

Final

A Review of Studies Examining the Cost Effectiveness of Pharmacological Treatments for Overactive Bladder in Adults with Symptoms of Urinary Frequency, Urgency and Urge Incontinence

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Executive Summary

A review of studies examining the cost effectiveness of pharmacological treatments for overactive bladder in adults with symptoms of urinary frequency, urgency and urge incontinence.

Introduction: This report is a review of studies examining the cost effectiveness of anticholinergics in the treatment of overactive bladder. The medications examined within the review include: fesoterodine, oxybutynin immediate release (IR), oxybutynin extended release (ER/XL), oxybutynin controlled release (CR), oxybutynin transdermal patch, oxybutynin topical gel, tolterodine IR, tolterodine ER, solifenacin, darifenacin and trospium.

Research questions:

What is the comparative cost effectiveness of the drugs under review as first line therapy versus oxybutynin IR formulation from a Canadian perspective?

What is the cost effectiveness of the drugs under review as second line therapy for overactive bladder in those who have either failed or are intolerant to oxybutynin IR ?

With respect to the medications under review, do they differ in their cost effectiveness?

What recommendation regarding funding within the BC Pharmacare system does this evidence support?

Search strategy and findings:

A comprehensive search of the medical literature was conducted including the following databases: Medline, Embase, Cochrane and NHS EED. From this search, 17 studies met the inclusion criteria for the review. Some studies were useful in addressing more than one of the research questions. Six studies compared the newer anticholinergics with oxybutynin IR and may therefore be helpful in answering the first research question. Only one study examined the cost effectiveness of a newer anticholinergic as second line therapy in those who discontinue therapy with oxybutynin IR. Five studies compared the cost effectiveness of the newer anticholinergics with either placebo or no treatment. Lastly, the relative cost effectiveness of the newer anticholinergics was compared in 12 studies.

Overall summary:

In general, the literature examining the cost effectiveness of the newer anticholinergics in the treatment of overactive bladder is of poor quality, with almost all studies explicitly citing financial support from the pharmaceutical industry. There are a number of common limitations that are persistent in much of the literature which significantly reduce its usefulness in aiding in decision making. Following is a brief summary of these issues.

In most cases, estimates of the effect of the medication on quality of life and utilities are not derived from direct measurement within clinical trials, but rather, are extrapolated from a correlation of clinical symptoms (micturitions (number of voids) and leakages) with a Euroqol value measured at a single time-point, based on a small study conducted in 1997. The questionable validity of an assumed linear relationship between symptoms and quality of life and the lack of evidence of a change in utility or quality of life with a change in symptoms bring into question this approach to measuring the efficacy of these medications. Additionally, this measure does not incorporate the effect of adverse effects of the medications on patient's quality of life.

Secondly, the approach to managing discontinuations within the models varies greatly from one study to another and can significantly influence the results. Issues are related to the use of clinical trial discontinuation rates, rather than "real world" database rates, the lack of accounting for different reasons for discontinuation and various assumptions regarding the costs and utilities assigned to those who discontinue therapy.

Thirdly, many of the studies include the cost of incontinence pads and appliances, which are generally not funded by the Canadian healthcare payer which may reduce the applicability of the results of these studies for the Canadian decision maker.

Finally, the handling of adverse events within the trials is generally approached through the assumption that those who experience adverse events discontinue therapy. A disutility is not applied to those who experience adverse events but remain on therapy. Given the small benefits in utility seen with these drugs, this may have a significant impact on the estimated cost effectiveness. In the majority of studies dry mouth was the only adverse event considered. Additionally, none of the studies incorporate the potential for CNS adverse effects of these drugs. In clinical practice these drugs have been associated with CNS types of adverse effects, particularly in the elderly. As cited within the clinical review, the trials examining the efficacy and safety of these drugs generally did not include frail elderly patients or those with concomitant diseases and therefore the applicability of the cost effectiveness studies for these patients is limited. These weaknesses should be kept in mind when using this literature to make funding decisions.

With respect to the first research question regarding the cost effectiveness of the newer anticholinergic agents as compared with oxybutynin IR in the treatment of overactive bladder, six studies were identified which addressed this question. Although all the evidence had significant weaknesses, a study by Cardoza et al from a UK perspective is likely to provide the best available estimate of the cost effectiveness. They found that oxybutynin IR was the least costly treatment. Solifenacin was more effective than oxybutynin IR, but also more costly with an estimated ICER of £80,000/QALY (~\$164,000 CAN). Other treatments including, fesoterodine, propiverine ER, tolterodine IR and tolterodine ER, were dominated by solifenacin.

With regards to the second research question, examining the cost effectiveness of the newer anticholinergics as a second line treatment in OAB after either failure with or intolerance to oxybutynin IR there was only one study which specifically addressed this question. The study by O'Brien et al, from a Canadian perspective compared the cost effectiveness of tolterodine IR with that of no

treatment in patients who had discontinued oxybutynin IR therapy. The ICER was estimated to be \$9,982/QALY for oxybutynin IR followed by tolterodine IR as compared with oxybutynin IR followed by no treatment. It is likely that the true ICER is higher than this estimate as a number of assumptions within this analysis serve to optimize the results for tolterodine IR.

There are five studies which compared the cost effectiveness of the newer anticholinergics with either no treatment and/or placebo. Caution should be exercised in using these results to inform decisions about the cost effectiveness of these medications as second line therapy, given that none of the studies were conducted in the population of interest (those who had discontinued oxybutynin IR). Consequently, they are likely to provide an overestimate of the cost effectiveness of these medications. Additionally, there were many assumptions within these analyses relating to estimates of efficacy, costs and utility derivation which serve to optimize the cost effectiveness estimates for the newer anticholinergics. Correcting these assumptions would likely lead to higher cost effectiveness ratios for the newer anticholinergics. Although difficult to predict, given the lack of appropriate data, it is likely that the ICER would be greater than \$50,000/QALY; therefore, at a minimum, a price reduction for the newer anticholinergics would be required for these agents to have the potential of being cost effective.

Conclusions:

Overall, the evidence available for examining the cost effectiveness of these medications is generally of poor quality. As is evident from the conclusions of the clinical review, evidence of meaningful differences in efficacy and adverse events of these medications is limited and therefore makes estimation of the comparative cost effectiveness challenging.

The evidence available supports the cost effectiveness of oxybutynin IR as first line therapy in the treatment of overactive bladder. Many patients, however, withdraw from therapy due to the rate of dry mouth with this treatment. As stated within the clinical review, the risk of dry mouth is likely to be lower with extended release formulations.

With respect to the cost effectiveness of the newer anticholinergics as second line therapy after discontinuation of oxybutynin IR due to either lack of response or adverse effects there are no well-designed economic studies which can help to answer this question. The available evidence suggests that at their current price, these agents are unlikely to be considered cost effective second line therapies as compared with no treatment or placebo.

With respect to the relative cost effectiveness of the newer anticholinergic medications there appears to be inadequate evidence to support conclusions regarding differences in cost effectiveness.

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List of Abbreviations

CAD – Canadian dollars

CDR – Common Drug Review

CNS – central nervous system

CR – controlled release

ER – extended release

GP – general practitioner

ICER – incremental cost effectiveness ratio

ICUR – incremental cost utility ratio

IR – immediate release

mg - milligrams

n/a – not applicable

NHS EED – National Health Service Economic Evaluation Database

NICE – National Institute for Health and Clinical Excellence

OAB – overactive bladder

QALY – quality adjusted life year

SEK – Swedish Krona

SF-36 – Short Form Health Survey

UTI – urinary tract infection

XL – extended release

XR – extended release

Title: A review of the cost effectiveness of pharmacological therapies for overactive bladder, urge and mixed urinary incontinence

1. REQUEST:

To review the cost effectiveness studies examining antimuscarinic treatments for overactive bladder with symptoms of urinary frequency, urgency, or urge incontinence, or any combination of these symptoms. To provide a recommendation regarding a drug coverage strategy for those who cannot tolerate and/or have insufficient response to oxybutynin IR, based on the findings of the review.

2. RESEARCH QUESTION(S):

Currently, the BC Ministry of Health provides Regular Benefit coverage for oxybutynin IR. Other medications under consideration, for which coverage is not currently provided include: other formulations of oxybutynin (ER, CR, transdermal patch, topical gel), fesoterodine, tolterodine (IR and ER), solifenacin, darifenacin and trospium. This review is focused on summarizing and critiquing the cost effectiveness literature with respect to the following three questions:

1. What is the cost effectiveness of the medications under consideration relative to oxybutynin IR (i.e. as first line therapy)?
2. What is the cost effectiveness of these medications when used as second line therapy in patients who are either intolerant or who have not responded adequately to a trial of oxybutynin IR?
3. When choosing between the medications under consideration, what is the comparative cost effectiveness of these medications? (Appendix A)

3. SEARCH STRATEGY AND SEARCH FINDINGS

a) SEARCH STRATEGY

A search of the medical literature from 1948 to present in Medline (indexed, in-process and other non-indexed), Embase, Cochrane database, NHS EED was conducted in order to capture all relevant literature based on the NHS EED recommended search strategy. Key search words included, "economics", "costs", "cost", "costly", "price", "pricing", "pharmacoeconomics", "expenditure", "value", "budget", "oxybutynin", "fesoterodine", "tolterodine", "solifenacin", "darifenacin", "trospium", "overactive bladder", "urge incontinence", "urinary frequency", "urinary urgency", and "incontinence". In addition, the reference lists of retrieved studies were hand searched.

a. SEARCH FINDINGS

Number of studies identified.

Two reviewers (KC and DC) independently reviewed the literature searches in order to identify potential articles for inclusion within the critical appraisal. Any disagreements were resolved through consensus. A total of 23 studies were identified for potential inclusion within the report.

Number of studies included and excluded and reason for exclusion.

The 23 potential studies identified during the literature review were reviewed by two reviewers (KC and DC). Of the 23 studies, the seventeen studies which addressed the objectives of the review were selected for inclusion. Some studies addressed more than one objective; consequently, there were six studies which addressed the first objective, six studies that addressed the second objective, and 12 studies that addressed the comparative cost effectiveness of the newer anticholinergics. Those studies that were not included within the review along with the reasons for exclusion are detailed in Table 1.

Table 1. Excluded Studies

Study Reference	Reason for Exclusion
Bolge SC, Cerulli A, Kahler KH et al. Impact of successful treatment of overactive bladder on health care resource use and productivity. <i>Drug Benefit Trends</i> 2006;18:244-255.	Cost and resource study
Getsios D, El-Hadi W, Caro I et al. Pharmacological management of overactive bladder. A systematic and critical review of published economic evaluations. <i>Pharmacoeconomics</i> 2005;23(10):995-1006.	Systematic review
Hashim J, Abrams P. Drug treatment of overactive bladder. Efficacy, cost and quality-of-life considerations. <i>Drugs</i> 2004;64(15):1643-1656.	Review article
Reeves P, Irwin D, Kelleher C et al. The current and future burden and cost of overactive bladder in five European countries. <i>Europ Assoc Urol</i> 2006;50:1050-1057.	Cost study
Siddiqui NY, Amundsen CL, Visco AG et al. Cost-effectiveness of sacral neuromodulation versus intravesical botulinum A toxin for treatment of refractory urge incontinence. <i>J Urol</i> 2009;182:2799-2804.	Excluded treatment
Verheggen BG, Lee R, Lieuw On MM et al. Estimating the quality-of-life impact and cost-effectiveness of alpha-blocker and anti-muscarinic combination treatment in men with lower urinary tract symptoms related to benign prostatic hyperplasia and overactive bladder. <i>J Med Econ</i> 2012;15(3):586-600.	Wrong patient population

b. INCLUDED STUDIES

The following is a listing of the studies included within the review.

Comparative studies versus oxybutynin IR

Armstrong EP, Malone DC, Bui CN et al. Cost-effectiveness analysis of anti-muscarinic agents for the treatment of overactive bladder. *J Med Econ* 2012;15(Suppl S1):35-44.

Cardozo L, Thorpe A, Warner J et al. The cost-effectiveness of solifenacin vs fesoterodine, oxybutynin immediate-release propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK National Health Service. *BJU Intern* 2010;106:506-514.

Guest JF, Abegunde D, Ruiz FJ. Cost effectiveness of controlled-release oxybutynin compared with immediate-release oxybutynin and tolterodine in the treatment of overactive bladder in the UK, France and Austria. *Clin Drug Invest* 2004;24(6):305-321.

Herschorn S, Vicente C, Piwko C. Canadian cost-effectiveness analysis of solifenacin compared to oxybutynin immediate-release in patients with overactive bladder. *J Med Econom* 2010;13(3):508-515.

Hughes DA, Dubois D. Cost-effectiveness analysis of extended-release formulations of oxybutynin and tolterodine for the management of urge incontinence. *Pharmacoeconomics* 2004;22(16):1047-1059.

Nilsson FOL, Linner L, Samuelsson E et al. Cost-effectiveness analysis of newer anticholinergic drugs for urinary incontinence vs oxybutynin and no treatment using data on persistence from the Swedish prescribed drug registry. *BJU Intern* 2011;110:240-246.

Cost effectiveness of second line treatment

O'Brien BJ, Goeree R, Bernard L et al. Cost-effectiveness of tolterodine for patients with urge incontinence who discontinue initial therapy with oxybutynin: A Canadian perspective. *Clin Therap* 2001;23(12):2038-2048.

Comparative studies versus placebo to no treatment

Hakkaart L, Verboon P, Phillips R et al. The cost utility of solifenacin in the treatment of overactive bladder. *In Urol Nephrol* 2009;41:293-298.

Kobelt G, Jonsson L, Mattiasson A. Cost-effectiveness of new treatments for overactive bladder: The example of tolterodine, a new muscarinic agent: A Markov model. *Neurourol Urodynam* 1998;17:599-611.

Milsom I, Axelsen S, Kulseng-Hansen S et al. Cost-effectiveness analysis of solifenacin flexible dosing in patients with overactive bladder symptoms in four Nordic countries. *Acta Obstetrica et Gynecologica* 2009;88:693-699.

Nilsson FOL, Linner L, Samuelsson E et al. Cost-effectiveness analysis of newer anticholinergic drugs for urinary incontinence vs oxybutynin and no treatment using data on persistence from the Swedish prescribed drug registry. *BJU Intern* 2011;110:240-246.

Pradelli L, Iannazzo S. Solifenacin in the treatment of overactive bladder syndrome in Italian patients: pharmacoeconomic evaluation. *J Med Econom* 2009;12(1):25-35.

4. SUMMARY AND CRITICAL APPRAISAL OF INCLUDED STUDIES:

The following sections provide a summary of the cost effectiveness studies comparing the newer anticholinergics with oxybutynin IR, the newer anticholinergics as second line therapy and the newer anticholinergics versus placebo or no treatment. The comparative cost effectiveness of the newer anticholinergics is reviewed within Appendix A. For each study a brief summary of the methodology and results is provided, followed by a critique of the paper to assist in assessing its value in decision making. However, as many of the studies suffer from the same limitations, a discussion of the persistent issues is provided below and should be kept in mind when evaluating all of the literature.

Issues to consider in examining the cost effectiveness literature for overactive bladder include the derivation of utility values, handling of discontinuation rates, the resource use and cost of incontinence pads, handling of adverse events and the sponsorship of the trials.

4.1 General Common Issues

Utility Value Derivation

The large majority of studies within this review based their utility values on a paper by Kobelt et al published in 1997. (Kobelt 1997) The paper examined three different outcome measures for assessing the burden of illness of urge incontinence in patients; however, the details of the study design and results are very limited within the published paper. The willingness-to-pay for a reduction in micturitions (urinary voids) and leakages was studied within a Swedish population and correlations between these two clinical measures and quality of life scores derived using the SF-36 and the EuroQol were also assessed within a Swedish and North American population, respectively.

Based on the Swedish willingness-to-pay study, the authors reported that patients were willing to pay 466 SEK per month (~\$75/month CAD) for a 50% reduction in symptoms and 240 SEK per month (~\$38/month CAD) for a 25% reduction in symptoms. In interpreting the results of this study one should consider the potential for “isolation bias” which is inherent in willingness-to-pay studies. This refers to the fact that in isolation, when asked only about the improvement of symptoms, an individual may be willing to pay a set amount; however, if this is coupled with information relating to where this money may come from, for example, an increase in taxes, or with multiple treatment options for various diseases, the willingness to pay often decreases.

In the second North American study reported in the Kobelt paper the baseline score for micturitions and leakages in a sample of patients with OAB was correlated with the SF-36 score in five of the eight domains; however, the 12 week score after receiving treatment (n=244) or placebo (n=106) was correlated in only three of the eight domains. Furthermore, the change in symptoms with treatment was correlated in only two of the eight domains. The correlation coefficients were not reported, only the p values, so it is impossible to determine the extent of effect of symptoms on these domains. This provides only very weak evidence for a relationship between symptoms and quality of life.

In the third analysis within this paper the mean EuroQol score derived from the participants of the Swedish willingness to pay study was correlated with micturitions and leakages. The correlation coefficient was reported to be -0.2 ($p < 0.001$). When these results were used within cost effectiveness analyses, patients were placed into groups based on the combined number of symptoms (micturitions and leakages) they experienced in a 24 hour period. Those with fewer than 9 symptoms were assigned a utility of 0.742, 9-11 symptoms a value of 0.712, 12-14 symptoms, a value of 0.676, 15 to 17 symptoms a value of 0.640 and 18 or more symptoms a value of 0.598. (Kobelt 1998) Unfortunately, the relationship between symptoms and the EuroQol score was based on the quality of life measure at a single time point and not based on a change in score with treatment. In order to demonstrate that micturitions and leakages impact quality of life it is important to show that a change in these clinical parameters results in a change in quality of life. A simple correlation between these two values at one time point may be due to a tertiary factor that is responsible for the micturitions and leakages. Improvement in the micturitions and leakages may not lead to improvement in this tertiary factor and therefore may not improve quality of life.

From this analysis, the only evidence in support of a relationship between quality of life and micturitions and leakages is the correlation of the change in SF-36 scores with treatment, of which only two of the 8 domains were significant at a $p < 0.05$ level. From this weak evidence, most studies have assumed a linear relationship between micturition and leakages and quality of life, generally as measured using the EQ5D, and have used this relationship in converting clinical symptoms to utility gains, rather than collecting quality of life data within the clinical trials.

Discontinuations of Therapy

Discontinuation of treatment is common with all of the drugs used in the treatment of OAB. How discontinuations are handled within the model analysis both with respect to the estimation of the discontinuation rates and with regards to what assumptions are made regarding costs, utilities and treatment post discontinuation of therapy may significantly affect the results of the cost effectiveness analyses. The methods adopted within the identified studies to incorporate discontinuations varied substantially limiting the ability to contrast study results.

The discontinuation rates within clinical trials are substantially lower than those seen in practice. It is generally accepted that “real world” data from prescription databases will more accurately reflect the true discontinuation rate and should therefore be used within analyses. The difficulty with this data is that it typically does not provide any information regarding the reason for discontinuation. Patients may have discontinued due to adverse events, due to resolution of symptoms or due to inefficacy of the medication. If they discontinued due to adverse events, a move to an alternative medication with a better safety profile may be appropriate; however, if they discontinued due to a resolution of symptoms, no further treatment may be required. Lastly, if the discontinuation was due to inefficacy of the medication, a switch to another medication may be appropriate; however, the benefit of switching to a medication which is from the same class of drugs is unclear. Given the limited data to inform these transitions, it would be important that they are tested within sensitivity analyses.

Furthermore, the assumptions regarding the management of patients after discontinuing therapy may also significantly impact the results of a study. There is the question of both whether patients receive further pharmacological treatment and, if so, what benefit they gain. If they receive no further treatment, it would be reasonable to assume they resort to baseline, provided they did not discontinue due to a resolution of symptoms. If they receive treatment with an alternative medication, for example tolterodine, then they would generally not return to baseline, but the estimated efficacy in this situation is unclear. Given the uncertainty surrounding the second option, it would be best to assume that patients receive no further treatment and return to baseline. If patients return to baseline, they will accrue utilities as they had during the run in period of the trial; however, they will also have costs associated with incontinence pad usage, if a societal perspective is taken.

Costs of Incontinence Pads

The results of many of the studies are influenced by the incorporation of the costs of incontinence pads within the analysis. As healthcare payers do not generally bear this cost within Canada, the influence of assumptions regarding incontinence pads should be taken into consideration when examining the literature. The use of these appliances varies greatly from one country to another, as does their cost, which can have a significant impact on the conclusions drawn from these studies.

Adverse Events

Another concern with these analyses is the handling of adverse events. In most cases it is assumed that those who experience adverse events discontinue therapy. Consequently, no utility deficit is assigned to those who experience adverse events and remain on therapy. Both dry mouth and constipation are reported to some extent with all of these drugs and, given the very small benefit in quality of life seen with these medications, accounting for the disutility due to these adverse events may have a significant impact on the cost effectiveness results. Additionally, the potential for CNS adverse effects of these drugs is not considered in **any** of the models. This class of medications has been shown in real world utilization to be associated with CNS effects, particularly in the elderly; however, the trials are generally of short duration which may have affected the ability to detect the occurrence of these side effects.

Sponsorship

The final common issue to consider is that there are no truly independent analyses conducted within this area. NICE, within the UK, conducted a review of drugs for the treatment of urinary incontinence in women in 2006, and although they incorporated a cost minimization analysis of these therapies, details of the design of the study were not reported in enough detail to allow an assessment of its value. (NICE 2006) All other studies, bar one, had an explicit statement relating to the receipt of funding from industry sponsors and in the single study that did not report direct funding, a number of potential conflicts were cited by the authors.

All of these factors together result in the literature being of generally poor quality reducing its usefulness in supporting any recommendation regarding the cost effectiveness of these drugs. This

should be considered when reading the following two sections focused on the comparative cost effectiveness of the newer anticholinergic medications with oxybutynin IR and the cost effectiveness of the newer anticholinergics as second line therapy.

4.2 Cost effectiveness of the medications under consideration (“newer anticholinergics”) as compared with oxybutynin IR for OAB

Of the studies identified within the literature review, six included comparisons between the newer anticholinergic drugs/formulations and oxybutynin IR. (Herschorn 2010, Guest 2004, Armstrong 2012, Cardoza 2010, Nilsson 2011, Hughes 2004) One of the studies was from a Canadian perspective (Herschorn 2010), one from a US perspective (Armstrong 2012), one from a Swedish perspective (Nilsson 2011), and the remaining three incorporated a UK perspective, although the study by Guest also included an Austrian and French perspective (Hughes 2004, Carzoda 2010, Guest 2004). Each of them suffers from a number of drawbacks which limit their usefulness in determining the relative cost effectiveness of the newer anticholinergics versus oxybutynin IR. All except Nilsson were sponsored by the pharmaceutical industry; however, Nilsson also cites industry conflicts of interest.

The three most relevant studies were Cardoza, Hughes and Nilsson, although they suffer from significant drawbacks and limited applicability within this setting.

Cardoza et al. 2010

Cardoza and colleagues compared the cost effectiveness of fesoterodine 4 mg/day and 8 mg/day (flexible dosing), propiverine ER 20mg/day, solifenacin 5mg/day and 10 mg/day (flexible dosing), tolterodine ER 4mg/day and tolterodine IR 2 mg and 4mg per day (flexible dosing) with oxybutynin IR 15 mg/day using a decision tree model. Efficacy of the treatments was derived from a systematic review of the literature and subsequent meta-analysis. Results of the trials were extrapolated from the 12 week timeframe to 1 year. To model persistence with the medications a real world database of drug persistence was used. Those who discontinued treatment were assumed to receive no further treatment and to have equivalent utility values to those with no response and to accrue no costs. The disutilities and costs of adverse events were not modeled except as they led to medication discontinuation. The Kobelt study was used to model utilities; however, rather than using a linear relationship between incontinence episodes and micturitions and utility values, patients were classified as either non-responders, partial responders or full responders. Partial responders were given a utility value halfway between the 2 other categories. Costs included within the model were OAB drug costs, GP consultations and outpatient contacts. Resource use was based on expert clinical opinion.

Oxybutynin IR was found to be the least costly therapy; whereas, solifenacin resulted in the greatest QALY gain. The ICER for solifenacin versus oxybutynin IR was £80,000 (~\$164,000 CAN) per QALY. Solifenacin dominated treatment with fesoterodine, tolterodine ER and tolterodine IR. Deterministic and probabilistic sensitivity analyses supported the robustness of the results.

Strengths of the study include the fact that many relevant comparators were included within the analysis. Additionally, the derivation of effectiveness data from a systematic review and meta-analysis

reduces the potential for bias within the results. The use of a real world database for persistence data is more representative of real world practice; however, as data was not available for fesoterodine, the values were based on assumptions for this treatment. The division of response into 3 categories may be more likely to estimate a clinically relevant change in disease than the assumed linear relationship between symptoms and utilities; however, measurement of quality of life within the trials would still be more credible.

Weaknesses of this study include:

- There may be differences in clinical practice and costs between Canada and the UK in applying the results of this analysis, particularly due to the fact that resource use was based solely on expert opinion and will therefore reflect UK practice. However, the omission of the cost of incontinence pads means that the results may be more relevant to healthcare decision makers than many other studies.
- An additional drawback of the methodology of this analysis is that each of the three symptoms were individually converted to a utility value and analyzed separately, which is unlikely to represent the full benefit the patient is experiencing.
- Disutility due to adverse events on treatment was not accounted for within the model.
- Finally, the assumptions regarding those who discontinued therapy were not tested within sensitivity analyses. Assuming they accrue no costs and have utilities of non-responders is unlikely to represent true outcomes in these patients.

Overall, this study found that, of the newer anticholinergic mediations, solifenacin was the most cost effective treatment; however, the ICER for solifenacin versus oxybutynin IR far exceeds the \$50,000 per QALY which is often used as a guide within Canada.

Hughes et al. 2004

Hughes and colleagues compared the cost effectiveness of oxybutynin IR, oxybutynin XR, tolterodine IR, tolterodine ER and no treatment from a UK healthcare payer perspective. Effectiveness data was derived from a systematic review of the literature and subsequent modeling of the pooled results with adjustments for baseline differences. Efficacy measures included the number of incontinence free weeks and persistence with therapy. The 3 month efficacy data from the clinical trials was extrapolated to 1 year within a decision analytic model. Patients who discontinued therapy were divided into two groups, those who discontinued due to adverse events and those who discontinued due to other reasons. The incidence of dry mouth was used as a proxy to estimate the proportion of discontinuations due to adverse events. These patients were assumed to return to baseline characteristics; whereas, those discontinuing due to other reasons were assumed to have experienced a health benefit. Costs included within the model were OAB drug costs, incontinence appliances and pads, medical professional fees and surgical costs.

Oxybutynin IR was the least costly treatment relative to no treatment. The incremental cost per incontinent free week for oxybutynin IR versus no treatment ranged from £2.58 to £16.59 (~\$5.75 to \$37.00 CAN). Relative to oxybutynin IR, tolterodine ER resulted in an ICER of £7.14 (~\$16.00 CAN) per incontinence free week. Relative to tolterodine ER, oxybutynin XR resulted in an ICER of £84.82

(~\$189.00 CAN) per incontinent free week. Tolterodine IR was dominated by tolterodine ER therapy. The results were sensitive to assumptions regarding the reason for discontinuing in those patients who stopped therapy.

This study combined the results of clinical trials sourced through a systematic review of the literature in order to estimate the relative efficacy of treatments. Although not as sound as using either a meta-analysis or indirect treatment comparison, it reduces the bias that may be introduced by selecting a single comparative study. An additional strength of this study is the avoidance of the assumption that all patients discontinued therapy due to adverse events and the testing of this assumption within sensitivity analyses.

There are a number of weaknesses of the study:

- A drawback of this study stems from the derivation of discontinuation rates from clinical trials and not a “real world” database, which has been shown to overestimate persistence with therapy.
- Similar to most studies in this area, this study received pharmaceutical industry sponsorship.
- Interpretability of this study is limited due to the difficulty of valuing an incontinent free week.
- Applicability of this study is limited given it is not from a Canadian perspective and the cost of incontinence pads and appliances is included within the analysis.

Nilsson et al. 2011

This study compared the cost effectiveness of the newer anticholinergics, as a group, with oxybutynin IR 5 mg three times daily, no treatment and placebo treatment. In the no treatment arm patients were assumed to achieve no improvement in symptoms or quality of life; whereas, in the placebo arm, the placebo response from trials was used to estimate the improvement in quality of life. This study was conducted from the perspective of the Swedish healthcare payer. The efficacy of treatment was derived from a Swedish prescribed drug registry with the assumption that the medication was effective in all patients who refilled their prescription at least once within 120 days of the original prescription. Discontinuation rates were also derived from this database. A Markov model was created which followed patients with OAB for a period of one year. Those with treatment success were assigned utilities derived from two fesoterodine studies which used the King’s Health Questionnaire to estimate improvements in quality of life. On the other hand, serious adverse events were derived from a randomized controlled trial comparison of solifenacin with tolterodine. Costs included were physician visits, incontinence pads, OAB drugs and dementia investigations.

The incremental cost per QALY was €21,045 (~\$29,000 CAN) for the newer anticholinergics versus no treatment, €65,435 (~\$89,000 CAN) versus placebo treatment and €37,119 (~\$51,000 CAN) versus oxybutynin IR. Deterministic univariate sensitivity analyses found the results to be sensitive to changes in the cost of pads, very serious adverse events, and the probability of non-responders receiving alternative therapy.

There are a number of weaknesses with this study.

- The use of “real world” discontinuation rates from a prescription database rather than those from clinical trial data is a strength of this study; however, the data from the database was for persistence with therapy at 12 weeks, which was then extrapolated to 1 year, rather than deriving 1 year data from the database. This is likely to overestimate the compliance with therapy.
- The validity of the assumption that those who renewed their prescription within 120 days experienced efficacy; whereas, those who did not renew it did not experience efficacy is highly questionable. There are many reasons why a person may not renew their prescription including a possible resolution of symptoms. There are also cases in which a person may renew their prescription even though they are not experiencing efficacy. This is not a validated approach to the measurement of a drug’s efficacy.
- Although the study did not report direct funding, the authors cite a number of pharmaceutical industry potential conflicts of interest.
- The applicability of the study may be limited by differences between the Swedish and Canadian healthcare systems, the inclusion of the costs of incontinence pads and the fact that all of the newer anticholinergic drugs were compared as a group.
- The use of trials for different drugs to estimate adverse effects and quality of life improvements may lead to selection bias in the choice of model inputs.
- Efficacy is based on fesoterodine studies which may have an effectiveness benefit over alternative newer anticholinergics; however, fesoterodine also appears to have a greater risk of adverse events than other newer anticholinergics which is not accounted for in the model.
- The assumptions within this study are likely to provide the most optimistic result for the newer anticholinergics and therefore it is unlikely that they would be considered cost effective based on this evidence.

Armstrong et al. 2012

From the perspective of a third party payer within the United States, this analysis compared the cost effectiveness of darifenacin, fesoterodine, oxybutynin IR, oxybutynin gel, oxybutynin patch, solifenacin, tolterodine IR, tolterodine ER, trospium IR and trospium ER in patients with OAB. A 3 month decision analytic model was created with the efficacy of the treatments derived from a pooled analysis of the results from a systematic review of the literature. Efficacy was defined as 3 to 7 days with no incontinent episodes. The discontinuation rates were reported to have been extracted from clinical trials; however, the results used within the model were not reported within the paper. The costs included within the model were for OAB drugs, co morbidities including urinary tract infections, skin irritations, depression, falls and fractures and incontinence pads. The rate of co morbidities varied based on the continent rate of patients.

Oxybutynin IR was found to be the least costly treatment alternative. All other treatments apart from solifenacin were dominated. Solifenacin resulted in an ICER of \$1,338 per additional continent patient. Both one-way deterministic and probabilistic sensitivity analyses were conducted. Results were found

to be sensitive to the continence rate with solifenacin; however, no other details were provided from the deterministic analysis.

There are a number of issues regarding this study which limit its usefulness in aiding in decision making.

- The study is from a US perspective, which has a significantly different healthcare system than Canada.
- This is a cost effectiveness study rather than a cost utility study which limits its interpretability. The value of increasing the number of continent patients by one is unclear and limits the application of the results. The study is also limited by the fact that it only examined a 3 month period and did not appear to test this duration within sensitivity analyses. It is unlikely that patients would be treated for so short a period of time.
- Of particular concern is the inclusion of the costs of co morbidities associated with overactive bladder. Although there are some studies that show there is a higher rate of these morbidities in patients who are incontinent, there are no clinical trials with any of these drugs which show a reduction in these co morbidities. Additionally, the references sighted show a link between incontinence and falls, rather than incontinence and fractures. The authors appear to erroneously assume these are the same, and incorporate a cost for fractures rather than falls.
- It is very unclear where the values for the probability of the co morbidities are derived from, particularly with respect to the adjustments for low, medium and high risk patients. There is no evidence that these assumptions have been tested within sensitivity analyses and they would be expected to have a significant impact on the results of the study.
- The discontinuation rates used within this trial were derived from clinical trials; which have been shown to significantly underestimate the true discontinuation rate in clinical practice.
- Caution should be exercised in using this study to assess differences between the newer anticholinergics particularly with respect to solifenacin, as the higher continence rate with this drug is most likely due to the fact that the clinical trials used only a 3 day micturition diary rather than the 7 day diary commonly used within other earlier trials. This provides a significant bias in favor of solifenacin given that the longer you record the data, the more likely you are to capture an incontinent episode. The results were sensitive to this measure within sensitivity analyses.
- Caution should be paid when interpreting with results with respect to fesoterodine as the efficacy measure was imputed for this medication as the continence rate was not reported within the clinical trials.
- As with many other analyses, the cost of incontinence pads is included within this analysis, which would therefore provide a patient perspective rather than a healthcare payer perspective.

Herschorn et al. 2010

The only Canadian comparative study was conducted by Herschorn and colleagues which examined the cost effectiveness of solifenacin 5 mg/day versus oxybutynin IR 5 mg three times daily from the perspective of the society. The analysis used a 1 year Markov model. Efficacy data relating to

frequency of micturitions and leakages was derived from a single head to head 8 week trial whose primary objective was to assess the comparative incidence of dry mouth with the two medications. The 8 week efficacy results were assumed to be maintained throughout the year provided the patient did not discontinue therapy. A linear relationship between frequency of symptoms and utilities was assumed as derived by Kobelt et al. Discontinuation rates were derived from provincial claims databases. Drop outs were assumed to be treated with tolterodine ER 4 mg/day and were assigned the average utility of the five health states incorporated within the model. Costs included within the model were OAB drugs, adjusted to real world compliance, and incontinence pads.

Solifenacin resulted in an incremental cost per QALY of \$14,092 versus oxybutynin IR. Both deterministic and probabilistic sensitivity analyses were conducted. Solifenacin was found to be cost effective in >90% of simulations at a willingness to pay of \$50,000 per QALY. The results were most sensitive to the discontinuation rates and the cost of incontinence pads. If the cost of tolterodine ER was reduced to \$0, the ICER for solifenacin versus oxybutynin IR rose to \$30,149 per QALY. If the utility of the drop outs was changed to health state 2, the ICUR rose to \$318,117/QALY.

It is difficult to place much value on the results of this study as the assumptions regarding those who discontinued therapy appear inappropriate and biased in favor of solifenacin. Of note, if all discontinued patients received tolterodine, it would seem plausible that they would achieve utility benefits associated with this treatment rather than simply assigning the mean value of the health states within the model. Alternatively, if patients do not receive tolterodine, it would be reasonable to assume that the patients would return to their baseline utility value. In the base case analysis discontinuing patients received tolterodine, but achieve utility gains lower than their baseline values. In the sensitivity analysis in which patients do not incur the cost of tolterodine their utility gains are still lower than their baseline values. In one sensitivity analysis which assumed utility values for those discontinuing therapy to be slightly greater than the baseline average for the cohort, the ICUR was \$318,117/QALY for solifenacin versus oxybutynin IR. Thus, it is clear that the utility value associated with discontinuation appears to have a significant impact on the results and conclusions of the study.

The Canadian perspective of this study should support its applicability within this setting; however, a number of weaknesses make it difficult to provide a clear interpretation of the results.

- The main concern is with respect to the sensitivity of the results to the assumptions regarding the costs and utilities assigned to those patients who discontinue therapy.
- Additional concerns are with respect to the fact that the efficacy data is derived from a single 8 week safety study rather than either a head to head efficacy study or a meta-analysis of trials.
- Concerns regarding the derivation of utilities as previously discussed also apply to this study.

Guest et al. 2004

A study by Guest et al compared the cost effectiveness of oxybutynin CR (up to 10 mg/day), oxybutynin IR (up to 10 mg/day) and tolterodine IR (up to 4 mg/day). The authors created a decision tree model which modeled the course of overactive bladder over a period of 6 months from the perspective of the Austrian, French and UK societies. Efficacy of treatments was derived from pooling the results of published clinical trials with respect to the percentage reduction in incontinence episodes and

micturitions. Costs included within the analysis were OAB drugs, laboratory tests, UTI treatment, incontinence pads, other medical practitioners, surgery, GP visits, specialist visits, hospitalizations and lost productivity. The relative cost effectiveness of the therapies was assessed based on the cost to reduce the daily frequency of incontinence and the cost to reduce the daily frequency of micturition.

This study found that starting therapy with oxybutynin CR was a dominant strategy (less costly and more effective than the alternatives) in both the UK and Austria and it was a cost effective strategy within France. The authors conducted both probabilistic and univariate deterministic sensitivity analyses. They reported that the French results were most sensitive to the probability of continuing therapy for 6 months and the number of outpatient visits; whereas, the UK and Austrian results were most sensitive to the percentage reduction in the frequency of incontinence and micturitions.

There are a number of weaknesses with this study

- The study used the pooled results of comparative clinical trials sourced from a systematic review of the literature which helps to reduce potential bias with respect to efficacy estimates. Unfortunately, a formal meta-analysis was not conducted and it is therefore unclear as to whether adjustments for differences in variability were appropriately accounted for.
- The model assumes a reduction in urinary tract infections and surgery in patients who benefit from treatment which has not been supported by clinical trial evidence. Although OAB patients are at higher risk than the general population for UTI's and surgery, there is no evidence that treatment with anticholinergic medications reduce this risk.
- The bulk of the cost differences between treatments were due to either surgery and hospitalizations or the use of electrotherapy (in Austria). The use of these resources was derived from expert opinion, and was heavily influenced by the discontinuation rate for the drugs under study.
- The sources for the discontinuation rates differed between therapies with the rates for oxybutynin IR and tolterodine IR being derived from a real world prescription database and the rates for oxybutynin CR derived from an open label trial. This is likely to result in an overestimation of the true compliance with oxybutynin CR and therefore an overestimate of its cost effectiveness.
- As with many other studies in this area it was not conducted from a Canadian perspective and received industry funding. The societal perspective of the analysis limits the relevance to healthcare payer decision makers.

Summary

There were six studies that compared the cost effectiveness of the newer anticholinergics with oxybutynin IR and thereby may assist in making a decision about the use of these agents as first line therapy in overactive bladder. All of the studies received industry sponsorship and suffer from a number of limitations which generally served to ensure an optimistic estimate of the cost effectiveness of the new agents. Even with these assumptions, either in the base case or when tested within sensitivity analyses, in most cases the ICER for the new anticholinergics compared with oxybutynin IR exceeds the value of \$50,000/QALY. Although the literature is of poor quality and there is a need for a

more objective analysis from a Canadian perspective, the currently available evidence does not appear to support the use of any alternative therapies to oxybutynin IR as first line therapy in OAB.

4.3 Cost effectiveness of the newer anticholinergic drugs/formulations as second line treatment

Given the high discontinuation rates with oxybutynin IR, of interest is whether the newer anticholinergic drugs are cost effective when compared with the alternative of no further pharmacologic treatment after failure on oxybutynin IR or in patients who experience adverse effects with oxybutynin IR leading to discontinuation. The only study designed to answer this question is one from a Canadian perspective, conducted by O'Brien et al in 2001. It compared the cost effectiveness of two strategies for managing patients who discontinue treatment with oxybutynin IR. In the first scenario patients were treated with tolterodine IR and in the second patients were given no treatment.

In addition, there are a number of studies which compared the cost effectiveness of the newer anticholinergics with either placebo or no treatment which may be of use in assessing this question; however, caution should be exercised in interpreting these studies as they have a number of drawbacks. The most significant one being that they are not focused on the population of interest (i.e. those who have discontinued oxybutynin IR).

In addition to the issues discussed regarding the use of these agents as first line therapy, many of which also apply to these studies, there are some further issues discussed below that are of particular relevance to second line therapy.

First, in comparing the newer anticholinergics against no further pharmacological treatment consideration must be made to the efficacy of the no treatment arm. As is evident in most of the studies in OAB there is significant placebo response which may in part be due to a traditional placebo effect, but may also be due to alternative approaches the patients may be engaged in to control symptoms of OAB. Applying the placebo response values to a group of patients who are receiving no therapy for OAB is likely to overestimate the benefit experienced by this group. On the other hand, applying the baseline values to the no treatment group is likely to overestimate the benefit of therapy and the cost effectiveness of treatment. A more appropriate solution would be to provide both, with the true benefit lying between the two estimates.

Secondly, there is a lack of clinical trials examining the efficacy of newer anticholinergics in the population of interest, specifically, those who have failed oxybutynin IR therapy. In most cases the trials included a mixed population of patients who have previously received pharmacological treatment for OAB, those who were receiving pharmacological therapy up until the start of the trial and those who have not received pharmacologic therapy for OAB. It is unclear as to whether the efficacy of these medications would be comparable in those who failed oxybutynin IR therapy, especially given that all the medications are from the same class.

O'Brien et al. 2001

O'Brien conducted a cost utility analysis comparing oxybutynin IR treatment followed by no treatment for those who discontinued oxybutynin IR versus oxybutynin IR treatment followed by tolterodine IR 2 mg BID for those who discontinued. The analysis was conducted from a Canadian perspective using Canadian costs and was sponsored by the pharmaceutical industry. Efficacy data regarding the effect of treatments on OAB symptoms was derived from pooling the patient level data from 3 head to head 12 week comparative trials for oxybutynin IR versus tolterodine IR. A Markov model was created that modeled the course of treatment over 1 year. The efficacy data from the clinical trials was extrapolated to one year assuming that the 12 week efficacy persisted throughout the time period. Adverse events were not explicitly incorporated within the model aside from accounting for them within the estimated discontinuation rates. Discontinuation rates were derived from two sources: the clinical trial discontinuation rate and the Quebec provincial drug claims database. This resulted in the clinical trial discontinuation rates being inflated by a factor of 2.9 which lead to a discontinuation rate of 47.8% with oxybutynin and 14.96% with tolterodine. The Kobelt utilities were used to convert OAB symptoms to utility values. The analysis was conducted from a societal perspective including both the cost of OAB drugs, GP visits and incontinence pads. Pad usage was derived from data collected during the trials.

The ICER for oxybutynin IR followed by tolterodine IR was \$9,982 per QALY compared with oxybutynin IR followed by no treatment. The authors conducted a univariate deterministic sensitivity analysis. They found the results to be insensitive to changes in the baseline cohort disease state distribution, the oxybutynin dose distribution and changes in costs and utilities. The discontinuation rates were not tested within sensitivity analyses.

The relevance of this study is strengthened by the fact that it is conducted from a Canadian perspective with Canadian cost estimates; however, there are also some limitations particularly with respect to the assumptions regarding discontinuations.

- The model assumes that all patients discontinued oxybutynin IR due to intolerance or lack of efficacy and no one discontinued due to a resolution of symptoms. This would affect the proportion of patients eligible for tolterodine IR therapy.
- The discontinuation rates are derived from a combination of clinical trial data and a real world drug claims database. Based on the drugs claims database, the discontinuation rate for oxybutynin IR was 2.9 times higher at 4 weeks than the discontinuation rate within the clinical trials. Consequently, the clinical trial discontinuation rates for both drugs were multiplied by 2.9 to arrive at a discontinuation rate of 47.8% and 14.96% for oxybutynin IR and tolterodine IR, respectively, at 4 weeks. This assumes that there is a relative difference between the 2 treatments rather than an absolute difference. A published study by Gopal examining a matched cohort of patients receiving tolterodine and oxybutynin found that the 6 month discontinuation rate with oxybutynin was 71% compared with 61% with tolterodine. (Gopal 2008) These results support an absolute difference of 10% between the two treatments rather than a proportional difference as assumed within the O'Brien study. These assumptions were not tested within sensitivity analyses, so the impact on the results cannot be explicitly

estimated, but would be expected to result in a significant overestimation of the cost effectiveness of the tolterodine arm.

- Within the model, patients who discontinued oxybutynin IR and did not receive further pharmacological treatment were assumed to experience no benefits. To give a more objective estimate of the cost effectiveness of therapy, a sensitivity analysis allowing for a placebo response in this group would provide a more thorough analysis on which to base decisions.
- The use of the Kobelt approach to convert OAB symptoms to utility values has been critiqued earlier and the drawbacks of this method apply to this study.
- Adverse events were only accounted for through discontinuation of therapy and no utility decrement was applied for those continuing on therapy with adverse events. This may be particularly relevant given the small magnitude of utility benefit experienced with treatment.
- The results may also have been significantly affected by the inclusion of the costs of incontinence pads, which are generally not borne by the healthcare payer within Canada and therefore reduce the relevance of this study in healthcare decision making.
- Finally, it should be noted that the estimated efficacy of tolterodine IR within this model was based upon head to head trials versus oxybutynin IR. It was therefore not derived from the population of interest, those who have failed therapy with oxybutynin IR. It is unclear whether this would accurately estimate the efficacy of tolterodine, particularly given that the medications are from the same therapeutic class.

Summary

There is only one study which specifically addresses the cost effectiveness of a newer anticholinergic after discontinuation of oxybutynin IR. Although, the ICER for oxybutynin IR followed by tolterodine IR as compared with oxybutynin IR followed by no treatment was under \$50,000 per QALY as reported within the study, it is likely that the true ICER is higher than this estimate as a number of assumptions within this analysis serve to optimize the results for tolterodine IR.

4.4 Newer Anticholinergics versus Placebo/No treatment

Although the following studies compared the newer anticholinergics with placebo or no treatment, which may be an appropriate comparator when deciding if those who either failed treatment with oxybutynin IR or were intolerant to treatment with oxybutynin IR should receive further therapy, none of these studies were conducted specifically within this population. The efficacy of these medications in people who have failed therapy with oxybutynin IR, particularly given that these medications are from the same class, is unclear. If the efficacy is lower, the following studies are likely to overestimate the cost effectiveness of these medications.

Five studies were identified within the literature search comparing the newer anticholinergics with the alternative of either placebo and/or no treatment. One study, by Nilsson et al, compared the newer anticholinergics as a group versus both placebo and no treatment, with the assumption that all the newer anticholinergics have comparable efficacy and safety. (Nilsson 2011) Three studies compared solifenacin with either placebo or no treatment, two of which also included tolterodine ER. (Haakart

2009, Milsom 2009, Pradelli 2009) Finally, one study compared tolterodine IR with no treatment. (Kobelt 1998)

One study was from a UK perspective (Haakart 2009), 3 from a Scandinavian perspective (Milsom 2009, Kobelt 1998, Nilsson 2011) and one from an Italian perspective (Pradelli 2009). All except Nilsson include a direct statement acknowledging the receipt of funding from the pharmaceutical industry; however, Nilsson cited a number of potential industrial funding conflicts.

Nilsson et al. 2011

This cost utility analysis was discussed above and compared the newer anticholinergics as a group (i.e. solifenacin, tolterodine, fesoterodine, darifenacin and oxybutynin (patch)) with oxybutynin IR 5 mg TID and with no treatment and placebo in urgency urinary incontinence from a Swedish societal perspective. The incremental cost per QALY was €21,045 (~\$28,000 CAN) for the newer anticholinergics versus no treatment and €65,435 (~\$87,000 CAN) versus placebo. The incremental cost per QALY versus oxybutynin IR was €37,119 (~\$49,000 CAN). A univariate deterministic sensitivity analysis was conducted which found the results were sensitive to the frequency of very serious adverse events, the cost of incontinence pads and the percentage of non-responders receiving an alternative prescription (5.77% in base case based on Swedish prescribed drug registry).

Strengths of this study include the direct measurement of quality of life within the fesoterodine clinical trial using a validated instrument and the fact that the rate of discontinuation of therapy was derived from a real world database.

There are a number of weaknesses with this study.

- Rather than use 1 year discontinuation rates from the database, the 12 week discontinuation rates were used within the model which may overestimate long term compliance.
- Additionally, few patients within the drug database were new to oxybutynin IR bringing into question the accuracy of the estimates for this treatment.
- The fact that it is from a Swedish societal perspective may limit its applicability in assisting Canadian healthcare decision makers as they generally do not bear the costs of incontinence pads and the treatment patterns may differ between countries.
- The validity of grouping all the newer anticholinergics with the assumption of comparable efficacy and safety was not well justified within the paper. Published meta-analyses have found differences between the therapies both with respect to efficacy and adverse events.
- This analysis selected fesoterodine efficacy data, which has been shown to offer an effectiveness benefit over other newer anticholinergics; whereas, adverse events were derived from solifenacin and tolterodine studies, which may have fewer adverse effects than fesoterodine. This may have biased the results in favour of the new anticholinergics.
- Additionally, no utility decrement for patients who experience adverse events but remain on therapy was incorporated.
- Finally, the validity of the assumption that those who refill their prescription may be considered responders to treatment; whereas those who don't are none responders may not be justified.

The significant number of issues with this study limit its usefulness in informing decisions.

Haakart et al. 2009

This study compared the cost effectiveness of solifenacin 5 mg/day and 10 mg/day with placebo from the perspective of the UK healthcare system. The population was based on solifenacin clinical trials including males and females with OAB defined as at least 3 episodes of urgency and/or three episodes of urinary incontinence during a 3 day micturition diary. The analysis was based on a 1 year Markov model. Efficacy of solifenacin was derived from four placebo controlled clinical trials of 12 weeks duration (n=1890). Twelve week efficacy was assumed to be maintained for the duration of the 1 year model. The utility gained by patients was based on Kobelt utilities assuming a linear relationship between micturitions and leakages and an EQ-5D score. Adverse events were not incorporated within the model, apart from accounting for patients discontinuing therapy. Discontinuation rates were derived from the 12 week clinical trials and the discontinuation rate between 3 months and 12 months was assumed to be similar to the discontinuation rate in the first 12 weeks. Those who discontinued therapy were assumed to generate no utilities and to accrue no costs. Both OAB drug costs and the cost of incontinence pads were incorporated within the model with the use of incontinence pads derived from clinical trials.

Solifenacin 5 mg and 10 mg resulted in an incremental cost per QALY of £17,602 (~\$42,000 CAN) and £24,464 (~\$58,000 CAN), respectively, versus placebo. A deterministic univariate sensitivity analysis found the results to be sensitive to assumptions regarding those who discontinued therapy. Assuming that those who discontinued had no symptoms (i.e. their OAB resolved) resulted in an ICER of £25,470/QALY (~\$61,000 CAN) and £44,000/QALY (~\$105,000 CAN) for solifenacin 5 mg and 10 mg, respectively versus placebo. If the utility of patients who discontinue was assumed to be equivalent to baseline, the ICERs for solifenacin 5 mg and 10 mg versus placebo were £20,391/QALY (~\$49,000 CAN) and £23,122/QALY (~\$55,000 CAN), respectively.

There are a number of weaknesses with this study:

- This study is from a UK perspective which makes it difficult to generalize the results to a Canadian setting.
- Only very limited sensitivity analyses were conducted on the results.
- The baseline results incorporate the assumption that those who discontinue treatment accrue no utilities which is inaccurate. When tested in sensitivity analyses the results proved very sensitive to this assumption leading to significant increases in the ICER.
- The discontinuation rates were based on clinical trial data and were unfortunately not tested within sensitivity analyses. In general, the discontinuation rates within OAB clinical trials have been shown to be significantly lower than those in a real world situation and the impact of greater discontinuations on the results was not considered.
- The results are likely to be highly influenced by the inclusion of the cost of incontinence pads as they are the only cost associated with placebo treatment and the cost is much higher for this product in the placebo group than in the solifenacin group. If the cost of incontinence pads was

not included within the analysis, the ICER for solifenacin 5 mg and 10 mg versus placebo would be £34,571 (~\$82,000 CAN) and £42,643 (~\$102,000 CAN), respectively.

- Issues associated with the use of Kobelt's utility conversion, as discussed previously, also apply to this study.
- The selection criteria for the studies which were used to estimate the efficacy of the treatments within the model is not clearly laid out within the methods of the paper.
- As with many other papers, this study received financial support from the pharmaceutical industry.

The significant number of issues with this study limit its usefulness in informing decisions.

Milsom et al. 2009

Milsom and colleagues also compared solifenacin 5 mg/day and 10 mg/day, flexible dosing with placebo and tolterodine ER 4 mg/day with placebo in a cost effectiveness/utility analysis from both a societal and healthcare payer perspective in Norway, Finland, Sweden and Denmark. The efficacy of the treatments was based on pooled data from 2 clinical trials for the comparison of solifenacin versus placebo. In one of these studies patients were also randomized to receive tolterodine ER and this data was used for the comparison of tolterodine ER versus placebo. Unfortunately this clinical trial was not powered for a comparison of solifenacin versus tolterodine ER. The 12 week efficacy was assumed to be maintained for the 1 year treatment period. The authors converted the clinical results to utilities using Kobelt's method of modeling the clinical symptoms with EQ-5D scores. Costs included within the model were for OAB drugs, physician visits, laboratory tests, pad usage and productivity loss, measured using the human capital method.

From both a societal and healthcare payer perspective solifenacin was dominant over tolterodine ER. From a societal perspective the cost per QALY for solifenacin versus placebo ranged from €14,318 to €27,603 (~\$21,000 to ~\$40,000 CAN), depending on the country. From the healthcare system perspective the cost per QALY for solifenacin versus placebo ranged from €24,084 to €33,757 (~\$35,000 to ~\$50,000 CAN). A univariate deterministic sensitivity analysis found the results to be insensitive to changes in unit costs, frequency of adverse events and to separate analyses for 5 mg and 10 mg solifenacin.

There are a number of weaknesses with this study:

- The criteria used for selecting the 3 studies used in estimating the efficacy of solifenacin, tolterodine ER and placebo within this analysis were not reported within the paper.
- The derivation of placebo efficacy from two alternative studies from the ones that were used to estimate the efficacy of solifenacin and tolterodine brings into question the validity of the efficacy data.
- The authors state that the 12 week efficacy data from clinical trials was linearly extrapolated to one year, although the actual data used in the model is not reported within the paper. Most studies have assumed that the efficacy at 12 weeks is maintained throughout the 52 weeks of treatment. The assumption of continued improvement over the course of the year is justified

based on an open label extension of a solifenacin trial in which all patients received solifenacin. Use of these results to justify further improvement over the course of the year is inappropriate due to the lack of a placebo control, the lack of blinding, the fact that 9% of patients elected not to continue onto the open label study and 19% of patients did not complete the open label study. The conditions of this trial are biased in that they select specifically for patients who have responded to therapy.

- The drawback of the use of the Kobelt study to convert clinical symptoms to quality of life has been discussed previously and applies also to this study.
- The transferability of the results of this trial to a Canadian setting is reduced by the fact that much of the resource use patterns, including the frequency of specialist visits and laboratory testing are based on typical clinical practice within the respective country within the analysis.
- Additionally, in the direct cost analysis the price of incontinent pads is included which may not be borne by Canadian healthcare payers and the cost of which may vary significantly from one location to another.
- Although the actual data regarding adverse events used within the model are not reported within the publication the discontinuation rates from placebo, solifenacin and tolterodine appear to be set at 0%, 4.2% and 3.8%. These rates appear to be based on 12 week discontinuations due to adverse events from the clinical trials and do not represent real world discontinuation rates, which tend to be significantly higher. There is no evidence of adjustment of these rates to reflect clinical practice nor to account for the extended duration of the model.

The significant number of issues with this study limit its usefulness in informing decisions.

Pradelli et al. 2009

This cost effectiveness/utility analysis compared solifenacin 5 mg/day with tolterodine ER 4 mg/day and with both placebo and no treatment in an analysis based on those in the Italian population suffering from overactive bladder. A Markov model was created to follow patients over the course of 1 year of treatment. The dry rate (no leakages over the 3 day micturition diary period) was derived from a head to head trial comparing solifenacin with tolterodine ER. For other efficacy measures, episodes of incontinence, micturition frequency and use of incontinence pads, the data was derived from separate studies comparing either solifenacin to placebo or tolterodine ER to placebo. The micturition and leakage frequency was used to estimate the quality of life of patients based on the algorithm developed by Kobelt. The results were then adjusted based on a UK study to increase the utilities for those who were dry by 15% and to decrease it by 7% for those who were wet. The costs of OAB drugs, incontinence pads, medical examinations, creams and other local treatments, productivity losses and costs for falls or fractures were incorporated within the model.

From the patient perspective the incremental cost for solifenacin 5 mg/day was €18,613 (~\$27,000 CAN) per QALY as compared with placebo; whereas, for tolterodine ER it was €33,309 (~\$49,000 CAN) per QALY versus placebo. The incremental cost per continent patient was €5,810 (~\$9,000 CAN) for solifenacin versus placebo and €10,467 (~\$15,000 CAN) for tolterodine ER versus placebo. Based on the deterministic sensitivity analysis, the results were most sensitive to the costs of OAB drugs, to the perspective of the analysis and to the utility value derivation and its adjustment for the dry rate.

There are a number of weaknesses with this study:

- The validity of using separate placebo controlled trials to estimate efficacy with adjustments from a head to head trial for dry and wet rates is questionable. Additionally, the method of selection of these trials is not detailed within the publication.
- Of particular concern is the fact that the solifenacin efficacy data was derived from trials which used a 3 day continence diary; whereas the tolterodine data was derived from a trial that used a 7 day continence diary.
- The validity of the utility value adjustments for continent and incontinent patients is questionable and insufficiently justified. This is a problem given that it had a significant impact on the results within the sensitivity analyses.
- Another factor which serves to significantly lower the estimated cost effectiveness ratio is the fact that only the 5 mg/day dose of solifenacin is considered; whereas, a proportion of patients require the 10 mg dose, which is associated with greater side effects and therefore would result in a higher ICER if included.
- Finally, the inclusion of the costs for falls and fractures is questionable given that there is no evidence within the clinical trials that treatment affected either of these measures.

The significant number of issues with this study limit its usefulness in informing decisions.

Kobelt et al. 1998

This analysis compared the cost effectiveness and cost utility of tolterodine IR with no treatment from a Swedish healthcare payer perspective. A Markov model was developed to model the transitions of patients over the course of one year. The efficacy of treatment was based on pooled data from three multinational 12 week clinical trials with the assumption that the twelve week efficacy would be maintained for the full year of treatment. To establish the utility gain associated with therapy, the number of micturitions and leakages over a 24 hour period from the clinical trials were converted to EQ5D scores using the method developed by Kobelt. (Kobelt 1997) The discontinuation rate appeared to be derived from the 12 week clinical trials and was assumed to be consistent over the 1 year period. Those who discontinued therapy were assigned the mean baseline value for utilities and costs for the remainder of the year. OAB drug costs, GP visits and incontinence pads were included in the costs of management. Pad usage was derived from the clinical trials, using only the Swedish data.

The incremental cost effectiveness ratio for tolterodine IR versus no treatment was SEK 213,042 (~\$39,000 CAN) per QALY. The incremental cost per time spent with minimal symptoms was SEK 1,869 (~\$340 CAN) for tolterodine versus no treatment. A univariate sensitivity analysis indicated the results were insensitive to increases in drop outs (up to 50% discontinuing therapy), the time horizon (up to 2 years) and to utility values.

There are a number of weaknesses with this study:

- The applicability of the results of this study within the Canadian setting may be limited by the fact that the study was conducted from a Swedish perspective and included the cost of incontinence pads which is generally not borne by the Canadian healthcare payer.
- Concerns regarding the validity of the Kobelt utility conversion as discussed previously also apply to this study.
- Additionally, the derivation of a discontinuation rate from clinical trials is unlikely to approximate the discontinuation rate within the real world; however, these results were relatively insensitive to this value within sensitivity analyses.
- Finally, given the relatively small gains in utility seen with treatment, it is particularly relevant for disutilities due to adverse events to be considered within the analysis as this may affect the results.

The significant number of issues with this study limit its usefulness in informing decisions.

Summary

There are five studies which compared the cost effectiveness of the newer anticholinergics with either no treatment and/or placebo. Caution should be exercised in using these results to inform decisions about the cost effectiveness of these medications as second line therapy, given that none of the studies were conducted in the population of interest (those who had discontinued oxybutynin IR). Consequently, they are likely to provide an overestimate of the cost effectiveness of these medications. Additionally, there were many assumptions within these analyses relating to estimates of efficacy, costs and utility derivation which serve to optimize the cost effectiveness estimates for the newer anticholinergics. Correcting these assumptions would likely lead to higher cost effectiveness ratios for the newer anticholinergics. Although difficult to predict, given the lack of appropriate data, it is likely that the ICER would be greater than \$50,000/QALY; therefore, at a minimum, a price reduction for the newer anticholinergics would be required for these agents to have the potential of being cost effective.

4.5 CDR REVIEWS

A number of submissions have been made to CDR for newer anticholinergics including darafenacin, trospium, fesoterodine and solifenacin. All except solifenacin applied only for consideration as second line therapy as an alternative to tolterodine ER. Each submission contained a cost minimization analysis which assumed that all newer anticholinergics had comparable efficacy and safety. In all cases the studies in which the efficacy and safety were assessed did not appear to be specific to the patient population who had failed oxybutynin IR therapy. As most jurisdictions fund tolterodine ER for patients who are either intolerant of or do not respond to oxybutynin IR the main focus was on the relative pricing of the newer anticholinergics compared with tolterodine ER. In most cases the recommendation was to fund the newer medications with the same restrictions as tolterodine ER, after the manufacturer provided a reduced price for their medications. In many cases, the reduced price was confidential. As BC does not currently fund tolterodine IR or ER, consideration must be given to the funding of any of the newer anticholinergics.

Although the solifenacin submission also contained a cost utility analysis which included tolterodine ER, oxybutynin IR and placebo as comparators, the evidence was not deemed supportive of a recommendation for use of solifenacin as first line therapy as an alternative to oxybutynin IR.

5. OVERALL SUMMARY

This review critically appraised the literature examining the cost effectiveness of newer anticholinergics including (tolterodine IR, tolterodine ER, solifenacin, darafenacin, oxybutynin ER, oxybutynin CR, oxybutynin patch, oxybutynin gel, trospium, fesoterodine) in the treatment of overactive bladder. The critical appraisal was divided into two subsections, specifically, the comparative cost effectiveness of oxybutynin IR versus the newer anticholinergics as first line therapy in OAB and secondly the cost effectiveness of the newer anticholinergics as compared with no further therapy as second line therapy after discontinuation of oxybutynin IR. A summary of the evidence on the comparative cost effectiveness of the newer anticholinergics is provided within an appendix. The following is a summary of the quality of the literature within this area of study followed by a summary of the results of the review within the two primary areas of interest.

The cost effectiveness literature within this area is of generally poor quality and the literature search did not reveal any independent studies examining the use of these agents in OAB, with the majority of studies receiving direct sponsorship from the pharmaceutical industry. In general, the available studies tend to make assumptions which provide an optimistic estimate of the cost effectiveness of the newer agents.

First the utility derivation using the method introduced by Kobelt is of questionable validity. The evidence for a link between a significant change in quality of life with the modest improvements in symptoms with treatment is tenuous. It is based upon an improvement in 2 of the 8 domains of the SF-36 with the addition of treatment for OAB; however, it is the relationship between the EuroQol score and clinical symptoms that is actually used within cost utility analyses. Unfortunately this correlation is based on the measurement of symptoms at a single time point, not derived from a change in quality of life with treatment, and does not necessarily support a linear relationship between symptoms and utilities. The link between small changes in clinical symptoms and changes in quality of life is so tenuous as to call into question the results of the studies using this approach to value improvements with therapy.

Secondly, in most cases the disutility due to adverse events is not considered within the models, but rather it is accounted for through the discontinuation rate. The assumption that all discontinuations are due to adverse events is common within the literature, with varying assumptions regarding the cost and utilities accumulated by patients who discontinue and with respect to further treatment. All of these assumptions are generally taken in favour of the newer anticholinergics, are often not tested within sensitivity analyses and are likely to provide biased estimates of the cost effectiveness of these medications. The use of clinical trial discontinuation rates, rather than real world data is likely to further bias the results, as the true number of patients discontinuing therapy has been shown to be much greater in general practice as compared with trials.

Finally, many of the studies are conducted from the perspective of healthcare systems outside Canada with the inclusion of the costs of incontinence pads being common. As these costs are not borne by the Canadian healthcare system their inclusion makes the use of these studies in decision making challenging.

All of these concerns regarding the literature must be kept in mind when making recommendation regarding funding.

There were six studies which examined the comparative cost effectiveness of newer anticholinergics versus oxybutynin IR in first line treatment of OAB. In all of the studies oxybutynin IR was the least costly treatment for OAB. There appears to be limited evidence to support an efficacy advantage of the newer anticholinergics as compared with oxybutynin IR; however, most models include a lower withdrawal rate due to dry mouth with the newer anticholinergics. Although the evidence is of poor quality available publications indicate that the incremental cost per QALY for the newer anticholinergics versus oxybutynin IR is likely to be greater than \$50,000. Thus, the literature within this area does not support the cost effectiveness of the newer anticholinergics relative to oxybutynin IR as first line therapy for OAB.

With respect to the use of these medications as second line therapy in patients who either did not respond to or experienced adverse effects to oxybutynin IR there is only one cost utility study that specifically addresses this question. The study was conducted from a Canadian healthcare payer perspective and found that the use of tolterodine IR after discontinuation of oxybutynin IR was \$9,982 per QALY as compared with no treatment after discontinuation of oxybutynin IR. This is likely to be an underestimate of the true cost per QALY of this scenario due to the use of optimistic assumptions biasing results in favour of tolterodine IR.

Five studies compared the cost effectiveness of the newer anticholinergics with either placebo or no treatment. Caution should be exercised when using these studies to inform decisions regarding second line therapy as they are likely to provide an overestimate of the cost effectiveness of these medications as they were not specifically conducted as second line therapy. In three studies comparing solifenacin with placebo the ICER ranged from \$27,000 to \$58,000, with the lower value applying only to the 5 mg/day dose. In one study where the newer anticholinergics were considered as a group the ICER was ~\$28,000/QALY versus no treatment and ~\$87,000/QALY versus placebo. In the final study, the ICER for tolterodine IR versus no treatment was ~\$39,000/QALY. The significant number of assumptions made within these studies lead to a bias within the results in favour of the cost effectiveness of the newer anticholinergics. Correcting these assumptions would likely lead to higher cost effectiveness ratios for the newer anticholinergics. Although difficult to predict, given the lack of appropriate data it is likely that the ICER would be greater than \$50,000 per QALY; therefore, at a minimum, a price reduction for the newer anticholinergics would be required for these agents to have the potential of being cost effective.

In considering trospium, darafenacin, solifenacin and fesoterodine as second line therapy the submissions to CDR contained cost minimization analyses which assumed that the efficacy of these

agents is comparable to tolterodine ER, with any differences resulting from differential discontinuation rates due to adverse effects.

In deciding whether or not to fund the newer anticholinergics, consideration should also be given to the effect of the funding of these medications on the discontinuation rates with oxybutynin IR. The high discontinuation rates with oxybutynin IR indicate that there is a need for alternative medications which provide either improved efficacy and/or reduced side effects. The evidence for improved efficacy is limited and therefore much of the focus has been on potentially better adverse event profiles with the newer anticholinergics. Given the dissatisfaction with oxybutynin IR, even if the alternative agents offer little benefit, simply by funding these medications, there is likely to be an increase in the discontinuation of oxybutynin IR with a move to the newer agents. Even if the alternative agents do not provide greater benefits for the patient, they are unlikely to return to treatment with oxybutynin IR thereby leading to increased costs of therapy. The impact of this was not considered within any of the cost effectiveness models.

The recommendations within this report are to a large extent based on speculation of the effect of incorporating more appropriate assumptions and estimates within the available models. The literature in this area is of poor quality and all of it is sponsored by the pharmaceutical industry. To make a more confident recommendation regarding the place of the newer anticholinergics within the treatment of OAB one would need to conduct a better quality study which would include the following:

- an accurate estimate of the discontinuation rates for the drugs within a real world setting, in addition to an understanding of the reason for discontinuation, or a testing of the assumption regarding the reason for the discontinuation within sensitivity analyses
- incorporation of the disutility associated with adverse events for patients who remain on therapy
- direct measurement of effects on quality of life in patients within clinical trials, which were incorporated within the fesoterodine studies. Alternatively, considering alternative models to that of Kobelt that may be clinically relevant which might include a division of patients into categories of continent and incontinent.
- deriving efficacy estimates from a well conducted meta-analysis or multiple treatment comparison
- analysis from a Canadian perspective both incorporating and eliminating the costs of incontinence pads

6. CONCLUSIONS

Overall the literature with respect to the cost effectiveness of medications in treatment of overactive bladder is of poor quality. None of the studies were independently conducted and all suffer from a significant number of limitations which in most cases serve to overestimate the cost effectiveness of newer anticholinergics.

With respect to the choice of anticholinergic medication as first line therapy in the treatment of OAB, the currently available evidence supports the use of oxybutynin IR as a cost effective anticholinergic medication.

With respect to the cost effectiveness of the newer anticholinergics as second line therapy after discontinuation of oxybutynin IR due to either lack of response or adverse effects there are no well-designed studies which can help to answer this question. The available evidence suggests that at their current price, these agents are unlikely to be considered cost effective second line therapies as compared with no drug treatment.

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8. APPENDIX

Table A1: Characteristics of Included Studies focusing First Line treatment of OAB

Study	Armstrong et al. 2012	Cardozo L et al. 2010	Guest JF et al. 2004
Sponsorship	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry
Country	United States	UK	Austria, France & UK
Perspective	Third party payer	HCS	Societal
Study type	CEA	CUA	CEA
Comparators	Fesoterodine 8mg/day Oxybutynin IR 5 mg BID Oxybutynin ER 30 mg/day Oxybutynin TD gel 1 sachet daily Oxybutynin patch every 3.5 days Solifenacin 5 mg/day Tolterodine IR 2 mg BID Tolterodine ER 4 mg/day Trospium IR 20 mg BID Trospium ER 60 mg/day	fesoterodine 4 mg/day & 8 mg/day oxybutynin IR 15 mg/day propiverine ER 20 mg/day solifenacin 5 mg/day & 10 mg/day tolterodine ER 4 mg/day tolterodine IR 2 mg/day and 4 mg/day	oxybutynin CR (up to 10 mg/day) oxybutynin IR (up to 10 mg/day) tolterodine IR (up to 4 mg/day)
Time horizon	3 months	1 year	6 months
Type of model	Decision analytic model	Decision tree	Decision tree
Efficacy inputs	Pooled results from systematic review	Meta-analysis	Pooled results of RCTs and expert opinion
Utilities	not applicable	Kobelt utilities categorized as no response, partial response & full response	not applicable
Costs included	OAB medications, comorbidities (UTIs, skin irritation, depression, falls), incontinence pads	OAB medications, outpatient visits (resource use based on expert opinion)	OAB medications, laboratory tests, UTI treatment, doctor visits, surgery, transportation, hospitalizations and productivity
Outcomes	3 to 7 days with no incontinent episodes Discontinuation rates as per clinical trials	Cost per QALY Discontinuation rates as per real world database	Cost per additional reduction in the number of daily micturitions Cost per additional reduction in the number of daily incontinence episodes
Results	a) oxybutynin IR was the least costly treatment b) all other treatments apart from solifenacin were dominated c) solifenacin ICER \$1338±168 per additional continent free patients	a) oxybutynin IR was the least costly therapy b) fesoterodine, tolterodine ER & tolterodine IR dominated by solifenacin c) solifenacin - £80,000/QALY versus oxybutynin IR	a) oxybutynin was dominant therapy in UK and Austria and cost effective in France
Types of sensitivity analyses	Deterministic and probabilistic analysis	Deterministic and probabilistic analyses	Deterministic and probabilistic analyses
Results of sensitivity analysis	Results were sensitive to the continence rate with solifenacin	Results not reported but stated robust to changes in utility values, treatment effects & discontinuation rates	French perspective: results most sensitive to discontinuation rates, number of outpatient visits UK and Austrian perspective: results most sensitive to percentage reduction in frequency of incontinence and micturition

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, rct – randomized controlled trial, TD – transdermal, TID – three times daily, UTI – urinary tract infection

Table A1 (con't): Characteristics of Included Studies focusing First Line treatment of OAB

Study	Herschorn S et al. 2010	Hughes et al. 2004	Nilsson FOL et al. 2011
Sponsorship	Pharmaceutical Industry	Pharmaceutical Industry	Not stated, but COI cited for Pharmaceutical Industry
Country	Canada	UK	Sweden
Perspective	HCS	HCS	HCS
Study type	CUA	CEA	CUA
Comparators	Solifenacing 5 mg daily Oxybutynin IR 5 mg TID	Oxybutynin IR 5 mg TID Oxybutynin XL 10 mg daily Tolterodine IR 2 mg BID Tolterodine ER 4 mg daily	Oxybutynin IR 5 mg TID Newer anticholinergics as a group (solifenacin, tolterodine, fesoterodine, darifenacin and oxybutynin patch) No treatment (placebo effect) No treatment (no effect)
Time horizon	1 year	1 year	1 year
Type of model	Markov model	Decision analytic model	Markov model
Efficacy inputs	single randomized controlled trial (VECTOR)	Systematic review of the literature	Patients within the Swedish Prescribed Drug Registry receiving OAB medications
Utilities	Kobelt utilities	Not applicable	King's Health Questionnaire transformed to utilities using 2 fesoteridine clinical trials
Costs included	OAB medications	OAB medications, incontinence appliances and pads, medical personnel salaries, surgery	OAB medications, physician visits, incontinence pads, dementia investigation
Outcomes	Cost per QALY	Incremental cost per incontinent free week	Cost per QALY
Results	a) solifenacin ICER \$14,092/QALY versus oxybutynin	a) oxybutynin IR versus no treatment – £2.58 to £16.59 per incontinent free week b) tolterodine ER vs oxybutynin IR – £7.14 per incontinent free week c) oxybutynin XL vs tolterodine ER – £84.82 per incontinent free week d) tolterodine IR dominated by tolterodine ER	a) newer anticholinergics versus no treatment – £21,045 / QALY b) newer anticholinergics versus placebo – £65,435 / QALY c) newer anticholinergics versus oxybutynin IR £37,119 / QALY
Types of sensitivity analyses	Deterministic and probabilistic analyses	Deterministic univariate analysis	Deterministic univariate sensitivity analysis
Results of sensitivity analysis	Most sensitive to discontinuation rates and inclusion of cost of incontinent pads, assumptions regarding treatment and utility for those who discontinue therapy	Sensitive to outcomes for discontinuing patients	Sensitive to costs of pads, frequency of serious adverse events and percentage of non-responders receiving alternative medication

HCS – healthcare system, COI – conflict of interest, CEA – cost effectiveness analysis, CUA – cost utility analysis, ER – extended release, OAB – overactive bladder, QALY – quality adjusted life years, XL – extended release

Table A2: Characteristics of Included Studies focusing on newer anticholinergic drugs / formulation as second line treatment of OAB

Study	O'Brien BJ et al. 2001	Nilsson FOL et al. 2011	Hakkaart L et al. 2009
Sponsorship	Pharmaceutical Industry	Not stated, but COI cited for Pharmaceutical Industry	Pharmaceutical Industry
Country	Canada	Sweden	UK
Perspective	Societal	HCS	HCS
Study type	CEA / CUA	CUA	CUA
Comparators	Oxybutynin followed by no treatment in those who discontinue Oxybutynin followed by tolterodine 2 mg BID in those who discontinue	Oxybutynin IR 5 mg TID Newer anticholinergics as a group (solifenacin, tolterodine, fesoterodine, darifenacin and oxybutynin patch) No treatment (placebo effect) No treatment (no effect)	Solifenacin 5 mg daily Solifenacin 10 mg daily Placebo
Time horizon	1 year	1 year	1 year
Type of model	Markov model	Markov model	Markov model
Efficacy inputs	Pooled data from 3 RCTs, discontinuation rates from provincial database	Patients within the Swedish Prescribed Drug Registry receiving OAB medications	Four placebo controlled trials of 12 weeks duration
Utilities	Kobelt utilities	King's Health Questionnaire transformed to utilities using 2 fesoteridine clinical trials	Kobelt utilities
Costs included	OAB medications, physician visits, incontinence pads	OAB medications, physician visits, incontinence pads, dementia investigation	OAB medications, incontinence pads
Outcomes	Cost per number of months in "normal" health state (no leakage)	Cost per QALY	Cost per QALY
Results	a) oxybutynin followed by tolterodine versus oxybutynin followed by no treatment - \$9982 / QALY	a) newer anticholinergics versus no treatment – £21,045 / QALY b) newer anticholinergics versus placebo – £65,435 / QALY c) newer anticholinergics versus oxybutynin IR £37,119 / QALY	a) solifenacin 5 mg versus placebo – £17,602 / QALY b) solifenacin 10 mg versus placebo £24,464 / QALY
Types of sensitivity analyses	Deterministic univariate analysis	Deterministic univariate sensitivity analysis	Deterministic analysis
Results of sensitivity analysis	Insensitive to changes in baseline cohort disease state distribution, oxybutynin dose, costs and utilities	Sensitive to costs of pads, frequency of serious adverse events and percentage of non-responders receiving alternative medication	Sensitive to assumptions regarding health state of patients who withdrew

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, RCT – randomized controlled trial, TD – transdermal, BID – twice daily, TID – three times daily, UTI – urinary tract infection

Table A2 (con't): Characteristics of Included Studies focusing on newer anticholinergic drugs / formulation as second line treatment of OAB

Study	Milsom I et al. 2009	Pradelli L et al. 2009	Kobelt G et al. 1998
Sponsorship	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry
Country	Norway, Finland, Sweden and Denmark	Italy	Sweden
Perspective	Societal and HCS	Societal and HCS	HCS
Study type	CEA / CUA	CEA / CUA	CEA / CUA
Comparators	Solifenacin 5 mg/day and 10 mg/day (flexible dosing) Tolterodine ER 4 mg/day Placebo	Solifenacin 5 mg/day Tolterodine ER 4 mg/day No treatment (placebo effect) No treatment (no effect)	Tolterodine IR 2 mg BID No treatment (no effect)
Time horizon	1 year	1 year	1 year
Type of model	Decision analytic model	Markov model	Markov model
Efficacy inputs	Selected RCTs	Selected RCTs	Pooled data from three 12 week RCTs
Utilities	Kobelt utilities	Kobelt utilities adjusted for a wet and dry rate	Kobelt utilities
Costs included	OAB medication costs, physician visits, laboratory tests, incontinence pads, productivity loss (human capital method)	OAB medications, incontinence pads, medical examinations, creams and other local treatments, productivity losses and cost of falls or fractures	OAB medication costs, GP visits, incontinence pads
Outcomes	Cost per micturition episode, incontinence episode, urge incontinence episode, urgency episode Cost per QALY	Cost per QALY Cost per continent patient	Cost per additional month spent in state 1 (minimal symptoms) Cost per QALY
Results	Solifenacin dominated tolterodine from societal and HCS perspectives Solifenacin versus placebo – €14,318 to €27,603 per QALY, depending on country from societal perspective Solifenacin versus placebo – €24,084 to €33,757 per QALY, depending on country from HCS perspective	Solifenacin vs placebo – €18,613/QALY Solifenacin vs no treatment – €7,634/QALY Tolterodine vs placebo – €2,600/QALY Tolterodine vs no treatment – €3,979/QALY	Tolterodine vs placebo US\$23,032 per QALY Tolterodine vs placebo US\$215 per additional month spent with minimal symptoms
Types of sensitivity analyses	Deterministic univariate analysis	Deterministic univariate analysis	Deterministic univariate analysis
Results of sensitivity analysis	Results were insensitive to changes in unit costs, frequency of adverse events and separate analyses for 5 mg and 10 mg solifenacin.	Results were most sensitive to drug costs, utility derivation and utility adjustment for wet and dry rate and perspective of analysis	Results were insensitive to changes in drop outs, time horizon (up to 2 years) and utilities

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, RCT – randomized controlled trial, TD – transdermal, BID – twice daily, TID – three times daily, UTI – urinary tract infection

Table A3: Comparative cost effectiveness of the newer anticholinergic drugs / formulations

Study	Arlandis-Guzman S et al. 2011	Armstrong EP et al. 2012	Cardozo L et al. 2010	Getsios D et al. Clin Drug Invest 2004.
Sponsorship	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry
Country	Spain	United States	UK	UK
Perspective	Societal	Third party payer	HCS	HCS
Study type	CUA	CEA	CUA	CEA / CUA
Comparators	Fesoterodine 4 mg/day Tolterodine ER 4 mg/day Solifenacin 5 mg/day	Darifenacin 7.5 mg/day Fesoterodine 8 mg/day Oxybutynin IR 5 mg BID Oxybutynin ER 30 mg/day Oxybutynin TD gel 1 sachet daily Oxybutynin TD patch every 3.5 days Solifenacin 5 mg/day Tolterodine IR 2 mg/day Tolterodine ER 4 mg/day Trosipium IR 20 mg BID Trosipium ER 60 mg/day	fesoterodine 4 mg/day & 8 mg/day oxybutynin IR 15 mg/day propiverine ER 20 mg/day solifenacin 5 mg/day & 10 mg/day tolterodine ER 4 mg/day tolterodine IR 2 mg/day and 4 mg/day	Oxybutynin XL 4 mg/day Tolterodine IR 4 mg/day
Time horizon	1 year	3 months	1 year	1 year
Type of model	Decision tree model	Decision analytic model	Decision tree	Markov model
Efficacy inputs	Selected 12 week RCTs	Pooled results from literature review	Meta-analysis	A 12 week RCT
Utilities	King's Health Questionnaire transformed to utilities base on continence category	Not applicable	Kobelt utilities categorized as no response, partial response & full response	Kobelt utilities
Costs included	OAB medications, physician visits, laboratory tests, incontinence pads, comorbidities (fractures, skin infections, UTIs, depression, nursing home admissions), productivity losses	OAB medications, comorbidities (skin irritations, depression, falls)	OAB medications, outpatient visits (resource use based on expert opinion)	OAB medications, incontinence pads and laundry
Outcomes	Cost per QALY	Cost per additional continent patient	Cost per QALY Discontinuation rates as per real world database	Cost per incontinent episode avoided Cost per additional patient achieving continence Cost per QALY
Results	Fesoterodine dominated tolterodine and solifenacin Fesoterodine QALY gain - 0.01014; solifenacin QALY gain - 0.00957; tolterodine QALY gain - 0.00846 Fesoterodine costs - €1,937; solifenacin costs - €1,960; tolterodine costs - €2,089	Oxybutynin IR was least costly All other treatment apart from solifenacin were dominated by solifenacin Solifenacin vs oxybutynin IR - \$1338 per additional continent patient	a) oxybutynin IR was the least costly therapy b) fesoterodine, tolterodine ER & tolterodine IR dominated by solifenacin c) solifenacin - £80,000/QALY versus oxybutynin IR	Oxybutynin XL dominated tolterodine IR for all endpoints
Types of sensitivity analyses	Deterministic univariate analysis	Deterministic univariate and probabilistic analysis	Deterministic and probabilistic analyses	Deterministic univariate analysis
Results of sensitivity analysis	Results were sensitive to the analysis perspective, time horizon and percent of continent patients	Results were sensitive to the analysis perspective, time horizon and percent of continent patients	Results not reported but stated robust to changes in utility values, treatment effects & discontinuation rates	Results were insensitive to discontinuation rates, time horizon, utilities, non-pharmaceutical costs, inclusion of comorbidity costs and drug costs

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, RCT – randomized controlled trial, TD – transdermal, BID – twice daily, TID – three times daily, UTI – urinary tract infection

Table A3 (con't): Comparative cost effectiveness of the newer anticholinergic drugs/formulations

Study	Getsios D et al. Clin Therap 2004.	Guest JF et al. 2004	Hughes et al. 2004	Milsom I et al. 2009
Sponsorship	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry	Pharmaceutical Industry
Country	Canada	Austria, France and UK	UK	Norway, Finland, Sweden and Denmark
Perspective	Patients	HCS	HCS	Societal and HCS
Study type	CEA	CEA	CEA	CEA / CUA
Comparators	Oxybutynin XL 10 mg daily Tolterodine IR 2 mg BID	Oxybutynin CR (up to 10 mg/day) Oxybutynin IR (up to 10 mg/day) Tolterodine IR (up to 4 mg/day)	Oxybutynin IR Oxybutynin ER Tolterodine IR Tolterodine ER	Solifenacin 5 mg/day and 10 mg/day (flexible dosing) Tolterodine ER 4 mg/day Placebo
Time horizon	1 year	6 months	1 year	1 year
Type of model	Markov model	Decision tree model	Decision analytic model	Decision analytic model
Efficacy inputs	A 12 week RCT	Pooled results of RCTS and clinical interviews	Systematic review of literature	Selected RCTS
Utilities	Not applicable	Not applicable	Not applicable	Kobelt utilities
Costs included	OAB medications, GP visits, incontinence pads, laundry costs	OAB medications, UTI treatment, laboratory tests, incontinence pads, GP and specialist visits, other practitioner visits, surgeries, hospitalizations, lost productivity	OAB medications, incontinence appliances, incontinence pads, medical personnel salaries, surgical costs	OAB medication costs, physician visits, laboratory tests, incontinence pads, productivity loss (human capital method)
Outcomes	Cost per additional incontinence-free day	Cost per incontinent episode avoided Cost per additional micturition	Incremental cost per incontinent free week	Cost per micturition episode, incontinence episode, urge incontinence episode, urgency episode Cost per QALY
Results	Oxybutynin XL dominated tolterodine IR with 16.5 additional incontinent free days and one year cost of \$32 lower than tolterodine IR	Starting treatment with Oxybutynin CR was a dominant strategy in UK and Austrai and was cost effective in France	Oxybutynin IR vs no treatment - incremental cost of £2.58 to £16.59 per incontinent free week Tolterodine ER vs oxybutynin IR – incremental cost of £7.14 per incontinent free week Oxybutynin XL vs tolterodine ER – incremental cost of £84.82 per incontinent free week Tolterodine IR dominated by tolterodine ER	Solifenacin dominated tolterodine from societal and HCS perspectives Solifenacin versus placebo – €14,318 to €27,603 per QALY, depending on country from societal perspective Solifenacin versus placebo – €24,084 to €33,757 per QALY, depending on country from HCS perspective
Types of sensitivity analyses	Deterministic univariate analysis	Deterministic univariate and probabilistic analyses	Deterministic univariate analysis	Deterministic univariate analysis
Results of sensitivity analysis	Results were sensitive to the relative cost of the two medications	French perspective: results most sensitive to discontinuation rates, number of outpatient visits UK and Austrian perspective: results most sensitive to percentage reduction in frequency of incontinence and micturition	Results were sensitive to outcomes for discontinued patients and persistence with therapy	Results were insensitive to changes in unit costs, frequency of adverse events and separate analyses for 5 mg and 10 mg solifenacin.

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, RCT – randomized controlled trial, TD – transdermal, BID – twice daily, TID – three times daily, UTI – urinary tract infection

Table A3 (con't): Comparative cost effectiveness of the newer anticholinergic drugs/formulations

Study	Noe et al. 2002	Perfetto et al. 2005	Pradelli L et al. 2009	Speakman M et al 2008
Sponsorship	Pharmaceutical Industry	None reported	Pharmaceutical Industry	Pharmaceutical Industry
Country	USA	US	Italy	UK
Perspective	Societal	HCS	Societal and HCS	HCS
Study type	CMA	CMA	CEA / CUA	CUA
Comparators	Oxybutynin ER 5 mg/day, 10 mg/day, 15 mg/day (flexible dosing) Tolterodine ER 2 mg/day and 4 mg/day (flexible dosing)	Oxybutynin ER 10 mg/day Tolterodine ER 4 mg/day	Solifenacin 5 mg/day Tolterodine ER 4 mg/day No treatment (placebo effect) No treatment (no effect)	Solifenacin 5 mg/day and 10 mg/day (flexible dosing) Tolterodine IR 2 mg BID Tolterodine ER 4 mg/day
Time horizon	3 months	1 year	1 year	1 year
Type of model	Decision analytic model	Decision analytic model	Markov model	Markov model
Efficacy inputs	Assumed equal efficacy of treatments	Assumed equal efficacy of treatments	Selected RCTs	A 12 week RCT
Utilities	Not applicable	Not applicable	Kobelt utilities adjusted for a wet and dry rate	Kobelt utilities
Costs included	OAB medications, other medications, physician visits, incontinence pads, non-pharmacologic OAB treatments, comorbid conditions, productivity losses, specialist visits, investigative tests	OAB medications, inpatient and outpatient medical management costs, incontinence pads	OAB medications, incontinence pads, medical examinations, creams and other local treatments, productivity losses and cost of falls or fractures	OAB medications, primary care visits, incontinent pads
Outcomes	Costs	Costs	Cost per QALY Cost per continent patient	Cost per QALY
Results	Tolterodine ER – \$1,207 for 3 months Oxybutynin CR - \$1,283 for 3 months	Tolterodine ER - \$8876 for 1 year Oxybutynin ER - \$9080 for 1 year	Solifenacin vs placebo – €18,613/QALY Solifenacin vs no treatment – €7,634/QALY Tolterodine vs placebo – €2,600/QALY Tolterodine vs no treatment – €3,979/QALY	Solifenacin was dominant treatment with lower costs versus tolterodine (£509 versus £526) and slightly greater QALY (difference of +0.04)
Types of sensitivity analyses	Decision univariate analysis	Decision univariate analysis	Deterministic univariate analysis	Deterministic univariate analysis
Results of sensitivity analysis	Results were relatively insensitive to changes in costs Results were sensitive to changes in resource utilization and discontinuation rates	Results were robust to changes in medication costs and discontinuation rates Results sensitive to medical management costs	Results were most sensitive to drug costs, utility derivation and utility adjustment for wet and dry rate and perspective of analysis	Results were insensitive to discontinuation rate, percent of patients treated with solifenacin 10 mg/day, baseline symptoms and utility scores

HCS – healthcare system, CEA – cost effectiveness analysis, CR – controlled release, CUA – cost utility analysis, ER – extended release, ICER – incremental cost effectiveness ratio, IR – immediate release, OAB – overactive bladder, QALY – quality adjusted life years, RCT – randomized controlled trial, TD – transdermal, BID – twice daily, TID – three times daily, UTI – urinary tract infection

Appendix A: Comparative cost effectiveness of the newer anticholinergic drugs/formulations

There were 12 studies which examined the comparative cost effectiveness of the newer anticholinergic drugs/formulations. One of the studies was from a Canadian perspective (Getsios 2004 (Clin Ther)), four were from the perspective of the United Kingdom (Cardoza 2010, Speakman 2008, Getsios 2004 (Clin Drug Invest), Hughes 2004), three from a US perspective (Armstrong 2012, Perfetto 2005, Noe 2002) and the remaining four were from various European perspectives (Guest 2004, Milsom 2009, Pradelli 2009, Arlandis-Guzman 2011).

Comparisons of oxybutynin ER and tolterodine IR/ER

There were three studies which compared oxybutynin ER with tolterodine IR. (Getsios 2004 (Clin Ther), Getsios 2004 (Clin Drug Invest), Guest 2004). In all three studies tolterodine IR was dominated by oxybutynin ER.

There were two cost minimization analyses that compared oxybutynin ER with tolterodine ER (Perfetto 2005, Noe 2002), with the assumption that the efficacy of the two medications was equivalent. Treatment with tolterodine ER was found to be less costly than treatment with oxybutynin ER, in both cases.

One additional study by Hughes compared oxybutynin IR, oxybutynin ER, tolterodine IR and tolterodine ER in a UK cost effectiveness analysis which supported the results of the previous five studies. Oxybutynin IR was found to be the least costly therapy with an incremental cost per incontinent free week of £2.58 to £16.59, depending on assumptions regarding discontinuers. Tolterodine ER was associated with an incremental cost per incontinent free week of £7.14 versus oxybutynin IR, but was dominated in sensitivity analyses where discontinuers either reverted to baseline or achieved efficacy of the placebo arm and when full persistence was assumed. Oxybutynin ER was more expensive again, with an incremental cost per incontinent free week of £84.82 versus tolterodine ER. Tolterodine IR was dominated by tolterodine ER within the base case and by oxybutynin IR within sensitivity analyses. The comparative efficacy of oxybutynin ER and tolterodine ER were not based on head-to-head clinical trials.

From this evidence the following may be concluded:

- Evidence supports oxybutynin IR as the least costly therapy for overactive bladder.
- Overall, these studies appear to support a cost effectiveness advantage of oxybutynin ER over tolterodine IR.
- The comparative cost effectiveness of the extended release formulation of oxybutynin and tolterodine is difficult to assess as the analyses were not based on head-to-head clinical trials. As stated within the clinical analysis, the only clinical trial comparing these medications was small and used non-equivalent doses. In two of the economics studies the medications were assumed to have equivalent efficacy and in the third, results from separate trials were used with baseline adjustment. Without clearer information regarding the comparative efficacy and safety of these medications a conclusion regarding their comparative cost effectiveness cannot be reached.

Other Newer Anticholinergics

There were three studies which compared solifenacin with only tolterodine IR or tolterodine ER (Milsom 2009, Pradelli 2009, Speakman 2008). In two of the studies which examined a flexible dose of solifenacin 5 mg and 10 mg, solifenacin was dominant over tolterodine ER and tolterodine IR (Milsom 2009, Speakman 2008). In the third study, by Pradelli, there was no direct comparison between solifenacin 5 mg and tolterodine ER; however, the ICER for solifenacin versus no treatment was lower than it was for tolterodine ER versus no treatment.

As stated within the clinical review differences in efficacy between solifenacin and tolterodine ER were modestly in favour of solifenacin; however, solifenacin was also associated with greater dry mouth and constipation than tolterodine ER. In the three cost effectiveness studies the clinical efficacy outcomes were converted to utilities using the method suggested by Kobelt. (Kobelt 1998) This resulted in a modest benefit in favour of solifenacin; however, the effect of adverse events on the quality of life of patients who remain on therapy was not accounted for in any of these trials. The clinical review found that patients on solifenacin may experience greater constipation and dry mouth. The only accounting for differences in adverse events in the economic analyses was through the assumption that those who experienced adverse events discontinued therapy. In two of the studies (Milsom 2009 and Pradelli 2009) clinical trial discontinuation rates were used, which are likely to significantly underestimate true discontinuation rates and in the third study two separate open label trials were used, which are likely to provide both an underestimation of the true discontinuation rate and an inaccurate reflection of the true difference between treatments as the patient populations of the studies may differ. Due to the significant number of drawbacks relating to these studies there is inadequate evidence to support a difference in cost effectiveness between solifenacin and tolterodine ER.

There were three studies which incorporated both solifenacin and fesoterodine into their analyses with conflicting results (Cardozo 2010, Arlandis-Guzman 2011, Armstrong 2012). Cardoza compared the cost effectiveness of oxybutynin IR, propiverine ER, solifenacin, tolterodine ER, tolterodine IR and fesoterodine from a UK perspective. They found oxybutynin IR to be the least costly therapy. Solifenacin dominated all other treatments, but resulted in an ICER of £80,000/QALY versus oxybutynin IR. Armstrong compared the cost effectiveness of darifenacin, fesoterodine, oxybutynin IR, oxybutynin ER, oxybutynin gel, oxybutynin patch, solifenacin, tolterodine IR, tolterodine ER, trospium IR and trospium ER. They also found that oxybutynin IR was the least costly therapy and solifenacin dominated all other treatments apart from oxybutynin IR. The incremental cost per additional continent patient was \$1338 (US) for solifenacin versus oxybutynin IR based on annualized costs and 3-7 day continence diaries administered during a 12 week trial. Finally, Arlandis-Guzman compared the cost effectiveness of fesoterodine with tolterodine ER and solifenacin from a Spanish perspective. In this case fesoterodine dominated the other two treatments resulting in greater QALYs at a lower cost.

As with all the literature in this area these studies suffer from a number of limitations, some of which have contributed to the conflicting results. The drawbacks of the Carodoza study have been reviewed

earlier within this paper; however, specifically with respect to a comparison between the newer anticholinergics the results for fesoterodine should be viewed as speculative as the discontinuation rate for fesoterodine was imputed and assumed to be equivalent to tolterodine ER. With respect to the other two studies, they both incorporated the costs of multiple co-morbidities including falls, depression, urinary tract infections and skin infections. None of these agents have been shown, within clinical trials, to have an impact on these comorbidities. In both analyses the discontinuation rates were based on 12 week clinical trial data. No extrapolation was required in the Armstrong study as the model was only 12 weeks in duration; however, within Arlandis-Guzman the rates were assumed to be equivalent to placebo for the 12 to 52 week period. The use of clinical trial discontinuation rates is likely to significantly underestimate the true discontinuation rate with these medications and does not allow for the examination of differences between the therapies. With respect to efficacy measurement within the trials, Arlandis-Guzman estimated the proportion of patients who were continent and those that were incontinent based on head to head trials for fesoterodine and tolterodine and abstracted from the literature for solifenacin. Armstrong, on the other hand, used the 3 to 7 day continence rates based on clinical trials. This provides a biased measure of comparative efficacy of the treatments as the studies of some drugs such as tolterodine ER used 7 day continence diaries; whereas, the newer agents, such as solifenacin used 3 day diaries. These are not equivalent measures as the longer you record data, the more likely you will record an incontinent episode. Lastly, none of the studies incorporated the disutilities or costs associated with those who remain on therapy with adverse events.

From this literature there does not appear to be adequate evidence to support conclusions regarding differences in cost effectiveness between the newer anticholinergics studied.