Managing Depression

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1

Disclosures

- I have no financial relationships with pharmaceutical companies
- I have received honoraria from:
  - Canadian Agency for Drugs and Technologies in Health (CADTH)
  - Patented Medicines Price Review Board (PMPRB)

2

Learning Objectives

Upon completion of this session, NDs will be able to:

1. Describe the clinical presentation and prevalence of major depressive disorder (MDD).
2. List the DSM 5-TR diagnostic criteria for MDD.
3. Describe the different treatment options for depression and list some advantages and disadvantages of various treatments for MDD.
4. Describe treatment options when the first antidepressant doesn't work
5. Describe several strategies to monitor therapy of patients with MDD

3

Presentation Outline

- Learning objectives
- Characteristics of depression
  - Prevalence, risk factors and course
  - Signs and symptoms
- Treatment options
  - Pharmacological
  - Non-pharmacological
- Monitoring parameters
- Key Messages

4

Major Depressive Disorder

Common and recurrent

Average age of onset: mid 20s

Annual Canadian prevalence: 5.4%

Lifetime prevalence: 11%

Lifetime risk

- 1 in 5 women
- 1 in 10 men
- 1 in 50 children (< 12 years old)
- 1 in 15 adolescents

Second-leading cause of disability worldwide

Drugs for MDD. *CADTH*. Feb 2020.
Patten SB, et al. *Can J Psychiatry*. 2015;60(1):23-30.
Ferrari AJ, et al. *PLoS Med*. 2013;10(11):e1001547.

5

Case: Sylvia Part 1

30-year-old female, with low mood x four months (first major depressive episode)

Feels fatigued, despondent and has difficulty concentrating. She also feels hopeless and hollow.

Lost her waitress job in March 2020

Sleeps 10-12 hrs/night and mentioned that she lacks any desire to get out of bed

Has gained 5 kg in the last two months

Denies suicidal thoughts

6

Case: Sylvia

Single and lives on her own

Eats fast food, frozen dinners and snacks

Drinks 2-4 glasses of wine and coolers/day and smokes occasionally

Family Hx: Mother has MDD and generalized anxiety disorder and takes sertraline and buspirone

Medical conditions: Psoriasis, chronic back pain

Medications: Betamethasone, apremilast, acetaminophen with codeine (T#3), ibuprofen

No known allergies

7

DSM 5-TR Major Depressive Episode (MDE) Symptoms	
Low mood	Fatigue (loss of energy)
Anhedonia	Feelings of unworthiness or guilt
Appetite or weight changes	Poor concentration
Agitation	Loss of interest in life or thoughts of suicide
Sleep disturbances	

Five or more of these symptoms > 2 weeks **Must impair function**

S - Sleep changes
A - Appetite (wt. change)
D - Dysphoria (low mood)
A - Anhedonia
F - Fatigue
A - Agitation
C - Concentration
E - Esteem/guilt
S - Suicide

8

RATING THE SEVERITY OF MDD

9

Commonly Used Depression Rating Scales

- Beck Depression Inventory (BDI)
- Hamilton Depression Rating Scale (HAM-D or HDRS)
- Montgomery-Åsberg Depression Rating Scale (MADRS)
- Patient Health Questionnaire-9 (PHQ-9)
- Patient Health Questionnaire (PHQ) three pages, screens for depression, general anxiety and eating disorders

https://www.apa.org/depression-guideline/assessment/

10

Validated rating scales for MBC

Outcome	Clinician-rated scales	Patient-rated scales
Symptoms/ severity	• Hamilton Depression Rating Scale (HAM-D, HAM-7) • Montgomery Åsberg Depression Rating Scale (MADRS) • Inventory for Depressive Symptomatology (IDS) • Columbia Suicide Severity Rating Scale (C-SSRS)** • Dimensional Anhedonia Rating Scale (DARS)	• Beck Depression Inventory II (BDI-II)* • Clinically Useful Depression Outcome Scale (CUDOS) • Patient Health Questionnaire (PHQ-9) • Patient Rated Outcome Measurement Information System (PROMIS) • Quick Inventory for Depressive Symptomatology, Self-Rated (QIDS-SR) • Suicidality Scale**

Patient-rated scales are well correlated with clinician-rated scales and take less time to administer

*Copyright may require a fee for clinical use.
**Scales can help assess suicide ideation, but they cannot reliably predict suicide attempts or behaviours; when scales for suicide risk are used, the results should be promptly reviewed and followed up with clinical assessment if scores indicate risk. Scales are examples for illustrative purposes and are not specifically endorsed by CANMAT. MBC, measurement-based care.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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11

Patient Health Questionnaire (PHQ-9)

Over the last two weeks, how often have you experienced the following?	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	(3)
2. Feeling down, depressed, or hopeless	0	1	(2)	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	(3)
4. Feeling tired or having little energy	0	1	2	(3)
5. Poor appetite or overeating	0	1	(2)	3
6. Feeling bad about yourself – or that you are a failure or have let yourself or your family down	0	1	(2)	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	(1)	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless than you have been moving around a lot more than usual	(0)	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	(0)	1	2	3

Adapted from: PHQ Screeners. Available at: http://www.phqscreeners.com/

12

Patient Health Questionnaire (PHQ-9)

GUIDE FOR INTERPRETING PHQ-9 SCORES		
Score	**Depression severity**	**Action**
0-4	None-minimal	Patient likely does not need depression treatment
5-9	Mild	Use clinical judgement about treatment, based on patient's duration of symptoms and functional impairment
10-14	Moderate	Use clinical judgement about treatment, based on patient's duration of symptoms and functional impairment
15-19	Moderately severe	Treat using antidepressants, psychotherapy or a combination of treatment
20-27	Severe	Treat using antidepressants with or without psychotherapy

Adapted from: PHQ Screeners. Available at: http://www.phqscreeners.com/

13

Risk Factors for Depression

- Family history of MDD
- Female gender
- Social isolation (e.g., single, widowed, divorced)
- Recent loss of a loved one or tragedy
- Uncontrolled chronic or severe pain
- Substance abuse
- Recent childbirth
- Lower socioeconomic status
- Insomnia
- Comorbid chronic conditions (e.g., MI, stroke, cancer, hypothyroid, diabetes, COPD, psoriasis, anxiety disorders)
- Medications

14

Medications Associated With Depression

MEDICATION CLASSES

- Opioids
- Steroids
- Hormones (progesterone, estrogen)
- Cardiac meds – clonidine, beta blockers, amiodarone, digoxin, calcium channel blockers, ACEI/ARBs
- Chemotherapy
- Benzodiazepines
- Anticonvulsants (phenytoin, carbamazepine, topiramate)

SPECIFIC MEDICATIONS

- Levodopa
- Varenicline
- Isotretinoin
- Bromocriptine
- Finasteride
- Mefloquine
- Alcohol
- Apremilast

15

Setting Goals of Therapy for Sylvia

SHORT-TERM (e.g., < 3 months)

- Stabilize depressive symptoms
- Minimize side effects
- Induce remission (not only response)
- Improve quality of life
- Prevent suicide
- Reintegrate with family and social environment
- Prevent drug interactions
- Reduce alcohol intake

16

Setting Goals of Therapy for Sylvia

LONG-TERM *(e.g., > 3 months)*

- Prevent relapse and recurrence
- Maintain a stable mood/remission
- Manage side effects
- Education
- Adherence
- Improve chronic pain and psoriasis symptoms
- Smoking cessation (when Sylvia is ready)
- Reduce alcohol and opioid intake

17

Treatment Options

Pharmacotherapy (Moderate-to-severe)

Antidepressants

Adjunctive or combination therapies

Psychotherapy (Mild-to-moderate/severe)

Cognitive behavioural therapy (CBT)

Interpersonal therapy (IPT)

Virtual options ("Betterhelp", "ReGain", "Talkspace", "Pride Counselling")

Alternative treatments

- Electroconvulsive therapy (ECT) (Treatment-resistant)
- Ketamine (esketamine [Spravato®]) (Treatment-resistant)
- Transcranial magnetic stimulation (TMS) therapy (Treatment-resistant)
- Others (Mild-to-moderate)
  - Natural health products (e.g., St. John's Wort, SAM-e)
  - Mindful meditation (Free apps "Calm", "Headspace" or "Mindfulness")
  - Exercise

18

What do you think Sylvia should do?

19

First-Line Antidepressant Options		
SSRIs	Selective serotonin reuptake inhibitors (*sertraline, citalopram, escitalopram, fluoxetine, paroxetine, fluvoxamine*)	6 agents
NaSSA	Noradrenergic and serotonergic specific antidepressant (*mirtazapine*)	1 agent
NDRIs	Norepinephrine dopamine reuptake inhibitor (*bupropion*)	1 agent
SNRIs	Serotonin norepinephrine reuptake inhibitors (*venlafaxine, desvenlafaxine, duloxetine, levomilnacipran*)	4 agents
Serotonin modulator	Serotonin reuptake inhibitor, partial agonist/antagonist (*vortioxetine*) Serotonin reuptake inhibitor, partial agonist (*vilazodone*)	2 agent
Second- and Third-Line Options		
TCAs	Tricyclic antidepressants (*desipramine, nortriptyline, amitriptyline, clomipramine, imipramine, doxepin, protriptyline, amoxapine, trimipramine*)	9 agents
RIMA	Reversible inhibitor of monoamine oxidase-A (*moclobemide*)	1 agent
Reserved Treatment Options		
SARIs	Serotonin antagonists/reuptake inhibitor (*trazodone*)	1 agent
MAOIs	Monoamine oxidase inhibitors (*phenelzine, tranylcypromine*)	2 agents
Heterocyclics	Maprotiline	1 agent

20

1st-line antidepressants

Line of Treatment	Antidepressant	Daily dose[1]	Mechanism	Level of Evidence
1st Line	Citalopram	20-40 mg	SSRI	
	Escitalopram	10-20 mg	SSRI	
	Fluoxetine	20-60 mg	SSRI	
	Fluvoxamine	100-300 mg	SSRI	
	Paroxetine	20-50 mg	SSRI	
	Sertraline	50-200 mg	SSRI	
	Desvenlafaxine	50-100 mg	SNRI	
	Duloxetine	60-120 mg	SNRI	
	Levomilnacipran*	40-120 mg	SNRI	
	Venlafaxine-XR	75-225 mg	SNRI	
	Bupropion	150-450[2] mg	NDRI	
	Mirtazapine	30-60 mg	α2 antagonist; 5-HT2 antagonist	
	Vilazodone*	20-40 mg	SRI; 5-HT1A agonist	
	Vortioxetine	10-20 mg	SRI; 5-HT1A, 5-HT1B agonist; 5-HT1D, 5-HT3A, 5-HT7 antagonist	
	Agomelatine#	25-50 mg	MT1, MT2 agonist; 5-HT2 antagonist	
	Mianserin#	30-90 mg	α2 antagonist; 5-HT2 antagonist	
	Milnacipran#	50-200 mg	SNRI	

LoE, Level of Evidence: Level 1, Level 2, Level 3, Level 4

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*Change since CANMAT 2016 guidelines, based on updated evidence; # Not available in Canada. See speaker notes for additional footnotes.
5-HT, 5-hydroxytryptamine receptor; α2, alpha-2 adrenergic receptor; MT, melatonin receptor; NDRI, norepinephrine-dopamine reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

15

21

2nd-line and 3rd-line antidepressants

Line of Treatment	Antidepressant	Daily dose[1]	Mechanism	Level of Evidence
2nd Line	Amitriptyline	75-300 mg	TCA	
	Clomipramine	150-300 mg	TCA	
	Desipramine	100-300 mg	TCA	
	Doxepin	75-300 mg	TCA	
	Imipramine	75-300 mg	TCA	
	Nortriptyline	75-150 mg	TCA	
	Protriptyline	30-60 mg	TCA	
	Trimipramine	75-300 mg	TCA	
	Moclobemide	150-450 mg[2]	RIMA	
	Trazodone	150-400 mg	SRI; 5-HT2 antagonist	
	Quetiapine	150-300 mg	DA, 5-HT, α1 & α2 antagonist; NRI	
	Dextromethorphan-bupropion*#	45 mg/105 mg-90 mg/210 mg	NMDA antagonist; NDRI, sigma-1 agonist	
	Nefazodone#	300-600 mg	SRI; 5-HT2 antagonist	
	Selegiline transdermal#	6-12 mg	MAO-B inhibitor	
3rd Line	Phenelzine	45-90 mg	MAO inhibitor	
	Tranylcypromine	30-60 mg	MAO inhibitor	
	Reboxetine#	8-12 mg	NRI	

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5-HT, 5-hydroxytryptamine receptor; α1/2, alpha-1/2 adrenergic receptor; DA, dopamine; MAO, monoamine oxidase; NMDA, N-methyl-D-aspartate receptor; NRI, norepinephrine reuptake inhibitor; RIMA, reversible inhibitor of monoamine oxidase A; SRI, serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

16

22

Recommendations for CAM treatments

Line of treatment	CAM treatment	Level of evidence
1st Line	• St. John's wort for mild MDE	Level 1
2nd Line	• Acupuncture for mild MDE	Level 2
	• St. John's wort for moderate MDE	Level 2
	• Adjunctive acupuncture for moderate MDE	Level 2
	• Adjunctive L-methyl folate for mild-moderate MDE	Level 2
3rd Line	• Adjunctive SAM-e for mild to moderate MDE	Level 2
	• DHEA for mild MDE	Level 3
	• Omega-3 fatty acids for mild MDE	Level 3
	• Saffron, lavender, or roseroot for mild MDE	Level 4

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

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DHEA, dehydroepiandrosterone; MDE, major depressive episode; SAM-e, S-adenosyl-L-methionine.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

23

SELECTING AN ANTIDEPRESSANT

24

Based on the available evidence, is there any one antidepressant (or antidepressant class) that is superior to all the rest for treating MDD?

A. Vortioxetine is the most effective
B. SSRIs are the most effective
C. SNRIs are the most effective
D. TCAs are the most effective
E. They are all equally effective

25

Comparing Antidepressants

CADTH

- Updated systematic review and network meta-analysis based on Cipriani's review (*Lancet* 2018)
- 522 double-blind RCTs of 21 different antidepressants vs. placebo or active comparators in adults with MDD (*304 were placebo-controlled; 116,447 participants*)
- Primary efficacy outcome: at least 50% response (measured at eight weeks or greater)
- Acceptability outcome: treatment discontinuation for any reason


TECHNOLOGY REVIEW: FOCUSED CRITICAL APPRAISAL

Drugs for Major Depressive Disorder

Articles

Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Drugs for Major Depressive Disorder. Focused Critical Appraisal. *CADTH*. Feb 2020 (24). Accessed on April 21, 2020. https://cadth.ca/sites/default/files/hta-he/he0022-major-depressive-disorder-critical-appraisal.pdf

26

"This study concluded that all included antidepressants were more efficacious than placebo in their response rates…."

Drugs for Major Depressive Disorder. Focused Critical Appraisal. *CADTH*. Feb 2020 (24). Accessed on April 21, 2020. https://cadth.ca/sites/default/files/hta-he/he0022-major-depressive-disorder-critical-appraisal.pdf

27

"Overall, these observations illuminate that all currently available treatments, regardless of novelty and price, are likely equal and can be used for patients with MDD based on their clinical attributes and personal preferences as part of a shared decision-making process."

Drugs for Major Depressive Disorder. Focused Critical Appraisal. *CADTH*. Feb 2020 (24). Accessed on April 21, 2020. https://cadth.ca/sites/default/files/hta-he/he0022-major-depressive-disorder-critical-appraisal.pdf

28

Factors to Consider When Selecting an Antidepressant

- Severity of episode
- Patient's age
- Long-term adherence
  - Risk of relapse increases if discontinued early (35%-60% vs. 10%-25%)
- Previous treatment response
- Comorbid psychiatric or medical disorders
- Effectiveness
- Drug interactions
- Accessibility/affordability
- Pharmacokinetics
- Side effects
- Suicide risk
- Patient preferences
- Clinician experience

29

Recommendations for selecting initial treatment[1]

For mild MDE severity with low safety risk

Psychotherapy and pharmacotherapy demonstrate similar benefits

Psychotherapy (if accessible) associated with **fewer risks** but limited evidence for efficacy when delivered less frequently than once weekly

Exercise, certain **CAM** treatments, and guided **DHIs** may be considered as monotherapy (especially if preferred by patient)

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

[1] There is stronger evidence for efficacy and safety of pharmacotherapy and psychotherapy compared to exercise, complementary and alternative medicine treatments, and digital health interventions. The level of evidence refers to the choice of treatment, not to the treatments themselves.
CAM, complementary and alternative medicine; DHI, digital health intervention; MDE, major depressive episode.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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30

Recommendations for selecting initial treatment[1]

For moderate MDE severity with low-moderate safety risk

Initial choice can be **pharmacotherapy, psychotherapy, or both combined**

Pharmacotherapy is **slightly more efficacious** in reducing **depressed mood, guilt, suicidal thoughts, anxiety, and somatic symptoms** during acute treatment

Structured **psychotherapy**, specifically CBT, is slightly **more efficacious** in the **medium-term** (6-12 months)

Exercise, certain **CAM** treatments, and **DHIs** may be considered as **adjuncts** to psychotherapy and/or pharmacotherapy (especially if preferred by patient)

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

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5

31

Recommendations for selecting initial treatment[1]

For severe MDE with moderate-high safety risk

Without psychotic symptoms: combination of **pharmacotherapy and psychotherapy**

With psychotic symptoms: combination of **antidepressant and antipsychotic medication**

Very severe and/or life-threatening situations: consider **electroconvulsive therapy**

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

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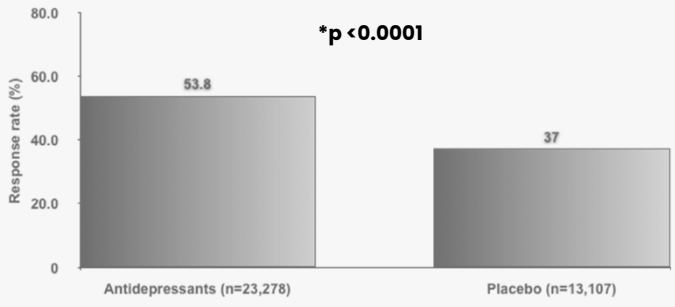
32

HOW EFFECTIVE ARE ANTIDEPRESSANTS?

33

Overall Response Rates: Antidepressants

Meta-analysis including 262 drug-placebo comparisons from 182 clinical trials (n=36,385)



Papakostas F. *Eur Neuropsychopharmacol.* 2009:19:34-40.

34

Sequenced Treatment Alternatives to Relie Depression (STAR*D) Study

- Objective: Assess effectiveness of depression treatments in MDD – NIMH-funded study ($35 million)
- 2,876 outpatients (18-75 yrs old)
- 76% Caucasian, 64% female
- Mean age 40.8 yrs (average of six MDE over 15 yrs)
- 41 US centres (18 primary care and 23 psychiatric settings)
- Baseline HAM-D17 score > 21.8 (had to be ≥ 14)
- Open-label (no placebo)
- (Pseudo) Randomized

Article

Acute and Longer-Term Outcomes in Depressed Outpatients Requiring One or Several Treatment Steps: A STAR*D Report

A. John Rush, M.D.
Madhukar H. Trivedi, M.D.
Stephen R. Wisniewski, Ph.D.
Andrew A. Nierenberg, M.D.
Jonathan W. Stewart, M.D.
Diane Warden, Ph.D., M.B.A.
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Patrick J. McGrath, M.D.
Jerrold F. Rosenbaum, M.D.
Harold A. Sackeim, Ph.D.
David J. Kupfer, M.D.
James Luther, M.A.
Maurizio Fava, M.D.

Rush AJ, et al. *Am J Psychiatry.* 2006;163:1905-1917.
https://www.nimh.nih.gov/funding/clinical-research/practical/stard/allmedicationlevels.shtml

35

(STAR*D) Sequence

Step 1: Citalopram (3,671 people start and 2,876 take citalopram for up to 14 wks)

Move to step 2 if not in remission

Step 2: 7 options (1,439 people)

Move to step 3 if not in remission

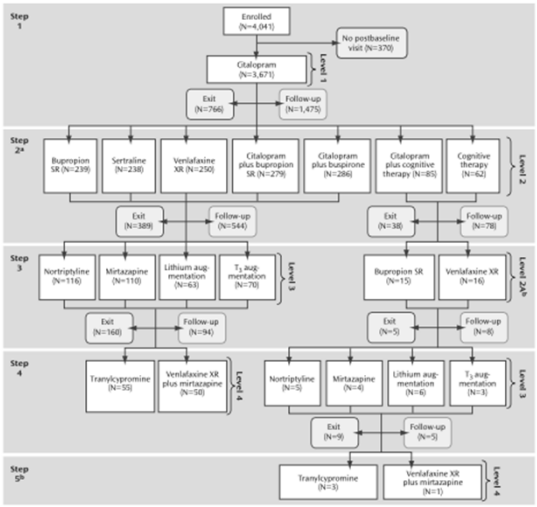
Step 3: 4 options (390 people)

Move to step 4 if not in remission

Step 4: 2 options (123 people)

Primary Outcome: Remission

HAMD ≤ 7 or QIDS-SR ≤ 5



Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.

36

(STAR*D) Results for Step 1 and 2

Citalopram mean dose = 42 mg

Avg. treatment duration 10 wks

Remission rates after phase 1:

- 27.5% using HAM-D
- 32.9% using QIDS-SR

Response rate (≥ 50% reduction) = 47%

Remission after step 2 was ~25% using QIDS-SR (NSS)

Response rate after step 2 was ~28% (NSS)

Article

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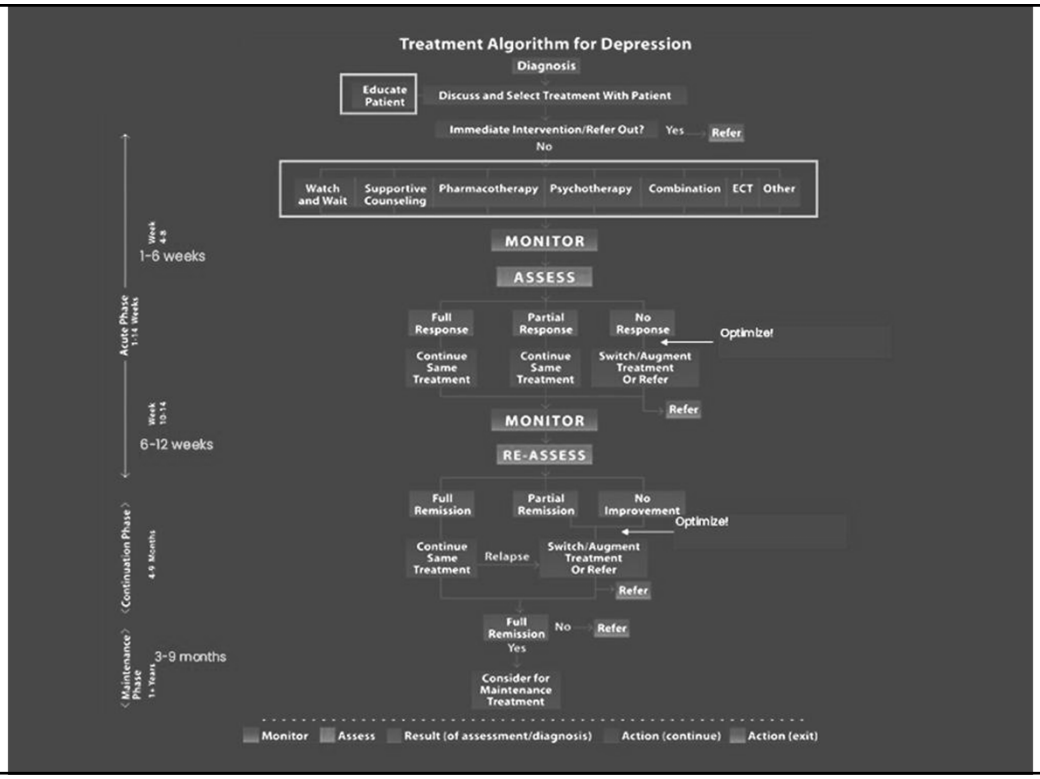
Rush AJ et al; *Am J Psychiatry*. 2006;163:1905-1917.

37



38

Antidepressant Adverse Effects

Anticholinergic
- Constipation
- Blurred vision
- Urinary retention
- Confusion/delirium

CNS effects
- Headaches
- Agitation
- Sedation
- Seizures

- Cognitive
- Cardiovascular
  - Postural hypotension
  - QTc Prolongation
- GI (SSRI bleed, N/V/D/C)
- Serotonin syndrome
- Sexual dysfunction
- Hyponatremia (SIADH)
- Weight gain

Santarsieri D, Schwartz TL. Antidepressant efficacy and side effect burden. A quick guide for clinicians. *Drugs Context*. 2015;4:212290. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630974/

39

Antidepressant Adverse Effects

CLASS	EXAMPLES	ADVERSE EFFECTS	OTHER COMMENTS
TCA	Imipramine Amitriptyline Doxepin Desipramine Nortriptyline	Weight gain, sedation, dry mouth, nausea, blurred vision, constipation, tachycardia	Generally not first-line therapy due to increased anticholinergic and cardiotoxic SE
MAOI	Phenelzine Tranylcypromine	Weight gain, fatigue, sexual dysfunction, hypotension	Generally not first-line therapy due to serotonin syndrome and hypertensive crises
SSRI	Fluoxetine Paroxetine Sertraline Citalopram Escitalopram	Headaches, GI distress, insomnia, fatigue, anxiety, sexual dysfunction, weight gain	Often first-line treatment due to safer SE profile. Subtle SE differences must be weighed by the prescriber.
SNRI	Venlafaxine Desvenlafaxine Duloxetine Levomilnacipran	Nausea, insomnia, dry mouth, headache, increased blood pressure, sexual dysfunction, weight gain	SEs are similar to but may be slightly more frequent than with SSRI
Atypical	Bupropion	Headache, agitation, insomnia, loss of appetite, weight loss, sweating	Increased seizure risk in eating disorder and epilepsy patients. No sexual dysfunction or weight gain. May also help to quit smoking.
	Mirtazapine	Sedation, increased appetite, weight gain	Sedation may be less with higher dose. Much reduced nausea and sexual dysfunction compared with SSRI/SNRI. Some risk of reduced white blood cell count.
	Trazodone	Sedation, nausea, priapism (rare)	Lower risk of weight gain and sexual dysfunction, but may cause priapism. Often used to induce sleep as a positive effect.
	Vilazodone	Nausea, diarrhea, insomnia	Better SE profile than most ADTs with lower risk of sexual dysfunction or weight gain
	Vortioxetine	Nausea, diarrhea, dizziness	Similar SE profile to the SSRI. May have precognitive benefits in adults with MDD

40

Adverse effects of 1st-line antidepressants

- **Side effect profiles vary** across antidepressants
- **Inform patients about potential side effects** before prescribing and inquire about side effects **within 2 weeks** of treatment initiation

	Nausea	Vomiting	Constipation	Diarrhea	Dry mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased appetite
SSRIs																		
Citalopram	21	4		8	19			17	4	3	2		5	11		8	4	
Escitalopram	15		4	8	7	2	6	4	2	2		8	5	3		2	2	2
Fluoxetine	21				10			13	14	12		16		8	9	10	11	
Fluvoxamine			18	6	26	22	15	26	2	2	16	14		11	5	11	15	
Paroxetine	26	2	14	12	18	18	13	23	5	5	2	13		11	15	8	6	1
Sertraline	26	4	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1
SNRIs																		
Desvenlafaxine[1]	22	3	9	11	11	20	13	4	<1	3	0	9	7	10		2	5	2
Duloxetine	20	5	11	8	15		9	7		3		11	8	6		3	8	
Levomilnacipran	17	5	9		10	17	8			2		6		9			3	
Milnacipran[2]	37	7	16		5	18	10			4		12		9		2	2	
Venlafaxine-IR		6	15	8	22	25	19	23	13	6	2	18		12	12	5	11	
Venlafaxine-XR	37	4	8	8	12	26	20	17	10	2	3	17		14	8	5	8	
Others																		
Agomelatine	≤9	≤9	≤9	≤9		≥10	≤9	≤9		≤9	<1	≤9	≤9	<1			<1	≤9
Bupropion SR[3]	11		≥10	4	≥10	≥10	7	3	5	5		≥10		2	2	3		
Bupropion XL	15	2	10		19		8			5		10		2		4	5	
Mirtazapine			13		25		7								8	2		17
Vilazodone[4]	24	5		29	7	14	8	5				6	3					3
Vortioxetine[5]	23	4	4	5	6		5	3				3	3	2			1	

LoE, Level of Evidence: Level 1, Level 2, Level 3, Level 4

0-9% | 10-29% | ≥ 30%

When data from multiple doses were reported separately, the data from the minimum therapeutic dose was used (indicated by footnotes).
Percentage rates taken from product monographs (based on clinical trial data and not placebo adjusted). Blank squares indicate no data reported.
[1]Data from 50 mg dose; [2]data from 50 mg dose; [3]data from 100–150 mg dose; [4]data from 40 mg dose; [5]data from 10 mg dose.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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17

41

Comparable favourability ratings for 1st-line antidepressants

- Choice depends on **balance of efficacy and tolerability**
- These are **not absolute ratings** and **agents may be selected for other clinical reasons** despite less favourable ratings

	Efficacy and drug-specific issues[1]				Tolerability issues			
	Efficacy	Acceptability[2]	Drug interactions	Discontinuation	Sedation	Weight gain	Sexual Dysfunction	Other tolerability[2]
SSRIs								
Citalopram			QTc[3]					
Escitalopram								
Fluoxetine								
Fluvoxamine								
Paroxetine								
Sertraline								
SNRIs								
Desvenlafaxine								
Duloxetine								
Levomilnacipran								
Venlafaxine-XR								
Others								
Bupropion								
Mirtazapine								
Vilazodone								
Vortioxetine								
Not available in Canada								
Agomelatine			LFTs[4]					
Mianserin								
Milnacipran								

More favourable | Less favourable | Neutral[5]

These comparative favourability ratings are based on a variety of data sources, including meta-analyses and RCTs, supplemented with expert consensus. Clear squares indicate neutral ratings and do not imply intermediate favourability. See speaker notes for additional footnotes.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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18

42

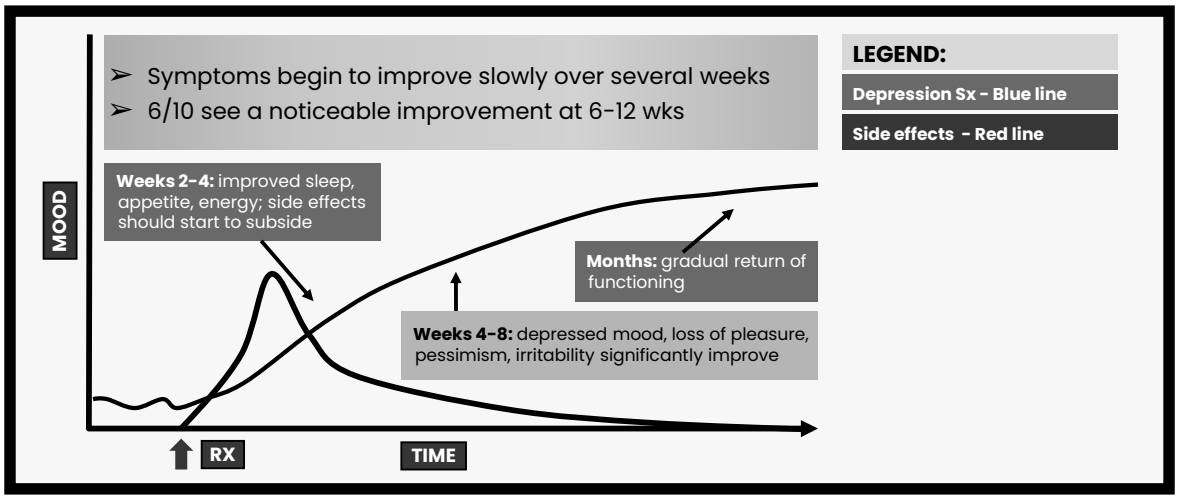
Discontinuation Syndrome

F	Flu-like symptoms (chills, coryza, myalgia)
I	Insomnia
N	Nausea
I	Imbalance
S	Sensory disturbances (headache, dizziness, anxiety, 'electric shock')
H	Hyperarousal

Michelson, et al. *Br J Psychiatry* 2000.

43

Antidepressants: Onset of Effect



https://medicationinfoshare.ca/gallery/getting-started-with-antidepressants/

44

OPTIMIZING RESPONSE TO ANTIDEPRESSANTS

45

Optimal Use of Antidepressants: Time for Clinical Response

An improvement of at least 25% at 2-4 weeks suggests good probability of a response (> 50% decrease in symptoms) and remission after 6-12 weeks

Lack of a response (e.g., < 25%) at 2-4 weeks is a predictor of later non-response (e.g., < 20% probability of full response at 8 weeks)

Note: the evidence for switching an antidepressant at 2-4 weeks due to lack of efficacy is of low quality

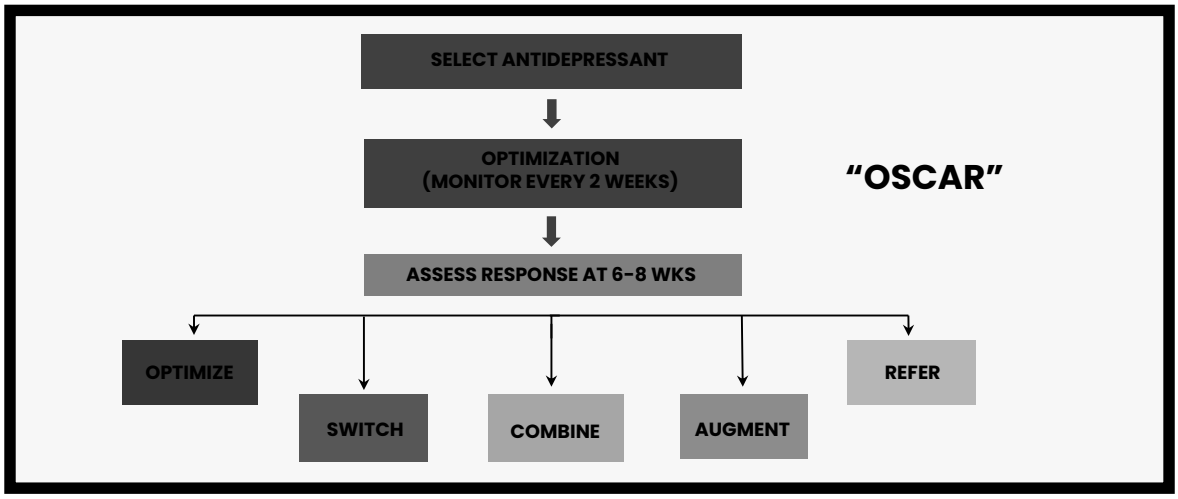
CANMAT recommends increasing the dose at 2-4 weeks if the antidepressant is tolerated in a non-improver or switch therapy if the antidepressant is not tolerated

One study looking specifically at fluoxetine improvement suggested there isn't a strong correlation between early non-response and likelihood of remission

CANMAT. *Can J Psychiatry*. 2016;61(9):540–560. https://ajp.psychiatryonline.org/doi/full/10.1176/appi.ajp.160.4.734

46

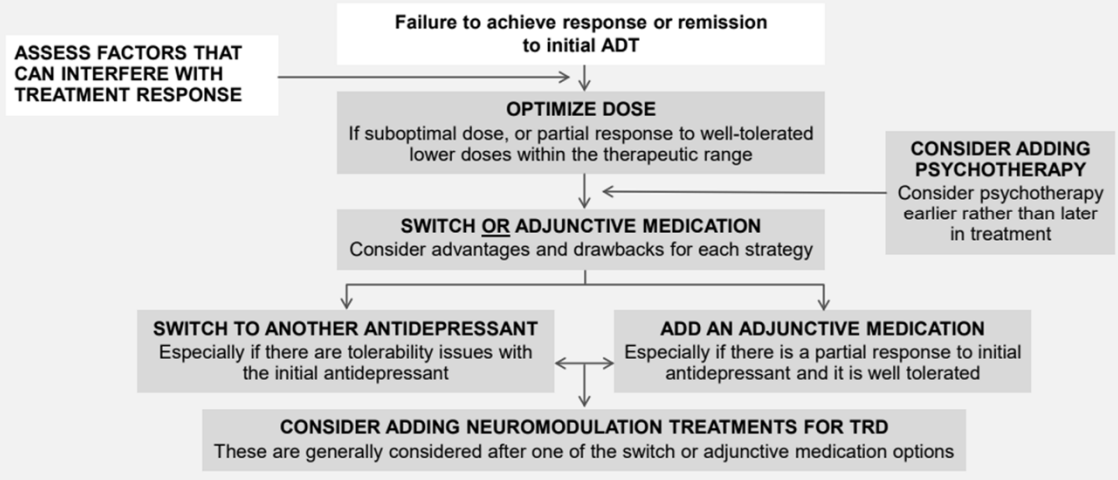
Strategies for Reaching Remission



Kennedy, et al. *Can J Psychiatry.* 2001.

47

Algorithm for sequential treatment after suboptimal response



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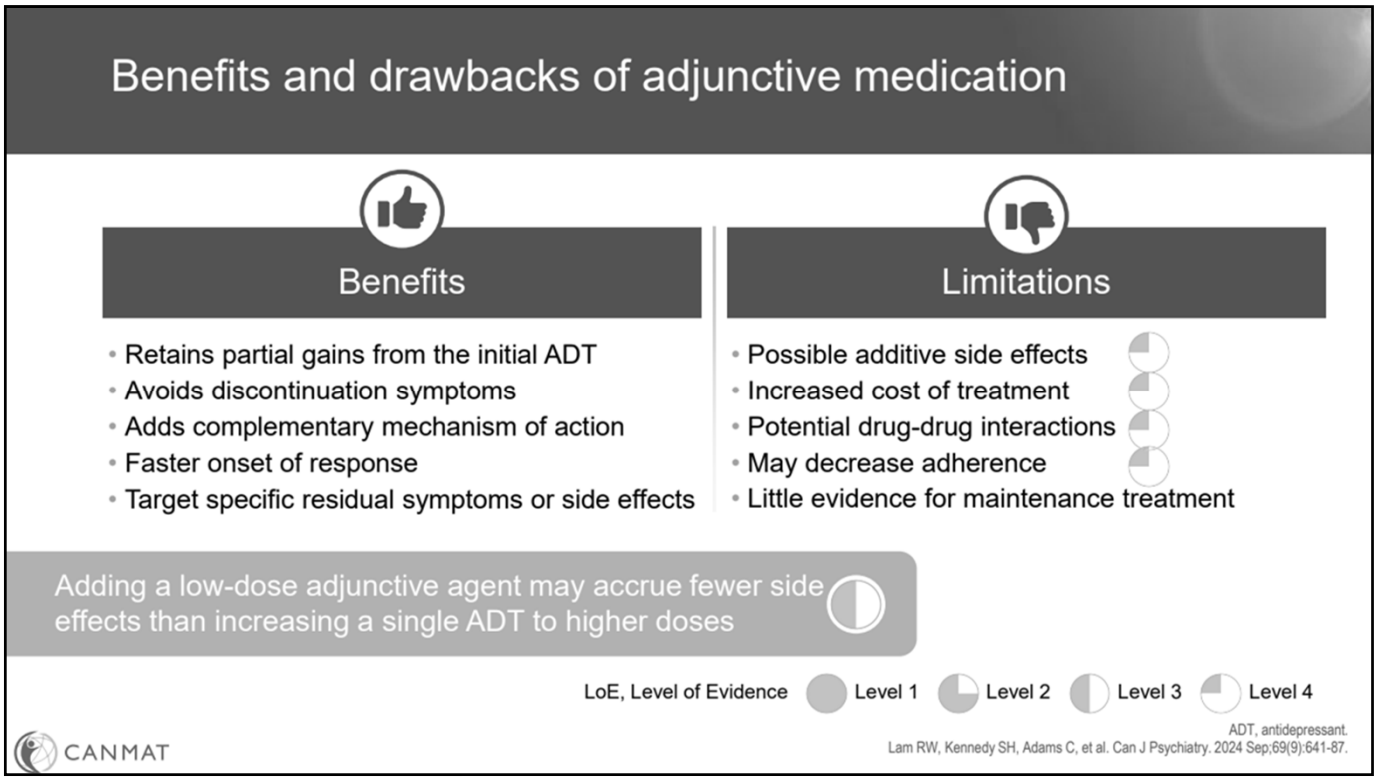
ADT, antidepressant; TRD, treatment-resistant depression.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

48



49

Augmentation and Combination Strategies

Lithium

Second-generation antipsychotics (e.g., quetiapine, aripiprazole, olanzapine, brexpiprazole, risperidone)

Thyroid hormone (primarily triiodothyronine)

Buspirone

Psychostimulants

Combination antidepressants

(SSRI + bupropion or mirtazapine or TCA)

(Venlafaxine + mirtazapine)

50

Recommendations for adjunctive treatments (part 1)

Line of Treatment	Adjunctive Agent	Target Dose[1]	Level of Evidence
1st Line	Aripiprazole	2-10 mg	Level 1
	Brexpiprazole*	0.5-2 mg	Level 1
2nd Line	Bupropion	150-450 mg	Level 1
	Intranasal esketamine*	56-84 mg IN	Level 1
	IV racemic ketamine*	0.5-1.0 mg/kg IV	Level 1
	Olanzapine	2.5-10 mg	Level 1
	Quetiapine XR*	150-300 mg	Level 1
	Risperidone*	1-3 mg	Level 1
	Lithium	600-1200 mg (0.5-0.8 mmol/L)	Level 1
	Cariprazine*	1.5-3 mg	Level 2
	Mirtazapine/mianserin	30-60 mg / 30-90 mg	Level 2
	Modafinil	100-400 mg	Level 2
	Triiodothyronine	25-50 mg	Level 2

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

*Change since CANMAT 2016 guidelines, based on updated evidence. See speaker notes for additional footnotes.
IN, intranasal; IV, intravenous; XR, extended release.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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51

Recommendations for adjunctive treatments (part 2)

Line of Treatment	Adjunctive Agent	Target Dose[1]	Level of Evidence
3rd Line	Other ADTs including TCAs	Varies	Level 3
	Stimulants	Varies	Level 3
	Lamotrigine*	100-300 mg	Level 3
	Non-IV racemic ketamine*	Varies	Level 3
	Pramipexole*	1-2 mg b.i.d.	Level 3
	Ziprasidone	20-80 mg b.i.d.	Level 3
Investigational	Psychedelic-assisted psychotherapy*	Moderate to high doses with psychotherapy	Level 3
Not recommended	Cannabis* (insufficient evidence for efficacy; risk of harms)	n/a	n/a

LoE, Level of Evidence — Level 1 — Level 2 — Level 3 — Level 4

*Change since CANMAT 2016 guidelines, based on updated evidence. See speaker notes for additional footnotes.
ADT, antidepressant; b.i.d., twice daily; IV, intravenous; TCA, tricyclic antidepressant.
Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

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52

Continuing Antidepressants

Acute phase (getting to remission): at least 6-9 months after remission

Maintenance phase (preventing relapse and recurrence): Continue for at least 2 years if at high risk for recurrence

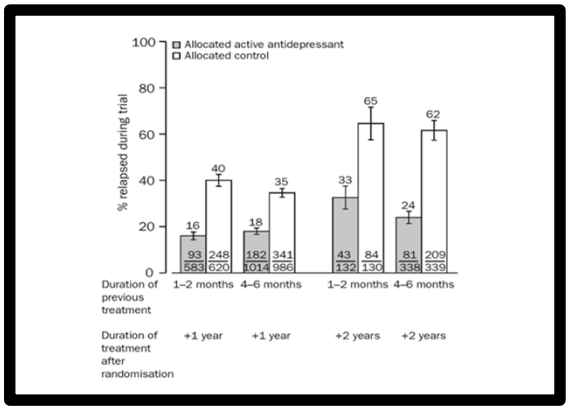
Likelihood of relapse/recurrence reduced by approximately 50% when adhering to an antidepressant compared to a placebo for 1-2 years

There is limited evidence to guide if antidepressants should be continued beyond 2 years

53

Antidepressant Relapse Prevention

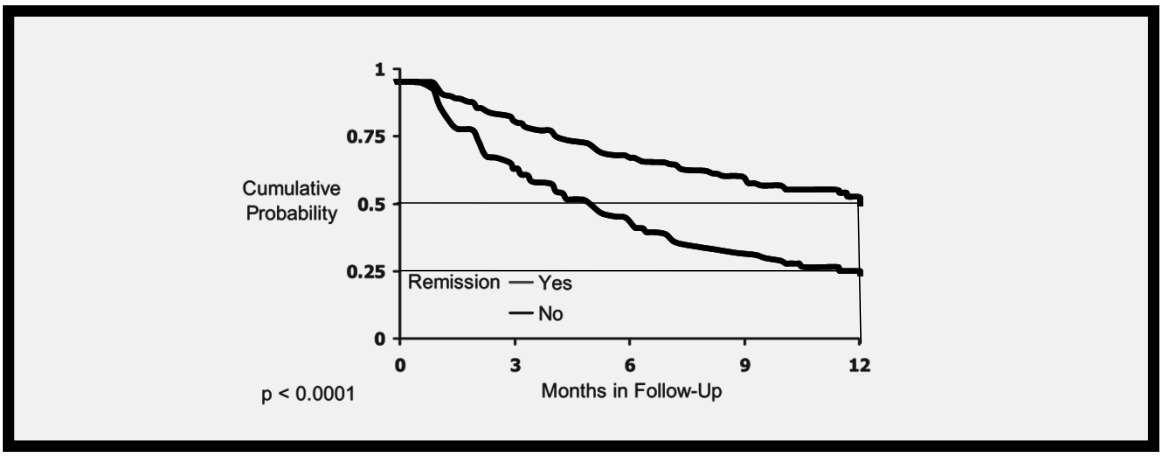
Relapse rates after 1 or 2 years of antidepressant treatment in patients already treated for 1–2 or 4–6 months after an acute episode of depression!



Geddes, et al. *Lancet*. 2003.

54

One-Year Relapse Rates in Remitters vs. Non–Remitters From STAR*D Trial



Relapse = QIDS-IVR$_{16}$ ≥ 11

Adapted from: Rush AJ, et al. *Am J Psychiatry*. 2006;163:1905-1917.

55

	MONITORING PARAMETERS	TIMELINE
1	Target symptoms for depression, severity of symptoms and functioning (efficacy of antidepressant – aim for remission)	q7-14 days for 4-6 wks then q1-3 months (to watch for relapse)
2	Antidepressant adverse effects (depends on the medication selected)	q7-14 days for 4 wks then q3 months
3	Suicidal thoughts/behaviours	q7-14 days for 4-8 wks
4	Drug interactions/serotonin syndrome	First 2 wks of adding a serotonergic agent or new medication
5	Discontinuation syndrome	At discontinuation of therapy

56

Great Monitoring Tool

www.moodfx.ca

- ✓ Interactive
- ✓ Appointment reminders
- ✓ Tracks symptoms
- ✓ Charts results of different mood scales
- ✓ Can print and share results with clinicians
- ✓ Weekly text/email tips
- ✓ Free!

57

Clinical Pearls: The Pharmacist's Role in Managing MDD

Build rapport first (discuss your role and their role)

Use SAD-A-FACES and/or PHQ-9 to determine the key target symptoms (and their severity)

Use the counselling checklist as a guide

Develop a monitoring plan (including frequency of monitoring and when to seek help)

Optimize medications aiming for REMISSION

Assess for adverse effects

Listen carefully for the patient's concerns – ensure you've addressed them

58

Key Messages

- MDD is common, often unrecognized and can be successfully treated
- Risk and severity assessments help with treatment selection and monitoring
- Antidepressants are equally efficacious and more EFFECTIVE than placebo at reducing the symptoms of depression
- Antidepressants help reduce symptoms of (moderate-to-severe) depression in 50-60% of adults and decrease the risk of relapse by approximately 50% (at 1 year)
- Reduce reliance on antidepressants in mild-to-moderate depression

59

Key Messages

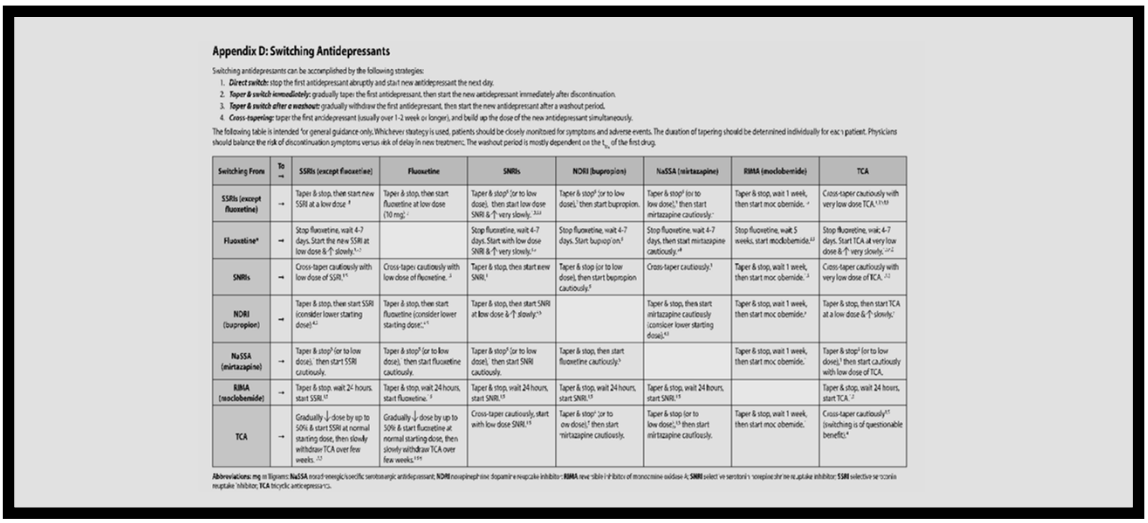
- The selection of an antidepressant is based on side-effect profiles, previous response, comorbidities and potential drug interactions
- Optimize outcomes for patients with depression through:
  - Enhanced patient contact (e.g., follow-up calls, medication review)
  - Frequent monitoring (use websites like moodfx and rating scales)
- Consider combining antidepressants with psychotherapy
- NDs are well-positioned to assess for risk factors and screen for depression as well as improve MDD outcomes!

60

Questions?

61

Switching Antidepressants



Appendix D: Switching Antidepressants

Switching antidepressants can be accomplished by the following strategies:

1. ***Direct switch:*** stop the first antidepressant abruptly and start new antidepressant the next day.
2. ***Taper & switch immediately:*** gradually taper the first antidepressant, then start the new antidepressant immediately after discontinuation.
3. ***Taper & switch after a washout:*** gradually withdraw the first antidepressant, then start the new antidepressant after a washout period.
4. ***Cross-tapering:*** taper the first antidepressant (usually over 1-2 week or longer), and build up the dose of the new antidepressant simultaneously.

The following table is intended for general guidance only. Whichever strategy is used, patients should be closely monitored for symptoms and adverse events. The duration of tapering should be determined individually for each patient. Physicians should balance the risk of discontinuation symptoms versus risk of delay in new treatment. The washout period is mostly dependent on the $t_{1/2}$ of the first drug.

Switching From	To →	SSRIs (except fluoxetine)	Fluoxetine	SNRIs	NDRI (bupropion)	NaSSA (mirtazapine)	RIMA (moclobemide)	TCA
SSRIs (except fluoxetine)	→	Taper & stop, then start new SSRI at a low dose.[a]	Taper & stop, then start fluoxetine at low dose (10 mg).[c]	Taper & stop[b] (or to low dose), then start low dose SNRI & ↑ very slowly.[b,d,e]	Taper & stop[b] (or to low dose),[f] then start bupropion.	Taper & stop[b] (or to low dose),[f] then start mirtazapine cautiously.[c]	Taper & stop, wait 1 week, then start moc obemide.[c,e]	Cross-taper cautiously with very low dose TCA.[c,f,g,g]
Fluoxetine*	→	Stop fluoxetine, wait 4-7 days. Start the new SSRI at low dose & ↑ slowly.[a,c,e]		Stop fluoxetine, wait 4-7 days. Start with low dose SNRI & ↑ very slowly.[b,e]	Stop fluoxetine, wait 4-7 days. Start bupropion.[b]	Stop fluoxetine, wait 4-7 days, then start mirtazapine cautiously.[c,e]	Stop fluoxetine, wait 5 weeks, start moclobemide.[c,f]	Stop fluoxetine, wait 4-7 days. Start TCA at very low dose & ↑ very slowly.[c,e,f,g]
SNRIs	→	Cross-taper cautiously with low dose of SSRI.[a,b]	Cross-taper cautiously with low dose of fluoxetine.[c]	Taper & stop, then start new SNRI.[b]	Taper & stop (or to low dose), then start bupropion cautiously.[b]	Cross-taper cautiously.[b]	Taper & stop, wait 1 week, then start moc obemide.[c,e]	Cross-taper cautiously with very low dose of TCA.[c,f,g]
NDRI (bupropion)	→	Taper & stop, then start SSRI (consider lower starting dose).[a,c]	Taper & stop, then start fluoxetine (consider lower starting dose).[a,c]	Taper & stop, then start SNRI at low dose & ↑ slowly.[a,b]		Taper & stop, then start mirtazapine cautiously (consider lower starting dose).[c,f]	Taper & stop, wait 1 week, then start moc obemide.[c]	Taper & stop, then start TCA at a low dose & ↑ slowly.[c]
NaSSA (mirtazapine)	→	Taper & stop[b] (or to low dose), then start SSRI cautiously.	Taper & stop[b] (or to low dose), then start fluoxetine cautiously.	Taper & stop[b] (or to low dose), then start SNRI cautiously.	Taper & stop, then start fluoxetine cautiously.[b]		Taper & stop, wait 1 week, then start moc obemide.	Taper & stop[b] (or to low dose),[f] then start cautiously with low dose of TCA.
RIMA (moclobemide)	→	Taper & stop, wait 24 hours, start SSRI.[c,f]	Taper & stop, wait 24 hours, start fluoxetine.[c]	Taper & stop, wait 24 hours, start SNRI.[c,f]	Taper & stop, wait 24 hours, start SNRI.[c,f]	Taper & stop, wait 24 hours, start SNRI.[c,f]		Taper & stop, wait 24 hours, start TCA.[c,f]
TCA	→	Gradually ↓ dose by up to 50% & start SSRI at normal starting dose, then slowly withdraw TCA over few weeks.[c,f,g]	Gradually ↓ dose by up to 50% & start fluoxetine at normal starting dose, then slowly withdraw TCA over few weeks.[c,f,g]	Cross-taper cautiously, start with low dose SNRI.[c,f]	Taper & stop[b] (or to low dose),[f] then start mirtazapine cautiously.	Taper & stop (or to low dose),[c,f] then start mirtazapine cautiously.	Taper & stop, wait 1 week, then start moc obemide.	Cross-taper cautiously[c,f] (switching is of questionable benefit).[g]

Abbreviations: mg in figures; **NaSSA** noradrenergic/specific serotonergic antidepressant; **NDRI** norepinephrine dopamine reuptake inhibitor; **RIMA** reversible inhibitor of monoamine oxidase A; **SNRI** selective serotonin norepinephrine reuptake inhibitor; **SSRI** selective serotonin reuptake inhibitor; **TCA** tricyclic antidepressants.

Available at: http://www2.gov.bc.ca/assets/gov/health/practitioner-pro/bc-guidelines/depress_appd.pdf
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62

Vortioxetine

Serotonin (5-HT) modulator

- Inhibits reuptake of post-synaptic 5-HT
- Increases 5-HT, NE, DA, Ach and histamine in the synapse
- Antagonistic effect post-synaptic 5HT receptors (5-HT3, 5-HT1D, 5-HT7)
- 5-HT1A receptor agonist and partial agonist of 5-HT1B

Studied in 22 RCTs in MDD

Dosing (5-20 mg daily)

60-70-hour half-life

Drug interactions with CYP2D6 inhibitors and CYP inducers

Adverse effects similar to SSRIs: nausea, diarrhea, sexual dysfunction (< SSRIs), SIADH

Cost ~$3/day

Adil's recommended place in therapy:

- Those who have not responded to other drug therapies

CADTH CDEC Vortioxetine Recommendation, Feb 2020.

63

Venlafaxine (SNRI)

Dual reuptake blockade of 5HT and NA at intermediate-to-high doses
(> 225 mg/day); DA blockade at high doses

Drug interactions: < SSRIs; CYP2D6 inhibition; potentiates 5HT effects

May be helpful with neuropathic pain

Similar side effects to SSRIs

Intermediate sexual side effects

Noradrenaline side effects may be observed at higher doses

Insomnia, restlessness, tremor, sweating, BP increase

Withdrawal reactions with abrupt cessations

64