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Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Section 3. Pharmacological Treatments

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Abstract

Background: The Canadian Network for Mood and Anxiety Treatments (CANMAT) conducted a revision of the 2009 guidelines by updating the evidence and recommendations. The scope of the 2016 guidelines remains the management of major depressive disorder (MDD) in adults, with a target audience of psychiatrists and other mental health professionals.

Methods: Using the question-answer format, we conducted a systematic literature search focusing on systematic reviews and meta-analyses. Evidence was graded using CANMAT-defined criteria for level of evidence. Recommendations for lines of treatment were based on the quality of evidence and clinical expert consensus. "Pharmacological Treatments" is the third of six sections of the 2016 guidelines. With little new information on older medications, treatment recommendations focus on second-generation antidepressants.

Results: Evidence-informed responses are given for 21 questions under 4 broad categories: 1) principles of pharmacological management, including individualized assessment of patient and medication factors for antidepressant selection, regular and

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frequent monitoring, and assessing clinical and functional outcomes with measurement-based care; 2) comparative aspects of antidepressant medications based on efficacy, tolerability, and safety, including summaries of newly approved drugs since 2009; 3) practical approaches to pharmacological management, including drug-drug interactions and maintenance recommendations; and 4) managing inadequate response and treatment resistance, with a focus on switching antidepressants, applying adjunctive treatments, and new and emerging agents.

Conclusions: Evidence-based pharmacological treatments are available for first-line treatment of MDD and for management of inadequate response. However, given the limitations of the evidence base, pharmacological management of MDD still depends on tailoring treatments to the patient.

Keywords
major depressive disorder, pharmacotherapy, clinical practice guidelines, antidepressants, evidence-based medicine, meta-analysis, antipsychotics, clinical trials, randomized controlled trial

In 2009, the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, published a revision of evidence-based clinical guidelines for the treatment of depressive disorders.[1] CANMAT has updated these guidelines in 2016 to reflect new evidence in the field.

The scope of these guidelines remains the management of adults with unipolar major depressive disorder (MDD) with a target audience of psychiatrists and other mental health professionals. CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2] This section on "Pharmacological Treatments" is 1 of 6 CANMAT guidelines articles; other sections of the guidelines expand on burden and principles of care, psychological treatments, neurostimulation treatments, complementary and alternative medicine treatments, and special populations. These recommendations are presented as guidance for clinicians who should consider them in the context of individual patients and not as standards of care. Some medications discussed may not be available in Canada or other countries.

Methods

The full methods have been previously described,[3] but in summary, relevant studies in English and French published from January 1, 2009, to December 31, 2015, were identified using computerized searches of electronic databases (PubMed, PsychInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other guidelines and major reports. Each recommendation includes the level of evidence for each graded line of treatment, using specified criteria (Table 1). The level of evidence criteria now reflect the primacy of meta-analysis because of its increasing use in the evaluation of evidence.

Because of the very large number of randomized-controlled trials (RCTs), this section will primarily focus on systematic reviews and individual and network meta-analyses. Although meta-analyses have advantages in summarizing data, they still have limitations that can lead to erroneous or conflicting results depending on the comprehensiveness of the review, criteria for study selection and quality, and generalizability of the included studies.[4] We also focus on second-generation antidepressants because there is little new information on the older tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors.

3.1. Who Should be Treated with Pharmacotherapy?

Despite earlier reports questioning the efficacy of antidepressants,[5] subsequent meta-analyses have continued to support the efficacy of antidepressants in MDD.[6] The 2009 CANMAT guidelines identified most second-generation antidepressants as first-line treatments for patients with a major depressive episode (MDE) of moderate or greater severity (as determined by symptom scales and/or functional impairment), and this recommendation is unchanged. First-line treatments for individuals with depression of mild severity include psychoeducation, self-management, and psychological treatments. Pharmacological treatments can be considered for mild depression in some situations, including patient preference, previous response to antidepressants, or lack of response to nonpharmacological interventions.

3.2. Which Antidepressants Are Newly Approved?

Several new antidepressants have been approved in Canada, the United States, and elsewhere since the publication of the 2009 CANMAT guidelines.

Levomilnacipran is an active enantiomer of the racemic drug, milnacipran, a serotonin and noradrenaline reuptake inhibitor (SNRI). Levomilnacipran has greater selectivity for noradrenaline than for serotonin reuptake inhibition compared to other SNRIs. It is available as an extended-release formulation for once-daily administration. There are no published meta-analyses for levomilnacipran, but a pooled analysis of 5 placebo-controlled RCTs ($N = 2598$) confirmed its efficacy for response and remission.[7] One relapse-prevention study did not show significant differences between levomilnacipran and placebo.[8] There are no comparison studies of levomilnacipran with other antidepressants.

Vilazodone is a multimodal antidepressant that acts as a serotonin reuptake inhibitor and a partial agonist at 5-HT_{1A}

Table 1. Criteria for Level of Evidence and Line of Treatment.

	Criteria
Level of evidence[a]	
1	Meta-analysis with narrow confidence intervals and/or 2 or more RCTs with adequate sample size, preferably placebo controlled
2	Meta-analysis with wide confidence intervals and/or 1 or more RCTs with adequate sample size
3	Small-sample RCTs *or* nonrandomized, controlled prospective studies *or* case series *or* high-quality retrospective studies
4	Expert opinion/consensus
Line of treatment	
First line	Level 1 or Level 2 Evidence, plus clinical support[b]
Second line	Level 3 Evidence or higher, plus clinical support[b]
Third line	Level 4 Evidence or higher, plus clinical support[b]

RCT, randomized controlled trial.
[a]Note that Level 1 and 2 Evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, and hence the highest level of evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgement of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence.
[b]Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are feasible and relevant to clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side effects or safety profile.

receptors. Published meta-analyses are lacking, but 4 published and 8 unpublished or recently completed RCTs were identified.[9-11] A review of the clinical basis for approval has also been published.[12] Although 5 early-phase vilazodone trials failed to show efficacy, 4 subsequent studies (phases III and IV) reported efficacy for vilazodone 20 mg and 40 mg over placebo. There are no published relapse-prevention data for vilazodone or comparison studies with other antidepressants. Vilazodone must be taken with food to ensure adequate absorption and a titration dose schedule (10 mg/d for 7 days, 20 mg/d for 7 days, then 40 mg/d if needed) is recommended to avoid adverse gastrointestinal effects.[9]

Vortioxetine, another multimodal antidepressant, acts as a serotonin reuptake inhibitor, an agonist at 5-HT_{1A} receptors, a partial agonist at 5-HT_{1B} receptors, and an antagonist at 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 receptors. In 1 meta-analysis (12 RCTs, $N = 4947$), vortioxetine was superior to placebo in standardized mean difference and in odds ratios for response and remission.[13] Vortioxetine also has positive effects on neuropsychological performance in multiple cognitive domains in patients with MDD.[14-17] A relapse-prevention study showed superiority of vortioxetine over placebo.[18] Comparator studies are published for vortioxetine and agomelatine, duloxetine, and venlafaxine.

Table 2. Principles of Pharmacotherapy Management.

Recommendations (Level 4 Evidence)
• Conduct a detailed clinical assessment, including evaluation of suicidality, bipolarity, comorbidity, concomitant medications, and symptom specifiers/dimensions.
• Discuss evidence-based pharmacologic and nonpharmacologic treatment options.
• Elicit patient preference in the decision to use pharmacological treatment.
• Evaluate previous treatments, including dose, duration, response, and side effects of antidepressant and related medications.
• Where clinically indicated, refer for laboratory testing, including lipids, liver function tests, and electrocardiograms.
• Reassess patients for tolerability, safety, and early improvement no more than 2 weeks after starting a medication. Further follow-up may be every 2 to 4 weeks.
• Follow measurement-based care by using validated rating scales to monitor outcomes and guide clinical decisions.

3.3. How Do You Select an Antidepressant?

General principles of depression management are reviewed in Section 1.[3] Table 2 summarizes principles as they apply to pharmacological treatment. The process of selecting an antidepressant should involve both physician expertise and patient perceptions and preferences.

The selective serotonin reuptake inhibitors (SSRIs), SNRIs, agomelatine, bupropion, and mirtazapine remain first-line recommendations for pharmacotherapy for MDD (Table 3). Vortioxetine is also a first-line recommendation. Recommended second-line agents include TCAs, quetiapine and trazodone (owing to higher side effect burden), moclobemide and selegiline (potential serious drug interactions), levomilnacipran (lack of comparative and relapse-prevention data), and vilazodone (lack of comparative and relapse-prevention data and the need to titrate and take with food). Third-line recommendations include MAO inhibitors (owing to higher side effect burden and potential serious drug and dietary interactions) and reboxetine (lower efficacy).

Many clinical features and medication characteristics influence the choice of a first-line antidepressant (Table 4). There are no absolutes, and relative differences between medications are small. Hence, selecting an antidepressant involves an individualized needs assessment for each patient. Figure 1 shows a summary algorithm. The questions that follow summarize the evidence for selection factors.

3.4. What Clinical Factors Influence Antidepressant Selection?

Several clinical features, including increasing age, presence of anxiety, and long episode duration are associated with poorer response to medications.[19-22] However, few clinical features have high-quality evidence to support specific

Table 3. Summary Recommendations for Antidepressants.

Antidepressant (Brand Name(s))	Mechanism	Dose Range
First line (Level 1 Evidence)		
Agomelatine[a] (Valdoxan)	MT_1 and MT_2 agonist; 5-HT_2 antagonist	25-50 mg
Bupropion (Wellbutrin)[b]	NDRI	150-300 mg
Citalopram (Celexa, Cipramil)	SSRI	20-40 mg
Desvenlafaxine (Pristiq)	SNRI	50-100 mg
Duloxetine (Cymbalta)	SNRI	60 mg
Escitalopram (Cipralex, Lexapro)	SSRI	10-20 mg
Fluoxetine (Prozac)	SSRI	20-60 mg
Fluvoxamine (Luvox)	SSRI	100-300 mg
Mianserin[a] (Tolvon)	α_2-Adrenergic agonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic agonist; 5-HT_2 antagonist	15-45 mg
Paroxetine (Paxil)[d]	SSRI	20-50 mg 25-62.5 mg for CR version
Sertraline (Zoloft)	SSRI	50-200 mg
Venlafaxine (Effexor)[e]	SNRI	75-225 mg
Vortioxetine (Brintellix, Trintellix)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} agonist; 5-HT_{1B} partial agonist; 5-HT_{1D}, 5-HT_{3A}, and 5-HT_7 antagonist	10-20 mg
Second line (Level 1 Evidence)		
Amitriptyline, clomipramine, and others	TCA	Various
Levomilnacipran (Fetzima)[f]	SNRI	40-120 mg
Moclobemide (Manerix)	Reversible inhibitor of MAO-A	300-600 mg
Quetiapine (Seroquel)[e]	Atypical antipsychotic	150-300 mg
Selegiline transdermal[a] (Emsam)	Irreversible MAO-B inhibitor	6-12 mg daily transdermal
Trazodone (Desyrel)	Serotonin reuptake inhibitor; 5-HT_2 antagonist	150-300 mg
Vilazodone (Viibryd)[f]	Serotonin reuptake inhibitor; 5-HT_{1A} partial agonist	20-40 mg (titrate from 10 mg)
Third line (Level 1 Evidence)		
Phenelzine (Nardil)	Irreversible MAO inhibitor	45-90 mg
Tranylcypromine (Parnate)		20-60 mg
Reboxetine[a] (Edronax)	Noradrenaline reuptake inhibitor	8-10 mg

5-HT, 5-hydroxytryptamine (serotonin); MAO, monoamine oxidase; MT, melatonin; NDRI, noradrenaline and dopamine reuptake inhibitor; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]Not available in Canada.
[b]Available as sustained-release (SR) and extended-release (XL) versions.
[c]Available as rapid-dissolving (RD) version.
[d]Available as controlled-release (CR) version
[e]Available as extended-release (XR) version.
[f]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.

Table 4. Factors to Consider in Selecting an Antidepressant.

Patient Factors	Medication Factors
• Clinical features and dimensions • Comorbid conditions • Response and side effects during previous use of antidepressants • Patient preference	• Comparative efficacy • Comparative tolerability (potential side effects) • Potential interactions with other medications • Simplicity of use • Cost and availability

antidepressant recommendations. For example, there is no consistent evidence that age, sex, race, or ethnicity predicts outcomes using specific antidepressants.

The fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-5*)[23] uses episode and course specifiers to subtype clinical presentations of MDD. Other clinical dimensions, including cognitive dysfunction, sleep disturbance, and somatic symptoms (e.g., pain, fatigue), are proposed.[3] Many antidepressants have been studied for these depressive subtypes, but most studies only examine efficacy against placebo, and there are few comparative studies to suggest differential antidepressant efficacy. Table 5 summarizes the recommendations for these specifiers/dimensions.

Large trials examining response with *DSM-IV* specifiers (melancholic, atypical, anxious) found no differences in efficacy between escitalopram, sertraline, and venlafaxine XR or between escitalopram and nortriptyline.[24,25] The US STAR*D study also did not find differences in remission rates with citalopram in atypical or melancholic subtypes.[26,27]

For psychotic depression, a Cochrane meta-analysis (12 studies, $N = 929$) found that an antidepressant-antipsychotic combination was more effective than placebo (2 RCTs),

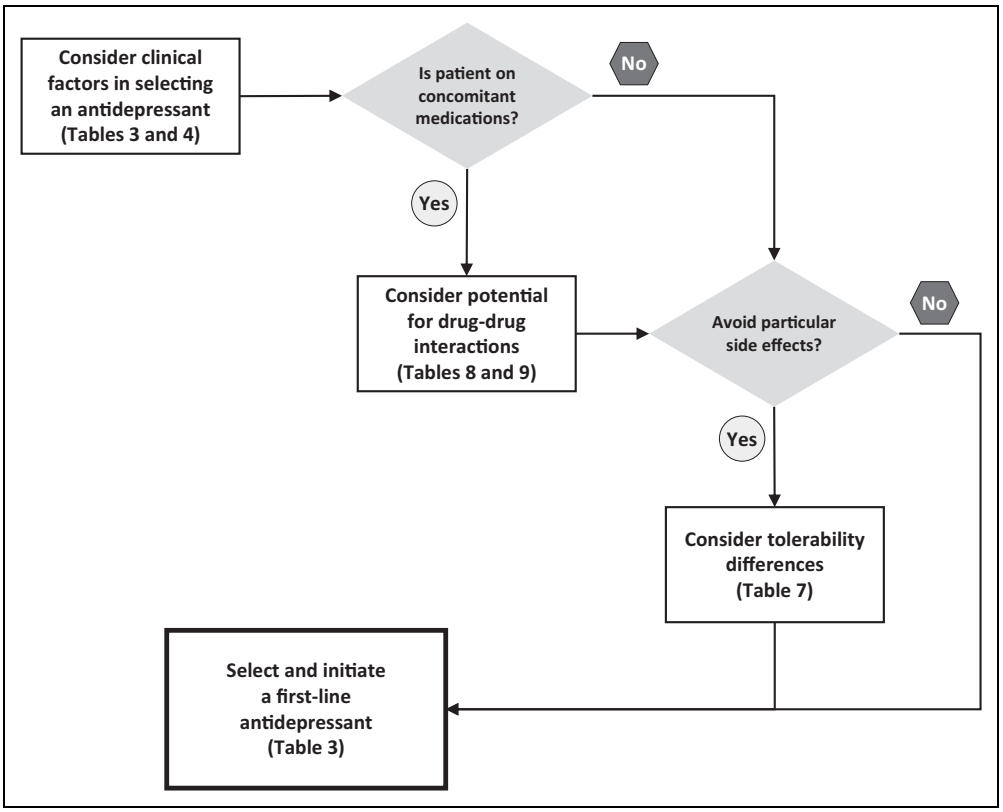

Figure 1. Summary algorithm for selecting an antidepressant.

antidepressant monotherapy (3 RCTs), and antipsychotic monotherapy (4 RCTs).[28] There is no evidence to address the question of how long individuals should remain on combination treatment once the psychotic depressive episode has remitted.

Mixed features is a new *DSM-5* specifier for MDD, and no trials have used these *DSM-5* criteria. In studies of MDE with variants of mixed symptoms similar to *DSM-5* mixed features, monotherapy with lurasidone and with ziprasidone was efficacious compared with placebo.[29,30]

For cognitive dysfunction, a systematic review (35 studies) found low-quality evidence that SSRIs, bupropion, duloxetine, moclobemide, and tianeptine (an antidepressant with limited availability) improve cognitive domains such as learning, memory, and executive function.[31] In a meta-analysis (17 studies, $N = 3653$) reviewing the cognitive effects of antidepressants based on neuropsychological tests, vortioxetine had the largest effects on processing speed, executive control, and cognitive control, while duloxetine had the largest effects on delayed recall.[17] The quality of these data is limited by small samples sizes and heterogeneity in cognitive testing. There were few differences between individual or classes of antidepressants, but those comparisons were also limited by small sample sizes.

Some antidepressants, including agomelatine, mirtazapine, and trazodone, and the atypical antipsychotic, quetiapine, have shown superior effects on subjective or objective sleep measures. However, mirtazapine, quetiapine, and trazodone also have the highest adverse event rates of somnolence and daytime sedation.[32]

There are few comparative studies of antidepressants for somatic symptoms such as pain and fatigue.[33] SNRIs, especially duloxetine,[34] are efficacious for painful conditions, including neuropathic pain and fibromyalgia.[35] There are no comparative studies on fatigue or low energy.

3.5. How Do Psychiatric and Medical Comorbidities Influence Antidepressant Selection?

There is limited evidence to guide antidepressant choice in the management of MDD with comorbid conditions. A comprehensive review was conducted by a CANMAT task force in 2012.[36] Readers are referred to their summary recommendations for mood disorders and comorbid anxiety,[37] attention-deficit/hyperactivity disorder,[38] substance use disorders,[39] personality disorders,[40] metabolic conditions, and common medical conditions.[41-43]

3.6. How Do Second-Generation Antidepressants Compare in Efficacy?

The 2009 CANMAT guidelines identified that, based on evidence from RCTs and early meta-analyses, some antidepressants had superior efficacy, although differences were small. Since then, meta-analyses with individual comparisons (see Suppl. Table S1) have reported superiority of

Table 5. Recommendations for Clinical Specifiers and Dimensions of Major Depressive Disorder.

Specifiers/ Dimensions	Recommendations (Level of Evidence)	Comments
With anxious distress[a]	• Use an antidepressant with efficacy in generalized anxiety disorder (Level 4)	• No differences in efficacy between SSRIs, SNRIs, and bupropion (Level 2)
With catatonic features[a]	• Benzodiazepines (Level 3)	• No antidepressants have been studied
With melancholic features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• TCAs and SNRIs have been studied
With atypical features[a]	• No specific antidepressants have demonstrated superiority (Level 2)	• Older studies found MAO inhibitors superior to TCAs
With psychotic features[a]	• Use antipsychotic and antidepressant cotreatment (Level 1)	• Few studies involved atypical antipsychotics
With mixed features[a]	• Lurasidone[b] (Level 2) • Ziprasidone[b] (Level 3)	• No comparative studies
With seasonal pattern[a]	• No specific antidepressants have demonstrated superiority (Level 2 and 3)	• SSRIs, agomelatine, bupropion, and moclobemide have been studied
With cognitive dysfunction	• Vortioxetine (Level 1) • Bupropion (Level 2) • Duloxetine (Level 2) • SSRIs (Level 2)[b] • Moclobemide (Level 3)	• Limited data available on cognitive effects of other antidepressants and on comparative differences in efficacy
With sleep disturbances	• Agomelatine (Level 1) • Mirtazapine (Level 2) • Quetiapine (Level 2) • Trazodone (Level 2)	• Beneficial effects on sleep must be balanced against potential for side effects (e.g., daytime sedation)
With somatic symptoms	• Duloxetine (pain) (Level 1) • Other SNRIs (pain) (Level 2) • Bupropion (fatigue) (Level 1) • SSRIs[b] (fatigue) (Level 2) • Duloxetine[b] (energy) (Level 2)	• Few antidepressants have been studied for somatic symptoms other than pain • Few comparative antidepressant studies for pain and other somatic symptoms

MAO, monoamine oxidase; SNRI, serotonin and noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]*DSM-5* specifiers.
[b]Comparisons only with placebo.

agomelatine (over sertraline), citalopram (over paroxetine and reboxetine), escitalopram (over citalopram), fluoxetine (over milnacipran), mirtazapine (over SSRIs as a class and venlafaxine), paroxetine (over fluoxetine), and sertraline (over fluoxetine). Unfortunately, many drug comparisons are not represented in these meta-analyses because of lack of head-to-head RCTs.

Network meta-analysis (also known as multiple or mixed-treatments meta-analysis) provides additional comparative information because it uses both direct (comparing 2 drugs head to head) and indirect (comparing 2 drugs based on their comparisons to a common third drug) comparisons.[44] Several network meta-analyses have been conducted since 2009 (see Suppl. Table S2). Cipriani and colleagues[45] examined 12 second-generation antidepressants in a network meta-analysis and found superior response for escitalopram, mirtazapine, sertraline, and venlafaxine. In direct head-to-head trials, Gartlehner et al.[46] found superior response of escitalopram over citalopram, sertraline over fluoxetine, and venlafaxine over fluoxetine. In the indirect treatments analysis, there was superior response to escitalopram over duloxetine and escitalopram over fluoxetine. The differences in response rates were modest, ranging from 5% to 6%.[46] A network meta-analysis of only head-to-head trials found that agomelatine, escitalopram, mirtazapine, and venlafaxine were superior to fluoxetine.[47] Additionally, mirtazapine and venlafaxine were superior to duloxetine, paroxetine, and sertraline, and agomelatine was superior to sertraline. A multiple-treatments meta-analysis of 10 antidepressants, including only studies conducted in primary care settings, found that escitalopram had superior remission rates.[48] In contrast, a network meta-analysis examining only classes of antidepressants in primary care found few differences in response, although SSRIs and TCAs were superior to mianserin/mirtazapine and moclobemide.[49]

In summary, meta-analyses continue to show that some antidepressants have modest superiority for treatment response, particularly escitalopram, mirtazapine, sertraline,

Table 6. Antidepressants with Evidence for Superior Efficacy Based on Meta-Analyses.

Antidepressant	Level of Evidence	Comparator Medications
Escitalopram	Level 1	Citalopram, duloxetine, fluoxetine, fluvoxamine, paroxetine
Mirtazapine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine
Sertraline	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Venlafaxine	Level 1	Duloxetine, fluoxetine, fluvoxamine, paroxetine
Agomelatine	Level 2	Fluoxetine, sertraline
Citalopram	Level 2	Paroxetine

and venlafaxine (Table 6). There is more limited evidence for the superiority of agomelatine and citalopram. Although considered small effects, 5% to 6% differences in response rate may be clinically relevant from a population basis.

3.7. How Do Antidepressants Compare on Measures of Functional Outcomes?

CANMAT recommendations for assessment of functional outcomes highlighted the critical impact of depressive symptoms on social, occupational, and physical functioning and that recovery from depression involves both relief of symptoms and improvement of functioning.[50] Systematic reviews show that functional outcomes are only modestly correlated with symptom outcomes, and functional improvement may lag behind symptom improvement.[51] Few studies of antidepressants assess functional outcomes. A systematic review (247 studies) found that 80% of treatment studies reported only symptom outcomes.[52] Another systematic review (35 studies) examined the relationships between antidepressants, cognitive dysfunction, and functional ability.[31] Antidepressants were generally associated with improvement in cognitive domains, but there was no conclusive evidence that improved cognition led to improved overall functioning. In the absence of high-quality studies comparing the efficacy of individual antidepressants on functional outcomes in MDD, no medication can be cited as demonstrating superior functional improvement.

3.8. What Is the Comparative Tolerability of Second-Generation Antidepressants?

Comparing tolerability is challenging to assess by RCTs, and meta-analyses have found few differences in tolerability between antidepressants (see Suppl. Tables S1 and S2). CANMAT chose to illustrate differences in side effect profiles of antidepressants by using the summary information contained in product monographs, which is reported in a standard format from the evidence submitted to regulatory authorities. While this information is not placebo-adjusted and is not based on direct comparisons, it can show a qualitative profile of side effects for each antidepressant (Table 7).

Because sexual side effects are inconsistently and inadequately reported, clinical trial data are not reliable for assessing antidepressant-associated sexual dysfunction. A network meta-analysis of second-generation antidepressants (63 studies, $N > 26{,}000$)[53] found low-quality evidence that bupropion had statistically lower rates of sexual side effects and that escitalopram and paroxetine had higher rates compared to other antidepressants. In studies that used standardized rating scales or interviews, which are more likely to reliably detect sexual side effects, agomelatine, bupropion, mirtazapine, vilazodone, and vortioxetine demonstrated lower risk.[54]

3.9. Are Antidepressants Associated with Suicidality?

Suicidal ideation and acts are important risks associated with MDD and require diligent assessment, monitoring and management during psychiatric treatment (see Section 1[3]). A signal for increased suicidality in adolescents and young adults in antidepressant clinical trials led many regulatory agencies to issue "black box" warnings in 2004. Since 2009, 3 large meta-analyses have addressed the effect of antidepressants on suicidal ideas or behaviour. The first included data from 372 RCTs comparing 12 antidepressants to placebo and reported a reduced risk of suicidal ideas or acts in those aged 25 to 64 years and a reduced risk of suicidal acts in those older than 65 years.[55] A meta-analysis of fluoxetine and venlafaxine showed no difference in suicidality compared to placebo, while another meta-analysis showed a trend toward reduced risk of suicidal ideas or acts with paroxetine versus placebo in the same age groups.[56,57] A systematic review of observational studies involving more than 200,000 patients with moderate to severe depression found that exposure to SSRIs reduced the risk of suicide by more than 40% among adults and more than 50% among elderly people.[58]

In contrast, exposure to SSRIs almost doubled (odds ratio = 1.92) the risk of suicide and suicide attempts among adolescents in these observational studies.[58] It is possible that only the most severely ill adolescents would have been prescribed antidepressants, and so this observational sample may well have had a particularly high risk for suicide actions. Nevertheless, caution and close monitoring are recommended when antidepressants are prescribed in this age group (see Section 6[59]). Large observational studies have not shown differences in suicide risk with particular antidepressants or classes of antidepressants, and therefore caution should be exercised for all antidepressants.

3.10. What Are Uncommon but Serious Adverse Effects of Antidepressants?

Prolongation of the corrected QT interval (QTc), a surrogate marker for Torsade de Pointes (TdP) arrhythmia, has been the subject of warnings by regulatory agencies for

Table 7. Prevalence of Adverse Events among Newer Antidepressants: Unadjusted Frequency (%) of Common Adverse Events as Reported in Product Monographs.

	Nausea	Constipation	Diarrhea	Dry Mouth	Headaches	Dizziness	Somnolence	Nervousness	Anxiety	Agitation	Insomnia	Fatigue	Sweating	Asthenia	Tremor	Anorexia	Increased Appetite	Weight Gain	Male Sexual Dysfunction
Citalopram	21		8	19				3	3	2		5	11		8	4			9
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2	10
Fluoxetine	21			10			13	14	12		16		8	9	10	11			2
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15			1
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1		16
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1		16
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2				6
Duloxetine	20	11	8	15		8	7		3		11	8	6		3				10
Levomilnacipran	17	9		10	17	8			2		6		9						11
Milnacipran	12	7		9	10				4		7	3	4		3				
Venlafaxine IR	37	15	8	22	25	19	23	13	6	2	18		12	12	5	11			18
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8			16
Agomelatine[c]	C	C	C		C	C	C		C		C	C	C						
Bupropion SR[d]	11	7	4	13	28	7	3	5	5	2	8		2	2	3				
Bupropion XL	13	9		26	34	6			5	2	16				3				
Mirtazapine		13		25		7	54							8	7		17	12	
Moclobemide	5	4	2	9	8	5	4	4	3	5	7	3	2	1	5				
Vilazodone[e]	24		29	7	14	8	5				6	3					3	2	5
Vortioxetine[f]	23	4	5	6		5	3				3	3	2						<1

When data from multiple doses were reported separately, the data from the minimum therapeutic dose were used (indicated by footnotes). Data sources and references are available in Supplemental Table S3. Clear cells represent 0% to 9%; shaded cells, 10% to 29%; and black cells, 30% and higher.

[a]Data from all indications.

[b]Data from 50-mg dose.

[c]C, common effects, $\geq$1% and <10%.

[d]Data from 100- to 150-mg dose.

[e]Data from 40-mg dose.

[f]Data from 10-mg dose.

citalopram, escitalopram, and quetiapine.[60] However, TdP is often an idiosyncratic event, and its associations with antidepressants, medication dose, and QTc prolongation remain unclear.[61] For example, a systematic review of antidepressants, QTc prolongation, and TdP found that 95% (36 of 38) of published case reports of QTc prolongation associated with antidepressants had 1 or more additional risk factors for TdP.[61] Most cases of TdP occurred at therapeutic doses of the antidepressant, and several cases of TdP occurred with QTc interval within the normal range.[61] Accordingly, in the absence of other known risk factors for TdP, the use of citalopram, escitalopram, and other antidepressants at therapeutic doses carries only a very low risk of TdP and other arrhythmias.[60,61]

The long-term use of SSRI antidepressants has been associated with increased risk of falls and fractures that is unrelated to postural hypotension. Systematic reviews and meta-analyses of observational studies indicate a small increased relative risk for fractures associated with SSRIs, with the highest risk in the first 6 weeks of exposure.[62-64] Hyponatremia is also associated with SSRI use, primarily in elderly patients with other risk factors for hyponatremia.[65]

SSRIs can inhibit platelet aggregation by altering platelet serotonin receptors and modestly increase the risk of gastrointestinal bleeding, but this risk may be doubled with concomitant use of nonsteroidal anti-inflammatory drugs (NSAIDs).[66] Concomitant use of acid-suppressing drugs can significantly reduce the risk of gastrointestinal bleeding.[67]

Elevation of liver enzymes is uncommonly seen with most antidepressants, and routine testing is not required. However, regulatory agencies in countries where agomelatine is approved have mandated regular liver function testing owing to the drug's potential to elevate liver enzymes (1.3%) and sporadic cases of toxic hepatitis.[68]

3.11. Are There Differences in Formulations of Specific Antidepressants?

A systematic review and network meta-analysis (7 studies for direct comparisons and 68 studies for indirect) found no differences in efficacy or tolerability with extended-release antidepressants compared to immediate-release formulations, although there was some evidence that adherence was lower with the immediate-release agents.[69] Extended-release antidepressants should be considered if adherence or compliance to medication is an issue.

Generic substitution for branded medications is a common practice in some countries and may involve alternative drug formulations.[70] The Canadian and US regulatory agencies define pharmacokinetic similarity for generics as bioequivalence between 80% and 125% of brand-name agents. Bioinequivalence, which may result in loss of efficacy or increased side effects, can occur and in some cases led to withdrawal of an approved generic agent.[71] Although generic medications are safe and reliable for most patients, for some who are well and maintained on a branded medication, a careful risk-benefit assessment (taking into account potential loss of efficacy) should be conducted prior to switching to a generic version.

3.12. What Are Clinically Relevant Drug-Drug Interactions?

Many patients with MDD take other medications for comorbid psychiatric and medical conditions. Drug-drug interactions can potentially reduce the efficacy of an antidepressant or other medications and increase adverse effects. Antidepressants and antipsychotics are primarily metabolized through the cytochrome P450 (CYP) enzyme metabolic pathway.[72,73] Most antidepressants are substrates for several CYP enzymes (Tables 8 and 9), but agomelatine and duloxetine are metabolized primarily via the CYP1A2 pathway and should not be coadministered with drugs that potently inhibit CYP1A2, such as cimetidine, ticlopidine, and ciprofloxacin. Similarly, vilazodone is metabolized primarily through CYP3A4 and should be used with caution when prescribed with CYP3A4 inhibitors such as ketoconazole.

Several antidepressants and atypical antipsychotics act as inhibitors of specific CYP isoenzymes (Table 9). Clinically relevant drug-drug interactions are usually caused by agents that are potent CYP inhibitors, including fluoxetine (CYP2D6), paroxetine (CYP2D6), and fluvoxamine (CYP1A2, 2C19, and 3A4). Drug-drug interactions with moderate CYP inhibitors, including bupropion, duloxetine, and sertraline (CYP2D6), are rarely clinically relevant except at higher doses.

P-glycoprotein is an important component of the blood-brain barrier and the intestinal barrier and affects efflux of medications, including psychotropic, cardiac, and cancer agents.[74] However, there is no consistent evidence of clinically relevant P-glycoprotein interactions with antidepressants or antipsychotics.[74,75]

Although not a pharmacokinetic drug-drug interaction, serotonin syndrome and/or hypertensive crisis can occur when serotonergic or sympathomimetic drugs are combined with MAO inhibitors, including the reversible MAO-A inhibitor, moclobemide, and the irreversible MAO-B inhibitor, selegiline (Table 9). Serotonin syndrome is rare except in cases of overdose, but it can also occur with combination use of multiple serotonergic medications (e.g., SSRIs, SNRIs, tramadol).[76]

3.13. Can Pharmacogenetic Testing or Therapeutic Drug-Level Monitoring Help to Select or Optimize an Antidepressant?

Pharmacogenetic testing for CYP enzymes is now available in many regions, and comprehensive recommendations for antidepressants have been suggested by the Clinical Pharmacogenetics Implementation Consortium (CPIC).[77] Since large-scale RCTs to examine the utility of pharmacogenetic tests are still lacking,[78] CANMAT does not recommend routine use of pharmacogenetic testing.

Table 8. Some Clinically Significant Drug-Drug Interactions Resulting from Inhibition of Cytochrome P450 (CYP) Isoenzymes.

Cytochrome P450 Inhibition of	Increases Serum Levels of These CYP Substrates	
CYP1A2	• **Agomelatine** • Caffeine • **Clozapine** • **Duloxetine** • Mexiletine	• Naproxen • **Olanzapine** • **Risperidone** • Tacrine • Theophylline • Warfarin
CYP2C19	• Antiarrhythmics • Antiepileptics (diazepam, phenytoin, phenobarbital) • Indomethacin	• Omeprazole • Primidone • Propanolol • Warfarin
CYP2D6	• Tricyclic antidepressants • Beta-blockers (metoprolol, propranolol) • Codeine and other opioids (reduces effect) • **Olanzapine**	• **Risperidone** • **Vortioxetine** • Tamoxifen (reduces effect) • Tramadol
CYP3A4	• Amiodarone • Antiarrhythmics (quinidine) • Antihistamines (astemizole, chlorpheniramine) • Calcium channel antagonists (e.g., diltiazem, verapamil) • **Haloperidol** • HIV protease inhibitors • Statins • Immune modulators (cyclosporine, tacrolimus)	• **Levomilnacipran** • Macrolide antibacterials (clarithromycin, erythromycin) • **Methadone** • **Phenothiazines** • **Quetiapine** • Sildenafil • Tamoxifen • **Vilazodone**

This is only a limited selection of interactions. For more comprehensive lists, see references in the text. Psychotropic medications in bold. HIV, human immunodeficiency virus.

Table 9. Potential Drug-Drug Interactions Involving Newer Antidepressants and Atypical Antipsychotics.

Potential for Drug-Drug Interaction	Antidepressants	Atypical Antipsychotics
Minimal or low potential	• Citalopram • Desvenlafaxine • Escitalopram • Mirtazapine • Venlafaxine	• Paliperidone
Moderate potential	• Agomelatine (1A2 substrate[a]) • Bupropion (2D6 inhibitor) • Duloxetine (2D6 inhibitor; • 1A2 substrate[a]) • Levomilnacipran (3A4 substrate) • Sertraline (2D6 inhibitor) • Vilazodone (3A4 substrate) • Vortioxetine (2D6 substrate)	• Aripiprazole (2D6, 3A4 substrate) • Olanzapine (1A2 substrate[b]) • Risperidone (2D6, 3A4 substrate)
Higher potential	• Fluoxetine (2D6, 2C19 inhibitor) • Fluvoxamine (1A2, 2C19, 3A4 inhibitor) • Moclobemide (MAO inhibitor precautions[c]) • Paroxetine (2D6 inhibitor) • Selegiline (MAO inhibitor precautions[c])	• Clozapine (3A4, 1A2 substrate) • Lurasidone (3A4 substrate) • Quetiapine (3A4 substrate)

Moderate and higher potential interactions are noted in parentheses. MAO, monoamine oxidase.
[a]Coadministration with CYP1A2 inhibitors (e.g., cimetidine, ciprofloxacin and other fluoroquinolone antimicrobials, ticlopidine) should be avoided because serum antidepressant levels will be higher, leading to increased potential for side effects.
[b]Also metabolized through the uridine diphosphate glucuronosyltransferase (UGT) pathway.
[c]Precautions similar to those of older MAO inhibitors. Avoid coadministration of other antidepressants, serotonergic drugs (e.g., meperidine), and sympathomimetic drugs (e.g., pseudoephedrine, stimulants).

Similarly, CANMAT does not recommend routine therapeutic drug-level monitoring (TDM) for second-generation antidepressants because the poor correlation between blood antidepressant levels and clinical response limits TDM utility. Pharmacogenetic testing and/or TDM may be helpful in individual circumstances, including inability to tolerate minimum doses (i.e., to detect poor metabolizers), repeated failure to respond to high doses (i.e., to detect ultrarapid metabolizers), and to detect nonadherence.

3.14. How Long Do You Wait for a Response from an Antidepressant?

Early improvement (defined as >20%-30% reduction from baseline in a depression rating scale after 2-4 weeks) is correlated with response and remission at 6 to 12 weeks.[79] The lack of early improvement at 2 to 4 weeks is also a predictor of later antidepressant nonresponse/nonremission. However, there is only low-quality evidence to support early switching at 2 or 4 weeks for nonimprovers to an initial antidepressant.[80,81] CANMAT recommends increasing the antidepressant dose for nonimprovers at 2 to 4 weeks if the medication is tolerated and switching to another antidepressant if tolerability is a problem.

3.15. How Long Do You Continue an Antidepressant?

The CANMAT guidelines identify 2 phases of depression treatment: an acute phase (getting to symptomatic remission) and a maintenance phase (preventing relapse and recurrence) (see Section 1[3]). The 2009 guidelines recommended that patients maintain treatment with antidepressants for 6 to 9 months after achieving symptomatic remission, while those with risk factors for recurrence extend antidepressant treatment to 2 years or more.[82] New evidence continues to support this recommendation for antidepressant maintenance. A meta-analysis found significant benefit of antidepressants over placebo in maintenance studies of 1 to 12 months (72 trials, $N = 14450$) and $\geq$12 months (35 trials, $N = 7253$).[83] Similarly, a review of all 16 maintenance RCTs ($N > 4000$) submitted to the Food and Drug Administration (FDA) found a 2-fold difference in recurrence during 24- to 52-week follow-up with antidepressants versus placebo (18% vs 37%, respectively).[84] The drug-placebo benefit also narrowed after 6 months, consistent with meta-analyses showing higher relapse/recurrence risk when antidepressants are discontinued within 6 months.[85]

Few RCTs have specifically evaluated risk factors to guide longer term treatment. In 1 study, patients with recurrent MDD were less likely to experience recurrence and more likely to have improved psychosocial outcomes with 2 years of maintenance treatment with venlafaxine ER versus 1 year.[86] The recommendation to extend maintenance treatment to 2 years or beyond in the presence of clinical risk factors (Table 10) is based on Level 3 and 4 Evidence.

Table 10. Risk Factors to Consider Longer Term (2 Years or Longer) Maintenance Treatment with Antidepressants (Level 3 and 4 Evidence).

- Frequent, recurrent episodes
- Severe episodes (psychosis, severe impairment, suicidality)
- Chronic episodes
- Presence of comorbid psychiatric or other medical conditions
- Presence of residual symptoms
- Difficult-to-treat episodes

Discontinuation symptoms, described by the FINISH mnemonic (flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, hyperarousal), may be experienced by up to 40% of patients when antidepressants are stopped abruptly.[87,88] These are generally mild and transient, but more severe symptoms have been described. Immediate-release formulations of paroxetine and venlafaxine are the most likely to be associated with discontinuation effects while long half-life agents such as fluoxetine and vortioxetine are the least likely.[89] Unless there are clinical reasons otherwise, we recommend slowly tapering the dose over several weeks when discontinuing antidepressants.

3.16. How Do You Manage Inadequate Response to an Antidepressant?

Figure 2 shows an algorithm for inadequate response to an initial antidepressant. If a patient has partial (e.g., 25%-49% reduction in symptom scores) or no response (e.g., <25% reduction) to the initial treatment, clinicians should ensure the treatment is optimized.[90,91] There is substantial evidence that many patients receive subtherapeutic doses and/or inadequate duration of treatment, and up to 20% may have poor adherence.[92] The clinician should then reevaluate the diagnosis and consider treatment issues that may be affecting response.[93] Psychotherapy and neurostimulation approaches should also be considered for patients with an inadequate antidepressant response (see Section 2[94] and Section 4[95] respectively).

Research on strategies for inadequate response to an initial antidepressant has been hampered by a lack of consensus on the concept and definition of treatment-resistant depression (TRD). The most commonly employed definition is inadequate response to 2 or more antidepressants.[91] However, this definition does not take into account adjunctive strategies, nor does it differentiate between patients who have had partial response versus those who have had no response. Additionally, few studies address residual symptoms (e.g., $\geq$50% improvement but symptom score is not in remission range).

In 2012, the United States Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review examining the various strategies to treat depression following inadequate response to an SSRI.[96] It concluded there was insufficient evidence to differentiate between monotherapy switch within the SSRI class or switching to a non-SSRI agent. There was low strength of evidence, indicating that augmenting with an atypical

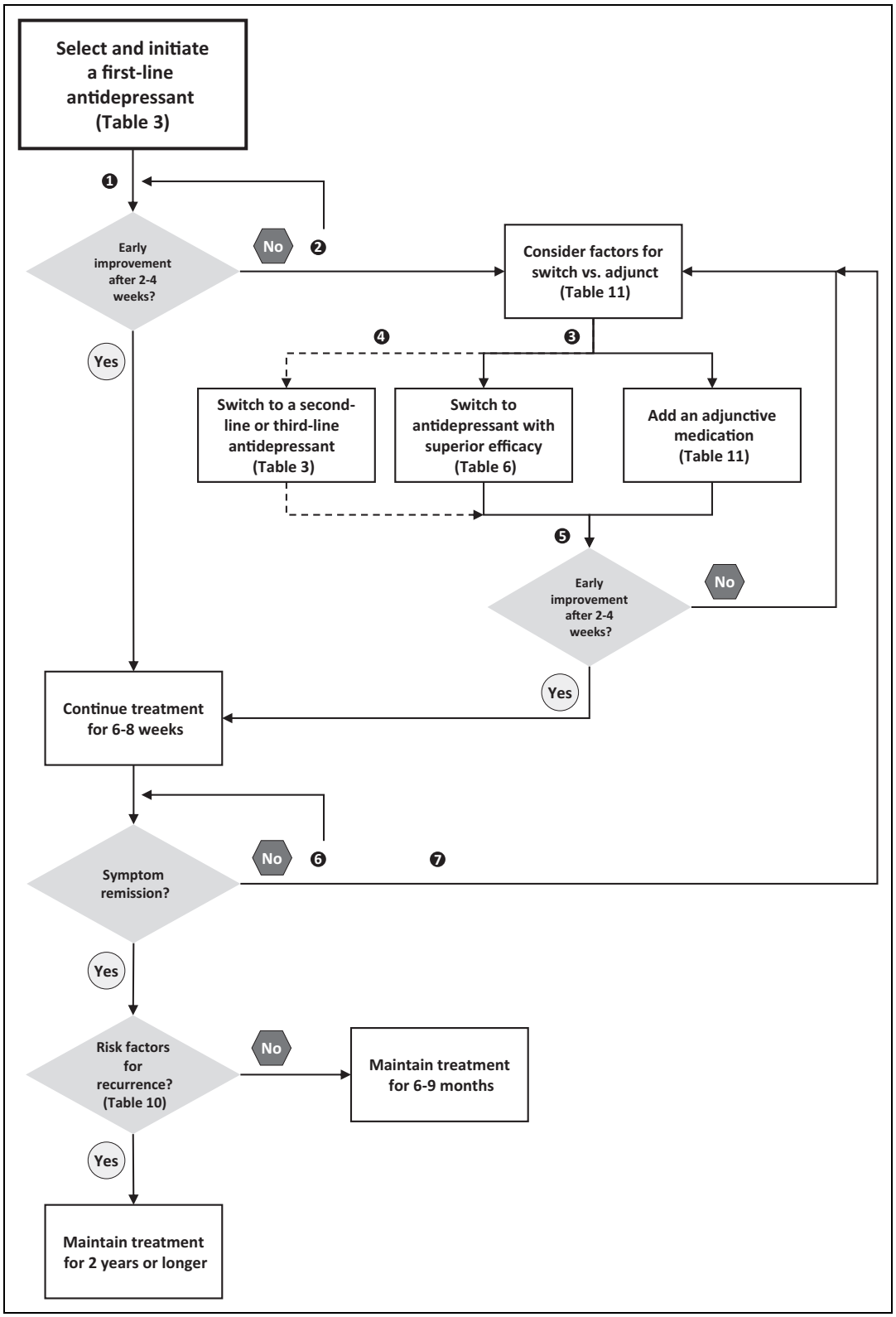

Figure 2. Summary algorithm for managing inadequate response to an antidepressant. (1) Monitor outcomes using measurement-based care. (2) Depending on tolerability, first optimize antidepressant by increasing dose. (3) For early treatment resistance, consider adjunctive use of psychological and neurostimulation treatments. (4) After failure of 1 or more antidepressants, consider switch to a second-line or third-line antidepressant. (5) For more resistant depressions, consider longer evaluation periods for improvement. (6) Depending on tolerability, increase dose if not at maximal doses. (7) For more chronic and resistant depressions, consider a chronic disease management approach, with less emphasis on symptom remission and more emphasis on improvement in functioning and quality of life.

antipsychotic was more effective than antidepressant monotherapy. There was also insufficient evidence about the benefits of individual atypical antipsychotics or other adjunctive agents. The following questions summarize subsequent evidence for these strategies.

3.17. How Effective Are Switching Strategies?

The 2009 CANMAT guidelines summarized evidence showing that switching nonresponders to another antidepressant results in good response and remission rates. Studies with newer antidepressants support this finding. Switching has also been studied as a control condition in RCTs of adjunctive treatments, with several studies demonstrating benefit of the switch compared to placebo.[97,98] However, there are few RCTs comparing a switch strategy to continuing the same antidepressant. A systematic review identified only 3 RCTs ($N = 495$), all of which investigated adjunctive strategies as the primary aim but included conditions for switching to a new antidepressant and continuing on the original antidepressant.[99] There were no differences in response or remission rates between switch and continuing strategies and no consistent evidence of differential efficacy between switching within class (e.g., from one SSRI to another SSRI) or across classes of antidepressants.[99]

The value of switching between classes or within classes of antidepressants remains controversial.[100] A previous meta-analysis (4 studies, $N = 1496$) found a modest, but statistically significant, remission advantage for patients on an SSRI switched to an antidepressant in a different class (bupropion, mirtazapine, venlafaxine) versus a second SSRI trial (28% vs. 23.5%, respectively).[101] These results are difficult to interpret because specific antidepressants have shown superior efficacy within both SSRI and non-SSRI classes (see 3.6., "How Do Second-Generation Antidepressants Compare in Efficacy?"). Consequently, CANMAT continues to recommend switching to an antidepressant with evidence of superior efficacy (Table 5).

3.18. How Effective Are Adjunctive Strategies?

An adjunctive strategy refers to the addition of a second medication to an initial medication. The term *adjunctive* is preferred over terms such as *combination* (adding a second antidepressant to the first) or *augmentation* (adding another medication that is not an antidepressant, e.g., triiodothyronine) because some augmentation agents (e.g., lithium, quetiapine) also have antidepressant effects as monotherapy.

Recommendations for adjunctive agents are based on efficacy and tolerability (Table 11). A network meta-analysis of RCTs (48 trials, $N = 6654$) examined the comparative adjunctive effects of aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone with each other and with placebo.[102] Only aripiprazole, lithium, quetiapine, and triiodothyronine were more effective than placebo, with stronger efficacy estimates for aripiprazole and quetiapine than for lithium and thyroid hormone.[102] There were no significant differences between the active treatments, but the network meta-analysis was limited due to few head-to-head comparisons, which reduces the power of indirect comparisons and the reliability of the results. This is apparent when examining the evidence base for lithium and triiodothyronine relative to other agents (summarized below).

Atypical antipsychotics. Adjunctive treatment with atypical antipsychotic medications has the most consistent evidence for efficacy in TRD. Four independent meta-analyses[103-106] comprising 12 to 17 trials ($N = 3208$-3807) and a network meta-analysis[107] (18 trials, $N = 4422$) all found superior efficacy when compared to placebo for adjunctive aripiprazole, olanzapine, quetiapine, and risperidone, with small to medium effect sizes. The network meta-analysis did not find evidence for differences in efficacy among the atypical antipsychotics studied.[107] Although not included in these meta-analyses, placebo-controlled RCTs have also shown efficacy for adjunctive brexpiprazole[108,109] and for ziprasidone.[110] All the meta-analyses and RCTs also found evidence for worse tolerability compared to placebo.

Antidepressants. The adjunctive strategy of adding another antidepressant to an existing one for TRD was examined in a systematic review, but only 5 placebo-controlled RCTs ($N = 565$) were identified: 3 trials with mirtazapine/mianserin and 2 trials with low-dose desipramine added to an SSRI.[111] The studies were too heterogeneous to conduct a meta-analysis, but there was a signal for efficacy of adjunctive mirtazapine/mianserin.[111] A meta-analysis (23 studies, $N = 2435$) focusing on adverse effects found that adjunctive antidepressant use was associated with increased side effects compared to monotherapy, especially when adding mirtazapine/mianserin or TCAs to SSRIs.[112]

Combinations of antidepressants have also been investigated as comedications in the initial treatment of MDD. While initial pilot studies were encouraging,[113,114] large-sample RCTs found no differences in efficacy with the combination of bupropion + escitalopram over each agent alone[115] or with the combinations of escitalopram + bupropion SR and mirtazapine + venlafaxine XR over escitalopram alone.[116] In addition, adverse effects were higher in the combination treatments. A combination of antidepressants at initiation of treatment is not recommended.

Other medications. A systematic review of lithium augmentation trials concluded that it was effective but acknowledged that extant studies mostly involved lithium in combination with TCAs in trials with small sample sizes.[117] This was highlighted in a meta-analysis of placebo-controlled RCTs (9 trials, $N = 237$) that identified only 3 trials ($N = 74$) of adjunctive lithium with SSRIs[118]; while the overall comparison and the SSRI-only comparison were both significant, the confidence intervals were

Table 11. Recommendations for Adjunctive Medications for Nonresponse or Partial Response to an Antidepressant.

Recommendation	Adjunctive Agent	Level of Evidence	Dosing
First line	Aripiprazole	Level 1	2-15 mg
	Quetiapine	Level 1	150-300 mg
	Risperidone	Level 1	1-3 mg
Second line	Brexpiprazole[a]	Level 1	1-3 mg
	Bupropion	Level 2	150-300 mg
	Lithium	Level 2	600-1200 mg (therapeutic serum levels)
	Mirtazapine/mianserin	Level 2	30-60 mg
	Modafinil	Level 2	100-400 mg
	Olanzapine	Level 1	2.5-10 mg
	Triiodothyronine	Level 2	25-50 mcg
Third line	Other antidepressants	Level 3	Various
	Other stimulants (methylphenidate, lisdexamfetamine, etc.)	Level 3	Various
	TCAs (e.g., desipramine)	Level 2	Various
	Ziprasidone	Level 3	20-80 mg bid
Experimental	Ketamine	Level 1	0.5 mg/kg, single intravenous dose[b]
Not recommended	Pindolol	Level 1 (lack of efficacy)	Not applicable

TCA, tricyclic antidepressant.
[a]Newly approved since the 2009 Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines.
[b]For acute treatment.

wide, indicating Level 2 Evidence for efficacy. There have been no studies of triiodothyronine augmentation since the systematic review in 2008 that identified only 2 placebo-controlled RCTs.[119] The STAR*D trial, although not placebo-controlled, is the largest RCT ($N = 142$) to compare the 2 strategies.[120] There were no significant differences in remission rates, but triiodothyronine was better tolerated than lithium and had lower dropout rates.

A meta-analysis of modafanil, an atypical stimulant, in MDD identified 4 trials ($N = 568$), but only 2 ($N = 211$) were adjunctive studies.[121] After excluding an outlier study, there was only marginal evidence for efficacy in modafinil-treated patients compared to placebo on both response and remission rates. Adverse effects did not appear to differ from placebo.[121] Two placebo-controlled RCTs of lisdexamfetamine, a stimulant, found evidence of efficacy as an adjunctive agent for partial responders to SSRIs[122,123]; however, 2 unpublished phase III trials ($N = 830$) of adjunctive lisdexamfetamine were negative, and the clinical development program was discontinued.[124] To date, other stimulants (e.g., methylphenidate) have only negative studies.[125]

Several meta-analyses have shown that single doses of intravenous ketamine, which preferentially target N-methyl-D-aspartate (NMDA) receptors, have rapid antidepressant effects in TRD.[126-128] However, ketamine is associated with psychotomimetic adverse effects, carries potential for abuse, and still has very limited data on safety and efficacy with longer term use.[126,129,130] CANMAT considers ketamine an experimental treatment and recommends its use be limited to academic depression treatment centres.

A meta-analysis (5 trials, $N = 154$) examined adjunctive use of the beta-blocker pindolol. There was no significant benefit for pindolol versus placebo in combination with SSRI therapy and no differences in tolerability or safety between the 2 groups.[131] Pindolol is not recommended as an adjunct treatment.

3.19. How Do you Choose between Switching to Another Antidepressant and Adding an Adjunctive Agent?

An RCT ($N = 101$) found that adjunctive aripiprazole was superior to antidepressant switch on efficacy outcomes, including response and remission.[132] In a retrospective comparison of the STAR*D switch and adjunctive studies, patients who tolerated citalopram and who had partial response were more likely to benefit from adjunctive strategies compared to switching.[133] A few studies have addressed residual symptoms, such as fatigue or sexual dysfunction.[134,135] However, there is no consistent evidence to support specific adjunctive agents to target specific residual symptoms or side effects.

In summary, given the limited evidence, a pharmacologic approach for TRD would include diagnostic reevaluation, consideration of previous medication trials (including degree of response and tolerability), rational use of adjunctive medications, discontinuation of medications that have not been beneficial, and careful monitoring of symptoms, side effects, and functioning to evaluate outcomes. The decision between switching and adjunctive strategies should be individualized based on clinical factors (Table 12).

Table 12. Factors to Consider in Choosing between Switching to Another Antidepressant Monotherapy or Adding an Adjunctive Medication (Level 3 Evidence).

Consider switching to another antidepressant when:
- It is the first antidepressant trial.
- There are poorly tolerated side effects to the initial antidepressant.
- There is no response (<25% improvement) to the initial antidepressant.[a]
- There is more time to wait for a response (less severe, less functional impairment).
- Patient prefers to switch to another antidepressant.

Consider an adjunctive medication when:
- There have been 2 or more antidepressant trials.
- The initial antidepressant is well tolerated.
- There is partial response (>25% improvement) to the initial antidepressant.
- There are specific residual symptoms or side effects to the initial antidepressant that can be targeted.
- There is less time to wait for a response (more severe, more functional impairment).
- Patient prefers to add on another medication.

[a]For the initial antidepressant trial. In subsequent trials, lack of response (<25% improvement) may not be a factor for choosing between switch and adjunctive strategies.

3.20. How Do You Manage Persistent and Chronic Depression?

The *DSM-5* has added a new diagnosis of persistent depressive disorder (PDD) that subsumes the *DSM-IV* diagnoses of dysthymic disorder and chronic MDD (see Section 1[3]). A systematic review and network meta-analysis examined efficacy (response) and acceptability (all-cause discontinuation) of treatments for PDD (depression >2 years' duration) with a network of 45 RCTs ($N = 5804$) involving 28 drugs.[136] Most of the studied drugs were more effective than placebo, including fluoxetine, paroxetine, sertraline, moclobemide, and imipramine, with no differences in acceptability compared to placebo. The only differences between treatments were superior efficacy of sertraline over imipramine and superior acceptability of moclobemide over fluoxetine.[136] These results confirmed a meta-analysis (20 trials, $N = 2918$) of chronic depression showing that SSRIs were similar in efficacy but superior in tolerability compared with TCAs.[137] The network meta-analysis also identified differences in effects between combined psychotherapy + medication and medication-only studies in dysthymia studies compared to studies of chronic MDD, suggesting that the new diagnosis of PDD may not have homogeneous treatment response.[136]

Although there are positive results in treating chronic depression and PDD with antidepressants, some experts have argued that patients with repeated treatment failures and a chronic course of depression require a chronic disease management approach (i.e., with less emphasis on remission of symptoms and cure, greater emphasis on improving functioning and quality of life, and greater use of psychotherapeutic and nonmedication treatments).[138]

3.21. What Novel Treatments Are Being Investigated?

The link between the rapid antidepressant effect of ketamine and the glutamate system has stimulated drug development on related compounds, including esketamine (the S-enantiomer of ketamine, delivered intranasally),[139] lanicemine, and memantine.[140] Other promising compounds include GluN2B antagonists (e.g., CERC-301)[141]; GLYX-13, which targets the glycine coagonist site on the NMDA receptor[142]; and basimglurant, which targets the metabotropic glutamate (mGlu) receptors.[143] Other potential candidates for antidepressant actions include drugs that target the endocannabinoid system and drugs with neuroplasticity mechanisms, which are thought to play a role in sustained antidepressant effects.[144]

Preliminary studies have shown promise for several currently available medications with diverse effects. In a meta-analysis (4 studies, $N = 150$) of adjunctive celecoxib, higher response and remission rates and lower dropout rates were reported with the NSAID compared to placebo.[145] In contrast, a subsequent small trial ($N = 30$ female patients with first episode of MDD) did not demonstrate efficacy of adjunctive celecoxib with sertraline.[146] Preliminary studies of pramipexole, a dopaminergic D2, D3, and D4 receptor agonist that has evidence for efficacy in bipolar depression,[147] found some benefit in TRD.[148,149] Other investigational drugs for MDD include novel atypical antipsychotics such as cariprazine.[150]

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