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CANMAT 2023 UPDATE:
CLINICAL GUIDELINES FOR THE MANAGEMENT OF MDD IN ADULTS

QUESTION 3:

How Are Treatments Selected?

How is the initial treatment selected?

Recommendations are based primarily on **severity of depression,** but **also consider** past treatment response, patient preference, and treatment availability

Collaborative decisions made by clinician and patient considering:

- Range of potential treatments
- Evidence supporting each
- Nature and severity of depression
- Personal situation
- Expectations
- Patient preference

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

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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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

[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; CBT, cognitive behavioural therapy; DHI, digital health intervention; MDE, major depressive episode.

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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

[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.

MDE, major depressive episode.

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When should pharmacotherapy and psychotherapy be combined?

Combining **psychological treatment with pharmacotherapy is more effective than either alone** for acute treatment and may **reduce risk of recurrence**

The strongest evidence supports **in-person CBT initiated sequentially after establishing antidepressant treatment**

- Psychological treatment may address **residual symptoms** that remain after pharmacotherapy
- May include **MBCT**

A smaller body of evidence supports addition of **psychodynamic psychotherapy to an antidepressant**

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CBT, cognitive behavioural therapy; MBCT, mindfulness-based cognitive therapy.

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

When should pharmacotherapy and psychotherapy be combined?

- Best chances of sustained recovery occur when an **antidepressant is continued with added psychological treatment**
- Consider **risks and benefits** of continuing/tapering medications
- **Sequential treatment** is useful for individuals with **recurrent and severe** forms of depression and **high risk of relapse**

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

How is a psychological treatment selected?

CBT, IPT, and BA are recommended as **1st-line psychological treatments** for acute treatment of MDD

Psychotherapy is similarly effective across sex, age, level of education, culture, and ethnicity

Illness severity primarily affects the **urgency** of beginning treatment but **does not predict outcomes** in CBT versus pharmacotherapy

Combination psychological & pharmacological treatment is **more effective** than either alone

CBT reduces suicide attempts by half in those who attempted in the previous 6 months

CBT is effective in **individual, group, and telephone/digital delivery**

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

BA, behavioural activation; CBT, cognitive behavioural therapy; IPT, interpersonal therapy; MDD, major depressive disorder.

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

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Recommendations for psychological treatments

Line of Treatment	Psychological Treatment	Level of Evidence
1st Line	• Cognitive behavioural therapy (CBT)	
	• Interpersonal therapy (IPT)	
	• Behavioural activation (BA)	
2nd Line	• Cognitive behavioural analysis system of psychotherapy (CBASP)	
	• Mindfulness-based cognitive therapy (MBCT)	
	• Problem-solving therapy (PST)	
	• Short-term psychodynamic (STPP)	
	• Transdiagnostic psychological treatment of emotional disorders*	
3rd Line	• Acceptance & commitment therapy (ACT)	
	• Long-term psychodynamic psychotherapy (PDT)	
	• Metacognitive therapy (MCT)*	
	• Motivational interviewing (MI)	

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

*Change since the CANMAT 2016 guidelines, based on updated evidence.

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

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How many sessions of psychological treatment are required?

Most improvement occurs during the **early psychological treatment** sessions

Optimal dose for a 1st-line psychotherapy is **12-16 sessions**

Increased frequency (2 sessions/week) for CBT and IPT produce better outcomes

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

CBT, cognitive behavioural therapy; IPT, interpersonal therapy.

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Which psychological treatments have new evidence?

1st Line

New evidence supports **CBT, IPT, and BA** for acute treatment of depression

2nd Line

Evidence for **CBASP, MBCT, PST, STPP** continues to grow but may be **subject to limitations** including heterogeneity and risk of bias

3rd Line

ACT is effective compared to inactive controls and in patients with **mild depression**

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

ACT, acceptance and commitment therapy; BA, behavioural activation; CBASP, cognitive behavioural analysis system of psychotherapy; CBT, cognitive behavioural therapy; IPT, interpersonal therapy; MBCT, mindfulness-based cognitive therapy; PST, problem-solving therapy; STPP, short-term psychodynamic psychotherapy.

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Which psychological treatments have new evidence?

Transdiagnostic or "unified" psychological treatment of emotional disorders, including anxiety and depression

- Motivational enhancement
- Psychoeducation
- Training in emotional awareness
- Cognitive restructuring
- Emotion-driven behaviours
- Tolerance of physical sensations
- Relapse prevention
- **2nd-line treatment for MDD** and particularly useful for concurrent anxiety issues 

MCT focuses on awareness and understanding of thoughts and feelings of oneself and others

- Goal-directed
- Enhances metacognitive capacities to gain more flexibility in attention, monitoring, control, and regulation of cognitive processes
- **3rd-line treatment for MDD** 

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

MCT, metacognitive therapy; MDD, major depressive disorder.

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How is a pharmacological treatment selected?

Choice of **31 antidepressants**

- **17 are 1st-line** treatments with robust evidence for safety and efficacy in placebo-controlled RCTs

Considerations for prescribing

- Efficacy
- Adverse effects
- Clinical presentation
- Cost
- Patient preference

Use psychoeducation to discuss

- Risk & benefits
- Time course of effects
- Myths & misbeliefs

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

RCT, randomized controlled trial.

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

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	

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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.
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2nd-line and 3rd-line antidepressants

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

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

*Change since CANMAT 2016 guidelines, based on updated evidence; # Not available in Canada. See speaker notes for additional footnotes.
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.
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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	31	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	

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.
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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	Discontin-uation	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.

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Further considerations for pharmacological treatment selection

Sexual dysfunction may be a symptom of depression
Assessment of baseline sexual functioning could identify emergent side effects

Patient and clinical factors, **episode specifiers, and symptom dimensions**

Most antidepressants are effective irrespective of **sex, gender, race, ethnicity, baseline severity**

Age

<25 years old: Efficacy, adverse reactions, and risk of discontinuation symptoms may favour fluoxetine or agomelatine

>65 years old: SSRIs may be less effective and SNRIs may be more effective

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SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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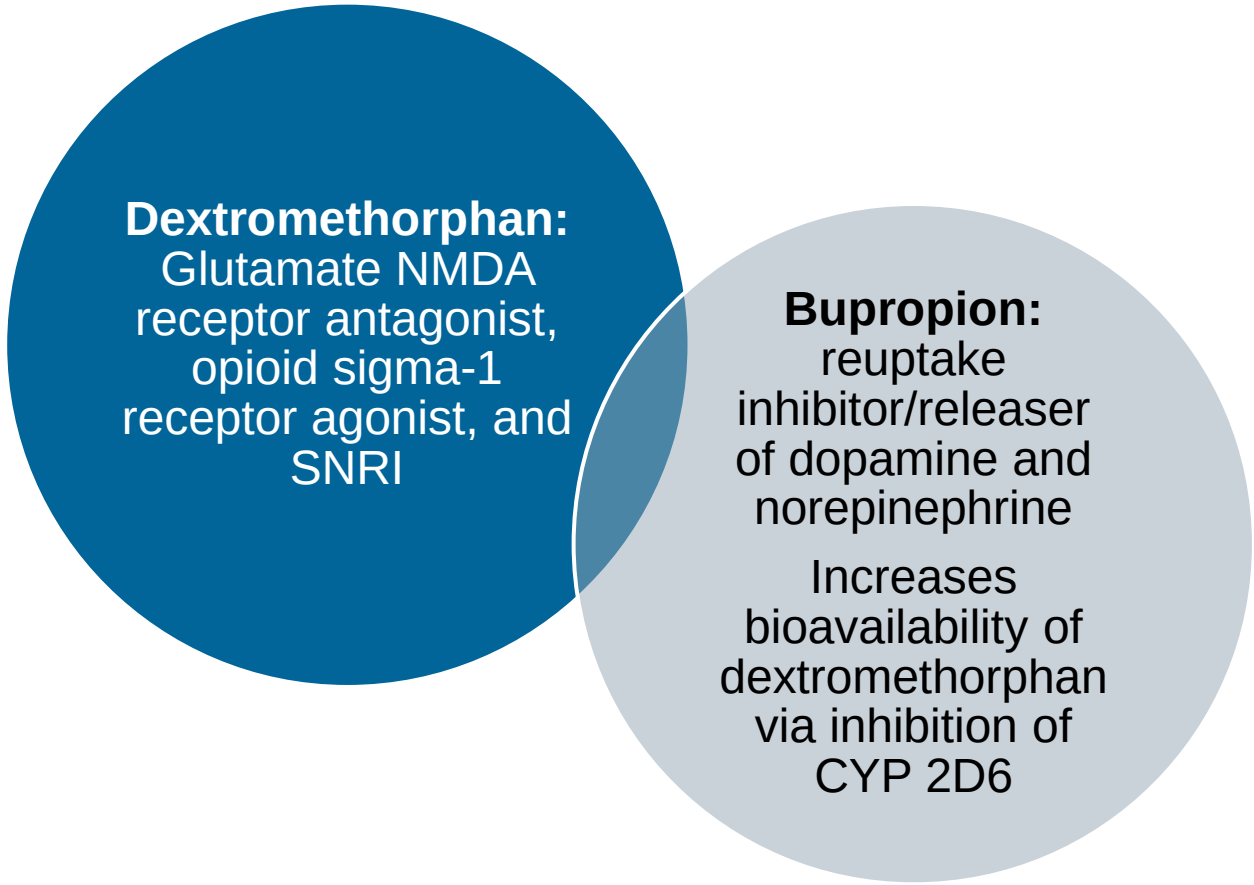
Which pharmacological treatments have new evidence?

- **Dextromethorphan combination with low-dose bupropion*** is recommended as a **2nd-line** treatment
- **Brexanolone and zuranolone: allopregnanolone agonists** approved for treatment of postpartum depression in the U.S.



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*Not available in Canada.

NMDA, N-methyl-D-aspartate; SNRI, serotonin-norepinephrine reuptake inhibitor; CYP, cytochrome P450.

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How do DSM-5-TR specifiers and symptom dimensions influence medication selection?

No changes have been made to the following CANMAT 2016 recommendations:

- **Melancholic features and atypical features:** no specific recommendations
- **Catatonic features:** benzodiazepines or ECT
- **Psychotic features:** combination antidepressant and antipsychotic treatment or ECT
- **Anxious distress features:** any 1st-line antidepressant*

*MDE with anxiety is associated with poorer response to standard treatment.

DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision; ECT, electroconvulsive therapy; MDE, major depressive episode.

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DSM-5-TR mixed features specifier

Mixed features: MDE with **depressive symptoms and subsyndromal manic** symptoms

- Manage in consultation with psychiatry to **differentiate from mixed states found in bipolar disorders**
- Closely monitor for **activating side effects and manic/hypomanic switch** when initiating antidepressants
- **1st-line antidepressants** are recommended
  - **Lurasidone is recommended for 2nd-line treatment**

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DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision; MDE, major depressive episode.

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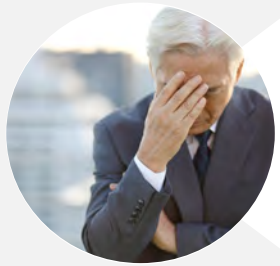
Symptom dimensions not included in DSM-5-TR that may have treatment specificity

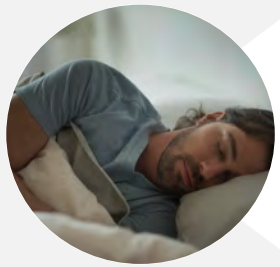


Cognitive dysfunction

Vortioxetine, bupropion, and SNRIs may have superior efficacy than SSRIs

Comorbid pain conditions

Duloxetine and other SNRIs show more benefit than SSRIs



Energy, fatigue, and motivation

Preferentially respond to SNRIs than SSRIs

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

DSM-5-TR, Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

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Anhedonia as a potential treatment target

Anhedonia: reduced ability to experience **pleasure** and reduced **motivational drive** and **consummatory pleasure**

Up to **70% of patients with MDD** experience anhedonia

- Associated with **reduced likelihood of remission** with SSRI treatment
- A **promising symptom dimension** for future clinical trials
- **No evidence that any specific agent is superior** in treating anhedonia
- **Monoaminergic antidepressants, ketamine, methylphenidate and psilocybin** may improve anhedonia severity

MDD, major depressive disorder; SSRI, selective serotonin reuptake inhibitor.

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Recommendations for DSM-5-TR episode specifiers and symptom dimensions

Line of Treatment	DSM-5-TR Episode Specifiers			
	Anxious distress Atypical features Melancholic features	**Mixed features**	**Psychotic features**	**Catatonic features**
1st Line	• Any 1st-line ADT	• Any 1st-line ADT*	• Any 1st-line ADT + AAP	• Benzodiazepine + any 1st-line ADT
2nd Line	• Any 2nd-line ADT	• Lurasidone**		

Line of Treatment	Symptom Dimensions		
	Cognitive dysfunction	**Sleep disturbance**	**Somatic symptoms**
1st Line	• Vortioxetine	• Agomelatine†	• Duloxetine (pain) • Bupropion (fatigue)
2nd Line	• Bupropion • Duloxetine • SSRIs**	• Mirtazapine • Quetiapine-XR • Trazodone	• Duloxetine** (fatigue) • Other SNRIs (pain) • SSRIs** (fatigue)

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*When initiating medications, monitor for activating side effects and potential switch to (hypo)mania; ** Comparisons only with placebo; † Not available in Canada.
AAP, atypical antipsychotic; ADT, antidepressant; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.
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Are antidepressants associated with an increased risk of suicide?

Antidepressants reduce suicidal thoughts and behaviours, with a greater effect on **suicidal ideation** than on prevention of suicide attempts and death

Antidepressants may also **increase suicidality** in a **subset of patients**

Age

- Meta-analysis of RCTs:
  - **Increased** risk of suicidal behaviour **among young adults <25 years**
  - **Reduced** risk among **≥65 years**
  - **No effect** between ages **25-65** years
- Meta-analysis of observational studies:
  - Modest increase in suicidal behaviour that were **not age-dependent**

Treatment time period

- Suicidal behaviours are highest:
  - Month **before antidepressant initiation**
  - Month **after initiation**
  - Month **after discontinuation**

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RCT, randomized controlled trial.

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Recommendations for management of suicide risk

Routine monitoring of suicide risk during antidepressant treatment

Enhanced attention during the first **4 weeks following initiation and cessation** of treatment

Educate patients on **risk of increased suicidal thoughts and behaviours** (especially adolescents and young adults)

Educate patients that **if they experience increased suicidal thoughts** when starting a new medication, they should**:**

A) Understand them as a **medication side effect**
B) Recognize a need for **urgent action** to address distress and other symptoms
C) Implement a **safety plan**
D) **Reach out** to care provider, crisis line, or emergency department

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Are there differences in formulations of specific antidepressants?

- Meta-analysis found **no difference in efficacy** between **extended-release** and **immediate-release** formulations
- **Generic versions of antidepressants**
  - **Bioequivalent** to reference brand-name products
  - Increase accessibility to **cost-effective** treatment
  - Differences in bioavailability and efficacy between brand-name and generic preparations have been reported*

Use **generic or brand-name** antidepressants in **immediate- or extended-release** formulations and **minimize change** in formulation or brand if the treatment is effective

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

*Not systematically studied.

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

Safety concerns and drug interactions with SSRIs and SNRIs

Most 1st-line antidepressants have a **well-established safety record** and **can be combined with other commonly prescribed medications** without significant risk of interactions

SSRIs

- Modestly increased risk of **fractures and falls**
- Citalopram and escitalopram: **low risk of hepatic AEs**
- **Drug interactions:**
  - Fluoxetine and paroxetine: inhibit CYP2D6
  - Fluvoxamine: inhibits CYP1A2, CYP2C19, CYP3A4
  - SSRI + NSAIDs: GI bleeding
  - SSRI + diuretics: hyponatremia

SNRIs

- Risk of **increased blood pressure**
- Duloxetine: **higher risk of hepatic AEs**
- **Drug interactions:**
  - SNRI+ NSAIDs: GI bleeding
  - SNRI+ diuretics: hyponatremia

SSRIs and SNRIs may have age dependent adverse effects

- **<25 years old:** akathisia, agitation, and aggression
- **>65 years old:** GI bleeding, hyponatremia, liver damage, and QTc prolongation

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

AE, adverse effect; CYP, cytochrome P450; GI, gastrointestinal; NSAID, nonsteroidal anti-inflammatory drug; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI; selective serotonin reuptake inhibitor.

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Safety concerns and drug interactions with other antidepressants

TCAs

- **With overdose**, TCAs have a higher risk of **life-threatening effects** including:
  - Altered mental state
  - Cardiac toxicity
  - Seizures
- **SSRIs are preferred** for those at risk for overdose
- **Reserved as a 2nd-line option**

MAOIs

- May have **life-threatening interactions** with:
  - Medications that affect monoamine metabolism
  - Herbal remedies
  - Foods containing high levels of tyramine
- **Reserved as a 3rd-line option**

AEs of other antidepressants

- Agomelatine (MT1, MT2 agonist; 5-HT2 antagonist)#, bupropion (NDRI), and nefazodone (SRI, 5-HT2 antagonist)#: **high risk of hepatic AEs**
- Mirtazapine (α2 antagonist; 5-HT2 antagonist): increased **appetite, weight gain, and long-term metabolic risks**

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

#Not available in Canada.

5-HT, 5-hydroxytryptamine receptor; α2, alpha-2 adrenergic receptor; AE, adverse effect; MAOI, monoamine oxidase inhibitor; MT, melatonin; NDRI, norepinephrine-dopamine reuptake inhibitor; SRI, serotonin reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

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

CANMAT

Can pharmacogenetic testing inform medication selection?

Commercially available pharmacogenetic tests can **inform antidepressant selection and dosing**

- Based on gene variants for:
  - Enzymes that **metabolize psychotropic medications**
  - **Serotonin transporter and receptors**
- May minimize likelihood of **AEs** and increase likelihood of **positive responses**
- Meta-analyses show **higher response and remission rates** compared to usual care (modest effect sizes)

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AE, adverse effect.

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

Role of pharmacogenetic testing

CANMAT does not recommend

- **Routine pharmacogenetic testing**: clinical benefits are too modest and inconsistent 
- **Routine monitoring of antidepressant plasma levels:** relationship to clinical outcomes is weak 

Indications for pharmacogenetic testing

- When there **are severe or unusual adverse effects** with low doses of medications
- When there are **poor responses** to therapeutic doses
- **Sequence2Script** website may facilitate interpretation of results*

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*According to Clinical Pharmacogenetics Implementation Consortium 7 guidelines. Lam RW, Kennedy SH, Adams C, et al. Can J Psychiatry. 2024 Sep;69(9):641-87.

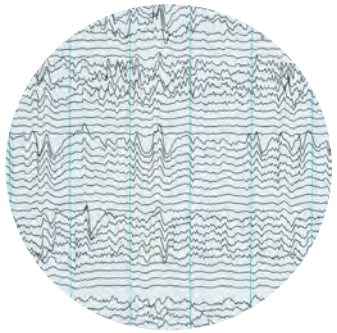
CANMAT

Can other biomarkers inform treatment selection?

CANMAT does not recommend biomarker measurement or use of EEG for routine antidepressant selection

Inflammatory markers in blood

- IL-8 and C-reactive protein: associated with **worse responses to SSRIs**
- Small effect size



Electrophysiological measures of brain function

- Stronger EEG loudness dependence of the auditory evoked potentials: associated with **better response to SSRIs**
- Early state of evidence, modest effect size, lack of evidence of better response with alternative treatments, need for specialized equipment

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

EEG, electroencephalography; IL-8, interleukin 8; SSRI, selective serotonin reuptake inhibitor.

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

What CAM treatments are effective?

Consider **CAM treatments alone only for mild severity MDE or as adjuncts** to standard treatment in **moderate severity** illness

- CAM treatments have **not shown sufficient evidence for comparison to 1st-line psychotherapy or pharmacotherapy** for moderate-severe depression
- Therapeutic **dose ranges are inconsistent** for most CAM treatments

CAM, complementary and alternative medicine; MDE, major depressive episode.

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

Recommendations for CAM treatments

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

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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.

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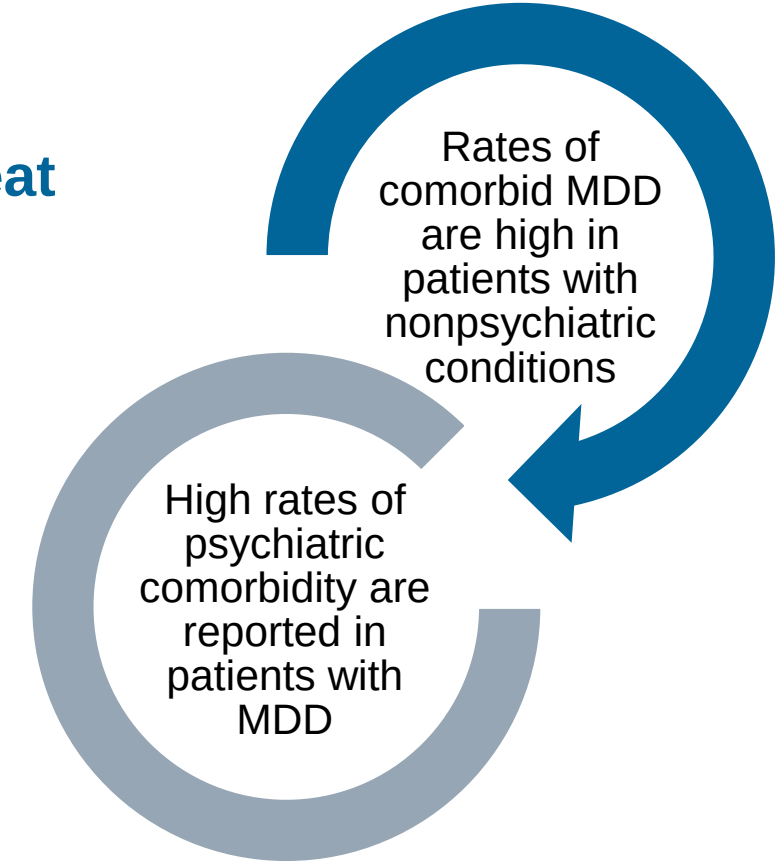
How are comorbid conditions managed?

Psychiatric and nonpsychiatric comorbidities are common in MDD and require treatment

Comorbidities may make MDD more **difficult to treat**

- Depressive symptoms may be conflated by symptoms of other conditions
- Difficulty distinguishing side effects of depression treatment and concomitant medications
- Minimize polypharmacy and check for drug interactions



MDD, major depressive disorder.

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

Impact of comorbidities on MDD treatment

Pharmacological treatments

- Patients with comorbidities have a **worse treatment response to antidepressants** than those without
- However, antidepressants are **more effective than placebo** across many comorbidities:
  - Myocardial infarction
  - Coronary artery disease
  - Stroke
  - IBD
  - Diabetes mellitus
  - Cancer

Psychological treatment

- Patients with other medical conditions **benefit from psychological treatments** like those without
- **CBT and BA** are effective for individuals with:
  - Coronary artery disease
  - Neurological conditions
- **CBT is recommended** for patients with:*
  - Personality disorder (16-20 sessions)
  - Anxiety
  - Substance use
  - ADHD

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

*CBT of greater complexity should be considered for psychiatric comorbidities.

ADHD, attention-deficit/hyperactivity disorder; BA, behavioural activation; CBT, cognitive behavioural therapy; IBD, inflammatory bowel disease.

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

CANMAT

How are cultural and religious practices integrated into treatment?

Cultural and religious adaptations of evidence-based psychotherapies are recommended where available and appropriate

- Research supporting **evidence-based psychological treatment** for depression often relies on data from **White North Americans and Europeans**
  - Evidence supporting these treatments in other countries and cultural groups is growing

Cultural adaptations may require

- **Cultural adaptations**
- **Therapist adaptations**
- **Integration of religion and spirituality**
- **Local remedies and practices**

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