Antidepressants for Major Depressive Disorder:
Drug Information to Support Drug Therapy Decisions

B.C. Provincial Academic Detailing (PAD) Service **March 2020**

Background

This PAD education session focuses on commonly prescribed and recently marketed antidepressants for major depressive disorder.

After achieving remission of an initial depressive episode, clinical practice guidelines recommend several months of continued antidepressant therapy (recommendations vary from 4 to 12 months) and longer if someone is at risk for relapse or has experienced recurrent episodes.[1-6]

A recent primary care trial found that discontinuing antidepressant therapy can be challenging even for people considered candidates for discontinuation according to guidelines.[7] 51% of people in the trial agreed to try a taper to discontinue their antidepressant therapy when provided with the recommendation from their primary care physician. Ten of 146 people considered eligible for antidepressant discontinuation were no longer taking an antidepressant at the end of follow up.

Acknowledging that the most appropriate duration of antidepressant therapy is not known,[8] participants in this PAD session will have the opportunity to discuss drug information that informs several decisions regarding antidepressants for non-pregnant adults, including:

1. How the efficacy of antidepressants is measured in clinical trials and reported in meta-analyses

2. The quality and quantity of evidence that informs conclusions regarding antidepressant comparisons and combinations

3. Drug information relevant to the prescribing, deprescribing and monitoring of antidepressants, including:
   - dose response
   - adverse events
   - clinical toxicology
   - drug interactions
   - available dosage forms and ability to taper practically
   - cost and coverage

Antidepressant	Brand Name	Marketed[9]
Fluoxetine	Prozac	1989
Sertraline	Zoloft	1992
Paroxetine	Paxil	1993
Venlafaxine	Effexor	1994
Bupropion	Wellbutrin	1998
Citalopram	Celexa	1999
Mirtazapine	Remeron	2001
Escitalopram	Cipralex	2005
Duloxetine	Cymbalta	2008
Desvenlafaxine	Pristiq	2009
Vortioxetine	Trintellix	2014
Levomilnacipran	Fetzima	2015
Vilazodone	Viibryd	2018

Antidepressant Clinical Trials

The most common efficacy measures used in antidepressant randomized controlled trials are symptom severity scales (clinician administered), eg:[1-3]

- Hamilton Depression Rating Scale (17 item) (HDRS-17: score range 0 to 52), and the
- Montgomery Asberg Depression Rating Scale (MADRS: score range 0 to 60).

Antidepressant trials have often excluded people with:[2,4-7]

- less severe depression scores (eg, HDRS < 19),
- depression with psychotic features,
- suicidal ideation,
- substance use disorder, or
- serious medical comorbidity.

In the largest dataset of published and unpublished trials, (522 trials; 116,477 participants):[2]

- mean age was 44; two-thirds were women,
- mean HDRS-17 score was 26 at baseline, and the
- median duration of the trials was 8 weeks.

Efficacy is often reported as a:

- continuous outcome: mean difference in depression severity scores achieved in the antidepressant group compared to the placebo group, or a
- dichotomous outcome: proportion of people achieving at least a 50% improvement in symptom severity scores.

Antidepressant Onset of Effect

Health Canada and the US Food and Drug Administration generally do not detail the time course of treatment response for antidepressants, but:[24-57]

- meta-analyses demonstrate evidence of improvement in depression symptom scales within the first 1 to 2 weeks, and[58,59]
- the effect appears largely maximized by 6 to 8 weeks.[24,59,60]

Antidepressant Dose Response

Antidepressants are generally approved by Health Canada and the US Food and Drug Administration:

- with a defined dosage range, but
- the relationship between dose and response is often not well characterized.[24-57]

For several antidepressants, efficacy appears optimized below the maximum approved dose, and:

- there is a more consistent relationship between higher doses and adverse events leading to drug discontinuation (See Table 1).[61,62]

Antidepressant Meta-Analyses & Systematic Reviews

The mean difference in improvement achieved in the antidepressant group as compared to the improvement achieved in the placebo group is:

- approximately 2 points (HDRS-17),[3,8,9]
- eg, in one meta-analysis: mean 9.6 point improvement in the antidepressant group versus 7.8 point improvement in the placebo group.[8]

Proportion of people achieving at least a 50% improvement in their symptom severity score (median 8 weeks):

- 45-50%* in the antidepressant group, and
- 35% in the placebo group.[2,10]

*citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, vortioxetine, venlafaxine, desvenlafaxine, duloxetine, levomilnacipran, mirtazapine, bupropion

In short-term (6 to 12 week) antidepressant trials:

- approximately 1 in 3 people discontinue treatment (antidepressant or placebo).[11]

Systematic reviews and network meta-analyses of antidepressant comparisons:

- do not claim substantial differences in efficacy;[2,12-22]
- the largest network meta-analysis did not identify high quality evidence for comparisons.[2]

Direct comparisons of recently marketed antidepressants (eg, levomilnacipran, vilazodone, vortioxetine) to more commonly prescribed antidepressants are limited.[2,21,22]

Evidence is incomplete for functional outcomes, quality of life, specific and serious* adverse events.[2,9-23]

*eg, death, disability, hospitalization

Combining Antidepressants

When response to initial antidepressant therapy is considered inadequate, available evidence does not reliably inform next drug therapy steps:[2,63,64]

- switching antidepressants,
- adding another antidepressant, or
- adding a non-antidepressant.

Combining antidepressants with dissimilar pharmacologic profiles has been proposed (eg, adding mirtazapine or bupropion to an SSRI or SNRI), but:

- few methodologically rigorous trials have examined the efficacy and safety of these combinations.[63,65-68]

Table 1: Antidepressant Drug Information

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]	**Selected Adverse Events and Comparisons** not intended to reproduce a product monograph
Organized by conventional pharmacologic classifications, however the mechanism of antidepressant effect is not known.[4-36] **There are no accepted biomarkers for assessing antidepressant effects (US Food and Drug Administration).**[37]				
serotonin reuptake inhibitors (SSRIs)[4-15]				▪ **adverse events:** information on specific adverse events, serious adverse events, and long-term safety is incomplete;[40-54] direct comparisons of more recently marketed antidepressants (vilazodone, vortioxetine, levomilnacipran) to commonly prescribed antidepressants are particularly limited;[41,45,53] cautious interpretation of comparative risks: in the largest network meta-analysis, antidepressant comparisons were not informed by high quality evidence[41] ▪ **adverse events leading to discontinuation:** statistically more with venlafaxine compared to citalopram, escitalopram, fluoxetine, sertraline, vortioxetine; statistically more with duloxetine compared to escitalopram, venlafaxine, desvenlafaxine; statistically more with mirtazapine compared to sertraline (low to moderate quality evidence)[41] ▪ **agitation-type adverse events**: Health Canada advises monitoring for suicidal ideation, agitation and behaviour changes (eg, akathisia, agitation, emotional lability, hostility, aggression, depersonalization) when initiating antidepressant therapy or during change in dose or regimen[1] ▪ **clinical toxicology** (case series, observational studies of acute overdoses, poisonings): SSRIs: associated with lower risk of morbidity and mortality (cardiovascular, seizures) relative to other antidepressants such as venlafaxine, desvenlafaxine, bupropion;[20,21,55-59] citalopram, escitalopram: increased risk of seizures and QTc prolongation compared to other SSRIs;[55] vilazodone: serotonin toxicity and seizures potentially more common in overdose and poisonings than SSRIs but information is limited;[60] British Columbia Drug and Poison Information Centre → dpic.org ▪ **withdrawal symptoms:** potentially greater prevalence with paroxetine, venlafaxine, desvenlafaxine, duloxetine[43,44,61-65]
citalopram Celexa, generic 10, 20, 40 mg TAB	initial: 10-20 mg once a day max: 40 mg $T_{1/2}$ ~ 37 hrs Css ~ 1-2 weeks	▪ maximum: 40 mg due to QTc prolongation ▪ dose response: efficacy increases up to ~20-40 mg; discontinuation due to adverse events linear to exponential relationship; balance of efficacy + tolerability ~20-40 mg (systematic review)[38] ▪ ▼ dose: advanced age, hepatic impairment, CYP2C19 poor metabolizers ▪ ▼ dose: CYP2C19 inhibitor, cimetidine	10 mg: $2.50 20 mg: $5 40 mg: $5 **regular benefit**	
escitalopram Cipralex, generic 10, 20 mg TAB (S-isomer of citalopram)	initial: 5-10 mg once a day max: 20 mg $T_{1/2}$ ~ 27-32 hrs Css ~ 1 week	▪ maximum: 20 mg due to QTc prolongation ▪ dose response: efficacy increases up to ~10-20 mg; discontinuation due to adverse events linear to exponential relationship; balance of efficacy + tolerability ~10-20 mg (systematic review)[38] ▪ ▼ dose: advanced age, hepatic impairment, CYP2C19 poor metabolizers ▪ ▼ dose: CYP2C19 inhibitor, cimetidine	5 mg: $5 10 mg: $10 20 mg: $10 **regular benefit**	
fluoxetine Prozac, generic 10, 20, 40, 60 mg CAP 20 mg/5 mL SOLUTION	initial: 20 mg once a day in the morning max: 60 mg $T_{1/2}$ ~ 4-16 days Css ~ 4-5 weeks	▪ dose response: efficacy increases up to ~20-40 mg; discontinuation due to adverse events linear to exponential relationship; balance of efficacy + tolerability ~20-40 mg (systematic review)[38] ▪ ▼ dose: advanced age, renal or hepatic impairment	10 mg: $10 20 mg: $10 40 mg: $20 60 mg: $30 solution 20 mg: $50 **regular benefit**	
paroxetine Paxil, generic 10, 20, 30 mg TAB **paroxetine** Paxil CR 12.5, 25 mg TAB controlled release do not crush or chew	initial: 10-20 mg once a day max: 50 mg initial: 12.5-25 mg CR once a day max: 62.5 mg $T_{1/2}$ ~ 24 hrs Css ~ 1-2 weeks	▪ dose response: efficacy increases up to ~20-40 mg; discontinuation due to adverse events linear to exponential relationship; balance of efficacy + tolerability ~20-40 mg (systematic review)[38] ▪ ▼ dose: advanced age, renal or hepatic impairment	10 mg: $35 **non benefit** 20 mg, 30 mg: $10 50 mg: $25 **regular benefit** 12.5 mg CR: $60 25 mg CR: $65 62.5 mg CR: $190 **non benefit**	
sertraline Zoloft, generic 25, 50, 100 mg CAP	initial: 25-50 mg once a day with food max: 200 mg $T_{1/2}$ ~ 26 hrs Css ~ 1 week	▪ dose response: efficacy increases up to ~50-100 mg; discontinuation due to adverse events linear to exponential relationship; balance of efficacy + tolerability ~50-100 mg (systematic review)[38] ▪ ▼ dose: hepatic impairment	25 mg: $5 50 mg: $10 100 mg: $10 200 mg: $20 **regular benefit**	

Table 1: Antidepressant Drug Information continued

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]	**Selected Adverse Events and Comparisons** not intended to reproduce a product monograph
serotonin reuptake inhibitor, serotonin partial agonist[16,17]				▪ **insomnia versus somnolence:** most SSRI and SNRI antidepressants increase the risk of both insomnia and somnolence compared to placebo (meta-analysis);[66] mirtazapine increased risk of somnolence but not insomnia;[66] bupropion increased risk of insomnia but not somnolence[66] ▪ **cardiovascular** SNRIs, bupropion: increase blood pressure and heart rate; effect increases with dose;[20-27,31-34] levomilnacipran: contraindicated in heart failure NYHA Class III or IV, uncontrolled tachyarrhythmia or hypertension, recent myocardial infarction or cardiac intervention, history of cerebrovascular accident;[26] QTc prolongation: CredibleMeds QT drug lists → crediblemeds.org ▪ **sexual dysfunction:** defined and reported inconsistently in trials which makes comparisons uncertain;[67-69] mirtazapine, bupropion: potentially lower risk than SSRI comparators;[43,44,48,68,69] vortioxetine: 2-point improvement on 70-point sexual dysfunction scale compared to escitalopram (one trial);[19,70] case reports of sexual dysfunction persistence after SSRI or SNRI discontinuation (European Medicines Agency)[71,72] ▪ **antimuscarinic (anticholinergic):** consider antidepressants as potential contributors to anticholinergic burden[73] ▪ **hyponatremia:** SSRIs, SNRIs, vilazodone, vortioxetine, mirtazapine, bupropion[4-34] ▪ **body weight:** mirtazapine: potentially greater risk of weight gain;[43,44,48,74,75] bupropion, fluoxetine: consider potential for unintended weight loss in people with anorexia or weight loss (Health Canada)[8,31,32]
vilazodone Viibryd 10, 20, 40 mg TAB	initial: 10 mg once a day with food for 7 days max: 40 mg $T_{1/2}$ ~ 25 hrs Css ~ 3 days	▪ dose response: not adequately characterized (US FDA)[35] ▪ ▼ dose: CYP3A4 inhibitor	10 mg: $100 20 mg: $100 40 mg: $135 **non benefit**	
serotonin reuptake inhibitor, serotonin partial agonist, serotonin antagonist[18,19]				
vortioxetine Trintellix 5, 10, 20 mg TAB	initial: 5-10 mg once a day max: 20 mg $T_{1/2}$ ~ 66 hrs Css ~ 2 weeks	▪ dose response: possible relationship between dose and efficacy across 5-20 mg range but results inconsistent (systematic review);[39] nausea increases with dose (US FDA)[36] ▪ ▼ dose: advanced age, CYP2D6 poor metabolizer ▪ ▼ dose: CYP2D6 inhibitor ▪ contraindicated: severe hepatic impairment	5 mg: $95 10 mg: $100 20 mg: $105 **limited coverage** (as of July 2021)	
serotonin norepinephrine reuptake inhibitors (SNRIs)[20-27]				
venlafaxine Effexor XR, generic 37.5, 75, 150 mg CAP extended release do not crush or chew	initial: 37.5 mg once a day for 4 to 7 days, then 75 mg max: 225 mg $T_{1/2}$ ~ 5-11 hrs Css ~ 3-5 days	▪ dose response: efficacy increases up to 75-150 mg then modest increase >150 mg; discontinuation due to adverse events steep linear relationship; balance of efficacy + tolerability ~75-150 mg (systematic review)[38] ▪ ▼ dose: renal or hepatic impairment	37.5 mg: $5 75 mg: $5 150 mg: $5 225 mg: $10 **regular benefit**	
desvenlafaxine Pristiq, generic 50, 100 mg TAB extended release do not crush or chew (major metabolite of venlafaxine)	initial: 50 mg once a day max: 100 mg $T_{1/2}$ ~ 11 hrs Css ~ 4-5 days	▪ dose response: no additional benefit above 50 mg; adverse events and discontinuations more frequent at higher doses (Health Canada, US FDA)[22,23] ▪ ▼ dose: renal impairment	50 mg: $75 100 mg: $75 **non benefit**	
duloxetine Cymbalta, generic 30, 60 mg CAP delayed release do not crush or chew	initial: 30 mg once a day for 7 to 14 days, then 60 mg max: 60 mg $T_{1/2}$ ~ 8-17 hrs Css ~ 3 days	▪ dose response: no additional benefit above 60 mg (Health Canada, US FDA);[24,25] in anxiety disorder trials, incidence of sweating, diarrhea, vomiting doubles at 120 mg (Health Canada)[24] ▪ ▼ dose: renal impairment ▪ contraindicated: any hepatic impairment, CrCl < 30 mL/min	30 mg: $15 60 mg: $30 **non benefit**	

Table 1: Antidepressant Drug Information continued

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]	**Selected Adverse Events and Comparisons** not intended to reproduce a product monograph
serotonin norepinephrine reuptake inhibitors (SNRIs)[20-27]				▪ **gastrointestinal:** venlafaxine: higher rate of nausea and vomiting than SSRIs;[43,44] sertraline: higher rate of diarrhea than comparators;[43,44,47] vilazodone: diarrhea, nausea, vomiting ~50% participants (US FDA);[76] desvenlafaxine: tablet is a non-absorbable shell, potential for obstruction in people with gastrointestinal stricture;[22] duloxetine: enteric coating protects pellets against degradation to naphthol in acidic environment which can cause abdominal pain, cramping, nausea, vomiting and other severe systematic effects[77] ▪ **glaucoma:** link between antidepressant use and the occurrence of glaucoma but Health Canada could not differentiate risk between antidepressants;[78] duloxetine: contraindicated in people with uncontrolled glaucoma[24] ▪ **mirtazapine:** somnolence ~50% participants;[28] half-life increases, drug clearance decreases significantly with age;[28] more likely to cause dry mouth, weight gain, fatigue, somnolence than SSRIs but less likely to cause sweating, nausea or vomiting (systematic review)[48] ▪ **bupropion:** epileptogenic: contraindicated in seizure disorder, bulimia, anorexia, alcohol or sedative withdrawal (Health Canada);[31,32] consider risk factors: head trauma, CNS tumour, hepatic impairment, substance or alcohol misuse, insulin or hypoglycemics, other medications that lower seizure threshold (Health Canada);[31,32] agitation, insomnia, tremor, tinnitus: dose related and potential for prescribing cascade with addition of sedative hypnotics (Health Canada);[31,32] amphetamine-like pharmacology (US FDA);[79] misuse potential: oral, intranasal, injection;[57,80] urine toxicology: potentially false positive for amphetamine[55]
levomilnacipran Fetzima 20, 40, 80, 120 mg CAP extended release do not crush or chew	initial: 20 mg once a day for 2 days, then 40 mg max: 120 mg $T_{1/2}$ ~ 12 hrs Css ~ 3 days	▪ dose response: additional benefit not consistently demonstrated above 40 mg; urinary hesitancy, erectile dysfunction increases with dose (Health Canada)[26] ▪ ▼ dose: advanced age, renal impairment ▪ ▼ dose: CYP3A4 inhibitor ▪ not recommended: CrCl < 15 mL/min	20 mg: $120 40 mg: $125 80 mg: $130 120 mg: $140 **non benefit**	
alpha 2 antagonist, noradrenergic, serotonergic, antihistaminic, antimuscarinic, alpha 1 antagonist[28-30]				
mirtazapine Remeron, generic 15, 30, 45 mg TAB Remeron RD, generic 15, 30, 45 mg TAB orally disintegrating	initial: 15 mg once a day in the evening max: 45 mg $T_{1/2}$ ~ 20-40 hrs Css ~ 5 days	▪ dose response: efficacy increases up to 30 mg then decreases at higher doses; discontinuation due to adverse events steep linear relationship; balance efficacy + tolerability at 30 mg maximum (systematic review)[38] ▪ ▼ dose: advanced age, renal and hepatic impairment	15 mg: $5 30 mg: $10 45 mg: $10 **regular benefit**	
dopamine norepinephrine reuptake inhibitor[31-34]				
bupropion Wellbutrin SR, generic 100, 150 mg TAB sustained release do not crush or chew	usual: 100 to 150 mg SR once a day in the morning max: 300 mg SR per day; if > 150 mg SR, dose twice a day, 8 hours apart	▪ maximum: 300 mg per day and 150 mg SR per dose due to seizure risk (Health Canada)[31,32] ▪ dose response: discrepancy, flat dose response relationship across the 100-300 mg range for the SR formulation whereas 300 mg defined as the target dose for XL formulation (Health Canada)[31,32] ▪ ▼ dose: advanced age, renal and hepatic impairment ▪ not recommended: severe hepatic impairment	100 mg SR: $5 150 mg SR: $7.50 300 mg SR: $15 **limited coverage**	
bupropion Wellbutrin XL, generic 150, 300 mg TAB extended release do not crush or chew	initial: 150 mg XL once a day in the morning max: 300 mg $T_{1/2}$ ~ 21-37 hrs Css ~ 5-8 days		150 mg XL: $5 300 mg XL: $10 **limited coverage**	

▼ **dose:** Health Canada recommendation to lower the initial dose and/or lower the maximum dose
$T_{1/2}$ half-life; **Css** time to steady state
Cost without markup, calculated from McKesson Canada (accessed March 25, 2020) → www.mckesson.ca
British Columbia PharmaCare Special Authority Criteria → www.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority

Table 2: Select Antidepressant Drug Interactions[1-39]

= contraindicated

= strong effect, more than 80% change in metabolism; dose modification of affected drugs often suggested

= moderate effect, 50-80% change in metabolism

= antidepressant dose reduction recommended

= consider antidepressant dose increase

= caution warranted; ensure compelling rationale for combination, increase monitoring for adverse events

Antidepressant alters metabolism of other drugs via cytochrome P450 inhibition (▲ increased activity; ▼ decreased activity of affected medication)														
Cytochrome	Medications	CITA	ESCIT	FLUO	PARO	SERT	VILA	VORT	VENL	DESV	DULO	LEVO	MIRT	BUPR
2C19	▲ diazepam, phenytoin ▼ clopidogrel													
2D6	▲ aripiprazole, dextromethorphan, metoclopramide, risperidone, TCAs, vortioxetine, several beta blockers (carvedilol, metoprolol, nebivolol, propranolol, timolol) ▼ codeine, tamoxifen, tramadol													
Antidepressant is a major substrate altered by other drugs via cytochrome P450 inhibition (▲ antidepressant levels) or induction (▼ antidepressant levels)														
1A2 inhibitor	ciprofloxacin, fluvoxamine													
3A4 inducer	carbamazepine, phenytoin, rifampin													
3A4 inhibitor	clarithromycin, ketoconazole, some antiretrovirals						**20 mg max**					**80 mg max**		
2B6 inhibitor	clopidogrel, ticlopidine													**300 mg max**
2C19 inhibitor	cannabidiol, fluconazole, fluvoxamine, omeprazole	**20 mg max**	**10 mg max**											
2D6 inhibitor	bupropion, fluoxetine, paroxetine							**↓ dose 50%**						
Interactions not mediated via Cytochrome P450														
anticoagulants, antiplatelets, NSAIDs (▲ bleeding risk)													data limited	data limited
MAOIs (serotonin toxicity)														
other serotonergic medications (serotonin toxicity)														

Serotonin Toxicity Infographic Canadian Family Physician October 2018 → www.cfp.ca/content/64/10/720
QTc Prolongation Resource CredibleMeds QT drug lists → crediblemeds.org (note: antidepressant safety not evaluated in people with congenital QTc prolongation)

CITA citalopram; **ESCIT** escitalopram; **FLUO** fluoxetine; **PARO** paroxetine; **SERT** sertraline; **VILA** vilazodone; **VORT** vortioxetine; **VENL** venlafaxine; **DESV** desvenlafaxine; **DULO** duloxetine; **LEVO** levomilnacipran; **MIRT** mirtazapine; **BUPR** bupropion; **TCA** tricyclic antidepressants; **MAOIs** monoamine oxidase inhibitors

This is not intended as an exhaustive drug interaction list, but serves to summarize select clinically-relevant antidepressant drug interactions.
For complete information, please consult a drug interaction resource.

Antidepressant Withdrawal and Tapering

50% of people who discontinue antidepressant therapy may experience withdrawal symptoms, which can be severe and long-lasting in some cases.[1-5]

Table 3: Risk factors for antidepressant withdrawal symptoms[2,7]
Doses in the higher end of dosage range
History of withdrawal symptoms after missed or omitted doses
Previous unsuccessful attempts to discontinue antidepressant

Possible indicators of withdrawal rather than relapse or recurrence:[2,4-8]

- New symptoms that differ from original depressive symptoms, including diverse somatic and psychological symptoms
- Early onset (hours to days) after stopping antidepressants with shorter half-lives, but potentially later for antidepressants with a longer half-life, such as fluoxetine
- Rapid improvement when the antidepressant is restarted or, if tapering, the previous higher dose is resumed

Antidepressant Tapering Strategies (See Table 4)

Tapering strategies have not been evaluated to determine if they reduce risk of withdrawal or improve deprescribing.

General clinical principles:[2,6-8]

- Consider clinical context and urgency for antidepressant discontinuation
- Assess risk factors for withdrawal (See Table 3)
- More conservative approach if risk factors for antidepressant withdrawal symptoms are present
- Reassess for withdrawal symptoms after each dose reduction
- Return to previously tolerated dose if withdrawal symptoms are troublesome

Dosage forms and strengths may limit the practicality of tapering:

- Recent recommendations include reducing the dose of SSRIs and SNRIs non-linearly (hyperbolic dose reductions)[2,7,8] but this involves doses that are not practically achievable in British Columbia
- Table 4 includes important adaptations to these recommendations, limited to practically achievable doses and expanded to include additional antidepressants

Table 4: Practical Tapering Possibilities

Without apparent risk factors for withdrawal					More conservative, mostly linear					
Reduce to the Step 1 dose (mg/day) over 2 to 4 weeks if at a higher starting dose										
Antidepressant	Dosage Form	Step 1 2 weeks	Step 2 2-4 weeks	Step 3 stop	Step 1 2 weeks	Step 2 1-2 weeks	Step 3 1 week	Step 4 1 week	Step 5 1 week	Step 6 stop
citalopram	tab IR	20	10	0	20	10	7.5	5	2.5	0
escitalopram	tab IR	10	5	0	10	5	2.5	X	X	0
fluoxetine	cap IR, solution	20	10	0	20	10	7.5 soln	5 soln	2.5 soln	0
paroxetine	tab IR	20	10	0	20	10	7.5	5	2.5	0
paroxetine	tab CR	25	12.5	0	25	12.5	switch to IR Step 2			0
sertraline	cap IR	50	25	0	X dosage form limits more conservative taper					
vilazodone	tab IR	20	10	0	20	10	7.5	5	2.5	0
vortioxetine	tab IR	10	5	0	10	5	3.75	2.5	1.25	0
venlafaxine	cap XR	75	37.5	0	X dosage form limits more conservative taper					
desvenlafaxine	tab ER	50	X	0	X dosage form limits more conservative taper					
duloxetine	cap DR	60	30	0	X dosage form limits more conservative taper					
levomilnacipran	cap ER	40	20	0	X dosage form limits more conservative taper					
mirtazapine	tab IR	30	15	0	30	15	11.25	7.5	3.75	0
bupropion	tab SR (XL)	150	100	0	X dosage form limits more conservative taper					

X unable to practically or safely decrease further, consult pharmacist for additional options or switch to alternate antidepressant; soln = solution; immediate release (IR) tablets can be split into quarters to achieve lower doses; controlled release (CR), sustained release (SR), and extended release (ER, XR, XL) tablets should not be split

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Drug Information to Support Drug Therapy Decisions

B.C. Provincial Academic Detailing (PAD) Service **March 2020**

Antidepressant clinical trials show a substantial placebo response rate and a small magnitude of antidepressant effect relative to placebo.

(US Food and Drug Administration 2018)[1]

"Paucity of knowledge about how antidepressants work."

(CIPRIANI et al. Lancet 2018)[2]

"When an antidepressant was the novel or experimental drug in a comparison, it appeared to be significantly more effective than when the same treatment was the older or control drug in a comparison."

(CIPRIANI et al. Lancet 2018)[2]

"For the most commonly used second-generation antidepressants, the lower range of the licensed dose achieves the optimal balance between efficacy, tolerability, and acceptability."

(FURUKAWA et al. Lancet Psychiatry 2019)[3]

"Prominent as a barrier to antidepressant discontinuation was the notion that antidepressants are necessary to counter a deficiency of serotonin."

(EVELEIGH et al. Ther Adv Psychopharmacol 2019)[4]

"Do primary outcomes chosen in clinical trials for psychiatric disorders capture what is most important to a patient?"

(The Lancet Psychiatry 2020)[5]

"Our clinical recommendation is that when considering the potential benefits of treatment with antidepressants, be circumspect but not dismissive. Efficacy measured in clinical trials does not necessarily translate into effectiveness in clinical practice."

(TURNER & ROSENTHAL BMJ 2008)[6]

"Depression rating scales used in clinical trials seldom measure quality of life, which has been suggested to be a reasonable measure of clinical significance."

(TURNER & ROSENTHAL BMJ 2008)[6]

Reference list is available upon request.

Materials are designed to be used in conjunction with an academic detailing session provided by a PAD pharmacist. For more information, or to schedule an academic detailing session, please contact:

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