout period was 7 days between treatments. The battery of cognitive tests included both interviewer-administered and computerized tests and a practice or training session was conducted (Tables 4 and 5, Appendix J).

Several statistical analyses were conducted including random regression, the main analysis, with two models varying in the way the oxybutynin dose was considered; the model that fit best made assumptions about the linearity of the dose-response. Significant oxybutynin effects ($P < 0.05$) were identified on 7 of the 15 cognitive measures, all effects in the direction of impaired performance. When a correction was made for multiple comparisons, drug effects for oxybutynin were significant for 3 of the 15 tests: Buschke Long-term Storage, Buschke Recall from Long-term Storage and Reaction Time. None of the effects for diphenhydramine remained significant after the correction for multiple comparison. Because of the small sample size, formal statistical tests were not conducted for the degree of fit of statistical models, effects of oxybutynin and diphenhydramine or the sensitivity of the cogntive tests.

Risk of bias/quality: The order of sequence of receiving oxybutynin, diphenhydramine and placebo was randomized (but not the dose of oxybutynin). There was no further information provided about the process of randomization itself or allocation concealment (both rated as ‘unclear’ risk of bias). Although the trial was described as “double-blind”, drugs were given in orange juice and not described as being identical in taste. The study did not identify any withdrawals so was rated ‘unclear’ for incomplete outcome reporting. The study was rated at low risk of bias for selective outcome reporting (Table 3, Appendix J).

Harms: were not reported in this study.

Non-randomized studies: Moga 2003, a controlled cohort analysis among residents of U.S. Veterans Administration long-term care facilities, compared initial users of antimuscarinic drugs with non-users. The majority of patients were elderly males, with 21-22% over the age of 85. 10% had moderate to severe cognitive impairment at baseline; 75% of users were on oxybutynin IR..All comparisons were to non-users. Results for cognition were reported for all anti-muscarinic drug users jointly.

A cognitive performance scale that is highly correlated with the mini-mental state exam (MMSE) was used to assess cognition; range in scores 0 (intact) to 6 (very severe impairment). No difference was observed between patients on antimuscarinics and non-users. However, the scale is not likely to be sensitive to mild differences in cognition. Therefore it is unclear whether the lack of detected difference reflects no effect on cognition or the scale's lack of ability to detect minor differences. Major short-term effects on cognition were excluded, over a median of 45 days, but a claim of no effect on cognition cannot be supported. This study does not provide comparative data between oxybutynin and other drugs or different oxybutynin formulations.

Summary – Cognition

Two short-term trials (4-12 weeks) on elderly females were identified. One trial (N=76) reported no difference between oxybutynin ER and IR in MMSE, a secondary outcome (Minassian 2007). The other trial (N=50), a placebo-controlled trial, did not detect development of delirium, agitation or change in MMSE with oxybutynin IR compared to placebo (Lackner 2008). The latter trial was conducted exclusively in women who were residents of nursing home facilities (mean age 89). MMSE is unlikely to detect mild differences in cognition, and the Confusion Assessment Method, the primary outcome in Lackner 2008, was designed to detect acute changes of delirium. The latter trial was an equivalence trial and the clinical meaningfulness of the margins chosen for equivalence (± 2 points on CAM) were not discussed. Neither study provides sufficient evidence to conclude oxybutynin does not cause cognitive impairment in the elderly when used on a long-term basis.

Two trials in healthy volunteers were identified. The largest trial (Kay 2012b; N=153) compared oxybutynin gel to oxybutynin IR and did not reveal a difference between formulations for the primary outcome, delayed recall on the name-face association test. The emphasis on name-face association test versus other outcomes such as reaction time may not be justified in terms of overall assessment of cognition (Janos 2008). Conclusions cannot be drawn on secondary outcomes or post hoc analyses, which are hypothesis-generating only. The issue of dose equivalence in this study is unresolved, limiting interpretation of the data.

A smaller placebo-controlled study in healthy volunteers (N=12) suggests cognitive changes can occur with a single-dose of oxybutynin IR. When a correction was made for multiple comparisons, drug effects for oxybutynin were significant for 3 of the 15 tests: Buschke Long-term Storage, Buschke Recall from Long-term Storage and Reaction Time. None of the effects for the antihistamine diphenhydramine remained significant after the correction for multiple comparison. This study used a higher-than-recommended dose as its maximum single dose of oxybutynin. It provides no information about steady-state (multiple dose) effects and no information about comparative effects with other antimuscarinic drugs.

Taken together, these studies do not provide sufficient evidence with which to conclude one formulation of oxybutynin has a therapeutic advantage in terms of cognitive effects in the elderly.

No RCTs were identified that assessed long-term cognitive effects of any formulation of oxybutynin.

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Direct Comparator RCTs

Different Formulations of the Same Drug
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Table of Contents – Part I Appendices

Appendix A. References for Included Studies and Systematic Reviews

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Appendix B. Pharmacokinetics of Antimuscarinic Drugs

Select features of each drug under review and its different formulations are presented below.

Oxybutynin

Oxybutynin is a nonselective muscarinic receptor antagonist. It also has a direct antispasmodic action on smooth muscle but this is much weaker than its anticholinergic properties and may not be clinically significant (Oxybutynin Chloride Immediate Release Product Monograph; Kennelly 2010). A local anesthetic and analgesic effect is claimed as well but is of unknown clinical significance. Oxybutynin is available in three oral and two transdermal formulations.

Oxybutynin immediate release (IR) has a short half-life of 2-3 hours, and low oral bioavailability of about 6% (range 1.6 to 10.9%) due to extensive first pass (pre-systemic) metabolism in the bowel and liver before it enters the bloodstream (Oxybutynin Chloride Immediate Release Product Monograph). Metabolism is predominantly due to the enzyme CYP 3A41, which is part of the cytochrome P450 system. An active metabolite, N-desethyloxybutynin (DEO), is equipotent to the parent compound. DEO has been hypothesized to account for some of the more common adverse effects. This has led to marketing claims based on differences in the amount of DEO produced by different routes of administration.

Oxybutynin is widely distributed in the body. The IR formulation has greater fluctuations in peak and trough plasma concentrations than longer-acting formulations. There is a wide interindividual variation in the pharmacokinetics of oxybutynin IR, with approximately 8-fold variation in peak plasma concentration, C_{max}, and area under the concentration curve over time (AUC), a measure of drug exposure. The limited data have not detected sex differences for any adult age group.

Published data on the pharmacokinetics of oxybutynin IR in the elderly are sparse, but indicate that oxybutynin concentrations tend to increase with age, particularly amongst frail elderly (Ouslander 1998; Hughes 1992). In frail elderly, C_{max} and AUC values are approximately twice those in elderly or young adult volunteers. The greater bioavailability frail elderly is likely due to increased absorption rather than differences in metabolism (Hughes 1992). The few published pharmacokinetic studies indicate a lower starting dose of 2.5 mg two or three times a day may be sufficient to attain therapeutic plasma levels in frail elderly. This information is reflected in the U.S. Package Insert (Oxybutynin Chloride Immediate Release (Ditropan®) U.S. Package Insert).

Oxybutynin ER (Ditropan XL) uses a nondeformable delivery system consisting of a semipermeable membrane surrounding a bi-layer core, which releases drug by osmosis over a 24 hour period. It has an increased relative bioavailability of oxybutynin and lower relative bioavailability of DEO than oxybutynin IR (Oxybutynin Chloride Extended Release (Ditropan XL®) Product Monograph). This may be due to greater absorption of this formulation from the colon where there may be less pre-systemic metabolism than in the small intestine. A second controlled release formulation (Uromax®) is also available (Oxybutynin Chloride Controlled Release (Uromax®) Product Monograph). Both long-acting oral formulations show less fluctuation in peak and trough plasma levels of oxybutynin and DEO, with lower maximum plasma concentrations and higher trough levels than oxybutynin IR. Onset of action is slower than oxybutynin IR for the initial dose (Table). Nondeformable formulations of other drugs have rarely been associated with intestinal obstruction.

Two transdermal formulations bypass first-pass gastrointestinal and hepatic metabolism, reducing the formation of DEO. Transdermal oxybutynin is absorbed through the skin and into systemic

circulation by passive diffusion. Interindividual variation in skin permeability is about 20% (Oxybutynin Transdermal (Oxytrol™) Product Monograph). Only small amounts of CYP 3A4 enzyme are present in the skin so pre-systemic metabolism is low. Oxybutynin TDS is an adhesive patch that delivers drug continuously for 3 to 4 days. Upon initial application of oxybutynin TDS, plasma concentrations increase for 24 to 48 hours and then steady concentrations are maintained for up to 96 hours. Oxybutynin gel is an alcohol-based gel that is applied daily (Oxybutynin Gel (Gelnique™) Product Monograph). Absorption of both the gel and the transdermal patch is estimated to be about 10% of the applied dose. Application has to be rotated; the small variations in absorption at recommended sites are within the range for 'bioequivalence'.

Tolterodine

The premise that tolterodine achieves a separation of the antimuscarinic effects on bladder versus salivary glands or ciliary muscle (visual accommodation) has been the basis of marketing claims. Evidence for tissue selectivity for the bladder rather than other M3 receptor-bearing tissues is weak and may not be clinically significant.

Like oxybutynin, tolterodine is available in short and long-acting forms (Tolterodine Immediate Release (Detrol™) Product Monograph; Tolterodine Extended Release (Detrol LA™) Product Monograph). The long-acting form has less fluctuation between peak and trough concentrations, with peak concentration 75% of that observed with tolterodine IR, and trough concentrations 150% of that observed with the IR formulation.

Tolterodine is extensively metabolized to an active metabolite, 5-hydroxymethyl tolterodine (5-HMT) by enzyme CYP 2D6. Tolterodine's clinical effects are due to the total concentration of the parent compound plus 5-HMT, which has similar activity.

The metabolism of tolterodine is affected by genetic polymorphisms of the CYP 2D6 enzyme, as are several other drugs under review (Bernard 2006) (Table). Nonfunctional alleles of the CYP 2D6 enzyme occur in 2 to 10% of various populations. 'Poor metabolizers' use an alternate pathway for metabolism of tolterodine, involving CYP 3A4, and have higher levels of the parent compound than 'extensive metabolizers'. Because of a ten-fold difference in protein binding of tolterodine and 5-HMT, exposures to overall active drug/metabolite (active moiety) are thought to be comparable (Larrson 1999; Pahlman and Gozzi 1999). However, there have been few clinical studies that have assessed clinical outcomes in poor and extensive metabolizers and some evidence that adverse event profiles may vary by metabolizer phenotype. Tolterodine is more lipophilic than its active metabolite 5-HMT. Lipophilicity plays a role in crossing membranes such as the blood brain barrier. Reduced metabolism of the more lipophilic parent compound could potentially increase the adverse event profile in the brain or the eye, compared with extensive metabolizers.

CYP 2D6 alleles that cause intermediate levels of activity occur in up to 51% of Asian populations ('intermediate metabolizers') (Bernard 2006). This group of people may have the greatest exposure to the active drug/metabolite, compared with extensive and poor metabolizers, because of the CYP 2D6 enzyme's involvement in the metabolism of 5-HMT as well as its production (Oishi 2010). The clinical relevance of an intermediate metabolizer phenotype has not been studied.

Fesoterodine

Fesoterodine shares the same active metabolite as tolterodine. Fesoterodine is a pro-drug and almost entirely absorbed form the gut. It is rapidly converted by nonspecific esterases to 5-HMT

so that the parent compound is not detectable in plasma. Some of the converted 5-HMT undergoes pre-systemic metabolism, with bioavailability still relatively high at 52%. (Fesoterodine (Toviaz™) Product Monograph).

Based on a comparison of mean AUC values of active drug in CYP 2D6 extensive metabolizers (the majority of Caucasian populations), the bioavailability of 5-HMT is about 39% and 27% higher, respectively, at 4 mg and 8 mg doses of fesoterodine than 5-HMT following identical doses of tolterodine (Malhotra 2011). However, active drug exposure (termed the 'active moiety', which consists of active parent drug and any active metabolites) for tolterodine involves two moieties (tolterodine plus 5-HMT) whereas for fesoterodine, it involves a single entity, 5-HMT (Malhotra 2011). In contrast to production of 5-HMT from tolterodine, the conversion of fesoterodine to 5-HMT does not depend on CYP 2D6. Because of this, CYP 2D6 metabolizer status does not affect the production of 5-HMT. Pharmacokinetics studies suggest there is less interindividual variability in 5-HMT exposure compared with administration of tolterodine (Malhotra 2009; Malhotra 2011). However, 5-HMT is further metabolized by CYP 2D6 as well as CYP 3A4. Poor metabolizers (CYP 2D6 deficiency) therefore have a 1.7-fold and 2-fold increase in peak concentration (C_{max}) and area under the concentration curve (AUC) of 5-HMT, respectively. In addition, potent CYP 3A4 inhibitors (ketoconazole) can increase 5-HMT C_{max} and AUC by 2-fold and 2.4 fold, respectively. An 8 mg dose in a poor CYP 2D6 metabolizer taking ketoconazole would produce similar exposures as 28 mg in a CYP 2D6 extensive metabolizer (Center for Drug Evaluation and Research NDA 22-030). Because of this the maximum dose is restricted to 4 mg once daily in patients taking concomitant potent inhibitors of CYP 3A4.

Claims of tissue selectivity have the same limitations as those for tolterodine. Theoretically because 5-HMT is less lipophilic than tolterodine and has lower permeability across biological membranes such as the intestinal wall and the blood brain barrier, there may be an advantage in terms of reduced adverse events (e.g., constipation, central nervous system effects, effects on the eye), and in using fesoterodine in patients with an intermediate or poor metabolizer phenotype (Malhotra 2011). There are no clinical data to confirm or refute these notions.

Drug-drug interactions with potent CYP 3A4 inhibitors can occur. There is no dosage adjustment for potent CYP 2D6 inhibitors based on the magnitude of increased plasma levels in the presence of maximum inhibition (i.e., CYP 2D6 deficiency) as noted above.

Solifenacin

Solifenacin has modestly greater selectivity for the M3 receptor over M1 and M2 receptors. Solifenacin has the longest half life of all the antimuscarinic drugs (45-68 hours with multiple doses) and is well absorbed, with bioavailability of ~90%. It is extensively metabolized predominantly by the liver via CYP 3A4 enzyme. There is one active metabolite, 4R-hydroxy solifenacin, and three inactive metabolites, which are excreted by the kidney. It is highly bound to plasma proteins.

Adults aged 65 to 80 years have increased exposure to solifenacin by 20 to 25% compared with younger adults (Solifenacin Product Monograph). Renal insufficiency prolongs the half-life and increases exposure to solifenacin (Health Canada Summary Basis of Decision Vesicare®). Although no adjustment of dose is required for age alone, renal and hepatic function need to be considered. Dose adjustment should be made for severe renal insufficiency and in moderate hepatic insufficiency. The drug is contraindicated in severe hepatic insufficiency.

In preclinical studies, tissue selectivity for the bladder over salivary glands is reported. However, these data are limited and the clinical relevance of relative tissue selectivity in humans is not established.

The long elimination half-life of solifenacin may be an issue with respect to potential drug interactions and adverse effects (Health Canada Summary Basis of Decision).

Darifenacin

Darifenacin shows the greatest selectivity (9 to 59-fold), in vitro, for human cloned M3 receptors, the subtype thought to be most important to target in the bladder of patients with OAB.

Darifenacin is available as an extended release formulation with time to peak concentration of ~7 hours, and half-life of 12-18 hours. Bioavailability is 15% to 19%. There is a reported 23% per decade increase in bioavailability of darifenacin in people older than age 65, and exposure is also 28% higher at steady state in females (Darifenacin (Enablex®) Product Monograph). No dosage adjustment has been recommended for these groups. Data for the very elderly (>age 75) is limited due to the small number of patients (Health Canada Summary Basis of Decision Enablex®).

Doubling the dose more than doubles total and steady state exposure suggesting saturation of first pass metabolism (Health Canada Summary Basis of Decision Enablex®). Darifenacin is extensively metabolized by CYP 2D6 and CYP 3A4, predominantly by the liver, with less than 15% recovered unchanged. Only 10% of the ingested dose is converted to an active metabolite, which has four-fold less potency than the parent compound. In CYP 2D6 poor metabolizers, pathway of elimination is metabolism by CYP 3A4.

Trospium

Trospium differs from other drugs under review in that it is a quaternary amine rather than tertiary amine. This makes trospium highly charged and less likely to cross the blood brain barrier (see page 20 in main text of report). Trospium has a low bioavailability of 10% due to low permeability across the intestinal epithelium (Trospium (Trosec™) Product Monograph; Madersbacher and Rovner 2006). Bioavailability is further reduced in the presence of food, particularly a high fat meal, so should be taken under fasting conditions.

Women, aged 60 to 70, had higher drug exposure, based on a 26% higher peak concentration and 68% greater AUC than men in the same age group. No dosage adjustments have been recommended by the manufacturer on the basis of age or sex.

Trospium demonstrates diurnal variability in exposure. C_{max} and AUC are decreased up to 50% and 33% respectively if taken in the evening compared to morning doses.

Trospium is only minimally metabolized by CYP enzymes, in contrast to other antimuscarinic drugs. Its major metabolic pathway is ester hydrolysis to two inactive metabolites. These undergo conjugation and excretion by the kidney. About 60% of trospium is excreted by the kidneys unchanged.

A table summarizing the pharmacokinetics of each drug or formulation is on the next page.

Table. Pharmacokinetics of Antimuscarinic Drugs

Parameter	Oxybutynin IR	Oxybutynin ER	Oxybutynin TDS	Oxybutynin Gel	Tolterodine IR	Tolterodine ER	Fesoterodine	Trospium IR	Darifenacin	Solifenacin
Bioavailability F (%)	1.6-10.9	Relative bioavailability 156% (R) and 187% (S) compared with IR	High	High	≥ 77% absorbed after 5 mg oral dose	≥ 77 (10%-74%) Relative bioavailability of ER vs IR: Tol 71% 5-HMT 73%	5-HMT 52%	< 10%	15-19% EM	90%
Peak, h (steady state)	~1 h	4-6h	single dose: 36-48 steady state: Oxy 10.0 DEO: 24.0	NA	1-2 h	2-6 h	~5 h	5-6 h	7h	3 – 8 h
Half-life, h	2-3 h 5 h elderly Biphasic elimination Oxy 64 h (both phases) DEO 82 h (both phases)	12-13 h	After removal of patch, half-life ~7-8 h	Biphasic elimination Oxy 64 h (both phases) DEO 82 h (both phases)	1.9-3.7 h EM ~10 PM	~7 EM (majority of people) ~18 PM NR for IM	5-HMT ~7-9 h	20 ~33 if CrCl < 30	13-19	45-68, chronic dosing
Duration, h	6-10 h	< 24 h	3-4 days	~24	1-2 h	2-6 h	~5 h	5-6 h	7h	~ 50 h
% protein bound	Oxy> 99% ; DEO > 97%				Tol > 90% 5-HMT 74%		5-HMT ~50% both to albumin and αl acid glycoprotein	48-78%	98%	98%
Vd, L	193				113 +/- 26.7		169	395	163	600
Elimination	< 0.1% Oxy excreted in urine unchanged < 0.1% Oxy excreted unchanged	Same as Oxy IR Insoluble shell excreted in feces	Same as Oxy IR	Same as Oxy IR	77% excreted in urine; 17% fecal < 1% (<2.5% in PM) excreted unchanged; 5-14% excreted as 5-HMT; 80% of metabolites in urine are inactive		70% excreted in urine 16% as 5-HMT 53% inactive 34% carboxy metabolite (CYP 2D6) 1% N-desisopropyl	85% fecal ~ 6% excreted in urine 3% unchanged	60% urine 3% unchanged	69% urine < 15% unchanged 23% fecal

							metabolite 7% recovered in feces			
Metabolism	Bowel, liver 1st pass extraction CYP 3A4	Bowel, liver 1st pass extraction CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4	Liver *Avoids* 1st pass metabolism CYP 3A4	1st pass extraction 2D6 major 3A4 minor	1st pass extraction 2D6 major 3A4 minor	Pro-drug converted to 5-HMT by nonspecific esterases 5-HMT is metabolized by CYP 2D6 and CYP 3A4	Kidney – actively secreted	3A4 major 2D6 minor	Liver CYP 3A4 4 metabolites, one active but low concentration metabolites excreted by kidney
Active metabolite(s)	DEO	DEO	DEO	DEO	5-HMT	5-HMT	5-HMT	None	None	4-R hydroxy .
DEO:Oxy Ratio (steady state)	11.9:1	NA	1.3:1	1:1	--	--	--	--	--	--
M3 vs. M2 relative selectivity	10				1.1		1.0	1.3	58.2	12.5

F = fraction absorbed, the proportion of the administered dose that reaches systemic circulation. Bioavailability is determined by comparing the area under the concentration-time curve (AUC) after the test route of administration with the AUC after intravenous administration. The AUC ratio, corrected for any differences in dose, provides an estimate of F. EM, extensive metabolizer; PM=poor metabolizer; DEO=N-desethyl-oxybutynin; 5-HMT=5-hydroxymethyl tolterodine; NA=not available; Oxy=oxybutynin

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Tolterodine L-tartrate (Detrol™) Immediate Release Tablets 1 mg and 2 mg Product Monograph. Pfizer Canada Inc. 2011. Date of revision: Feb 10, 2010.

Tolterodine L-tartrate (Detrol LA™) extended release capsules 2 mg and 4 mg Product Monograph. Pfizer Canada Inc. 2011. Date of revision: June 20, 2011.

Trospium Chloride Coated Tablet (Trosec®) Product Monograph. Sunovion Pharmaceuticals Canada Inc. Date of Revision: May 8 2012.

Appendix C. Search Strategies

Search Strategy for Systematic Reviews

Database: EBM Reviews – Cochrane Database of Systematic Reviews <2005 to November 2012>, EBM Reviews – Database of Abstracts of Reviews of Effects <4th Quarter 2012>, EBM Reviews – Health Technology Assessment <4th Quarter 2012>
Search Date: 10 January 2013

1 (overactive adj2 bladder).mp. (47)
2 ((urge or urgency or urinary) adj incontinen$).tw. (326)
3 urinary urgenc$.tw. (26)
4 urina$ frequen$.tw. (53)
5 mixed ui.tw. (1)
6 stress ui.tw. (3)
7 or/1-6 (377)
8 (anti-muscarinic or muscarinic).mp. (93)
9 oxybutynin.mp. (30)
10 tolterodine.mp. (18)
11 fesoterodine.mp. (5)
12 darifenacin.mp. (9)
13 trospium.mp. (9)
14 solifenacin.mp. (7)
15 or/8-14 (117)
16 7 and 15 (39)

Database: Ovid MEDLINE® 1946 to Present with Daily Update
Search Date: 10 January 2013

1 urinary bladder, overactive/ (1884)
2 (overactive adj2 bladder?).tw. (2486)
3 ((urge or urgency or urinary) adj incontinen$).tw. (15642)
4 urinary urgenc$.tw. (480)
5 urina$ frequen$.tw. (1121)
6 mixed ui.tw. (73)
7 stress ui.tw. (100)
8 or/1-7 (18826)
9 muscarinic antagonists/ (6251)
10 oxybutynin.mp. (1105)
11 tolterodine.mp. (671)
12 fesoterodine.mp. (92)
13 darifenacin.mp. (235)
14 trospium.mp. (180)
15 solifenacin.mp. (253)
16 or/9-15 (7228)
17 8 and 16 (1262)
18 limit 17 to “reviews (maximizes specificity)” (80)
19 limit 18 to (“young adult (19 to 24 years)” or “adult (19 to 44 years)” or “young adult and adult (19-24 and 19-44)” or “middle age (45 to 64 years)” or “middle aged (45 plus years)” or “all aged (65 and over)” or “aged (80 and over)”) (36)

Database: Ovid MEDLINE® In-Process & Other Non-Indexed Citations <January 09, 2013>
Search Date: 10 January 2013

1 urinary bladder, overactive/ (0)
2 (overactive adj2 bladder?).tw. (329)
3 ((urge or urgency or urinary) adj incontinen$).tw. (898)
4 urinary urgenc$.tw. (38)
5 urina$ frequen$.tw. (57)
6 mixed ui.tw. (5)
7 stress ui.tw. (4)
8 or/1-7 (1188)
9 muscarinic antagonists/ (0)
10 oxybutynin.mp. (64)
11 tolterodine.mp. (58)
12 fesoterodine.mp. (11)
13 darifenacin.mp. (13)
14 trospium.mp. (13)
15 solifenacin.mp. (31)
16 or/9-15 (131)
17 8 and 16 (79)
18 limit 17 to "reviews (maximizes specificity)" (11)

Search strategies for controlled trials

Database: Ovid MEDLINE® 1946 to Present with Daily Update
Search Date: 10 January 2013

1 urinary bladder, overactive/ (1884)
2 (overactive adj2 bladder?).tw. (2486)
3 ((urge or urgency or urinary) adj incontinen$).tw. (15642)
4 urinary urgenc$.tw. (480)
5 urina$ frequen$.tw. (1121)
6 mixed ui.tw. (73)
7 stress ui.tw. (100)
8 or/1-7 (18826)
9 muscarinic antagonists/ (6251)
10 oxybutynin.mp. (1105)
11 tolterodine.mp. (671)
12 fesoterodine.mp. (92)
13 darifenacin.mp. (235)
14 trospium.mp. (180)
15 solifenacin.mp. (253)
16 or/9-15 (7228)
17 randomized controlled trial.pt. (336781)
18 controlled clinical trial.pt. (84885)
19 randomi?ed.ab. (286958)
20 placebo.ab. (134036)
21 drug therapy.fs. (1567914)
22 randomly.ab. (172858)
23 trial.ab. (247511)

24 groups.ab. (1130854)
25 or/17-24 (2926782)
26 animals/ not (humans/ and animals/) (3655446)
27 25 not 26 (2487257)
28 8 and 16 and 27 (1021)
29 28 and (2012$ or 2013$).ed. (73)

Database: Embase <1974 to 2013 January 09>
Search Date: 10 January 2013

1 (overactive adj2 bladder?).mp. (7545)
2 ((urge or urgency or urinary) adj incontinen$).tw. (23379)
3 urinary urgenc$.tw. (849)
4 urinary urgenc$.tw. (849)
5 urina$ frequen$.tw. (1729)
6 mixed ui.tw. (140)
7 stress ui.tw. (163)
8 oxybutynin.mp. (4439)
9 tolterodine.mp. (2666)
10 fesoterodine.mp. (383)
11 darifenacin.mp. (1011)
12 trospium.mp. (1083)
13 solifenacin.mp. (1049)
14 or/8-13 (6500)
15 randomized controlled trial/ (337546)
16 crossover procedure/ (35911)
17 double-blind procedure/ (115070)
18 (randomi?ed or randomly).tw. (625399)
19 (crossover$ or cross-over$).tw. (66429)
20 placebo.ab. (181302)
21 (doubl$ adj blind$).tw. (139866)
22 assign$.ab. (212374)
23 allocat$.ab. (71874)
24 or/15-23 (989431)
25 (animal$ not (human$ and animal$)).mp. (3659198)
26 24 not 25 (893825)
27 14 and 26 (1093)
28 27 and (2011$ or 2012$ or 2013$).em. (251)

Database: EBM Reviews – Cochrane Central Register of Controlled Trials <December 2012>
Search Date: 10 January 2013

1 urinary bladder, overactive/ (187)
2 (overactive adj2 bladder?).tw. (494)
3 ((urge or urgency or urinary) adj incontinen$).tw. (1508)
4 urinary urgenc$.tw. (61)
5 urina$ frequen$.tw. (150)
6 mixed ui.tw. (8)
7 stress ui.tw. (12)
8 or/1-7 (1965)
9 muscarinic antagonists/ (476)

10 oxybutynin.mp. (289)
11 tolterodine.mp. (300)
12 fesoterodine.mp. (47)
13 darifenacin.mp. (44)
14 trospium.mp. (89)
15 solifenacin.mp. (72)
16 or/9-15 (949)
17 8 and 16 (447)

Search terms for Cochrane Incontinence Specialized Register
Search date: 17 Jan 2013
{relevant.review.antichol*}
AND
{intvent.chem.drug.oxybut*} OR {INTVENT.CHEM.DRUG.TOLTERODINE.} OR {INTVENT.CHEM.DRUG.FESOTERODINE.} OR {INTVENT.CHEM.DRUG.DARIFENACIN.} OR {intvent.chem.drug.trosp*} OR {intvent.chem.drug.solifenacin.}
(in the keywords field of Reference Manager 12)

Cognition/Adverse Event Search
Database: Ovid MEDLINE® 1946 to Present with Daily Update, Ovid MEDLINE® In-Process & Other Non-Indexed Citations <January 15, 2013>
Search Date: 16 January 2013

Database: Ovid MEDLINE® 1946 to Present with Daily Update, Ovid MEDLINE® In-Process & Other Non-Indexed Citations <January 15, 2013>
Search Strategy:

1 urinary bladder, overactive/ (1890)
2 (overactive adj2 bladder?).tw. (2824)
3 ((urge or urgency or urinary) adj incontinen$).tw. (16563)
4 urinary urgenc$.tw. (519)
5 urina$ frequen$.tw. (1183)
6 mixed ui.tw. (78)
7 stress ui.tw. (105)
8 or/1-7 (20048)
9 muscarinic antagonists/ (6259)
10 oxybutynin.mp. (1172)
11 tolterodine.mp. (729)
12 fesoterodine.mp. (103)
13 darifenacin.mp. (248)
14 trospium.mp. (193)
15 solifenacin.mp. (284)
16 or/9-15 (7367)
17 (ae or co or de).fs. (4616903)
18 (safe or safety).tw. (392664)
19 side effect$.tw. (161168)
20 (adverse adj3 (effect$ or event$)).tw. (170986)
21 (serious adj3 (effect$ or event$)).tw. (20525)
22 complication$.tw. (542208)
23 exp follow-up studies/ (455835)
24 follow-up.tw. (543074)
25 tolerability.tw. (28114)

26 toxicity.tw. (226615)
27 or/17-26 (5759753)
28 exp mental disorders/ (874037)
29 (mental adj (function$ or process$ or status)).tw. (9395)
30 (cognitive adj (defect$ or disorder$ or dysfunction$ or impair$)).mp. (40836)
31 (confused or confusion).mp. (31530)
32 (disorientat$ or disoriented).mp. (3269)
33 (central nervous system or CNS).mp. (211118)
34 (delirious or delirium).mp. (18203)
35 dizziness.mp. (12401)
36 vertigo.mp. (12550)
37 dementia.mp. (79311)
38 exp amnesia/ (8024)
39 amnesia$.tw. (7718)
40 (drowsiness$ or restless$ or sleep$ or somnolen$).mp. (132172)
41 asthenia.mp. (5128)
42 (debilit$ or oligophren$).mp. (13720)
43 (delusion$ or hallucinat$).mp. (19891)
44 (mania or manic).tw. (12477)
45 or/28-44 (1240542)
46 exp cohort studies/ (1214478)
47 cohort$.tw. (223008)
48 exp case control studies/ (578125)
49 (case adj (series or control$)).tw. (97504)
50 case reports.pt. (1598626)
51 (case$ adj2 report$).tw. (351432)
52 (case$ adj2 stud$).tw. (129360)
53 ((follow-up or followup) adj (study or studies or trial$)).tw. (35444)
54 epidemiologic methods/ (28504)
55 limit 54 to yr=1966-1989 (11196)
56 or/46-53,55 (3097602)
57 animals/ not (humans/ and animals/) (3657678)
58 56 not 57 (3044324)
59 8 and 16 and (27 or 45) and 58 (206)

Database: Embase <1974 to 2013 Week 02>
Search Date: 16 January 2013

1 (overactive adj2 bladder?).mp. (7545)
2 ((urge or urgency or urinary) adj incontinen$).tw. (23382)
3 urinary urgenc$.tw. (849)
4 urinary urgenc$.tw. (849)
5 urina$ frequen$.tw. (1730)
6 mixed ui.tw. (140)
7 stress ui.tw. (163)
8 or/1-7 (30114)
9 oxybutynin.mp. (4439)
10 tolterodine.mp. (2666)
11 fesoterodine.mp. (383)
12 darifenacin.mp. (1011)

13 trospium.mp. (1083)
14 solifenacin.mp. (1049)
15 or/9-14 (6500)
16 (ae or co or si).fs. (2509835)
17 exp adverse drug reaction/ (341336)
18 exp drug safety/ (205650)
19 exp drug hypersensitivity/ (47297)
20 (safe or safety).tw. (542838)
21 side effect$.tw. (224332)
22 (adverse adj3 (effect$ or event$)).tw. (240139)
23 (serious adj3 (effect$ or event$)).tw. (29443)
24 complication$.tw. (727760)
25 follow-up.tw. (736674)
26 tolerability.tw. (43640)
27 toxicity.tw. (298607)
28 or/16-27 (4238466)
29 exp mental disease/ (1520659)
30 (mental adj (function$ or process$ or status)).tw. (13376)
31 (cognitive adj (defect$ or disorder$ or dysfunction$ or impair$)).mp. (100514)
32 exp confusion/ (19594)
33 (confused or confusion).tw. (38912)
34 (disorientat$ or disoriented).mp. (8096)
35 (central nervous system or CNS).mp. (602142)
36 (delirious or delirium).mp. (18100)
37 dizziness.mp. (44815)
38 vertigo.mp. (43559)
39 exp dementia/ (205076)
40 dementia.tw. (79826)
41 exp amnesia/ (27188)
42 amnesia$.tw. (9942)
43 (drowsiness$ or restless$ or sleep$ or somnolen$).mp. (218705)
44 asthenia.mp. (18677)
45 (debilit$ or oligophren$).mp. (18253)
46 (delusion$ or hallucinat$).mp. (37061)
47 exp mania/ (42847)
48 (mania or manic).tw. (17014)
49 or/29-48 (2276450)
50 exp cohort analysis/ (137983)
51 exp longitudinal study/ (57620)
52 exp prospective study/ (222838)
53 exp follow up/ (673165)
54 cohort$.tw. (314456)
55 exp case control study/ (78493)
56 (case$ and control$).tw. (387835)
57 exp case study/ (18281)
58 (case$ and series).tw. (144799)
59 case report/ (1914428)
60 (case$ adj2 report$).tw. (463328)
61 (case$ adj2 stud$).tw. (164935)
62 or/50-61 (3506863)
63 (animal$ not (human$ and animal$)).mp. (3659600)

64 62 not 63 (3443692)
65 8 and 15 and (28 or 49) and 64 (350)

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Appendix D. Tolterodine vs. Oxybutynin Tables and Figures
Tolterodine IR vs. Oxybutynin IR

Table 1. RCT Study Characteristics: Tolterodine IR vs Oxybutynin IR

Study Country N Sponsorship	Design	Inclusion criteria	Baseline Characteristics % of participants	Tol IR	Oxy IR	Placebo if included	Outcomes Assessed
Abrams 1998 (Study 008) UK, Ireland, Sweden N = 293 Pharmacia & Upjohn	Parallel group DB, MC Phase III RCT Double-dummy Placebo-controlled 2:2:1 randomization 2 week wash-out/run-in 12 weeks duration Designed as an equivalence trial	Urodynamically confirmed detrusor overactivity plus urinary frequency (≥ 8 micturitions/24 h), and ≥ 1 episode of either UUI or urgency per 24 h	76% female, 24% male Mean age 56 yrs Age range 19 to 80 yrs 76% had incontinence Most had received prior drug treatment, with 38% of these reporting beneficial responses ~ 30% had history of LUT surgery 87% were on concomitant medications for concurrent conditions incl. postmenopausal symptoms	Tol IR 2 mg bid* N = 118 UUI: N = 93 Baseline UUI: 2.9 (range 0.1-24.0) episodes	Oxy IR 5 mg tid* N = 118 UUI: N = 88 Baseline UUI: 2.6 (range 0.1-24.0) episodes	Placebo N = 56 UUI: N = 40 Baseline UUI: 3.3 (0.1-23.5) episodes	• Patient perception of bladder condition • Micturition frequency • Incontinence episodes • Volume voided per micturition • SAE, WDAE, Specific AE • Lab chemistry, hematology • BP within 6 hours of drug intake • Drug serum concentrations
Altan-Yaycioglu 2005 Turkey N = 52	Parallel group single-blind (assessor) RCT 4 weeks duration	Women with urodynamically proven detrusor overactivity and without any history or manifestation of eye disease	100% female Mean age Tol 42.2 yrs; Oxy 40.2 yrs Age range 22 to 60 yrs	Tol IR 2 mg bid N = 28 (56 eyes)	Oxy IR 5 mg tid N = 24 (48 eyes)	ND	• Ocular intermediate outcomes: o Accommodation amplitude and pupillary diameter, o Tear secretion • Ocular dryness, • Ocular burning sensation • Ocular foreign-body sensation • Dry mouth
Drutz 1999 (Study 010) US, Canada N= 277 Pharmacia & Upjohn	Parallel group DB, MC Phase III RCT Double-dummy Placebo-controlled 2:2:1 randomization 2 week wash-out/run-in 12 weeks duration	Urodynamically confirmed detrusor overactivity plus urinary frequency (≥ 8 micturitions/24 h), and ≥ 1 episode of either UUI or urgency per 24 h	75% female Mean age 64 yrs Age range 23 to 91 yrs 92% Caucasian 88% had incontinence 7% neurogenic cause 35% had history of LUT surgery, more in Oxy group	Tol IR 2 mg bid N = 109 UUI: N = 90 PP: N = 70	Oxy IR 5 mg tid N = 112 UUI: N = 103 PP: N = 41	Placebo N = 56 UUI: N = 50 PP: N = 36	• Patient perception of bladder condition (FDA review) • QOL (SF-36) • Micturition frequency • Incontinence episodes • Volume voided per micturition • SAE • WDAE

	Per protocol analysis ITT analysis in FDA review Equivalence trial		(45%) than Tol (27%) 50% had previously received drug treatment 6% of participants in Tol group (95% tested) were poor metabolizers	baseline UUI: 2.9 episodes	baseline UUI: 2.6 episodes	baseline UUI: 2.4 episodes	• Specific AE • BP within 6 hours of drug intake • Drug serum concentrations
Study Country N Sponsorship	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Tol IR**	**Oxy IR**	**Placebo if included**	**Outcomes Assessed**
Giannitsas 2004 Greece N = 128 Sponsorship not declared	Two-way crossover open-label RCT 3-4 week wash-out between drugs 6 week treatment period Per protocol analysis	Women with urodynamically confirmed detrusor overactiviy	100% female For N = 107 completers: Mean age 56 yrs Age range 23 to 91 yrs 36% incontinence in week prior to study ≥ 1 episode)	Tol IR 2 mg bid N = 107 completers UUI: N=38	Oxy IR 5 mg tid N = 107 completers UUI: N=38	ND	• Micturition frequency • Volume voided per micturition • Urodynamic parameters: - Volume at first desire to void - bladder volume at first overactive contraction - pressure of first overactive contraction - mean cystometric capacity - overactivity index • WDAE • Dry mouth • Constipation
Lee 2002 South Korea N = 228 Pharmacia	Parallel group DB, MC Double dummy RCT 2 week wash-out/run-in 8 weeks duration ITT, LOCF Designed as an equivalence trial	Frequency (≥ 8 micturitions per 24 h) plus ≥ 1 episode of UUI or urgency per 24 h	77% female Mean age 52 yrs Age range 22 to 86 yrs Asian population 27% had received prior drug treatment: 32% in Tol group and 22% in Oxy group 61-64% were on concomitant medication for other conditions	Tol IR 2 mg bid N = 112 UUI: N = 46 Baseline UUI: 2.6 (0.3-9.3) episodes	Oxy IR 5 mg bid N = 116 UUI: N = 42 Baseline UUI : 2.4 (3.0-14.7) episodes	ND	• Patient perception of benefit • Incontinence episodes • Micturition frequency • SAE • WDAE • Total AE • Specific AE
Leung 2002 Hong Kong N = 106 Pharmacia	Parallel group DB RCT 2 centres 10 weeks duration 1 week run-in phase 2 week follow-up post study	Women with urodynamically confirmed detrusor instability	100% female Median age 49.5 yrs (43-63) Asian population 59% of Oxy group and 72% of Tol group were on concomitant medication for other conditions	Tol IR 2 mg bid N = 53 baseline UUI episodes NR	Oxy 5 mg bid N = 53 baseline UUI episodes NR		• Tolerability (drug compliance, withdrawal rate) • Patient perception of severity of bladder symptoms • Total withdrawals • Micturition frequency • Incontinence episodes

							• Urgency episodes • Protective pad usage • Urinary pad test • Total AE • Dry mouth (Xerostomia Questionnaire)
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Tol IR**	**Oxy IR**	**Placebo if included**	**Outcomes Assessed**
Malone-Lee 2001 UK, Republic of Ireland N = 482 screened N = 379 randomized Pharmacia & Upjohn	Parallel group DB, MC RCT Double-dummy 2 week wash-out/run-in 10 weeks duration	Adults 50 years or older with urinary frequency (> 8 per 24 h) plus ≥ 1 episode of either UUI or urgency per 24 h	67% female Mean age 65 yrs Age range 49 to 90 yrs 54% incontinence 32% had received prior drug treatment (28-30% good efficacy response) 27% had a history of LUT surgery	Tol IR 2 mg bid N = 190 UUI: N = 104 Baseline UUI: 2.4 (2.6)	Oxy IR 2.5 mg titrated to 5 mg tid N = 188 UUI: N = 102 Baseline UUI: 2.9 (3.4)	ND	• Micturition frequency • Incontinence episodes • Pads per 24 h • Volume voided per micturition • SAE • WDAE • Total AE • Specific AE • Dry mouth (primary outcome)
Qiu 2002 China N=78 Sponsorship not declared	DB RCT Placebo-controlled 3 weeks duration ITT	Urgency, frequency, sensation of incomplete emptying with or without urgency incontinence, and normal urine examination	63% female, 37% male Asian population	Tol IR 1 mg once daily N = 30	Oxy IR 5 mg once daily N = 27	Placebo N = 21	• Patient subjective assessment of improvement (scale not described) • Micturition frequency • AE
Study 015 Netherlands, France, Switzerland N = 240 Pharmacia & Upjohn	Parallel group DB, MC, Phase III RCT Double-dummy 2 week wash-out/run-in 12 weeks duration Designed as an equivalence trial	Urodynamically proven detrusor overactivity plus urinary frequency (≥ 8 micturitions/24 h), and 1 or more episodes of either UUI or urgency per 24 h	70% female mean age ~56 yrs 6% neurogenic cause 95% Caucasian	Tol IR 2 mg bid N = 119 N = 93	Oxy IR 5 mg tid N = 119 N = 95	ND	• Patient perception of bladder condition • Incontinence episodes • Micturition frequency • Volume voided per micturition • SAE • WDAE • Total AE • Specific AE

Xia 2001 China N = 206 Sponsorship not declared	Parallel group DB, MC RCT ITT 2 weeks wash-out 6 weeks duration	Micturition frequency ≥ 8 per 24 h, urgency, average voided volume ≤ 100 mls, OAB symptoms for six months	56% female, 44% male 28% had incontinence Asian population Mean age Tol: 49 yrs; Oxy 51 yrs	Tol IR 2 mg bid N = 101 UUI: N = 29	Oxy IR 5 mg bid N = 105 UUI: N = 28		• Incontinence episodes • Micturition frequency • Voided volume per micturition • AE • Lab tests, ECG
DB, double blind; MC, multicentre; ND, not done; LOCF, last observation carried forward, LUT, lower urinary tract; PP, per protocol; UUI, urgency urinary incontinence; Table lists outcomes assessed but not all are reported e.g., Lee 2002 reports only AE in 5% or more of participants in either group. *Abrams 1999: optional starting dose in UK oxy 2.5 mg bid or tol 1 mg bid if participant > 65 years;							

Table 2. RCT Outcomes – Tolterodine IR vs Oxybutynin IR

Study	Abrams 1998 Study A008			Drutz 1999 Study A010			Study A015 NDA 20-771 1997		Malone-Lee 2001		Giannitsas2004 (crossover)	
Treatment	Placebo	Tol	Oxy	Placebo	Tol	Oxy	Tol	Oxy	Tol	Oxy	Tol	Oxy
N	N=57	N=118	N=118	N=55	N=108	N=111	N=120	N=120	N=190	N=188	N= 128 107 completers	N=128 107 completers
Mortality	0	0[1]	0	0	0	0	0	0	0[2]	0[2]	NA	
SAE	2 (4%)	4 (3%)	3 (3%)	2 (4%)	1 (1%)	3 (3%)			5 (3%)	5 (3%)	NA	
WDAE	7 (12%)	10 (9%)	20 (17%)	2 (4%)	7 (7%)	23 (21%)	13 (11%)	25 (21%)	22 (12%)	28 (15%)	7	10
QOL	Data collected but NA (no trends in support of efficacy for Tol according to FDA review)			SF-36 Data NA no difference stated in text			NA		NA		NA	
Cure (no incontinence episodes for 7 days)	NA			NA			NA		NA		NA	
Perception of improvement No. of patients	27 (47%)	59 (50%)	58 (49%)	NA					86	78	NA	
Incontinence episodes per 24 h Mean (SD) change from baseline or End of Tx	-0.9 (3.5)	-1.3 (3.2)	-1.7 (3.1)	-1.1 (2.1)	-1.6 (2.4)	-1.9 (2.3)	-1.7 (2.5)	-2.1 (3.2)	-1.3 (2.4)	-1.8 (2.8)		
N (evaluable patients)	N=40	N = 93	N = 88	N=50	N=90	N=103	N=93	N=95	N=104	N=102	NA	
Urgency Episodes	NA			NA			NA		NA		NA	
Nocturia Episodes	NA			NA			NA		NA		NA	
Total AE	46 (81%)	105 (89%)	114 (97%)	41 (75%)	84 (78%)	100 (91%)	76 (63%)	112 (93%)	132 (70%)	153 (81%)	NA	

Table 2. RCT Outcomes – Tolterodine IR vs Oxybutynin IR Continued

Study	Abrams 1998 Study A008			Drutz 1999 Study A010			Study A015 NDA 20-771 1997		Malone-Lee 2001		Giannitsas2004 (crossover)	
Treatment	Placebo	Tol IR	Oxy IR	Placebo	Tol IR	Oxy IR	Tol IR	Oxy IR	Tol IR	Oxy IR	Tol IR	Oxy IR
N	N=57	N=118	N=118	N=55	N=108	N=111	N=120	N=120	N=190	N=188	N= 128 107 completers	N=128 107 completers
Dry Mouth	12 (21%)	59 (50%)	102 (86%)	8 (15%)	32 (30%)	77 (69%)	46 (38%)	94 (78%)	71 (37%)	114 (61%)	20	52
Dyspepsia	3 (5%)	11 (9%)	27 (23%)	NA			NA		18 (10%)	23 (12%)	NA	
Nausea	6 (11%)	4 (3%)	7 (6%)	NA			NA		7 (4%)	10 (5%)	NA	
Abdominal pain	NA			NA			NA		11 (6%)	12 (6%)	NA	
Mean volume voided per micturition Change from baseline (SD)	6 (42) N =56	38 (54) N=118	47 (58) N=116	13(52) N=55	31 (45) N=108	46 (49) N=111	35 (53) N=119	54 (64) N=119	33 SD NA	34 SD NA	41 SD NA	44 SD NA
Difference in change frrom baseline		Tol vs Oxy: – 9 mls, (95% CI -20, 3) p = 0.15			Tol vs Oxy : -15.0 mls (95% CI -26.7, -3.3) p = 0.012		Tol vs Oxy: -19		Tol vs Oxy -0.6 mls (95% CI -0.03 – 1.03), p = 0.065		Tol vs Oxy: - 3 mls	
Urodynamics Bladder volume at first desire to void Mean	NA			NA			NA		NA		Baseline 105.6 (39.4)	
											117.9 (27.6) p < 0.05	129.0 (30.1) p < 0.05
Mean cystometric capacity	NA			NA			NA		NA		Baseline 362.8 (119.1)	
											415.6 (114.1)	419.2 (120.9) NS

All outcomes other than incontinence, urgency, nocturia and urodynamic parameters are reported as number of patients who experienced one or more events (or reported improvement).

Data for Abrams 1998 and Drutz 1999 are supplemented with data from the FDA review NDA 20-771, which was also the source of information for Study A015. Published, pooled meta-analyses were also checked for any additional data reported separately for individual trials. If numbers of patients varied in publication and FDA review, FDA numbers were used.

[1]One patient died two months after completion of the study. NA, not available (either not reported or not measured);

Table 2 Continued. RCT Outcomes – Tolterodine IR vs. Oxybutynin IR											
Study	Altan-Yaycioglu 2005		Lee 2002		Leung 2001		Qiu 2002			Xia 2001	
Treatment	Tol IR	Oxy IR	Tol IR	Oxy IR	Tol IR	Oxy IR	Placebo	Tol IR	Oxy IR	Tol IR	Oxy IR
N	N=28	N=24	N=112	N=116	N=53	N=53	N=21	N=30	N=27	N=101	N=105
Mortality	0[3]	0[3]	0[2]	0[2]	0[2]	0[2]	NA			NA	
SAE	0	0	1	1	0	0	NA			NA	
WDAE	0	0	11 (10%)	18 (16%)	3	1	NA			NA	
QOL	NA		NA		NA		NA			NA	
Cure (no incontinence episodes for 7 days)	NA		NA		NA		NA			NA	
Patient-Perception of Improvement	NA		50 (45%)	53 (46%)	Reported as change in VAS – no difference between groups		5 (24%)	22 (73%)	20 (74%)	NA	
Incontinence Episodes per 24 h Mean change (SD) from baseline or end of Tx	NA		-2.2 (2.3)	-1.4 (1.8)	NA		NA			-2.92 (2.44)	-2.32 (1.52)
N (evaluable patients)			N=46	N=42						N=29	N=28
Urgency Episodes	NA		NA		No improvement with either drug (data NA)		NA			NA	
Nocturia	NA		NA		NA		NA			NA	
Total AE	NA		62 (55%)	94 (81%)	26 (49%)	32 (60%)	NA			33 (33%)	58 (55%)
Dry Mouth	14 (50%)	20 (83%)	39 (35%)	72 (62%)	NA		4 (19%)	5 (17%)	13 (48%)	NA	
Dyspepsia	NA		8 (7%)	6 (5%)	NA		NA			NA	
Nausea	NA		NA		NA		NA			NA	
Abdominal pain	NA		6 (5%)	6 (5%)	NA		NA			NA	

Table 2 Continued. RCT Outcomes – Tolterodine IR vs. Oxybutynin IR											
Study	Altan-Yaycioglu 2005		Lee 2002		Leung 2001		Qiu 2002			Xia 2001	
Treatment	Tol IR	Oxy IR	Tol IR	Oxy IR	Tol IR	Oxy IR	Placebo	Tol IR	Oxy IR	Tol IR	Oxy IR
N	N=28	N=24	N=112	N=116	N=53	N=53	N=21	N=30	N=27	N=101	N=105
Dry Eye Burning sensation in eye Foreign body sensation in eye	4 (14%) 12 (43%) 6 (21%)	4 (17%) 14 (58%) 6 (25%)	NA		NA		NA			NA	
Mean volume voided per micturition	NA		NA		NA		NA			NA	
Urodynamics	NA		NA		NA		NA			NA	

NA, not available (either not reported or not measured); Tx, treatment;
[2]inferred from accounting of all SAE; [3]inferred from accounting of all patients completing study

Table 3. RCT Outcomes – Description of SAE – Tolterodine IR vs. Oxybutynin IR

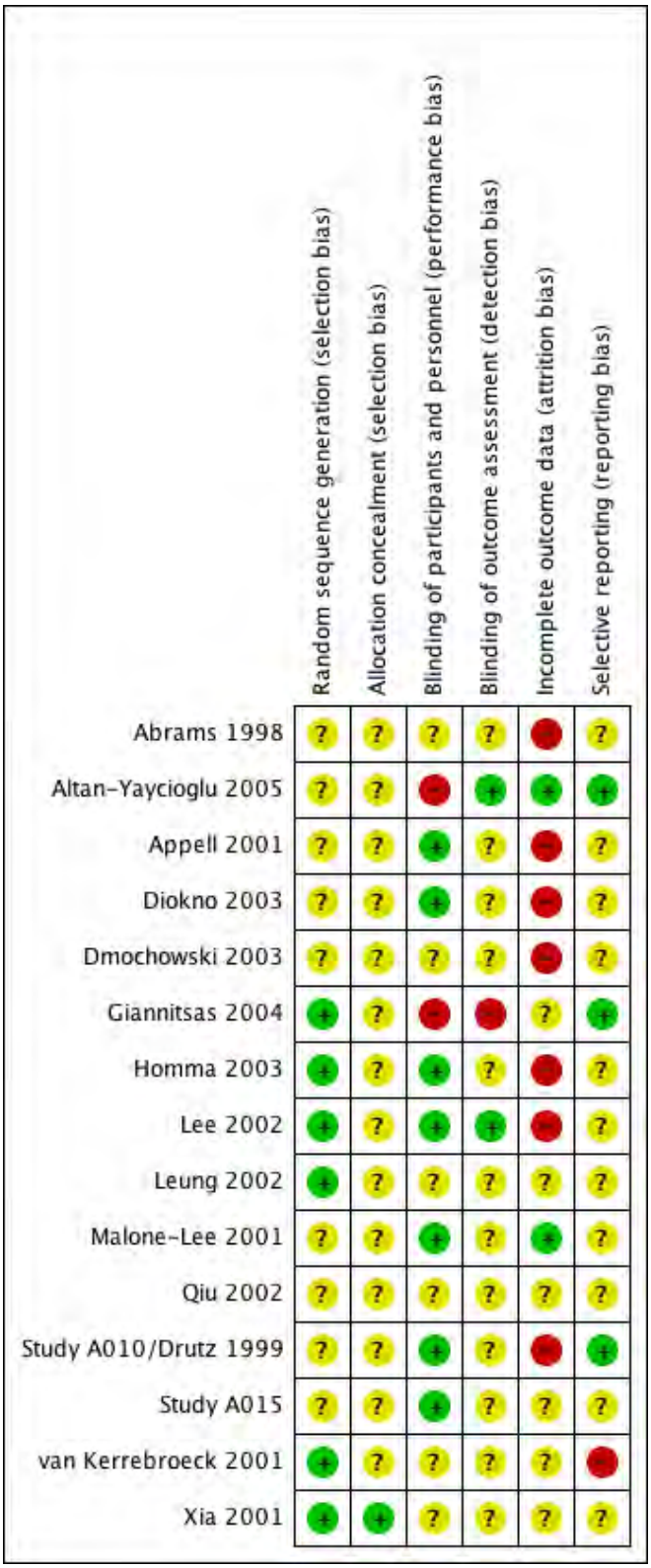
Study	Description of SAE	
	Tol IR	**Oxy IR**
Abrams 1998	N=4 1 syncope in an 80 year old male with prior history of syncope and cardiovascular disease; no identified arrhythmia. Patient died approx. 8 weeks post study (drug non-contributory, evaluated by FDA); syncope on study assessed as possibly related to drug 3 events thought likely to be unrelated: 1 rectal prolapse; 1 ovarian carcinoma; 1 arterial embolus post investigative procedure	N=3 Events not described. FDA reviewer agreed that SAE were not drug-related.
Drutz 1999	N=1 Details not provided, all patients who had SAE had significant concurrent disease such as diabetes and hypertension. FDA reviewer agreed SAE was not drug-related.	N=3 Details not provided, all patients had significant concurrent disease such as diabetes and hypertension, FDA reviewer agreed SAE were not drug-related.
Malone-Lee 2001	N=5 1 abdominal pain +/- vomiting 1 hematemesis + esophagitis 1 urinary retention 2/5 SAE were assessed by investigator as not related to drug and were not described.	N=5 None assessed by investigators as related to drug and none described.
Lee 2002	N=1 Fracture – no description, investigator-assessed as unrelated to drug.	N=1 Acute pyelonephritis, investigator-assessed as unrelated to drug.

Table 4. RCT Outcomes – Patient-Reported Perception of Improvement Tol IR vs. Oxy IR

Study	Abrams 1998	Lee 2002	Malone-Lee 2001	Leung 2002	Qiu 2002
Type of scale	6 point scale (PPBC) 0 = no problems 1 = very minor 2 = minor 3 = moderate 4 = severe 5= many severe problems	Binomial scale: Have you had any benefit from your treatment? Yes/No; If yes, patient was asked to evaluate benefit as either "little" or "much"	6 point scale 0 = no problems 5 = severe problems	oVAS scale: overall severity of bladder symptoms 0 = minimal effect; 10 = maximum severity cVAS scale: perceived changes in symptoms before and after treatment; +5 = maximum improvement -5 = maximum deterioration	Categories: Improvement or no improvement
Proportion of patients reporting improvement	$\geq$ 1 point decrease in scale Tol: 59/118 (50%) Oxy: 58/118 (49%) Pl: 27/57 (47%)	Much benefit: Tol: 50/112 (45%) Oxy: 53/112 (46%)	Improvement: Tol: 86/190 (45%) Oxy: 78/188 (41%) No change: Tol 42%; Oxy 51% Deterioration: Tol 12%; Oxy 8%	NA	Tol: 22/30 (73%) Oxy: 20/27 (74%)
Other				Week 10 difference between Tol and Oxy groups: oVAS: 0.417 favors Tol but NS cVAS: 0.053 favors Tol but NS	

NA, not available; NS, not significant; PPBC, Patient Perception of Bladder Condition, oVAS, visual analogue scale, overall severity; cVAS, visual analogue scale, perceived change
PPBC data for Drutz 1999 and Study A015 are not published.

Table 5. RCT Quality Assessment Tolterodine vs. Oxybutynin RCTs. Risk of Bias Assessment



The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

Studies for all tolterodine-oxybutynin comparisons are included in the table.

Study A010 is the same study reported by Drutz 1999. Drutz 1999 was assessed as high risk of bias for selective reporting as well as incomplete outcome data (see text of report). Because data from the FDA review were used to supplement the Drutz publication, in the table, we have assessed the study as it is reported in the FDA review NDA 20-771 as this is more indicative of the conduct of the study.

Other Tolterodine-Oxybutynin Comparisons

Table 6. RCT Study Characteristics – Other Tolterodine-Oxybutynin Comparisons

Study Country N	Design	Inclusion criteria	Baseline Characteristics % of participants	Tol	Oxy	Placebo if included	Outcomes Assessed
Diokno 2003 NCT00293839 US N = 790	Parallel group, DB, MC RCT 12 weeks duration 1 week run-in phase modified ITT (all patients who had received medication and had at least one efficacy outcome) 7 day bladder diary	Women with relatively severe UUI or urge predominant mixed UI, with or without prior history of treatment	100% female Median age 61 (Oxy); 56 (Tol) 85% Caucasian, 8% African-American 15% 75 yrs or older 46-48% prior Rx Baseline 21-60 UUI episodes per week	Tol ER 4 mg/d N = 399	Oxy ER 10 mg/d N = 391	ND	• UUI episodes • Total incontinence episodes • Micturition frequency • Proportion of participants with no UUI episodes • Proportion of participants with no incontinence episodes • SAE • WDAE • Specific AE
Dmochowski 2003 Study O00011 US N = 361	Parallel group DB. MC, RCT, Double-dummy, Placebo-controlled 2 week wash-out and 1-2 week run-in period Modified ITT analysis (all patients who had received medication and had at least one efficacy outcome) LOCF Equivalence trial 3 day bladder diary	Previously treated patients with OAB, all of whom were required to have had a *beneficial* response to pre-study treatment (established by patient report and investigator assessment)	93% female, 7% male Mean age 63.5 yrs (range 18 to 89 years) 4% Black, 95% Caucasian 100% prior drug treatment with 100% having a beneficial response 50% had prior Oxy treatment; 47% had prior Tol treatment, and 5-6% had prior "other" treatment (including non-anticholinergics) Baseline severity: mean incontinence episodes/day mean approx. 5, median 4	Tol ER 4 mg/d N = 123	Oxy TDS 3.8 mg/d N = 121	Placebo N = 117	• Patient-reported global assessment of condition (IIQ, UDI) • Incontinence episodes • Proportion of patients with complete continence • Micturition frequency • Volume per void • WDAE • "Treatment-related" SAE • "Treatment-related" Systemic AE • Application site AE
Homma 2003 Korea, Japan N = 608	Parallel group DB, MC, RCT Double dummy, Placebo-controlled 1-2 week wash-out/run-in phase 2:2:1 randomization ITT, LOCF	urgency, urgency incontinence $\geq$ 5 per week, frequency $\geq$ 8 voids per day and symptoms for $\geq$ 6 months	70% female, 30% male Mean age 58-61 48% Japanese, 52% Korean 25% had prior drug therapy (of these 48-53% reported poor efficacy) Baseline severity: median 2 UUI per 24 hours (13-15 per	Tol ER 4 mg/d N= 240	Oxy IR 3 mg tid N = 246	Placebo N = 122	• QOL (KHQ) • Patient perception of treatment benefit • Patient perception of urgency • Incontinence episodes • Micturition frequency per 24 h • Incontinence pads per 24 hours • Volume voided per micturition

	Designed as a noninferiority trial 3 day bladder diary		week; range 4 - 168)				• Patient perception of bladder condition • SAE • WDAE • Specific AE • Lab tests, ECG
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Tol**	**Oxy**	**Placebo if included**	**Outcomes Assessed**
Appell 2001 US N = 378	Parallel group DB RCT Completer analysis for efficacy Stratification on basis of severity at baseline (≤ 21 or > 21 UUI episodes per week) 7 day bladder diary	Patients with urgency incontinence (7-50 episodes per week) and micturition frequency ≥ 10 voids per 24 h or patients with urge predominant mixed UI	All participants had OAB with urgency incontinence 7-50 episodes of urgency incontinence per week and 10 or more micturitions per 24 hours or predominant urge mixed incontinence mean age 59-60 (age range 21-87) 38-41% had prior treatment 86-87% Caucasian; 5-7% African American; 2% Asian	Tol IR 2 mg bid N = 193	Oxy ER 10 mg/d N = 185	ND	• Incontinence episodes (UUI – primary outcome; total episodes including stress UI) • Micturition frequency • WDAE • Specific AE
DB, double-blind; h, hours; IIQ = incontinence impact questionnaire; ITT, intention-to-treat; KHQ, King's Health Questionnaire: LOCF, last observation carried forward; MC, multicenter; ND, not done; UDI = urogenital distress inventory; UUI, urgency urinary incontinence;							

Table 7. RCT Outcomes – Other Tol-Oxy Comparisons

Study	Homma 2003			Diokno 2003		Dmochowski 2003			Appell 2001	
Treatment	Tol ER	Oxy IR	Placebo	Tol ER	Oxy ER	Tol ER	Oxy TDS	Placebo	Tol IR	Oxy ER
N	240	246	122	399	391	123	121	117	193	185
Mortality	0	0	0	0	1[1]	NA			NA	
SAE	8	7		0	0		0			
WDAE	12	42	11	19	20	4[2]	16[2]	3[2]	15	14
QOL	No significant difference between active drugs for any of the domains for KHQ (data nor provided)			NA		Global assessment of disease state[1] -33 (28) .IIQ-travel -22 (29) UDI – irritative symptoms -28 (26)	-30 (30) -23 (25) -25 (26)	-21 (31) -11 (30) -18 (24)	NA	
PPBC proportion (%) reporting improvement	72%	73%	59%	NA		NA			NA	
Continence No (total) incontinence episodes (no. of days for diary)[2] No urge incontinence episodes (no. of days for diary)	NA			16.8% (7 day diary) 20.9% (7 day diary)	23.0% (7 day diary) 26.7% (7 day diary)	47 (39%) (3 day diary)	47 (38%) (3 day diary)	26 (22%) (3 day diary)	NA	
Incontinence episodes End of Tx	NA			NA		NA			Total UI per week End of Tx 9.3 (13.4) N=172 Per 24 h 1.33 (1.91) Urgency UI per week End of Tx 7.8 (11.1)	Total UI per week End of Tx 7.1 (12.0) N=160 Per 24 h 1.01 (1.71) Urgency UI per week End of Tx 6.1 (9.7)
Incontinence episodes Mean (SD) change from	median (range) per 24 h			mean		mean (SD) per 24 h			NA	

baseline	-2.0 (-11.3-4.0)	-2.1 (-13.1-7.5)	-1.1 (-16.-5)	UUI per week -18.6 Per 24 h -2.7 SD NR	UUI per week -31.1 Per 24 h -4.4 SD NR	-3.2 (2.8)	-2.9 (3.0)	-2.1 (3.0)	. .

Table 7. RCT Outcomes – Other Tol-Oxy Comparisons Continued

Study	Homma 2003			Diokno 2003		Dmochowski 2003			Appell 2001	
Treatment	Tol ER	Oxy IR	Placebo	Tol ER	Oxy ER	Tol ER	Oxy TDS	Placebo	Tol IR	Oxy ER
N	240	246	122	399	391	123	121	117	193	185
Incontinence pads per 24h	median absolute change (range): 0 (-11.4-2.9)	0 (-13-3.3)	0 (-5.9-6.0)	NA		NA			NA	
Urgency	NA			NA		NA			NA	
Nocturia	NA			NA		NA			data collected but not analyzed separately	
Total AE	NA			NA		NA			NA	
Total CNS AE	NA			33	35	NA				
Dizziness	4	6	2	10	15	NA				
Somnolence	1	4	4	9	4	NA			3	8
Asthenia	NA			NA		NA			7	3
Insomnia	NA			3	7	NA			3	1
Asthenia	NA					NA			7	3
Depression	NA			3	5	NA				
nervousness	NA					NA			2	0
Hypertonia	NA			4	2	NA				
Dry Mouth	80	131	12	86	110	9	5	2	64	52
Abnormal vision	3	8	0	”<5%”	“<5%”	NA			2	4
Dry eyes	3	7	0	NA		NA			NA	
Headache	10	11	8	24	22	NA			17	15
Dyspepsia	9	20	4	NA		NA			10	11
Nausea	NA			NA		NA			3	6
Abdominal pain	14	12	4	NA		NA			NA	
	17	15	6	31	25	7	4		12	13

Constipation										
Dry skin	0	4	1							
Application Site AE	NA			NA		7	32	8	NA	
UTI	NA			13	20	NA			NA	
acute urinary retention	1	8	0	NA		0	0	0	NA	
post void residual volume > 150 mls				NA		4	4	3	PVR measured but not reported	
Study	Homma 2003			Diokno 2003		Dmochowski 2003			Appell 2001	
Treatment	Tol ER	Oxy IR	Placebo	Tol ER	Oxy ER	Tol ER	Oxy TDS	Placebo	Tol IR	Oxy ER
N	240	246	122	399	391	123	121	117	193	185
"difficulty in micturition"	3	21	2							
"urinary hesitation"	1	1	0	NA		NA			6	6
Mean (SD) change from baseline in volume voided per micturition	median 17.2 mls	median 22.3 mls	median 6.6 mls	NA		29.3(56.9)	32.0 (55.2)	9.3 (63.1)	NA	
Urodynamics	NA			NA		NA			NA	

[1] Global Assessment of Disease State scoring system is not further defined in the publication. [2] Separate numbers for total and urgency incontinence episodes are provided for those studies that enrolled patients with mixed UI.
[1]Another patient who had received oxybutynin in Diokno 2003 died following completion of study. [2] Numbers as reported in NDA 21-351 (Amendment) Statistical Review
Absolute numbers are reported in this table.

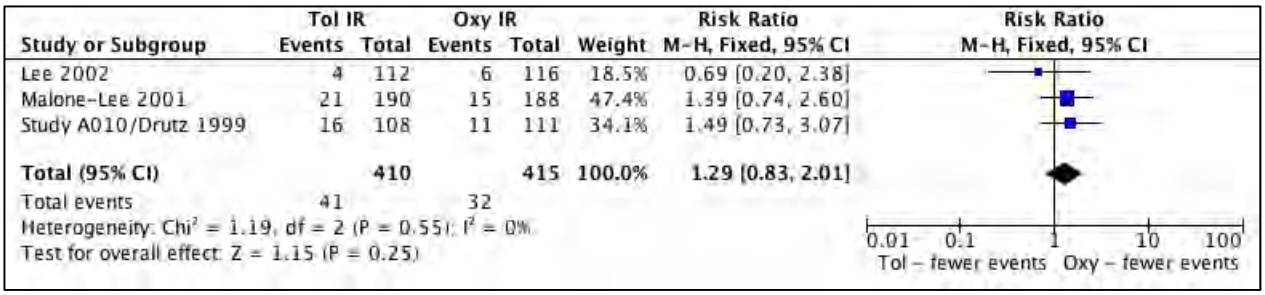
Table 8. RCT Outcomes – Description of SAE – Other Tol-Oxy Comparisons

Study	Comparison	Description of SAE	
		Tol	Oxy
Diokno 2003	Tol ER vs. Oxy IR	Total SAE NR 0 "attributable to drug"	Total SAE NR 0 "attributable to drug" 1 death during study and 1 death following study No details provided on deaths.
Homma 2003	Tol ER vs. Oxy IR vs. Placebo	N=8 Details not provided, not thought to be related to drug	N=7 1 "possibly related to treatment; cardiac failure" Details not provided for other SAE
Dmochowski 2003	Tol ER vs. Oxy TDS	N=1	Total SAE NR

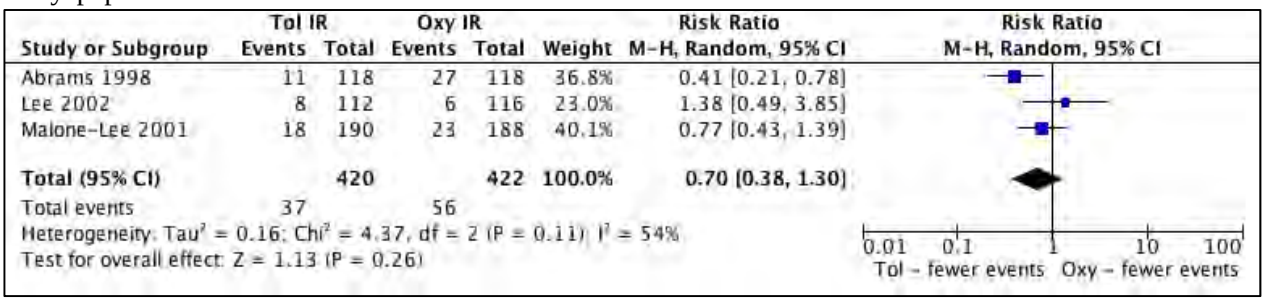
		Fecal impaction requiring hospitalization for treatment	N=0 “treatment-related” SAE
Appell 2001	Tol IR vs. Oxy ER	NR	NR
NR, not reported			

Additional Meta-Analyses: Tolterodine IR vs. Oxybutynin IR

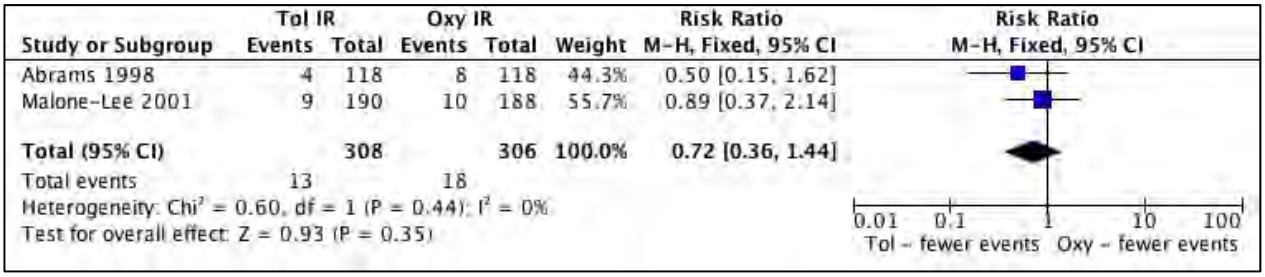
1. Headache:



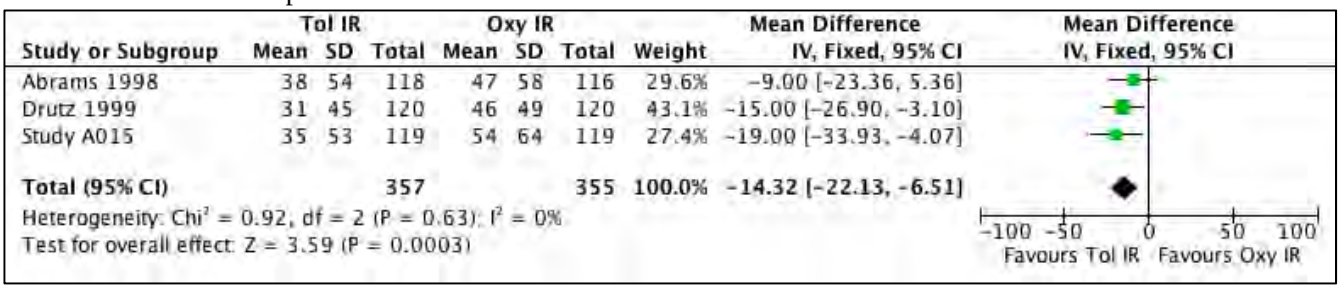
2. Dyspepsia:



3. Blurred vision:

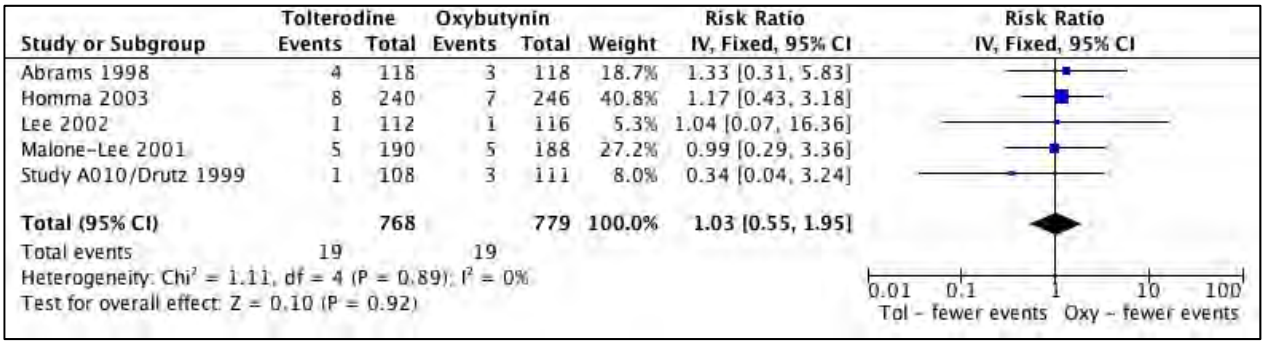


4. Mean volume voided per micturition:

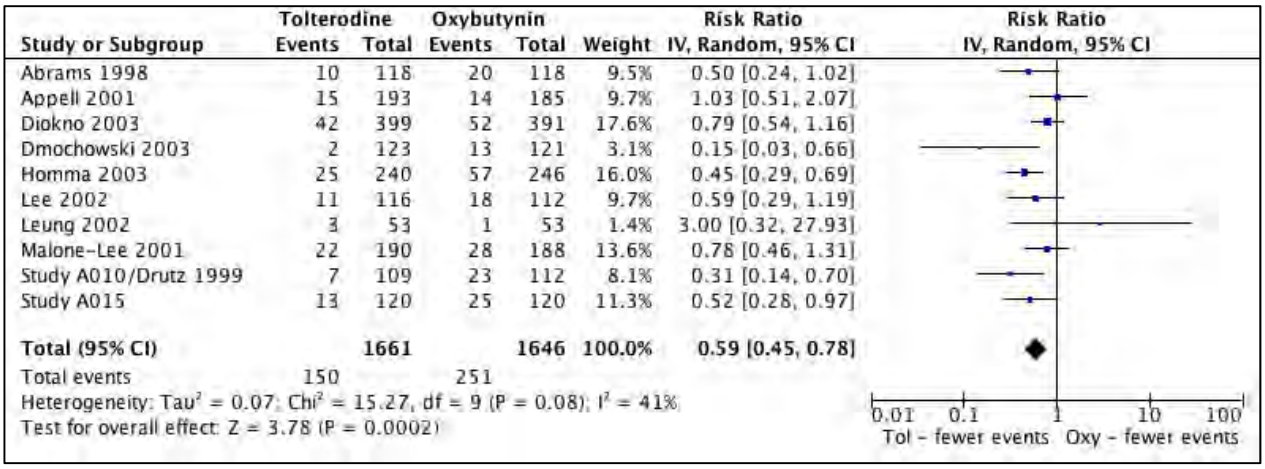


Meta-analyses Tolterodine vs. Oxybutynin (All formulations)

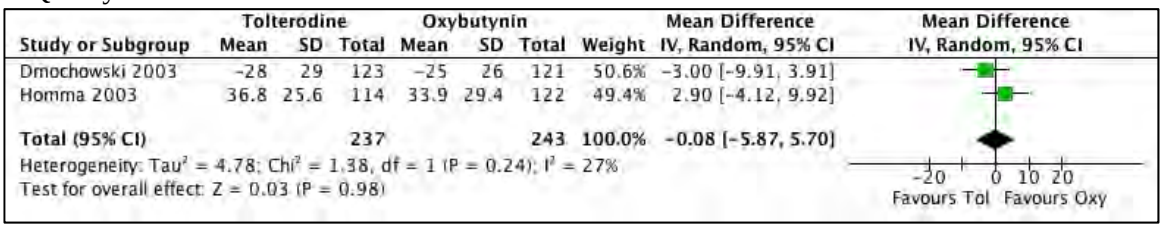
1. SAE:



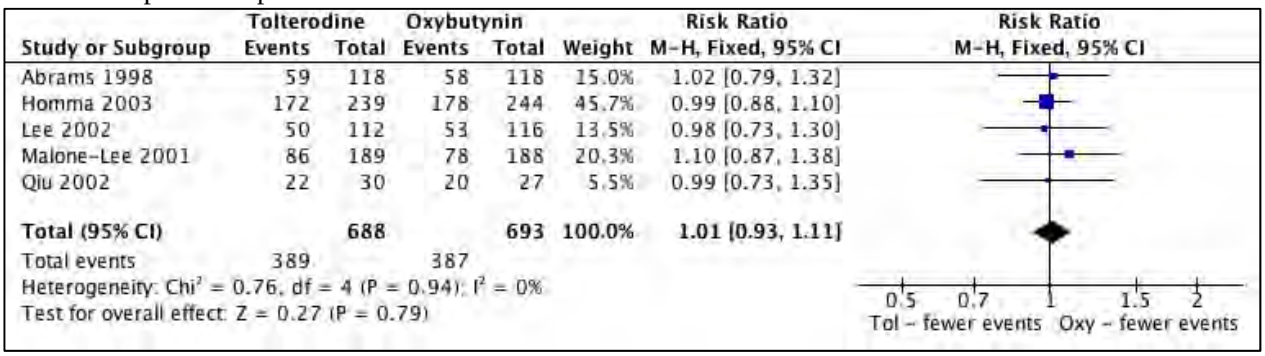
2. WDAE:



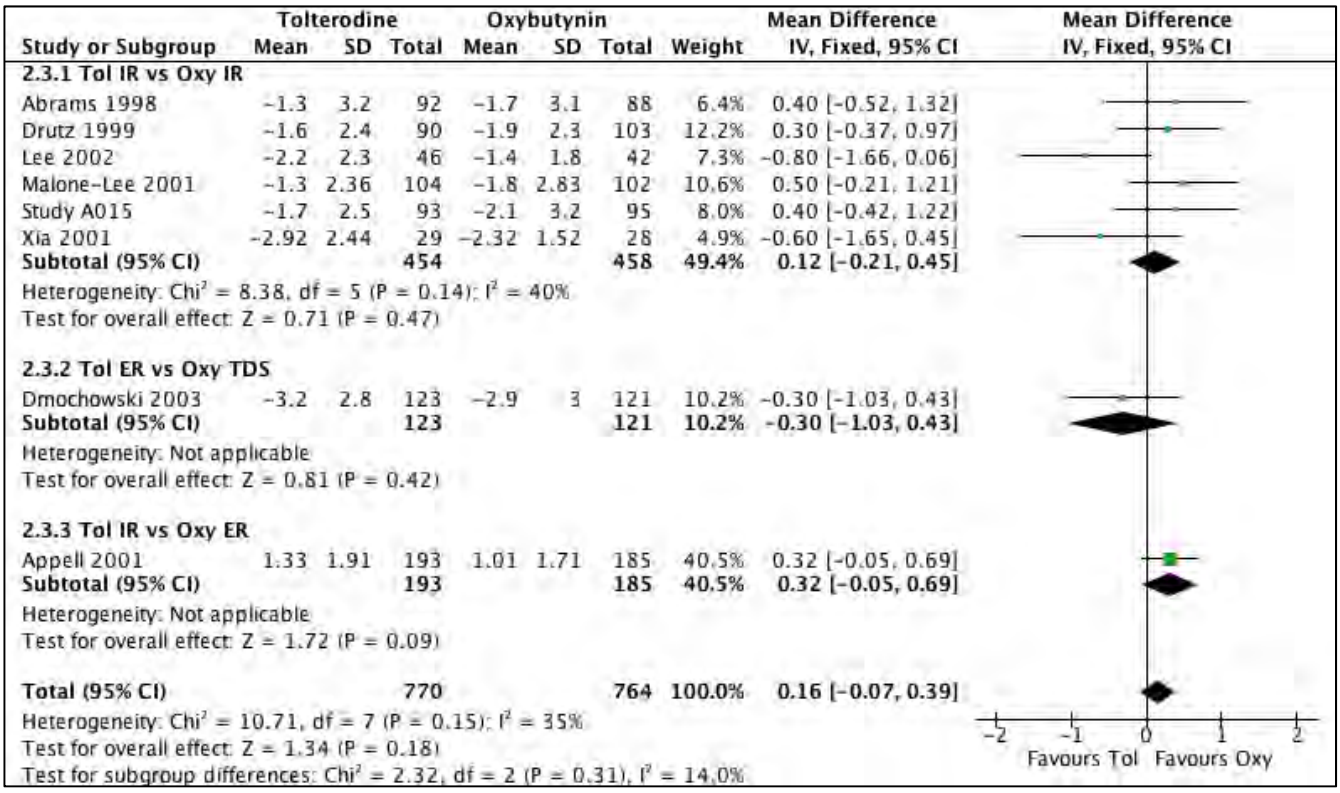
3. Quality of Life:



4. Patient-reported improvement:



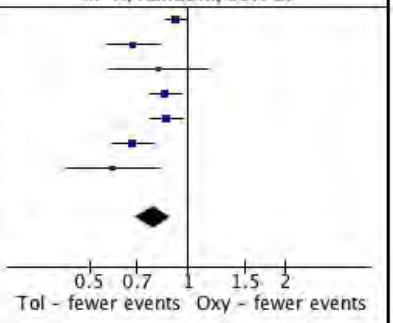
5. Incontinence:



6. Total AE:

Study or Subgroup	Tolterodine Events	Total	Oxybutynin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abrams 1998	105	118	114	118	18.9%	0.92 [0.86, 0.99]
Lee 2002	62	112	94	116	14.0%	0.68 [0.57, 0.82]
Leung 2002	26	53	32	53	8.0%	0.81 [0.57, 1.15]
Malone-Lee 2001	132	190	153	188	17.3%	0.85 [0.76, 0.96]
Study A010/Drutz 1999	84	108	100	111	17.2%	0.86 [0.77, 0.97]
Study A015	76	120	112	120	16.0%	0.68 [0.59, 0.78]
Xia 2001	33	101	58	105	8.6%	0.59 [0.43, 0.82]
Total (95% CI)		**802**		**811**	**100.0%**	**0.78 [0.69, 0.89]**
Total events	518		663			

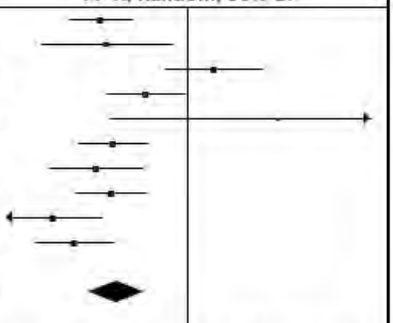
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 31.32$, df = 6 ($P < 0.0001$); $I^2 = 81\%$
Test for overall effect: $Z = 3.77$ ($P = 0.0002$)



7. Dry mouth:

Study or Subgroup	Tolterodine Events	Total	Oxybutynin Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Abrams 1998	59	118	102	118	12.5%	0.58 [0.48, 0.70]
Altan-Yaycioglu 2005	14	28	20	24	8.0%	0.60 [0.40, 0.91]
Appell 2001	64	193	52	185	10.1%	1.18 [0.87, 1.60]
Diokno 2003	86	399	110	391	11.4%	0.77 [0.60, 0.98]
Dmochowski 2003	9	123	5	121	2.2%	1.77 [0.61, 5.13]
Homma 2003	80	240	131	246	12.1%	0.63 [0.51, 0.78]
Lee 2002	39	112	72	116	10.4%	0.56 [0.42, 0.75]
Malone-Lee 2001	71	190	114	188	12.0%	0.62 [0.50, 0.77]
Study A010/Drutz 1999	32	108	77	111	9.9%	0.43 [0.31, 0.59]
Study A015	46	120	94	120	11.4%	0.49 [0.38, 0.63]
Total (95% CI)		**1631**		**1620**	**100.0%**	**0.64 [0.54, 0.76]**
Total events	500		777			

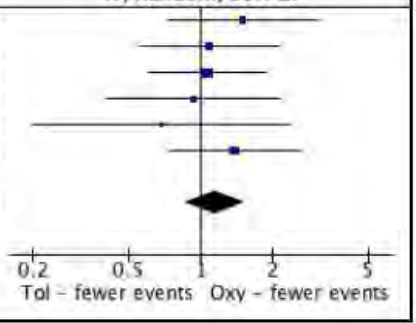
Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 34.01$, df = 9 ($P < 0.0001$); $I^2 = 74\%$
Test for overall effect: $Z = 5.11$ ($P < 0.00001$)



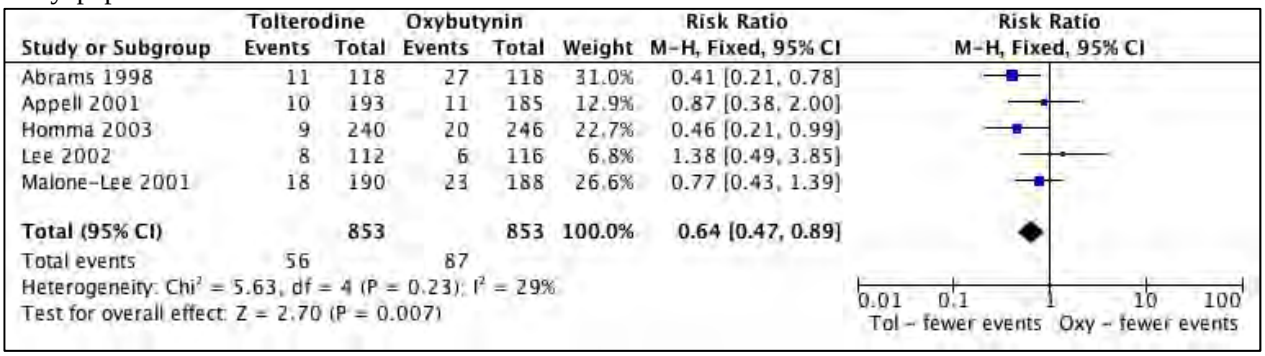
8. Headache:

Study or Subgroup	Tolterodine Events	Total	Oxybutynin Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Abrams 1998	16	108	11	111	16.1%	1.49 [0.73, 3.07]
Appell 2001	17	193	15	185	19.0%	1.09 [0.56, 2.11]
Diokno 2003	24	399	22	391	26.5%	1.07 [0.61, 1.87]
Homma 2003	10	240	11	246	11.9%	0.93 [0.40, 2.15]
Lee 2002	4	112	6	116	5.5%	0.69 [0.20, 2.38]
Malone-Lee 2001	21	190	15	188	21.0%	1.39 [0.74, 2.60]
Total (95% CI)		**1242**		**1237**	**100.0%**	**1.15 [0.86, 1.53]**
Total events	92		80			

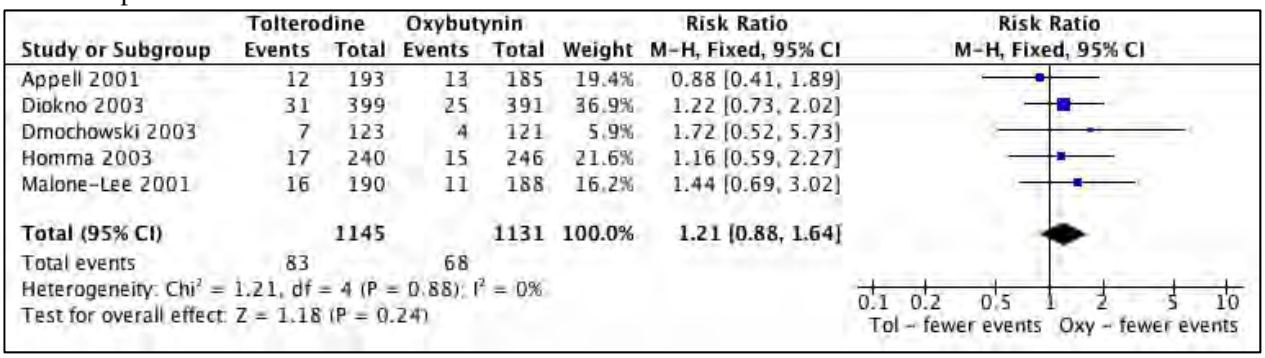
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.83$, df = 5 ($P = 0.87$); $I^2 = 0\%$
Test for overall effect: $Z = 0.94$ ($P = 0.35$)



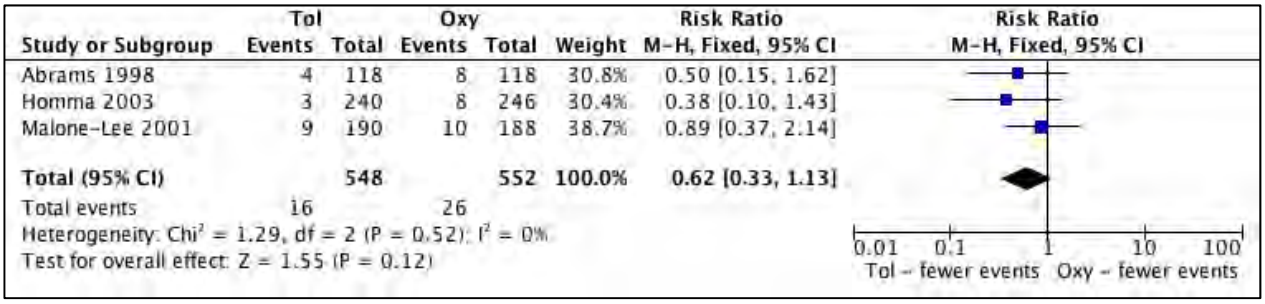
9. Dyspepsia:



10. Constipation:



11. Blurred vision:



Appendix E. Additional Tolterodine Adverse Event Data

Canada Vigilance Adverse Reaction Online Database

Non-fatal SAE: There were 110 non-fatal SAEs (omitting three duplicates). The classification below is the scheme used in reporting for designating the AE as serious and is reporter-dependent. There is overlap in the classification in that some of the events in categories other than hospitalization, for example, do lead to hospitalization. Under the category of 'other important medical conditions', adverse events have been classified designating one event as the primary event. Note that many cases are associated with more than one adverse event or organ system, and that the classification may not reflect the relative importance of each event in the individual circumstances. In 11 of the serious cases, 'drug ineffective' was also listed.

- Life-threatening (3): oedema/puritus/respiratory distress (1); agitation/dizziness/hypersensitivity/suicidal ideation/urinary retention/violence-related symptom (1); circulatory collapse/tongue oedema (1);
- Disability (5): memory impairment (1); condition aggravated/urinary tract infection/drug ineffective (1); abdominal discomfort/pelvic pain/bipolar disorder/condition aggravated, infection/drug ineffective (1); balance disorder/hallucination visual/feeling abnormal/drug interaction (1); halo vision/ visual acuity reduced (1);
- Congenital Anomaly (1): Aplasia cutis congenital [congenital focal absence of epidermis with or without other layers of the skin]/foetal exposure during pregnancy (1);
- Leading to hospitalization (17)
    - *Neurological*: delirium/echolalia/hallucination/psychotic disorder (1); agitation/drug ineffective/loss of consciousness/urinary tract infection/medication error (1); confusional state (1); convulsion (1);
    - *Gastrointestinal*: faecaloma (1); ileus/abdominal distension/abdominal pain (1);
    - *Urinary tract*: urinary retention (1); 1 urinary retention/uterovaginal prolapse (1); cystitis (1); dysuria/pain (1);
    - *Cardiac*: arrhythmia/blood pressure increased (1); heart rate irregular (1)
    - *Unclear or multiple body system*: abdominal pain/dizziness/lethargy/nausea/ porphyria/vision blurred (1), bacterial infection/drug ineffective/dry mouth (1); bladder pain/concussion/diarrhoea/hip fracture (1); drug interaction/ INR increased/retroperitoneal hemorrhage (1); compression fracture/dehydration;diarrhea/fall/gastrointestinal infection (1);

- Other 'medically important conditions' (84):

o *Neurological*: hallucination (2); decreased appetite/fear/hallucination/somnolence/irritability (1); amnesia/drug ineffective (1); amnesia/speech disorder (1); amnesia/activities of daily living impaired (1); coma/epilepsy/life support/lung neoplasm malignant (1); cerebrovascular accident/drug ineffective (1); loss of consciousness/vision blurred (1); balance disorder/fall/diarrhea (1); balance disorder/dementia (1); dizziness/fall/upper limb fracture (1); confusional state/condition aggravated/drug interaction (1);

o *Immune system*: anaphylactic reaction/ loss of consciousness (1); loss of consciousness/pain/swelling face (1); chest discomfort/dyspnea/eye irritation and edema/hypersensitivity/throat tightness (1); hypersensitivity/lip swelling/rash generalized/pyrexia/hyperhidrosis (1); hypersensitivity/oral mucosal blistering/hypertonic bladder (1); dyspnea/heart rate increased/ hypersensitivity/pyrexia/rash generalized (1); hypersensitivity/nasal congestion/dyspnea/dysphonia/dry throat/nasal

polyps/allergies/sinus disorder/streptococcal infection (1); hypersensitivity (3); eczema/puritus/rash (1); lip swelling (1); tongue oedema/headache/abdominal discomfort (1);

- *Cardiac*: QT prolongation/chest pain/palpitations/dyspnea/hypertension/urinary tract infection (1); ateriospasm coronary/chest pain/hypoperfusion (1); atrial fibrillation (1); cardiac pacemaker insertion (1); dizziness/headache/heart rate irregular /nausea (1); heart rate irregular (2); dizziness/heart rate irregular (1); heart rate increased (1); hypertension (2); blood pressure increased/chest discomfort/tachycardia (1); blood pressure inadequately controlled/blood pressure increased (1); blood pressure increased/chest discomfort; tachycardia/diverticulitis/urinary retention/drug interaction (1); angina (1); cardiac disorder /palpitations/drug interaction (1); palpitations (1);
- *Respiratory*: respiratory failure (1); interstitial lung disease/lung neoplasm/ cough/dyspnea/drug ineffective (1);
- *Gastrointestinal*: constipation/condition aggravated/dysphonia/dehydration/dry mouth/dysuria/nasal dryness/vitreous detachment/other (1); constipation/fatigue/drug ineffective (1); condition aggravated/ Crohn's disease (1); diarrhea/flatulence (1); dysphagia/gastric banding (1);
- *Renal and urinary*: renal failure (1); urinary retention (9); dry mouth/nocturia/urine flow decreased (1); urinary incontinence (2); urinary incontinence/drug ineffective (1); catheter placement/dysuria/pain (1); bladder pain/cystitis (1); cystoplexy/oedema peripheral (1); condition aggravated/hypertonic bladder (1);
- *Eye disorders*: eye disorder (3); visual acuity decreased (1); diplopia/vision blurred (1); cataract/vision blurred (1); vision blurred/pollakiuria (1); accommodation disorder/vision blurred/visual field defect (1); cataract (1); glaucoma (1);
- *Other/metabolic/multiple*: diabetes mellitus (1); gait disturbance/pain (1); back pain (1); blood potassium decrease/drug interaction (1); drug ineffective (1); blood glucose increased/eye irritation/muscle spasms/drug ineffective (1); dental caries/dry mouth/increased disability/multiple sclerosis relapse/speech disorder/headache/blood pressure fluctuation (1); asthenia/headache/malaise /nausea/renal failure (1);

Additions to Tolterodine Product Information from Post Market Experience

Contraindications:
Known hypersensitivity to the drug or its ingredients, or to fesoterodine fumarate extended-release tablets (2011)

Warnings:
Anaphylaxis and angioedema (2011)

Precautions:
Central Nervous System (CNS) Effects: [Tolterodine] is associated with anticholinergic central nervous system (CNS) effects including dizziness and somnolence (2012)

The ability to drive and use machinery may be negatively affected. Patients should be advised to exercise caution.

Tolterodine should be used with caution in the following patients:
- *With myasthenia gravi*

Cardiovascular system safety concerns:

In a study of the effect of tolterodine immediate-release tablets on the QT interval, the effect on the QT interval appeared greater for 8 mg/day (two times the therapeutic dose) compared to 4 mg/day and was more pronounced in CYP2D6 poor metabolizers (PM) than extensive metabolizers (EMs)…. These observations should be considered in clinical decisions to prescribe tolterodine extended-release capsules for patients with:
- Congenital or documented acquired QT prolongation;
- Patients who are taking Class IA (e.g., quinidine, procainamide) or Class III (e.g.,amiodarone, sotalol) antiarrhythmic medications.

Adverse Events
Psychiatric Disorders: *disorientation*, hallucinations
Nervous System Disorders: *memory impairment*

Cases of aggravation of symptoms of dementia (e.g. confusion, disorientation, delusion) have been reported after tolterodine therapy was initiated in patients taking cholinesterase inhibitors for the treatment of dementia.

Gastrointestinal Disorders: *diarrhea*

General: anaphylaxis and angioedema

Part II and III Appendices – Table of Contents

Appendix F – Fesoterodine vs. Comparators. Evidence Tables and Figures

Table 1. RCT Study Characteristics: Fesoterodine vs. Tolterodine ER

Study Country N	Design	Inclusion criteria Exclusions	Baseline Characteristics % of participants	Feso 8 mg	Feso 4 mg	Tol ER 4 mg	Placebo	Outcomes Assessed
Chapple 2007 SP583 (19 countries: Belgium, Bulgaria, Czech Republic Estonia, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Russia, Spain, Sweden, Ukraine, UK, South Africa, Aus, NZ) Schwartz Pharma and Pfizer	four-arm, DB, double-dummy, placebo- and active controlled parallel group RCT; Phase III study MC 2 week placebo run-in phase 3 day bladder diary Assessments week 0, 2, 4, 8 and 12 modified ITT with LOCF 12 weeks duration	• OAB ≥ 6 months • ≥ 8 micturitions /24 h (3 day diary) AND • Either ≥ 3 UUI episode per 24 h, OR • ≥ 6 urgency episodes per 24 h (recorded in 3 day diary) • patients had to indicate on Likert scale that condition caused them at least moderate problems Protocol amended later to include ≥ 3 UUI episodes per 24 h in remaining subjects Exclusions genitourinary pathology; neurological conditions; prior history of acute urinary retention	Screened: 1463; Placebo run-in: 1409 Randomized: 1135 Mean age 57 yrs 41% prior treatment for OAB 96-98% white 80% female; 20% male 78% incontinent mean duration 8-9 years Percent ≥ age 65 NR	4 mg x 1 initial week, 8 mg x 11 weeks N=288 ≥ 1 dose: 287 Completed: N=252 Baseline UUI: 3.7 (SD 3.0) Nocturia: 2.0 (SD 1.6) Urgency: 11.5 (4.2)	N=272 ≥ 1 dose: 271 Completed N=231 Baseline UUI: 3.4 (SD 3.8) Nocturia: 1.9 (SD 1.3) Urgency: 11.0 (4.2)	N=290 Completed N=253 Baseline UUI: 3.8 (SD 3.1) Nocturia: 2.0 (SD 1.2) Urgency: 11.0 (3.4)	N=285 ≥1 dose N=284 Completed N=252 Baseline UUI: 3.7 (SD 3.1) Nocturia: 1.8 (SD 1.2) Urgency: 11.4 (4.0)	• Micturitions per 24 h, change from baseline (at 12 weeks) (co-primary outcome) • UUI episodes, change from baseline per 24 h (co-primary outcome) • Treatment response - 4 point scale 1 = greatly improved; and 2= improved regarded as 'yes'; 3= not changed and 4= worsened considered 'no'. • Mean volume voided per micturition • Daytime micturitions per 24 h • Urgency episodes per 24 h • Continent days per week (calculated based on 3 day diary • AE • Laboratory parameters (hematology, chemistry, urinalysis) • Residual urinary volume • ECG • Physical examination • Subject assessment of treatment tolerance

		requiring catheterization; no predominant stress UI; lower urinary tract pathology that could be cause of urgency or incontinence; symptomatic or recurrent UTI; post void residual urine volume > 100 mls; polyuria; clinically relevant BOO; pelvic organ prolapse; QT prolongation, arrhythmia or unstable angina						• Median percentage change in bladder diary variables from baseline (post hoc)

Table 1 Continued. RCT Study Characteristics – Fesoterodine vs. Tolterodine ER							
Study Country N	**Design**	**Inclusion criteria Exclusions**	**Baseline Characteristics % of participants**	**Feso 8 mg**	**Tol ER 4 mg**	**Placebo**	**Outcomes Assessed**
Herschorn 2010 A1008 NCT00444925 MC Canada (9 sites, 56 patients) US, Central and South America, Europe and Asia Pfizer	three-arm, DB, double-dummy placebo- and active-controlled parallel group RCT 2 week single-blind run-in phase 2:2:1 randomization modified ITT with LOCF using data from interim visits but not baseline data ANCOVA model for parametric data Winsorized means; Van Elteren's test for non-parametric data	• OAB ≥ 3 months • 1 UUI episode on average per 24 h • ≥ 8 micturitions per 24 h in 3 bladder day diary Exclusions No genitourinary pathology; no neurological conditions; no prior history of acute urinary retention requiring catheterization; no predominant stress UI; other;	Screened: 2685 Randomized:1712 ≥ 1 dose:1697 82% women 78% Caucasian mean age ~ 58 years 33% were ≥ age 65 ~ 50% prior drug treatment ~ 1% reported no UUI episodes and "were in violation of the study inclusion criterion". They were excluded from analyses of baseline to week 12 change in UUI episodes/24 h and of the diary-dry rates.	fesoterodine 4 mg x 1 week, then 8 mg x 11 weeks ≥ 1 dose: N = 679 Baseline UUI: 2.4 (SD 2.0) Nocturnal voids: 2.2 (SD 1. 3) Urgency: 9.3 (3.9) Completed N=598	≥ 1 dose N=684 Baseline UUI: 2.5 (SD 2.2) Nocturnal voids: 2.2 (SD 1.3) Urgency: 9.3 (SD 3.7) Completed N=628	≥ 1 dose N=334 Baseline UUI:2.6 (SD 2.3) Nocturnal voids: 2.3 (SD 1.3) Urgency: 9.4 (SD 4.2) Completed N=304	• UUI episodes/24 h (change from baseline) = primary outcome; UUI episodes defined as those with urinary sensation scale (USS) rating of 5 in bladder diary • Proportion of evaluable§ participants who had 0 incontinence episodes in 3-day diary (diary dry rate) • Mean volume voided • Micturitions per 24 h • Nocturnal voids per 24 h • Percent change of nocturnal micturition per 24 h • Urgency episodes (scale rating of 3 or more on Urinary Sensation Scale) (Scale 1=no urgency; 2=mild urgency; 3=moderate urgency; 4=severe urgency; 5=UUI) • Severe urgency episodes using 5-point urinary sensation scale (scale rating 4 or more) • PPBC • Urgency Perception Scale (3 point categorical response scale; higher scores = less urgency)* • Frequency-urgency sum per 24 h • OAB-q for QoL* • Median percentage change in bladder diary variables from baseline to week 12 (exploratory) • SAE • WDAE • Selected AE • Laboratory parameters (hematology, chemistry)

							• BP and pulse rate • ECG • Physical examination
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Feso 8 mg**	**Tol ER 4 mg**	**Placebo**	**Outcomes Assessed**
Kaplan 2010 A1046 MC North America, South America, Europe, Asia, Africa (Canada 8 sites, 24 patients) Pfizer	three-arm, DB, double-dummy parallel group RCT 2 week single blind run-in phase with placebo 2:2:1 randomization 3 day bladder diary Assessment visits week 0, 1,4 and 12 12 weeks duration LOCF - post baseline data imputed on LOCF basis; baseline data were not carried forward.	• OAB symptoms for ≥ 3 months • 1 urgency incontinence episode on average per 24 h as verified by 3 day bladder diary in run-in phase • 8 micturitions per 24 h (3 day bladder diary) <u>Exclusions</u> renal or hepatic disease; genitourinary pathology; neurological conditions; history of acute urinary retention requiring catheterization; predominant stress UI; other exclusions similar to other RCTs for this comparison	Screened: 4136 Randomized: 2417 ≥ 1 dose: 2411 Mean age ~ 59 yrs Age range 18 to 89 yrs 36% were ≥ age 65 2% had fewer than 1 incontinence episode per day in violation of eligibility criteria but were included in analyses Prior antimuscarinic therapy: 33%	N=960 (≥ 1 dose) Evaluable for UUI: 851 Completed 431 <u>Baseline</u> UUI: 2.6 (SD 2.2) per 24 h Nocturia: 2.2 (SD 1.3) per 24h Urgency: 9.7 (SD 4.0) per 24 h	N = 973 (≥ 1 dose) Evaluable for UUI: 864 Completed 885 <u>Baseline</u> UUI: 2.6 (SD 2.1) per 24 h Nocturia 2.3 (SD 1.2) per 24 h Urgency: 9.7 (SD 3.6) per 24 h	N = 472 (≥ 1 dose) Evaluable for UUI: 373 Completed 432 <u>Baseline</u> UUI: 2.4 (SD 1.9) per 24 h Nocturia 2.1 (SD 1.3) per 24 h Urgency: 9.5 (SD 3.9) per 24 h	• UUI episodes change from baseline (= primary outcome) • Micturitions per 24 h • Severe urgency episodes (urinary sensation scale) • Frequency-urgency sum per 24 h - sum of all urinary sensation scale ratings associated with all micturitions over 24 h averaged over diary period • Nocturnal voids per 24 h • % change in nocturnal voids per 24 h • 3-day diary dry rate: proportion of evaluable subjects who had 0 UUI episodes on post baseline diary§ • PPBC • OAB-q • Mean volume voided • SAE • WDAE • Laboratory parameters (hematology, serum chemistry) • BP and pulse rate • ECG • Physical exam

*comparisons fesoterodine vs. tolterodine, and tolterodine vs. placebo were post hoc analyses and not prespecified.

§Evaluable patients were those who had incontinence as recorded in baseline diary; protocols specified incontinence as an eligibility criterion for Kaplan 2010 and Herschorn 2009 but 10 to 20% in Kaplan 2010 were in violation of this, and ~1% in Herschorn 2009 were in violation of this.

ANCOVA=analysis of covariance; BP=blood pressure; h=hours; ITT=intention-to-treat analysis; LOCF=last observation carried forward; mITT=modified intention-to-treat analysis; ND=not done; PPBC=patient perception of bladder condition; OAB-q=OAB-questionnaire; QoL=quality of life; SAE=serious adverse events; SD=standard deviation; UUI=urgency urinary incontinence; WDAE=withdrawals due to adverse events

Table 2. RCT Outcomes Fesoterodine vs. Tolterodine ER										
Study	Chapple 2007				Herschorn 2009[1]			Kaplan 2010[2]		
Treatment	Placebo	Tol ER	Feso 4 mg	Feso 8 mg	Placebo	Tol ER 4 mg	Feso 8 mg	Placebo	Tol ER 4 mg	Feso 8 mg
N randomized	285	290	272	288	NA	NA	NA	NA	NA	NA
N ≥ 1 dose	283	290	272	287	334	684	679	478	973	960
Mortality	1[3] (0.4%)	0	0 (0.3%)	1	2 (0.5%)	0 (0%)	2 (0.2%)	1 (0.2%)	0	0
SAE	8 (2.8%)	7 (2.4%)	12 (4.4%)	11 (3.8%)	6 (2%)	9 (1%)	16 (2%)	7 (2%)	6 (1%)	13 (1%)
WDAE	6 (2%)	9 (3%)	7 (3%)	14 (5%)	6 (2%)	28 (4%)	44 (6%)	9 (2%)	28 (3%)	45 (5%)
OAB-q change from baseline - Symptom bother	NA				-16.3	-22.5	-27.1	-21.8	-24.3	-28.9
Symptom Bother LSM (SE) difference Feso vs. Tol[3]	NA				-4.6 (95% CI -7.7 to -1.6)			-4.6 (95% CI -6.6 to -2.7)		
-Coping	NA				14	18.5	22.6	19	22	25.9
- Concern	NA				13.4	19.3	22.6	20.2	22.6	26.8
- Sleep	NA				12.2	15.1	17.1	16.6	18.7	21
- Social	NA				6.8	9.4	11.6	10.8	12	13.9
- HRQL score	NA				12	16.3	19.3	12.2	19.5	22.9
HRQL LSM (SE) difference Feso vs. Tol[3]					3.0 (NR) (95% CI 0.23 to 5.8)			3.3 (0.1) 95% CI (1.5 to 5.2)		
KHQ - severity (coping)	-9	-12.6	--	-14.0	NA			NA		
- emotions	-10.1	-16.3	--	-17.4						
- role limitations	-11.8	-22.1	--	-21.7						
- physical limitations	-11.4	-19.7	--	-21.7						
- social limitations	-8.7	-14.1	--	-15.4						
- sleep/energy	-9.6	-11.7	--	-13.6						
- personal relationship	-6.2	-10.4	--	-11.9						
- incontinence impact	-16.1	-23.3	--	-24.6						
- general health	-3.8	-4.3	--	-4.0						
ICIQ-SF	-2.55	-3.95	--	-4.41						
Perception of improvement					54%	63%	71%	60%	70%	74%
					N=313	N=626	N=619	N=455	N=937	N=918
Cure (no incontinence episodes) (days)					(3 days) 45.0%	(3 days) 57.2%	(3 days) 64.0%			
					N=307	N=626	N=619			

Study	Chapple 2007				Herschorn 2009[1]			Kaplan 2010[2]		
Treatment	Placebo	Tol ER	Feso 4 mg	Feso 8 mg	Placebo	Tol ER 4 mg	Feso 8 mg	Placebo	Tol ER 4 mg	Feso 8 mg
N randomized	285	290	272	288	NA	NA	NA	NA	NA	NA
N ≥ 1 dose	283	290	272	287	334	684	679	478	973	960
Continent Days per Wk Change from baseline LSM (SE)[4]	2.07 (0.20)	2.48 (0.20)	2.84 (0.21)	3.32 (0.19)	NA			NA		
Incontinence per 24 h Change from baseline LSM (SE) or WInsorized mean (SE)	-1.14 (SD 0.16)	-1.74 (SD 0.16)	-1.95 (SD 0.17)	-2.22 (SE 0.16)	-1.46^ (SE 0.1)	-1.61^ (SE 0.06)	-1.72^ (SE 0.06)	-1.62^ (SE 0.07)	-1.74^ (SE 0.06)	-1.95^ (SE 0.05)
N (evaluable patients)	N=211	N=223	N=199	N=223	N=307	N=626	N=619	N=448	N=926	N=908
Urgency per 24 h Change from baseline Mean (SD)*	NA	7.4 (3.84)	NA	7.9 (5.14)	NA	6.23 (4.31)	5.8 (4.52)	NA	6.01 (4.33)	5.32 (4.17)
Urgency per 24 h Change from baseline LSM (SE)	-1.07 (0.19)	-2.03 (0.19)	-1.88 (2.0)	-2.36 (0.20)	-2.0 (SE NA)	-3.1 (SE NA)	-3.5 (SE NA)	graph only	graph only	graph only
No. of patients	279	283	265	276				413	933	915
Nocturia Change from baseline Mean (SD)**	-0.30 (1.120)	-0.44 (1.049)	-0.41 (1.153)	-0.43 (1.154)	-1.46 (0.1)	-1.61 (0.06)	-1.72 (0.06)	NA	NA	NA
Nocturia Change from baseline LSM (SE)	-0.32 (0.06)	-0.40 (0.06)	-0.39 (0.06)	-0.39 (0.06)	-0.5 (0.1)	-0.6 (0.0)	-0.7 (0.0)	0.5 (0.1)	-0.6 (0.1)	-0.6 (0.1)
Total AE	107/283 (38%)	144/290 (50%)	135/272 (50%)	167/287 (58%)	125 (37.4%)	280 (40.9%)	353 (52.0%)	145 (30.3%)	375 (38.5%)	459 (47.8%)
Nocturia End of treatment Mean (SD)**	1.5 (1.35)	1.6 (1.28)	1.5 (1.33)	1.6 (1.73)	1.6 (1.3)	1.6 (1.3)	1.5 (1.3)	1.8 (1.4)	1.7 (1.3)	1.6 (1.4)
No. of patients	N=279	N=283	265	N=276	N=293	N=596	N=601	N=413	N=933	N=915
No. of patients with one or more AE (%)	107 (38%)	144 (50%)	135 (50%)	167 (58%)	125 (37.4%)	280 (40.9%)	353 (52.0%)	145 (30.3%)	375 (38.5%)	459 (47.8%)
QT prolongation (%)	0	0	1 (0.4%)	2 (0.7%)						
Dry Mouth	20 (7.1%)	49 (16.9%)	59 (21.7)	97 (33.8%)	20 (5.99%)	112 (16.4%)	189 27.80%	26 (5%)	130 (13%)	265 (28%)
Dyspepsia	3 (1%)	5 (2%)	6 (2%)	12 (4%)	1 (0.3%)	8 (1.2%)	12 (1.8%)	2 (0.4%)	8 (0.8%)	10 (1.0%)
Nausea	1 (0.3%)	6 (2.1%)	1 (0.4%)	4 (1.4%)	6 (1.8%)	7 (1.02%)	12 (1.77%)	3 (0.6%)	13 (1.3%)	11 (1.1%)
Abdominal pain	NA				4 (1.2%)	4 (0.58%)	10 (1.47%)	NA		
Upper abdominal pain	NA				3 (0.9%)	6 (0.88%)	9 (1.33%)	NA		

Constipation	4 (1.4%)	8 (2.8%)	9 (3.3%)	13 (4.5%)	10 (3.0%)	28 (4.1)%	37 (5.4%)	26 (5.4%)	30 (3.1%)	42 (4.4%)
Dizziness	7 (2.5%)	4 (1.4%)	4 (1.5%)	3 (1.0%)	4 (1.2%)	10 (1.5%)	8 (1.2%)	2 (0.4%)	8 (0.8%)	10 (1.0%)
Headache	14 (4.9%)	14 (4.8%)	12 (4.4%)	7 (2.4%)	8 (2.4%)	23 (3.4%)	38 (5.6%)	6 (1.3%)	20 (2.1%)	27 (2.8%)
Fatigue	1 (0.3%)	10 (3.4%)	1 (0.4%)	1 (0.4%)	0 (0%)	4 (0.6%)	12 (1.8%)	NA	NA	NA
Dry eye	0	1 (0.3%)	6 (2.2%)	12 (4.2%)	6 (1.8%)	8 (1.17%)	12 (1.77%)	0	1 (0.3%)	6 (2.2%)
Urinary tract infection	6 (2%)	4 (1%)	8 (3%)	9 (3%)	2 (0.60%)	10 (1.46%)	15 (2.21%)	5 (.10%)	12 (1.2%)	14 (1.5%)
Acute Urinary Retention	0	0	1	2						
Mean volume voided per micturition End of Treatment	159.9 (62.0)	178.0 (66.2)	187.0 (92.6)	187.5 (73.7)	164.2 (74.6)	176.1 (74.9)	186.2 (81.2)	147.6 (54.9)	142 (55.4)	146.6 (54.9)
Mean volume voided change from baseline LSM (SE) or Winsorized mean (SE)[3]	9.8 (43.5)	23.6 (52.1)	27.0 (70.3)	33.5 (54.2)	16.8 (3.9)	23.5 (3.0)	32.9 (3.1)	17.3^ (2.4)	28.4^ (1.82)	34.5^ (2.1)
Urodynamics	NA				NA			NA		

KHQ=King's Health Questionnaire;AE=adverse events; LSM=least squares mean; NA=either not reported or not measured; SAE=serious adverse events; SD=standard deviation; SE=standard error; total AE= the proportion of patients experiencing one or more AE; WDAE=withdrawals due to adverse events; * from Madhuvrata 2012 (investigator-provided data); ** from Fesoterodine CDR Review; ^ Winsorized mean (SE)

[1] Herschorn 2009: 107 patients excluded from efficacy analysis

[2] Kaplan 2010: 77 patients excluded from efficacy analysis

[3] Data and calculations as reported in Fesoterodine CDR Review

[4] Results extrapolated by study investigators from a 3 day bladder diary

Table 3. SAE – Fesoterodine vs. Tolterodine				
		Description of SAE		
Study	Comparison	Fesoterodine	Tolterodine	Placebo
Chapple 2007* SP583	Feso 4mg Feso 8 mg Tol ER 4 mg Placebo	8 mg dose: Deaths*: 1 myocardial infarction 1 day post discharge for an eight day hospitalization for bronchitis; female, age NR; 26 days post discontinuation of fesoterodine, with initial event (hospitalization for bronchitis) occurring 2 weeks post discontinuation Non-fatal SAE: 8 (2.8%) details NR 4 mg dose: Deaths: 0 Non-fatal SAE: 12 (4.4%)	0 deaths* Non-fatal SAE 7 (2.4%) details NR	1 death* – details NR Non-fatal SAE: 8 (2.8%) details NR
Herschorn 2010 A1008 NCT00444925	Feso 8 mg Tol ER 4 mg Placebo	2 deaths: traumatic brain injury as a result of a car accident in 73 year old female (1); cause of death not verified in 70 year old female with cardiac failure listed on death certificate (1)** The SAE listed on clinicaltrials.gov for 15 participants who had one or more SAE (16 AE in total) are: iron deficiency anemia 1 myocardial ischemia 1 abdominal pain 1 appendicitis perforated 1 hypertensive heart disease 1 rectal hemorrhage 1 bronchiectasis 1 traumatic brain injury 1 upper limb fracture 1 cervical disc protrusion 1 hepatic neoplasm 1 prostate cancer 1 intracranial hemorrhage 1	0 deaths The SAE listed on clinicaltrials.gov for 9 participants (10 AE in total) are: chest pain 1 biliary colic 1 cystitis 1 herpes zoster 1 head injury 1 cervical disc protrusion 1 breast cancer 1 lymphoma 1 breast mass 1 dyspnea exertional 1	2 deaths – details NR The SAE listed on clinicaltrials.gov for 8 participants (18 AE in total), as listed on clinicaltrials.gov: nausea 1 vomiting 1 abdominal wall abscess 1 hand fracture 1 seroma 1 cervical spine stenosis 1 MSK pain 1 pain in extremity 1 spinal column stenosis 1 prostate cancer 1 dizziness 1 metastic lung cancer 1

		suicidal behaviour 1 urinary incontinence 1 uterine hemorrhage 1		noeplasm malignant 1 skin cancer 1 dizziness 1 vertobrobasilar insufficiency 1 mental status change 1asthma 1 arteriosclerosis 1
Kaplan 2010 A1046	Feso 8 mg N=960 Tol ER 4 mg N=973 Placebo N=478	0 deaths 13 participants experienced SAE (1.4%) in fesoterodine group – 2 considered treatment-related are described: acute pyelonephritis in a 49 year old female (1); acute urinary retention (1) in a 72 year old male The SAE listed for 13 participants as recorded on clincialtrials.gov (21 AE in total): unstable angina 1 atrial fibrillation1 atrial tachycardia1 chronic cardiac failure 1 chest pain 1 bronchopneumonia 1 pneumonia 1 pyelonephritis 1 acute pyelonephritis 1 sepsis 1 therapeutic agent toxicity 1 colon cancer 1 balance disorder 1 dizziness 2 ischemic stroke 1 bipolar disorder 1 mania 1 renal failure acute 1 hyperhidrosis 1 cholecystectomy 1	0 deaths 6 participants had SAE (0.6%)as described on clinicaltrials.gov (6 AE in total): fibula fracture 1 spinal compression fracture 1 breast cancer 1 colon cancer 1 gastric cancer 1 allergic respiratory disease 1	1 death Non-fatal SAE: 7 (1.5%) 8 participants had SAE in 8 participants as recorded on clinicaltrials.gov (12 AE) in total) cardiac failure congestive 1 mitral valve stenosis 1 diverticulum intestinal hemorrhagic 1 large intestine perforation 1 peritonitis 1 hepatitis acute 1 cellulitis 1 pneumonia 1 delayed recovery from anesthesia 1 lower limb fracture 1 hepatic neoplasm 1 deep vein thrombosis 1
*deaths not reported in publication – information obtained from CDR Review 2012; ** details obtained from CDR review 2012				

Table 4. Fesoterodine 4 mg vs. Tolterodine ER 4 mg: Chapple 2007		
Outcome	**N**	**Feso vs. Tol RR or mean difference**
All-cause mortality	562	0 events
SAE (non-fatal)	562	RR 1.83 [95% CI 0.73 to 4.57]
QoL General Health Perception (KHQ)	546	MD 1.10 [95% CI -2.15 to 4.35]
QoL Incontinence severity	538	MD -0.50 [95% CI -4.31 to 3.31]
WDAE	562	RR 0.83 [95% CI 0.94 to 1.15]
Patient-reported improvement/cure	403	RR 1.04 [95% CI 1.06 to 1.16]
Incontinence episodes Mean change from baseline	422	MD -0.23 [95% CI -0.71 to 0.25]
Continent days per week	422	MD 0.26 [95% CI -0.32 to 0.84]
Nocturia	548	MD -0.03 [95% CI -0.15 to 0.21]
Total AE	562	RR 1.0 [95% CI 0.85 to 1.8]
Dry mouth	562	RR 1.28 [95%CI 0.91 to 1.81]

AE=adverse events; **ER**=extended release; **MD**=mean difference; **RR**=relative risk;
QoL=quality of life; **SAE**=serious adverse events; **WDAE**=withdrawals due to adverse events

Table 5. QoL- King's Health Questionnaire: Chapple 2007	
Fesoterodine 8 mg/d vs. Tolterodine ER 4 mg/d	
KHQ domain	**Mean difference (95% CI) Feso 8 mg/d vs. Tol ER 4mg/d**
Incontinence impact	-2.20 (95% CI -6.59 to 4.19)
Role limitation	0.00 (95% CI 5.09 to 5.09)
Physical limitation	-1.70 (95% CI -6.74 to 3.34)
Social limitation	-1.00 (95% CI -5.42 to 3.42)
Personal relationships	2.40 (95% CI -3.74 to 8.54)
Emotions	-3.00 (95% CI -8.15 to 2.15)
Sleep and energy	-4.30 (95% CI -9.12 to 0.52)
Severity coping measure	-1.70 (95% CI -6.15 to 2.75)
General health perception	1.20 (95% CI -2.28 to 4.68)

From Mudhuvrata 2012; **CI**=confidence intervals;
feso=fesoterodine; **tol**=tolterodine; **QoL**=quality of life;

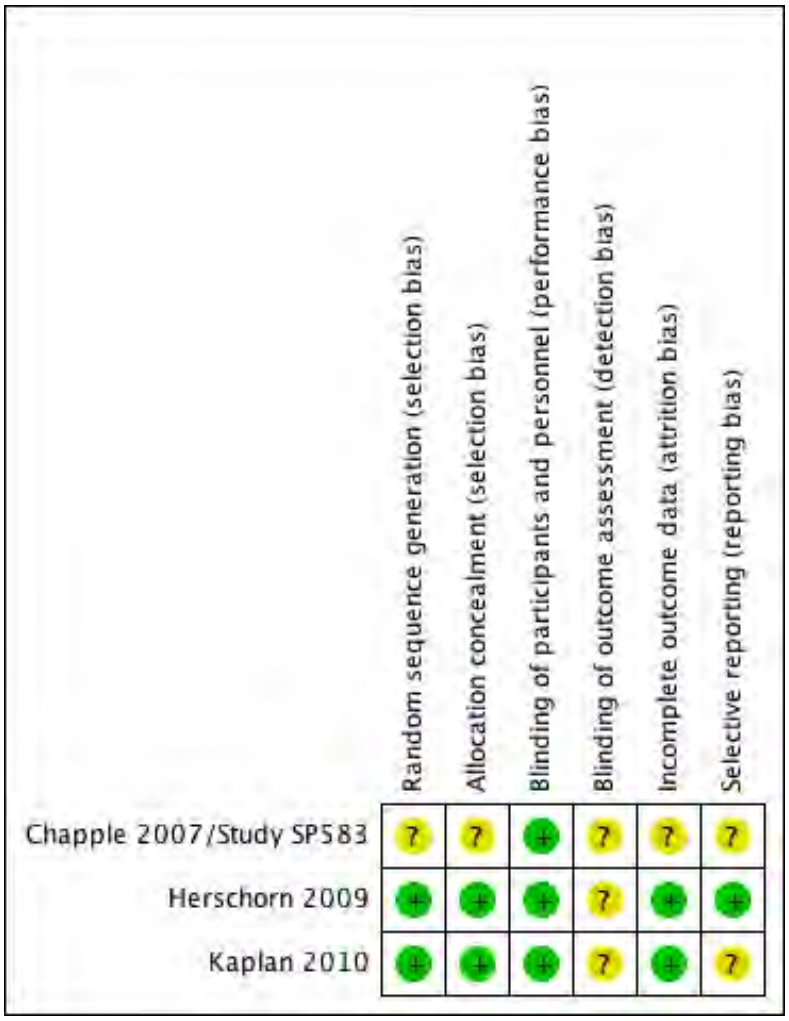


Table 6. Risk of Bias/Quality Assessment

The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

The Chapple 2007 publication did not report patient disposition. However, this information was available in the Fesoterodine CDR Review (Study SP583) and was assessed on the basis of those data.

Appendix G – Solifenacin vs. Comparators Evidence Tables and Figures

Table 1. RCT Study Characteristics – Solifenacin vs. Oxybutynin							
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Soli**	**Oxy IR**	**Placebo if included**	**Outcomes Assessed**
Herschorn 2010 NCT00431041 VECTOR trial Canada N=132 Astellas	MC, Parallel group DB RCT Double-dummy 14 day washout period required if on medication 8 weeks duration 3 day bladder diary Outcome assessment at baseline, weeks 2, 4 and 8 ITT, no data imputation Superiority design	Adults (18 years or older) with ≥ 1 urgency episode per 24 h and ≥ 8 micturitions per 24 h Patients not required to have urgency incontinence No use of tricyclic antidepressants, alpha blockers, 5 alpha-reductase inhibitors or anti-Parkinsons drugs; no history of stress UI, UTI, clinically significant outflow obstruction or urinary retention	Adults with ≥ 1 urgency episode per 24 hours and ≥ 8 micturitions per 24 h on average for ≥ 3 months (documented in a 3-day bladder diary) 78% female; 22% male Mean age 61 years Age range 22 to 87 43% > age 65 17% > 75 years 90% Caucasian 7 (5%) black; 3 Asian (2%); 1 Aboriginal (<1%); 2 Other 89% on ≥ 1 concomitant medications (e.g., lipid lowering agents, anti-HT, antacids)	Soli 5 mg once daily N=68 Completers: N=52	Oxy IR 5 mg tid N=64 Completers: N=40	ND	- Dry mouth incidence and severity (primary outcome) - Urgency - Incontinence episodes - Frequency of micturitions - Nocturia - Volume voided per micturition - PPBC - OAB-q - Total withdrawals - WDAE - SAE - Total AE - Specific AE

Table 2. RCT Outcomes – Solifenacin vs. Oxybutynin IR		
Study	**Herschorn 2010**	
Treatment	Solifenacin 5 mg N=68	Oxybutynin IR 5 mg tid N=64
All-cause Mortality	0 (0%)	0 (0%)
SAE (non-fatal)	3 (4%)	0 (0%)
Total withdrawals	16 (24%)	24 (38%)
WDAE	9 (13%)	19 (30%)
CNS only WDAE	NA	NA
OAB-q evaluable patients N	N=64	N=61
OAB-q Symptom bother (SD)	-21 ± 20	-25 ± 24
OAB-q Coping (SD)	19 ± 27	25 ± 24
OAB-q Concern (SD)	23 ± 24	24 ± 24
OAB-q Sleep (SD)	20 ± 27	23 ± 26
OAB-q Social (SD)	11 ± 21	15 ± 20
OAB-q HRQL score (SD)	19 ± 22	22 ± 21
PPBC	N=67	N=62
Mean change from baseline (SD)	-0.9 ± 1.3	-1.4 ± 1.3
Proportion reporting continence	NA	NA
Incontinence Episodes per 24 h	N=63	N=48
Mean change from baseline (SD)	-0.6 ± 1.5	-1.0 ± 1.9
Urgency episodes per 24 h	N=63	N=48
Mean (SD) change from baseline	-2.5 ± 4.4	-3.5 ± 4.4
Nocturia episodes per 24 h	N=63	N=48
Mean (SD) change from baseline	-0.4 ± 1.0	-0.7 ± 1.5
Total AE	49 (72%)	59 (83%)
Total CNS AE	NA	NA
Confusion	0 (0%)	1 (2%)
Dizziness	2 (3%)	6 (9%)
Somnolence	1 (2%)	3 (5%)
Fatigue	4 (6%)	6 (9%)
Insomnia	NA	NA
Nervousness	NA	NA
Headache	2 (3%)	4 (6%)
Dry Mouth	24 (35%)	53 (83%)
Dysgeusia	1 (2%)	2 (3%)
Dysphonia	0 (0%)	6 (9%)
Dysphagia	1 (2%)	5 (8%)
Nasopharyngitis	0 (0%)	3 (5%)
Nasal dryness	0 (0%)	9 (14%)
Cough	1 (2%)	3 (5%)
Dry throat	0 (0%)	3 (5%)
Sinusitis	0 (0%)	2 (3%)
Epistaxis	0 (0%)	2 (3%)
Abnormal vision	2 (3%)	0 (0%)
Ocular dryness	0 (0%)	3 (5%)
Dyspepsia	3 (4%)	1 (2%)
Nausea	2 (3%)	2 (3%)
Abdominal pain	0 (0%)	1 (2%)
Constipation	10 (15%)	4 6%)

Study	**Herschorn 2010**	
Treatment	Solifenacin 5 mg N=68	Oxybutynin IR 5 mg tid N=64
UTI	3 (4%)	3 (5%)
Acute urinary retention	0 (0%)	2 (3%)
Dysuria	3 (4%)	0 (0%)
Hypothyroidism	0 (0%)	2 (3%)
Dry skin	0 (0%)	3 (5%)
Contusion	1 (2%)	2 (3%)

AE, adverse events; **NA,** not available (either no events or not reported); **OAB-q**, overactive bladder questionnaire; **PPBC**, patient perception of bladder condition; **SD**, standard deviation; **UTI**, urinary tract infections; **WDAE** withdrawals due to AE; **SAE**, serious adverse events.

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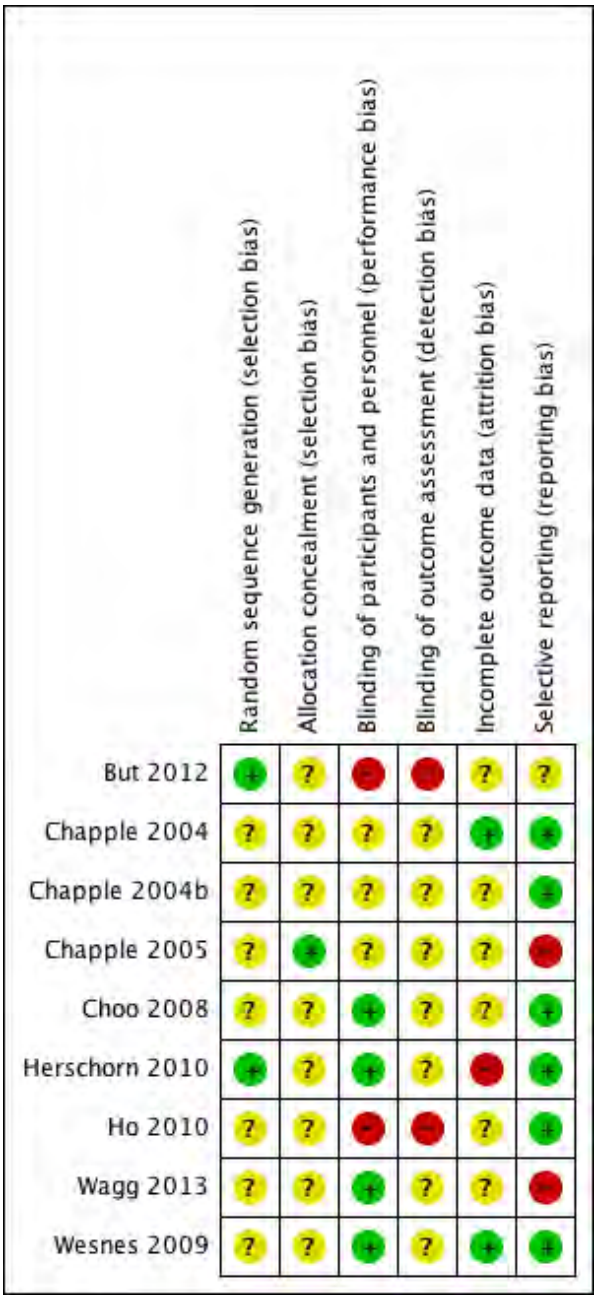
Table 3. Solifenacin vs. Comparators – RCT Risk of Bias



The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

Table 4. RCT Study Characteristics – Solifenacin vs. Tolterodine ER							
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Solifenacin**	**Tolterodine**	**Placebo if included**	**Outcomes Assessed**
Chapple 2005 STAR trial NCT00802373 905-EC-001 Europe (17 countries) N=1355 screened N=1200 randomized Per protocol analysis: 1049 Efficacy analysis: 1177* Yamanouchi/ Astellas	MC, DB, double-dummy parallel group RCT 2 week single blind placebo run-in phase pre-randomization 12 weeks duration 3 day bladder diary Non-inferiority trial based on micturition frequency (delta 0.2) Outcomes assessed at weeks 4, 8 and 12	Adults who had OAB symptoms (including urinary frequency, urgency or urge incontinence) for ≥ 3 months and who were being treated as outpatients ≥ 8 micturitions per 24 h ≥ 1 urgency episode OR 1 incontinence episode per 24 h during 3-day bladder diary	mean age Soli 56.5 years; Tol 56.4 years (range 53 -59 yrs) Soli: 169 (29.2%) > 65 years and 39 (6.7%) > 75 years; Tol 176 (29.4%) > 65 years and 36 (6.0%) > 75 years 99.4% Caucasian; 7 individuals other racial/ethnic groups Baseline total incontinence episodes: Soli 2.77 (2.65); Tol 2.55 (2.37) Baseline urgency incontinence episodes: Soli 2.31 (2.35); Tol 2.12 (2.14) Baseline nocturia episodes: Soli 2.02 (1.33); Tol 1.92 (1.22) No. of evaluable patients for incontinence NR in publication From PBAC: Soli 364; Tol 378	Soli 5-10 mg once daily 5 mg starting dose Patient could request increase to 10 mg at 4 weeks (48% increased dose) Randomized N=593 Full analysis dataset N=578 Per protocol N=525 Evaluable for incontinence: 364 (PBAC) Evaluable for nocturia (PBAC): 479	Tol ER 4 mg once daily Randomized N=607 Full analysis dataset N=599 Per protocol N=524 Evaluable for incontinence: 378 (PBAC) Evaluable for nocturia: 496	ND	• Micturition frequency • Urgency episodes • Urge incontinence • Total incontinence (with and without the sensation of urgency) • Nocturia • Proportion experiencing a 50% reduction in incontinence episodes • Proportion of patients who were incontinent at baseline but continent at study endpoint • PPBC • Patient pad usage per 24 h • Volume voided per micturition • % patients who wished to increase study medication dose after 4 weeks • Patient assessment of treatment benefit Physician assessment of treatment benefit
Ho 2010 Taiwan N=75 Per protocol analysis for	Open label parallel group RCT 12 weeks duration Outcomes assessed at weeks 4, 8 and 12 3 day bladder diary	Adults able to fill out a bladder diary and who had OAB symptoms (urinary frequency, urgency or urge incontinence) for ≥ 3 months No clinically significant bladder obstruction or other urogenital pathology, no contraindications to anticholinergic medication; post	67% female, 33% male Mean age Soli 59 yrs; Tol 55 yrs Baseline incontinence episodes: Soli 3.21 (3.05); Tol 6.19 (5.83) Prior drug therapy: Soli 46%;	Soli 5 mg once daily N=39	Tol ER 4 mg once daily N=36	ND	• Micturition frequency • Urgency episodes • Incontinence episodes • Void volume • Pad usage • PPBC • Post void residual volume (ultrasound)

efficacy:72		void residual volume < 200 mls	Tol 56% Comorbidiites: Soli 72%; Tol 82% Drugs for comorbid conditions: Soli 77%; Tol 64%				• Patient assessment of treatment benefit • Physician assessment of treatment benefit • Total AE • WDAE • Specific AE

DB, double-blind; ER=extended release; MC=multicenter; ND=not done; PPBC=patient perception of bladder condition: soli=solifenacin; tol=tolterodine; yrs=years;

Table 5. RCT Outcomes – Solifenacin vs. Tolterodine ER

Study	**Chapple 2005 (STAR trial)**		**Ho 2010**	
Treatment	Solifenacin 5-10 mg once daily N=593	Tolterodine 4 mg ER once daily N=607	Solifenacin 5 mg once daily N=39	Tolterodine ER 4 mg once daily N=36
Full analysis dataset[1]	578	599	PP 35	PP 33
Mortality	0^	0^		
SAE	3 (0.5%)^	7 (1.2%)^	1	1
WDAE	20^	18^	1	1
QOL	NA	NA		
Cure (no incontinence episodes for bladder diary duration)	218/364[1] (60%)	191/378[1] (51%)		
PPBC	-1.51 ± 1.44	- 1.33 ± 1.45	-1.40 ± 1.40	-1.40 ± 1.60
Proportion self-reported "much" improved	NA	NA	17.1%	27.3%
Proportion reported as "much" improved by physician	NA	NA	31.4%	21.2%
Urge incontinence per 24 h Mean (SD) change from baseline	-1.42 ± 2.40	-0.83 ± 2.36	-2.79 ± 2.82	-4.67 ± 9.29
	N=NR	N=NR		
Total Incontinence episodes per 24 h Mean (SD) change from baseline	-1.6 (2.26)	-1.11 (2.49)	Did not enrol participants with mixed UI	
	N=364[1]	N=378[1]		
	-2.85 ± 3.57	-2.42 ± 3.55	-1.70 ± 3.07	-1.15 ± 2.68

Urgency Episodes	N= NR	N=NR		
Nocturia Episodes	-0.71 ± 1.10 N=479[1]	-0.63 ± 1.07 N=496[1]	NA	NA
Proportion with no nocturia at study end	100/479[1] (21%)	111/496[1] (22%)	NA	NA
Pad use per 24 h	-1.72 ± 2.34	-1.19 ± 1.84		
Total AE	282 (47.6%)^	265 (43.7%)	15	9
Dry Mouth	178	146	7	3
Blurred vision	4	10	NA	NA
Dizziness	NA	NA	1	0
Fatigue	NA	NA	1	0
Constipation	36	15	5	1
Hiccup	NA	NA	1	0
Palpitation	NA	NA	1	1
Mean volume voided per micturition Change from baseline (SD)	37.95 ± 48.1	31.00 ± 51.47	27.61± 51.74	10.60 ± 50.29
Urodynamics	NA	NA	Female subgroup – no difference between drugs	
Proportion requesting dose increase	48%	51%	--	--

[1]Full analysis dataset was a modified intent-to-treat population for efficacy outcomes, requiring data at baseline and during double-blind treatment.
PP, per protocol;

Table 6. RCT Study Characteristics – Solifenacin vs. Tolterodine IR							
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Soli**	**Tol**	**Placebo if included**	**Outcomes Assessed**
Chapple 2004 Study 005 Europe (9 countries) N= 279 screened N=225 randomized Yamounouchi/ Astellas	MC, DB placebo-controlled parallel group RCT single-blind placebo run-in phase of 2 weeks 4 weeks treatment and 2 week follow-up Dose-finding for solifenacin 3 day bladder diary	Men and women, age 18 to 80 years, with idiopathic detrusor overactivity (defined as phasic contractions of >10 cm H2O as assessed by filling cystometry) within 6 months of study initiation; mean ≥ 8 voids/24 h for 3 days and ≥ 3 episodes of incontinence or urgency during 3 day bladder diary No significant bladder outlet obstruction or other pelvic or urogenital pathology, no diabetic neuropathy, and normal ECG and lab test results	mean age 53-59 years approx. 60% women > 98% Caucasian 100% had history of incontinence 72% pure UUI 28% mixed urge predominant incontinence 30 to 59% had prior use of anticholinergic medication	Soli 2.5, 5, 10 or 20 mg once daily 2.5 mg: N=41 5.0 mg: N=37 10 mg: N=35 20 mg: N=37	Tol IR 2 mg bid N=37	Placebo N=38	• Micturition frequency (primary outcome) • Volume voided/void • Incontinence episodes per 24 h • Urgency episodes per 24 h • QoL Contilife items • total sum score; • sum scores of the 5 domains (daily activities, effort, self-image, emotional consequences, sexuality); • overall Contilife QOL score • QoL U-UDI • SAE (only 'treatment-related') • AE • WDAE • Laboratory measures • Vital signs • ECG • -Post-void residual volume
Chapple 2004b 905-CL-015 Study sites not specified N=1281 screened N=1081 randomized N=1077 treated Yamanouchi/ Astellas	MC, DB parallel group RCT 2 week placebo run-in period 12 weeks duration Outcomes assessed at weeks 4, 8 and 12 weeks 3 day bladder diary	Adults with symptoms of OAB (including urgency, urge incontinence, or frequency) for ≥ 3 months; average frequency of ≥ 8 voids per day and ≥ 3 episodes of urgency and/or 3 episodes of incontinence No significant bladder outlet obstruction or other urogenital pathology or risks for AE and no cholinergic or anticholinergic drugs	75% female, 25% male Mean age 57-58 yrs Age range 19 to 85 yrs 34% ≥ age 65 9.4% ≥ age 75 63% had UI only 30% had urge predominant mixed UI 7% had no incontinence Majority had nondrug therapy 25% prior drug therapy	Soli 5 or 10 mg once daily 5 mg: N=279 10 mg: N=269 UUI: 5 mg: N=172 10 mg: 162 Mixed UI 5 mg N=79 10 mg N=81	Tol IR 2 mg bid N=266 UUI: N=142 Mixed UI: N=90	Placebo N=267 UUI: N=177 Mixed UI: N=59	• Micturition frequency per 24 h (primary outcome • Total incontinence episodes per 24 h • Urgency incontinence episodes per 24 h • Urgency episodes per 24 h • Mean voided volume/void • SAE (only 'treatment-related') • AE • WDAE • vital signs • ECG • Post-void residual volume • Laboratory measures

Table 6 Continued. RCT Study Characteristics – Solifenacin vs. Tolterodine IR							
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Soli**	**Tol**	**Placebo if included**	**Outcomes Assessed**
Choo 2008 NCT00189800 Korea N=538 screened N=357 randomized N=354 treated Astellas	MC, DB, parallel group Phase III RCT 2 week placebo run-in period 3 day bladder diary 12 weeks duration outcomes assessed at week 4, 8 and 12 Noninferiority trial (margin lower limit of 95% CI -1) hierarchical design re doses of solifenacin; comparison of Soli 10 mg first, then if non-inferior, Soli 5 mg compared to Tol ITT, LOCF for efficacy analysis. Modified ITT - all randomized patients who had efficacy data at baseline and at least one on-treatment visit	Adults with frequency ≥ 8 voids/day ≥ 3 urgency episodes or urgency incontinence episodes during 3-day bladder diary period post void residual volume < 200 ml	20.7% male; 79.3% female Mean age 53 yrs Asian population (Korea) 24-30% had prior drug treatment for OAB 42-52% had urgency incontinence	Soli 5 mg or 10 mg 5 mg N=120 10 mg N=120	Tol IR 2 mg bid N=118	ND	• Micturition frequency per 24 h (primary outcome) • Volume per void • Urgency incontinence episodes per 24 h • Urgency episodes per 24 h • Nocturia episodes per 24 h • QOL KHQ • AE • Laboratory tests • Vital signs • Post-void residual volume

* Efficacy analysis included treated patients for whom efficacy data were available at baseline and at least one on-treatment efficacy assessment. KHQ=King's Health Questionnaire; U-UDI=Urge Urinary Distress Inventory; ITT=intention-to-treat; LOCF=last observation carried forward;

Table 7. RCT Outcomes –Solifenacin vs. Tolterodine IR											
Study	Chapple 2004				Chapple 2004b				Choo 2008		
Treatment	Placebo	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d	Placebo	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d
N randomized	38	37	35	37	267	279	269	266	120	119	118
N ≥ 1 dose (AE analysis)	36	37	33	37	267	279	268	263	118	118	118
Mortality	0	0	0	0							
Non-fatal SAE	0	0	0	0	NR	2 (0.7%)^	1 (0.4%)^	0^	1	0	0
WDAE	0	1	3	1	10	9	7	5	5	7	2
QOL											
Contilife Sum Score	57.9 (-8%)	48.5 (-22%)	44.4 (-27%)	50.8 (-15%)	NA				NA		
KHQ mean change from baseline											
- general health perception	NA	-3.4	-2.6	-4.2					-3.3	-2.3	-2.0
- incontinence impact	NA	-21.8	-23.7	-25.6					-13.6	-15.9	-12.1
-role limitations	NA	-19.1	-20.7	-23.7					-18.4	-23.8	-19.5
-physical limitations	NA	-16.3	-17.1	-18.2					-21.0	-25.3	-20.4
-social limitations	NA	-10.3	-10.5	-13.3					-14.0	-23.4	-18.8
- personal relationships	NA	-8.9	-9.5	-7.6					-9.3	-7.1	-7.8
- emotions	NA	-15.1	-17.5	-17.7					-16.9	-20.4	-15.3
- sleep/energy	NA	-11.7	-13.1	-11.3					-15.7	-18.8	-13.7
- severity measures	NA	-11.6	-13.3	-11.6					-12.8	-13.8	-9.9
-symptom severity	NA	-3.2	-3.4	-3.2					-3.4	-4.0	-3.5
U-UDI Mean Change from Baseline ± SD*	NR	-5.2, SD NR	-6.3 SD NR	-4.9, SD NR							
Cure/Continence	NA				NA				NA		
PPBC	NA				NA				NA		
Urgency incontinence per 24 h; Mean (SD) change from baseline					- 0.62 ± 1.96 N=127	-1.41 ± 1.74 N=113	-1.36 ± 2.13 N=127	-0.91 ± 2.01 N=119			
Total Incontinence Episodes per 24 h Change from baseline Mean ± SD	-0.29, SD NR	-0.83, SD NR	-0.79, SD NR	-1.07, SD NR	-0.76 ± 2.26 N=153	-1.42 ±1.82 N=141	-1.45 ±2.24 N=158	-1.14 ± 2.15 N=157	0.78 ± 1.74	0.75 ± 1.49	0.72 ± 1.18
Urgency Episodes	-1.03	-2.35	-2.46	-1.62	-1.20 ± 3.26	-2.19 ± 2.87	-2.61 ± 3.24	-1.88 ± 3.0	-2.5	-2.35	-2.2
Nocturia Episodes	-1.03	-2.21	-2.47	-1.79	NA				-0.67	-0.6	-0.54

*Solifenacin CDR Review 2006

Table 7 Continued. RCT Outcomes – Solifenacin vs. Tolterodine IR											
Study	Chapple 2004				Chapple 2004b				Choo 2008		
Treatment	Placebo	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d	Placebo	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d	Soli 5 mg/d	Soli 10 mg/d	Tol IR 4 mg/d
N	38	37	35	37	267	279	269	266	120	119	118
N ≥ 1 dose (AE analysis)	36	37	33	37	267	279	268	263	118	118	118
mITT									118	118	118
Total AE	6	12	12	12	NR	NR	NR	NR	NR	NR	NR
Dry Mouth	0	5	5	9	13	39	57	49	9	23	22
Blurred vision	1	1	5	2	7	10	15	4	16	19	12
Headache	0	2	2	0							
Dizziness											
Fatigue											
Dyspepsia	0	1	1	0					3	4	2
Constipation	0	5	2	1	5	20	21	7	8	17	3
GU total									6	10	14
Acute urinary retention	0	0	0	0							
Difficulty in micturition									1	6	6
Urine flow decreased									3	3	3
Vesical tenesmus									1	1	3
Cystitis									3	2	2
Nasopharyngitis									1	1	3
Infections and infestations									7	5	6
Increased sweating	0	2	0	0							
Mean Volume Voided Change from baseline (SD)	9.7	38	43.2	14.7	7.4 ± 36.3	32.9 ± 47.7	39.2 ± 50.5	24.4 ± 49.2	30.2	45.0	29.3
Change in post void residual volume (SD)									male +10.3 (48.6); female +8.0 (39.3)	male +9.9 (54.3); female +2.8 (49.3)	male +6.3 (39.6); female +4.4 (29.4)

Table 8. RCT Study Characteristics – Solifenacin vs. Darifenacin							
Solifenacin vs. Darifenacin							
Study Country N	**Design**	**Inclusion criteria**	**Baseline Characteristics % of participants**	**Soli**	**Dari**	**Placebo if included**	**Outcomes Assessed**
But 2012 Slovenia (4 centres) N=80 screened N=77 randomized	MC, open label RCT 3-day bladder diary outcomes assessed baseline, 4 weeks and 12 weeks	Ambulatory women with idiopathic OAB (urgency intensity and urgency urinary incontinence of ≥ 3 on the Urgency Perception Scale and ≥ 1 urgency episode per day No anticholinergic drugs for at least 6 months prior to study and free of bladder disease	100% female median age 54 years	Soli 5 mg once daily N=40 PP: N=32	Dari 7.5 mg once daily N=37 PP: N=29	ND	• Urgency Perception Scale (urgency frequency and intensity = primary outcome) • UDI • IIQ • AEs - pre-defined list • Treatment success - subjective (VAS)

VAS=visual analogue scale; UDI=Urogenital Distress Inventory; IIQ=Incontinence Impact Questionnaire

See darifenacin Appendices But 2012 RCT outcomes.

Table 9. Cognition RCT Study Characteristics – Solifenacin vs. Oxybutynin							
Study Country N	Design	Inclusion criteria	Baseline Characteristics % of participants	Solifenacin	Oxy IR	Placebo if included	Outcomes Assessed
Wagg 2013 NCT01126424 UK N=36 screened N=26 randomized Astellas	DB, triple-crossover trial MC (3) on volunteers with mild cognitive impairment 21 day treatment period Each treatment period separated by 21 day washout period. Assessment on day prior to first dose of each treatment period was used as baseline for tests at time points predose and 1,2,4,6 hours postdose at end of same treatment period Randomized to one of 6 different treatment sequences Assessed at times predose, 1, 2, 4 and 6 h post dose in each treatment period on last day	Adult volunteers aged 75 years or older with mild cognitive impairment MMSE > 23 Geriatric depression scale < 5 BMI of 18 - 30 kg/m^2 No history of urinary retention	Mild cognitive impairment (etiology not determined) 53.8% male mean age 78.8 years Age range 75 to 88 yrs 100% Caucasian MMSE score 17.5 (SD 1.4) GDS score 1.2 (SD 1.1) 25/26 taking concomitant medication - most commonly simvastatin (6), paracetamol (6), ramipril (5), None were taking acetylcholinesterase inhibitors	Soli 5 mg once daily N=26 (crossover)	Oxy IR 5 mg bid N=26 (crossover)	Placebo N=26 (crossover)	• Composite outcomes of cognitive function at time, change from baseline to time of peak concentration (6 h post dose for solifenacin and 2h post dose for oxybutynin) • (power of attention; continuity of attention; • quality of working memory; • quality of episodic memory; speed of memory) • Secondary endpoints: • Change from baseline in cognitive function at time points other than predicted C_{max} • Composite scores from 2 time points close to respective C_{max} for each agent (4+6 h for solifenacin; 1+2 h for oxybutynin) (Post hoc) • Self-rated alertness, contentment and calmness (Bond-Lader visual analogue scales) (Post hoc) • AE • Physical examination

Table 9 Continued. Cognition RCT Study Characteristics – Solifenacin vs. Oxybutynin

Study Country N	Design	Inclusion criteria	Baseline Characteristics % of participants	Solifenacin	Oxybutynin IR	Placebo if included	Outcomes Assessed
Wesnes 2009 SCOPE (Country not specified) N=28 screened N=12 randomized Astellas	Single dose pilot study; placebo-controlled three-way crossover RCT on healthy volunteers Single center Washout period between treatment 14 days Assessed at 2, 4, 6, 8, 10, 12 and 24 h post dose in each of the three treatment periods.	Healthy volunteers > 65 years willing and able to complete the study test battery (had to perform at or above a minimum level on at least one occasion for each individual cognitive function task measure) MMSE > 27 on screening	50% female mean age 69.1 yrs age range 65-76 11/12 Caucasian, 1 Asian	Solifenacin 10 mg single dose N=12 (crossover)	Oxybutynin IR 10 mg single dose*	Placebo N=12 (crossover)	• Composite outcomes of cognitive function (power of attention; continuity of attention; quality of working memory; quality of episodic memory; speed of memory • Self ratings of alertness, contentment and calmness • Postural Stability Test • BP, HR, ECG • Blood and urine samples (lab tests not specified)
* Dose is twice the maximum single recommended dose for Oxybutynin IR							

Table 10. Cognition RCT Outcomes Wagg 2013 Adverse Events			
Study	**Wagg 2013 (crossover)**		
Treatment	Solifenacin 5 mg once daily for 21 days	Oxybutynin IR 5 mg bid for 21 days	
Withdrawals	7 (2 in period one; 1 in period two; 3 in period three)		
Adverse events (%)	Solifenacin N=23	Oxy IR N=25	Placebo N=22
Total AE	14 (60%)	21 (84%)	11 (50%)
Dry mouth	4 (17%)	13 (52%)	5 (23%)
Dyspepsia	0 (0%)	4 (16%)	0 (0%)
Constipation	1 (4%)	0 (0%)	1 (5%)
Nausea	1 (4%)	1 (4%)	0 (0%)
Diarrhea	0 (0%)	1 (4%)	1 (5%)
Nervous system disorders	2 (9%)	3 (12%)	1 (5%)
Balance disorder	2 (9%)	0 (0%)	0 (0%)
Memory impairment	0 (0%)	1 (4%)	0 (0%)
Eye disorders	2 (9%)	3 (12%)	0 (0%)
Vision blurred	1 (4%)	1 (4%)	0 (0%)
Psychiatric disorders	2 (9%)	1 (4%)	0 (0%)

Appendix H. U.S. FDA Post-market Labeling Changes for Solifenacin

The following changed have been required by the US Food and Drug Administration post market (2007-2013).

March 2013

Adverse reactions

Post-Marketing Experience

- muscular weakness

July 2012

Adverse Reactions - Post-Marketing Experience

- Central Nervous: delirium
- Hepatic: liver disorders mostly characterized by abnormal liver function tests (AST,ALT, GGT) Renal: renal impairment
- Metabolism and nutrition disorders: decreased appetite, hyperkalemia

June 2012

Warnings and Precautions- Central Nervous System Effects

- [Solifenacin] is associated with anticholinergic central nervous system (CNS) effects. A variety of CNS anticholinergic effects have been reported, including headache, confusion, hallucinations and somnolence. Patients should be monitored for signs of anticholinergic CNS effects, particularly after beginning treatment or increasing the dose. Advise patients not to drive or operate heavy machinery until they know how [solifenacin] affects them. If a patient experiences anticholinergic CNS effects, dose reduction or drug discontinuation should be considered.

August 2012

Adverse Reactions- Post-Marketing Experience

- Eye disorders: glaucoma
- Gastrointestinal disorders: gastroesophageal reflux disease and ileus
- Respiratory, thoracic and mediastinal disorders: dysphonia

January 2012

Adverse Reactions- Post-Marketing Experience

- Dermatologic: exfoliative dermatitis and erythema multiforme

July 2010

Warnings

- Angioedema of the face, lips, tongue, and/or larynx have been reported with solifenacin. In some cases angioedema occurred after the first dose. Angioedema associated with upper airway swelling may be life threatening. If involvement of the tongue, hypopharynx, or larynx occurs, solifenacin should be promptly discontinued and appropriate therapy and/or measures necessary to ensure a patent airway should be promptly provided.

Adverse Reactions - Post-Marketing Surveillance

- with airway obstruction

November 2008

Adverse Reactions – Post-Marketing Experience

- General
  - peripheral edema
- Central Nervous System
  - Headache

Part IV Appendices - Darifenacin vs. Comparator Drugs

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Appendix H. Darifenacin vs. Comparator Drugs RCT Evidence Tables

Table 1. RCT Study Characteristics Darifenacin ER vs. Comparator Drugs

Darifenacin ER vs. Oxybutynin IR

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	DARI ER	OXY IR	Placebo	Outcomes Assessed
Zinner 2005 Study 137-666 U.S. N=76 randomized (crossover) Novartis	DB, double-dummy Placebo-controlled four-way crossover study # of centres NR Single-blind placebo run-in phase, 2 weeks Randomization to one of 4 sequences Each treatment period 14 days with 10 day washout period between treatments 2 week paper bladder diary Completer analysis for efficacy (data available for ≥ 1 efficacy outcome in week 2 for each of the 4 treatment periods) For AE (tolerability): completer analysis consisted of exposure to all 4 treatments for at least 7 days (or less if	• Men and women aged 18 to 85 yrs • Patients with OAB who had undergone cystometry within the previous 12 months • Urgency incontinence ≥4 significant incontinent episodes per week (requiring a change of clothing or absorbent pad) • Frequency ≥ 8 voids per day on average Exclusions: • Neurogenic bladder or stress incontinence • Contraindications to antimuscarinic therapy • Prior bladder or prostate surgery; other urinary tract pathology including significant urinary bladder obstruction • 'Clinically significant concomitant disease' • Patients starting or modifying an existing bladder training program;	71/76 female (93%) Mean age 59.9 yrs (age range 33-84 yrs) Baseline incontinence episodes/week 20.4 (SD 17.7) = 2.9 episodes per day Baseline urgency: 9.3 (SD 3.4) episodes per day	DARI ER 15 mg qd DARI ER 30 mg qd (not recommended dose) N=19 for each period/dose (crossover)	OXY IR 5 mg tid N=19 for each period (crossover)	Placebo tablet qd and capsules tid N=19 for each period (crossover)	• 7 day bladder diary • Antimuscarinic AE rates (primary outcome for sample size calculation) • Incontinence episodes per day • Micturitions per day • Urgency episodes per day • Severity of urgency episodes (mild; moderate; severe) • WDAE • AE (observed or volunteered) • Vital signs • ECG • Laboratory (hematology, biochemistry, urinalysis)

	antimuscarinic AE were observed earlier)	• Treatment with thyroid or estrogen hormone replacement • Concomitant medications with antimuscarinic effects or known to affect bladder function					
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**DARI**	**OXY IR**	**Placebo**	**Outcomes Assessed**
Chapple 2005 Study 137-307 U.K. N=65 total randomized in 3 separate cohorts N=24 for the one cohort of interest Novartis, Pfizer	DB, two-way crossover trial # of centres NR 3 separate cohorts of patients testing different comparisons 7 day treatment period with ≥ 14 day washout period One cohort of interest in terms of intervention/dosage = cohort 2	• Men and women with evidence on cystometry of detrusor overactivity within the previous 6 months, either idiopathic or neurogenic plus two or more of the following symptoms: o Average of ≥ 7 micturitions per day; o ≥ 7 episodes of urgency per week; o ≥ 1 urge incontinence episode necessitating a change of clothing or pads <u>Exclusions</u> • Prior bladder surgery for detrusor overactivity; Prostatectomy in last 6 months; • Antimuscarinic drugs within prior 2 weeks; Stress and mixed UI unless detrusor overactivity was the	32% female, 68% males overall; Mean age 50-53 yrs age range 32 –74 yrs Majority had idiopathic detrusor activity 2/24 (8%) in cohort 2 had neurogenic detrusor overactivity	DARI ER 15 mg qd N=12 Period 1 (Crossover)	OXY IR 5 mg tid N=12 Period 1 (Crossover)	ND	• Parameters derived from 6 hour ambulatory bladder pressure measurements o duration of phasic contractions o number of phasic contractions o log-transformed activity index (<u>A</u>rea <u>u</u>nder the duration of activity <u>e</u>ffect time <u>c</u>urve, AUEC) • Salivary flow • Visual nearpoint • Heart rate; heart rate variability • Laboratory tests – hematology, biochemistry, urinalysis • Physical examination

		principal urodynamic observation and < 1 stress incontinence episode per week; • Other exclusions as per text					
Darifenacin ER vs. Tolterodine							
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**DARI ER**	**TOL**	**Placebo**	**Outcomes Assessed**
Study 137-1001 Unpublished Phase III pivotal trial included in FDA review 21-513 U.S., Canada N=680 total N=335 for active drug/ doses of interest Novartis	DB placebo-controlled parallel group RCT MC Randomization: 1:1:2 for placebo; DARI 15; TOL 2 week wash-out period if necessary 2 week treatment-free run-in phase (no placebo) Assessments based on a 2 week bladder diary (electronic diary) Assessments at baseline, weeks 2, 6 and 12 ITT (all those who were randomized, took ≥ 1 dose of medication and had some bladder diary data), LOCF Multiplicity handled by a step down testing procedure	Men and women ≥ age 18 yrs OAB ≥ 6 months; all 3 of the following symptoms based on a 14-day run-in diary: o incontinence 5-50 episodes per week; o micturitions ≥ 8 per day; o urgency ≥ 1 episode per day Exclusions:* • Clinically significant hepatic disease or clinically significant laboratory test results; • Drugs with anticholinergic effects (e.g., tricyclic antidepressants); • Opioids and other drugs causing constipation; • Contraindications to anticholinergic use; >1 stress incontinence episode per week; • BOO or post residual void volume > 200 mL;	79% female; 21% male mean age 60 (range 32-85) 34% prior treatment (drug or bladder training) < 5% prior urogenital surgery 93% Caucasian	DARI ER 15 mg qd N=112 DARI ER 30 mg qd N=230 DARI ER 15: 92/112 (82%) completer (significantly lower than placebo)	TOL 2 mg bid N=223 Completers: NA	PL N=115 Completers: 104 (90%)	• Incontinence episodes per week (primary efficacy outcome) • Micturitions per 24 h • Mean volume voided • Urgency episodes • Severity of urgency episodes • incontinence episodes per week resulting in change of clothing or pads • Nocturia • QoL: KHQ • Patient global satisfaction; Patient global preference; patient willingness to use medication again • Incontinence treatment responders (>50% reduction from baseline in incontinence episodes per week) • Micturition responders (achieved < 8 micturitions per day) • AE (observed or volunteered) • Laboratory data

	Non-parametric approach for data that were skewed Used 2.5% significance level to test difference vs. placebo	• Clinically significant pelvic prolapse; • Urogenital surgery < 6 months prior; bladder biopsy < 30 days prior; local urinary pathology; • UTI history (3 or more over preceding 2 years); • Clinically significant systemic disease that would interfere with participation; • Intention to start a bladder training program – had to be on stable regimen; • Hypersensitivity to darifenacin or other anticholinergic drugs; • Alcohol or drug abuse; • Intention to donate blood products during study or within one month of completion					

Darifenacin ER vs. Solifenacin							
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**DARI ER**	**SOLI**	**Placebo**	**Outcomes Assessed**
But 2012 Slovenia (4 centres) N=80 screened N=77 randomized Astellas	Open-label RCT MC 3-day bladder diary Randomization 1:1 Assessments at baseline, 4 weeks and 12 weeks Per protocol analysis	Ambulatory women with idiopathic OAB (urgency intensity and urgency urinary incontinence of ≥ 3 on the Urgency Perception Scale) and ≥ 1 urgency episode per day No anticholinergic drugs for at least 6 months prior to study and free of bladder disease Exclusions: • Angular glaucoma; • UTI; • Urinary tract stones; • Bladder disease; • Neurogenic OAB; • Severe orthopedic difficulties (e.g., need for crutches or wheelchair)	100% female median age 54 years	DARI ER 7.5 mg qd N=37 PP: N=29	SOLI 5 mg qd N=40 PP: N=32	ND	• Urgency Perception Scale (urgency frequency and intensity = primary outcome) • UDI • IIQ • Incontinence pad usage • AEs - pre-defined list • Treatment success - subjective (VAS)

AE= adverse events; **BOO**= bladder outlet obstruction; **DARI**= darifenacin; **DB**= double-blind; **ER**= extended-release; **IIQ**= Incontinence Impact Questionnaire; **IR**= immediate-release; **ITT**= intent-to-treat; **KHQ**= King's Health Questionnaire; **LOCF**= last observation carried forward; **MC**= multicentre; **NA**= not available; **ND**= not done; **NR**= not reported; **OAB**= overactive bladder syndrome; **OXY**= oxybutynin; **PL**= placebo; **PP**= per protocol; **qd**= every day; **QoL**= quality of life; **SD**= standard deviation; **SOLI**= solifenacin; **tid**= three times a day; **TOL**= tolterodine; **UDI**=Urogenital Distress Inventory; **UTI**= urinary tract infection; **VAS**= visual analogue scale; **WDAE**= withdrawals due to adverse events
* exclusions for Study 137-1001 obtained from the FDA NDA review 21-513

Table 2. RCT Outcomes: Darifenacin ER vs. Oxybutynin IR					
Study	Zinner 2005			Chapple 2005	
Treatment	Placebo	DARI ER 15 mg qd	OXY IR 5mg tid	DARI ER 15 mg qd	OXY IR 5 mg tid
N randomized	N=76 (crossover)			N=24 (crossover)	
Completer analysis	N=58 (efficacy); N= 61 (AE)			--	
All-cause Mortality	0	0	0	0	0
SAE	1	0	1	1	0
Total withdrawals	4	2	6	1 (4%)	0
WDAE	NR	NR	NR	1 (4%)	0
'Treatment-related' WDAE	0	0	4	1 (4%)	0
QoL	NA			NA	
Perception of improvement/cure	NA			NA	
Incontinence Episodes/week at Baseline Mean ± SDξ	20.4 ± 17.7 [=2.9/day], N=76			NA	
Incontinence Episodes/week at Study End Meanξ	14.64/week	10.93/week	9.45/week	NA	
Incontinence Episodes/week Mean change from baselineξ	-6.38/week	-10.09/week [=1.4/day]*	-11.57/week [=1.7/day]*	NA	
	N=58				
Urgency Episodes/Day at Baseline Mean ± SDξ	9.3 ± 3.4, N=76			NA	
Urgency episodes/day at Study End Meanξ	8.71	7.95	8.12	NA	
Urgency Episodes: Mean Change from Baseline§	-0.51	-1.1*	-1.27*	NA	
	N=58				
Nocturia	NA			NA	
Total AE	32/68 (47%)	36/64 (56%)	47/69 (68%)	16 (67%)	19 (79%)
	--	RR 0.83** [95% CI 0.63 to 1.08]		RR 0.84 [95% CI 0.59 to 1.19]	
'Treatment-related' AE	--	--	--	14 (20%)	19 (79%)
Dry Mouth	4.9%	13%	36%	13 (54%)	17 (71%)
		DARI vs. OXY P <0.05			
Constipation	3.3%	9.8%	8.2%	8 (33%)	6 (25%)
Dyspepsia	NA			3 (13%)	5 (21%)
Headache	NA			1 (4%)	3 (13%)
Dizziness	0	0	1.6%	NA	
Somnolence	NA			1 (4%)	1 (4%)
Asthenia	NA				
Blurred vision/abnormal vision	0	0	3.3%	1 (4%)	3 (13%)
Dysphagia	NA			1 (4%)	3 (13%)
Pharyngitis	NA			0	1 (4%)
Pruritus	NA			0	1 (4%)
Urinary Tract Disorder	NA			2 (8%)	1 (4%)
Mean volume voided	NA			NA	
Urodynamics:				N=20	N=23
Duration of detrusor activity (seconds) (LSM difference)	NA			-176.4	-214.6

Activity index ($cmH_20.s$) (LSM difference)	NA	-10375	-14922
# of phasic detrusor contractions (LSM difference)	NA	-12.8	-15.9

AE= adverse events; **CI**= confidence intervals; **DARI**= darifenacin; **ER**= extended-release; **IR**= immediate-release; **KHQ**= King's Health Questionnaire; **OXY**= oxybutynin; **LSM**= least squares mean; **NA**= not available, either not measured or not reported; **NR**= not reported; **PL**= placebo; **qd**= every day; **RR**= relative risk; **s**= seconds; **tid**= three times a day; **WDAE**= withdrawals due to adverse events;

§ Means are adjusted for sequence and period from a crossover analysis of variance.
*P< 0.05 vs. placebo, accounting for multiplicity by the least significant difference method
**Common Drug Review 2009, Appendix IV, p. 73. It is unclear whether this analysis took into account the lack of dependence of observations in each arm of the crossover trial.

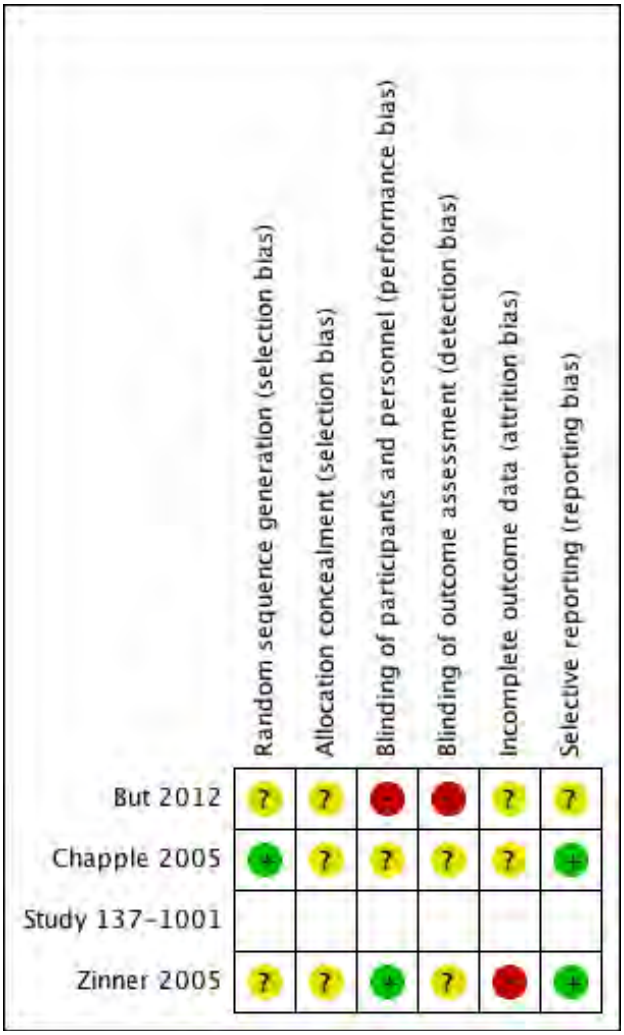


Table 3. Risk of bias assessment of active comparator trials.

The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

Study 137-1001 has not been assessed for risk of bias as a full study report (requested) was not available at time of draft.

Table 4. RCT Outcomes: Darifenacin ER vs. Tolterodine IR				
Study	Study 137-1001			
Treatment	**Placebo**	**DARI ER 15 mg qd**	**TOL 2 mg bid**	**Difference DARI vs. TOL (unless otherwise specified)**
N randomized	115	112	223	--
Completed	104 (90%)	92 (82%)		--
Full analysis set	114 (99%)	109 (97%)		--
Mortality	0	0	0	--
SAE	1/115 (0.9%)	1/112 (0.9%)	4/223 (1.8%)	0.5 [95% CI 0.06 to 4.40] P=0.53^
Total withdrawals	11/115 (9.6%)	20/112 (17.9%)	NR	--
WDAE	4 /115 (4%)	8/112 (7%)	17/223 (8%)	DARI vs. PL: RR 0.94 [95% CI 0.4 to 2.1], P=0.87
QoL: KHQ Mean change				
- Severity (coping) Mean change Baseline	-5.6 52.0	-11.9 47.5	-9.5 48.4	-2.4 points
- Emotions	NR	NR	NR	NR
- Role limitations Baseline	-20.6 64.4	-22.0 58.2	-20.6 61.5	-1.4 points
- Physical limitations	NR	NR	NR	NR
- Social limitations	NR	NR	NR	NR
- Sleep/energy	NR	NR	NR	NR
- Personal relationship	NR	NR	NR	NR
- Incontinence impact Baseline	-6.1 77.0	-18.0 74.9	-16.9 78.4	-1.1 points
- General health	NR	NR	NR	NR
Dryness rate (no incontinence episodes) (days)	NR	NR	NR	--
Patient perception of improvement	NR	NR	NR	--
Incontinence episodes per week: baseline median	15.5/week	16.2/week	NR	--
Incontinence episodes per week: Median (% change) at week 12	-9.0 /week (-71%)	-11.4/week (-83%)	-10.3/week (74%)	DARI vs. PL: -2.4/week [97.5% CI -5.2 to 0.30], P=0.049§ DARI vs. TOL -0.9/week [97.5% CI -3.4 to 1.4], ND
Urgency per 24 hours baseline	8.5	8.6	NR	--
Urgency per 24 hours Median change/day (%) to week 12	-1.9 (-25%) N=113	-2.6 (-33%) N=109	-2.3 (-26%) N=221	DARI vs. PL: -0.7 [97.5% CI -1.6 to 0.1], P=0.61§ DARI vs. TOL -0.3 [97.5% CI -1.1 to 0.6], ND
Total AE	69 (60%)	85 (76%)	148 (66%)	RR 1.14 [95% CI 0.99 to 1.32]
Dry mouth	11 (9.6%)	39 (34.8%)	60 (26.9%)	RR 1.29 [95% CI 0.93 to 1.81]
Constipation	7 (6.1%)	28 (25.0%)	28 (12.6%)	**RR 1.99 [95% CI 1.24 to 3.19]**
Dyspepsia	3.5%	8.9%	7.6%	RR 1.17 [95% CI 0.55 to 2.47]
UTI*	5 (4.3%)	7 (6.3%)	NR	--
Nervous system AE**	5 (4.3%)	2 (1.8%)	6 (2.7%)	RR 0.66 (95% CI 0.14 to 3.24)
Volume voided per micturition Change from baseline in median at week 12	4.6 (3) N=111	26.7 (18) N=107	22 (NR) N=219	DARI vs. PL: 20 mls [97.5 % CI 6 to 34], P=0.002

				DARI vs. TOL:15 mls [97.5% CI 4 to 26], ND

AE= adverse events; **bid**= twice a day; **DARI**= darifenacin; **ER**= extended-release; **KHQ**= King's Health Questionnaire; **IR**= immediate-release; **LSM**= least squares mean; **mls**= millimeters; **ND**= not done due to step down testing procedure; **NR**= not reported; **OXY**= oxybutynin; **PL**= placebo; **qd**= every day; **QoL**= quality of life; **SAE**= serious adverse events; **UTI**= urinary tract infection; **SD**= standard deviation; **TOL**= tolterodine; **WDAE**= withdrawals due to adverse events;

Data are from CDR Review 2009, Appendix IV, p.68-76 unless otherwise specified
*FDA Review, Table VII –C.5.1.4
** Foote 2004; identified nervous system AE were dizziness and depression but details were not provided.
^ Calculated in RevMan v5.2
§ p-value statistically significant at the 0.025 significance level
Note: Statistically significant differences are bolded.

Table 5. RCT Outcomes: Darifenacin ER vs. Solifenacin

Study	**But 2012 (SOLIDAR Study)**	
Treatment	**DARI 7.5 mg/day**	**SOLI 5 mg/day**
N randomized	37	40
Per protocol analysis	29	32
Mortality	NR	NR
SAE	NR	NR
Total withdrawals	8/37 (22%)	8/40 (20%)
WDAE	4/37 (11%)	4/40 (10%)
QoL Total Score Treatment Difference Median, p-value Mean (SD)	-34.9, p=0.018* -35.9 (79.1)	
IIQ – Emotional health Median, p-value	-8.3, p=0.057* -11.0 (21.6)	
IIQ – Physical Activity	-5.6, p=0.14* -6.9 (19.7)	
IIQ – Social Relationship	-8.7, p=0.020* -8.7 (18.0)	
IIQ – Transport	-5.7, p=0.051* -9.31 (21.3)	
UDI Score – Irritative Symptoms Median, p value Mean (SD)	-5.6, p=0.34* -5.7 (25.4)	
UDI – Stress Symptoms Median, p-value Mean (SD)	0.0, p=0.46* -7.5 (30.9)	
UDI – Obstructive Symptoms	-1.4, p=0.58* -1.1 (14.7)	
Subjective Success (VAS Score) Median (25-75 percentile)	55 (33.0-88.0)	84 (55.0-92.5)
Median Treatment Difference	22.5, p=0.010*	
Incontinence Episodes//day	NR	NR
Pad Usage/day: Baseline Median Mean (SD)	2.4 2.8 (2.9)	2.9 2.8 (2.4)
Pad Usage/day: Median Treatment Difference at Study End	-0.6	
p-value	p=0.19*	
Urgency Episodes/day: Baseline Mean (SD) Median	5.9 (1.5) 7.0	5.7 (0.99) 6.0
Urgency Episodes/day: Median Treatment Difference at Study End	0.0	
p-value	p=0.66*	

Urgency Episodes: Mean (SD) Change from Baseline	-0.4 (1.9)	
Nocturia Episodes/day: Baseline Mean (SD) Median	2.6 (1.3) 2.3	2.5 (1.6) 2.5
Nocturia Episodes/day: Median Treatment Difference at Study End; p-value	-0.3	
	p=0.43*	
Nocturia Episodes: Mean (SD) Change from Baseline	-0.3 (1.2)	
Total AE	NR	NR
Dry Mouth at baseline	17/36 (47%)	17/36 (47%)
Dry Mouth at 3 months	18/29 (62%)	18/29 (62%)
Constipation at baseline	10/36 (28%)	10/36 (28%)
Constipation at 3 months	8/29 (28%)	8/29 (28%)
Blurred Vision at baseline	16/36 (44%)	16/36 (44%)
Blurred Vision at 3 months	9/29 (21%)	9/29 (21%)
Headache at baseline	16/36 (44%)	16/36 (44%)
Headache at 3 months	4/29 (14%)	4/29 (14%)
Dizziness at baseline	15/36 (42%)	15/36 (42%)
Dizziness at 3 months	8/29 (28%)	8/29 (28%)
Lack of concentration at baseline	14/36 (39%)	14/36 (39%)
Lack of concentration at 3 months	8/29 (28%)	8/29 (28%)
Memory problems at baseline	20/36 (56%)	20/36 (56%)
Memory problems at 3 months	9/29 (31%)	9/29 (31%)
Insomnia at baseline	18/36 (50%)	18/36 (50%)
Insomnia at 3 months	7/29 (24%)	7/29 (24%)

AE= adverse events; **DARI**= darifenacin; **ER**= extended-release; **IIQ**= Incontinence Impact Questionnaire; **IR**= immediate-release; **NR**= not reported; **OAB**= overactive bladder syndrome; **OXY**= oxybutynin; **PL**= placebo; **qd**= every day; **QoL**= quality of life; **SAE**= serious adverse events; **UTI**= urinary tract infection; **SD**= standard deviation; **SOLI**= solifenacin; **UDI**=Urogenital Distress Inventory; **VAS**= visual analogue scale; **WDAE**= withdrawals due to adverse events;
* p-value calculated by Wilcoxon Rank Sum Test

Table 6. Darifenacin ER vs. Placebo RCTs: Study Characteristics

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	DARI ER	Placebo	Outcomes Assessed*
Chapple 2007 NCT00171184 US, Poland, Hungary, Sweden, UK, Germany, South Africa N=400 randomized Novartis	DB, single-dummy Parallel group RCT MC 2 week screening period 1 week placebo run-in phase 2:1 randomization (DARI: PL) 12 weeks duration 7-day bladder diary (paper) baseline and week 12 3-day diary weeks 1, 2 and 6 Flexible dose – voluntary up-titration Assessment baseline, week 1, 2, 6 and 12 ITT, LOCF	• Men and women ≥ age 65, recruited from specialty and primary care practices; • OAB ≥ 6 months • had to be capable of independent toileting and able to complete bladder diary independently • completion of at least 5 days of 7-day diary during screening • ≥ 1 urge incontinence episode per day on average • ≥ 10 micturitions per day, as demonstrated in 7-day bladder diary • Patients with BPH on stable doses of alpha blockers of 5-alpha-reductase inhibitors during 3 months or 6 months respectively prior to screening could be included. <u>Exclusions</u> • Treatment with drugs known to affect urinary bladder function or external urethral sphincter; • Polyuria; mean volume voided per micturition of > 300 ml; • Post void residual volume >	77% female, 23% male Mean age 72 years; > 75 years: DARI 31% vs. PL 43% Overall 35% > age 75 92% were taking at least one additional medication; most common co-morbidities were hypertension and hypercholesterolemia Baseline comorbidities include: Condition / DARI / PL Arrhythmia 3.4% 6.0% CAD 6.0% 8.3% HT 60.5% 52.6% High cholesterol 21.1% 21.1% Constipation 6.4% 10.5% Gastritis 6.0% 0.8% GE reflux 6.8% 13.5% Osteoarthritis 17.7% 18.0% Diabetes 8.3% 3.0% BPH 9.4% 10.5% Aspirin DARI 26%; PL 32% Simvastatin DARI 15%; PL 11% Levothyroxine DARI 15%; PL 12%	DARI ER 7.5 mg starting dose with option to increase to 15 mg qd at 2 weeks N=266 <u>Baseline: median (range)</u> UUI/week 19.8 (4.0-142.0) Urgency/day 7.6 (1.0-24.4)	PL Voluntary sham increase at 2 weeks N=133 <u>Baseline: median (range)</u> UUI/week 21.0 (7.0-155.4) Urgency/day 7.4 (1.3-22.2)	• Urgency urinary incontinence episodes: change from baseline at week 12 (primary outcome); multiple other time points weeks 1, 2 and 6 • Incontinence pads used/week • Micturition frequency/day • Urgency episodes/day • Nocturnal voids/week • Responder rates (response defined as ≥ 30%, ≥50%, ≥70% or ≥90%) • 3-day dry rate (based on dryness for at least 3 consecutive days during week 12) • 7-day dry rate (dryness all 7 diary days during week 12) • QoL OAB-q

		100 mls as assessed by ultrasound. • Women with marked cystocele or other clinically significant stage 3 or 4 pelvic prolapse; • Participation in bladder-training program or electrical stimulation therapy within 3 months; urinary tract pathology • Any significant condition that in investigator's opinion made the patient unfit for study participation such as cognitive impairment, uncontrolled severe hypertension, severe heart failure, recent MI, uncontrolled thyroid disease	Diuretics: DARI 23%; PL 11%			• PPBC • Patient assessment of treatment benefit (no; yes; a little; yes; very much) in response to specific Q "Has the treatment been of benefit to you?") • Physician's assessment of treatment benefit (no; yes; a little; yes; very much in response to "Has the patient received any benefit from the treatment?") • SAE • WDAE • Total AE; • Specific AE • Post void residual volume • ECG day 1 and week 12 • Vital signs
AE= adverse events; **BPH**= benign prostatic hypertrophy; **CAD**= coronary artery disease; **DB**= double-blind; **DARI**= darifenacin; **ER**= extended-release; **GE**= gastroesophageal; **HT**= hypertension; **ITT**= intent-to-treat; **LOCF**= last observation carried forward; **MC**= multicentre; **ND**= not done; **NR**= not reported; **OAB**= overactive bladder; **OAB-q**= overactive bladder questionnaire; **OXY**= oxybutynin; **PPBC**= patient perception of bladder condition; **qd**= every day; **QoL**= quality of life; **SAE**= serious adverse events; **SD**= standard deviation; **UUI**= urgency urinary incontinence; **WDAE**= withdrawals due to AE; * all outcomes are listed but only AE are considered in this review.						

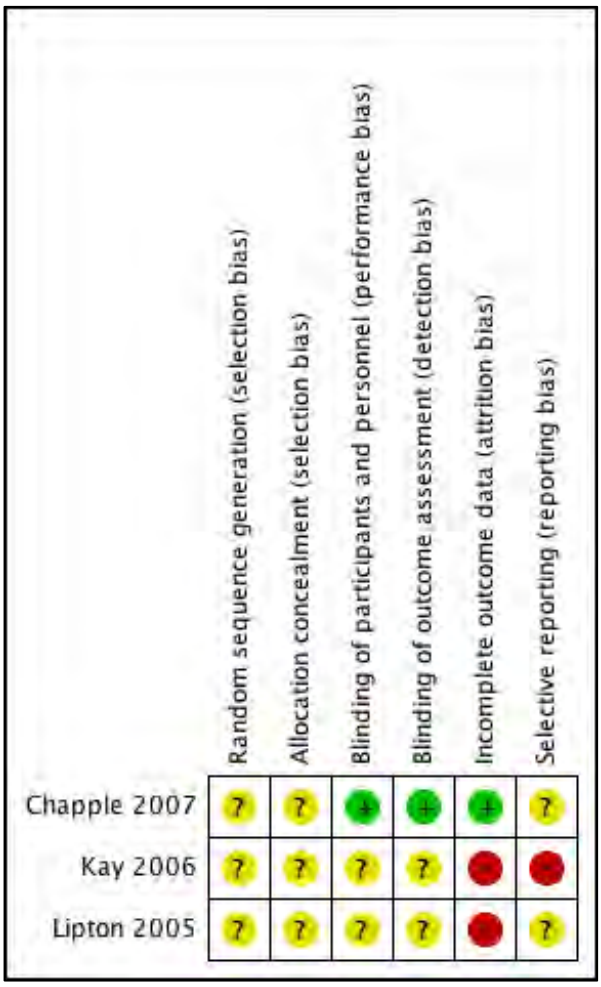


Table 7. Risk of bias assessment of placebo-controlled trials and cognition trials.

The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

Table 8. Cognition RCTs – Healthy Volunteer Study Characteristics							
Darifenacin ER vs. Oxybutynin ER							
Study Country N Sponsor	**Design**	**Inclusion criteria Exclusions**	**Baseline Characteristics**	**DARI ER**	**OXY ER**	**Placebo**	**Outcomes Assessed**
Kay 2006 NCT00170768 U.S. N=150 randomized Novartis	3-arm DB placebo- and active-controlled parallel group RCT; healthy volunteers; dose titration >2 weeks on darifenacin; > 1 week on oxybutynin; sham titration week 2 DARI; week 2 & 3 PL Duration 3 weeks barrage of memory tests (15 types) Per protocol analysis	• Healthy male and female • Age ≥ 60 • Able to carry out computerized testing • No anticholinergic Rx for 2 weeks prior to baseline • No benzodiazepines, opioids or sedating antihistamines • No drugs that affect CYP 2D6 or CYP 3A4 enzymes <u>Exclusions:</u> contraindications to anticholinergics; dementia, MMSE ≤27; depression	Mean age: Dari 66.4 (range 60-82) Oxy 68.0 (range 60-81) Placebo 67.4 (range 61-83) 62% female 94% Caucasian	Week1: 7.5mg qd Week 2: 7.5mg qd sham dose increase Week 3: 15mg qd N=49 completers N=40	Week 1: 10mg qd Week 2: 15mg qd Week 3: 20mg qd N=50 completers N=44	Week 1: Placebo qd Week 2: Sham dose increase Week 3 Sham dose increase N=51 completers N=50	• Cog screen battery of computerized cognitive function tests • Performed at baseline, week 1, 2, 3 o Recent (delayed) memory (delayed recall Name-face association o Immediate memory recall o Delayed memory recall o Visual attention & memory o Psychomotor/reaction time & info processing • Memory assessment clinics self-rating scale (MAC-S) • WDAE • SAE • Total AE

Table 8 Continued. Cognition RCTs – Healthy Volunteer Study Characteristics						
Darifenacin vs. Placebo						
Study Country N Sponsor	**Design**	**Inclusion criteria Exclusions**	**Baseline Characteristics**	**DARI**	**Placebo**	**Outcomes Assessed**
Lipton 2005 U.S. and/or U.K. N=239 screened; N=129 randomized (crossover) Pfizer Novartis	DB, placebo-controlled 3-way crossover RCT double-dummy Participants randomized to receive 3 of the 5 interventions 2 week treatment 1 week washout in between treatments Superiority design (DARI vs. PL)	Healthy males and females ≥ age 65 <u>Exclusions:</u> clinical dementia, depression, any other medical, psychological or social condition that would impair participation, clinically significant or unstable hematological, renal, hepatic or cardiac disease use of cimetidine, psychotropic drugs, anticholinergic drugs, antihistamines or other drugs known to affect cognitive function, any history of drug allergy or contraindications to antimuscarinic drugs	58% female, 42% male Mean age 71 (age range 65-84) 96% Caucasian 3% Black 1% Asian 88% concomitant medical conditions (predominantly essential hypertension) 93% on concomitant medications	DARI ER 7.5 mg qd DARI ER 15 mg qd DARI ER 3.75 mg qd (not dose of interest) DARI IR 5 mg tid (not formulation of interest)	Matching placebo, double dummy	• Battery of cognitive function tests performed at baseline and 2 weeks: o simple reaction time o digit vigilance task o memory scanning task o choice reaction time o delayed word recognition • Bond-Lader Questionnaire (subjective alertness, contentment, calmness – 16 VAS scales) • AE • ECG • Laboratory – hematology, clinical chemistry, urinalysis

AE= adverse events**; DB**= double blind; **DARI**= darifenacin; **ER**= extended-release; **IR**= immediate-release; **MMSE**= mini-mental status examination; **OXY**= oxybutynin; **PL**= placebo; **qd**= every day; **SAE**= serious adverse events; **tid**= three times a day; **WDAE**= withdrawals due to adverse events; **VAS**= visual analogue scale;

Part V Appendices - Table of Contents

Appendix I. Trospium vs. Comparator Drugs RCT Evidence Tables

Table 1. RCT Study Characteristics: Trospium vs. Comparators

Trospium IR vs. Oxybutynin IR

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	TROS IR	OXY IR	Outcomes Assessed
Zellner 2009 Germany N=1995 screened; N=1659 randomized Sponsor: Dr. R. Pfleger GmbH	12-week, MC (153 centres), DB parallel group, non-inferiority, flexible-dose Phase IIIb RCT 1:1 Randomization Treatment-free run-in phase (wash-out phase) Assessments 4 and 12 weeks 7-day bladder diary Full analysis set: subjects with any post randomization efficacy data PP= primary	Men and women ≥ 18 yrs with ≥ 8 micturitions/day and ≥ 5 urge incontinence episodes/week Exclusions: did not complete diary correctly for 7 consecutive days at baseline; polyuria > 2.8L per day; clinically significant BOO i.e., post void residual volume > 100; indwelling catheter or intermittent self catheterization; other significant medical problems; other urogenital conditions e.g., UTI; interstitial cystitis and/or hematuria; contraindications to anticholinergic therapy (e.g., untreated narrow-angle glaucoma; mechanical	Mean age; TROS 62 (12) OXY: 61 (12) Age range 20 -91 16 to 18% on urinary antispasmodics and discontinued prior to run-in phase > 10% on each group had selective Beta-blockers, ACEI, thyroid hormone, salicylate derivatives, or statins 4.6% took prohibited medications (urinary antispasmodics 0.7%; selective beta2-adrenoceptor agonists 0.6%); not clear how this was determined to be a major protocol violation	Flexible dose: 45 mg per day starting dose; option to increase to 90 mg (30 mg tid) at 4 weeks N=829 ≥ 1 dose: N=828 FAS population: N=810 PP population N=615 Completers: N=755 Dose adjustment: increase 261/828(32%) Subsequent dose decrease: 19/261 (7%)	Flexible dose: OXY 7.5 mg/d (2.5 mg tid) starting dose; option to increase to 15 mg/day at 4 weeks N=830 ≥ 1 dose: N=830 FAS population: N=798 PP population N=611 Completers N=738 Dose adjustment: increase 223/830 (27%) Subsequent dose decrease: 30/223 (14%)	• Urgency incontinence episodes per week - reduction from baseline to week 12 (primary outcome) Secondary outcomes: • Urgency incontinence episodes per week – reduction from baseline to week 4 • Subjective assessment of treatment success (VAS) • QoL – KHQ and SF-36 • Intensity of urgency • Change in mean volume voided • Intensity of dry mouth (no change, improved, or worsened) • SAE • WDAE • Total AE • Specific AE

	analysis Noninferiority design (margin 3.5 UUI episodes)	gastrointestinal stenosis, myasthenia gravis); tachycardic arrhythmia; severe psychiatric illness; hypersensitivity to trospium or oxybutynin or vehicle ingredients participation in bladder-training program or another study within 30 days before screening; alcohol and drug abuse; pregnancy, breastfeeding; insufficient contraception; other anticholinergic drugs; drugs with significant anticholinergic or sympathomimetic effects; drugs that could interact with trospium or oxybutynin				
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**TROS IR**	**OXY IR**	**Outcomes Assessed**
Halaska 2003 MP94.D2.04 Austria, Bulgaria, Czechoslovakia, Germany Russia, Spain N=358 Sponsorship not	52-week, MC (52 centres), DB, parallel group RCT Randomization 3:1 2-day bladder diaries 0, 2, 26 and 52 weeks (bladder	Adults > 18 (or 19) years with one of the following, as confirmed by pre-trial urodynamic measurements: • urge syndrome (frequency, nocturia, overwhelming urge, wetting); • urge incontinence; • mixed incontinence; • neurogenic (detrusor	86% female; 14% male Mean age 53.7 (range 19-89) 71% prior illnesses (not specified) 41% prior medication (not specified)	TROS 20 mg bid N=267	OXY IR 5 mg bid N=90	• Patient and Physician-reported subjective improvement; • Incontinence episodes; • Perceptions of urgency; • Micturition frequency; • Urodynamic testing o maximum cystometric bladder capacity; o volume at first uninhibited detrusor

declared – one author from Madaus AG	diaries) Assessments baseline, 2, 6, 12, 20, 26, 32, 40, 52 and 56 weeks modified 'ITT' ('patients who had not shown any obvious deviations from protocol; data before and after ingestion of trial medication; for bladder diary variables, this meant ≥ 4 micturitions or incontinence episodes per day recorded)	hyperreflexia) <u>Exclusions:</u> tachycardia; closed angle glaucoma; myasthenia gravis; severe arteriosclerosis of the cerebral vessels; stress incontinence; frequency due to heart failure, renal failure or diuretic therapy; BOO; acute UTI; hiatus hernia in combination with reflux esophagitis; stenoses in gi tract; megacolon; colonic ulceration; allergy or intolerance of atropine, OXY, TROS or other constituents of the trial medication; concurrent medication within the last 7 days –anticholinergics, tri or tetracyclic antidepressants, alpha blockers or beta-sympathomimetics; urological or gynecological surgery within 3 mo; serious illnesses or conditions; pregnancy or lactation				contraction; o volume at first sensation to void; o maximum detrusor pressure at first unstable contraction; o volume at maximum unstable detrusor contraction; o residual urine; o maximum flow rate • Total AE, Specific AE • 20-item questionnaire about general health plus side effects (checklist-anticholinergic AE – nausea, vomiting, constipation, heart palpitations, hot flushes, light sensitivity, double vision, dryness of mouth; severity of each) • physical examination • ECG, BP, HR • Laboratory data (hematology, clinical chemistry, urinalysis)

Trospium IR vs. Tolterodine IR							
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**TROS IR**	**TOL IR**	**Placebo**	**Outcomes Assessed**
Study MP94D2.15 (Unpublished; 2001) Poland Russia Bulgaria N=232 Madaus AG	3-week, MC (10 centres), DB, double-dummy placebo-controlled, parallel group non-inferiority RCT Washout period 10 days Assessments: -10, 0, 10 and 21 days 10-day bladder diary during washout period and 21 day treatment period (21 days); study end regarded as last 3 days Sequential testing: Superiority TROS vs. PL (ITT, LOCF analysis)	Males and females aged 18 to 80 years Micturition frequency $\geq$ 10 days Urodynamic measurement • motoric urge-syndrome with unstable detrusor contractions; • combined form of motoric urge-syndrome and stress incontinence; • sensoric urge-syndrome with provable first desire to void a bladder filling of 150 ml at most • motoric urge syndrome combined with sensoric urge syndrome; Exclusions: Stress incontinence; neurogenic bladder; maximum cystometric capacity > 500 ml; tachyarrhythmia; angle glaucoma, myasthenia gravis; pollakiuria or nocturia because of cardiac insufficiency, renal insufficiency or diuretic	77% female, 23% male 100% Caucasian Mean age 51.1 years (SD 15.8) Range 18 to 78) 54% unstable detrusor contractions ('motoric urge-syndrome')= a; 9% combined with stress incontinence '=combined' = b; 36% 'sensoric urge-syndrome with first desire to void $\leq$ 150 mls = c; motoric urge-syndrome combined with sensoric urge-syndrome = d TROS: a: 35 (61%); b: 7 (12%) c: 14 (15%); d: 1 (2%) TOL:	TROS 20 mg bid N=76 Baseline UI: N=37 (49%) 3.7 (3.3)	TOL 2 mg bid N=77 Baseline UI: N=42 (55%) 3.4 (3.5)	N=79 Baseline N=42 (53%) 2.8 (2.4)	• Micturition frequency per 24 hours (primary outcome) • AUC of micturition frequency • Incontinence episodes per 24 hours • Mean volume voided • Frequency of changing diapers • Days without incontinence • Patient assessment of efficacy on VAS [-1=worsening of symptoms; 0 =no improvement to 10 =cured] • Physician VAS (as above) • Patient-reported opinion on restriction of work and everyday activities, hobbies and recreational activities; social gathering; eating and drinking habits at baseline and study end (VAS) • Laboratory – hematology, biochemistry, urinalysis • Physical examination incl. BP, HR

	Then non-inferiority of TROS vs. TOL on PP analysis (region of equivalence = 50% of treatment effect of TROS vs. PL)	therapy; BOO; UTI; disease with complicated evacuation of gastro-intestinal tract; recurrent retention of urine, allergies or drug intolerance; treatment with anticholinergics, tri- or tetra-cyclic antidepressants, alpha blocker, beta-sympathomimetics within the 10 days prior to urodynamic measurement; concomitant medication (anticholinergics, tri or tetracyclic antidepressants; alpha blocker, beta sympathomimetics, amantadine, quinide, disopyramid, calcium antagonists if unstable dose or started within 8 weeks; urological or gynaecological surgery within 3 mo; serious disease (e.g., kidney, liver disease); participation in a clinical trial during last 30 days except trials on trospium;	a: 25 (40%) b: 7 (11%) c: 31 (49%) d: 0 25% prior medication				

AE= adverse events; **bid**= twice a day; **BOO**= bladder outlet obstruction; **BP**= blood pressure; **DB**= double blind; **FAS**= full analysis set as defined by investigators; **HR**= heart rate; **IR**= immediate release; **ITT**= intention-to-treat; **KHQ**= King's Health Questionnaire; **LOCF**= last observation carried forward; **MC**= multicentre; **mo**= months; **OXY**= oxybutynin; **PL**= placebo; **PP**= per protocol; **SAE**= serious adverse events; **SD**= standard deviation; **TROS**= trospium; **UTI**= urinary tract infection; **UUI**= urge urinary incontinence; **VAS**= visual analogue scale; **WDAE**= withdrawals due to adverse events;

Table 2. RCT Outcomes: Trospium IR vs. Other Antimuscarinic Drugs				
Trospium IR vs. Oxybutynin IR				
Study	**Zellner 2009**		**Halaska 2003**	
Treatment	**TROS IR 45-90 mg/day**	**OXY IR 7.5-15 mg/day**	**TROS IR 20mg bid**	**OXY IR 5 mg bid**
N randomized	829	830	267	90
Safety analysis (≥ 1 dose)	828	830		
Full analysis set	810	798		
Per protocol analysis	615	611		
Completers	755	738		
Total withdrawals	72 (8.7%)	92 (11.1%)	67 (25.0%)	24 (26.7%)
All-cause Mortality	0	0	2/267 (0.7%)	0
SAE	13/828 (1.6%)	9/830 (1.1%)	19/267 (4.9%)	6/90 (6.7%)
WDAE	48/828 (5.8%)	61/830 (7.4%)	16/267 (6.0%)	9/90 (10%)
QoL: SF-36 Health Transition: improvement	368/810 (45.4%)	374/798 (46.9%)	NA	
SF-36 all 8 multi-item categories mean scores	mean changes from 4.4 to 11.7 points; NR by group or by individual category		NA	
QoL: KHQ Total Score Median Difference (range)	-16.17 (-84.57 to 48.16)	-15.76 (-84.75 to 69.31)	NA	
- KHQ Total score difference§	-0.23 [95% CI -2.11 to 1.72]			
Perception of improvement/cure	See SF-36 Health Transition Item		60/207 (29%) 'cure'	11/65 (17%) 'cure'
Problems caused by incontinence (VAS) Median (range)	-33.0 mm (-99 to 42 mm)	-32.0 mm (-98 to 68 mm)	NA	
Median Difference §	0.00 (-2.00 to 3.00)			

Incontinence Episodes at Baseline Median or mean	median 14/week (FAS) median 15/week (PP)	median 14/week (FAS) median 14/week (PP)	mean 1.5/day	mean 2.1/day
Incontinence Episodes: mean reduction from baseline	--	--	~1	~1
Incontinence Episodes/week	-10.42/week* (FAS) (N=788) -11.0/week* (PP)	-10.00/week* (FAS) (N=784) -11.0/week* (PP)		
Median change from baseline§	PP: 0.00 [95% CI -1.00 to 1.00] FAS: 0.00 [95% CI -1.00 to 0.83] Men: -1.00 [95% CI -4.00 to 1.67] Women 0.00 [95% CI -1.00 to 1.00]			
Nocturia	NA		NA	
Urgency Episodes per day at baseline	NA		10.2	11.0
Urgency Episodes per day at study end	NA		-3.5	-3.6
Total AE	188 (22.7%)	220 (26.5%)	173/267 (64.8%)	69/90 (76.7%)
Specific 'treatment-related' AE as judged by investigators**				
Dry mouth	34/828 (4.1%)^	64/830 (7.7%)^	87/267 (33%)	45/90 (50%)
Dysphagia	NA	NA	9 (3%)	5 (6%)
Constipation	10 (1.2%)	1 (0.1%)	18 (7%)	4 (4%)
Dyspepsia	1 (0.1%)	9 (1.1)	13 (5%)	3 (3%)
Diarrhea	10 (1.2%)	1 (0.1%)	1 (0.1%)	8 (1.0%)
Abdominal pain	NA		5 (2%)	0 (0%)
Nausea	8 (1.0%)	9 (1.1%)	6 (2%)	2 (2%)
Headache	NA		11 (4%)	8 (9%)
Blurred vision/abnormal vision	NA		9 (3%)	5 (6%)
Insomnia	NA		10 (4%)	2 (2%)
Urinary Tract Infection	NA		33 (12%)	10 (11%)
Mean volume voided Mean (SD)	48.0 (58.94)	52.38 (63.41)	NA	
Mean difference	-4.4			
Median	41.0	44.2		
Median difference	-4.00 (-9.90 to 1.90)			

Urodynamics: Maximum cystometric capacity (52 wks)§	NA		115 mls N=189	119 mls N=62
			6.0 mls (90% CI -33.0 to +23.0 ml)	
Mean increase in volume at first unstable contraction	NA		46.0 mls N=51	36.7 mls N=18
Median difference in increase in volume at first unstable contraction (52 wks)§	NA		11 mls NS	
Volume at first sensation to void	NA		78.6 N=186	70.2 N=62
Dose adjusted to higher dose Dose readjusted (to lower dose)	242/810 (29.2%) 19/810 (2.3%)	193/798 (23.3%) 30/798 (3.6%)	--	--

§ Hodges-Lehmann point estimate; * P< 0.001 for noninferiority hypothesis

^Summed for categories of mild, moderate and severe mouth dryness at end of study; Total dry mouth is not reported only those possibly, definitely or probably related to drug. At baseline, 52% in the trospium group and 54% in the oxybutynin group experienced mouth dryness.

**as identified by investigators – for Halaska 2003, this consisted of AE with possible/probable connection to medication. Total specific AE were not reported.

bid= twice a day; **CI**= confidence intervals; **FAS**= full analysis set; **IR**= immediate release; **KHQ**= King's Health Questionnaire; **NA**= not available, either not measured or not reported; **NR**= not reported; **OXY**= oxybutynin; **PP**= per protocol; **QoL**= quality of life; **SAE**= serious adverse events; **SD**= standard deviation; **TROS**= trospium; **WDAE**= withdrawals due to adverse events; **wks**= weeks;

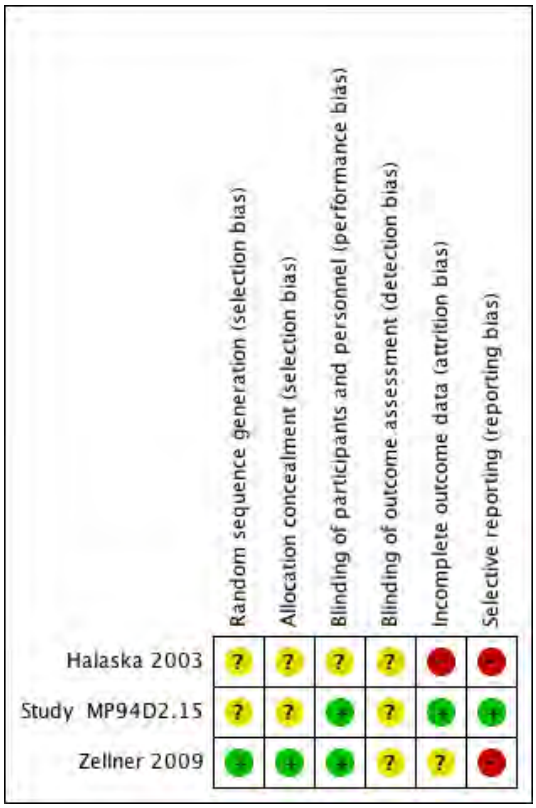
Table 2 Continued. RCT Outcomes: Trospium IR vs. Comparators			
Trospium IR vs. Tolterodine IR			
Study	**Study MP94D2.15**		
Treatment	**TROS 20 mg bid**	**TOL 2 mg bid**	**Placebo**
N randomized	76	77	79
Per protocol analysis	57 (75%)	63 (82%)	60 (76%)
Completers	73	74	76
All-cause Mortality	0	0	0
SAE	0	0	0
Total withdrawals	3	3	3
WDAE	1	0	1
QoL	NR	NR	NR
Patient-reported improvement in restriction of: Work and everyday activities (PP analysis only): Mean difference in VAS from baseline (SD) (%)	36.6 (30.9) (52%)	14.7 (30.7) (24%)	17.6 (28.2 (26%)
Patient assessment of improvement (PP analysis only)	5.3 (3.0)	4.9 (3.0)	3.3 (3.1)
Incontinence Episodes/day: baseline	3.7 (3.3) N=37	3.4 (3.5) N=42	2.8 (2.4) N=42
Incontinence Episodes: change from baseline	-2.5 (3.1)	-2.2 (2.8)	-1.6 (2.3)
Diaper Usage	-1.8 (1.8) N=31	-1.4 (1.8) N=29	-1.5 (2.1) N=29
Continent (dry) Days during treatment day 1 to day 20	13.5 (7.2) N=74	12.6 (7.1) N=74	12.3 (7.9) N=76
Urgency Episodes: Mean Change from Baseline	NR	NR	NR
Nocturia	NR	NR	NR
Total AE	26 (34.2%)	25 (32.5%)	12 (15.2%)
Total gastrointestinal disorders	22 (28.9%)	22 (28.6%)	7 (8.9%)
Dry Mouth	22 (28.9%)	21 (27.3%)	5 (6%)
Central and peripheral system disorders	1 (1.3%)	1 (1.3%)	1 (1.3%)
Psychiatric disorders*	1 (1.3%)	1 (1.3%)	1 (1.3%)
Headache	0	0	3 (5.8%)
Abnormal accommodation	2 (2.6%)	0	2 (2.5%)
Vision abnormal	2 (2.6%)	0	0
Cardiovascular disorders, general	0	1 (1.3%)	0
Tachycardia, palpitation	2 (2.6%)	1 (1.3%)	0
Urinary Tract Infection	0	2 (2.6%)	2 (2.5%)
Mean volume voided: change from baseline (SD) (% change) N	36.0 (59.2) (30%) N=72	45.0 (46.4) (39%) N=70	18.6 (47.6) (15%) N=75
Urodynamics:	NR	NR	NR

* Psychiatric AE: TROS: insomnia; TOL: aggressive reaction, somnolence; Placebo: anorexia

AE= adverse events; **bid**= twice a day; **NR**= not reported; **PP**= per protocol; **QoL**= quality of life; **SD**= standard deviation; **TOL**= tolterodine; **TROS**= trospium; **VAS**= visual analogue scale; **WDAE**= withdrawals due to adverse events;

Table 3. Risk of Bias/Quality Assessment

A. RCTs on Patients with OAB



The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

A risk of bias assessment could not be conducted for Study NCT0118827 because a full study report was not available.

B. Healthy Volunteer RCTs (Cognition)

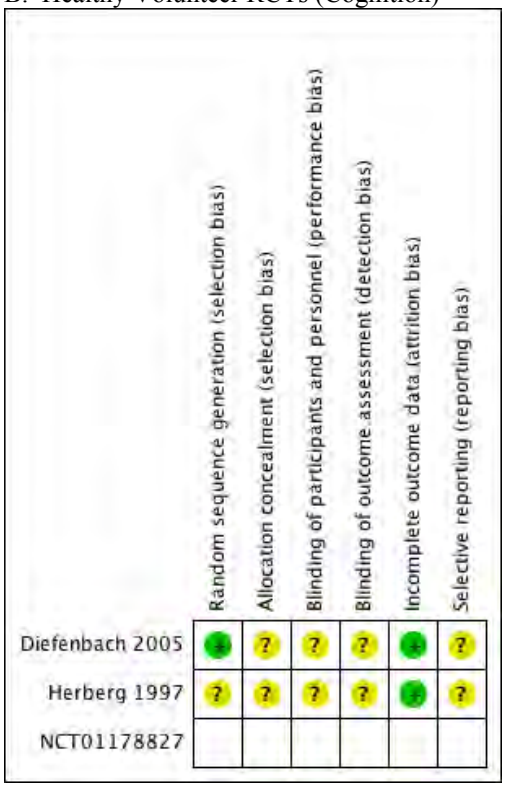


Table 4. Adverse events reported in the Canada Online Vigilance Database
Database last updated March 31, 2013 (N=12)

Adverse Reaction Case Reports
o Atrial fibrillation/BP increased dizziness/dyspnea/headache/HR increased/palpitations/ventricular extrasystoles – serious (hospitalization) (1)
o Dysuria – serious (hospitalization) (1)
o Dizziness/nausea/vision blurred (1)
o Choking sensation/dry mouth/dysphagia (1)
o Abdominal pain/diarrhea (1)
o Discomfort/vomiting (1)
o Anticholinergic syndrome/asthenia/HR irregular/palpitations/tremor (1)
o Night sweats (1)
o Urinary retention (1)
o Constipation/dry mouth/dry throat/pollakiuria (1)
o Drug ineffective (1)
o Drug ineffective/hot flush (1)

Table 5. Cognition RCT Study Characteristics					
OAB Patient RCTs: Trospium ER vs. Oxybutynin IR					
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**Interventions**	**Outcomes Assessed**
NCT01178827 Unpublished U.S. N=20 Allergan	SC, single-blind, placebo-controlled parallel group RCT Per protocol analysis	Males and females ≥ age 60 with symptoms of OAB and age-associated memory impairment; No acute or unstable medical conditions; Exclusion criteria: history of alcohol or substance abuse within 1 year prior to study Donations of > 500 mls blood or plasma in 30 days prior to study; known bleeding disorder (hemophilia); prior abdominal bypass surgery for obesity	11 female (55%), 9 male (45%) Mean age: 72 (8) TROS: 74 (6) OXY IR: 68 (6) OXY PL: 77 (12)	Trospium ER 60 mg once daily x 10 days, N=6 Oxybutynin IR 5 mg tid x 2 days, N=10 Placebo tid x 2 days (placebo for oxybutynin IR), N=4	• CSF drug levels: o trospium ER levels 10 day post dose o CSF oxybutynin IR and DEO levels 2 day post dose • HTVLT-R o Total recall score o Delayed recall score • BVMT-R o Free recall o Delayed recall o Yes/no delayed recognition trial o Total recall score

Table 4 Continued. Healthy Volunteer RCTs: Trospium IR vs. Oxybutynin IR or Tolterodine IR

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	Interventions	Outcomes Assessed
Diefenbach 2005 Germany N=25 Dr R. Pfleger GmbH	SC, DB, placebo-controlled crossover RCT 4 2-night periods of polysomnography in a sleep lab separated by 12-day washout. Night 1 – adaptation to study situation Night 2- study medication, 2h before polysomnography started	Healthy volunteers ≥ aged 50 years Exclusions: sleep disturbances; organic or psychiatric diseases which influence sleep, or which were contraindications to one of study medications	Mean age 60 (SD 3) Age range 51-65 12 men; 12 women; 1 of unspecified sex withdrew	Single dose of total recommended daily dose at 9:30 pm: o Oxy IR 15 mg (3 x 5 mg) o Tolterodine IR 4mg (2 x 2 mg) o Trospium IR (3 x15 mg)	• Duration of REM as a percentage of sleep duration (primary outcome) • Prolongation of REM latency (exploratory): time between sleep onset and first period of REM • Cognitive tests 1 hour after administration of study medication: o number-combination test (information-processing capacity and working velocity) o d2 test of attention for assessing individual sustained attention and concentration • ECG • Laboratory variables • AE
Herberg 1997 Germany N=54 randomized	SC, DB RCT – does not specify parallel group or crossover; no washout period identified so likely parallel group Assessment at baseline and end of treatment (morning of day 8)	healthy volunteers aged 35-70 yrs Exclusions: No acute medical condition; no chronic disease; no pregnancy or lactation; non-compliance		Oxy IR t mg t.i.d. x 7 days Trospium 20 mg bid x 7 days	Precision of visual orientation Concentration Vigilance Motor co-ordination Reaction in stress situations Word Match List AE (spontaneously reported)

AE= adverse events; **BVMT-R**: Brief Visuospatial Memory Test-Revised; **CSF**= cerebrospinal fluid; **DB**= double-blind; **DEO**= N-desethyl-oxybutynin; **HVLT-R** Hopkins Verbal Learning Test-Revised; **IR**= immediate-release; **OXY**= oxybutynin; **REM**= rapid eye movement; **TROS**= trospium; **SC**= single centre;

Table 6. RCT Outcomes: Studies on Cognition			
Trospium ER vs. Oxybutynin IR and other comparators			
NCT 01178827			
Treatment	**TROS ER 60 mg x 10 days**	**OXY IR 5 mg tid x 2 days**	**Placebo for OXY IR tid x 2 days**
N	6	10	4
Plasma levels post dose (10 days for TROS; 2 days for OXY)	1.47 ± 1.03 ng/ml (=1470 ± 1030 pg/ml)	OXY: 8800 ± 2840 pg/ml DEO: 47,000 ± 11,200	
CSF fluid levels post dose (10 days for TROS; 2 days for OXY)	Below level of detection	OXY: 59.7 ± 30.9 DEO: 386 ± 23.5	--
HVLT-R Total Recall Score up to 10 days Mean (SD) change from baseline	Baseline: 22.5 ± 2.9	Baseline 24.4 ± 3.3	Baseline 24.0 ± 3.7
	-0.3 ± 3.3	-3.3 ± 5.4	-2.0 ± 4.8
HVLT-R Delayed Recall Score up to 10 days Mean (SD) change from baseline	Baseline 8.2 ± 1.2	Baseline	Baseline
	-1.2 ± 1.5	-1.3 ± 1.6	-0.3 ± 3.7
BVMT-R Total Recall Score up to 10 days Mean (SD) change from baseline	Baseline 15.8 ± 6.6	Baseline 20.3 ± 9.9	Baseline 16.8 ± 11.3
	1.2 ± 7.4	-1.1 ± 5.3	0.0 ± 3.5
BVMT-Delayed Recall Score up to 10 days Mean (SD) change from baseline	Baseline 6.0 ± 4.2	Baseline 8.0 ± 3.6	Baseline 4.5 ± 5.3
	0.2 ± 3.4	-1.8 ± 3.5	2.3 ± 3.9
SAE	0/6	0/10	0/4
Hypoacusis	0/6	1/10 (10.0%)	0/4
Tinnitus	1/6 (16.7%)	0/10	0/4
Dry Mouth	0/6	2/10 (20.0%)	0/4
Nausea	2/6 (33.3%)	2/10 (20.0%)	0/4
Diarrhea	1/6 (16.7%)	0/10	0/4
Dyspepsia	0/6	1/10 (10.0%)	0/4
Edema peripheral	0/6	1/10 (10.0%)	0/4
Arthralgia	1/6 (16.7%)	0/10	0/4
Back pain	4/6 (66.7%)	3/10 (30.0%)	1/4 (25.0%)
Muscle spasms	1/6 (16.7%)	1/10 (10.0%)	1/4 (25.0%)
MSK stiffness	1/6 (16.7%)	0/10	0/4
Neck pain	0/6	1/10	0/4
Headache	1/6 (16.7%)	4/10 (40.0%)	2/5 (50.0%)
Lethargy	1/6 (16.7%)	0/10	0/4
Dizziness	1/6 (16.7%)	0/10	0/4
Anxiety	0/6	1/10	0/4

BVMT-R= Brief Visuospatial Memory Test-Revised; **DEO**= N-desethyl-oxybutynin; **ER**= extended-release; **HVLT-R**= Hopkins Verbal Learning Test-Revised; **IR=** immediate-release; **MSK**= musculoskeletal; **OXY**= oxybutynin; **SD**= standard deviation; **SAE**= serious adverse events; **TROS**= trospium;
For both HVLT-R and HVLT-R, a negative change indicates deterioration.
Data are results posted on clinicaltrials.gov.

Table 6 Continued. RCT Outcomes: Studies on Cognition				
RCTs in Healthy Volunteers: Trospium IR vs. Oxybutynin IR and other comparators				
Diefenbach 2005				
Treatment	**TROS IR 45 mg single dose**	**OXY IR 10 mg single dose**	**TOL IR 4 mg single dose**	**Placebo**
N	N=24 (crossover)			
ZVT, reaction time, Median (1st and 3rd quartile), seconds	75 (66-82)	76 (67-99)	73 (61-89)	79 (65-88)
d2: error corrected, total Median (1st and 3rd quartile)	343 (306-365)	345 (313-393)	342 (292-401)	340 (316-400)
Total AE	NR by group			
Dry mouth	5	8	4	3

Herberg 1997 (translated)		
Treatment	**TROS IR 20 mg bid x 7 days**	**OXY IR 5 mg tid x 7 days**
N randomized	18	18
Completers	18	18
Total withdrawals	0	0
All-cause Mortality	0	0
SAE	0	0
Withdrawals due to AE	0	0
Total AE	8 (events, not participants)	23 (events, not participants)
Dry Mouth	1	11
Efficacy outcomes (psychomotor function)		
Precision of visual orientation	No difference (data NR)	
Concentration	No difference (data NR)	
Vigilance	No difference (Figure 2)	
Motor co-ordination	No difference (data NR)	
Reaction in stress situations	No difference (data NR)	
Precision of visual orientation	No difference (data NR)	

AE= adverse events; **D2**= test of attention for assessing individual sustained attention and concentration; **IR**= immediate release; **NR**= not reported; **ZVT=** Der Zahlen-Verbindungs-Test, a number-combination test for evaluating information-processing capacity and working velocity

Appendices for Different Formulations of the Same Drug: Table of Contents

Appendix J. Different Formulations of the Same Drug: RCT Evidence Tables

Table 1. RCT Study Characteristics: Different Formulations of Oxybutynin						
Oxybutynin CR or ER vs. Oxybutynin IR						
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**OXY CR or ER**	**OXY IR**	**Outcomes Assessed**
Anderson 1999 C-95-049-05 U.S. N=158 screened; N=105 randomized ALZA	MC (13 centres), DB parallel group dose-titration Phase II RCT 1-week washout period 1-week baseline period 2 weeks at final dose 7-day bladder diary at baseline and final week PP analysis (baseline and endpoint diary data) Equivalence trial (95% CI upper boundary not to exceed 4	Community dwelling men and women with urge incontinence or urge predominant mixed UI ≥ 6 urge incontinence episodes per week All patients had previously responded to oxybutynin treatment Exclusions Known treatable urinary pathology that could cause incontinence Men with prostate surgery < 9 months before study enrolment or PSA > 10 ng/mL; Post void residual volume of > 100 mL (pelvic ultrasound); CrCl < 50 mL; Glaucoma or untreated anterior chamber angles; Hb < 100 g/L; hypersensitivity to OXY; History of drug or	92% female, 8% male Mean age CR 59.2 (SD 10.6); IR 59.6 (SD 10.0) Race/ethnicity NR 100% had prior medication for OAB and responded	OXY ER (OROS or XL)) initiated at 5 mg daily and increased or decreased by 5 mg increments q 4-7 days; Maximum 30 mg Titration goals: o No urge incontinence episodes during final 2 days of 4-7 day period; o Maximum tolerated dose (5 mg dose below that at which intolerable anticholinergic effects were reported) o Maximum allowed dose At study end: 5 mg N=10;	OXY IR 5 mg 1-4X daily, initiated at 5 mg daily and increased (or decreased) q 4-7 days Maximum 20 mg Titration goals: o No urge incontinence episodes during final 2 days of 4-7 day period; o Maximum tolerated dose (5 mg dose below that at which intolerable anticholinergic effects were reported) o Maximum allowed dose At study end: 5 mg N=13 10 mg N=14;	• Urge incontinence episodes per week (primary outcome) • Total incontinence episodes (stress + urgency) • Micturition frequency • Proportion with no UUI episodes; • Proportion achieving continence • Subjective Assessment of Symptoms Severity (5-point scale, 0-4) • Patient Satisfaction and Overall Rating • Total void frequency • Voided volume • Post-void residual volume • Clinical chemistry, hematology, urinalysis; • ECG • Vital signs • AE (based on anticholinergic effects assessment questionnaire and spontaneous reporting)

	episodes in favor of IR*)	alcohol abuse or +ve urine drug screen; those at risk for complete urinary retention or other disorders caused by anticholinergic therapy; pregnant or lactating women; Severe narrowing of the gi tract; Myasthenia gravis		10 mg N=8; 15 mg N=12; 20 mg N=12; 25 mg N=4; 25 mg N=6; 30 mg N=6	15 mg N=12; 20 mg N=8	

* From FDA NDA Review 20-897

Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**OXY ER**	**OXY IR**	**Outcomes Assessed**
Barkin 2004 Canada N=125 randomized Purdue	MC, Parallel group DB RCT Double-dummy drug packaging technique Total duration 9 weeks: • 3 week no-treatment baseline period • 2 week dose-titration period • 4 week stable-dose period Efficacy	Adult men and women ≥ age 18 with urgency incontinence ≥ 7 episodes per week and ≥ 8 voids per day during last 2 weeks of baseline period Exclusions: post void residual volume > 100 mLs; unstable dose of any drug with anticholinergic or diuretic/antidiuretic side effects; allergy or previous life-threatening side effects with anticholinergic/antispas	Of the 100 evaluable patients, 85% were female 15% male Mean age (SD): OXY CR 58.0 (12.4) yrs (range 26 to 78); OXY IR 60.6 (14.8) yrs (range 26 to 83) > 65 years: 20 (38%); 18 (44%) Race/ethnicity NR	OXY CR (Uromax) 5 -20 mg/d Mean dose (SD) 15.2 mg/d (4.4) N=65 randomized but only evaluable patients are included in the mean i.e., those who completed ≥ 2 weeks of stable-dose phase N=53 Titration Goal: best balance between continence and AE: (increase or	OXY IR 5-20 mg per day Mean dose (SD) 14.0 (5.3) mg/d N=60 randomized but only evaluable patients are included in the mean: N=41 Titration Goal: best balance between continence and AE: (increase or decrease in) 5 mg	• Voids per day (primary outcome) • Incontinence episodes • Pad usage • Urgency episodes • Any AE in a 24 hour patient diary • Physician-assessment of tolerability based on number and severity of anticholinergic AE reported by patient • Purdue Urgency Questionnaire (newly developed) • Incontinence Impact Questionnaire (IIQ (4-point scale) • Urogenital Distress Inventory (UDI) (4-point

	population: those who completed ≥ 2 weeks in the stable-dose phase and did not have major protocol violations 'Safety' population: all randomized patients ITT population - all patients randomized and who had ≥ 1 post baseline evaluation Discussion suggests the trial was an equivalence trial	modic medications; primary diagnosis of stress UI; conditions contraindicating anticholinergic therapy; daily fluid intake > 3L; hepatic/renal disease; painful bladder syndrome; uninvestigated voiding difficulty with risk of urinary retention; uninvestigated hematuria or hematuria secondary to malignant disease; UTI or history of recurrent UTI (> 3/year); indwelling catheter or bladder training within 14 days of screening; untreated psychiatric conditions affecting completion of voiding diaries; drug/alcohol abuse; BOO; chronic untreated constipation; pregnancy or breastfeeding; failure to use reliable contraception in women of childbearing potential		decrease in) 5 mg increments based on the severity of anticholinergic AE	increments based on the severity of anticholinergic AE	scale) • Lab: clinical chemistry (full list provided) and hematology (CBC and differential)

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	OXY CR or ER	OXY IR	Outcomes Assessed
Birns 2000 U.K. N=162 screened N=130 randomized Leiras Oy and Pharmacia & UpJohn	MC (15 centres) DB, double-dummy parallel group RCT 2 week screening during which patients received OXY IR 5 mg bid Bladder diary throughout the study 4 weeks duration post randomization Assessment baseline, 2, 4 and 6 weeks ITT (N=128)	Males and females whose voiding problems are currently stabilized on and tolerant to treatment with OXY IR <u>Exclusions:</u> Any medical condition for which anticholinergic medication is contraindicated; history of myasthenia gravis, glaucoma or functional or organic gastrointestinal obstructive disorders; symptomatic UTI BOO or symptoms of only nocturnal enuresis; females who were pregnant, lactating or of child-bearing age and not using adequate contraception	Mean age 56 yrs (range 18 to 76) Race/ethnicity NR 100 patients had specific diagnosis of detrusor instability; 7 patients had neuropathic bladder; 5 patients had mixed UI and 2 patients had stress UI.	OXY CR 10 mg once daily N=63	Oxy IR 5 mg bid N=67	• Proportion with daytime continence at study completion (primary outcome) • Proportion with night time continence at study end • Median change in voluntary daytime voids from week prior to treatment to study end • Median change in voluntary night-time voids from week prior to treatment to study end • Median change in daytime episodes of incontinence from week prior to treatment to study end • Median change in night-time episodes of incontinence from week prior to treatment to study end in last week • Blood concentrations of OXY and DEO pre and post dose • AE - total • Specific AE

Study Country N Sponsor	Design	Inclusion Criteria Exclusions	Baseline Characteristics	OXY CR or ER	OXY IR	Outcomes Assessed
Minassian 2007 N=72 randomized Canada Janssen-Ortho	Open label, single centre, parallel group RCT 2-week wash-out 12 weeks duration Assessments baseline, 4 and 12 weeks clinic visit; 8 weeks telephone follow-up 3-day bladder diary ITT Study terminated due to poor recruitment and interim analysis that indicated a priori sample size calculation did not reflect sample in study	Community dwelling women > age 65 with symptoms of OAB (urgency, frequency and nocturia); mixed urge predominant incontinence; MMSE > 24 <u>Exclusions:</u> Bedridden; permanent indwelling catheter; MMSE < 24; incontinence due to other causes; evidence of glaucoma; gastric retention or bowel obstruction; allergy to OXY or anticholinergic drugs; taking tricyclic antidepressants or anticholinesterase inhibitors; post void residual volume > 100 mL; neurologic disease	Mean age (SD) OXY ER 75 (6); OXY IR 73 (5) 94-95% had urge incontinence Stress Incontinence OXY ER: 67% OXY IR: 52% Fecal incontinence: OXY ER: 23% OXY IR: 9% Prior prolapse/incontinence surgery: OXY ER: 13% OXY IR: 49% +ve cough test lying: OXY ER: 26% OXY IR: 15% standing: OXY ER: 33% OXY IR: 15% Incontinence Median (IQR) OXY ER: 2 (0-4) OXY IR: 1 (0-3) MMSE Median (IQR)	OXY ER (XL) 5 mg once daily - after 4 weeks increased to 10 mg daily N=39 dose adjustment on the basis of non-response between week 1 to 4 = difference in mean daily frequency of < 1.5 according to voiding diaries	OXY IR 2.5 mg tid - increased after 4 weeks to 5 mg tid N=33 dose adjustment on the basis of non-response between week 1 to 4 = difference in mean daily frequency of < 1.5 according to voiding diaries	• Micturition frequency (primary outcome) • Incontinence episodes per day • Voided volume per micturition • Pad usage • IIQ • U-UDI • Uroflowmetry and post void residual volume > 100 mls • MMSE

			OXY ER: 29 (29-30) OXY IR: 30 (28-30)			
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**OXY CR or ER**	**OXY IR**	**Outcomes Assessed**
Versi 2000 C-97-020-03 U.S. N=417 screened; N= 226 randomized ALZA	MC (20 centres); DB parallel group RCT Baseline run-in period for 2 weeks Dose titration period (attaining a 5-mg final dose required approximately 2 weeks, whereas a final dose of 20 mg required approximately 5 weeks) Maintenance period (with optimal dose) for 1 week 7-day urinary diary during placebo baseline period and during the final week of OXY dose.	Adult, community-dwelling men and women with 7-45 urge incontinence episodes per week and at least 4 days of incontinence per week during the placebo baseline period, and had previously responded to treatment with anticholinergic medications or to a trial of oxybutynin before enrolment Exclusions: clinically significant medical problems, a post void residual urine volume over 100 mL, or other conditions in which oxybutynin is contraindicated.	89.4% female; 10.6% male Mean age: CR: 58.8 yrs; IR: 59.6 yrs Race (CR vs IR): White 86.5% vs 90.4% Black 5.4% vs 3.5% Asian 0.9% vs 0% Hispanic 5.4% vs 5.2% Native American 0% vs 0.9% Other 2% vs 0% “no statistically significant differences in patient age, gender distribution, race, baseline urge episodes, prior experience of controlled-release oxybutynin, or severity and duration of urgency and frequency between the two treatment groups”	OXY ER (OROS or XL) 5 mg qd Dose range: 5-20mg Increased in 5 mg/day increments every 7 days to a dose that achieved a balance between improvement in incontinence symptoms and tolerability of side effects (max dose 20 mg/day). Doses were decreased by 5 mg if side effects were intolerable.	OXY IR 5 mg qd Dose range: 5-20 mg Increased in 5 mg/day increments every 7 days to a dose that achieved a balance between improvement in incontinence symptoms and tolerability of side effects (max dose 20 mg/day). Doses were decreased by 5 mg if side effects were intolerable.	• The numbers of weekly urge incontinence episodes and total incontinence episodes determined from 7-day urinary diaries • Rates of dry mouth • AE • Physical examination • Standard laboratory tests • Urinalysis • Elimination of incontinence episodes by dose • Dry mouth risk by dose (Post hoc Kaplan-Meier survival analysis)

			20% had previously been enrolled in other studies of OXY ER			
Oxybutynin TDS or Gel vs. Oxybutynin IR						
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**OXY TDS**	**OXY IR**	**Outcomes Assessed**
Davila 2001 Country NR (U.S. Authors) N=76 randomized Watson Laboratories	MC, DB, double-dummy parallel group RCT Baseline evaluation on usual therapy 2 week washout period 6 weeks duration 3-day bladder diary Assessments 2, 4 and 6 weeks Equivalence study	Men and women with history of urge UI or urge predominant mixed UI, minimum of 3 incontinent episodes daily and a greater than 30% increase after 2 week washout. Detrusor instability urodynamically confirmed by cystometrogram <u>Exclusions:</u> history of allergy to oxybutynin, intolerability of TDS system, current pregnancy or lactation; overflow incontinence secondary to underactive or noncontractile detrusor or outlet obstruction, impaired bladder compliance, including tonic increase in pressure > 15 cm during filling cystometry; current medical conditions that	92% women, 8% male (5/6 males were assigned to TDS OXY) Mean age: TDS 63 (13) yrs; OXY IR 64 (15) 95% Caucasian 5% Black Mean baseline incontinence episodes per 24 h post washout (SD): OXY TDS: 7.2 (4.5); OXY IR: 7.2 (4.1)	Twice weekly application of TDS (delivery of 1.3 mg/day) Dose range: 1-4x 13 cm2 patches, up to 52 cm^2 (above approved dose of 36 cm^2 or 3.9mg/day) Patients started out with 2, 3 or 4 patches twice weekly depending on prior oral OXY dose. This was continued for 2 weeks, then adjusted by increasing if no or mild side effects or decreasing if intolerable side effects. 71% started with 2.6 mg/d	2.5 mg OXY (in capsules) - titration 2.5 mg bid or tid; or 5 mg bid or tid; 74% started with 10mg daily Dose range: 5-22.5 mg Titration based on 10 symptoms in questionnaire: o palpitations o constipation o dry mouth o nausea o urinary hesitancy o urinary retention o blurred vision o drowsiness o dizziness o (men) impotence	• Responders ≥ 30% reduction in incontinence episodes from baseline (primary outcome)* • Incontinence episodes per 24 h • Dry mouth on anticholinergic symptoms questionnaire • Patient assessment of efficacy (VAS) • Plasma concentration of OXY and DEO • Multichannel cystometry maximum cystometric capacity; average bladder volume at first detrusor contraction; post void residual volume • AE on basis of questionnaire • Local tolerability and appearance of skin* • Laboratory*; chemistry; hematology; urinalysis

		could contribute to or cause urinary incontinence; medical conditions that could be worsened by OXY		Titration based on 10 symptoms in questionnaire: o palpitations oconstipation o dry mouth o nausea o urinary hesitancy o urinary retention o blurred vision o drowsiness o dizziness o (men) impotence		
AE= adverse events; CI= confidence intervals; CR= controlled-release; DEO= N-desethyl-oxybutynin; ER= extended release; IIIQ= incontinence impact questionnaire; QR= interquartile; IR= immediate release; ITT= intention-to-treat; MMSE= mini-mental status examination; NR= not reported; OXY= oxybutynin; q= every; UDI= urogenital distress inventory; U-UDI= urge-UDI: UI= urinary incontinence; UUI= urge urinary incontinence; UTI= urinary tract infection; SD= standard deviation; VAS= visual analogue scale;						

* based on information from FDA review

Table 2. RCT Outcomes: OXY ER or CR (Oral) vs. OXY IR		
Study	**Anderson 1999**	
Treatment	OXY ER (Ditropan XL) 5-30 mg qd	OXY IR 5-30 mg qd
N	53	52
N for analysis (e.g., if per protocol)	N= 46 (efficacy); N= 53 (safety)	47 (efficacy); N= 52 (safety)
All-cause mortality	NR	NR
SAE	0*	1*^
WDAE	5 (9.6%) [1 subdural hematoma secondary to fall; 3 UTI; 1 dry mouth]	5 (9.4%) [3 UTI, 1 blurred vision; 1 dyspepsia]
Total Withdrawals	7	6
Quality of Life (QoL)	NA	NA
Cure (Dryness rate) : % of continent subjects at study end	41%	40% (p=0.9 ER vs IR)
Patient Perception of Improvement or Cure	NA	NA
% patients with no urge incontinence episodes at study end	52%	51% (p=0.7 CR vs IR)
Total Incontinence episodes per week: Baseline mean	29.3/week [=4.2/day]	26.3/week [=3.8/day]
Total incontinence episodes per week (mean % change from baseline) at study end	6/week [=0.9/day] (82%)	3.8/week [=0.5/day] (88%) (p=0.5 ER vs IR)
Urge urinary incontinence episodes per week: Baseline mean	27.4/week [=3.9/day]	23.4/week [=3.3/day]
Urge urinary incontinence episodes per week (mean % change from baseline) at study end	4.8/week [=0.7/day] (-84%)	3.1/week [=0.4/day] (-88%) (P=0.7 ER vs IR)
Nocturia	NA	NA
Total AE	NR	NR
Total Anticholinergic AE^	46 (87%)	49 (94%)
Dry mouth	36 (68%)	45 (87%); p=0.04 ER vs IR
Somnolence	20 (38%)	21 (40%); p=0.8 ER vs IR
Blurred vision	15 (28%)	9 (17%); p=0.3 ER vs IR
Constipation	16 (30%)	16 (31%); p=1.0 ER vs IR
Dizziness	15 (28%)	20 (38%); p=0.3 ER vs IR
Impaired urination	13 (25%)	15 (29%); p=0.7 ER vs IR
Nervousness	13 (25%)	12 (23%); p=1.0 ER vs IR
Nausea	10 (19%)	9 (17%); p=1.0 ER vs IR
Void volume: baseline mean ± SD	134.2 ± 82 mL	161.2 ± 92; p=0.2 ER vs IR
Void volume: Endpoint (change from baseline) mean ± SD	176.6 ± 138 (+42.4 ±124)	194.5 ± 152; p=0.9 ER vs IR (+33.3 ± 172; p=0.9 ER vs IR)
Post-void residual volume: baseline mean ± SD	15.4 ± 21mL	18.0 ± 24; p=0.6 ER vs IR
Post-void residual volume: Endpoint (change from baseline) mean ± SD	33.5 ± 77 (+18.0 ±72)	36.1 ± 59; p=0.2 ER vs IR (+18.1 ± 64; p=1.0 ER vs IR)
Total bladder volume:	149.7 ± 90	179.2 ± 95; P=0.2 ER vs IR)

baseline mean ± SD		
Total bladder volume: Endpoint (change from baseline) mean ± SD	210.1 ± 148 (+60.4 ± 133)	230.6 ± 176; p=0.9 ER vs IR (+51.4 ± 186; p=0.9 ER vs IR)
Normal void frequency (% change from baseline)	+54%	+17% (p<0.001 ER vs IR)
EKG changes*	Sinus bradycardia: 10% First degree AV block: 6%	Sinus Bradycardia: 2% First degree AV block: 2% ER vs. IR NS
AE= adverse events; ER= extended-release; IR= immediate release; NA= not available (either not measured or not reported); NR= not reported; qd= every day; SAE= serious adverse events; SD= standard deviation; UTI= urinary tract infection; WDAE= withdrawals due to adverse events;		

*reported in the FDA Review NDA 20-897;

^ Based on routinely administered questionnaire; NS= not statistically significant

Study	**Barkin 2004**	
Treatment	**OXY ER 5-20 mg/day**	**OXY IR 5-20 mg/day**
N	N=65	N=60
N for analysis (e.g., if per protocol)	N=53 (efficacy); N=65 (safety)	N= 41 (efficacy); N=60 safety
All-cause mortality		
SAE		
WDAE	11 (17%)	12 (20%); p=0.047
Total Withdrawals	13 (20%)	22 (37%)
Quality of Life (QoL) –		
IIQ scores: Baseline mean ± SD	2.6 ± 0.8	2.3 ± 0.8
IIQ scores: Study End mean ± SD	1.9 ± 1.7; p<0.001 vs baseline	1.6 ± 0.6; p<0.001 vs baseline (p=NS CR vs IR)
UDI scores: Baseline mean ± SD	2.6 ± 0.6	2.5 ± 0.4
UDI scores: Study End mean ± SD	2.0 ± 0.6; p< 0.001 vs baseline	1.8 ± 0.5; p<0.001 vs baseline (p=NS CR vs IR)
Cure (dryness rate)	NA	NA
Patient Perception of Improvement or Cure	NA	NA
Incontinence episodes per week: Baseline mean ± SD	24.3 ± 19.0	23.0 ± 17.7
Incontinence episodes per week at study end ± SD	10.4 ± 18.8; p<0.001 vs baseline	6.1 ± 8.8; p<0.001 vs baseline (p=0.404 CR vs IR)
Mean number of pads per day: Baseline vs Study end	2.3 vs 1.7; p<0.001	2.4 to 1.9; p=NS
Urgency measured using Purdue Urgency Questionnaire		
Frequency Baseline mean ± SD	3.3 ± 1.1	3.2 ± 0.9
Frequency Study end mean ± SD	2.3 ± 1.2; p<0.001 vs baseline	1.9 ± 0.9; p<0.001 vs baseline (p=0.116 CR vs IR)
Nocturia	NA	NA
Total AE	NR	NR
Dry mouth	44 (68%)	43 (72%)
Dry mouth - Moderate to severe	25 (38%)	27 (45%)
Pharyngitis	23 (35%)	24 (40%)
Dry skin	11 (17%)	7 (12%)

Diarrhea	9 (14%)	3 (5%)
Headache	8 (12%)	13 (22%)
Urinary tract infection	8 (12%)	11 (18%)
Dizziness	7 (11%)	11 (18%)
Dyspepsia	7 (11%)	10 (17%)
Rhinitis	7 (11%)	9 (15%)
Abdominal pain	6 (9%)	6 (10%)
Asthenia	5 (8%)	9 (15%)
Constipation	5 (8%)	6 (10%)
Taste perversion	5 (8%)	7 (12%)
Cough increased	4 (6%)	8 (13%)
Dysphagia	4 (6%)	8 (13%)
Dry eyes	2 (3%)	9 (15%)
Nausea	3 (5%)	10 (17%)
Volume per void: Baseline mean ± SD	177 ± 77 mL	221 ± 137 mL
Volume per void: Study End mean ± SD	202 ± 80 mL; p=0.064 vs baseline	261 ± 119 mL; p=0.077 vs baseline (p=0.533 CR vs IR)
AE= adverse events; ER= extended-release; IIQ= incontinence impact questionnaire; IR= immediate release; NA= not available (either not measured or not reported); NR= not reported; qd= every day; QoL= quality of life; SAE= serious adverse events; SD= standard deviation; UDI= urogenital distress inventory; UTI= urinary tract infection; WDAE= withdrawals due to adverse events;		

Study	**Birns 2000**	
Treatment	**OXY ER 10 mg qd**	**OXY IR 5 mg bid**
N	63	67
N for analysis (e.g., if per protocol)	N=62 (efficacy and safety)	N=66 (efficacy and safety)
All-cause mortality	0	0
SAE	0	1/66 (1.5%)* (An additional 2 patients reported SAE during screening and were not randomized)
WDAE	0	1/66 (1.5%)
Total Withdrawals	2/63 (3.2%)	3/67 (4.5%)
Quality of Life (QoL)	NA	NA
Cure (dryness rate)	NA	NA
Patient Perception of Improvement or Cure	NA	NA
Median change in daytime episodes of incontinence	Data not provided. “No statistically significant difference between the treatments”.	
Median change in night-time episodes of incontinence	Data not provided. “No statistically significant difference between the treatments”.	
Median change in voluntary night-time voids	Data not provided. “No statistically significant difference between the treatments”	
Total AE	34 (55%)	44 (67%)
Dry mouth	22.6 (14%)	11 (16.7%)
Dizziness	1 (1.6%)	6 (9.1%)
Vision abnormality	4 (6.5%)	3 (4.5%)
Coughing	2 (3.2%)	3 (4.5%)
Headache	0	3 (4.5%)
Proportion of patients with daytime	33/62 (53%)	38/66 (58%); p=0.62 CR vs IR

continence at completion of the study		
Proportion of patients with night-time continence at completion of the study	Data not provided. "No statistically significant difference between the treatments"	
Median change in the number of voluntary daytime voids	Data not provided. "No statistically significant difference between the treatments"	
AE= adverse events; bid= twice a day; ER= extended-release; IR= immediate release; NA= not available (either not measured or not reported); NR= not reported; qd= every day; QoL= quality of life; SAE= serious adverse events; SD= standard deviation; UTI= urinary tract infection; WDAE= withdrawals due to adverse events;		

Study	**Minassian 2007**	
Treatment	OXY ER 5-10 mg qd	OXY IR 2.5-5 mg tid
N	39	33
ITT (follow-up at 12 weeks)	N=37/39 (Efficacy)	N=28/33
All-cause mortality	NA	NA
SAE	NA	NA
WDAE	25/68	
Total Withdrawals	n=1/39 did not receive treatment; n=12/38 discontinued treatment	n=3/33 did not receive treatment; n=13/30 discontinued treatment
Quality of Life (QoL) at 12 weeks: Mean ± SD		
U-IIQ Activities	2.2 ± 1.0 (n=37)	2.1 ± 1.2 (n=28)
U-IIQ Travel	2.0 ± 1.1 (n=37)	1.9 ± 1.2 (n=28)
U-IIQ Physical activities	2.3 ± 1.3 (n=18)	1.9 ± 1.2 (n=13)
U-IIQ Feelings	2.0 ± 1.1 (n=37)	1.9 ± 1.3 (n=28)
U-IIQ Relationships	1.4 ± 0.9 (n=37)	1.5 ± 1.0 (n=28)
U-UDI	2.1 ± 1.0 (n=37)	1.7 ± 1.0 (n=28)
MMSE score Median (IQR)	30 (29-30); n=35	30 (29-30); n=2735
Cure (dryness rate)	NA	NA
Patient Perception of Improvement or Cure	NA	NA
Incontinence episodes/24 h at study end: median (IQR)	1 (0-2); n=34	0 (0-1); n=26
Urge urinary incontinence episodes	NA	NA
Median number of pads per day (IQR)	0 (0-2); n=34	0 (0-1); n=26
Nocturia	NA	NA
Total AE	19/37 (51%)	16/28 (57%)
Dry mouth	14	16
Moderate to severe dry mouth	6	2
Volume voided per micturition: median (IQR)	164 (129-187); n=34	161 (114-109); n=26
Post-void residual volume: median (IQR)	0 (0-29) mls; n=35	4 (0-87) mls; n=26
IQR= interquartile range		

Study	Versi 2000	
Treatment	OXY ER (OROS) 5-20 mg qd	OXY IR 5-20 mg qd
N	111	115
N for analysis (e.g., if per protocol)	111 (both safety and efficacy)	115 (both safety and efficacy)
All-cause mortality	0	0
SAE	0^	1^§
WDAE	3	7
Total Withdrawals	3+3+1	7+2
Quality of Life (QoL)	NA	NA
Cure (dryness rate)	NA	NA
Patient Perception of Improvement or Cure	NA	NA
Total incontinence episodes per week: Baseline mean	20.2	22.4
Total incontinence episodes per week (mean % change from baseline) at study end.	3.5 (-81%; p<0.001)	5.4 (-75%; P<0.001) (p=0.36 ER vs IR)
Urge urinary incontinence episodes per week: Baseline mean	18.6	19.8
Urge urinary incontinence episodes per week (mean % change from baseline) at study end	2.9 (-83%) p<0.001 vs. baseline	4.4 (-75%); p<0.001 vs. baseline p=0.36 ER vs IR
Nocturia	NA	NA
Total AE*	NR	NR
Total Anticholinergic AE^	70%	57% ER vs. IR NS
Dry Mouth	47.7%	59.1% (p=0.09 ER vs IR)
Volume voided	NA	NA
Urodynamics	NA	NA
ECG	3 (3%) (2 bradycardia)	1 (1%) (1 bradycardia)

AE= adverse events; bid= twice a day; CR= controlled release (=ER); ER= extended-release; IR= immediate release; NA= not available (either not measured or not reported); NR= not reported; qd= every day; QoL= quality of life; SAE= serious adverse events; SD= standard deviation; UTI= urinary tract infection; WDAE= withdrawals due to adverse events;

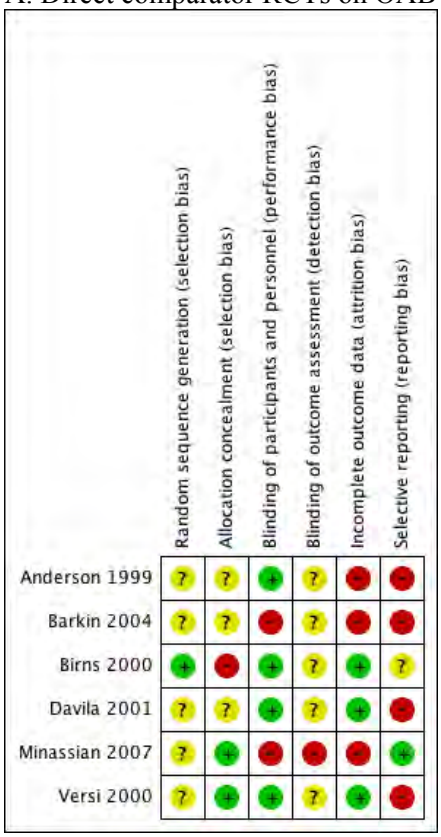
*Total AE =Proportion of patients with one or more AE; specific AE are also reported as proportion of patients experiencing the event. ^ From NDA Review 20-897;
§ 1 SAE was a small bowel obstruction in a patient with a history of a left colon resection for diverticulitis.

Study	Davila 2001	
Treatment	OXY TDS 1.3 mg/day (twice weekly)	OXY IR 2.5 mg bid to 5mg tid
N	38	38
N for analysis (e.g., if per protocol)	N=72 (Primary efficacy) N=76 for safety	
All-cause mortality	NA	NA
SAE	NA	NA
WDAE	n=1	0
Total Withdrawals	n=1 due to AE and n=1 due to personal reasons.	
Quality of Life (QoL)	NA	NA
Cure (dryness rate)	NA	NA
Visual analog scale score for efficacy (patient assessment): end of treatment	Difference of 0.1cm (p=0.9) between groups	
Visual analog scale score for efficacy (patient assessment): mean change at end of treatment	5.8 ± 4.2 cm; p< 0.0001	6.0 ± 3.3 cm; p< 0.0001
Incontinence episodes per day: Washout (baseline) mean ±SD	7.2 ± 4.5	7.2 ± 4.1
Total incontinence episodes per day: Study end (Change from washout at end of treatment) mean ±SD	2.4 ± 2.4; p<0.0001 vs baseline	2.6 ± 3.3; p<0.0001 vs baseline (P=NS TDS vs IR)
Urgency	NA	NA
Nocturia	NA	NA
Total AE	NR	NR
Erythema at patch application sites	38%^	23%^
Dry mouth	38%	94%; p<0.001
Dry mouth symptoms reported on unvalidated anticholinergic symptom questionnaires (patient assessment of symptom severity)	6% none; 26% mild; 59% tolerable; 9% intolerable	62% none; 27% mild; 11% tolerable; 0% intolerable
Treatment related AEs		
Dry mouth	15 (39%)	31 (82%)
Constipation	8 (21%)	19 (50%)
Somnolence	7 (18%)	14 (37%)
Nausea	3 (8%)	10 (26%)
Dizziness	6 (16%)	10 (26%)
Blurred vision	7 (18%)	9 (24%)
Urinary retention	9 (24%)	13 (34%)
Impaired urination	9 (24%)	9 (24%)
Palpitation	3 (8%)	5 (13%)
Bladder volume at first detrusor contraction: Washout mean ± SD	165 ± 158 mL	267 ± 187 mL
Bladder volume at first detrusor contraction: Last visit mean ± SD (change from washout)	229 ± 189 mL (+66 ± 126 mL; p=0.0055)	302 ± 198 mL (+45 ± 163 mL; p=0.1428) p=0.57 TDS vs IR
Maximum bladder capacity: Washout mean ± SD	244 ± 168 mL	342 ± 167 mL
Maximum bladder capacity: Last visit mean ± SD (change from washout)	297 ± 176 mL (+53 ± 88 mL; p=0.0011)	387 ± 162 mL (+51 ± 138 mL; p=0.0538)
Post-void residual volume: Washout mean ± SD (change at last visit)	25 ± 27 mL +16 ± 46; p=NS	41 ± 56 mL +13 ± 74; p=NS
Proportion of patients with no incontinence episodes recorded	8	10

^ summed from mild, moderate

Table 3. RCT Risk of Bias Assessment

A. Direct comparator RCTs on OAB patients



The Cochrane Risk of Bias Tool was used to assess the internal validity of individual trials as part of the quality assessment. Key elements of trial methodology and reporting are assessed, using a standardized set of criteria. If there is high risk of bias (red colour dots in the table), it is usually because of inadequate methods. If the risk of bias is "unclear" (yellow colour dots), usually the trial report did not adequately describe what was done. The green color dots represent low risk of bias.

Anderson 1999 and Versi 2000 were assessed based on information available in the FDA review as well as publication data.

B. Placebo RCTs on elderly or healthy volunteer RCTs (cognition)0

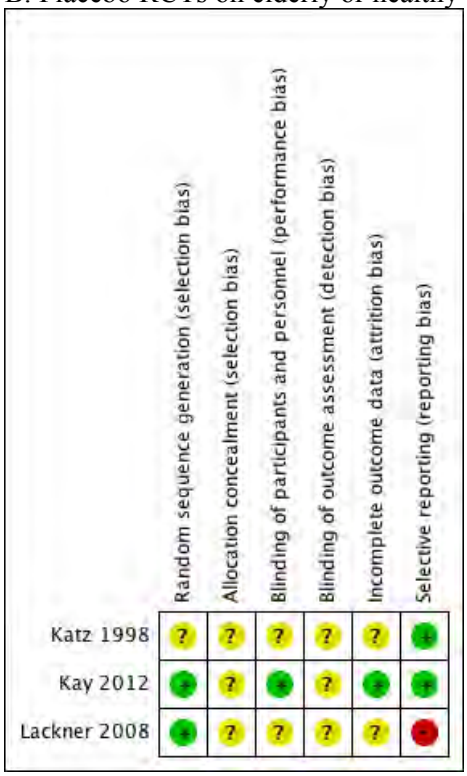


Table 4. RCT Study Characteristics: Placebo RCTs on Elderly and/or Cognition					
OAB patients					
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**Interventions**	**Outcomes Assessed**
Lackner 2008 U.S. N=50 ALZA Ortho-MacNeil	MC (12 nursing home facilities), DB, placebo-controlled RCT Randomization stratified according to cognition: MMSE 5-10 or 11-23 Duration 4 weeks Equivalence RCT (based on a 2-point or less difference in mean change in CAM score	Females ≥ age 65; resident of nursing home for ≥3 mo (not subacute facility, transitional care or rehabilitation unit); MMSE 5-23; global deterioration scale score of 3-6; urinary incontinence; ≥ 1 symptom or sign of urge incontinence, defined as ≥ 4 micturitions or wet checks or request to toilet within an 8-hour period of prompted voiding schedule on 2 consecutive days; nocturia or nocturnal enuresis > 2 per night; staff observation or incontinence on way to toilet or resident reports urgency or medical record documentation of detrusor overactivity or urgency; ability to swallow medication intact; medication adherence rate ≥ 80% during week before screening; <u>Exclusions:</u> terminal illness; bed-bound. Non-communicative; delirium; Lewy body dementia; history of ≥ 3 UTI in prior year or current UTI; post void residual volume ≥ 150 mls; urethral diverticulum; bladder stone; genitourinary surgery within past 6 mo; hepatic disease; severe CVS disease; myasthenia gravis; spinal cord injury; bowel movement M every	Mean age 88.6 (SD 6.2) years MMSE 11-23: N=37 MMSE 5-10: N=13 Mean MMSE14.5 ± SD 4.3 White non-Hispanic 49 1 Hispanic	Oxybutynin ER (Ditropan XL) 5 mg qd N=26 Placebo N=24	• Monitoring: weekly for AE, UTI and urinary retention (using ultrasound); • Confusion Assessment Method (CAM) Algorithm; mean change in CAM scores from baseline (primary outcome) Secondary: • Delirium (presence/absence) based on CAM • MMSE • Severe Impairment Battery • Brief Agitation Rating Scale • AE based on participant self-report; staff/providers; progress notes; checklist and post void residual measurement days 1, 3, 7, 14, 21 and 28. • Falls in prior 3 mo, during and 3 mo after trial

		3 days; history of gastrointestinal obstruction or decreased motility; current drug therapy for urinary incontinence; current use of acetylcholinesterase inhibitor or bisphosphonate; cholinomimetic drug, diphenhydramine or gastrointestinal antispasmodic within 2 weeks, investigational drug			

CAM= Confusion Assessment Method algorithm; mo= months

Study Country N Sponsor	**Design**	**Inclusion Criteria** **Exclusions**	**Baseline Characteristics**	**Interventions**	**Outcomes Assessed**
Kay 2012 U.S. N=176 screened; N=153 randomized (n=1 took no study medication) Watson Laboratories	MC (5 centres), DB placebo- and active-controlled phase I RCT. Day 1: Baseline evaluation Days 2-7: Treatment period Day 8: Observed dosing; participants received only two doses of oral test product. Assessment at screening, day 1 and day 8. Efficacy population: All randomized participants who received at	Study participants were **healthy** men and women aged 60–79 years with English as their primary language. <u>Exclusions:</u> contraindications or hypersensitivity to oxybutynin treatment, use of medications within 2 weeks before screening that are known to have anticholinergic properties or to affect cognition or have been identified as cytochrome P450 (CYP) 3A4 inhibitors, dementia score of ≤ 27 on the Mini-Mental State Examination, Name–Face Association	Safety population (n=152): 65% female, 35% male Mean age: OXY Gel 68.2 (SD 5.9) IR 69.0 (SD 5.9) Placebo: 67.3 (SD 5.5) 92% White; 6% Black; 2% Other NFAT Delayed Recall Score (p=0.366 ANCOVA): OTG 7.63 (SD 2.87) IR 8.43 (2.80) Placebo 7.77	OXY Gel 1g (100mg oxybutynin) once daily (plus placebo capsules); instructed to apply gel each morning to rotating sites on the abdomen, upper arm/shoulder or thigh, N=49 OXY-IR 5mg t.i.d (plus placebo gel); No special instructions were given to patients regarding timing of doses with respect to meals, N=52	Cognitive and psychomotor functions: • Psychologix Test Battery: - NFAT; - Misplaced Objects Test - Face Recognition Test • Cogscreen Test Battery: - Matching to sample test; - Visual Sequence Comparison Test; - Symbol Digit Coding Test; - Divided Attention Test-Visual Monitoring Response Time Specific outcomes: • NFAT delayed recall test vs. placebo = (using a 30-minute interval between acquisition and assessment) • Delayed recall scores for the First–Last Name Association Test, Misplaced Objects Test, and HVLT-R; • HVLT-R: measures of retention, delayed recognition, and learning ; • Immediate recall measures of learning from the NFAT and the First–Last Name Association Test;

	least one dose of study drug and provided data at baseline and day 8 for a specific end point were included in the analysis for that end point. Modified ITT: Participants with comparative data for the primary analysis N=149 Safety population: all randomized participants who took at least one dose of study medication N=152 (1 did not receive medication)	Test (NFAT) Delayed Recall score of ≤ 2 at baseline, and depression score of ≥ 9 on the Geriatric Depression Scale. Pre- or perimenopausal women also were excluded from study participation.	(3.22)	Placebo gel plus placebo capsules, N=51	• Recognition memory score from the Facial Recognition Test responses; • Additional measures of visual attention (Matching to Sample test), information processing speed (Symbol Digit Coding), psychomotor reaction time (Divided Attention Visual Monitoring), and self reported memory complaints (MAC-S). • Proportion of participants who had a decline of $\geq$ 4 points in NFAT delayed recall score • Vital signs • AE • Clinical laboratory tests

Cognition RCTs on Healthy Volunteers					
Study Country N Sponsor	**Design**	**Inclusion Criteria Exclusions**	**Baseline Characteristics**	**Interventions**	**Outcomes Assessed**
Katz 1998 U.S. N=12 National Institutes of Aging	DB, SC crossover placebo-controlled RCT Random regression analyses Also conducted repeated measures analysis of variance	≥ age 65 Medically stable euthymic (Geriatric Depression Scale ≤ 13) ≥ 8 years of school English language by age 6 <u>Exclusions:</u> History of CNS disease, alcohol or substance abuse within past 5 years; mental retardation, schizophrenia, bipolar or psychotic disorders; current evidence or a history of diseases leading to increased risk of anticholinergic medications; medications that are centrally acting or capable of causing drug-related cognitive impairment	7 men and 5 women mean age 69 (SD 4) (range 65-76) Average education 13.7 years cognitively intact, no depression	Oxybutynin IR 5 mg Oxybutynin IR 10 mg Diphenhydramine 50 mg Placebo	Interviewer-administered tests: • Buschke Selective Reminding Test (verbal learning and memory), • Digit Span (attention and short-term verbal memory) • Verbal Fluency-Letters (word production) • Tralmaking Parts A and B (attention and concentration and cognitive flexibility (B) • Digit Symbol Substitution (incidental memory) Computerized tests: • Finger tapping (motor speed) • Reaction Time • (reaction speed to simple stimulus) • Continuous Performance (vigilance and concentration) • Contingent Continuous Performance Task (speed of information processing) • Pattern Recognition (spatial perception)

Table 5. RCT Outcomes: Healthy Volunteer Cognition RCTs				
Study	**Kay 2012**			
Treatment	**OXY Gel 1 g qd**	**OXY IR 5 mg tid**	**Placebo**	**P value between groups***
N randomized	N=153			
Safety population	N=152			
Efficacy analysis (modified ITT)	n=49/49	n=49/52	n=51/51	
All-cause mortality	0	0	0	
SAE	0	0	0	
WDAE	0	3/52 (5.8%)	0	
Total Withdrawals	0	3/52 (5.8%)	0	
Day 8 Cognitive Function: Number of correct responses (LSM ± SD)				
- Name–Face Association Delayed Recall	7.02 ± 3.17	7.06 ± 3.68	7.77 ± 3.71	0.27
- Name–Face Association Learning Trial 1	4.14 ± 1.95	4.53 ± 2.62	4.72 ± 2.80	0.40
- Name–Face Association Learning Trial 2	7.81 ± 3.08	8.24 ± 3.36	8.65 ± 3.55	0.21
- First–Last Name Association Learning Trial 5	2.92 ± 1.58	3.44 ± 1.93	3.30 ± 1.76	0.21
- First–Last Name Association Delayed Recall	2.24 ± 1.34	2.63 ± 1.86	2.65 ± 1.71	0.29
- Facial Recognition, total correct	20.16 ± 3.43	20.64 ± 3.48	20.67 ± 4.11	0.64
- Misplaced Objects, correct first try	13.64 ± 3.03	12.38 ± 3.48	13.16 ± 3.44	0.03
- Misplaced Objects, change from baseline (Mean	1.00 ± 2.25	-0.29 ± 2.97	0.67 ± 2.36	
Reliable change scores: Proportion of subjects who had a decline of > 4 points in NFAT Delayed Recall	12.2%	14.3%	11.8%	0.923^
Day 8 Cognitive Function: Test score (LSM ± SD)				
- HVLT-R Total Free Recall	27.08 ± 4.33	27.22 ± 5.03	28.20 ± 5.09	0.34
- HVLT-R Delayed Recall	9.90 ± 1.98	10.25 ± 1.72	9.83 ± 2.15	0.39
- MAC-S Questionnaire	36.14 ± 5.74	36.30 ± 4.64	36.10 ±.97	0.94
Hopkins Verbal Learning Test–Revised, HVLT-R				
Total Free Recall: Mean change from baseline (SD)	-0.5 ± 5.0; p=0.475	-1.8 ± 3.7; p=0.002	-1.1 ± 4.1; p=0.067	
Total Free Recall: Reliable change - (decline in score ≥6 points	n= 5 (10.2%)	n=10 (20.4%)	n=6 (11.8%)	
Delayed Free Recall: Mean change from baseline (SD)	-0.3 ± 1.7; p=0.322	-0.7 ± 1.5; p=0.003	-0.5 ± 1.8; p=0.059	
Total AE	NR	NR	NR	
Dry Mouth	3 (6.1%)	38 (73.1%)	4 (7.8%)	
Headache	0	4 (7.7%)	2 (3.9%)	
Nausea	0	4 (7.7%)	0	
Constipation	0	3 (5.8%)	0	
Cough	0	3 (5.8%)	0	
Dizziness	0	3 (5.8%)	0	
Nasal dryness	0	3 (5.8%)	0	
Urinary hesitation	0	3 (5.8%)	0	
Dry eye	0	2 (3.8%)	0	
Dry throat	0	2 (3.8%)	0	
Urine flow decreased	0	2 (3.8%)	0	

Vital Signs	"No clinically significant changes"
Laboratory test	"No clinically significant changes"

* p-Value determined by all-group analysis of covariance unless otherwise specified; No statistically significant differences between active treatments and placebo were observed in pairwise comparisons; ^ Pearson's Chi-squared test **HVLT-R** = Hopkins Verbal Learning Test–Revised; **LSM**= least squares mean; **MAC-S** =Memory Assessment Clinics Self-Report; **SD**= standard deviation.

Table 6. RCT Study Characteristics Tolterodine ER vs. Tolterodine IR					
Study Country N Sponsor	**Design**	**Inclusion criteria Exclusions**	**Baseline Characteristics % of participants**	**Interventions**	**Outcomes Assessed**
van Kerrebroeck 2001 14 countries (Europe, North America, Australasia) N=1529 Pharmacia	DB placebo-controlled RCT 12 weeks duration 1-2 week wash-out/run-in phase 7 day bladder diary ITT with LOCF Baseline and 12 week measurements	Men and women with urinary frequency ≥ 8 micturitions every 24 h, urge incontinence (≥5 episodes per week) and symptoms of OAB ≥ 6 months estrogen treatment allowed if initiated ≥ 2 months pre study. Exclusion criteria: stress incontinence; daily urine vol > 3L; contraindications to antimuscarinic drugs; significant hepatic or renal disease (biochemical markers 2X upper limit of normal); symptomatic or recurrent UTI, interstitial cystitis, hematuria or BOO; current electrostimulation or bladder training; catheterization; Drugs that inhibit CYP 3A4 isozymes not allowed;	81% female, 19% male 53-54% had prior treatment for OAB, 41% of whom had poor response 97% had ≥ 5 incontinence episodes per week baseline incontinence episodes per week: Tol ER: 22.1 (0-168.0) Tol IR:23.2 (0-168.0) Placebo: 23.3 (0-168.0)	TOL IR 2 mg bid N=514 TOL ER4 mg once daily, N=507 Placebo, N=508	• Incontinence episodes per week: change from baseline; • Number of incontinence episodes per week • Micturitions every 24 hours • Volume voided per micturition • Number of pads per 24 h • KHQ* • SF-36* • Subject's perception of treatment benefit* • WDAE, SAE, some specific AE • Intensity of dry mouth (mild, moderate, severe) • Clinical chemistry and Hematology • Subset (N=154) 65 years or older underwent ECG
*According to FDA review NDA 21-228					
AE= adverse events; **BOO**= bladder outlet obstruction; **CR**= controlled release; **d**= day; **DB**= double-blind; **DEO**= N-desethyoxybutynin; **gi**= gastrointestinal; **IQR**= interquartile range; **IR**= immediate release; **KHQ**= King's Health Questionnaire; **MMSE**= mini mental status examination; **NR**= not reported; **OXY**= oxybutynin; **q**= every; **SD**= standard deviation; **UI**= urinary incontinence; **U-IIQ**= urge incontinence impact questionnaire; **U-UDI**= urge-urinary distress inventory; **UUI**= urgency urinary incontinence; **VAS**= visual analogue scale;					

Table 7. RCT Outcomes: Tolterodine ER vs Tolterodine IR			
Study	van Kerrebroeck 2001		
Treatment	Tol ER 4 mg	Tol IR 2 mg bid	Placebo
N	507	514	508
Safety analysis	505	512	507
Mortality	1	0	1
SAE	7	12	18
WDAE	27 (5%)	28 (5%)	33 (6%)
QoL	NA		
Cure (Dryness Rate)			
Incontinence episodes per week. Mean (SD) change from baseline	-11.8(17.8)/week	-10.6 (16.9)/week	-6.9 (15.4)/week
No. of pads per 24 h	-0.5 (1.4)	-0.5 (1.8)	-0.2 (1.4)
Urgency	NA		
Nocturia	NA		
Total AE	NA		
Dry mouth	118 (23%)	156 (30%)	39 (8%)
Abnormal vision	6 (1%)	4 (1%)	2 (0.5%)
Ocular dryness	17 (3%)	12 (2%)	10 (2%)
dyspepsia	15 (3%)	16 (3%)	7 (1%)
Nausea	7 (1%)	10 (2%)	10 (2%)
Constipation	30 (6%)	35 (7%)	22 (4%)
Diarrhea	10 (2%)	16 (3%)	11 (2%)
Abdominal pain	19 (4%)	13 (3%)	8 (2%)
Flatulence	10 (2%)	14 (3%)	9 (2%)
Headache	32 (6%)	19 (4%)	23 (5%)
Dizziness	11 (2%)	9 (2%)	5 (1%)
Somnolence	14 (3%)	13 (3%)	9 (2%)
fatigue	11 (2%)	6 (1%)	4 (1%)
Insomnia	7 (1%)	2 (0.5%)	9 (2%)
UTI	16 (3%)	13 (3%)	20 (4%)
Dysuria	5 (1%)	8 (2%)	1 (0.5%)
Peripheral edema	7 (1%)	7 (1%)	4 (1%)
Mean volume voided per micturition, change (SD) from baseline	+34 (51)	+29 (47)	-6.9 (15.4)
Urodynamics	NA		

Appendix K. Additional Meta-Analyses
Pooled Extended-Release Formulations of Oxybutynin (Oral or Transdermal) vs. Oxybutynin IR

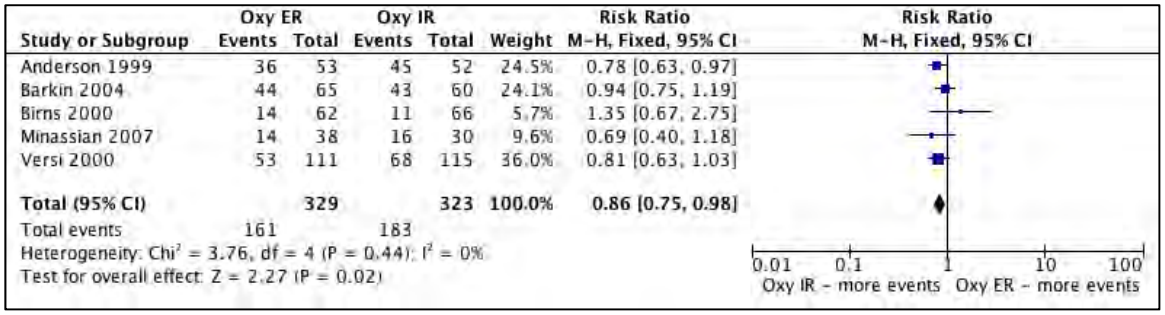


Figure 1. Dry mouth: extended-release (oral or transdermal) vs. oxybutynin IR

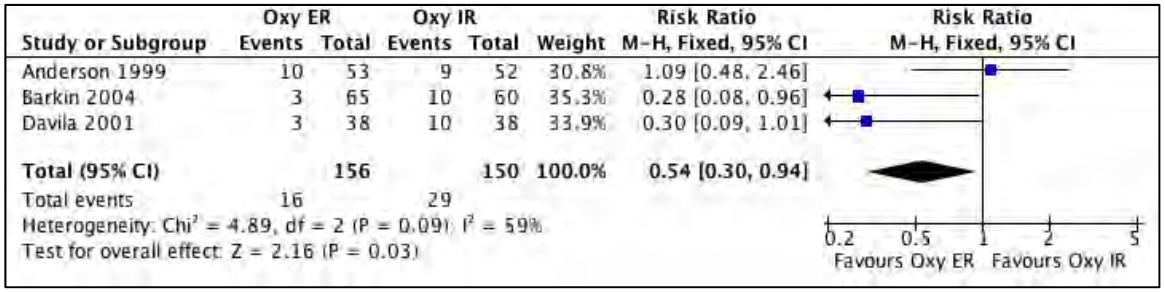


Figure 2. Nausea: oxybutynin extended-release (oral or transdermal) vs. oxybutynin IR

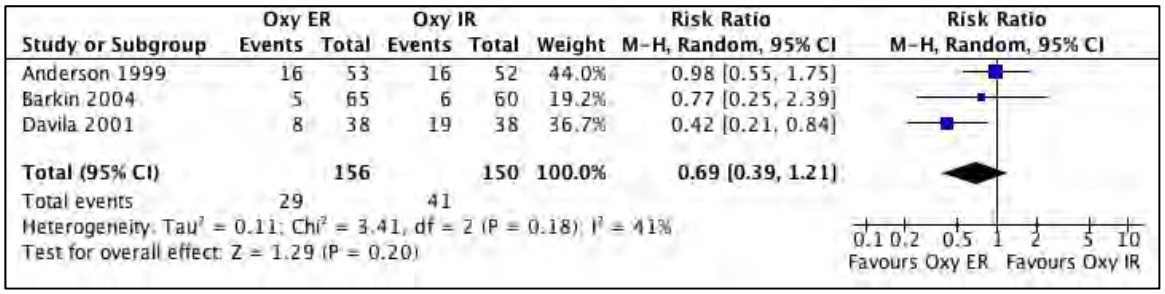


Figure 3. Constipation: oxybutynin extended-release (oral or transdermal) vs. oxybutynin IR

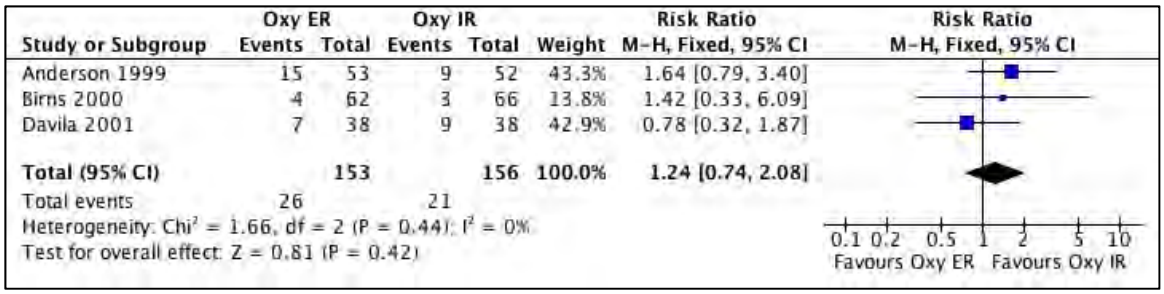


Figure 4. Blurred vision: oxybutynin extended-release (oral or transdermal) vs. oxybutynin IR

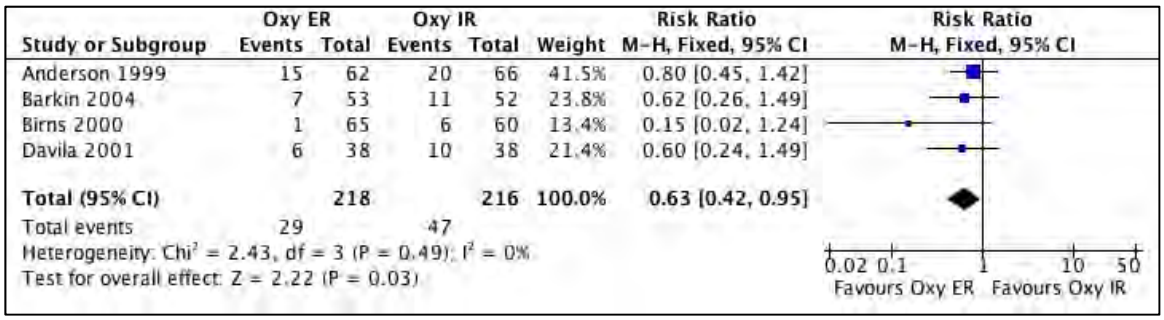


Figure 5. Dizziness: oxybutynin extended-release (oral or transdermal) vs. oxybutynin IR

Appendix L. Canada Vigilance Adverse Reaction Reports - Oxybutynin

Nervous system disorders – Serious Cases, N=34 aged 18 years or older
Ditropan or unspecified (IR or ER)*

- Agitation/confusional state/hallucination/syncope
- Asthenia/ataxia/confusional state
- Arrhythmia/syncope – (identified in nervous system but likely cardiac)
- Dizziness/dry mouth/fatigue/headache/edema peripheral/somnolence
- Aphasia/irritability/insomnia/thirst
- Asthenia/confusional state/somnolence
- Dizziness/hypotension/drug interaction (on beta blocker)
- Hepatic function abnormal/LOC/renal impairment
- Convulsions/muscle spasm
- Convulsion
- Convulsion/drug level decreased (on anticonvulsants)
- Agitation/confusional state/hallucination/hypomagnesaemia/insomnia/sedation/tremor
- Convulsion
- Agitation/drug interaction/speech disorder
- Dysgeusia/abdominal pain/diarrhea/drug ineffective/abnormal feces/rectal tenesmus/dry throat
- Feeling cold/hyperhidrosis/tremor
- Hallucination/respiratory disorder/tongue discoloration/tremor
- Dry eye/headache/photosensitivity reaction
- Depressed level of consciousness/hypokinesia
- Aggression/balance disorder/confusional state/hallucination, visual
- Dizziness/dry mouth/eye disorder/influenaz-like syndrome/somnolence
- BP increased/CVA/confusional state/fatigue/speech disorder/visual impairment
- Cerebrovascular accident/drug inefective/drug interaction
- Balance disorder/confusional state/cyanosis/erythema/fall/memory impairment/feeling abnormal/swelling face/pupillary disorder/eye discharge
- Feeling abnormal/erythema/headache/pruritus
- Burning sensation/dry mouth/erythema/pruritus/xeroderma
- Dizziness/HR increased/nausea/palpitations
- Speech disorder/cough/dyspnea/fatigue
- Anticholinergic syndrome

*Type of oral formulation could not be determine in the majority of reports because necessary details were not provide; majority were listed as Ditropan but dosing regimens did not clearly indicate IR.

Oxybutynin TDS (Oxytrol)

- Dizziness/fatigue/headache/leukemia/leucopenia/
- Amnesia/back pain/fall/spinal fracture/
- Amnesia/confusional state/dissociation/somnolence

Oxybutynin Gel (Gelnique)

- Angina/hypoaesthesia/drug effect incomplete
- Dizziness/orthostatic hypotension

Psychiatric disorders –Serious Cases, N=29 aged 18 years or older
Ditropan or unspecified (IR or ER)*

Aggression/confusional state
Aggression/agitation/insomnia/nervousness
Depression/dry mouth/malaise
Depression/psychotic disorder
Euphoric mood/therapeutic response unexpected
Bipolar disorder/abdominal discomfort/condition aggravated/drug ineffective/infection/micturition urgency/pelvic pain
Depression
Depression/dry mouth/dysuria/mouth ulceration/psychotic disorder/self-injurious ideation/skin exfoliation
Drug interaction/impaired self-care/UTI
Completed suicide (XL-ER) overdose
Completed suicide/feeling abnormal/thinking abnormal – 38 year old male (death)
Anxiety/palpitations

* Most reports did not clearly specify which formulation.

Cardiac – Serious cases

- Arrhythmia/syncope (also reported in nervous system disorders) (Ditropan)
- Cardiac failure, congestive/thirst (Ditropan)
- Heart rate irregular/tachycardia (Ditropan XL)
- Blood creatinine increased/cyanosis/diarrhea/dyspnea/nausea/palpitations/tachycardia (Uromax)
- Anxiety/palpitations (also reported in psychiatric disorders) (Oxybutynin generic)
- Balance disorder/confusional state/cyanosis/erythema/fall/feeling abnormal/memory impairment/swelling face/other (also reported in nervous system disorders) (Oxybutynin generic)
- Dizziness/heart rate increased/nausea/palpitations (Oxybutynin NOS)
- Angina pectoris/chest pain/drug effect incomplete/hypoesthesia (also reported in nervous system disorders) (Oxybutynin gel)

NOS= not otherwise specified