BC PAD Service
Spring 2023

Antidepressants for Major Depressive Disorder

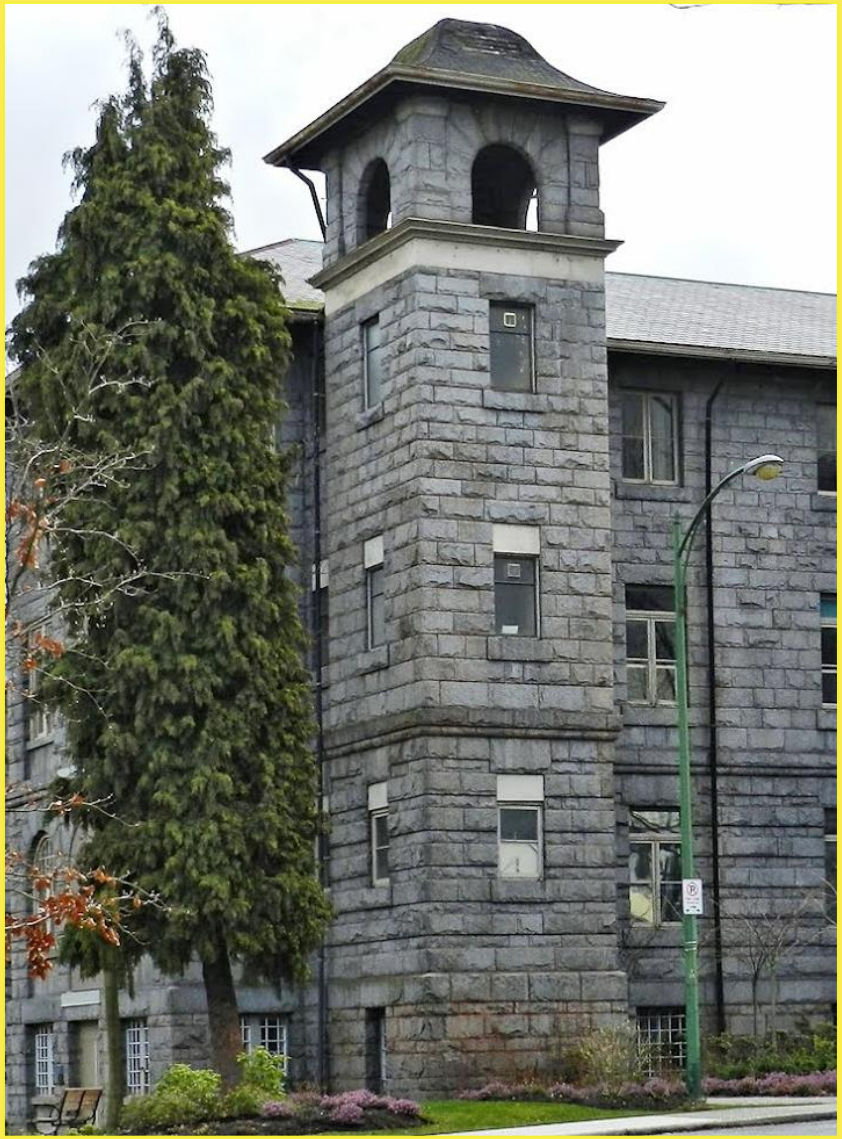
Drug Information

Disclosures

I am an employee of Vancouver Coastal Health which receives funding from the British Columbia Ministry of Health's Pharmaceutical, Laboratory and Blood Services Division for the purpose of delivering the BC Provincial Academic Detailing Service.

I have no other conflict of interests.

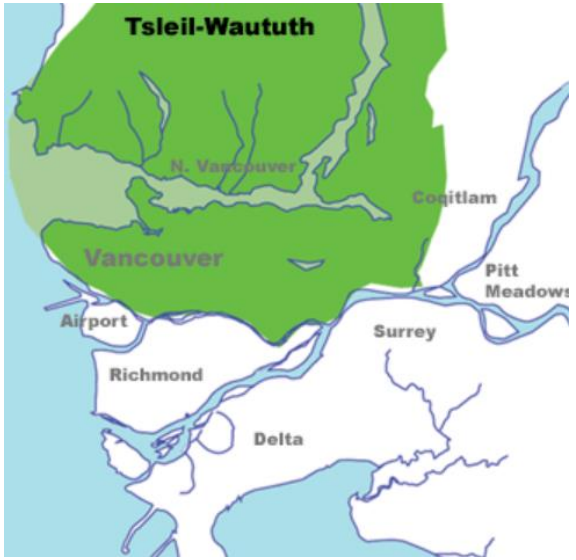
Information provided is a summary of the evidence. The content has been peer-reviewed by clinicians and experts in critical appraisal.



BC's Provincial Academic Detailing (PAD) Service is offered free of charge to health care professionals. This service is provided by health authorities and supported by the Ministry of Health. Relevant topics are indentified in consultation with various groups. All written materials are externally reviewed by clinicians and experts in critical appraisal.

Land Acknowledgment

In the spirit of reconciliation, I respectfully acknowledge that I am working and residing on the unceded Coast Salish territories of the Squamish, Musqueam and Tsleil-Waututh First Nations.



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01

BACKGROUND

SSRIs (serotonin reuptake inhibitors)

ANTIDEPRESSANT	BRAND NAME	MARKETED
Fluoxetine	PROZAC	1989
Sertraline	ZOLOFT	1992
Paroxetine	PAXIL	1993
Citalopram	CELEXA	1999
Escitalopram	CIPRALEX	2005

SNRIs (serotonin norepinephrine reuptake inhibitors)

ANTIDEPRESSANT	BRAND NAME	MARKETED
Venlafaxine	EFFEXOR	1994
Duloxetine	CYMBALTA	2008
Desvenlafaxine	PRISTIQ	2009
Levomilnacipran	FETZIMA	2015

ANTIDEPRESSANT	BRAND NAME	MARKETED	***dopamine norepinephrine reuptake inhibitor***
Bupropion	WELLBUTRIN	1998	

ANTIDEPRESSANT	BRAND NAME	MARKETED	**alpha 2 antagonist, noradrenergic, serotonergic, antihistaminic, antimuscuranic, alpha 1 antagonist**
Mirtazapine	REMERON	2001	

ANTIDEPRESSANT	BRAND NAME	MARKETED	**serotonin reuptake inhibitor, serotonin partial agonist, serotonin antagonist**
Vortioxetine	TRINTELLIX	2014	

ANTIDEPRESSANT	BRAND NAME	MARKETED	***serotonin reuptake inhibitor, serotonin partial agonist***
Vilazodone	VIIBRYD	2018	

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 of relapse or has experienced recurrent episodes. [1-6]

KEY NUMBERS

n=146

45 family practices

Conclusion: Changing inappropriate long-term antidepressant use is difficult.

INTERVENTION GROUP:
"consider discontinuing antidepressant"

70

DID NOT WANT TO DISCONTINUE

34 (49%)

AGREED TO DISCONTINUE

36 (51%)

CONTROL GROUP:

n=76

SUCCESSFUL AT DISCONTINUING

6 (8%)

SUCCESSFUL AT DISCONTINUING

4 (6%)

Eveleigh R et al. BJGP Open ; DOI: 10.3399/bjgpopen17X101265

Table 1. Baseline characteristics of participants (inappropriate long-term antidepressant users) in the overtreatment trial at individual level in frequencies, unless stated otherwise. Overtreatment: ≥9 months antidepressant use, without a current indication for maintenance therapy

	Overtreatment trial, *n* (%)	
	Control (*n* = 76)	Intervention (*n* = 70)
Mean age, years (SD)	56 (14.3)	56 (12.9)
Male	24 (32)	20 (29)
Marital status		
Married or living together	60 (79)	56 (80)
Separated or divorced	0 (0)	2 (3)
Widow/widower	7 (9)	2 (3)
Single	9 (12)	9 (13)
Lifetime psychiatric diagnosis		
Any lifetime psychiatric diagnosis	48 (63)	53 (76)
Depression	35 (46)	39 (56)
Panic disorder or agoraphobia	13 (17)	13 (19)
Generalised anxiety disorder	13 (17)	22 (31)
Social phobia	20 (26)	16 (23)
Antidepressant		
Selective serotonin reuptake inhibitors	50 (66)	57 (81)
Serotonin–norepinephrine reuptake inhibitors	11 (14)	7 (10)
Other (non-tricyclic antidepressant drug)	10 (13)	2 (3)
Tricyclic antidepressant drugs	5 (7)	4 (6)
Median duration of antidepressant use at inclusion, years (range)	9.5 (1–56)	8.0 (1– 48)
Comorbidity		
Cardiovascular disease	7 (9)	9 (13)
Cancer	6 (8)	8 (11)
Chronic obstructive pulmonary disease/asthma	12 (16)	9 (13)
Diabetes mellitus	11 (14)	3 (4)

SD = standard deviation.

Eveleigh R et al. BJGP Open ; DOI: 10.3399/bjgpopen17X101265

“For me this isn’t a psychoglogical illness, it’s physical. And my body is not able to make enough serotonin…”

“…She (my wife) said please take the pills, because you’re must easier to handle… ha ha “

“I have found a balance, emotionally that is…I don’t want to disturb this balance”.

— quotes from participants who did not agree to discontinue long-term antidepressant use

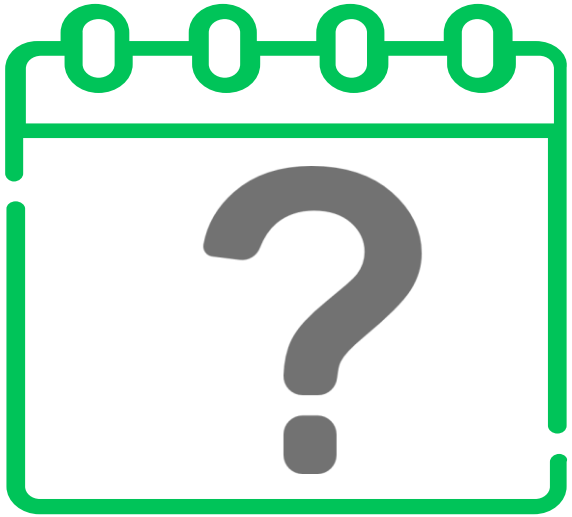
Ther Adv Psychopharmacol
2019, Vol. 9: 1–9 DOI: 10.1177/2045125319872344

"My GP made it very clear, it (the antidepressant) is only a temporary solution, it will help but the problem lies elsewhere".

"…And that my GP is willing to say no we won't wait and see, but will take my symptoms seriously. Then I thought, now I can try (to taper), if I have a kind of safety net. I had more confidence in myself, so I gave it a go. It was scary".

— quotes from participants who did agree to discontinue long-term antidepressant use

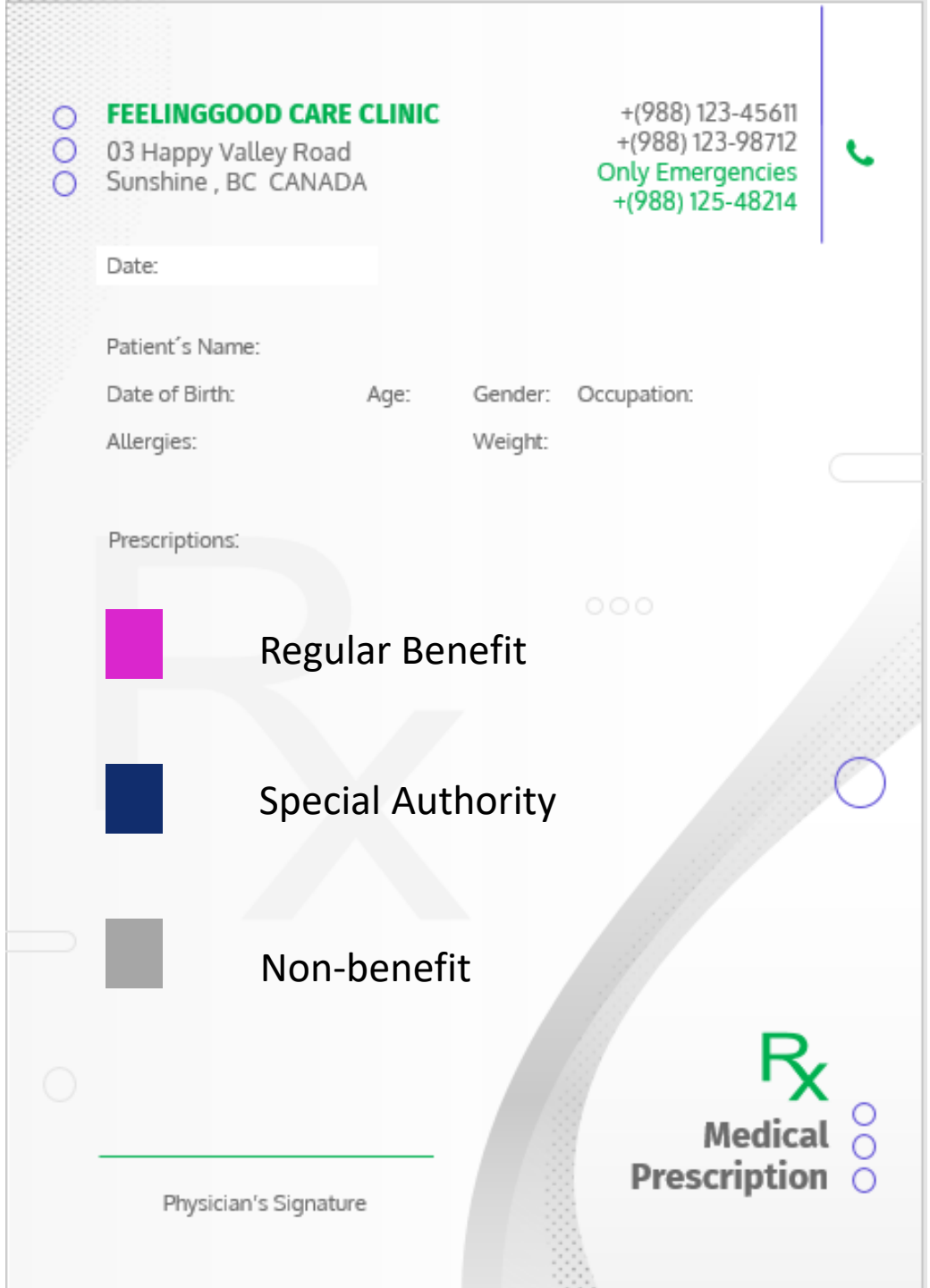
Ther Adv Psychopharmacol
2019, Vol. 9: 1–9 DOI: 10.1177/2045125319872344



The most appropriate duration of antidepressant therapy is **not known** [8]

02

COST & COVERAGE



SSRIs

Excluding Paxil 10mg tab & CR tablets

SNRIs

Venlafaxine is a regular benefit

VILAZODONE

MIRTAZAPINE

VORTIOXETINE

Major depressive disorder (MDD) in adult patients AND treatment failure or intolerance to ≥ 2 other specified antidepressants for MDD

BUPROPION

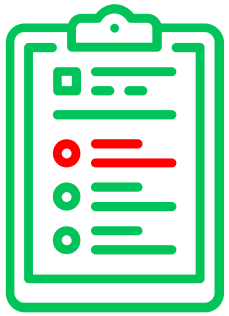
Diagnosis indicating depression

03

EVIDENCE

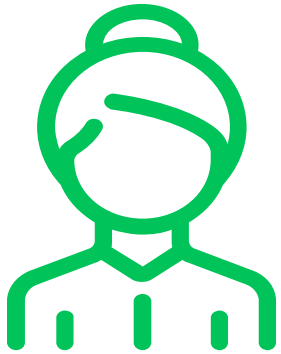
In the largest dataset of published and unpublished trials,
(522 trials; 116,477 participants):[2]

HDRS-17 Score
26 (baseline)

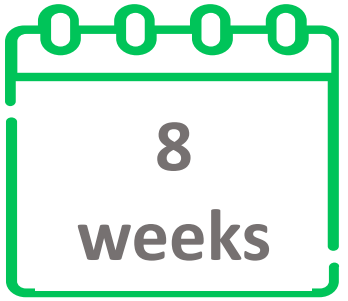


moderate depression

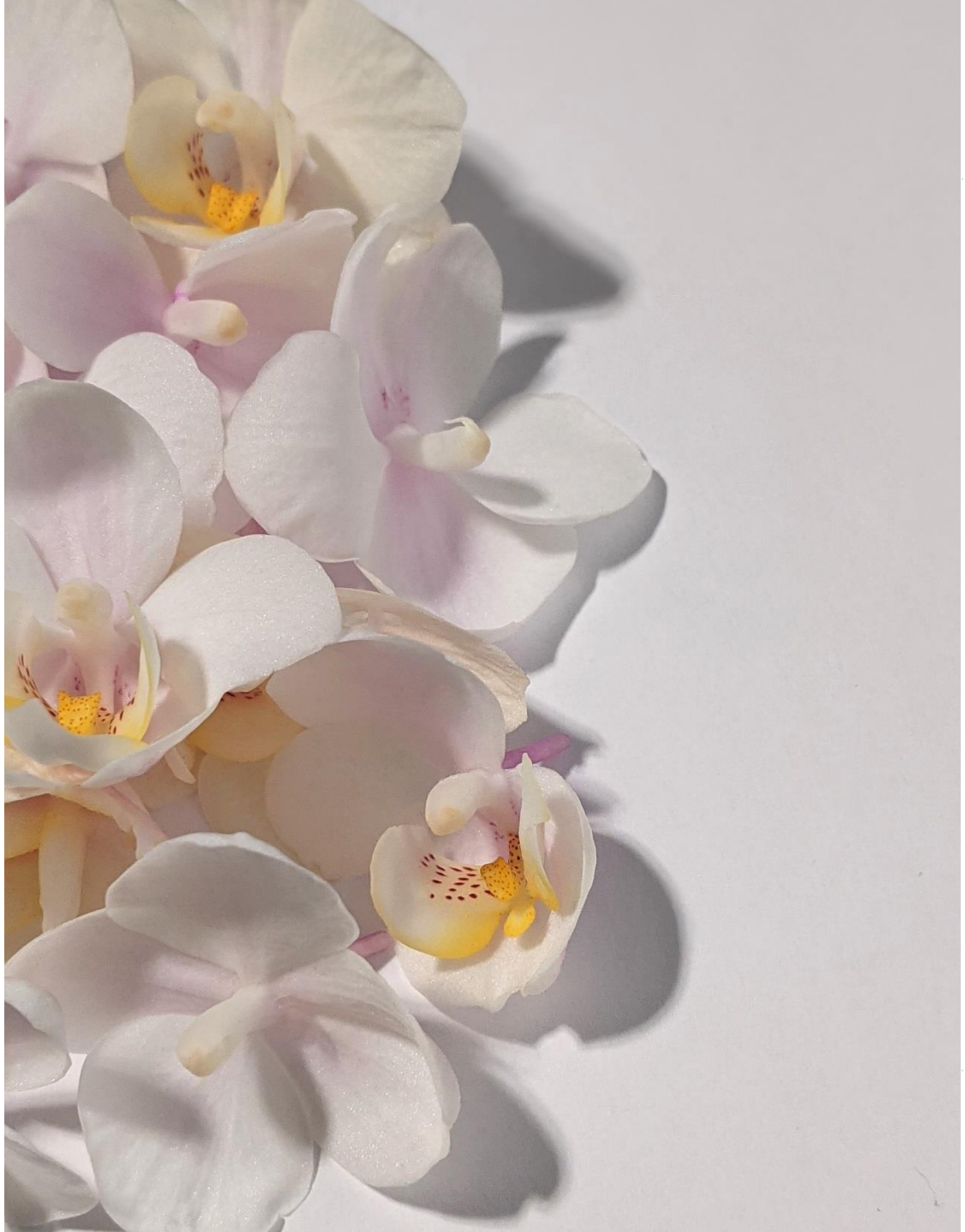
severe depression



~66%



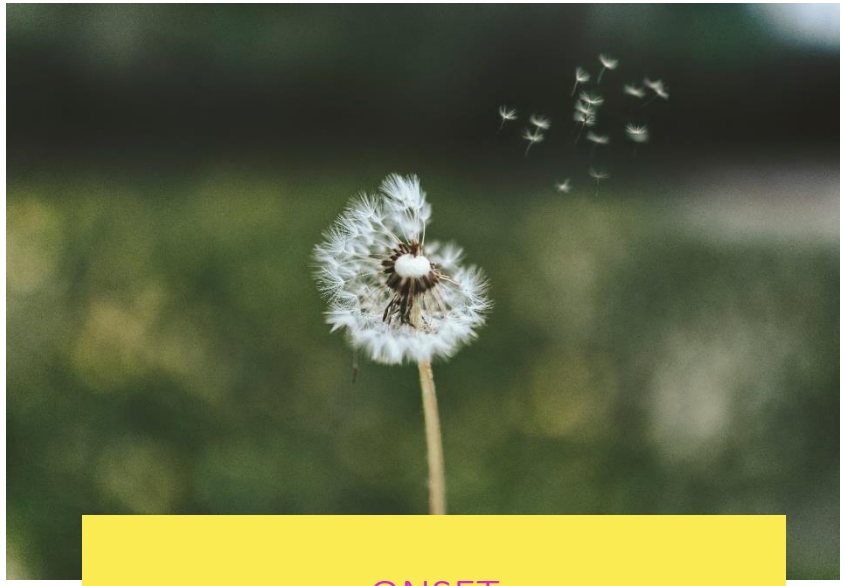
median duration of trials



EXCLUDED POPULATIONS

- Less severe depression scores (HDRS < 19)
- Depression with psychotic features
- Suicidal ideation
- Substance use disorder, or
- Serious medical co-morbidity

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



ONSET

meta-analyses demonstrate evidence of improvement in depression symptom scales within

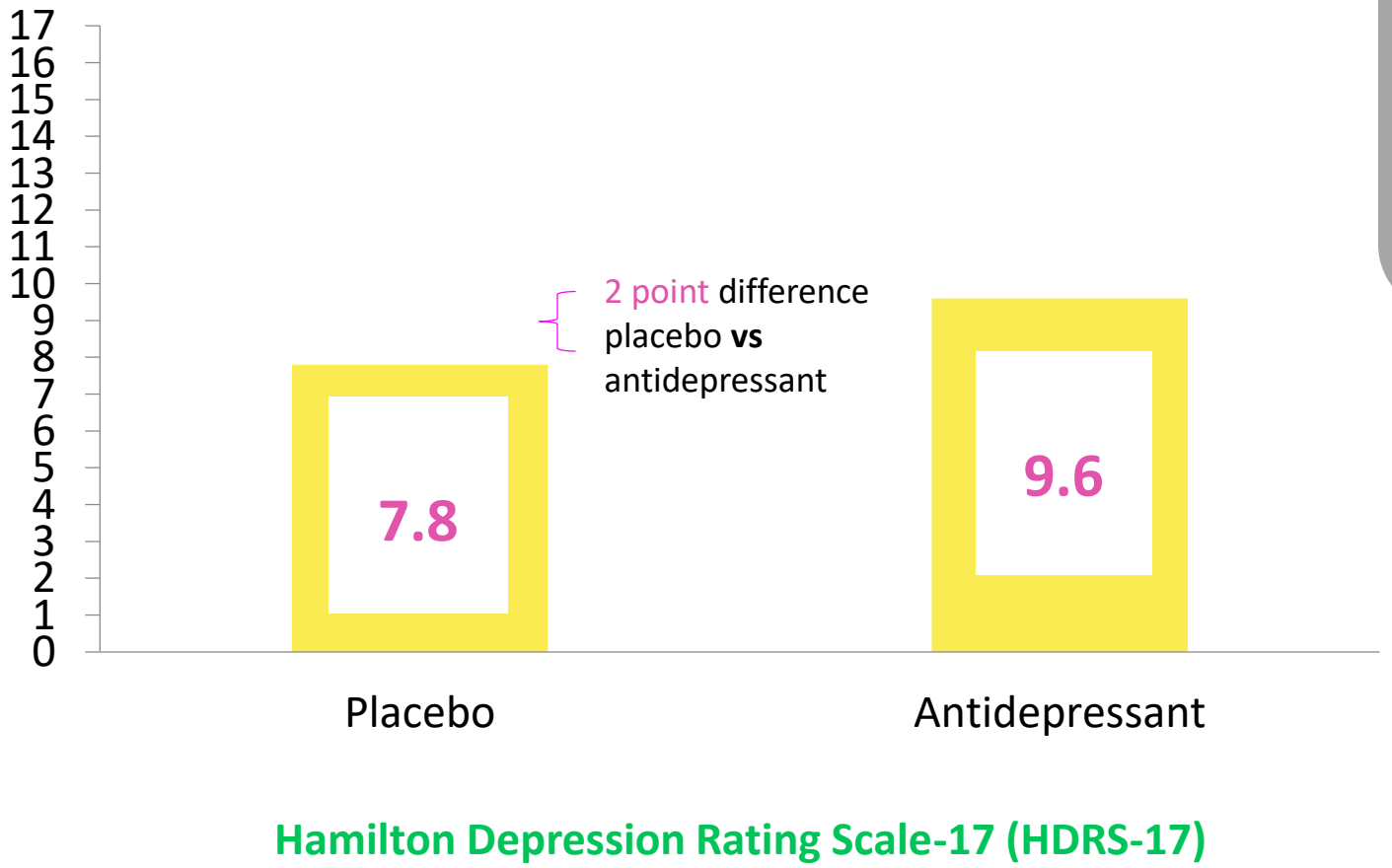
1-2 WEEKS

MAINTENANCE

the effect appears largely maximized by

6-8 WEEKS

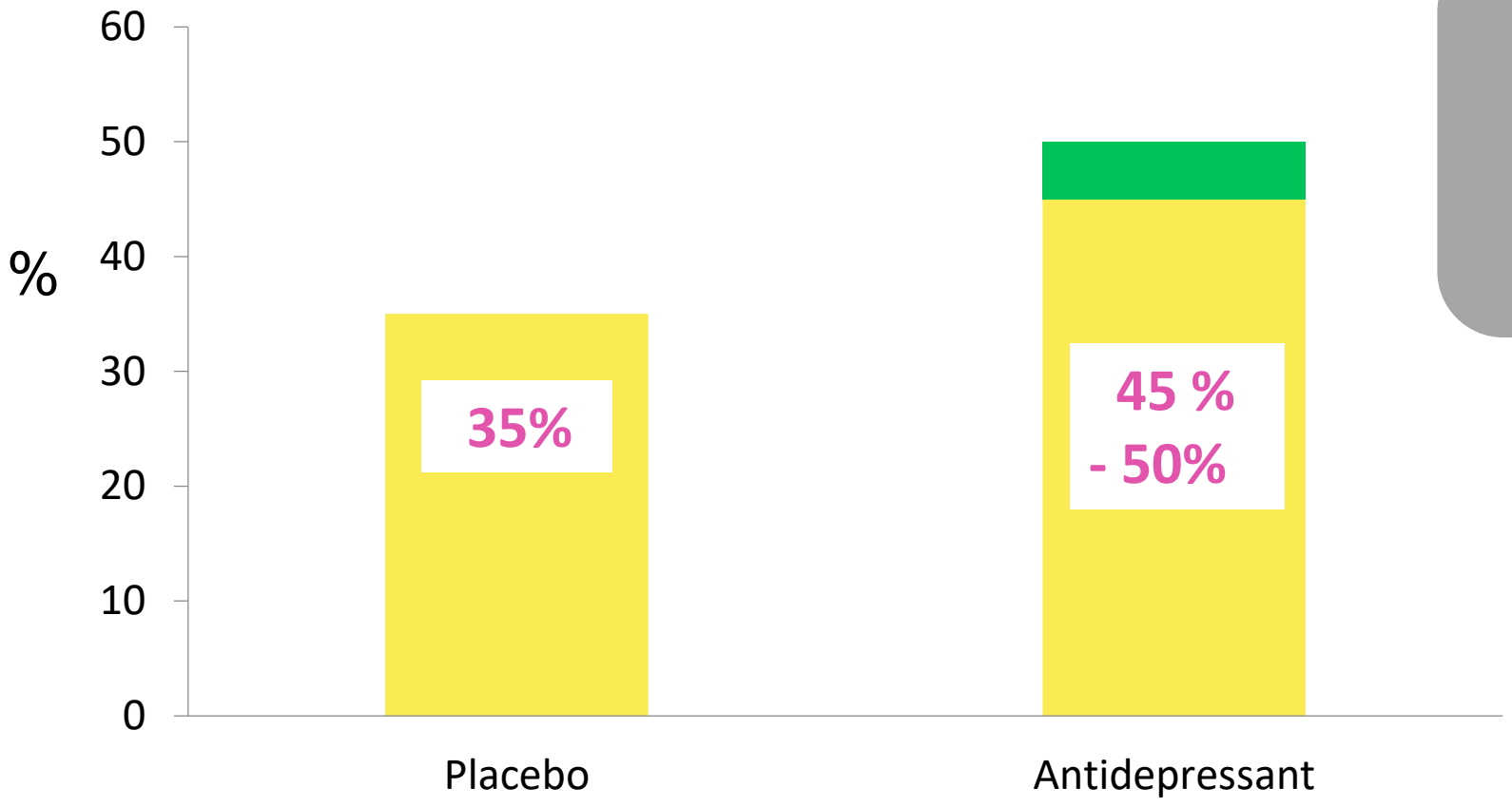
Mean Difference in Depression Severity Scores



Hamilton Depression Rating Scale-17 (HDRS-17)

Continuous outcome:
mean difference in **depression severity scores** achieved in antidepressant group compared to the placebo group

Proportion of People Achieving ≥ 50% Improvement in Symptom Severity Score



Dichotomous outcome:
Proportion of people achieving **at least a 50%** improvement in symptom severity scores

Median = 8 weeks

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

Hamilton Depression Rating Scale-17 (HDRS-17)

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:

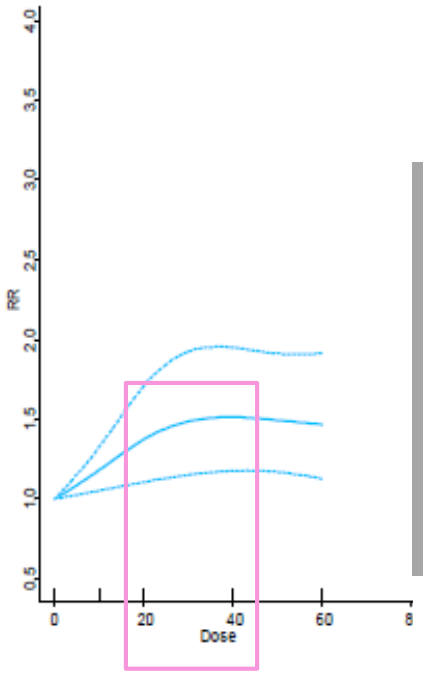
there is a more consistent relationship between higher doses and adverse events leading to drug discontinuation [61,62]

FURUKAWA 2019 SYSTEMATIC REVIEW: DOSE RESPONSE

RR = relative risk of response

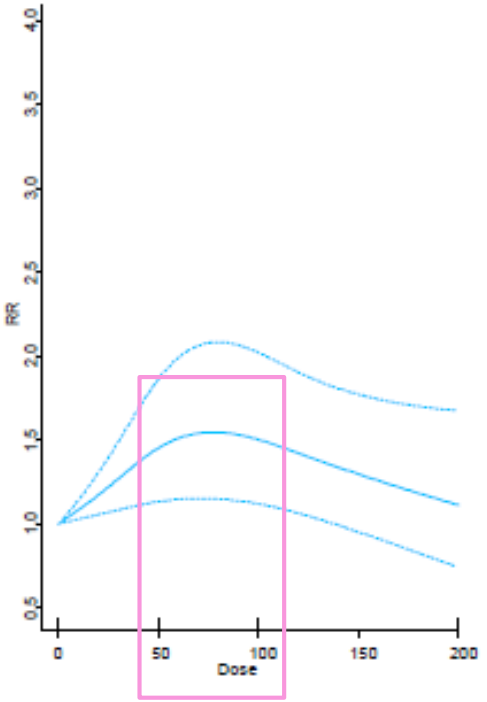
efficacy increased up to 20-40 mg and then decreased

Citalopram (17 arms)



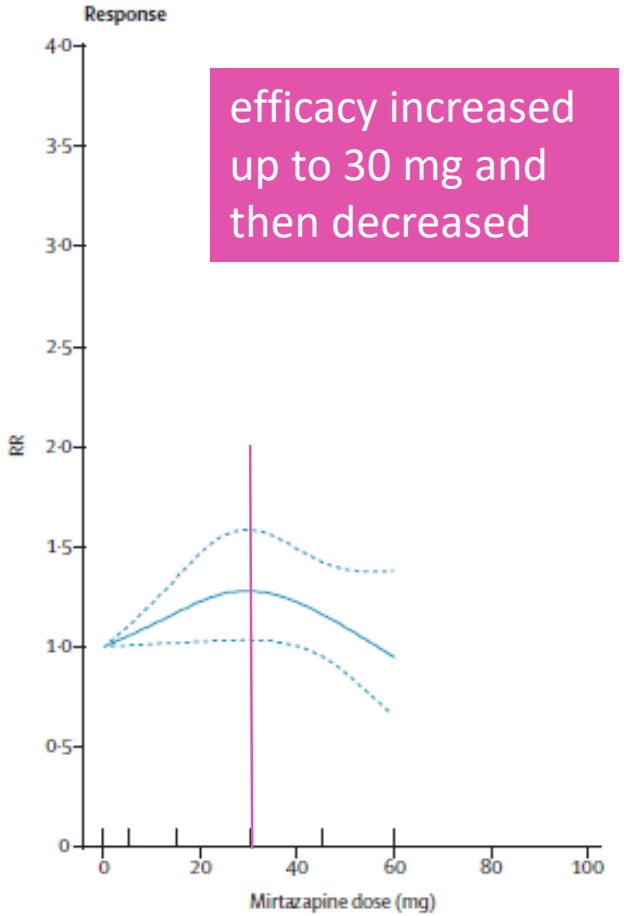
efficacy increased up to 50-100 mg and then decreased

Sertraline (11 arms)



Mirtazapine

efficacy increased up to 30 mg and then decreased



FURUKAWA Lancet Psychiatry 2019;6:601-609

citalopram

Maintenance Treatment

Evaluation of CELEXA in two placebo-controlled studies has shown that its antidepressant efficacy was maintained for periods of up to 24 weeks, following 6 or 8 weeks of initial treatment (total of 32 weeks) (see 14.2 Study Results). In the flexible dose study, the great majority of patients were receiving 20 or 40 mg/day doses both at 12 and 24 weeks. During maintenance therapy, the dosage should be kept at the lowest effective level and patients should be periodically reassessed to determine the need for continued treatment.

mirtazapine

While a relationship between dose and anti-depressant response for REMERON® has not been established, patients not responding to the initial 15 mg dose may benefit from dose increases up to a maximum of 45 mg/day (see CLINICAL TRIALS, Clinical Trials Showing Efficacy). REMERON® has an elimination half-life of approximately 20 - 40 hours, therefore, dose changes should occur in intervals of not less than one week. Dosage adjustments may be made according to the tolerance and based on the patient's response.

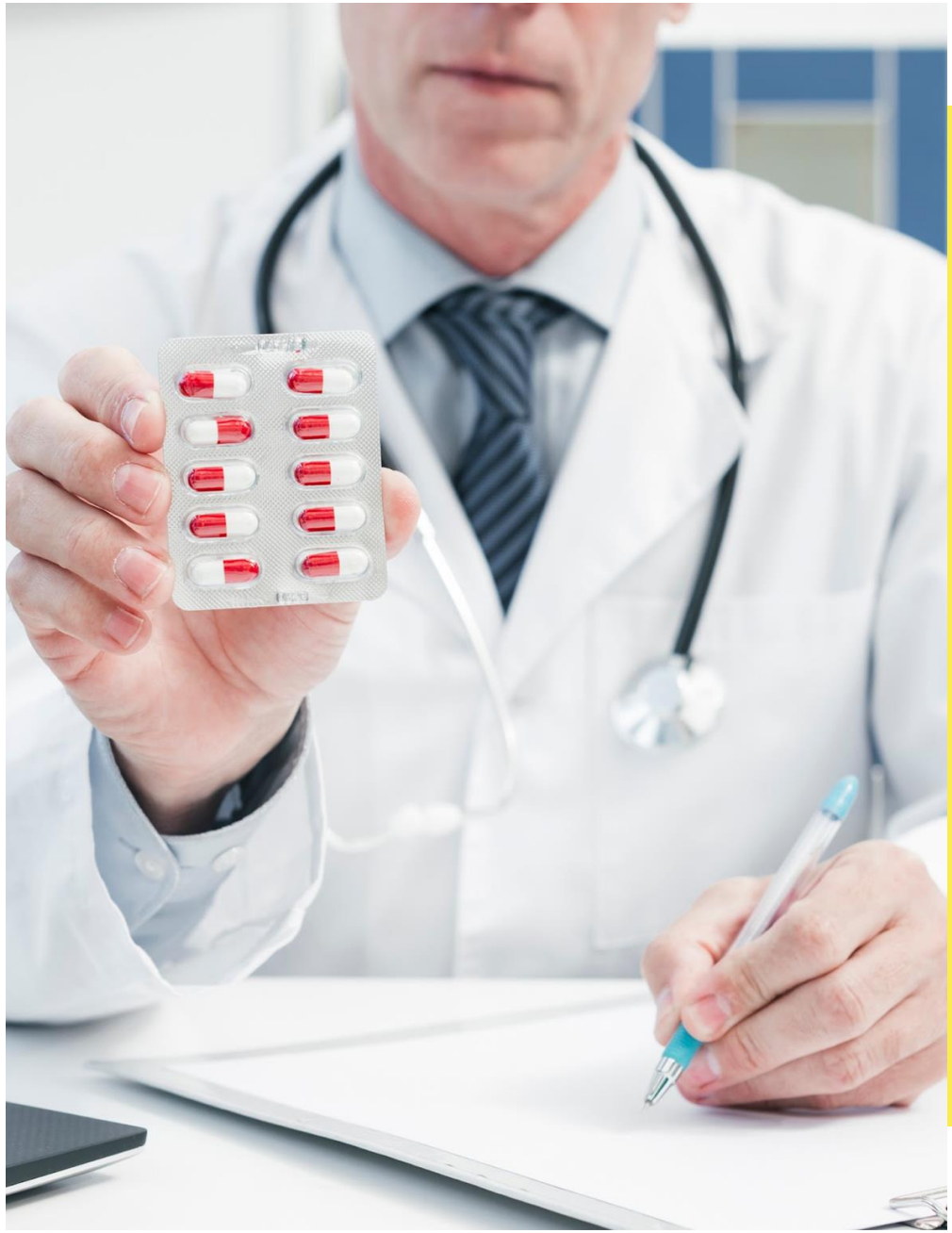
sertraline

4.2 Recommended Dose and Dosage Adjustment

Depression and Obsessive-Compulsive Disorder

As no clear dose-response relationship has been demonstrated over a range of 50-200 mg/day, a dose of 50 mg/day is recommended as the initial dose.

https://pdf.hres.ca/dpd_pm/00064174.PDF
https://www.pfizer.ca/sites/default/files/202110/ZOLOFT_PM_EN_253527_2021.09.29.pdf
https://www.merck.ca/static/pdf/REMERON-PM_E.pdf



In short-term (6-12 weeks) anti-depressant trials:

1/3 people discontinue treatment

(anti-depressant or placebo)[11]

META-ANALYSES & SYSTEMATIC REVIEWS

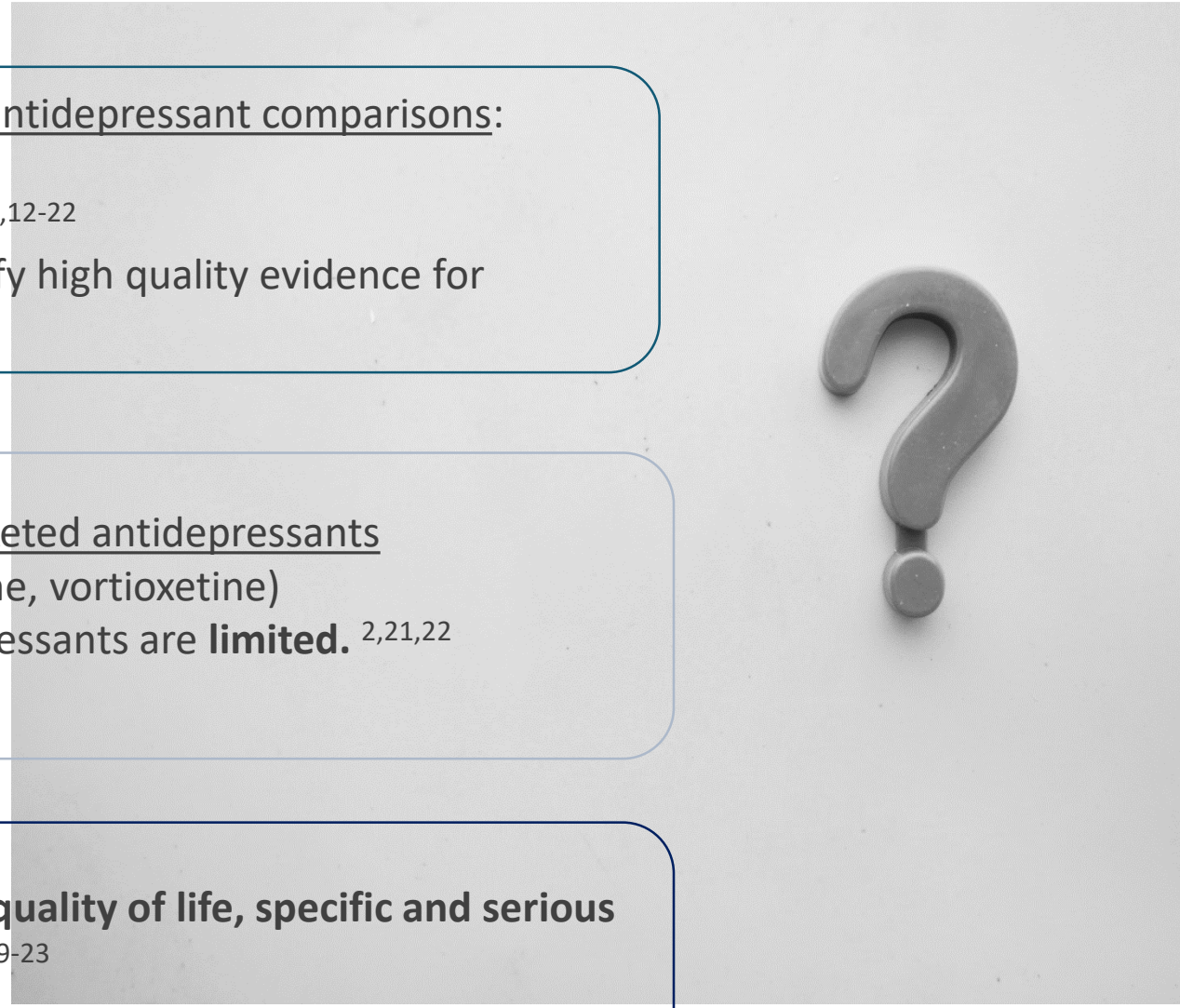
Systematic reviews and network meta-analyses of antidepressant comparisons:

- 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



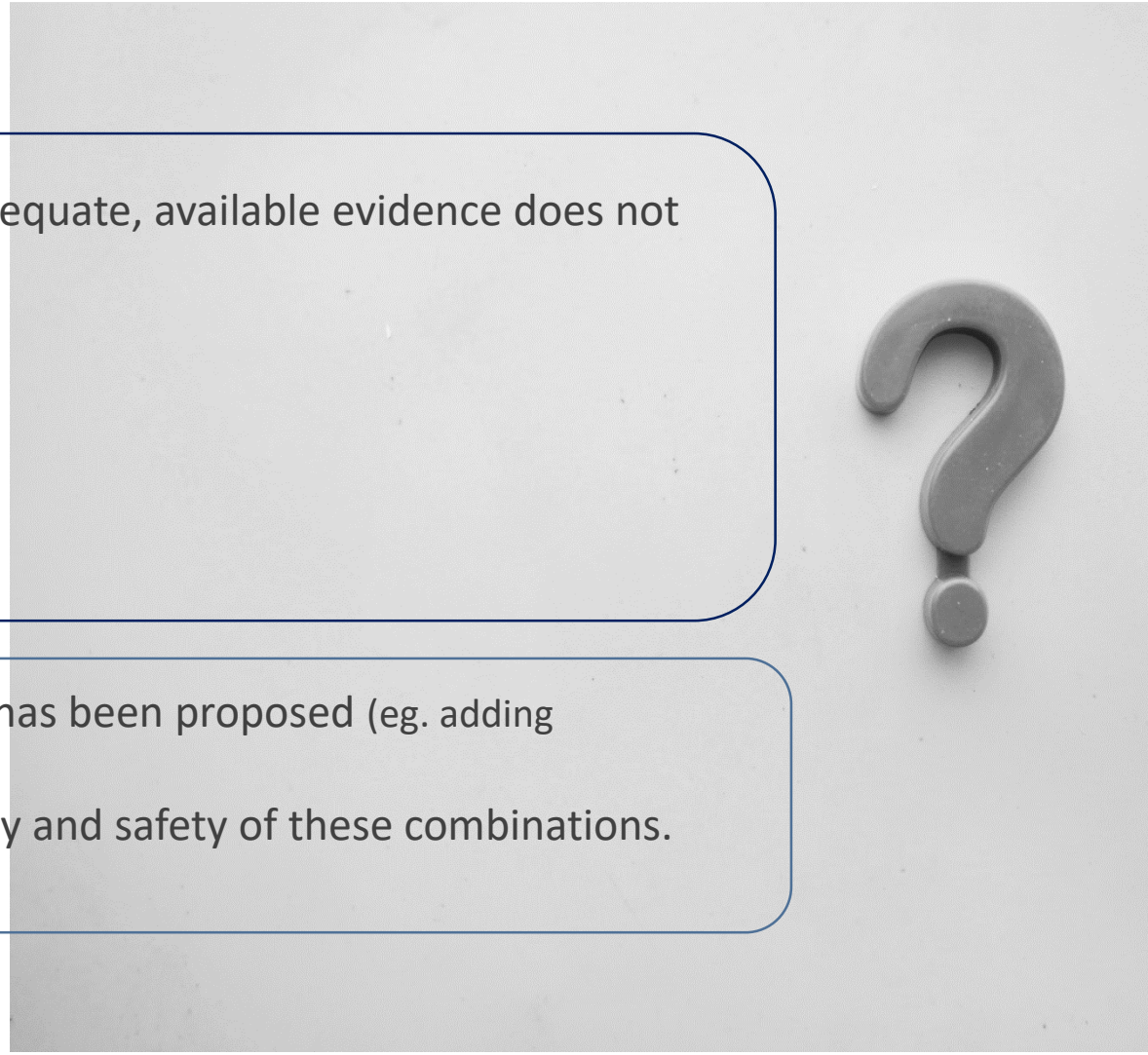
COMBINING ANTIDEPRESSANTS

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]



04

CLINICAL CONSIDERATIONS DRUG INFORMATION

adverse events

INCOMPLETE INFORMATION:

specific adverse events, serious adverse events, long term safety

LIMITED INFORMATION:

direct comparisons of vilazodone, vortioxetine, levomilnacipran vs commonly prescribed antidepressants

CAUTIOUS INTERPRETATION OF COMPARATIVE RISKS:

in the largest network meta-analysis, antidepressant comparisons were not informed by high quality evidence

ADVERSE EVENTS LEADING TO DISCONTINUATION [41]

venlafaxine > citalopram, escitalopram, fluoxetine, sertraline, vortioxetine

duloxetine > escitalopram, venlafaxine, desvenlafaxine

mirtazapine > sertraline

(low to moderate quality evidence)

WITHDRAWAL [43,44,61-65]

Potentially greater prevalence with

paroxetine

venlafaxine

desvenlafaxine

duloxetine

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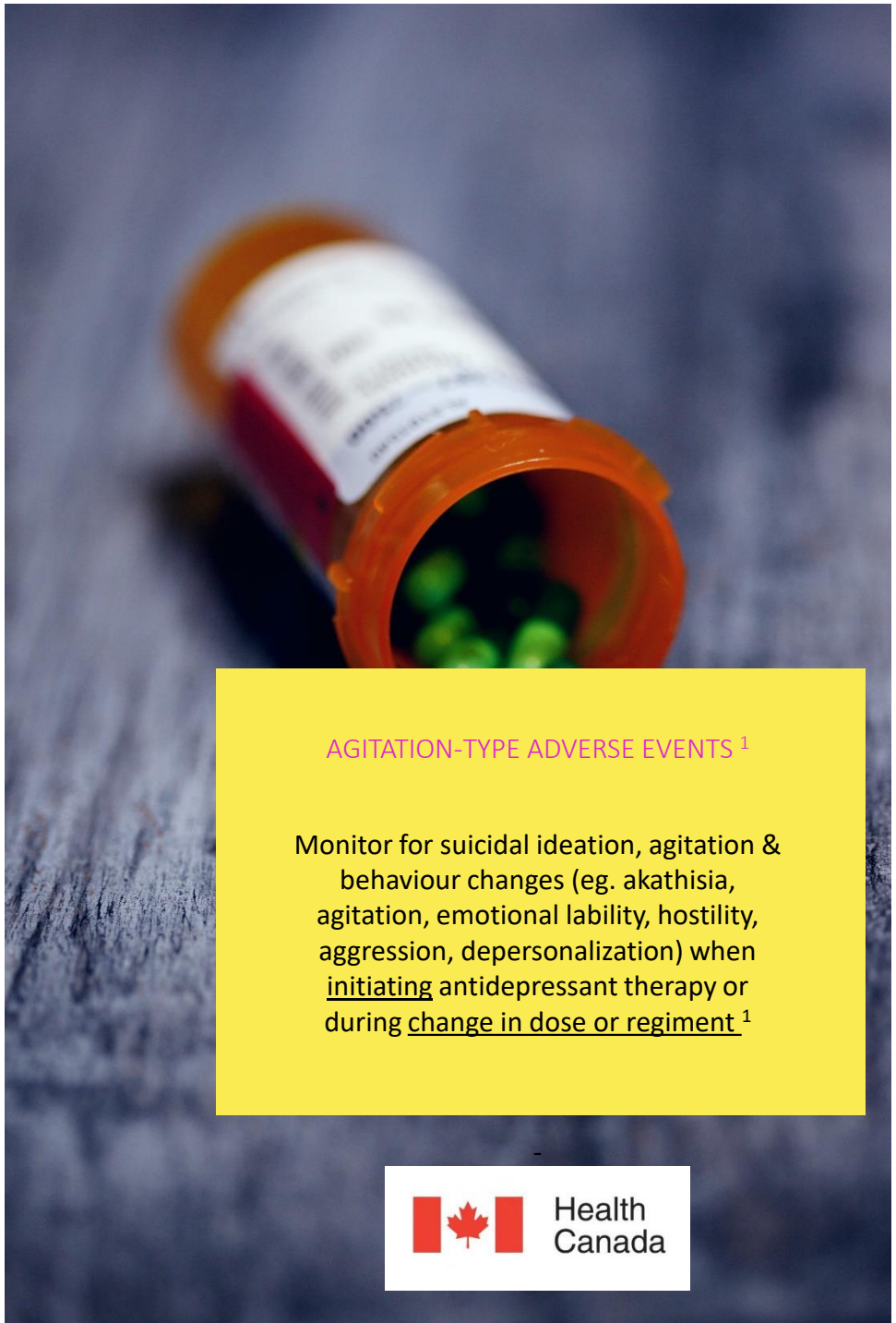

AGITATION-TYPE ADVERSE EVENTS [1]

Monitor for suicidal ideation, agitation & behaviour changes (eg. akathisia, agitation, emotional lability, hostility, aggression, depersonalization) when initiating antidepressant therapy or during change in dose or regiment [1]

Health Canada

- **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

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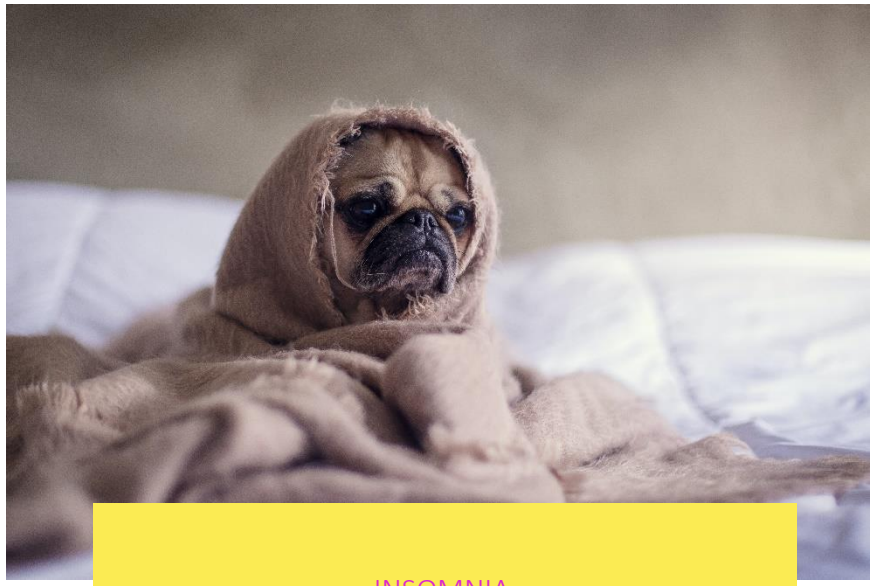
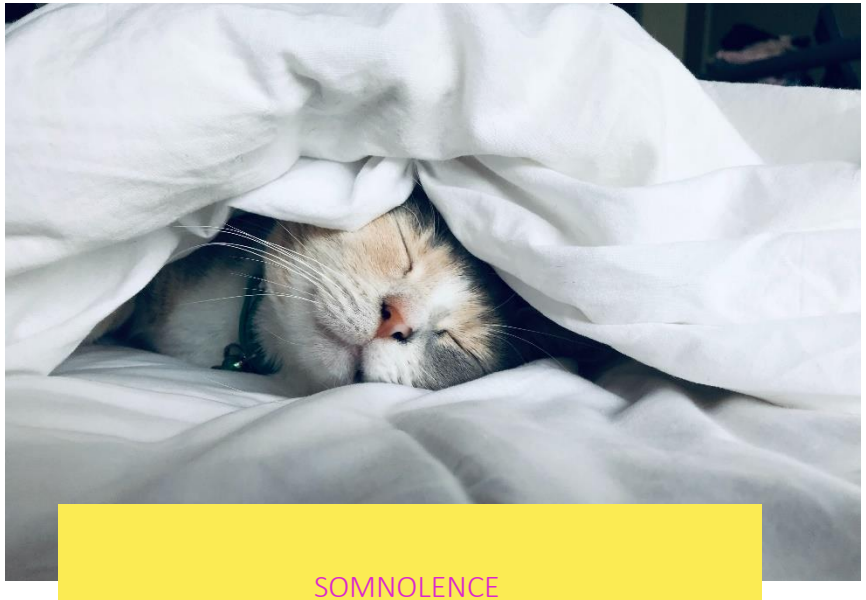


INSOMNIA

Most SSRIs and SNRIs > placebo

(meta-analysis [66])

Bupropion



SOMNOLENCE

Most SSRIs and SNRIs > placebo

(meta-analysis [66])

Mirtazapine

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CARDIOVASCULAR

↑BP ↑HR : SNRIs and Bupropion

- effect increases with dose

-

CARDIOVASCULAR

Levomilnacipran contraindications:

heart failure NYHA III and IV

uncontrolled tachyarrthymias

uncontrolled hypertension

recent myocardial infarction

recent cardiac intervention

history of cerebrovascular accident

QT_c Interval Prolongation:

crediblemeds.org

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CREDIBLEMEDS®

Gastrointestinal Adverse Events

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VENLAFAXINE

Higher rate of nausea and vomiting than SSRIs [43,44]

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]

SERTRALINE

Higher rate of diarrhea than comparators; [43,44,47]

VILAZODONE

Diarrhea, nausea, vomiting ~ 50% participants (US FDA) [76]

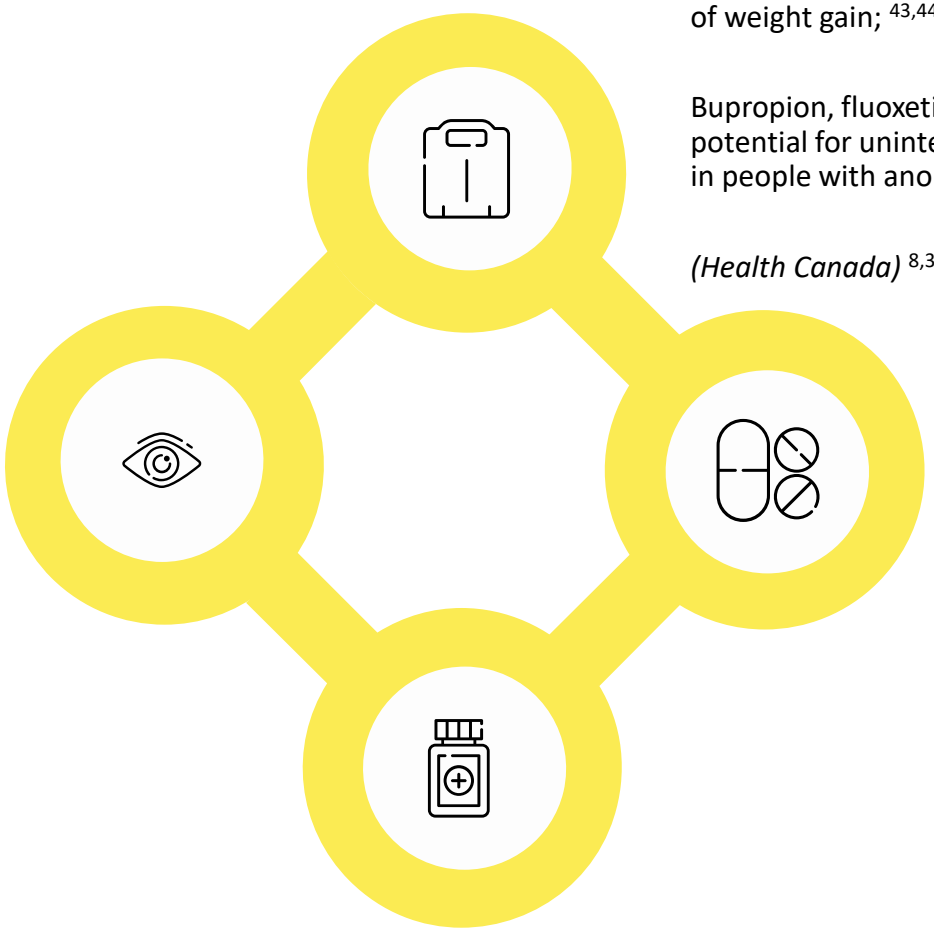
Not intended to reproduce a product monograph

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]



ANTIMUSCARINIC/ ANTICHOLINERGIC

Consider antidepressants as potential contributors to anticholinergic burden [73]

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]

HYPONATREMIA

SSRIs, SNRIs,vilazodone, vortioxetine, mirtazapine, bupropion [4-34]

SEXUAL DYSFUNCTION

Inconsistently defined & reported in trials-> comparisions uncertain [67-69]

Mirtazapine, bupropion: potentially lower risk than SSR 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 persistance after SSRI or SNRI discontinuation *(European Medicines Agency)* [71,72]

AGITATION, INSOMNIA, TREMOR, TINNITUS:

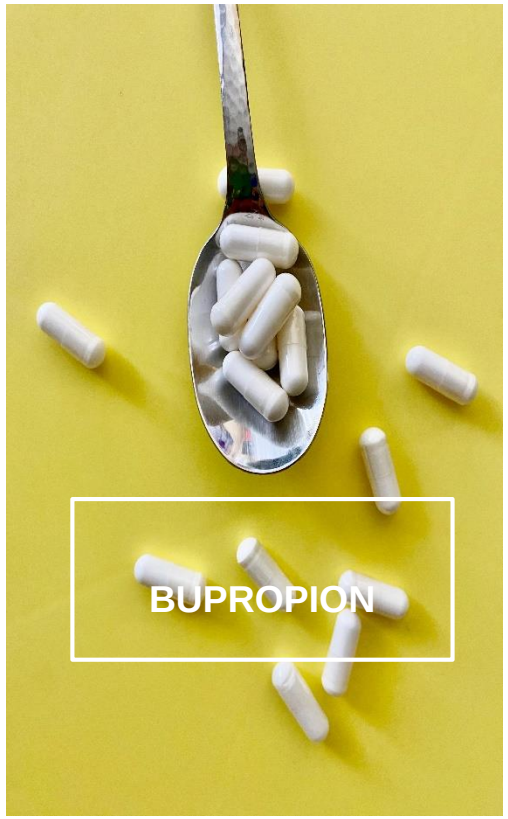
dose related & potential for prescribing cascade with addition of sedative hypnotics,

(Health Canada) [31,32]

AMPHETAMINE-LIKE pharmacology (US FDA)[79]

Misuse potental: oral, intranasal, injection [57,80]

URINE TOXICOLOGY: potentially false positive for amphetamine [55]



EPILEPTOGENIC:

Contraindicated in seizure disorder, bulima, alcohol or sedative withdrawal (Health Canada) [31,32]

RISK FACTORS:

head trauma, CNS trauma, hepatic impairment, substance or alcohol misuse, insulin or hypoglycemics, other medications that lower seizure threhold

(Health Canada) [31,32]

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Somnolence ~ 50% participants[28]

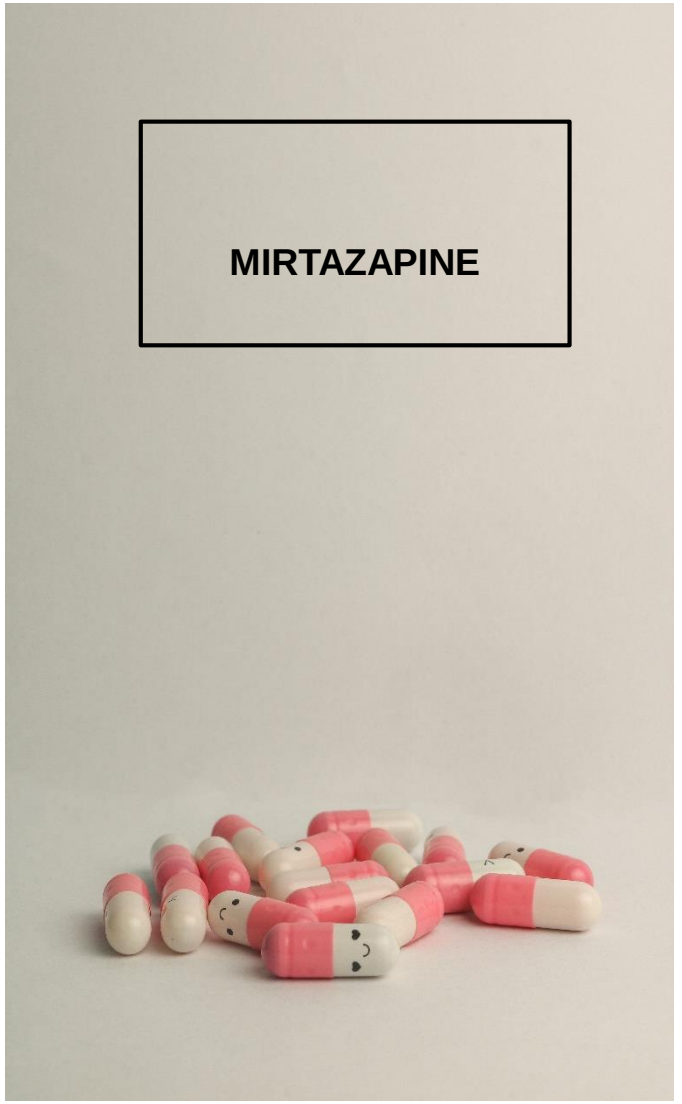
Age: ↑ half life

↓ drug clearance[28]

Dry Mouth, Weight Gain, Fatigue, Somnolence > SSRIs*

Sweating, Nausea, Vomitting < SSRIs*

**Systematic Review*



Drug Information

- **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 https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/pharmacare/prescribers/special-authority

SSRIs *serotonin reuptake inhibitors*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

SSRIs *serotonin reuptake inhibitors*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

SSRIs *serotonin reuptake inhibitors*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

VILAZODONE *serotonin reuptake inhibitor, serotonin partial agonist*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

VORTIOXETINE *serotonin reuptake inhibitor, serotonin partial agonist, serotonin antagonist*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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 **non benefit**

SNRIs *serotonin norepinephrine reuptake inhibitors*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

SNRIs *serotonin norepinephrine reuptake inhibitors*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**
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**

MIRTAZAPINE *alpha 2 antagonist, noradrenergic, serotonergic, antihistaminic, antimuscuranic, alpha 1 antagonist*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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**

March 2021

pad Refills

Your dose of drug information in between details

Drug information question: Is there a relationship between mirtazapine (Remeron®) dose and sedation?

Conclusion: The relationship between mirtazapine dose and sedation is unclear but available evidence indicates that the risk of adverse events causing patients to discontinue mirtazapine increases with dose.

We frequently receive this question during academic detailing sessions: *Is mirtazapine less sedating at higher doses?*

The Health Canada prescribing information for mirtazapine states that approximately **50% of patients experience somnolence** which may be due to its potent antihistaminic effects.[1] Common tertiary references report that mirtazapine is more sedating at lower doses (< 30 mg) than it is at higher doses (≥ 30 mg).[2,3] It is speculated to be more noradrenergic at higher doses.[2,3] This may lead to the prescribing of higher doses in an effort to overcome the drug's sedative effects.

In 1996 during the regulatory review of mirtazapine, the US Food and Drug Administration (FDA) identified that somnolence was the most common adverse event causing patients to discontinue mirtazapine.[5] The review states "One of the most troublesome of the common adverse events associated with mirtazapine use is its somnolent properties. What is unknown from the available data is the dose dependency for this event and whether or not and to what extent there may be adaptation."[5] The FDA requested a postmarketing trial examining the relationship between dose and sedation. Our literature search did not identify a completed, postmarketing dose-response trial fulfilling this requirement.

We contacted the manufacturer of Remeron® requesting relevant information and they provided three publications: a single case report,[6] one retrospective review[7] and one pharmacokinetic analysis.[8] None of these publications adequately address whether mirtazapine becomes less sedating at higher doses.

[1]Health Canada Drug Product Database; [2]UpToDate® Atypical antidepressants; [3]Clinical Handbook of Psychotropic Drugs 23rd edition; [4]FURUKAWA Lancet Psychiatry 2019;6:601-9 (PMID: 31178367); [5]US FDA 1996 Mirtazapine Review; [6]LEONARD Proc UCLA Healthcare 2015 Volume 19; [7]SHUMAN Ment Health Clin 2019;9:41-7 (PMID: 30627503); [8]GRASMADER Pharmacopsychiatry 2005;38:113-7 (PMID 15902580)

BUPROPION *dopamine norepinephrine reuptake inhibitor*

Antidepressant brand, generic	**Dosage Range** Health Canada[1]	**Dosage Clinical Considerations** dose response, dose adjustment	**Cost 30 Days**[2] BC PharmaCare[3]
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 initial: 150 mg XL once a day in the morning max: 300 mg $T_{1/2}$ ~ 21-37 hrs Css ~ 5-8 days	▪ 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			150 mg XL: $5 300 mg XL: $10 **limited coverage**

FIVE THINGS TO KNOW ABOUT ...

Bupropion abuse and overdose

CMAJ, September 16, 2014, 186(13)

Bupropion abuse is a growing public health problem

2

Although bupropion shares some structural and pharmacologic properties with amphetamine, early research suggested the drug did not produce any psychostimulant effects.[1] However, clinical experience and an increasing number of case reports describe bupropion abuse,[2] including recreational ingestion, nasal insufflation of crushed tablets and, more recently, intravenous injection.[3] Bupropion abusers report receiving a "high" similar to cocaine abuse, but of lesser intensity.[4]

Clinicians should remain vigilant for signs of bupropion misuse

3

Bupropion abusers report that they easily obtained the drug from physicians under the pretense of seeking an antidepressant or smoking cessation aid.[3] Emerging reports also highlight bupropion misuse in correctional facilities.[5] Bupropion toxicity should be considered in patients presenting with new-onset seizures of unknown cause, particularly in the context of suspected substance abuse. Nonhealing skin ulcers may reflect surreptitious injection of crushed tablets.

Seizures are a hallmark of toxicity

4

Bupropion lowers the seizure threshold, even at therapeutic doses of 150–450 mg/d.[1] Acute overdose typically produces seizures within a few hours after ingestion, although seizure onset may be delayed up to 24 hours in patients who ingest extended-release preparations.[6] The median dose associated with seizures is about 4.4 g.[6] Other reported signs of toxicity include lethargy, tremor, vomiting and agitation.[7] Associated cardiac toxicity includes sinus tachycardia, and massive overdose can cause widening of the QRS complex, ventricular dysrhythmias and cardiovascular collapse.[8] Death can occur. Although reported data are limited, they suggest that less than 0.5% of reported cases of bupropion overdose result in death.[9]

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.

05

TAPERING

WITHDRAWAL & TAPERING

50% of people who discontinue antidepressant therapy may experience withdrawal symptoms, which can be severe and long lasting in some cases

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 antidepressant with a longer half-life, such as fluoxetine
- Rapid improvement when the antidepressant is restarted or, if tapering, the previous higher dose is resumed

Tapering Strategies

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

TAPERING POSSIBILITIES

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

Appendix 1: Antidepressant Switching Strategies

Primary Care

Strategies for switching include:	**General clinical principles include:**
1. taper & switch after washout (~ 5 $t_{1/2}$) 2. taper & stop, then switch immediately 3. cross-taper (typically over 1-2 weeks) Typical taper during a switch involves reducing dose to next lowest marketed strength every 4-7 days, with goal to stop within 1-4 weeks. Ideal intervals or increments not known.	▪ recognition that data is lacking on the best method for switching from one antidepressant to another ▪ conduct all switches cautiously and consider starting the new antidepressant at the lowest available dose ▪ cross-tapering should be avoided if combining antidepressants results in moderate to severe drug interactions (See Table 2: Select Antidepressant Drug Interactions) ▪ due to long terminal half-lives, longer washout periods are recommended for fluoxetine ($t_{1/2}$ ~ 4 to 16 days) and possibly vortioxetine ($t_{1/2}$ ~ 66 hours) ▪ the safest strategy to avoid drug interactions is to taper & switch after the washout period ▪ the most conservative approach is recommended in primary care ▪ a direct switch can be considered between medications with similar pharmacology (to, or from SSRI and/or SNRI) ▪ less guidance exists for switching to and from recently marketed antidepressants (e.g., vilazodone, vortioxetine)

The tapering strategies above can be used for switching; consider urgency & context. This table informs additional safety considerations.	
serotonin reuptake inhibitors (SSRI) excluding fluoxetine - direct switch to, or from SSRI or SNRI can be considered; use lower initial doses - if switching from a high dose SSRI, consider tapering to at least a moderate dose before starting the new SSRI - caution switching from citalopram or paroxetine → duloxetine or bupropion: CYP 2D6 interaction - caution switching from paroxetine → vortioxetine: CYP 2D6 interaction; reduce vortioxetine dose by 50% if co-administering during the switch - if cross-tapering an SSRI → fluoxetine, remain at 10 mg of fluoxetine until the previous SSRI is stopped	**fluoxetine** - long half-life (~4 to 16 days): choose the most conservative switching option, as pharmacologic activity can last as long as 5 weeks after last dose - alternate strategy: stop fluoxetine, wait approximately 7 days before starting next antidepressant - if currently on a high dose of fluoxetine, consider tapering to 20 to 40 mg before stopping - if cross-tapering to fluoxetine, remain at 10 mg of fluoxetine until previous antidepressant is discontinued and increase dose at 4 to 5 week intervals - caution when switching to and from vortioxetine: both drugs have long half-lives and CYP 2D6 interactions; reduce vortioxetine dose by 50% if overlapping during the switch - caution fluoxetine → bupropion/citalopram/duloxetine/paroxetine/vortioxetine: CYP 2D6 interaction - DO NOT cross taper with clomipramine, fluvoxamine or MAOIs: high risk of serotonin toxicity
serotonin norepinephrine reuptake inhibitors (SNRI) - direct switch to a low dose SNRI or SSRI can be considered; if switching from a high dose SNRI or SSRI, consider tapering first - caution switching from duloxetine → citalopram/fluoxetine/paroxetine/bupropion: CYP 2D6 interaction - do not combine duloxetine and fluvoxamine: CYP 1A2 interaction	**bupropion** - direct switch to, or from bupropion not suggested: differing pharmacology from other antidepressants, may precipitate withdrawal symptoms - caution switching from bupropion → citalopram/fluoxetine/paroxetine/vortioxetine/duloxetine: CYP 2D6 interaction; reduce vortioxetine dose 50% if co-administering during the switch
vilazodone - pharmacokinetic interactions unlikely with other antidepressants - limited guidance exists to inform switching strategies	**mirtazapine** - direct switch to, or from mirtazapine not suggested: differing pharmacology from other antidepressants, may precipitate withdrawal symptoms
vortioxetine - long half-life (~66 hours) - caution switching from vortioxetine → fluoxetine/paroxetine/bupropion: CYP 2D6 interaction; reduce vortioxetine dose 50% if co-administering during the switch	**tricyclic antidepressants (TCA)** - fluvoxamine, fluoxetine, and paroxetine can increase TCA blood levels for several weeks - do not combine clomipramine and SSRIs or SNRIs: high risk of serotonin toxicity - switching from most antidepressants → TCA: cross-taper cautiously (exception: fluoxetine, stop and wait 4 to 7 days, start TCA at low dose and increase slowly OR stop fluoxetine and wait 5 weeks to start TCA)
reversible monoamine oxidase inhibitors (MAOI) - switching from moclobemide → another antidepressant: taper and stop, wait 24 hours before initiating new antidepressant - switching from most antidepressants → moclobemide: taper and stop, wait 1 to 2 weeks before initiating moclobemide (exception: fluoxetine wait 5 to 6 weeks; vortioxetine wait 3 weeks)	**irreversible monoamine oxidase inhibitors (MAOI)** - switching from an MAOI → another antidepressant: taper and stop, wait 2 weeks before initiating new antidepressant - most antidepressants → MAOI: taper and stop, wait 2 weeks before initiating MAOI (exceptions: fluoxetine wait 5 to 6 weeks; vortioxetine wait 3 weeks)

pad

06

RESOURCES

Serotonin Syndrome

Group A

Non-selective and irreversible MAOi A and B
Isocarboxazid
Isoniazid
Phenelzine
Tranylcypromine

Non-selective and reversible MAOi A and B
Linezolid

Selective and irreversible MAOi B
Selegiline (non-selective at higher doses)
Rasagiline

Selective and reversible MAOi A
Moclobemide
Methylene blue (non-selective at higher doses)

Group B

Antidepressants
Selective Serotonin Reuptake Inhibitors (SSRI): Paroxetine, fluvoxamine, sertraline, citalopram, escitalopram, fluoxetine

Serotonin Norepinephrine Inhibitors (SNRI): Venlafaxine, desvenlafaxine, duloxetine

Tricyclic Antidepressants: Clomipramine, imipramine

Opioids and other pain medications
Tramadol, meperidine, methadone, fentanyl (unlikely with morphine, codeine, oxycodone, buprenorphine)

Cough, cold and allergy
Dextromethorphan ("DM"), chlorpheniramine

Natural health products
St. John's wort, L-tryptophan, diet pills

Illicit drugs
Ecstasy (MDMA), amphetamine, cocaine

SEROTONIN SYNDROME

AVOID:	Group A with Group A or Group A with Group B
CAUTION:	TWO or more Group B drugs especially when ONE is used at a high dose
MONITOR:	If a patient uses a Group B drug and a second Group B drug is added, start low, increase the dose cautiously, and watch for symptoms for 24-48h after every change

Commonly Listed but unlikely to cause Serotonin Syndrome

Triptans (e.g., sumatriptan)

Antidepressants: amitriptyline, mirtazapine, trazodone

Antiemetics: 5HT3 receptor antagonists (e.g., ondansetron), metoclopramide

Buspirone, lithium

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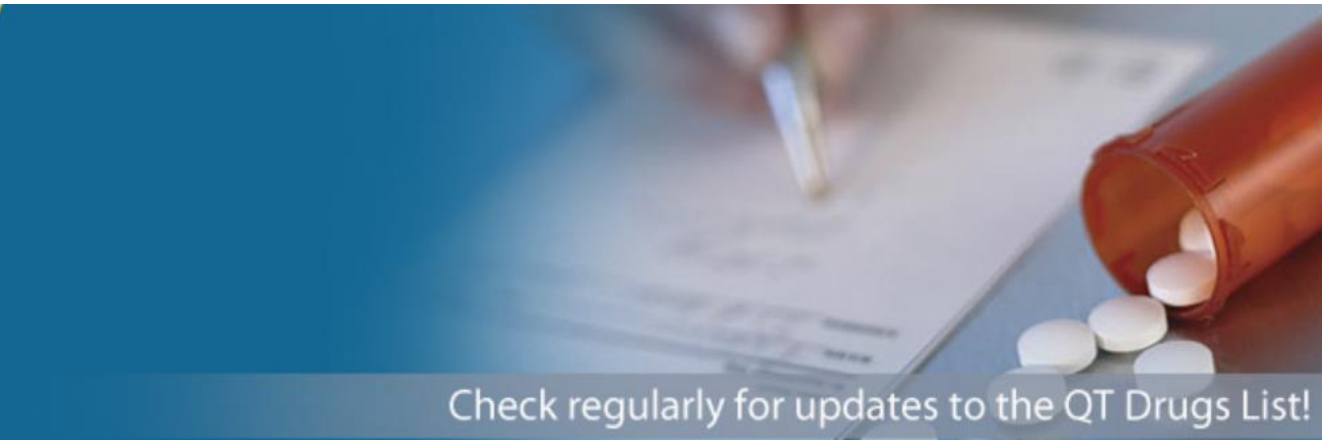

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ANCIENT STRESSORS

MODERN STRESSORS

Inspired by The Illustrated Happiness Trap by Russ Harris and Bev Aisbett

1. Acceptance and Commitment Therapy

Acceptance and Commitment Therapy (ACT) has been shown to be effective in the treatment of anxiety disorders, depression, addiction, and certain physical health issues (A-Tjak et al., 2015).

2. Cognitive Behavioral Therapy

Cognitive Behavioral Therapy, or CBT, is perhaps the most well-known and widely accepted form of treatment for many psychological issues.

In recent years, several independent meta-analyses have found solid evidence for the effectiveness of CBT in treating anxiety (Carpenter et al., 2018), depression (in all treatment delivery formats; Cuijpers, Noma, Karyotaki, Cipriani, & Furukawa, 2019), psychosis (Hazell, Hayward, Cavanagh, & Strauss, 2016), Body Dysmorphic Disorder (BDD; Harrison, de la Cruz,

One such effort examined the feasibility of internet-delivered cognitive behavior therapy (IBCT), which found that ICBT can be effective in treating children and adolescents with anxiety and depressive symptoms (Vigerland et al., 2016). CBT is an effective, evidence-based

https://positivepsychology.com/evidence-based-therapy

3. Dialectical Behavior Therapy

Dialectical Behavior Therapy (DBT) is also an evidence-based treatment, as it has been shown to be effective for relieving the symptoms and improving outcomes for patients with both borderline personality disorder (BPD) and substance abuse (Linehan et al., 1999) as well as for patients with trichotillomania (Keuthen et al., 2011).

4. Mindfulness-Based Cognitive Therapy

Mindfulness-Based Cognitive Therapy (MBCT) has been found to be effective in reducing relapse rates of Major Depressive Disorder (MDD) (Lilja et al., 2016).

As noted earlier, CBT research has proven it as effective for the treatment of both MDD and generalized anxiety disorder (GAD), along with several other disorders (Gratzer & Goldbloom, 2016); however, the addition of mindfulness to cognitive therapy may boost its effectiveness in some situations.

https://positivepsychology.com/evidence-based-therapy

RESOURCES

Parents & Caregivers

Youth & Young Adults

Health Professionals

School Professionals

www.keltymentalhealth.ca

RESOURCES

Useful Tools – Depression

Download reusable worksheets for Depression.

- Get Active
- Problem Solving
- Thought Challenging
- Multiple Thought Challenging
- Core Beliefs

Depression

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Depression is common and it can happen to anyone. The good news is that there are effective treatments that can help you feel better. Here you will learn more about depression and how to treat it.

You can use any lesson at any time. However, therapy for depression usually uses this order:

1. What is Depression?
2. Get Active
3. Problem Solving
4. Thought Challenging
5. Core Beliefs
6. Understanding Medication

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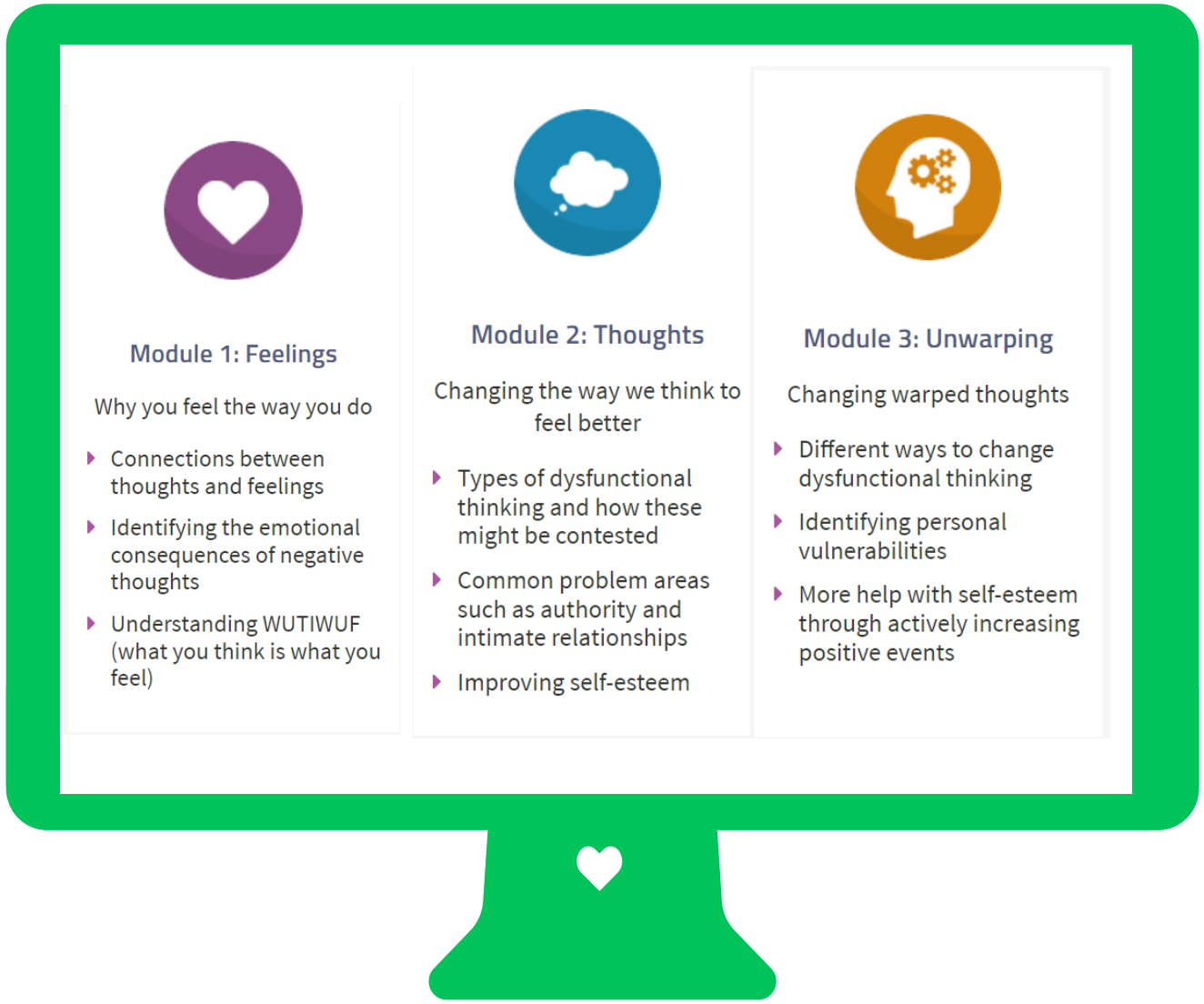
RESOURCES

moodgym®

Practise skills which can help to prevent and manage symptoms of depression and anxiety.

Cognitive behaviour therapy (CBT).



https://moodgym.com.au

moodgym®

Evaluation studies suggest that moodgym is a viable option for those who cannot access face-to-face therapy, and for those waiting for traditional services.

https://moodgym.com.au

Personal Quality of Life Scale

1. Work-occupation-school

Low									High
1	2	3	4	5	6	7	8	9	10

2a. Love-friends

Low									High
1	2	3	4	5	6	7	8	9	10

2b. Love-intimates

Low									High
1	2	3	4	5	6	7	8	9	10

2c. Love-family

Low									High
1	2	3	4	5	6	7	8	9	10

3. Play-recreation-hobbies-interests-sports

Low									High
1	2	3	4	5	6	7	8	9	10

Personal Quality of Life Scale

4.

Exercise
Smoke
Sleep
-spending extra time in bed when not asleep
- evening screen/device time

Recreational drugs
Alcohol
Gambling
Violence
Citizenship/community
Spiritual
Values
(trauma)

Rumi

the wound is where the light enters you

Health Coach Program

Self-Management
British Columbia

Trained peer coaches connect with you by telephone for 3 months once a week for 30 minutes

Peer Health Coaches provide support that complements and enhances professional health care; they do not provide medical/clinical advice or treatment.

Gain knowledge + skills + confidence

www.selfmanagementbc.ca

Rumi

the wound is where the light enters you

Health Coach Program

BounceBack®
reclaim your health

A trained BounceBack® coach will help participants learn skills to improve their mental health in up to six telephone sessions over three to six months.

To help adults and youth 15+ manage low mood, mild to moderate depression, anxiety, stress or worry.

A Canadian Mental Health Association (CMHA) funded (free) program.

www.cmha.ca/bounce-back

Suicide Prevention and Crisis Support

- **The Crisis Intervention and Suicide Prevention Centre of British Columbia** – provides local crisis centre phone numbers.

  Distress Line Numbers: BC-wide: **1-800-SUICIDE (1-800-784-2433)**
  Greater Vancouver: **604-872-3311**
  Toll free: Lower Mainland & Sunshine Coast: **1-866-661-3311**
  TTY: **1-866-872-0113**
  Seniors' Distress Line: **604-872-1234**

  Online Distress Services: www.youthinbc.com
  www.crisiscentrechat.ca
  www.crisiscentre.bc.ca

- **Centre for Suicide Prevention (Canada)** – provides information on suicide and suicidal behavior.
  Website: www.suicideinfo.ca

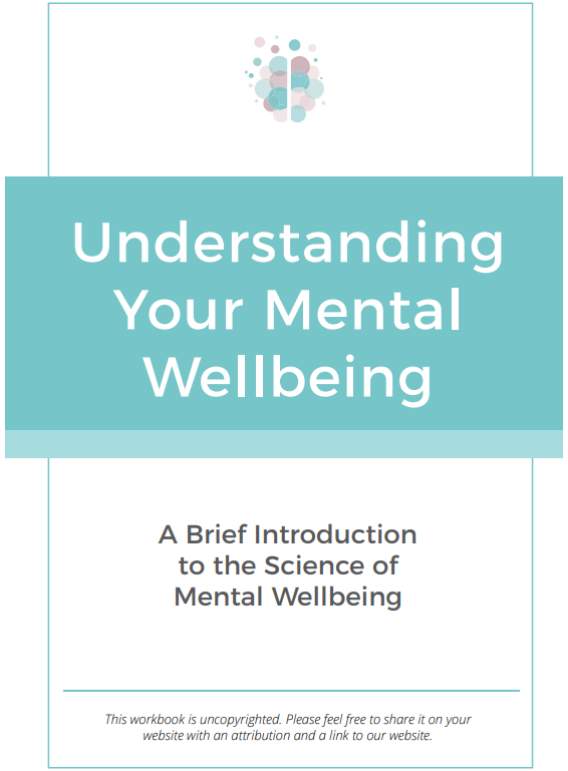
https://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/depression_resource_guide_physicians.pdf

THE WELLNESS SOCIETY

Can't afford therapy? Our self-help toolkit combining several therapeutic techniques is "like 10 therapy sessions in one."

"If you listen to your body when it whispers, you won't have to hear it scream."

Free Mental Wellbeing Tools



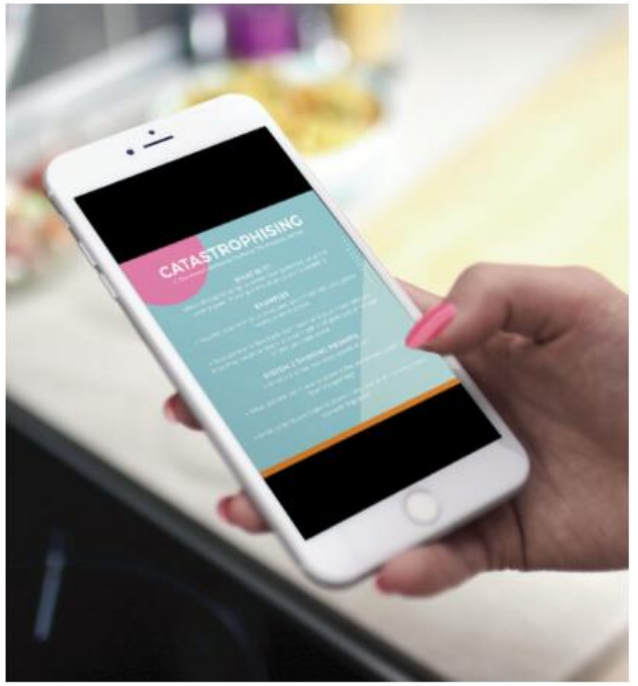
Our Tools Are Recommended By

NHS mind for better mental health Royal College of Nursing

https://thewellnesssociety.org

Discover The Mental Wellbeing Toolkit

THE WELLNESS SOCIETY



Save your time, energy and money with our concise, integrative framework combining valuable insights from:

- ✓ Cognitive behavioural therapy (CBT)
- ✓ Dialectical behavioural therapy (DBT)
- ✓ Mindfulness-based cognitive therapy (MBCT)
- ✓ Acceptance and commitment therapy (ACT)
- ✓ Positive psychology
- ✓ Problem solving therapy
- ✓ Behavioural activation (BA)
- ✓ Non-violent communication (NVC)
- ✓ Lifestyle medicine and more!

https://thewellnesssociety.org

THE WELLNESS SOCIETY

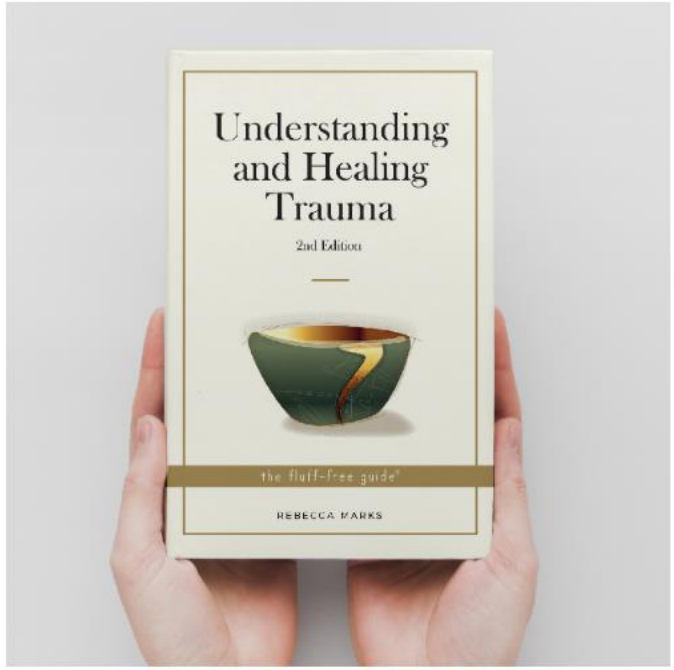
Therapy for Trauma Survivors Online Guide

Cognitive behavioural therapy (CBT), the most popular talking therapy on the NHS, may not always be the most helpful for trauma survivors.

Here are seven therapies recommended by trauma experts:

1. Eye Movement Desensitisation and Reprocessing (EMDR)
2. Somatic Experiencing (SE)
3. Sensorimotor Psychotherapy
4. Pesso Boyden System Psychomotor (PBSP)
5. Therapists trained in The Comprehensive Resource Model (CRM)
6. Internal Family Systems Therapy (IFS)
7. Tension, Stress and Trauma Release (TRE)

Free Book: Understanding and Healing Trauma



https://thewellnesssociety.org/7-types-of-therapy-for-trauma-survivors

THANKS!

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North Shore Primary Care Networks

Sanjeev Bains obtained her Bachelor of Science in Pharmacy degree and completed her Community Pharmacy Practice Residency through the University of British Columbia. She joins the North Shore PCN from her previous role as a clinical pharmacist in the BC Provincial Academic Detailing Service, a position that she has held for the past 13 years. Throughout her career, Sanjeev has maintained an active role in the community pharmacy setting by serving as a relief pharmacist for a number of local community pharmacies. Sanjeev also has previous experience as a Medication Management Pharmacist in the community of White Rock, where she provided pharmaceutical care to older adults that were recently discharged from the hospital. She looks forward to applying her knowledge in evidence-based medicine and experience in medication management in her new role. Outside of work, she enjoys keeping active by skiing, yoga, and baking.

Sanjeev will begin her role as a PCCP in a permanent full-time capacity on May 23, 2023.

Medications for Generalized Anxiety Disorder (GAD):

Evidence Summary for PAD Pharmacists

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

GAD Clinical Trials

Medications approved by Health Canada for the management of generalized anxiety disorder include:[1]

- escitalopram, paroxetine, venlafaxine, duloxetine, and buspirone.

The most common efficacy measure used in randomized controlled trials of medications for the treatment of GAD is a symptom severity scale (clinician administered):[2-4]

- Hamilton Anxiety Rating Scale (14 item) (HAM-A: score range 0 to 56).

In the largest dataset of published and unpublished trials, (89 trials; 25,441 participants):[5]

- two-thirds were women,
- mean HAM-A score was 25 at baseline,
- median duration of the trials was 8 weeks, and
- participants with major comorbidities (other than depression) were generally excluded.

The body of literature for GAD is smaller than that for major depressive disorder (MDD), with the largest dataset for MDD containing over four times as many participants.[6]

GAD Meta-Analyses & Systematic Reviews

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

- approximately 2 to 4 points (HAM-A score),[5]
- eg, in one meta-analysis (paroxetine, median 10 weeks):[7] mean 11.1 point improvement in the drug treatment group versus 8.8 point improvement in the placebo group.

Proportion of people achieving at least a 50% improvement in their symptom severity score:

- eg, in one meta-analysis (venlafaxine, median 8 weeks):[8]
  - 56% in the antidepressant group, and
  - 41% in the placebo group.

The largest systematic review and network meta-analysis shows that there is large variation in the quantity of evidence for different medications, eg,:[5]

- 2 trials, 37 participants received citalopram,
- 6 trials, 311 participants received buspirone,
- 6 trials, 485 participants received sertraline,
- 8 trials, 1355 participants received duloxetine,
- 13 trials, 1581 participants received escitalopram,
- 11 trials, 1957 participants received pregabalin,
- 14 trials, 2275 participants received venlafaxine.

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The following drugs were statistically more efficacious than placebo, have been studied in over 1000 participants, and participants were not more likely to discontinue the drug than placebo (ie, the acceptability point estimate favours the drug):[5]

- escitalopram, venlafaxine, and pregabalin.

The following drugs were statistically more efficacious than placebo, have been studied in over 1000 participants, but participants were more likely to discontinue the drug than placebo (ie, the acceptability point estimate favours placebo):[5]

- paroxetine, duloxetine, quetiapine, and benzodiazepines.

Recently marketed antidepressants (eg, vilazodone, vortioxetine) were not statistically more efficacious than placebo.[5]

5. Slee A, Nazareth I, Bondaronek P, Liu Y, Cheng Z, Freemantle N. Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. The Lancet. 2019;393(10173):768-777.

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