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

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Editorial

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Updated CANMAT Guidelines for Treatment of Major Depressive Disorder

Scott B. Patten, MD, PhD[1]

This issue of *The Canadian Journal of Psychiatry* (*CJP*) includes updates to the popular Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of major depressive disorder. This is the third iteration of these guidelines for major depressive disorder, the first being published in 2001[1] and then updated in 2009.[2] It is important to emphasize that these and other CANMAT guidelines are not endorsed by the Canadian Psychiatric Association. *CJP* has previously published guidelines developed by other independent groups.[3,4]

The series consists of 6 articles focusing on burden and principles of care,[5] psychological treatments,[6] pharmacological treatments,[7] neurostimulation treatments,[8] complementary and alternative medicine treatments,[9] and special populations.[10]

What is immediately apparent from the CANMAT guidelines is their distinctiveness. There are contemporary quality assessment and reporting guidelines for projects of this type, called Appraisal of Guidelines for Research & Evaluation II (AGREE II).[11,12] As a consequence of AGREE II, recently published guidelines have become increasingly standardized in their methodology and reporting. The CANMAT guidelines fulfill many of the items listed in AGREE II but not all. Rather than tailoring their reporting to AGREE II, CANMAT instead uses a question-and-answer format that has been well received by clinicians in previous versions of their guidelines. Central to the process of parsing evidence into clinical guidance is a grading of the quality of evidence and strength of recommendations. Internationally, the current standard for doing so is the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[13] CANMAT has chosen not to use this approach and instead uses its own level of evidence and 'lines of treatment' rating systems. Perhaps the most distinctive feature is CANMAT's explicit incorporation of expert opinion in assessment of lines of treatment. These are based on evidence plus 'clinical support', the latter being assigned through the expert opinion of the CANMAT committees. Most evidence-based guidelines emphasize minimization of the role of expert opinion. They view opinion as a weak source of evidence that risks distorting stronger forms of evidence (i.e., that deriving from randomized controlled trials and meta-analyses). CANMAT makes no apologies for going in a different direction. It believes that the integration of levels of evidence with expert opinion renders its recommendations more usable and realistic, and also that the 'lines of treatment' concept produces an alignment of the guidelines with stepped-care management concepts.

The AGREE II checklist includes an item assessing 'competing interests', which is a component of the AGREE II 'Editorial Independence' domain. Readers will note that some members of the CANMAT authorship group disclose multiple relevant financial activities, whereas other members report none. *CJP* requires disclosure of activities ''that could be perceived to influence, or that give the appearance of potentially influencing'' the work under consideration. In keeping with the editorial stance of most peer-reviewed journals, authors are encouraged to be inclusive, reporting ''interactions with ANY entity that could be considered broadly relevant to the work.'' This approach allows readers to decide the extent to which such information may affect their acceptance or interpretation of the guidance provided.

The approaches taken by the CANMAT group, while distinct from those of many other depression guidelines, have been embraced by clinicians and widely discussed both within Canada and internationally. These guidelines offer an interesting approach and texture to the provision of clinical guidance for the management of major depressive disorder. They also represent a considerable investment of effort by a notable group of Canadian psychiatrists and

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scientists, and we are proud to provide them to the readership of *CJP* in this issue.

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Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder: Introduction and Methods

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The Canadian Network for Mood and Anxiety Treatments (CANMAT) is a not-for-profit scientific and educational organization founded in 1995. In 2015, the CANMAT Depression Work Group began the process of producing new guidelines for the treatment of major depressive disorder (MDD), to update the previous 2009 guidelines.[1] The scope of the guidelines remains the management of adults with unipolar MDD with an identified target audience of community-based psychiatrists and mental health professionals. CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2]

The editorial group defined 6 sections for inclusion in the CANMAT 2016 Depression Guidelines: (1) Disease Burden and Principles of Care, (2) Psychological Treatments, (3) Pharmacological Treatments, (4) Neurostimulation Treatments, (5) Complementary and Alternative Medicine Treatments, and (6) Special Populations (children/adolescents, women, elderly). Treatment recommendations for patients with MDD and psychiatric/medical comorbidities were published by a CANMAT task force in 2012.[3]

The methods used were similar to the previous CANMAT guidelines that have been well regarded by clinicians. In contrast to other guidelines that use highly formalized evidence summaries that may be less accessible to users, we chose a clinically useful method that balances systematic evidence review with consensus expert opinion by experienced clinicians. Expert panels were established for each of the 6 sections. Members represented content experts from the fields of psychiatry, pharmacy, and psychology. The familiar question-answer format from previous editions was retained because feedback from clinicians affirmed the clinical practicality and ease of use. Each group updated the key questions based on internal and focus group discussions and held regular teleconferences during the guidelines development process.

We focused on evidence published since 2009. For each of the questions, a systematic literature search was conducted by research staff experienced in systematic reviews with medical librarian consultation as needed. Appropriate key words were used to identify English- and French-language studies published between January 1, 2009, and December 31, 2015, in electronic databases (including OVID Medline, PsycInfo, and EMBASE). Relevant studies were identified and reviewed, with an emphasis on meta-analyses and randomized controlled trials (RCTs). Studies were also identified by cross-referencing bibliographies, reviews of other major reports and guidelines, and feedback from experts. The evidence was summarized using evidence tables based on modified Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[4] for meta-analyses and on Consolidated Standards of Reporting

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Table 1. Canadian Network for Mood and Anxiety Treatments (CANMAT) Criteria for Level of Evidence.

Level of Evidence[a]	Criteria
1	Meta-analysis with narrow confidence intervals and/or 2 or more randomized controlled trials (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

[a]Note that Level 1 and 2 Evidence refers 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 judgment of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence.

Table 2. Canadian Network for Mood and Anxiety Treatments (CANMAT) Criteria for Line of Treatment.

Line of Treatment	Criteria
First line	Level 1 or Level 2 Evidence, plus clinical support[a]
Second line	Level 3 Evidence or higher, plus clinical support[a]
Third line	Level 4 Evidence or higher, plus clinical support[a]

[a]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.

Trials (CONSORT)[5] for RCTs. Supplemental Figure S1 (online supplemental materials) provides an example search strategy, PRISMA figure, and evidence table.

The evidence was graded using level of evidence criteria from the previous guidelines[1] (Table 1), supplemented by modified ratings from Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[6] These criteria now indicate the primacy of meta-analyses over RCTs, given the increasing use of individual and network[7] meta-analysis in evidence evaluation. 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.[8,9] RCTs were considered when systematic reviews and meta-analyses were not available. Small-sample (generally fewer than 30 participants per randomized condition) RCTs were considered Level 3 Evidence.

The recommendations were then expressed as lines of treatment, in which both the evidence base and clinical support were used to determine first-, second-, and third-line treatments (Table 2). In this context, clinical support reflects expert opinion on feasibility, availability, and clinical effectiveness. A first-line treatment recommendation indicates good-quality evidence (Level 1 or 2 Evidence) as well as clinical utility. However, treatments with Level 1 Evidence may be downgraded to second-line or third-line recommendation because of safety or side effect profiles. In a few instances where Level 1 or Level 2 Evidence was lacking, no first-line recommendation was made and the second-line recommendation may reflect expert consensus. We have indicated the rationale when these situations occur.

CANMAT recognizes that the level and quality of evidence vary widely with indication and type of treatment, that the majority of RCTs (and, hence, the meta-analyses based on them) may not reflect real-world clinical practice, and that there are very few predictors of treatment response for an individual patient. Therefore, there are few absolute or first-choice treatments. These CANMAT recommendations are presented as guidance for clinicians for consideration within the context of individual patients and not as standards of care.

Manuscript drafts were circulated amongst section members for discussion and consensus. If consensus could not be reached, a section member could submit a dissenting statement. The editorial team reviewed and revised each section, consolidating or merging questions as needed for consistency and succinctness. Final manuscripts were approved by all coauthors.

For transparency, we declare that the guidelines process and publication were funded entirely by internal CANMAT funds; no external support was sought or received. No honoraria were paid to authors, and no professional editorial assistance was used. All guidelines work group members disclosed potential conflicts of interest (available at www.canmat.org). CANMAT is a project-driven organization governed by a volunteer, unpaid advisory board, with no permanent staff or dedicated offices. Our diverse activities involve research, knowledge translation (e.g., guidelines dissemination, national and international conferences, publications), and continuing professional development (CPD). CANMAT has a conflict of interest policy that includes disclosures by all participants, and all CPD projects are accredited by academic institutions. CANMAT activities are funded from a variety of sources: for academic projects from peer-review or philanthropic foundations; for conferences from societies, registrations, and multiple industry sponsors; and for CPD from universities and industry sponsors. Research studies[10,11] are independently funded by agencies such as the Canadian Institutes of Health Research (CIHR) and are administrated by the academic institutions of the principal investigators. In the past 5 years (2011-2015), sources of CANMAT revenue (excluding CIHR and research funding) included national/international scientific conferences (28% of revenue), publications (26%), industry-supported CPD projects (26%), and academic projects (18%).

These updated CANMAT guidelines again encompass a variety of treatments, including psychological, pharmacological, neurostimulation, and complementary and alternative medicine (CAM) treatments. Choosing a first-line treatment among these treatment choices remains a collaborative decision between patient and clinician. However, there continues to be greater evidence and clinical experience with traditional treatments (psychotherapy and pharmacotherapy) and few studies directly comparing these with neurostimulation or CAM treatments. Also, many studies of neurostimulation are in populations of patients who have failed at least one previous treatment. Therefore, first-line psychological and/or pharmacological treatments usually should be considered before neurostimulation or CAM treatments.

Some medications and treatments discussed may not be available in Canada or other countries. As well, these guidelines are primarily addressed to specialists (psychiatrists and other mental health professionals) and hence may be more detailed than needed for primary care settings. As with previous versions, CANMAT will produce briefer summaries for primary care practitioners. To engage end users and obtain feedback, draft versions of these guidelines have been presented in interactive workshops at major psychiatric conferences in Canada. In addition, the Community Advisory Committee of the Canadian Biomarker Integration Network in Depression[12] (CAN-BIND, www.canbind.ca) research program, along with the Mood Disorders Association of Ontario, is currently engaged in developing a ''patient'' version of these guidelines as well as a strategy to disseminate the patient version directly to consumers. We hope that these updated guidelines will provide clinicians and their patients with evidence-informed recommendations to make personalized, collaborative treatment decisions.

Disclosures

Disclosures for all members of the CANMAT Depression Work Group are available at www.canmat.org.

The CANMAT guidelines are not officially endorsed by the Canadian Psychiatric Association.

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GMM has been on advisory board or speaker for Janssen, Lilly, Lundbeck, and Pfizer.

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AVR has received speaker and consultant honoraria or research funds from Bristol-Myers Squibb, Canadian Depression Research and Intervention Network, Canadian Foundation for Innovation and the Ministry of Economic Development and Innovation, Canadian Institutes of Health Research, Grand Challenges Canada, Janssen, Lundbeck, Ontario Mental Health Foundation, Pfizer, and Sunovion.

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Supplementary Material

The online supplement is available at http://cpa.sagepub.com/supplemental.

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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 1. Disease Burden and Principles of Care

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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. This section is the first of six guidelines articles.

Results: In Canada, the annual and lifetime prevalence of MDD was 4.7% and 11.3%, respectively. MDD represents the second leading cause of global disability, with high occupational and economic impact mainly attributable to indirect costs. *DSM-5* criteria for depressive disorders remain relatively unchanged, but other clinical dimensions (sleep, cognition, physical symptoms) may have implications for depression management. e-Mental health is increasingly used to support clinical and self-management of MDD. In the 2-phase (acute and maintenance) treatment model, specific goals address symptom remission, functional recovery, improved quality of life, and prevention of recurrence.

Conclusions: The burden attributed to MDD remains high, whether from individual distress, functional and relationship impairment, reduced quality of life, or societal economic cost. Applying core principles of care, including comprehensive assessment, therapeutic alliance, support of self-management, evidence-informed treatment, and measurement-based care, will optimize clinical, quality of life, and functional outcomes in MDD.

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Keywords
depressive disorders, clinical practice guidelines, major depressive disorder, systematic reviews, meta-analysis, clinical assessment, diagnosis, phenomenology, evidence-based medicine

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 mental health professionals. CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2] This section on Disease Burden and Principles of Care is the first of six guidelines articles; subsequent sections of the guidelines will expand on psychological, pharmacological, neurostimulation, and complementary and alternative medicine treatments, as well as on special populations (youth, women, and the elderly). The question-answer format has been retained for ease of use. These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

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. 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 judgment of the strength of evidence from various data sources and therefore are primarily Level 4 Evidence.

1.1. How Are the Depressive Disorders Classified?

The current classification of depression is based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) or "Recurrent Depressive Episodes" in the *International Classification of Diseases, 10th Revision* (*ICD-10*) classification of mental and behavioural disorders.[4,5] The *DSM-5*, introduced in 2013, removed the broad category of mood disorders and classifies depressive disorders separately from bipolar disorder.[4] For major depressive episode (MDE), the *DSM-5* core symptom and duration criteria (criterion A) are unchanged from the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (*DSM-IV-TR*) (Table 2).[6] The *DSM-IV-TR* "bereavement exclusion" criterion was eliminated in the *DSM-5*, reflecting evidence that bereavement may last longer than 2 months and is not different from other significant stressors or losses that may precipitate an MDE (Table 3). Instead, bereavement with more severe depressive symptomatology has been included in "Conditions for Further Study" as persistent complex bereavement disorder.

Other important changes in *DSM-5* include a new classification of chronic depression as persistent depressive disorder, which comprises the former *DSM-IV-TR* diagnoses of chronic MDE and dysthymic disorder. This change was in response to evidence showing it was difficult to differentiate the latter diagnoses and the fact that they frequently co-occurred. *DSM-5* also includes 2 new depressive disorders. Disruptive mood dysregulation disorder is applicable for children aged 6 to 18 years who exhibit severe and recurrent temper outbursts, uncontrollable behaviour, and persistent irritability. Premenstrual dysphoric disorder recognizes a serious form of premenstrual syndrome characterized by intense emotional symptoms, which may include symptoms of depressed mood, anxiety, mood swings, and irritability, in the final week before menses.

Despite these minor changes in criteria for MDD, the *DSM-5* field trials found poor interrater reliability for the diagnosis, and neither *DSM-5* nor *ICD-10* is based on aetiology or pathophysiology.[7] There are renewed efforts to use alternative frameworks, such as the US National Institute of Mental Health Research Domain Criteria Initiative (RDoC), which attempts to align diagnosis with current understanding of brain systems.[8]

1.2. What Are Important Clinical Specifiers and Dimensions of Depressive Episodes?

It is increasingly recognized that there is a spectrum of clinical presentations that are not captured by the symptom criteria for MDE. These represent important clinical dimensions that have implications for prognosis and treatment and may have different neurobiological substrates. *DSM-5* classifies these subtypes and dimensions as episode or course specifiers for MDE. *DSM-IV* specifiers, including melancholic, atypical, psychotic, and seasonal pattern, have been retained in the *DSM-5*, but the former postpartum

Table 1. Criteria for Level of Evidence[a] and Line of Treatment.

	Criteria
Level of evidence	
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 Canadian Network for Mood and Anxiety Treatments 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 effect or safety profile.

specifier is now termed "with peripartum onset" to reflect evidence that 50% of postpartum depressive episodes have an onset prior to delivery. New specifiers include anxiety and mixed features (Table 4). The *DSM-5* "with anxious distress" specifier recognizes that MDE is often accompanied by anxiety symptoms, even when a comorbid anxiety disorder is not present. Anxiety contributes to increased rates of suicide, poor response to treatment, and increased risk of chronicity and recurrence.[9]

The new *DSM-5* specifier "with mixed features" allows for the presence of manic or hypomanic symptoms in individuals diagnosed with unipolar MDEs, as well as the presence of depressive symptoms in patients diagnosed with mania/hypomania. Mixed features are found in up to a third of patients with MDE, although the prevalence rates vary widely depending on the diagnostic criteria employed.[10,11] Mixed depressive episodes are more common in younger patients, are more severe, and carry a higher risk for suicide,[12] but the specifier is controversial.[13]

Other clinical dimensions that are not recognized in the *DSM-5* may also have important assessment and treatment implications. For example, cognitive symptoms are included as a core diagnostic criterion for MDE, but these do not describe the full spectrum of cognitive dysfunction associated with depressive disorders, including disturbances in attention, memory, processing speed, and executive

Table 2. *DSM-5* Symptom Criteria for Major Depressive Episode.

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) or (2).

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

Note: Do not include symptoms that are clearly due to a general medical condition or mood-incongruent delusions or hallucinations.

Table 3. Summary of Changes from *DSM-IV-TR* to *DSM-5*.

DSM-IV-TR Item	*DSM-5* Item
MDD episode specifiers • With postpartum onset	New MDD episode specifiers • With anxious distress • With mixed features • Suicidality • With peripartum onset
Bereavement exclusion	Deleted
Premenstrual dysphoric disorder • In the appendix	Premenstrual dysphoric disorder • Now included as diagnosis
Dysthymic disorder, "double depression"—MDE superimposed on dysthymic disorder	Persistent depressive disorder • ± Full MDE criteria • "Dysthymia" when full MDE criteria not present

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; *DSM-IV-TR*, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*; MDD, major depressive disorder; MDE, major depressive episode.

Table 4. *DSM-5* Episode Specifiers and Other Clinical Dimensions Associated with MDE.

Subtype/ Dimension	*DSM-5* Specifier	Key Features
Melancholic depression	With melancholic features	Nonreactive mood, anhedonia, weight loss, guilt, psychomotor retardation or agitation, morning worsening of mood, early morning awakening, excessive or inappropriate guilt
Atypical depression	With atypical features	Reactive mood, oversleeping, overeating, leaden paralysis, interpersonal rejection sensitivity
Psychotic (delusional) depression	With psychotic features	Hallucinations or delusions
Catatonic depression	With catatonic features	Catalepsy (waxy flexibility), catatonic excitement, negativism or mutism, mannerisms or stereotypes, echolalia or echopraxia (uncommon in clinical practice)
Anxious depression	With anxious distress	Feeling keyed up or tense, restless, worried, something awful may happen, or afraid of losing control
Mixed states	With mixed features	Elevated mood, inflated self-esteem or grandiosity, more talkative, racing thoughts, increased energy and activity, decreased need for sleep, risky and impulsive activities
Seasonal affective disorder	Seasonal pattern	Regular onset and remission of depressive episodes during a particular season (usually fall/winter onset)
Postpartum and antepartum depression	With peripartum onset	Onset of depressive episode during pregnancy or within 4 weeks postpartum
Cognitive dysfunction	NA	Disturbances in attention, memory, processing speed, executive functioning and emotional processing
Sleep disturbance	NA	Insomnia or hypersomnia; circadian rhythm disturbance
Somatic symptoms	NA	Headaches, body aches, fatigue, anergia

DSM-5, *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*; MDE, major depressive episode; NA, not applicable.

functioning.[14-17] Cognitive deficits can be demonstrated with neuropsychological tests during acute MDEs and are associated with significant impact on daily functioning and quality of life.[16,18,19] Moreover, cognitive dysfunction is a common residual symptom during treatment and may continue even after mood symptoms have remitted.[20,21] These observations reflect the need and importance for clinical assessment and monitoring of cognitive symptoms during management of MDD.

Other putative clinical dimensions include sleep/circadian rhythms and physical symptoms. Insomnia and hypersomnia can be symptoms of acute MDD, residual symptoms of poor response, or side effects of treatments such as antidepressants. Disruption of social and biological rhythms can also interfere with sleep. There is a bidirectional relationship between sleep problems and depression (i.e., sleep disturbances can be an independent risk factor for onset of an MDE).[22] Similarly, somatic symptoms (e.g., painful physical symptoms, fatigue) are commonly associated with depressive episodes and are not well represented in the core MDD criteria.[23,24] The presence and severity of somatic symptoms, especially pain, is associated with poor outcomes in depression.[25]

1.3. How Common Are Depressive Disorders?

In Canada, the annual prevalence of MDE in the general population is 4.7%, indicating that over 1.5 million Canadians aged 15+ years experienced a current MDE in the past year, and lifetime prevalence is 11.3%.[26] Excluding bipolar disorders, the annual and lifetime prevalence of MDD was 3.9% and 9.9%, respectively.[26] These rates are intermediary between those in the United States and Asia and similar to those in Europe (Figure 1). Women have a greater annual prevalence of MDD (4.9%) than men (2.8%), and the prevalence has an inverse relationship with age.[26]

The incidence or the risk of developing a depressive disorder can only be estimated from longitudinal studies. There are few large population-based longitudinal studies based on the *DSM-IV* criteria. The Canadian estimates of incidence proportions of MDE were 2.9% in 2 years and 5.7% in 4 years,[27] similar to the 3-year incidence in the Netherlands (4.6%)[28] and in the United States (3.3%).[29]

Population-based surveys have shown consistently that about 50% of depressive episodes are brief, with resolution within 3 months. Figure 2 shows Canadian descriptive epidemiology for depressive episodes. Despite increases in mental health service in recent years, there have been no changes in the annual prevalence of MDE in Canada (4.8% in 2002 vs. 4.7% in 2012).[26] Similar trends are seen in the United States[30] and in Australia.[31]

1.4. What Is the Risk of Relapse or Recurrence?

Depressive disorders often have a chronic and episodic course. In a large American cohort of participants with

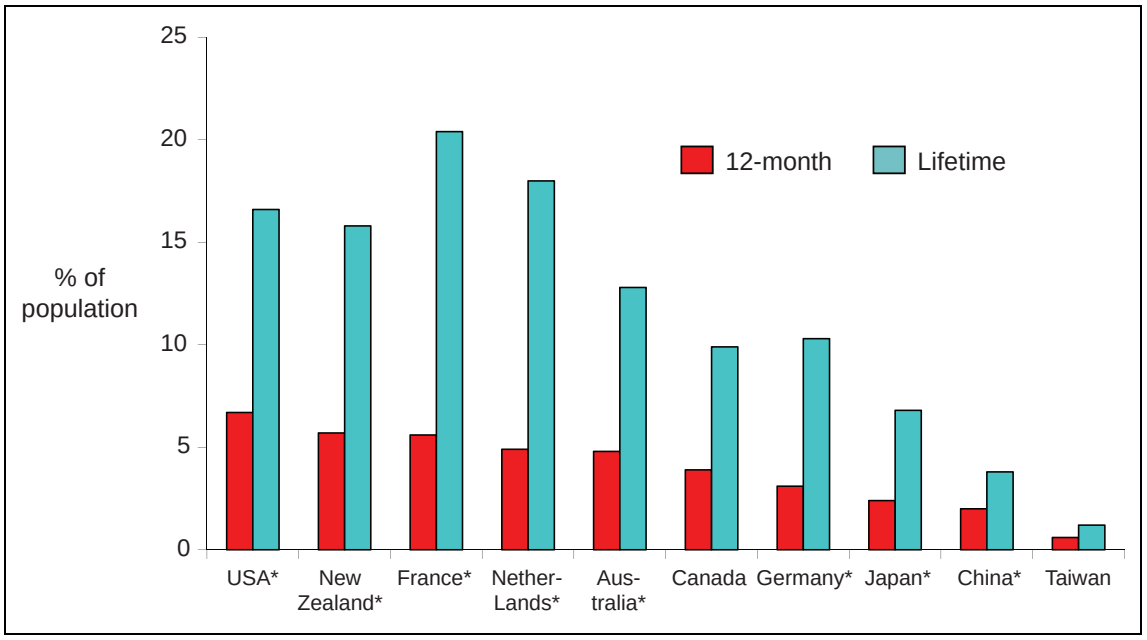

Figure 1. Prevalence of major depressive disorder by world region. *WMH, World Health Organization's World Mental Health Surveys, Canada, CCHS[113]; Taiwan Psychiatric Morbidity Survey.[114]

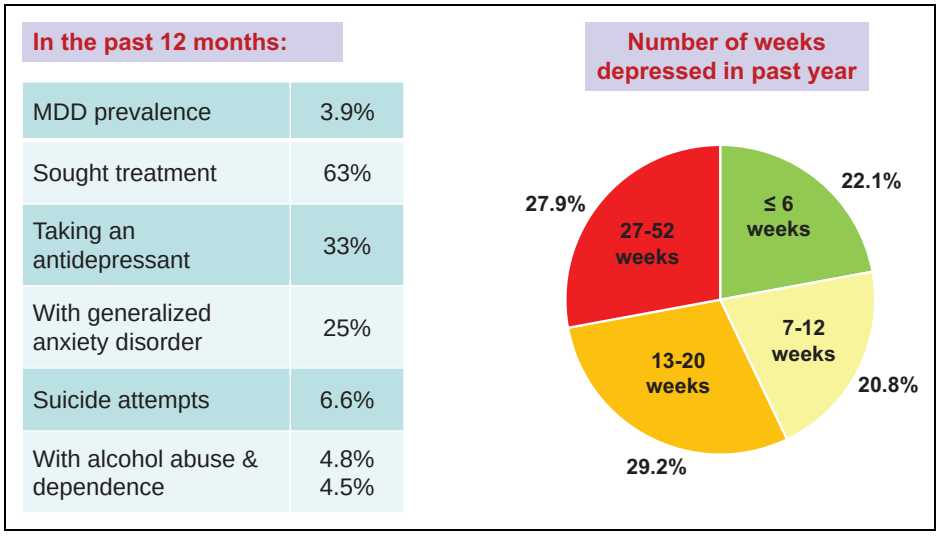

Figure 2. Descriptive epidemiology of depression in Canada, 2012.[26] MDD, major depressive disorder.

an MDE, 26.5% were experiencing a chronic episode of ≥2 years' duration.[32] Over the 3-year follow-up, 15.1% had a chronic course for the entire period.[33] *DSM-5* defines recurrence as a new MDE following a full-episode remission (i.e., 2 months with no significant symptoms).[4] In the US general population, of those with MDE at baseline and subsequent episode remission, 34.7% experienced a recurrent MDE in the next 3 years.[34] In the Netherlands, a 2-year follow-up of 375 patients with MDD in remission for 3 months found recurrence in 26.8% of patients treated in primary care and 33.5% in specialized mental health care.[35]

1.5. What Is the Disease Burden Associated with MDD?

Disease burden can be measured by metrics, such as disability-adjusted life years (DALYs) or health-adjusted life years (HALYs), that account for both early mortality and loss of functioning. The Global Burden of Disease Study 2010 found that depressive disorders represented the second leading cause of disability worldwide, and MDD was responsible for 2.5% of global DALYs.[36] In Ontario, the largest province in Canada, the disease burden in HALYs with MDD was greater than the combined burden of breast,

colorectal, lung, and prostate cancers.[37] MDD also is associated with serious impairment in quality of life[38] and has major economic impact owing to occupational costs, medical service costs, and suicide-related costs. In Canada, the economic burden of mental illness in 2003 was estimated at C$51 billion[39]; although there are no Canadian data for MDD specifically, in the United States, the economic cost of MDD in 2010 was estimated at US$210.5 billion.[40]

1.6. What Is the Occupational Impact of MDD?

MDD is associated with major productivity losses as a result of absenteeism (time away from work) as well as presenteeism (illness-related productivity loss while at work). The World Health Organization (WHO) Mental Health Surveys found that depression accounted for over 5% of the population illness-related productivity loss; participants with depression had a yearly mean of 34.4 "days out of role," which was largely invariant by country.[41] In Canada, workers with MDD, compared to those without depression, were twice as likely to leave work during a 10-year follow-up.[42]

Increased severity of illness,[43] concurrent medical conditions,[44] and comorbid anxiety disorders[45] result in a higher degree of work disability and greater absenteeism in people with MDD. In addition to overall severity, individual symptoms of MDD can differentially affect workplace performance. Work impairment is most closely associated with impaired concentration and depressed mood, followed by fatigue and insomnia.[46] Cognitive dysfunction is also more strongly associated with loss of workplace productivity than ratings of depression severity.[19] Depression treatment has a significant positive effect on work productivity.[47] Unfortunately, a substantial proportion of depressed workers do not receive evidence-based treatment.[48]

1.7. What Is the Impact of MDD on Other Domains?

Social factors (e.g., relationships and social activities) have a complex interrelationship with depressive disorders, including a substantial role in the causation of MDD.[49] It is therefore unsurprising to observe strong associations between MDD and social impairment, especially in social and close-relation domains.[50] Depressed mood, loss of interests, impaired concentration, and self-blame are the symptoms most associated with social impairment.[46]

Depression in parents may also affect the health of their children. Perinatal maternal depression is associated with multiple adverse outcomes in children, including increased problems with emotional regulation, internalizing disorders, behavioural disorders, hyperactivity, reduced social competence, insecure attachment, adolescent depression, and negative effects on cognitive development.[51] Adverse effects in offspring are also observed in the case of paternal depression.[52,53] Effective treatment and remission of maternal depression is associated with improved parenting and a reduction in psychiatric symptoms in the offspring.[54-56]

Table 5. Risk Factors for Depression Screening (Level 3 and 4 Evidence).

Clinical Factors	Symptom Factors
• History of depression • Family history of depression • Psychosocial adversity • High users of the medical system • Chronic medical conditions (especially cardiovascular disease, diabetes, and neurological disorders) • Other psychiatric conditions • Times of hormonal challenge (e.g., peripartum)	• Unexplained physical symptoms • Chronic pain • Fatigue • Insomnia • Anxiety • Substance abuse

1.8. What Is the Impact of MDD on Physical Health?

MDD is associated with many chronic medical conditions, including heart disease, arthritis, asthma, back pain, chronic pulmonary disease, hypertension, and migraine.[57] Depression is an independent risk factor for ischemic heart disease and cardiovascular mortality,[58,59] and vascular risk factors are also associated with onset of depression in later life.[60] The presence of depression substantially increases the level of disability[61] and reduces quality of life[62-64] in individuals with chronic medical illness.

MDD can affect medical conditions via multiple mechanisms. Depression reduces adherence to treatment[65,66] and interferes with participation in preventive health care.[67,68] Depression is also associated with important risk factors for physical illness, including sedentary lifestyle,[69] obesity,[70] and cigarette smoking.[71] The pathophysiology of depression appears to be related to other fundamental mechanisms of disease (e.g., MDD shares a complex and bidirectional relationship with obesity and associated metabolic problems[70,72]) and is associated with immune-inflammatory dysfunctions that are implicated in reduced neural plasticity and neuroprogression.[73-75]

1.9. How Does MDD Typically Present in Clinical Practice?

Depressive disorders have a broad range of presentations in clinical practice, especially in primary care settings. Emotional symptoms are often attributed to stressful work, relationship stress, or life stress, and presenting complaints are often physical symptoms because of the high degree of comorbidity with other medical conditions. Hence, MDD often goes unrecognized and untreated, even in clinical settings.

Screening for depression has been recommended by some agencies[76,77] and not by others.[78] The value of screening remains controversial because of the limited evidence base on effectiveness,[79] although screening is more effective when additional supports (e.g., treatment protocols, care management) are available.[80] CANMAT recommends that screening be done in primary and secondary care settings in individuals

Table 6. Principles of Clinical Management (Level 4 Evidence, Unless Indicated).

- Conduct a thorough biopsychosocial assessment, using clinical scales.
- Obtain collateral information whenever possible.
- Formulate a diagnosis and differential diagnosis.
- Establish a therapeutic alliance.
- Support education and self-management (Level 2 Evidence).
- Engage the patient as a partner to determine treatment goals.
- Construct a comprehensive management plan, including safety, together with the patient and his or her family (or other supports) if possible.
- Deliver evidence-based treatments.
- Monitor outcomes with measurement-based care (Level 2 Evidence).

with risk factors (summarized in Table 5) when there are available resources and services for subsequent diagnostic assessment and management. The quick 2-question screen ("In the last month, have you been bothered by little interest or pleasure in doing things?" and "In the last month, have you been feeling down, depressed or hopeless?") remains an effective and simple approach for screening in clinical practice.[81] An answer of "yes" to either question requires a more detailed assessment.

1.10. What Are the Basic Principles of Clinical Management?

Table 6 summarizes the principles of clinical management of MDD. A comprehensive assessment and management plan, including attention to safety, is the foundation of quality care. A thorough psychiatric assessment should include a comprehensive symptom inquiry, including an evaluation for bipolar disorder, anxiety disorders, and substance use disorders, as these are frequently comorbid with depression. Collateral information should be gathered whenever possible.

Stepped care[82] and chronic disease management models[83] are associated with significant improvements in depression outcomes compared to usual care. These models are consistent with the CANMAT delineation of recommended lines of treatment (see other sections). Common elements of these approaches are applicable to other treatment settings and include systematic monitoring of patient outcomes, patient education,[84] and treatment decisions that are evidence-based and responsive to therapeutic goals.

Poor treatment adherence and high discontinuation rates represent a major challenge, particularly for pharmacotherapy. Strategies for enhancing adherence include patient education and supported self-management, as well as use of collaborative care systems by practitioners. Treatment adherence should be discussed at an early stage and monitored frequently during treatment in a collaborative manner. A weak therapeutic alliance predicts poorer treatment adherence.[85]

Self-management refers to the individual's ability to manage depression and associated treatments, physical and psychosocial sequelae, and lifestyle modifications. Supported self-management typically includes action planning to change behaviour. Techniques include behavioural activation, communication skills, coping with emotion, patient education, healthy lifestyle, relapse-prevention planning, skill development, and self-monitoring.[86] In addition to decreasing patients' reliance on health care providers, effective self-management also serves to increase empowerment and self-efficacy.[86] Peer-support service delivery models are seeing broad uptake and may offer promise, but further research is required to fully evaluate effectiveness.[87]

Table 7. Risk Factors for Suicide During a Major Depressive Episode (Level 3 Evidence).

Nonmodifiable Risk Factors	Modifiable Risk Factors
• Older men • Past suicide attempt • History of self-harm behaviour • Being a sexual minority • Family history of suicide • History of legal problems	Symptoms and life events • Active suicidal ideation • Hopelessness • Psychotic symptoms • Anxiety • Impulsivity • Stressful life events such as financial stress (e.g., bankruptcy) and victimization Comorbid conditions • Substance use disorders (especially alcohol use disorder) • Posttraumatic stress disorder • Comorbid personality disorders (especially cluster B personality disorders) • Chronic painful medical conditions (e.g., migraine headaches, arthritis) • Cancer

1.11. How Do You Assess Suicidal Risk?

Suicidal ideation, plans, and attempts are highly prevalent among people with MDD.[88,89] Every clinical encounter with a patient with MDD should include an assessment of suicide risk. Table 7 shows the modifiable and nonmodifiable risk factors for suicide; history of suicide attempt is the strongest risk factor. The low base rate of suicide makes it difficult to predict suicide risk at an individual level.[90] Suicide risk assessment tools are available (e.g., SADPERSONS,[91,92] Columbia Suicide Severity Rating Scale,[93,94] Chronological Assessment of Suicide Risk interview guide[95]) and, while not particularly reliable in predicting future suicide attempts, can aid systematic assessment and documentation in clinical practice.

1.12. What Is Measurement-Based Care?

Measurement-based care refers to the systematic use of measurement tools, such as validated rating scales, to monitor

Table 8. Examples of Validated Outcome Scales.

Outcome	Clinician-Rated	Patient-Rated
Symptoms	• Hamilton Depression Rating Scale (HAM-D, HAM-7) • Montgomery-Asberg Depression Rating Scale (MADRS) • Inventory for Depressive Symptomatology (IDS)	• Patient Health Questionnaire (PHQ-9) • Quick Inventory for Depressive Symptomatology, Self-Rated (QIDS-SR) • Clinically Useful Depression Outcome Scale (CUDOS)
Functioning	• Multidimensional Scale of Independent Functioning (MSIF) • WHO Disability Assessment Scale (WHO-DAS) • Social and Occupational Functioning Assessment Scale (SOFAS)	• Sheehan Disability Scale (SDS) • WHO-DAS, self-rated • Lam Employment Absence and Productivity Scale (LEAPS)
Side effects	• UKU Side Effect Rating Scale	• Frequency, Intensity and Burden of Side Effects Rating (FIBSER)
Quality of life	• Quality of Life Interview (QOLI)	• Quality of Life, Enjoyment and Satisfaction Questionnaire (QLESQ) • EuroQoL-5D (EQ-5D)

Note: See online supplement for references to scales.

outcomes and support clinical decision-making. Using simple rating scales for measurement-based care of depression can improve outcomes such as symptom remission and adherence.[96,97]

Table 8 shows some clinically useful examples of the many available patient-rated and clinician-rated scales. Symptom scales can be useful tools for screening, diagnosis, and monitoring outcomes. For example, the important distinction between symptom response (usually defined as 50% or greater reduction in baseline score) and remission (a score in the nondepressed range) can be reliably determined using symptom scales.

Routine monitoring of patient outcomes must go beyond assessing the symptoms of depression and include the ongoing evaluation of functional impairment[98] and quality of life.[99] These outcomes are more important and relevant to patients, and each may vary independently of symptoms. Assessing functionality should include the evaluation of appropriate domains, such as occupational, social, or educational functioning.[100] Quality-of-life assessments, in comparison, offer the opportunity to evaluate patient well-being and overall health satisfaction more broadly.[99]

Measurement-based care can be incorporated into busy clinical settings using patient-rated questionnaires, which are highly correlated with clinician-rated scales but simpler to use and more efficient. Outcome scales are often used in conjunction with clinical algorithms, such as for decisions about medication adjustment.[101] The use of measurement tools should supplement and not replace clinician judgement.

1.13. What Are the Phases of Treatment?

The previous CANMAT guidelines proposed a 2-phase model (acute and maintenance phases)[102] for treatment, in contrast to the traditional 3-phase model (acute, continuation, and maintenance).[103] The distinction between continuation and maintenance phases was based on a theoretical difference between relapse (symptoms recurring before resolution of the current episode) and recurrence (symptoms that constitute a new episode, after recovery from the previous episode).[103] Recent reviews have highlighted the inconsistent use of these terms and lack of evidence to support distinct demarcations between episodes[104]; hence, CANMAT continues to endorse a single concept of relapse/recurrence and the 2 treatment phases (Table 9).

1.14. What Are the Goals of Acute and Maintenance Treatment?

The acute and maintenance treatment phases can be summarized with 2 clinical questions: "How do you get people with depression well?" and "How do you keep them well?" The primary target goals for acute treatment include symptom remission, which implies that signs and symptoms of depression are absent or almost so, and restoration of premorbid psychosocial functioning (Table 9). Full symptom remission is important because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcome.[105,106]

For the maintenance phase, a key goal is prevention of recurrence (Table 9). Clinicians should focus on healthy life strategies, personality vulnerabilities, long-term self-management, and clinical strategies to reduce recurrence.[104,107] In a significant proportion of patients with MDD, maintenance pharmacological, psychological, complementary and alternative medicine, and neurostimulation treatments have a role in the prevention of recurrence (see other sections).

Table 9. Phases of Treatments and Activities.

Treatment Phase	Duration	Goals	Activities
Acute	8 to 12 weeks	• Remission of symptoms • Restoration of functioning	• Establish therapeutic alliance • Educate and support self-management • Select and deliver evidence-based treatment(s) • Monitor progress
Maintenance	6 to 24 months, or longer	• Return to full functioning and quality of life • Prevention of recurrence	• Educate and support self-management • Rehabilitate • Treat comorbidities • Monitor for recurrence

Table 10. Risk Factors for Chronic or Recurrent Episodes (Level 3 Evidence).

- Earlier age of onset
- Greater number of previous episodes
- Severity of the initial episode (defined by the presence of a greater number of symptoms, suicidal ideation, or psychomotor agitation)
- Disruptions of the sleep-wake cycle
- Presence of comorbid psychopathology (particularly persistent depressive disorder/dysthymia)
- Family history of psychiatric illness
- Presence of negative cognitions
- High neuroticism
- Poor social support
- Stressful life events

Table 11. Examples of e-Mental Health Resources for Depression.

Purpose	e-Mental Health Application	Website
Information	Canadian Mental Health Association (CMHA)	www.cmha.ca/mental-health/understanding-mental-illness/depression/
	Mental Health Works; CMHA resources focusing on workplace mental health	www.mentalhealthworks.ca
	Mood Disorders Society of Canada (MDSC)	www.mooddisorderscanada.ca
	Here To Help; self-help information in many languages	www.heretohelp.bc.ca
Screening, assessment and monitoring	MoodFx; online tracking of symptoms (depression, anxiety, cognition) and functioning	www.moodfx.ca
	What's My M3; online and mobile app for mood tracking	www.whatsmym3.com
Self-management	MoodGym; evidence-based, interactive online self-help program for depression	https://moodgym.anu.edu.au
	eCouch; similar to MoodGym with self-help for depression and other diagnoses	https://ecouch.anu.edu.au
Social support	7 Cups of Tea; access to confidential online text chat to trained listeners	www.7cups.com
	BlueBoard; online anonymous community for people with depression and anxiety	https://blueboard.anu.edu.au
	Depression Support Group; online support groups	http://depression.supportgroups.com

Note: This is not a comprehensive list but includes examples that are evidence-based and/or from credible sources.

1.15. Who Needs Longer Term Treatment?

Following successful acute phase treatment (i.e., syndromal remission), clinicians must determine which patients require longer term (maintenance) treatment and for how long. The heterogeneity of MDD results in a varied longitudinal course, but half of patients will have a chronic or recurrent course of depression. Table 10 shows the risk factors for recurrence.[104,108]

Risk-prediction support tools have been developed to estimate risk of recurrence based on individuals' unique exposure to a key set of risk factors.[109] While risk-prediction

models may assist clinicians in stratifying baseline risks and making informed decisions about individualized maintenance treatments with patients, they require further validation in different clinical settings and do not replace clinical judgement.

1.16. Can e-Mental Health Help in Management of MDD?

Technology and the Internet have dramatically changed medicine. According to Statistics Canada, 83% of Canadians had Internet access in 2012, and more than 70% use the Internet daily; 62% were smartphone users.[110] e-Mental health refers to the use of computers, Internet, and mobile devices for mental health information and care.[111] e-Mental health applications are now widely available for information, screening, assessment and monitoring, interactive self-management and psychotherapy (see Psychological Treatments section), and social support. Clinicians should be aware that there are benefits and potential harms to using and recommending e-Mental health applications and that few have good-quality evidence to support effectiveness.[111,112] Table 11 lists some examples of e-Mental health resources that are evidence-based and/or come from credible sources.

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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 2. Psychological Treatments

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Abstract

Background: The Canadian Network for Mood and Anxiety Treatments (CANMAT) has revised its 2009 guidelines for the management of major depressive disorder (MDD) in adults by updating the evidence and recommendations. The target audiences for these 2016 guidelines are 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. "Psychological Treatments" is the second of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 25 questions under 5 broad categories: 1) patient characteristics relevant to using psychological interventions; 2) therapist and health system characteristics associated with optimizing outcomes; 3) descriptions of major psychotherapies and their efficacy; 4) additional psychological interventions, such as peer interventions and computer- and technology-delivered interventions; and 5) combining and/or sequencing psychological and pharmacological interventions.

Conclusions: First-line psychological treatment recommendations for acute MDD include cognitive-behavioural therapy (CBT), interpersonal therapy (IPT), and behavioural activation (BA). Second-line recommendations include computer-based and telephone-delivered psychotherapy. Where feasible, combining psychological treatment (CBT or IPT) with antidepressant treatment is recommended because combined treatment is superior to either treatment alone. First-line psychological treatments for maintenance include CBT and mindfulness-based cognitive therapy (MBCT). Patient preference, in combination

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with evidence-based treatments and clinician/system capacity, will yield the optimal treatment strategies for improving individual outcomes in MDD.

Keywords
major depressive disorder, clinical practice guidelines, evidence-based medicine, meta-analysis, systematic reviews, psychotherapy, biopsychosocial, cognitive-behavioural therapy, interpersonal therapy, mindfulness-based interventions

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). CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2] This section on Psychological Treatments is 1 of 6 CANMAT guidelines articles; other sections of the guidelines expand on burden and principles of care, pharmacological treatments, neurostimulation treatments, complementary and alternative medicine treatments, and special populations.

We use the term *psychological treatment* rather than *psychotherapy* as a broader term that involves treatment of psychiatric and behavioural disorders through a method of communicating that invokes a psychological model of illness. This method of communication begins with a patient who seeks alleviation of current symptoms or prevention of recurrence of symptoms. With the advent of computer, Internet, self-help, phone, and mobile apps, the relationship is now between the patient and the psychological model, with an implicit link to the ''therapist'' who designed the therapy. This guideline summarizes depression-specific psychotherapies as well as newer therapies that are promising and seeks to clarify the evidence and usefulness of each major treatment.

Psychological treatments for MDD share many common components: 1) the goal of treatment is alleviation of the core symptoms of depression; 2) there is careful attention to a specific method to deliver the therapy (typically a manual); 3) the psychotherapy focuses on the current problems of the patient; 4) high levels of activity are expected from both the therapist and the patient (who frequently has ''homework''); 5) careful symptom monitoring, preferably with rating scales, is expected; 6) psychoeducation about the illness is a frequent component; and 7) the treatment is generally time-limited, often paralleling the time course for pharmacotherapy.

Furthermore, many of these therapies have been modified to be delivered in a group format. While a group approach may allow for integration of new techniques involving peer feedback and may be more cost-effective, the core of the psychotherapy remains unchanged, so group interventions are not evaluated in these guidelines as a separate ''group therapy.'' Similarly, context-specific therapies (such as marital therapy for MDD coinciding with a severe marital dispute) are not evaluated, since such therapies do not generalize to the average person with depression. Indications for a specific therapy, as well as the choice of either psychological treatment or pharmacotherapy alone or in combination, are reviewed in a number of the following questions, along with discussion of self-help approaches and peer support. The recommendations are presented as guidance for clinicians who should consider them in the context of individual patients and not as standards of care.

Methods

The full methods have been previously described,[3] but in summary, relevant studies in English 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 psychological treatments 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, and various types of bias.[4] One additional limitation of both RCTs and subsequent meta-analyses needs to be highlighted: recruitment of individuals in standard MDD RCTs often excludes people with current suicidality, substance use, and other comorbidities.[5] This limits the generalizability of these studies. We have included separate sections on depression with various comorbidities to specifically highlight findings in those clinical conditions.

2.1. When Is Psychological Treatment Indicated?

In addition to patients' attitudes and preferences, a clinician must consider the availability of high-quality evidence-based psychological treatment and the risk from delay in treatment initiation. In more severe and high-risk cases, it is imperative to start a treatment that is immediately

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.

available and to consider all treatment modalities, including neurostimulation. In moderately severe and low-risk cases, the choice of initial treatment between psychological treatment and antidepressants may be determined by the balance of patient preferences and availability of each treatment modality. In addition, special circumstances may need to be taken into account. For example, women who are planning to conceive or are pregnant may be preferentially considered for psychological treatment, because of concerns that use of antidepressants in pregnancy may affect the fetus.[6,7] On the other hand, psychological therapies are not indicated for individuals with psychotic depression, who require pharmacotherapy with antidepressants and antipsychotics[8] or electroconvulsive therapy.

2.2. Which Individuals with Depression Are Most Likely to Benefit from Psychological Treatment?

Demographic factors. Psychological treatments benefit men and women to the same extent; psychological treatments are equally suitable for individuals of all ages, levels of education, and cultural and ethnic backgrounds.[9] Psychological treatments in general and cognitive-behavioural therapy (CBT) in particular appear to be equally effective for different subtypes of depression, including atypical depression, melancholic depression, and anxious depression.[9,10] In addition, a large individual-level meta-analysis confirmed that men and women derive similar benefits from CBT and from antidepressants.[11] In persistent depressive disorder (PDD), medication treatment or combination of medication with psychological treatment provides more benefit than psychological treatment alone.[12,13]

Severity. Early findings that CBT as a treatment for severe depression was less effective than medication[14] were followed by evidence of comparable efficacy for CBT and medication.[15] A subsequent meta-analysis confirmed that severity of depression does not differentially predict outcomes of treatment with antidepressants and CBT.[16] As in the case of antidepressant medication, the magnitude of benefit for psychological treatment appears to increase with increasing severity,[17] although there is evidence that psychological treatments are beneficial even for subthreshold depressive symptoms.[18] However, since the time course of improvement is typically faster with pharmacological than psychological treatment,[19] pharmacotherapy may still be preferred as the initial treatment in severe and high-risk cases.

2.3. How Do Co-occurring Psychiatric and Medical Conditions Affect the Efficacy of Psychological Treatments?

Psychiatric comorbidities. This question was addressed by a CANMAT task force in 2012[20] with individual studies on anxiety disorders,[21] attention-deficit/hyperactivity disorder (ADHD),[22] substance use disorders,[23] and personality disorders.[24] There is insufficient evidence to define formal treatment recommendations, so instead only evidence is summarized.

In summary, Level 2 Evidence supports a negative prognostic impact of comorbid personality disorder on treatment outcomes, including psychological treatments, in depression (Table 2). Insufficient evidence is available to support a positive or negative effect of anxiety symptoms or disorders on depression outcomes, but CBT may be more effective than other treatments. CBT is also effective for depressive symptoms in substance use disorders, and Level 2 Evidence supports integrated psychosocial treatment of alcohol misuse and depression. For ADHD, CBT can improve both depressive and ADHD symptoms.

Medical comorbidities. The CANMAT task force also addressed the management of mood disorders and comorbid medical conditions.[20,25,26] There is insufficient evidence to define formal treatment recommendations, so instead only evidence is summarized.

Several key limitations exist in summarizing this literature: 1) the comorbid medical disorders themselves represent a variety of illnesses grouped according to organ system

Table 2. Impact of Comorbid Psychiatric Disorders on Psychological Treatments in Major Depressive Disorder.

Comorbid Disorder	Summary Findings	Level of Evidence
Anxiety	Anxiety may not complicate or reduce responses to psychological treatments.	Conflicting/ insufficient evidence
	CBT more beneficial than other psychological treatments.	Level 2
Substance abuse	CBT improves both depression and substance abuse symptoms.	Level 2
	Integrated treatment is effective but with small effect size.	Level 2
Personality	Personality disorders have negative impact on depression outcomes.	Level 2
ADHD	CBT for ADHD helps both disorders, as adjunct to medications.	Level 2

ADHD, attention-deficit/hyperactivity disorder; CBT, cognitive-behavioural therapy.

(e.g., cancer includes a variety of diseases), 2) the medical disorders themselves include patients at varying stages or severity of medical illness, and 3) most studies measure improvement in depressive symptoms as opposed to only improvement of those with a full diagnosis of MDD.

In summary, there is Level 2 Evidence for treatment of depression with co-occurring cardiovascular disease for CBT, interpersonal therapy (IPT), and problem-solving therapy (PST).[25,27-29] Level 2 Evidence also exists for a variety of psychological treatments in cancer patients, but these are studied by cancer type and stage as noted in Table 3.[25,30] In the presence of human immunodeficiency virus (HIV), Level 1 Evidence supports a variety of psychological treatments, particularly CBT[31] and, importantly, improved adherence to medical interventions as well as improvement in depression.[32] For a variety of neurological disorders, psychological treatments (almost always CBT) have been tested for comorbid depression or depressive symptoms, with Level 2 Evidence of efficacy for multiple sclerosis and Parkinson's disease, and Level 3 Evidence for epilepsy and migraines.[25,33,34] Finally, for the strikingly high rates of depression accompanying hepatitis C, only Level 3 Evidence exists for psychological treatments, based primarily on expert recommendations with a single trial using both CBT and IPT approaches.[25,35]

2.4. How Do Gender and Age Influence the Decision to Use Psychological Treatment?

More women than men prefer psychological treatment over medication treatment.[36] Considerations for women during childbearing years include exposure of the fetus during gestation or neonate during lactation. The scope of evidence for psychological treatment is broader for postpartum rather than during pregnancy, with Level 1 Evidence to support psychological treatment as first-line for perinatal women with mild to moderate depressive illness.[37-40] Moreover,

Table 3. Impact of Comorbid Medical Disorders on Psychological Treatments in Major Depressive Disorder.

Comorbid Disorder	Summary Findings	Level of Evidence
Cancer	Evidence varies by type of psychological intervention and phase of cancer treatment, but multiple small positive RCTs[24]	Level 2
Cardiovascular disease	Effectiveness shown with CBT, IPT, and PST, alone or with antidepressants	Level 2
Multiple sclerosis	Various psychological treatments studied, primarily CBT; all beneficial	Level 2
HIV	CBT effective, most delivered in group format; IPT effective but with limited studies	Level 1 for CBT Level 2 for IPT
Epilepsy	Limited research, using CBT primarily, with moderate benefit for depressive symptoms	Level 3
Migraines	Various psychological treatments have moderate benefit for depressive symptoms	Level 3
Parkinson's disease	CBT effective for reducing depressive symptoms	Level 2
Hepatitis C	Psychological treatments may be useful	Level 3

CBT, cognitive-behavioural therapy; HIV, human immunodeficiency virus; IPT, interpersonal therapy; PST, problem-solving therapy; RCT, randomized-controlled trial.

many pregnant women prefer psychological treatment and report fear of potential adverse effects of antidepressants on the developing fetus or on their newborn via lactation, general worries about a negative outcome, and fears of dependency as well as balancing concerns about their own health or the fetus.[41,42] Treatment for adolescents is addressed elsewhere; for further advice, see the American Academy of Child and Adolescent Psychiatry.[43] Similarly, psychological treatments may have increased relevance in the elderly, since older patients with depression are more vulnerable to medication side effects and drug interactions, as many may already be taking multiple medications for comorbid medical disorders. Treatment of depression in youth/adolescents, women, and those in late life is reviewed in Section 6.[44]

2.5. What Are the Key Therapist Factors That Improve Clinical Outcomes?

Recommendations from the American Psychological Association Task Force on psychotherapy relationships[45] concluded that the best outcomes are likely to come from the concurrent use of evidence-based *therapy relationships*, not just evidence-based *treatments*. These conclusions were described as "demonstrably effective," "probably effective," and "promising, but insufficiently researched" (Table 4).[46,47] These recommendations are based on literature reviews and process

Table 4. Evidence-based Therapy Relationships: Therapist Factors That Improve Clinical Outcomes.[45,47,48,50,162-167]

	Elements of a Therapeutic Relationship
Demonstrably effective	• *Alliance* in individual psychotherapy—a collaborative stance predicated on agreement on goals, with consensus on the therapeutic tasks, and an emotional bond • *Empathy*—understanding with communicative attunement • *Collecting patient feedback*—monitoring treatment response with standardized scales
Probably effective	• *Goal consensus*—congruent understanding, agreement, and commitment to goals • *Collaboration*—mutual cooperative involvement of patient and therapist • *Positive regard*—in which patient feels respected and appreciated
Promising but insufficient research to judge	• *Congruence/genuineness*—therapist awareness and authentic use of his or her internal in-session experiences with the patient • *Repairing alliance ruptures*—recognizing and resolving tensions or impasses in the therapeutic alliance to restore collaboration, understanding, or communication • *Managing countertransference*—therapist awareness and self-management of strong feelings precipitated by the patient's manner of relating and/or the therapist's unresolved conflicts

Adapted with permission from Norcross (2011).

research using secondary analyses, rather than experimental trials of the specific principles; thus, they are supported by Level 3 Evidence and are recommended as a first-line treatment practice. Three evidence-based common factors found to predict positive outcomes are establishing a strong therapeutic alliance, using empathy, and collecting client feedback (Table 4).[46-49] Therapist characteristics that promote a therapeutic alliance include being genuinely respectful and interested in the well-being and safety of the patient, with empathy for subjective experience.[50] The collecting of patient feedback helps to track symptoms, experience of treatment, and functioning using validated scales (e.g., the Patient Health Questionnaire–9 [PHQ-9][51]) such that changes can be made if patients are not improving.

Additionally, therapist supervision and feedback can improve patient outcomes,[52,53] although the research was not exclusively focused on patients with depression. Therapist experience, adherence, and ability to be responsive to individual patient differences are associated with better outcomes.[54,55] Most importantly, the evidence for psychological therapies for depression is based on studies with highly competent therapists, hence the second-line recommendation (Level 3 Evidence) that psychological therapies for depression should be delivered by trained and proficient therapists, although even less-trained therapists can have efficacy in treating depression and indeed may be the only source of treatment.[56]

2.6. How Do You Choose a Psychological Treatment for MDD?

Choosing a specific type of psychological treatment should consider treatment efficacy, quality, and availability, as well as patient preference. Comparisons of different psychological treatments are fewer in number and quality, as well as complicated by methodological challenges, including lack of blinding and the effects of allegiance to a particular model.

Table 5 lists recommendations for acute and maintenance psychological treatments (respectively) for depression, with the evidence level conveying the efficacy in comparison to control conditions, not to alternative psychological treatments. When choosing psychological treatment for a patient with depression, we recommend preferentially selecting from first-line treatments. Second-line treatments should be used if first-line treatments have failed or are unavailable. Third-line treatments should be reserved for use in specialist centres where first- and second-line treatments are also available. All high-quality evidence in psychotherapy research is based on studies where extensively trained therapists receive regular supervision and adhere to principles of the given therapeutic model with high fidelity. Therefore, the evidence-based recommendations do not extend to psychological treatments that eclectically use elements of different models.

2.7. How Do Psychological Treatments for MDD Compare in Efficacy?

Some meta-analytic comparisons between specific models of psychological treatment have shown no significant differences in efficacy,[57] with others showing modest differences.[58] When only bona-fide therapies (defined as delivered by trained therapists, based on psychological principles, and designed to be a viable treatment) were considered, there were no differences between CBT and IPT, but CBT was more effective than other psychotherapies considered as a group[59]; using a different definition of bona-fide therapy, supportive therapy was less effective than other types of therapy, with no differences between CBT, IPT, and psychodynamic psychotherapy (PDT).[60] Short-term psychodynamic psychotherapy (STPP) compared to other types of

Table 5. Recommendations for Psychological Treatments for Acute and Maintenance Treatment of Major Depressive Disorder.

	Acute Treatment	Maintenance Treatment (Relapse Prevention)
Cognitive-behavioural therapy (CBT)	First line (Level 1)	First line (Level 1)
Interpersonal therapy (IPT)	First line (Level 1)	Second line (Level 2)
Behavioural activation (BA)	First line (Level 1)	Second line (Level 2)
Mindfulness-based cognitive therapy (MBCT)	Second line (Level 2)	First line (Level 1)
Cognitive-behavioural analysis system of psychotherapy (CBASP)	Second line (Level 2)	Second line (Level 2)
Problem-solving therapy (PST)	Second line (Level 2)	Insufficient evidence
Short-term psychodynamic psychotherapy (STPP)	Second line (Level 2)	Insufficient evidence
Telephone-delivered CBT and IPT	Second line (Level 2)	Insufficient evidence
Internet- and computer-assisted therapy	Second line (Level 2)	Insufficient evidence
Long-term psychodynamic psychotherapy (PDT)	Third line (Level 3)	Third line (Level 3)
Acceptance and commitment therapy (ACT)	Third line (Level 3)	Insufficient evidence
Videoconferenced psychotherapy	Third line (Level 3)	Insufficient evidence
Motivational interviewing (MI)	Third line (Level 4)	Insufficient evidence

psychotherapies resulted in slightly worse outcomes on some measures of depression at the end of treatment.[61]

Individual psychological treatments are discussed in more detail in the following, but in summary, CBT remains the most established evidence-based, first-line treatment for depression, both acute and maintenance. With more than 40 original reports and meta-analyses published on CBT for MDD or PDD since 2009, there is substantial evidence of efficacy even in severely affected individuals and in those who had not responded to treatment with antidepressants.[62,63] Similarly, there is evidence across populations (adult, adolescents, perinatal women) to support IPT as an alternative strong first-line treatment for acute MDD and second-line as a maintenance treatment.[64-66] Mindfulness-based cognitive therapy (MBCT) has new evidence to qualify as a second-line acute treatment. With several meta-analyses demonstrating efficacy[67,68] and a large, high-quality RCT ($N = 424$)[69] demonstrating equal efficacy of MBCT to medication as maintenance treatment for recurrent MDD, MBCT has emerged as a first-line maintenance treatment adjunctive to medication.

While there are new studies using Internet- or smartphone-delivered treatment, a single additional face-to-face study together with a new meta-analysis including many older, small studies elevate behavioural activation (BA) to first-line treatment.[70,71] The evidence base for STPP has expanded with recent studies, including comparisons with CBT[72] and antidepressant medication[73] and a recently updated meta-analysis.[61] A key limitation of the STPP literature is the conflation of different models of psychodynamic therapy (PDT) into the broad term *STPP*, whereby no single model has a replicated large RCT with positive findings for MDD, unlike CBT and IPT. Consequently, STPP is recommended as a second-line therapy with Level 2 Evidence. While long-term PDT is not within the scope defined earlier of an acute treatment for depression, there is limited evidence of efficacy for acute MDD treatment.[74] Thus, the limited evidence base confines general PDT—as separate from specific STPP—as a third-line treatment. While the amount of evidence for the cognitive-behavioural analysis system of psychotherapy (CBASP) has increased, results of the most recent large trial ($N = 491$ in 3 conditions) are inconsistent with previous results and do not support the efficacy of CBASP.[75] Therefore, CBASP remains a second-line treatment for chronic depression. An updated meta-analysis of acceptance and commitment therapy (ACT) concluded that there is insufficient evidence of efficacy[76]; therefore, ACT remains a third-line treatment. The evidence status for other types of psychotherapies has not changed significantly since the 2009 guidelines.

2.8. Does Group or Individual Format for Psychological Treatment Influence Outcome?

Meta-analyses that evaluated efficacy of group psychological therapy for depression concluded that it is more effective than treatment as usual.[77,78] However, group therapy was less effective than individual therapy at the end of treatment and had a higher dropout rate, although no differences were found at follow-up.[77] While efficacy evidence may slightly favour individual therapy, other factors, including availability, cost, and patient preference, are still important factors in choosing between group and individual treatments. Finally, given the gap between needed and available psychological treatments, group psychotherapy could improve access to treatment.

2.9. How Many Sessions of Psychological Treatment Are Required to Be Effective?

Recent research has examined shorter durations for various psychotherapies. Overall, there is Level 1 Evidence that brief interventions can be effective. A number of trials have demonstrated the efficacy of an 8-session CBT intervention.[79,80] A review of 4 small trials of an 8-session brief IPT intervention in depressed women also found efficacy,[81] while 2 other meta-analyses looking at brief (8 or fewer sessions) of CBT, MBCT, and PST noted significant efficacy in symptom reduction.[82,83] Studies comparing 8 versus 16 or more sessions are rare but suggestive of similar effectiveness.[84-86]

In the absence of definitive "dose-finding" trials, insufficient evidence exists to state a minimum dose; it is recommended that after selecting a first- or second-line psychological treatment, the specific treatment manual be followed. In several RCTs,[15,62,86,87] treatment was offered twice weekly for the first 2 to 8 weeks. Furthermore, in a recent analysis of 70 controlled studies ($N = 5403$), which account for natural recovery, there was no association between clinical improvement and the number of psychological treatment sessions or hours; however, a strong positive association was found for increased frequency of psychological treatment sessions per week and increased size of clinical improvement.[12] Thus, more frequent treatment sessions, particularly at the start of therapy, should be considered (Level 3 Evidence).

2.10. What Is Cognitive-Behavioural Therapy (CBT) and Its Efficacy in the Acute and Maintenance Phases of MDD Treatment?

CBT is an intensive, time-limited, symptom-focused psychological treatment built on the premise that depression is maintained by unhelpful behaviours and by inaccurate thoughts and beliefs about oneself, others, and the future. Behavioural interventions are aimed at increasing the patients' participation in activities that promote a sense of pleasure and achievement and thus lift their mood. Patients also assess the impact of various behaviours on their mood. The cognitive techniques help patients evaluate the accuracy of their negative thoughts and beliefs. Practising the new skills outside the therapy room (i.e., homework) is crucial for the effectiveness of therapy.

Since 2009, several meta-analyses have been published[57,88,89] using the same database (www.evidencebasedpsychotherapies.com). The authors found that CBT is as effective as antidepressant medication,[88] and the combination of CBT and an antidepressant is more effective than either alone.[57,88,89] Results of a recent RCT[62] suggested that when both CBT and pharmacotherapy are of high quality, the addition of CBT to pharmacotherapy increases recovery rates. When participant characteristics were taken into account, this effect was limited to participants with severe nonchronic depression. CBT is also effective for people with treatment-resistant depression (i.e., those who did not respond to at least 2 adequate antidepressant trials). An RCT of 469 primary care patients with depression with poor response to medication found CBT improved response and remission,[63] with sustained effects at 3-year follow-up.[89] In summary, CBT has Level 1 Evidence of efficacy and continues to be recommended as a first-line treatment for acute treatment of MDD.

Regarding maintenance treatment, a meta-analysis of 9 RCTs comparing CBT and pharmacotherapy concluded that after 1 year, those who received CBT in the *acute* phase of depressive illness had a lower rate of relapse than those who discontinued medication. There was no difference, however, between the CBT group and those who continued pharmacotherapy at 1-year follow-up.[57] A meta-analysis of 10 trials demonstrated a reduction in the risk of relapse by 21% in the first year and by 28% in the first 2 years.[90] In a subsequent meta-analysis, which included more heterogeneous studies, CBT delivered during remission decreased the likelihood of relapse by 32%. The comparison with pharmacotherapy did not show a significant difference.[91] To prevent depressive relapse/recurrence, CBT versus pharmacotherapy delivered during the acute phase offers better protection. During maintenance phase treatment, CBT and pharmacotherapy provide comparable prevention of relapse. In summary, CBT has Level 1 Evidence and is recommended as a first-line maintenance therapy, whether the CBT is delivered either in the acute or maintenance phase of MDD.

2.11. What Is Mindfulness-Based Cognitive Therapy (MBCT) and Its Efficacy in the Acute and Maintenance Phases of MDD Treatment?

MBCT for MDD was formally developed as an 8-week group treatment designed to teach patients how to disengage from maladaptive cognitive processes through an integration of mindfulness meditation training and cognitive-behavioural techniques.[92] MBCT improves clinical outcomes via changes in mindfulness, rumination, worry, compassion, and meta-awareness, consistent with underlying theory.[93]

MBCT was originally developed to prevent relapse in remitted patients. Clinical trials have supported its therapeutic value as an adjunct to treatment as usual[94,95] and its comparability to maintenance antidepressant medication[69,96] in this context. Of note, evidence has accrued to suggest that MBCT may only be efficacious or advantageous over other forms of aftercare for those patients with greater vulnerability, in the form of recurrent depression,[97,98] unstable remission,[99,100] or a history of childhood trauma[98] (although see also Geschwind et al.[101]).

MBCT has been increasingly applied to treatment of residual depressive symptoms following treatment and more recently to depressive symptoms in the context of a full MDD, particularly in patients who have not responded to an earlier treatment. MBCT has exhibited efficacy as an augmentation to treatment as usual in a heterogeneous sample of both currently and remitted depressed outpatients, albeit with modest effect sizes.[102,103] MBCT has also exhibited superior efficacy to a psychoeducation control treatment[104] and comparable efficacy to group CBT,[105] although a brief follow-up period and small sample size, respectively, were notable in these studies.

In summary, MBCT is recommended as a second-line adjunctive treatment (Level 2 Evidence) for acute depression and as a first-line maintenance treatment (Level 1 Evidence).

2.12. What Is Interpersonal Therapy (IPT) and Its Efficacy in the Acute and Maintenance Phases of MDD Treatment?

IPT focuses on patients' relational stressors involving losses, changes, disagreements, or interpersonal sensitivity, which are associated with the onset or perpetuation of present symptoms. The 4 focal interpersonal problem areas (i.e., bereavement, social role transitions, social deficits with interpersonal sensitivity, and disputes) each have a set of therapeutic guidelines.[106,107] The goals of IPT are to alleviate suffering, remit symptoms, and improve functioning.

A meta-analysis (16 RCTs, $N = 1472$) compared IPT to a control group for depression or depressive symptoms, with an effect size of 0.63.[65] A subsequent systematic review of comparative outcomes between IPT and other psychological treatments (8 studies, $N = 1233$) concluded that differences were small.[66] Finally, specific examination of IPT versus CBT for adults with MDD (7 trials, $N = 741$) found no differences between them.[64] In summary, Level 1 Evidence supports IPT as a first-line treatment for acute depression.

For maintenance treatment, a meta-analysis demonstrates that combined IPT with pharmacotherapy treatment was more effective than pharmacotherapy alone.[65] However, heterogeneity among the treatment formats (individualized vs. group) and small sample size in the studies reduce evidence to Level 2, and therefore IPT combined with medication is recommended as a second-line maintenance treatment for depression.

2.13. What Are Short-Term Psychodynamic Psychotherapy (STPP) and Long-Term Psychodynamic Therapy (PDT) and Their Efficacy in the Acute and Maintenance Phases of MDD Treatment?

Gunderson and Gabbard[108] have defined PDT as "a therapy that involves careful attention to the therapist/patient interaction with carefully timed interpretation of transference and resistance embedded in a sophisticated appreciation of the therapist's contribution to the two-person field." PDT has contributed deeply to understanding the importance of relationship/alliance issues (Table 4). Similarly, in the treatment of the depressed patient with comorbid personality disorder, PDT may have particular utility.[24] However, there is only weak evidence, and only after prolonged treatment, for efficacy of long-term PDT for acute treatment of MDD.[74,109] Hence, PDT is considered a third-line treatment for acute MDD.

For STPP, a meta-analysis identified 54 studies (33 RCTs).[61] STPP was significantly more effective than waitlist or treatment-as-usual control conditions, but some analyses indicated STPP was similar to other psychotherapies in outcomes while other findings noted STPP was significantly less effective on depressive symptoms than alternative psychotherapies at posttreatment.[61] Overall, the literature shows increasing evidence of a variety of improvements in outcomes related to STPP, but an absence of replication of specific models leaves evidence of efficacy at Level 2, and STPP models designed for depression should be considered second-line treatment. There is insufficient evidence to recommend STPP or PDT as a maintenance treatment for MDD.

2.14. What Is the Overall Level of Efficacy for Motivational Interviewing (MI) in the Acute and Maintenance Phases of MDD Treatment?

Motivational interviewing (MI) was originally designed for engaging and treating patients with substance use disorders[110] and takes the view that people approach change with ambivalence along a continuum of readiness.[111] There are no trials of MI as a stand-alone treatment for MDD; however, it has been used in conjunction with CBT, IPT, or medications to improve treatment engagement or adherence and for treatment of depression and comorbid substance misuse. For patients less likely to engage in or respond to unmodified treatments, it is worth considering integration of MI.[112] In the absence of specific MDD studies, evidence remains at Level 4 (expert opinion), and MI receives a third-line treatment recommendation.

2.15. What Is the Overall Level of Efficacy for Cognitive-Behavioural Analysis System of Psychotherapy (CBASP) in the Acute and Maintenance Phases of MDD Treatment?

CBASP was developed specifically for the treatment of chronic depression.[113] It involves cognitive, behavioural, and interpersonal strategies and is focused on helping patients to recognize how maladaptive cognitions and behaviours influence each other and lead to and perpetuate negative outcomes. Since the first CBASP trial published in 2000,[114] 5 CBASP studies have been published that provide only mixed results supporting CBASP.[75,115-118] Overall, Level 2 Evidence supports CBASP as a second-line monotherapy, or in combination with antidepressants, for partial-responding or nonresponding patients, in the treatment of PDD.

2.16. What Is Acceptance and Commitment Therapy (ACT) and Its Efficacy?

The aim of ACT is to mindfully increase acceptance of distressing experiences by taking an observer perspective and by clarifying and orienting behaviour towards valued directions, instead of struggling against or trying to control perceived suffering.[119] Since 2009, there have been 3 meta-analyses with a comparison of ACT to CBT.[120-122] In 16 studies of various diagnoses, there was

improvement in depressive symptoms and anxiety with ACT, although less than with CBT. ACT may also have particular value in the presence of comorbid medical conditions.[122] In the absence of specific large trials in MDD, evidence remains at Level 3 and ACT is recommended as a third-line treatment for MDD.

2.17. What Is Behavioural Activation (BA) for Depression and Its Efficacy?

The rationale for BA is that depression is caused and maintained by escape and avoidance of aversive emotions and stimuli that become self-reinforced and also prevents positive reinforcement of nondepressive behaviour, consequently causing longstanding patterns of inertia, avoidance, and social withdrawal.[123] Manuals are available to address techniques to be applied in BA.[124-126]

One meta-analysis (34 studies, $N > 2000$ patients with depressive symptoms, but not necessarily MDD)[127] found similar large effect sizes for BA and CBT compared to control conditions, as well as a similar effect to CBT. Subsequent clinical trials evaluating BA in MDD have almost exclusively involved Internet- or smartphone-delivered treatments as opposed to in-person therapy.[70,128,129] A subsequent meta-analysis (26 RCTs, $N = 1524$) that incorporated older studies, the Internet/smartphone studies, and 1 recent face-to-face trial reported a large effect size of BA compared to control conditions.[130,131] Overall, Level 1 Evidence supports BA as a first-line treatment for acute depression, with modest evidence that BA in acute depression provides protection against future relapse (Level 2), suggesting its role as a second-line treatment for maintenance.

2.18. What Are Peer Interventions and Their Efficacy for Depression?

Peer interventions for depression include self-help groups and peer-run organizations and services.[132] Peer support can be beneficial either alone or as a complement to clinical care. Guidelines from the Mental Health Commission of Canada provide direction to decision makers, program leaders, and the public about peer support training and practice.[133]

An initial meta-analysis of peer support for depression was positive, but subsequent results are mixed.[134-136] Given the general benefits of social and peer support, as well as the widespread availability of this resource,[137] peer interventions are recommended as a second-line adjunctive treatment for MDD (Level 2 Evidence).

2.19. What Is Problem-Solving Therapy (PST) and Its Efficacy?

PST is a structured brief, empirically tested intervention focusing on the adoption of adaptive problem-solving attitudes and skills to treat MDD. It has been shown to be more effective when training includes both positive problem orientation and problem-solving skills.[138]

PST has been tested most extensively in primary care settings in individuals with a variety of depressive symptoms spanning subclinical depression, adjustment disorders, and MDD, with clear efficacy in reducing depressive symptoms. Both telephone-delivered and in-person PST were effective for treating MDD in low-income homebound older adults.[139] Two separate meta-analyses found that the use of PST as an acute treatment for late life depression resulted in a significant reduction of depressive symptoms as well as disability in comparison to control treatments.[138,140]

Overall, since most studies include a focus on depressive symptoms rather than formal MDD, PST is recommended as a second-line acute treatment in primary care and geriatric depression (Level 2 Evidence); there is insufficient evidence to recommend PST as a maintenance treatment.

2.20. What Is Bibliotherapy and What Is Its Efficacy?

Bibliotherapy, the reading and use of self-help materials such as books to treat depression, has been tested in many older trials, particularly as RCTs involving a waitlist control compared to use of the book *Feeling Good* by David Burns.[141] With the expansion of computer/Internet approaches to self-help, very few bibliotherapy trials have been published since 2009. Although 1 RCT[142] highlighted the need for physician guidance to ensure active engagement, an RCT evaluating usual care versus prescription for *Feeling Good* found no difference in patient outcomes.[143] Overall, bibliotherapy has practical utility due to ease of use and low cost, may be useful for people waiting to be seen for clinical care, and remains a second-line treatment, either alone or as an adjunct to medication, ideally with clinician encouragement and monitoring.

2.21. How Effective Is Internet- and Computer-Delivered Therapy for Depression?

Meta-analyses and reviews of computer-based psychological treatment for the treatment of MDD, whether delivered over the Internet or as a stand-alone program, confirm efficacy.[144-150] Internet- and computer-delivered therapy (I/CT) can also be helpful in relapse prevention.[151] I/CT studies usually use adaptations of CBT, but 1 trial compared updated versions of CBT and IPT with the established "MoodGym" online version of CBT with over 600 participants in each of the 3 groups; self-guided IPT was similar to the other treatments in reducing depressive symptoms.[152] When the Internet therapy is guided by a clinician, both adherence and efficacy are much more substantial.[88] Across psychiatric disorders, 1 meta-analysis[153] found that guided Internet CBT was no different in outcomes from face-to-face CBT, while a noninferiority study[154] specifically for depression also found no differences between the 2 approaches.

I/CT remains a second-line treatment for depression, with improved efficacy if the I/CT is actively guided by a clinician.

2.22. How Effective Is Remote Interactive Psychological Treatment for Depression (Phone, Video, Internet) Compared to Face-to-Face Therapy?

Psychological treatments with a live therapist are being increasingly mediated by technology, whether by phone, videoconferencing, or live interaction over the Internet. In addition to CBT, a significant number of studies have evaluated other methods of telephone-delivered support and disease management.

Telephone-delivered psychological treatment remains the most studied model. In one of the first large trials (600 patients starting antidepressants in primary care offices), both 8-session CBT and disease management by phone improved clinical efficacy and satisfaction, compared to medication alone.[79] The same 8-session CBT phone intervention added to an antidepressant improved work performance and satisfaction compared to antidepressant alone.[80] Collectively, telephone-delivered CBT has Level 1 Evidence, while other therapies have Level 2 Evidence, positioning telephone-delivered therapy as a second-line treatment.

Videoconferencing approaches to psychological treatment may include use of traditional videoconference suites with television cameras in 2 different locations or, more recently, Internet technologies on personal computing devices, including Skype, Medeo, FaceTime, and many others. The broader application of such technologies to psychiatry has been extensively reviewed and found to be acceptable and generally equivalent to face-to-face care for many psychiatric conditions.[155,156] Relatively few studies have been done using videoconferencing for MDD, but there is limited evidence of efficacy in several small RCTs,[156-158] suggesting that videoconferenced psychological treatment for depression may be considered a promising third-line treatment.

2.23. Is Combined Psychological Treatment with Medication Superior to Psychological Treatment Alone?

Accumulated evidence shows that combined psychological and antidepressant treatment is more effective than psychological treatment alone or psychological treatment with placebo.[159,160] The evidence is mostly based on studies where either CBT or IPT was delivered alone and combined with selective serotonin reuptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs). There was a trend for SSRIs and IPT to be less effective in combinations than TCAs, CBT, and other psychotherapies. The small to moderate effect size of the differences suggests that combined treatment should be offered to individuals with moderate to severe depression based on a consideration of benefit-burden balance and preferences of a given patient.

2.24. Is Combined Psychological Treatment with Medication Superior to Medication Alone?

A recent meta-analysis shows that psychological treatment combined with antidepressants is more effective than antidepressants alone.[159] The evidence is primarily based on studies where individual CBT or IPT was combined with SSRIs or TCAs. The effect size of the difference was moderate, suggesting that combined treatment should be offered in preference to antidepressants alone to individuals with moderate to severe depression.

2.25. Is Sequential Treatment Superior to Monotherapy?

A meta-analysis of 8 studies found that psychological treatment after antidepressant treatment reduces the likelihood of relapse by 20%, compared to treatment as usual, which included discontinuation of antidepressants.[161] Although the meta-analysis aimed to examine the effect of any type of psychological treatment, the evidence was limited to CBT and MBCT.[161] In addition, a large pragmatic trial found that a course of up to 18 sessions of face-to-face individual CBT significantly reduced depressive symptoms and increased the likelihood of therapeutic response to antidepressants in treatment-resistant depression.[63] Another large primary care trial compared the effects of group MBCT and maintenance antidepressant therapy on time to relapse; while there were no significant differences between the 2 conditions, the risk of relapse was greater in those who had prematurely discontinued antidepressant treatment.[69] In contrast, PDT (up to 60 sessions over 18 months) did not significantly increase the likelihood of remission.[74]

In summary, CBT or MBCT is recommended as sequential first-line treatment (Level 1 Evidence) after a course of antidepressants, and MBCT is recommended as a second-line alternative to long-term maintenance antidepressant treatment (Level 2 Evidence).

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The CANMAT guidelines are not officially endorsed by the Canadian Psychiatric Association.

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GMM has been on advisory board or speaker for Janssen, Lilly, Lundbeck, and Pfizer.

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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 antagonist; 5-HT_2 antagonist	60-120 mg
Milnacipran[a] (Ixel)	SNRI	100 mg
Mirtazapine (Remeron)[c]	α_2-Adrenergic antagonist; 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),

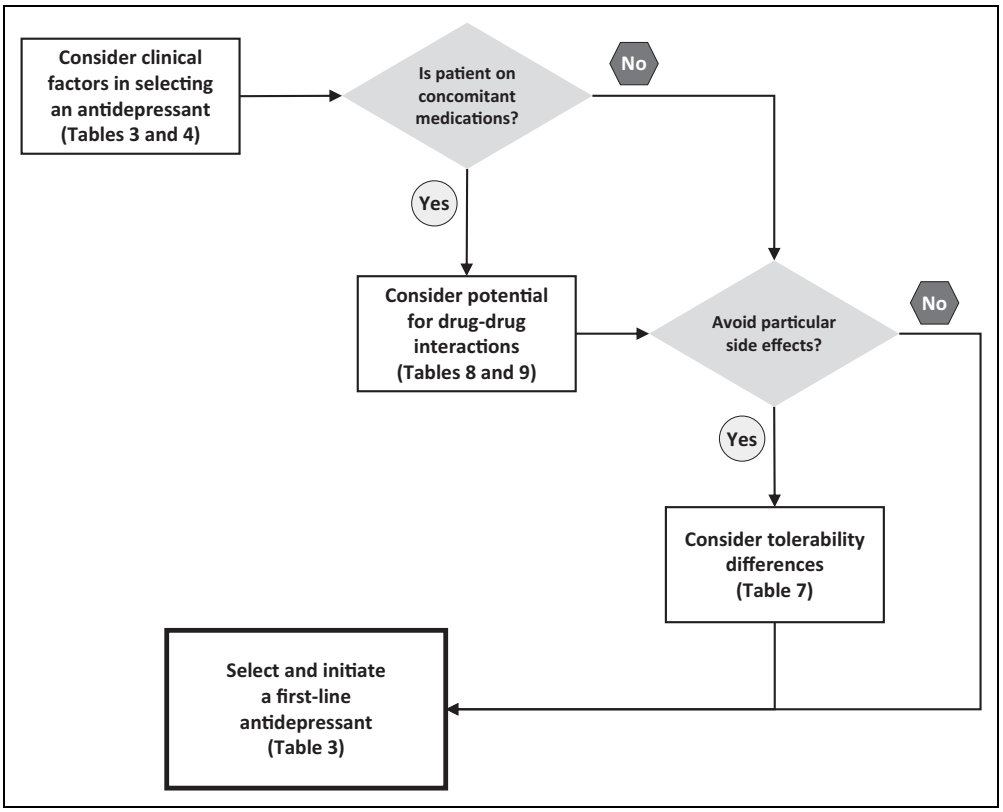

Figure 1. Summary algorithm for selecting an antidepressant.

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, desvenlafaxine, 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
Citalopram	21		8	19				3	3	2		5	11		8	4		
Escitalopram	15	4	8	7	3	6	4	2	2		8	5	3		2		2	2
Fluoxetine	21			10			13	14	12		16		8	9	10	11		
Fluvoxamine	37	18	6	26	22	15	26	2	2	16	14		11	5	11	15		
Paroxetine	26	14	11	18	18	13	23	5	5	2	13		11	15	8		1	
Sertraline[a]	26	8	18	16	20	12	13	3	3	6	16	11	8		11	3	1	
Desvenlafaxine[b]	22	9		11		13	4	<1	3		9	7	10		2			
Duloxetine	20	11	8	15		8	7		3		11	8	6		3			
Levomilnacipran	17	9		10	17	8			2		6		9					
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		
Venlafaxine XR	31	8	8	12	26	20	17	10	2	3	17		14	8	5	8		
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
Vortioxetine[f]	23	4	5	6		5	3				3	3	2					

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.

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.

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

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

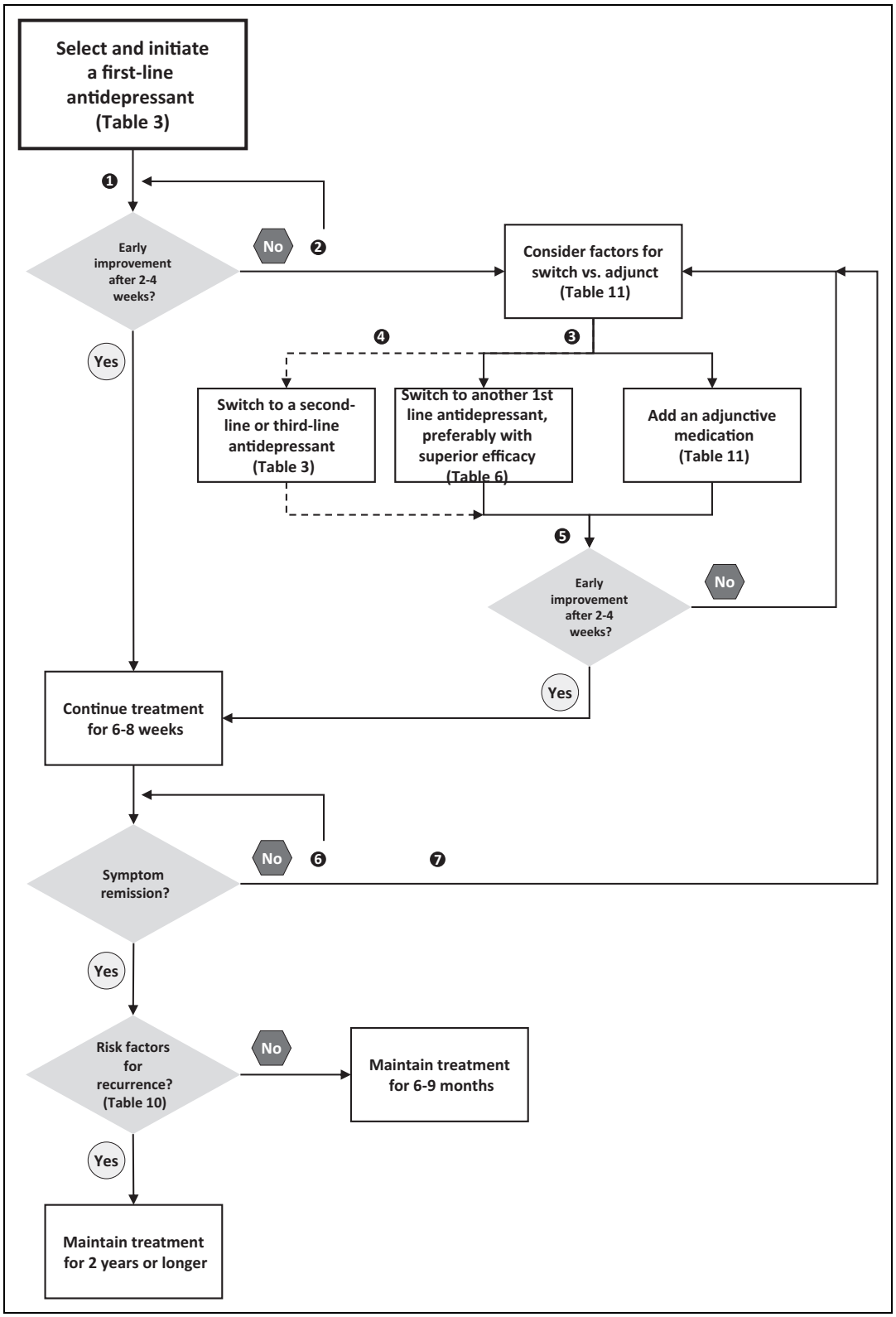

Figure 2. Summary algorithm for managing inadequate response to an antidepressant. (1) Monitor outcomes using measurement-based care. (2) Depending on tolerability, first optimize antidepressant by increasing dose. (3) For early treatment resistance, consider adjunctive use of psychological and neurostimulation 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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The CANMAT guidelines are not officially endorsed by the Canadian Psychiatric Association.

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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 4. Neurostimulation 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. "Neurostimulation Treatments" is the fourth of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 31 questions for 6 neurostimulation modalities: 1) transcranial direct current stimulation (tDCS), 2) repetitive transcranial magnetic stimulation (rTMS), 3) electroconvulsive therapy (ECT), 4) magnetic seizure therapy (MST), 5) vagus nerve stimulation (VNS), and 6) deep brain stimulation (DBS). Most of the neurostimulation treatments have been investigated in patients with varying degrees of treatment resistance.

Conclusions: There is increasing evidence for efficacy, tolerability, and safety of neurostimulation treatments. rTMS is now a first-line recommendation for patients with MDD who have failed at least 1 antidepressant. ECT remains a second-line treatment for patients with treatment-resistant depression, although in some situations, it may be considered first line. Third-line recommendations include tDCS and VNS. MST and DBS are still considered investigational treatments.

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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). CANMAT, in collaboration with the International Society for Bipolar Disorders, has published separate guidelines for bipolar disorder.[2] This section on "Neurostimulation Treatments" is 1 of 6 guidelines articles; other sections of the guidelines will expand on disease burden and principles of care, psychological treatments, pharmacological treatments, complementary and alternative medicine treatments, and special populations. These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

Neurostimulation, or neuromodulation, is an expanding area of research and clinical interest, driven in part by the increasing knowledge base on the neurocircuitry of depression. Neurostimulation treatments use electrical or magnetic stimulation targeting specific brain regions with noninvasive techniques, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), electroconvulsive therapy (ECT), and magnetic seizure therapy (MST), as well as invasive surgical techniques, such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS). Most of these neurostimulation treatments have been studied and are used in patients with treatment-resistant depression (TRD) who have failed to respond to standard treatments.

Methods

The full methods have been previously described,[3] but in summary, relevant studies in English 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.

Table 2 presents the overall neurostimulation treatment recommendations. More details for each modality are presented in the following questions. Because there is no consensus definition for TRD, we have specified the degree of treatment resistance whenever possible.

Transcranial Direct Current Stimulation (tDCS)

4.1. What Is tDCS and How Is It Delivered?

tDCS is a form of brain stimulation that delivers a continuous low-amplitude electrical current to a specified cortical region using scalp electrodes. *Anodal* stimulation over the cortex increases cortical excitability through depolarization of neuronal membrane potential. By contrast, *cathodal* stimulation decreases cortical excitability through hyperpolarization of the membrane potential.[4] Repeated use of tDCS may lead to neuroplasticity effects similar to long-term potentiation and/or long-term depression, perhaps mediated via N-methyl-D-aspartate receptor-dependent mechanisms.[4] Potential advantages of tDCS include ease of use, low cost, portability and potential for home-based use, ability for combination use with other treatments, and low potential for adverse effects.

4.2. What Are the Delivery Parameters for tDCS?

There is no cohesive summary evaluating the optimal stimulus parameters, frequency, or duration of tDCS for the treatment of MDD. Studies to date have used an electrode montage consisting of anodal stimulation over the left dorsolateral prefrontal cortex (DLPFC) with the cathode used as a ground over a noncortical region or a montage combining left DLPFC anodal stimulation with right DLPFC cathodal stimulation.[5] The exact frequency and duration of stimulation have not been established, but it seems that a minimum stimulation with 2 milliamperes (mA) for at least 30 minutes per day for 2 weeks is necessary to observe an antidepressant effect.[6] The largest randomized-controlled trial (RCT) to date ($N = 120$ in 4 conditions) using these parameters found higher remission rates at 6 weeks when combining tDCS with sertraline (47%) compared to tDCS (40%) or sertraline alone (30%),[7] which suggests that tDCS may have an additive or enhancing effect to other antidepressant treatments.[8] Furthermore, preliminary data suggest that tDCS may also enhance psychotherapeutic modalities.[9]

4.3. How Effective Is tDCS in Acute and Maintenance Treatment of MDD?

Studies evaluating the efficacy of tDCS have demonstrated mixed results. One meta-analysis (6 trials, $N = 200$) found no significant differences with tDCS compared to sham treatments,[10] while a subsequent meta-analysis (7 trials, $N = 269$) demonstrated modest differences between active and sham conditions with a small overall effect size of 0.37.[6] An individual patient-level meta-analysis (6 trials, $N = 289$)

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.

found a similar effect size ($\beta = 0.347$).[11] The most recent meta-analysis (10 trials, $N = 393$) also found superiority for tDCS over sham conditions with a small but significant effect size ($g = 0.30$).[5] There are no controlled studies of tDCS for maintenance treatment or relapse prevention. History of treatment resistance has been associated with poorer responses to tDCS.[5,6,11]

tDCS is thus recommended as a third-line treatment for MDD. It has Level 2 Evidence for acute efficacy (Table 2), but given the small number of studies with heterogeneous methodologies and the inconsistent results from meta-analyses, further research is needed to establish the optimal parameters of stimulation and the efficacy of tDCS as monotherapy or combination therapy for acute treatment of MDD.

4.4. What Are the Side Effects Associated with tDCS?

Most studies have found that tDCS is well tolerated. Reddening of the skin, itching, burning, heat, and tingling sensations at the site of stimulation are the most common reported adverse events with tDCS in more than half of patients.[5,6] Headaches, blurred vision, ringing in the ears, brighter or illuminated vision, fatigue, nausea, mild euphoria, reduced concentration, disorientation, insomnia, and anxiety have also been reported but at low rates with minimal difference between active and sham stimulation.[5] In the RCT examining tDCS and sertraline 50 mg/d, hypomania (3 patients, 10%) and mania (2 patients, 7%) were reported with the combined treatment compared to tDCS and sertraline alone (both with hypomania reported in 1 patient, 3%).[7] Adverse effects have not led to differences in dropout rates ($\sim$3%) between active and sham conditions across the RCTs.[5,6] There are no studies examining safety and tolerability over long-term use.

Repetitive Transcranial Magnetic Stimulation (rTMS)

4.5. What Is rTMS and How Is It Delivered?

rTMS uses powerful (1.0-2.5 Tesla), focused magnetic field pulses to induce electrical currents in neural tissue noninvasively, via an inductor coil placed against the scalp.[12] Therapeutic rTMS is usually delivered by a trained technician or nurse, under physician supervision. Unlike ECT, no anaesthesia is required. The therapeutic mechanism of rTMS is still under investigation, with mechanisms proposed at both cell-molecular and network levels.[13]

Standard protocols deliver rTMS once daily, 5 days/week (Table 3). Three-times-weekly stimulation has been reported as similarly effective, albeit with slower improvement and a similar number of sessions required overall.[14] 'Accelerated' protocols with multiple daily sessions (2-10/days) are being explored to complete the course more rapidly.[15,16]

Repeated rTMS sessions can exert therapeutic effects lasting several months. Clinical trials and naturalistic studies have found maximal effects at 26 to 28 sessions.[17,18] Clinical experience concurs in suggesting 20 sessions before declaring treatment failure, with extension to 25 to 30 sessions if improvements occur. There is currently no validated biomarker for predicting rTMS outcome in individuals[19] and limited evidence for clinical features to suggest rTMS-responsive depression.

4.6. What Are the Delivery Parameters for rTMS?

rTMS parameters include stimulation intensity, frequency, pattern, and site (Table 3). Conventional figure-8 or circular rTMS coils can target brain regions 1 to 4 cm deep to the scalp; helmet-shaped 'deep' rTMS coils can stimulate slightly deeper structures. For coil navigation, magnetic resonance imaging (MRI) guidance is the most precise method; however, scalp-based navigation is most common. Stimulus intensity is based on individually determined resting motor threshold (RMT, minimum intensity to elicit muscle twitches at relaxed upper or lower extremities, by visual inspection or electromyography). The most common intensity in all trials to date is 110% RMT[20]; most recent large trials have employed 120% RMT. Stimulation above this level falls outside conventional safety guidelines.[21] Newer theta-burst stimulation (TBS) protocols are more commonly delivered at lower intensities (e.g., 70%-80% active motor threshold).

Table 2. Summary of Neurostimulation Treatment Recommendations for Major Depressive Disorder.

Neurostimulation	Overall Recommendation	Acute Efficacy	Maintenance Efficacy	Safety and Tolerability
rTMS	First line (for patients who have failed at least 1 antidepressant)	Level 1	Level 3	Level 1
ECT	Second line First line in some clinical situations (see Table 5)	Level 1	Level 1	Level 1
tDCS	Third line	Level 2	Level 3	Level 2
VNS	Third line	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3
MST	Investigational	Level 3	Not known	Level 3

DBS, deep brain stimulation; ECT, electroconvulsive therapy; MST, magnetic seizure therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VNS, vagus nerve stimulation.

Table 3. Summary of Treatment Parameters for Repetitive Transcranial Magnetic Stimulation (rTMS).

Intensity, frequency, and site
- Stimulate at 110%-120% of resting motor threshold (70%-80% for theta-burst stimulation) (Level 1)
- Select stimulation frequency and site (Table 4)

Treatment course
- Perform stimulation 5 times weekly (Level 1)
- Deliver initial course until symptom remission is achieved, up to 20 sessions (4 weeks) (Level 1)
- Extend course to 30 sessions (6 weeks) in responders who have not achieved symptom remission (Level 3)

Maintenance course
- Use rTMS as needed to maintain response (Level 3)

Table 4. Recommendation for rTMS Stimulation Protocols.

Recommendation	Level of Evidence
First line	
High-frequency rTMS to left DLPFC	Level 1
Low-frequency rTMS to right DLPFC	Level 1
Second line	
Bilateral rTMS to DLPFC (left high-frequency and right low-frequency)	Level 1
Low-frequency rTMS to right DLPFC (in nonresponders to high-frequency left DLPFC-rTMS) or high-frequency rTMS to left DLPFC (in nonresponders to low-frequency right DLPFC-rTMS)	Level 3
TBS protocols	Level 3
Intermittent TBS to left DLPFC	
Left intermittent and right continuous TBS to DLPFC	
Intermittent TBS to bilateral DMPFC	
Third line	
High-frequency rTMS to bilateral DMPFC	Level 3

DLPFC, dorsolateral prefrontal cortex; DMPFC, dorsomedial prefrontal cortex; rTMS, repetitive transcranial magnetic stimulation; TBS, theta-burst stimulation.

Different stimulation frequency and patterns exert different effects. Conventionally, high-frequency rTMS (5-20 Hz) is considered excitatory, while low-frequency stimulation (1-5 Hz) is inhibitory. Conventional stimulation is delivered in 2- to 10-second trains at 10- to 60-second intervals, in 15- to 45-minute sessions. TBS protocols require only 1 to 3 minutes of stimulation and may achieve comparable or stronger effects.[22] Intermittent TBS (iTBS) is considered excitatory and continuous TBS (cTBS) inhibitory.

4.7. How Effective Is rTMS as an Acute Antidepressant Therapy?

More than 30 systematic reviews and meta-analyses have been conducted on rTMS in depression, with most studies involving patients with some degree of treatment resistance (i.e., having failed at least 1 or 2 antidepressant trials). Overall, rTMS is considered a first-line treatment for MDD for patients who have failed at least 1 antidepressant treatment (Table 2). Table 4 lists recommendations for rTMS stimulation protocols.

Both high-frequency ($\geq$10 Hz) rTMS of the left DLPFC and low-frequency ($\leq$1 Hz) rTMS of the right DLPFC have demonstrated efficacy in numerous meta-analyses,[20,23-25] with no differences in outcomes between them.[20] Hence, both high-frequency left DLPFC and low-frequency right DLPFC are first-line rTMS protocol recommendations. Low-frequency rTMS has the advantage of shorter treatment time. Published studies also suggest that nonresponders to high-frequency left DLPFC rTMS may respond to low-frequency right DLPFC rTMS[17] and vice versa.[26] Hence, a second-line recommendation is to switch nonresponders to the other stimulation protocol.

Bilateral stimulation combines high-frequency left and low-frequency right DLPFC rTMS and has not shown superiority over unilateral rTMS in meta-analyses.[27-29] Because bilateral stimulation requires more intensive setup without efficacy or safety advantages, it is considered a second-line rTMS protocol.

The efficacy of rTMS is established even in patients with TRD defined by stringent criteria.[30] The most recent

meta-analysis of high-frequency left DLPFC rTMS for TRD (23 trials, $N = 1156$) found significant efficacy of rTMS over sham, with a weighted mean difference of 2.31 and an effect size of 0.33.[31] For left DLPFC rTMS, RCTs with adequate sessions (20-30) and treatment durations of 4 weeks or more achieved ~40% to 55% response and ~25% to 35% remission rates, and a real-world effectiveness study reported 58% response and 37% remission rates.[18] Similarly, a meta-analysis (8 trials, $N = 263$) found that low-frequency right DLPFC rTMS had superior remission rates compared to sham (35% vs. 10%, respectively, $P < 0.0001$).[32]

Excitatory rTMS of the dorsomedial prefrontal cortex (DMPFC) has shown antidepressant effects in a small sham-controlled trial ($N = 45$ in 3 conditions)[33] and several larger case series.[22,34,35] The sham-controlled RCT directly compared DMPFC- and DLPFC-rTMS, reporting slightly better outcomes for DMPFC-rTMS.[33] A large case series ($N = 98$) of open-label DMPFC-rTMS reported 50% response and 36% remission rates, not significantly different from iTBS ($N = 87$).[22] Based on this Level 3 Evidence, stimulation to bilateral DMPFC is recommended as a third-line rTMS protocol.

Randomized pilot studies of TBS protocols for DLPFC have shown superiority over sham for left iTBS[36] but not for right cTBS,[36,37] while bilateral stimulation (left iTBS and right cTBS) had positive results in one study[36] but not in another.[38] For TBS of bilateral DMPFC, a retrospective case series found that iTBS achieved equivalent outcomes to longer conventional 10-Hz rTMS protocols.[22] Randomized comparisons of conventional rTMS and TBS are in progress but have not yet been published. Hence, TBS protocols are recommended as second line with Level 3 Evidence (Table 4).

4.8. How Effective Is Maintenance Treatment Post-rTMS?

Without maintenance treatment, relapse is common following successful rTMS. One naturalistic study ($N = 204$) reported median relapse time at 120 days, with relapse rates of 25%, 40%, 57%, and 77% at 2, 3, 4, and 6 months, respectively.[39] With maintenance rTMS, long-term outcomes appear more favourable. In a naturalistic study ($N = 257$), maintenance rTMS sessions as needed over 12 months sustained remission in 71% of rTMS remitters and response in 63% of rTMS responders.[40] Another study found that without maintenance, 38% of rTMS responders relapsed within 24 weeks, at a mean of 109 days posttreatment.[41] With reintroduction of rTMS as needed, 73% met response and 60% met remission criteria at 24 weeks.[41]

Various rTMS maintenance schedules have been proposed. An observational study ($N = 59$) compared a 20-week gradual taper of maintenance rTMS (from 3 sessions/week down to 1 session/month) to no maintenance; relapse rates were 38% with maintenance versus 82% without maintenance.[42] Another study ($N = 35$) provided 5 'clustered' maintenance sessions over 3 days, once monthly, extending relapse times to a mean 10.8 months among the 25 patients who relapsed.[43] As yet, there is insufficient evidence to support any one particular schedule of maintenance sessions over another.

4.9. How does rTMS Compare to ECT?

rTMS and ECT differ in mechanism, tolerability, and acceptability by patients and may be best understood as complementary rather than competing techniques. That said, several meta-analyses[28,31,44-46] evaluating a similar number of studies have consistently found that rTMS is less effective than ECT, particularly in patients with psychosis.[44] The most comprehensive meta-analysis (9 trials, $N = 425$) found significant superiority of ECT over left DLPFC rTMS in response and remission rates but no significant difference in weighted mean difference, in contrast to the other meta-analyses that found large differences in favour of ECT for all outcomes.[28,31,45,46] Likewise, rTMS response rates are poor in patients where ECT has failed.[35] These findings indicate that rTMS should be considered prior to pursuing ECT and that patients who have not responded to ECT are unlikely to respond to rTMS.

4.10. What Are the Adverse Effects Associated with rTMS?

The most common adverse effects for rTMS are scalp pain during stimulation (~40%) and transient headache after stimulation (~30%), both of which diminish steadily over treatment, typically respond to over-the-counter analgesia, and result in low rates of discontinuation.[47,48]

The cognitive safety profile of rTMS appears benign. A systematic review (22 studies, $N = 659$) of cognitive performance with rTMS found no worsening in cognitive domains but also little evidence of improvement, with no differences in cognitive performance between active rTMS and sham conditions.[49]

The most serious rTMS adverse event is seizure induction. To date, fewer than 25 cases of rTMS-induced seizure have been reported worldwide.[50] Seizure incidence with rTMS is estimated at ~0.01% to 0.1% versus 0.1% to 0.6% on antidepressant medications and 0.07% to 0.09% spontaneous incidence in the general population. High-frequency rTMS is contraindicated in patients with a history of seizures. Safety of low-frequency rTMS has been demonstrated in patients with epilepsy,[21] but safety in patients with depression and seizures has not been formally established. Most rTMS practitioners currently consider a history of seizures an absolute contraindication.

Consensus safety guidelines for therapeutic rTMS[21] list metallic hardware (e.g., cochlear implants, brain stimulators or electrodes, aneurysm clips) anywhere in the head, except the mouth, as an absolute contraindication. Relative contraindications include the presence of a cardiac pacemaker,

implantable defibrillator, a history of epilepsy, or the presence of a brain lesion (vascular, traumatic, neoplastic, infectious, or metabolic).

4.11. Should rTMS be Combined with Other Antidepressant Medications?

Most rTMS studies have delivered rTMS as an add-on to the preexisting antidepressant regimen. There is no evidence that discontinuing antidepressants prior to rTMS will improve outcomes. However, a meta-analysis (6 trials, $N = 392$) found that starting a new antidepressant with rTMS resulted in higher response and remission rates than rTMS alone.[51]

Electroconvulsive Therapy (ECT)

4.12. What Is ECT and How Is It Delivered?

ECT is a therapeutic procedure that entails induction of a seizure by applying an electrical stimulus to the brain. It is an effective and well-established treatment method for depressive and other mental disorders. ECT is delivered in a controlled clinical setting, after induction of general anaesthesia and application of a muscle relaxant. There are no absolute contraindications for ECT. The following conditions may be associated with an increased safety risk: space-occupying cerebral lesion, increased intracranial pressure, recent myocardial infarction, recent cerebral haemorrhage, unstable vascular aneurysm or malformation, pheochromocytoma, and class 4 or 5 anaesthesia risk. The exact mechanism of action is still under investigation, but the main hypotheses include seizure-induced changes in neurotransmitters, neuroplasticity, and functional connectivity. For example, ECT can increase levels of brain-derived neurotrophic factor (BDNF), which may contribute to the antidepressant effect.[52]

ECT is generally recommended as a second-line treatment for MDD because of adverse effects (Table 2), but ECT can be considered a first-line treatment in some clinical situations (Table 5).

Table 6 summarizes the recommendations for delivery of ECT. Current treatment parameters for ECT include electrode position, electrical intensity, and pulse width. The most common electrode placements are bilateral, either bitemporal (BT) or bifrontal (BF), or right unilateral (RUL). The electrical intensity is based on the minimum intensity to produce a generalized seizure, called the seizure threshold (ST). Bilateral treatments (both BT and BF) most often use 1.5 to 2.0 times ST and RUL 5 to 6 or even 8 times ST. A meta-analysis (8 trials, $N = 617$) found that BT, BF, and RUL have the same efficacy but may adversely affect specific cognitive domains differently.[53] Both BF and RUL ECT are first-line recommendations, but BT is recommended as second line because of higher rates of short-term cognitive adverse effects.

ECT generally uses brief pulse (BP) width, but in the past decade, there has been clinical and research interest into ultrabrief pulse width (UBP, pulse width below 0.5 ms) RUL and bilateral treatments. UBP may be associated with less short-term cognitive impairment and specifically the loss of autobiographical memory.[54] However, UBP may have slower speed of improvement and require more treatments than BP.[55] A systematic review[56] concluded there was no advantage of UBP over BP in RUL or bilateral ECT, and a meta-analysis (6 trials, $N = 689$) found that BP RUL had a small efficacy advantage and required fewer treatments than UBP but led to more cognitive impairment after an acute course.[57] Hence, UBP RUL is recommended as a second-line ECT treatment, especially to minimize short-term cognitive impairment.

The number of ECT treatments required to achieve response and/or remission, referred to as the index course, ranges between 6 and 15. ECT is usually delivered 2 to 3 treatments per week during the index course. More than 3 treatments per week are not recommended, as they are associated with higher frequency of cognitive side effects. A meta-analysis (8 studies, $N = 214$) found that twice-weekly ECT had similar efficacy compared to thrice-weekly ECT but had longer duration of treatment.[58]

Table 5. Clinical Indications for Electroconvulsive Therapy as a First-Line Treatment for Major Depressive Disorder.

- Acute suicidal ideation (Level 1)
- Psychotic features (Level 1)
- Treatment-resistant depression (Level 1)
- Repeated medication intolerance (Level 3)
- Catatonic features (Level 3)
- Prior favourable response to ECT (Level 3)
- Rapidly deteriorating physical status (Level 3)
- During pregnancy, for any of the above indications (Level 3)
- Patient preference (Level 4)

Table 6. Recommendations for Delivery of Electroconvulsive Therapy.

Recommendation	Level of Evidence
First line	
BP RUL (at 5-6 times seizure threshold)	Level 1
BP BF (at 1.5-2.0 times seizure threshold)	Level 1
Second line	
UBP RUL (up to 8 times seizure threshold) or UBP BF (at 1.5-2.0 times seizure threshold)	Level 1
BP BT (at 1.5-2.0 times seizure threshold)	Level 1
Twice-weekly ECT sessions have similar efficacy to thrice-weekly but have longer duration of treatment	Level 2
If no response to RUL after 4 to 6 treatments, switch to bilateral ECT (BT or BF)	Level 3
For maintenance pharmacotherapy post-ECT, use an antidepressant that has not been tried prior to ECT *or* nortriptyline plus lithium *or* venlafaxine plus lithium	Level 2
Maintenance use of ECT is as effective as pharmacotherapy in preventing relapse/recurrence after an acute course of ECT	Level 2

BF, bifrontal; BP, brief pulse; BT, bitemporal; ECT, electroconvulsive therapy; RUL, right unilateral; UBP, ultrabrief pulse.

4.13. How Effective Is ECT as an Acute Treatment?

ECT is one of the most effective treatments for MDD. Response rates can reach 70% to 80%, with remission rates 40% to 50% or higher, depending on the patient population and type of stimulus used. For example, 1 multicentre RCT ($N = 230$) reported remission rates of 55% for RUL, 61% for BF, and 64% for BT in a mixed sample of patients with unipolar (77%) and bipolar (23%) depression.[59] The strongest predictor of nonresponse to ECT is the degree of resistance to previous treatments. In patients with greater degrees of resistance to pharmacological and psychological treatments, response rates with ECT approximate 50%, compared to 65% in patients without a previous treatment failure.[60] Highest response rates have also been observed when patients are older, have psychotic features, have a shorter episode duration, and, possibly, have lesser depressive severity.[61]

The relapse/recurrence rate following an acute course of ECT, with or without maintenance treatment, is also high. A meta-analysis of 32 studies from 1962 to 2013 ($N = 1706$ patients) that assessed relapse rates following successful treatment with ECT reported that relapse rates are highest within the first 6 months post-ECT (37.7%).[62] Even in those receiving maintenance treatment post-ECT, relapse rates of 51.1% and 50.4% have been observed at 1 and 2 years, respectively. Baseline medication resistance is not associated with relapse, but lower relapse rates have been observed in cohorts with a greater percentage of psychotic patients and older patients.[62]

4.14. How Effective Is Maintenance Treatment Post-ECT?

Medications are most commonly used for maintenance after an acute treatment course of ECT. The use of antidepressant medication post-ECT reduced relapse rates by approximately half (relative risk of relapse on medication = 0.56).[62] However, there has been little study of specific medication strategies to minimize post-ECT relapse, and there is no clear evidence of the superiority of a specific antidepressant or class of medication. In RCTs, the combination of nortriptyline and lithium was superior to both nortriptyline monotherapy and placebo in reducing relapse rates,[63] and the combination of venlafaxine and lithium was found to be equally efficacious as nortriptyline and lithium.[64] In summary, the recommendation for pharmacotherapy post-ECT is to use an antidepressant that has not been tried prior to ECT, or nortriptyline plus lithium, or venlafaxine plus lithium.

Continuation/maintenance ECT (c/mECT) is also a safe and effective strategy to reduce relapse/recurrence.[65,66] Studies in which continuation ECT was used yielded comparable relapse-prevention results at 6 months as studies of pharmacological strategies (relapse rates: 37.2% vs. 37.7%, respectively).[62] This has also been demonstrated in a prospective RCT of continuation ECT versus continuation pharmacotherapy with nortriptyline and lithium.[67] Hence, maintenance ECT also can be used as a relapse-prevention strategy after an acute course of ECT. There are no studies investigating optimal frequency of c/mECT, so the schedule should be adjusted to the needs of an individual patient. The most commonly used schedule in studies of c/mECT involves weekly treatments for 4 weeks, then biweekly for 8 weeks, and then monthly. If signs of relapse occur, more frequent sessions are usually provided.

There has been a paucity of evidence regarding psychotherapeutic strategies to prevent post-ECT relapse.[68] A small RCT found that cognitive-behavioural group therapy plus continuation medication ($n = 17$) demonstrated a lower relapse rate at 6 and 12 months compared to continuation of UBP ECT plus medication ($n = 25$) and continuation of medication alone ($n = 18$).[69] There is insufficient evidence to recommend psychotherapy for maintenance treatment post-ECT.

4.15. What Are the Adverse Effects Associated with ECT?

The use of general anaesthesia, muscle relaxants, oxygenation, and monitoring has minimized the risks associated with ECT, and the mortality rate has been estimated to be less than 1 death per 73,440 treatments.[70] No clinical studies have demonstrated damage to the brain structures related to the administration of ECT. The most common adverse effects occur during a treatment course, are transient, and can be treated symptomatically: headaches (45%), muscle soreness (20%), and nausea (1%-25%). In a small number (7%), there can be a switch into a manic or mixed state.

Subjective and objective cognitive impairment are the adverse effects that have received the greatest attention. Cognitive effects include transient disorientation when recovering from an ECT session (in part due to postictal confusion and effects of general anaesthesia), retrograde amnesia (difficulty recalling information learned before a course of ECT, such as autobiographical memories), and anterograde amnesia (difficulty in retaining learned information after a course of ECT). There is mild, short-term impairment in memory and other cognitive domains during and immediately following a course of ECT. Clinical factors, including preexisting cognitive impairment, older age, and use of BT ECT, are associated with greater cognitive impairment, while use of UBP RUL ECT is associated with less impairment. However, these impairments are usually transient, with recovery of cognitive functioning occurring within weeks and months after an acute course of ECT, and no eventual cognitive differences between ECT parameters, including electrode placement and pulse width.[71,72] For example, 1 meta-analysis (84 studies, $N = 2981$) examined 24 cognitive variables (including processing speed, working memory, anterograde memory, and executive function) and found recovery or improvement in all neuropsychological

Table 7. Factors Associated with Higher Rates of Short-Term Adverse Cognitive Effects of Electroconvulsive Therapy Versus Those Associated with Lower Rates.

Factors	Level of Evidence
Bitemporal electrode placement versus bifrontal or unilateral placement	Level 1
Brief pulse width (1.0-1.5 ms) versus ultrabrief pulse width (0.3-0.5 ms)	Level 2
Suprathreshold stimulation versus lower electrical dose	Level 2
Treatment 3 times a week versus twice a week	Level 2
Concomitant use of lithium or agents with independent adverse cognitive effects versus reducing doses or discontinuing these agents	Level 3
Use of high doses of anaesthetic medications versus lower doses	Level 4

measures within 3 to 15 days after completing ECT.[72] There is less consistent information about retrograde amnesia, with some studies suggesting persistent effects, while a systematic review (15 studies, $N = 1128$) found that objective tests of autobiographical memory did not show effects beyond 6 months post-ECT.[73] Patient self-reports indicate some persistent cognitive dysfunction, especially retrograde amnesia, but self-reports of cognitive dysfunction are usually highly correlated with persistent depressive symptoms and are not correlated with objective testing.[73,74] Table 7 lists some of the factors that are associated with higher or lower rates of short-term adverse cognitive effects.

4.16. Should ECT Be Combined with Other Antidepressant Treatments?

Lower relapse rates have been reported in studies where concurrent antidepressant medication was permitted during the course of ECT compared to studies where maintenance pharmacotherapy was begun following the course of ECT (29.2% vs. 41.6%, respectively), suggesting that improved long-term outcomes are achieved with the use of concurrent, rather than sequential, use of ECT and medication.[62]

There is some evidence that concomitant use of lithium and ECT may increase cognitive side effects, encephalopathy, and spontaneous seizures, whereas benzodiazepines and anticonvulsants may raise the seizure threshold and decrease seizure efficacy, although lamotrigine may be less problematic than other anticonvulsants.[75]

Magnetic Seizure Therapy (MST)

4.17. What Is MST and How Is It Delivered?

MST is a noninvasive convulsive neurostimulation therapy that relies on the principle of electromagnetic induction to induce an electric field in the brain strong enough to elicit a generalized tonic-clonic seizure. Currently, MST is being investigated as an alternative to ECT. Like ECT, the seizure is elicited under general anaesthesia with assisted ventilation and EEG monitoring, but MST has the potential for fewer side effects such as cognitive dysfunction.[76]

The equipment used in MST consists of a neurostimulator and coil that is placed in direct contact with the skull. When electrical current passes through the coil, a strong focal magnetic field is generated (in the order of 2 Tesla). This magnetic field crosses the skull and soft tissue unimpeded to reach brain tissue, inducing an electrical current that causes neuronal depolarization and eventually triggering a generalized seizure.

4.18. What Are the Delivery Parameters of MST?

The optimal delivery parameters for MST are still being investigated. Most studies have used a coil placement at the vertex (i.e., Cz in 10-20 electroencephalogram [EEG] system) with a frequency of stimulation of 100 Hz, pulse width of 0.2 to 0.4 ms, and stimulation duration of 10 seconds. A summary of MST parameters used in studies is listed in Supplemental Table S1. MST has been given on a similar schedule as ECT, usually 2 to 3 times per week, with an index course of 12 treatments.

4.19. How Effective Is MST Compared to ECT?

There are no studies comparing MST versus sham stimulation. One small RCT ($N = 20$) comparing MST to RUL ECT found no significant differences in response rates (60% vs. 40%, respectively) or remission rates (30% vs. 40%, respectively).[77] In addition, the largest MST case series ($N = 26$, which included the 10 patients who received MST in the randomized trial) reported an overall response rate of 69% and remission rate of 46%,[78] which would be similar to those obtained with ECT. There are no studies of relapse following MST or of relapse prevention strategies. As a result, MST is recommended as an investigational treatment alternative for ECT based on Level 3 Evidence (Table 2).

4.20. What Are the Adverse Effects Associated with MST Compared to ECT?

MST seems to be associated with lower rates of headaches and muscle aches than ECT. In addition, MST has not shown a significant impact on anterograde or retrograde amnesia, and reorientation time (the time it takes after the seizure and emergence from anaesthesia to be fully oriented to person, place, and time) appears to be significantly shorter in patients receiving MST compared to ECT (2-7 minutes vs. 7-26 minutes, respectively).[76] However, the 1 randomized comparison of MST versus RUL ECT ($N = 20$) found no significant differences in neuropsychological testing after 12 treatments.[77]

Vagus Nerve Stimulation (VNS)

4.21. What Is VNS and How Is It Delivered?

VNS is an implantable neurostimulation technology originally approved in 1997 for the treatment of drug-resistant

epilepsy. The VNS system comprises an implantable pulse generator (IPG), which is surgically inserted underneath the skin of the chest, connected to an electrode placed in one of the vagus nerves in the neck. The vagus nerve is a cranial nerve that largely consists of fibers that transmit nerve impulses from the periphery to the brain. Electrical stimulation of the vagus nerve provides stimulation to the nucleus tractus solitarius, which in turn is able to modulate multiple regions of the brain via its neuronal connections to anatomically distributed subcortical and cortical regions of the brain.[79]

4.22. What Are the Delivery Parameters for VNS?

Optimal treatment parameters for VNS remain a research question. In an RCT of open-label VNS ($N = 331$) comparing low (0.25 mA current, 130 ms pulse width), medium (0.5-1.0 mA, 250 ms), or high (1.25-1.5 mA, 250 ms) electrical outputs, higher electrical charges were correlated with better improvement in depressive symptoms.[80] More sustained antidepressant responses and less frequent suicide attempts were reported in the medium- and high-stimulation groups than the low-dose group.

4.23. How Effective Is VNS in Acute Treatment?

VNS was approved by the Food and Drug Administration (FDA) in the United States in 2005 for the adjunct long-term treatment of chronic or recurrent depression for adult patients experiencing a major depressive episode who had failed to respond to 4 or more adequate antidepressant treatments. A meta-analysis of open-label studies (7 studies, $N = 426$) found a response rate of 31.8%.[81] However, only 1 RCT ($N = 235$) has evaluated the efficacy of VNS versus a sham-control condition, with no significant differences in efficacy between the conditions at 12 weeks.[82] Therefore, VNS is recommended as a third-line acute treatment with Level 3 Evidence for efficacy (Table 2).

4.24. How Effective Is VNS During Extended Treatment?

Recent systematic reviews and meta-analyses of open-label studies have suggested that the antidepressant effects of VNS may accrue over time. A patient-level meta-analysis (6 trials, $N = 1460$) of all randomized and open-label data with VNS found significantly higher odds ratios (ORs) for response (OR, 3.19) and remission (OR, 4.99) for VNS plus treatment as usual (TAU) compared to TAU alone.[83] However, absolute rates were low (e.g., remission rates for VNS plus TAU at 12, 24, 48, and 96 weeks were 3%, 5%, 10%, and 14%, respectively, vs. 1%, 1%, 2%, and 4% for TAU alone).[83] The median time to response with VNS was estimated to be 9 months in 1 study.[84] In another VNS study ($N = 74$), only 35% of patients had achieved a response by 3 months, but 61.5% and 50% of these 3-month responders maintained response at 12 months and 24 months, respectively.[85] Hence, the longer term results with VNS appear encouraging, and VNS can be considered for patients with chronic depression, particularly in situations where treatment adherence may be an issue.

4.25. What Are the Adverse Effects Associated with VNS?

Most patients with VNS are also on antidepressant medications, so adverse effects are for the combined treatment. The most commonly reported adverse effects after 1 year of VNS for TRD are voice alteration (69.3%), dyspnea (30.1%), pain (28.4%), and increased cough (26.4%).[83] Voice alteration and increased cough are often direct effects of VNS being actively delivered and can immediately improve by turning the stimulation off. The tolerability of VNS appears to improve over time with diminishing rates of adverse events reported by patients during their long-term treatment with VNS.[83] The reported rates of serious adverse psychiatric events have included suicide or attempted suicide (4.6%) and treatment-emergent hypomania or mania (2.7%).[80] A lower all-cause mortality rate, including suicide, has been observed in patients with TRD treated with adjunctive VNS compared to TAU.[86]

Deep Brain Stimulation (DBS)

4.26. What Is DBS and How Is It Delivered?

DBS is an invasive neurosurgical procedure involving the implantation of electrodes under MRI guidance into discrete brain targets. The electrodes are internalized and connected to an IPG that is typically implanted into the chest below the right clavicle. Similar to cardiac pacemakers and VNS, the IPG in DBS can be accessed using a handheld device, allowing the stimulation parameters to be monitored and/or programmed remotely. Modifiable DBS parameters include pulse width, frequency, and amplitude (voltage or current), which can be programmed by the treating physician and titrated to clinical effect. Currently, the most common indications for DBS are movement disorders (most specifically Parkinson's disease),[87] but DBS for difficult-to-treat psychiatric disorders, including TRD, is a growing research field.

4.27. How Effective Is DBS as an Acute Treatment in TRD?

DBS is still considered an experimental treatment, with Level 3 Evidence supporting efficacy (Table 2). Evidence for effectiveness of DBS has been based on nonrandomized, open-label trials with small sample sizes (fewer than 20 patients each) of patients with antidepressant-, psychotherapy-, and, often, ECT-refractory depression. The main anatomical targets for TRD are subcallosal cingulate (SCC) white matter, ventral capsule/ventral striatum

(VC/VS), nucleus accumbens, and medial forebrain bundle (MFB), with the majority of reports focused on the SCC.[88] The optimal stimulation parameters for various brain targets remain unknown. Generally, studies of DBS with these targets in highly refractory patients have reported response rates between 30% and 60% and remission rates between 20% and 40% at 3 or 6 months,[89,90] but a small study ($N = 7$) of open-label DBS of the MFB reported a response rate of 85.7% and a remission rate of 57.1%.[91]

The results from these open-label reports stand in contrast to the 2 multicentre, sham-controlled RCTs conducted to date, both of which were discontinued early because of lack of an efficacy signal. A study of VC/VS DBS ($N = 30$) found no differences between active and sham stimulation after the 16-week randomized phase, with response rates of 20% and 14.3%, respectively.[90] An open-label continuation phase showed response rates of 20%, 26.7%, and 23.3% at 12, 18, and 24 months, respectively. A multicentre, sham-controlled trial of SCC DBS ($N = 75$) was recently discontinued because of an interim futility analysis showing low probability of significant efficacy at 6 months.[88]

4.28. How Effective Is DBS During Extended Treatment?

Long-term data for DBS involves SCC DBS. A meta-analysis (4 open-label studies, $N = 66$) of SCC DBS for TRD revealed that depression severity was significantly reduced after 12 months (Hedges's $g = -1.89$, $P < 0.0001$).[89] At 3, 6, and 12 months, the pooled response rates were 36.6%, 53.9%, and 39.9%, respectively, while the pooled remission rates were 16.7%, 24.1%, and 26.3%, respectively.[89]

Higher rates of response have been observed in open studies beyond 1 year with SCC DBS. In 1 study ($N = 17$), the response rates were 36% and 92% at 1 and 2 years, respectively, and remission rates were 58% at 2 years.[92] In a long-term open study ($N = 20$) with follow-up to 6 years, response rates were 62.5%, 46.2%, and 75% at 1, 2, and 3 years, respectively, and remission rates were 20% and 40% at 2 and 3 years, respectively.[93] Improvements in health-related quality of life have also been reported with both long-term SCC and MFB DBS.[93,94]

In summary, the existing data from open-label studies are consistent with the premise that the antidepressant effects of SCC DBS continue to accrue over months and years of chronic stimulation, with improved rates of clinical and functional outcomes observed beyond 1 year postsurgery. However, the data from sham-controlled RCTs have yet to demonstrate efficacy of VC/VS and SCC DBS in acute treatment of TRD.

4.29. How Effective Is Maintenance Treatment Post-DBS?

Only 1 study has specifically addressed relapse prevention with DBS. Five patients were treated with SCC DBS to remission and randomized to on/off or off/on stimulation in blocks of 3 months.[95] At the end of active DBS, depression was remitted in 4 of 5 patients, and none of them had experienced a relapse, whereas at the end of sham stimulation, only 2 remained in remission, suggesting that ongoing DBS was required to maintain remission.

4.30. What Are the Adverse Effects Associated with DBS?

Adverse effects observed in longitudinal studies of DBS for TRD may be secondary to a multitude of factors, including those related to the surgical procedure itself (e.g., intracranial haemorrhage), perioperative risks (e.g., wound infection), factors unrelated to the DBS treatment, effects of stimulation on discrete brain regions, or changes in the DBS parameters. DBS has generally been well tolerated by patients, despite the inherent risks associated with an invasive neurosurgical procedure. The pooled dropout rate after 1 year of SCC DBS ($N = 63$) has been estimated to be 10.8% (95% CI, 4.3% to 24.4%).[89] There has been no evidence of worsening in neuropsychological performance with DBS, irrespective of the brain target,[94,96-98] and some studies report improvements in cognitive performance.

Reported psychiatric adverse events have included the emergence of psychosis and hypomania associated with a change in the stimulation parameters in patients receiving nucleus accumbens DBS.[99] These symptoms were transient and reversible with a change in DBS parameters. No episodes of hypomania have been reported with SCC DBS, including its use in patients with bipolar disorder.[92]

Oculomotor adverse events, including blurred vision and strabismus, have been reported with MFB DBS.[93] These effects were seen in all patients at higher amplitude settings. Suicidality and completed suicide have been reported,[92,93,99] although there was no evidence that these adverse events were secondary to device-related factors. The risk factors for suicidality with DBS are unclear but may be increased in those with a history of pre-DBS suicide or major concurrent psychosocial stressors.[92,93,99]

4.31. Should DBS Be Combined with Other Antidepressant Treatments?

To date, DBS has largely been used as an augmentation strategy to antidepressant medication, with very few patients receiving no psychotropic medication at the time of implantation. However, the optimal means of combining pharmacological, psychological, and other brain stimulation treatments with DBS remains unknown.

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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 5. Complementary and Alternative Medicine 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. "Complementary and Alternative Medicine Treatments" is the fifth of six sections of the 2016 guidelines.

Results: Evidence-informed responses were developed for 12 questions for 2 broad categories of complementary and alternative medicine (CAM) interventions: 1) physical and meditative treatments (light therapy, sleep deprivation, exercise, yoga, and acupuncture) and 2) natural health products (St. John's wort, omega-3 fatty acids; S-adenosyl-L-methionine [SAM-e], dehydroepiandrosterone, folate, *Crocus sativus*, and others). Recommendations were based on available data on efficacy, tolerability, and safety.

Conclusions: For MDD of mild to moderate severity, exercise, light therapy, St. John's wort, omega-3 fatty acids, SAM-e, and yoga are recommended as first- or second-line treatments. Adjunctive exercise and adjunctive St. John's wort are second-line recommendations for moderate to severe MDD. Other physical treatments and natural health products have less evidence

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but may be considered as third-line treatments. CAM treatments are generally well tolerated. Caveats include methodological limitations of studies and paucity of data on long-term outcomes and drug interactions.

Keywords
major depressive disorder, meta-analysis, systematic reviews, evidence-based medicine, clinical practice guidelines, complementary and alternative medicine, light therapy, sleep deprivation, exercise, natural health products

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. This section on complementary and alternative medicine (CAM) treatments is 1 of 6 guidelines articles; other sections expand on principles of care, psychological treatments, pharmacological treatments, neurostimulation treatments, and special populations. As before, the scope of these guidelines remains the management of adults with unipolar major depressive disorder (MDD). These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

While definitions of CAM treatments vary widely, they can be broadly defined as "a group of diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine."[2] The popularity of CAM continues to increase across the Western world,[3] in part because of a belief that "natural is better"[3] and a preference for self-directed over practitioner-directed therapies[4] and the favourable adverse event profiles, lower costs, and perceived efficacy of CAM treatments. Use by people with mental illness is estimated to range between 16% and 44%,[5,6] and a significant majority of these suffer from depression.[7] Unfortunately, although 10% to 30% of depressed patients are thought to use CAM treatments, there is generally no medical supervision, and these treatments are often used in combination with existing medications without considering possible interactions.[4]

As many as 120 different CAM therapies have been identified,[8] but only a small proportion has sufficient published evidence to warrant evaluation. Thus, this section focuses on 2 forms of CAM treatments: physical and meditative treatments (light therapy, sleep deprivation, exercise, yoga, and acupuncture) and natural health products (St. John's wort, omega-3 fatty acids, S-adenosyl-L-methionine (SAM-e), dehydroepiandrosterone (DHEA), tryptophan, folate preparations, acetyl-L-carnitine, *Crocus sativus*, *Lavandula*, and *Rhodiola rosea*). Many other CAM therapies, such as qi gong, aromatherapy, and massage therapy, are not reviewed because of a very limited evidence base.

Methods

The full methods have been previously described,[9] but in summary, relevant English-language publications 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 is informed by 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. Supplemental materials and citations, including small-sample randomized controlled trials (RCTs) not described in the text, are available online (Suppl. Tables S1-S10). The question-answer format adopted in the previous CANMAT guidelines has been retained for ease of use.

5.1. What Are General Caveats and Limitations of CAM Treatments?

As noted in the 2009 guidelines, the varying quality of RCTs (sample size, design, homogeneity of population) presents a major limitation to the systematic evaluation of CAM treatments.[10] In addition, variations within interventions (e.g., potency, dose, duration) across RCTs and frequent lack of long-term data impede the systematic evaluation of their benefit in practice. Blinding also poses a greater challenge for nonpharmacologic trials than pharmacologic trials.[11] Because of these limitations, as well as the volume of research on CAM therapies, we focused primarily on systematic reviews and meta-analyses, whenever available, to construct a global view of the literature for each CAM treatment. Publication bias must also be considered in evaluations of CAM research, given evidence suggesting bias in favour of CAM therapies as well as against.[12,13]

It is accepted that for most patients with MDD, evidence-based pharmacological treatments and/or psychological treatments should be considered ahead of CAM treatments because of a generally larger evidence base and often better quality evidence for efficacy. As well, it is emphasized that appropriate clinical judgement should be employed in determining the suitability of CAM treatments for individual patients. There remains a dearth of information on interactions between CAM therapies and conventional treatments for depression, as well as interactions between different CAM therapies. Such risk is compounded by the fact that patients often do not disclose self-directed CAM use to clinicians,[4,14] and clinicians may not ask.[15] In the absence of adequate safety information on treatment interactions, it is recommended that clinicians discuss the risks and benefits of CAM treatments with their patients and select and administer these therapies in an individual and tailored manner.

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.

Physical and Meditative Treatments

5.2. What Is Light Therapy? How Effective Is Light Therapy for the Treatment of MDD?

Light therapy (LT), or phototherapy, involves daily exposure to bright light and is typically administered at home with a fluorescent light box. Dosing of light may vary in intensity, spectrum (soft white to "blue enhanced" light), exposure duration, and time of administration (morning vs. evening).[7] The standard protocol is 10,000 lux (light intensity) for 30 minutes per day during the early morning for up to 6 weeks, with response usually seen within 1 to 3 weeks.[16,17] Proposed mechanisms of antidepressant action include the alteration of circadian rhythms[7] and modulation of serotonin and catecholamine systems.[18] Light therapy is generally well tolerated,[17] with common side effects being eye strain, headache, agitation, nausea, and sedation.[19]

Since 2009, 2 meta-analyses,[16,20] 4 systematic reviews[17,19,21,22] and 3 RCTs[23-25] have been generally confirmatory of recommendations in the 2009 guidelines (see Suppl. Table S1). While 1 meta-analysis (10 trials, $N = 714$) suggested that the efficacy of LT in seasonal depression has been overstated,[16] the other systematic reviews supported its benefit in seasonal depression. A large RCT also found that cognitive-behavioural therapy (CBT) had similar efficacy to LT as monotherapy or adjunctive in acute treatment of seasonal depression,[25] but a naturalistic follow-up study revealed that CBT was superior after 2 years.[26] Newer studies have expanded the LT evidence base for nonseasonal MDD. A recent meta-analysis (20 trials, $N = 881$) also found evidence to support the efficacy of LT as monotherapy in nonseasonal MDD.[20] In addition, an RCT reported that LT monotherapy and LT combined with fluoxetine were superior to placebo in nonseasonal MDD, with the combined treatment showing the most consistent effects.[23] Similarly, medication paired with chronotherapeutic techniques (LT, sleep deprivation, and sleep time stabilization) led to superior remission rates in nonseasonal MDD compared to medication combined with exercise at both 9-week and 29-week follow-up.[24,27]

In summary, the updated evidence continues to support LT as a first-line monotherapy for seasonal depression and as a second-line monotherapy or adjunctive treatment for mild to moderate nonseasonal MDD (Table 2).

5.3. What Is Sleep Deprivation? How Effective Is Sleep Deprivation for the Treatment of MDD?

Sleep deprivation (SD) continues to demonstrate rapid antidepressant effects in recent publications.[28] It involves keeping patients awake for extended periods, with total SD lasting up to 40 hours and partial SD allowing 3 to 4 hours of sleep per night.[29] Sleep deprivation is typically employed 2 to 4 times over the course of 1 week, with total SD often interspersed with partial SD or normal (recovery) sleep.[30,31] Several mechanisms of antidepressant action have been proposed, including increased activity of all neurotransmitter systems, synaptic potentiation, and glial signaling.[28] One systematic review[29] supported the efficacy of SD as augmentation to antidepressants in moderate to severe MDD (see Suppl. Table S2).

A practical limitation for the use of SD is maintaining its use for longer than a few weeks. Relapse after discontinuation is often rapid. However, combined chronotherapeutic techniques offer rapid onset of efficacy, greater clinical utility, and sustained response compared to total SD alone.[32] One such strategy is the combination of SD with sleep-phase advance (SPA), which involves scheduling bedtimes that are earlier than usual and then advancing the times on subsequent nights until a normal bedtime is reached. Several RCTs have demonstrated that an estimated 50% to 75% of SD responders experience continued improvement when SD and SPA are combined.[33] Tripartite interventions (total or partial SD + light therapy + SPA) implemented in small open trials also yielded remission rates of 60% to 75%.[31,34,35]

The most common side effect of SD is daytime sleepiness. Recurrence of panic attacks has been noted during SD,[24] but with no adverse impact on treatment of comorbid depression. The only established contraindication for SD is epilepsy, given the high risk of seizure induction with sleep

Table 2. Summary of Recommendations for Physical and Meditative Treatments.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
Exercise	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 1	Adjunctive
Light therapy	Seasonal (winter) MDD	First line	Level 1	Monotherapy
	Mild to moderate nonseasonal MDD	Second line	Level 2	Monotherapy and adjunctive
Yoga	Mild to moderate MDD	Second line	Level 2	Adjunctive
Acupuncture	Mild to moderate MDD	Third line	Level 2	Adjunctive
Sleep deprivation	Moderate to severe MDD	Third line	Level 2	Adjunctive

MDD, major depressive disorder.

reduction.[36] The risk of SD-induced mania is estimated to be low, with switch rates similar to or lower than with antidepressants and placebo.[36]

In summary, although there is Level 2 Evidence for SD in MDD, the findings are confounded by the challenges of blinding and sustaining treatment. SD is thus recommended as a third-line adjunctive treatment for more severe and refractory forms of MDD, in combination with other chronotherapeutic techniques (Table 2).

5.4. How Effective Is Exercise for the Treatment of MDD?

Exercise is a structured physical activity, often supervised, and undertaken with the aim of maintaining or improving physical fitness or health.[37] Potential mechanisms to explain its benefit in depression include biological factors (e.g., increased turnover of neurotransmitters, endorphins, or neurotrophic factors like brain-derived neurotrophic factor; reduction in cortisol levels; changes in kynurenine metabolism), and psychological factors (e.g., increased self-efficacy).[37] In general, exercise is well tolerated, with adverse events rarely reported in exercise and depression trials.[37] While both cardiovascular (aerobic) and resistance (anaerobic) exercise have been shown to be effective in reducing depressive symptoms, there is no clear evidence for the superiority of either form.[38] Recommendations for administration vary, but at least 30 minutes of supervised moderate-intensity exercise at least 3 times weekly for a minimum of 9 weeks is considered effective.[39,40] As with all physical activity interventions, however, the physical fitness of the participant must be taken into consideration.

Recent meta-analyses[37,41-44] and systematic reviews[39,45] have evaluated exercise as monotherapy or adjunct to antidepressants or psychotherapy for mild to moderate depression (Suppl. Table S3). Two meta-analyses (39 trials, $N = 2326$[31]; 13 trials, $N = 720$[36]) and 2 systematic reviews[43,45] reported that exercise was as effective as pharmacotherapy or psychotherapy. Other meta-analyses reported that adjunctive exercise was effective in the short term (13 trials, $N = 687$),[41] and superior to no-treatment control conditions (13 trials, $N = 720$)[42] and to control conditions like treatment as usual (10 trials, $N = 758$).[43] For moderate to severe MDD, 1 meta-analysis (20 trials, $N = 1298$) found exercise to be superior to control conditions.[44] Some methodological challenges, including suitability of control conditions, adequacy of blinding and self-selection bias, may limit interpretation of results. For example, when only high-quality trials were considered, the effect size for benefit of exercise became smaller.[37,42,44] There is also some evidence that exercise has better adherence when supervised by qualified practitioners, so feasibility may be an issue.[46]

The evidence for the long-term benefits of exercise in MDD is less clear. Meta-analyses have found only small effects[37] or no effects[41] for exercise in the long term, although a continued exercise regimen may help to maintain early benefits. A systematic review of large population-based, prospective studies suggested that participation in physical activity may also prevent the onset of depression.[47] Further research is therefore needed to assess the long-term benefits of exercise for depression.

In summary, there is Level 1 Evidence for exercise in treating MDD. It is recommended as first-line monotherapy for mild to moderate MDD and as second-line adjunctive treatment for moderate to severe MDD, based on the lack of long-term data and feasibility issues (Table 2).

5.5. What Is Yoga? How Effective Is Yoga for the Treatment of MDD?

Practitioners of the ancient Indian practice of yoga seek physical, mental, and spiritual balance. Thus, yoga "asanas" or postures aim to improve flexibility and strength, while controlled breathing exercises or "pranayama" target heightening of body awareness, and "dhyana" or meditation is thought to produce cognitive benefits.[48] The proposed neurobiological mechanisms for its benefit include increased turnover of dopamine and gamma-aminobutyric acid (GABA) levels in specific brain regions, regulation of the hypothalamic-pituitary-adrenal axis,[49] and normalization of heart rate variability.[50] The duration of yoga interventions varies, averaging 2 to 4 sessions a week over a course of 2 to 3 months.[49]

Since 2009, 1 meta-analysis (12 trials, $N = 619$)[49] has reported moderate advantage for yoga compared to usual care but only a modest benefit compared to relaxation and aerobic exercise (Suppl. Table S4). Integrated yoga forms,

incorporating breath control and meditation, may produce more benefits than those that focus on postures alone. Limitations of yoga studies include low quality of RCTs, variability in practice parameters and physical/mental health of participants, as well as difficulties with suitable control conditions.[49] Long-term efficacy and safety data are also lacking.

Side effects are rarely reported in studies of yoga, and the participant's level of physical fitness may play a role in the presence or severity of any adverse effects that are experienced.[48] There are case reports of meditation-induced mania or psychosis and of excessive or incorrect yoga practice possibly contributing to serious adverse effects such as artery occlusion or lotus neuropathy.[48]

Yoga continues to be recommended as a second-line adjunctive therapy in mild to moderate MDD with Level 2 Evidence (Table 2). Other treatments involving meditative practices (such as mindfulness-based cognitive therapy) are included in Section 2, Psychological Treatments.[51]

5.6. What Is Acupuncture? How Effective Is Acupuncture for the Treatment of MDD?

Acupuncture has been used for centuries in Asia as a treatment for a variety of health conditions, including chronic pain, gastrointestinal conditions, and musculoskeletal disorders. It involves the insertion of fine needles at specific physiological points to modulate the activity of nervous, hormonal, and immune systems. In recent years, electroacupuncture (transmission of a small, pulsed electrical current to the body through acupuncture needles) and laser acupuncture (use of low-level laser beams at specific acupuncture points) have also been evaluated, with comparable efficacy to manual acupuncture.[52] Acupuncture sessions may involve a variety of acupoints, are typically 20 to 30 minutes in duration, and range from 10 to 30 sessions, decreasing in frequency over time from daily to weekly intervals.[52]

While several RCTs and meta-analyses supported acupuncture as both a beneficial monotherapy[53,54] and as adjunct treatment,[54-56] others did not find evidence of efficacy for acupuncture either alone or as an adjunct therapy[52,57] (Suppl. Table S5).

The inconsistency in findings has been attributed to methodological issues. Sham acupuncture is often used as a control condition; however, there is no robust evidence that any specific acupoints are more relevant to depression than others, and as such, even sham treatment may produce benefits.[57] Small sample sizes, unclear randomization procedures, and heterogeneity of study protocols are other limitations.

Generally, acupuncture is well tolerated when performed by a trained and regulated practitioner. Adverse effects are usually mild and include headache, transient bleeding, bruising at needle insertion sites, skin irritation, and syncope.[11,52] To avoid infection, sterile, disposable needles and aseptic techniques should be used.

Acupuncture is recommended as a third-line treatment, with Level 2 Evidence in the adjunctive treatment of mild to moderate MDD (Table 2).

Natural Health Products

Natural health products are naturally occurring, nonprescription substances that promote or preserve good health, according to Health Canada. They include vitamins and minerals, herbal remedies, traditional and homeopathic medicines, and probiotics. As the list of available natural health products is extensive, only commonly used products with a reasonable body of published data are reviewed.

5.7. What Is St. John's Wort? How Effective Is St. John's Wort for the Treatment of MDD?

St. John's wort (SJW) (*Hypericum perforatum*) is a perennial plant that has been used as a herbal medicine for many centuries, with the total extract (which include hypericin/hyperforin and several other flavonoids) being regarded as active. Suggested mechanisms of antidepressant action include direct effect on serotonin receptors, monoamine oxidase inhibition, and neuroendocrine and ion channel modulation.[58,59] Formulations of SJW have varied widely, as has the dose range (500 to 1800 mg/day), while treatment duration has spanned 4 to 12 weeks.[58,60]

Since 2009, 2 systematic reviews[60,61] have confirmed the comparable efficacy of SJW to antidepressants and superiority to placebo for mild to moderate MDD (Suppl. Table S6). In MDD of greater severity, 1 systematic review[60] found SJW to be of equal efficacy to selective serotonin reuptake inhibitors, with a lower rate of withdrawals due to adverse events, whereas the other[61] reported no difference between SJW and placebo. In 2 subsequent RCTs, one found no significant difference between SJW, sertraline, or placebo monotherapy,[62] while the other found SJW monotherapy superior to placebo, particularly for individuals with moderate levels of atypical depression.[63]

Although SJW is significantly better tolerated than many first-line antidepressants,[64] side effects include gastrointestinal upset, headaches, skin irritation, photosensitivity, and dry mouth.[65] There is concern that higher potency extracts can interfere with the metabolism of various medications.[66] In addition, serotonin syndrome and hypomania have been reported when SJW is used concurrently with antidepressants.[67,68]

SJW is recommended as first-line monotherapy in mild to moderate MDD (Level 1 Evidence) and is recommended as a second-line adjunctive treatment for moderate to severe MDD (Level 2 Evidence) (Table 3).

5.8. What Are Omega-3 Fatty Acids? How Effective Are Omega-3 Fatty Acids for the Treatment of MDD?

Omega-3 fatty acids (ω-3 fatty acids) are polyunsaturated fatty acids that are primarily found in oily fish and certain nuts and seeds. Different formulations of ω-3 fatty acids have been

Table 3. Summary of Recommendations for Natural Health Products.

Intervention	Indication	Recommendation	Evidence	Monotherapy or Adjunctive Therapy
St. John's wort	Mild to moderate MDD	First line	Level 1	Monotherapy
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Omega-3	Mild to moderate MDD	Second line	Level 1	Monotherapy or adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
SAM-e	Mild to moderate MDD	Second line	Level 1	Adjunctive
	Moderate to severe MDD	Second line	Level 2	Adjunctive
Acetyl-L-carnitine	Mild to moderate MDD	Third line	Level 2	Monotherapy
Crocus sativus (saffron)	Mild to moderate MDD	Third line	Level 2	Monotherapy or adjunctive
DHEA	Mild to moderate MDD	Third line	Level 2	Monotherapy
Folate	Mild to moderate MDD	Third line	Level 2	Adjunctive
Lavandula (lavender)	Mild to moderate MDD	Third line	Level 3	Adjunctive
Inositol	Mild to moderate MDD	Not recommended	Level 2	
Tryptophan	Mild to moderate MDD	Not recommended	Level 2	
Rhodiola rosea (roseroot)	Mild to moderate MDD	Not recommended	Insufficient evidence	

DHEA, dehydroepiandrosterone; MDD, major depressive disorder; SAM-e, S-adenosyl-L-methionine.

studied, the most common being eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The typical dose range is 3 to 9 g/day of ω-3 or 1 to 2 g of EPA plus 1 to 2 g of DHA per day.[69] Duration of treatment ranges from 4 to 16 weeks.[70,71]

Four new meta-analyses[70-73] and 2 systematic reviews[69,74] have provided updates on the efficacy of ω-3 fatty acids in MDD (Suppl. Table S7). One reported no benefits (13 trials, $N = 731$),[70] another meta-analysis (25 trials, $N = 1438$)[72] and 1 review[74] reported equivocal outcomes, 1 meta-analysis (15 trials, $N = 916$) reported a positive outcome as monotherapy,[73] and 1 meta-analysis (11 trials, $N = 418$)[69] and 1 review[71] reported a positive outcome as adjunctive therapy.

Contradictory findings may be due to differences in study populations, methodology, and intervention parameters. The most recent and rigorous meta-analysis (11 trials, $N = 418$),[71] reporting specifically on DSM-defined MDD, found large effect sizes for the efficacy of ω-3 fatty acids. The variability in findings may also be due to differences in the composition and dosage of ω-3 fatty acids used. Two meta-analyses[71,73] found that EPA-dominant formulations were superior to DHA-based options for alleviation of depressive symptoms.

The ω-3 supplements are generally well tolerated with only mild side effects, including diarrhea, nausea, and a fishy aftertaste.[11,75] Patients on anticoagulant and antiplatelet medications may also require additional monitoring.[76] Manic induction has been reported in a few cases, although not in bipolar depressed patients.[77,78]

Thus, ω-3 fatty acids have Level 1 Evidence of efficacy but, because of the inconsistency in the evidence, are recommended as second-line monotherapy for mild to moderate MDD and adjunctive to antidepressants for moderate to severe MDD (Table 3).

5.9. What Is SAM-e? How Effective Is SAM-e for the Treatment of MDD?

SAM-e is a natural substrate in the human body, including in the brain, that is thought to function as a methyl donor in various physiological processes.[61] Proposed mechanisms of antidepressant action include modulation of monoaminergic neurotransmission.[79]

SAM-e is prescribed in Europe as an oral or parenteral treatment for several conditions, including MDD.[80] In the United States and Canada, SAM-e is available as an oral over-the-counter dietary supplement, often used in the dose range of 800 to 1600 mg/day given in divided doses with meals over 4 to 12 weeks.[81] Studies have also used intravenous and intramuscular formulations of SAM-e, at doses of 200 to 400 mg/day across 2 to 8 weeks,[61,81] which may be more effective than oral supplements.[69]

Two systematic reviews found SAM-e effective as a monotherapy versus placebo in mild to severe MDD[61] or versus comparator antidepressants in mild to moderate MDD[81] (Suppl. Table S8). There is also evidence to support adjunctive SAM-e with antidepressants in mild to moderate MDD.[69,81] There are concerns, however, about trial methodologies and paucity of data on SAM-e as maintenance therapy.[61]

Overall, SAM-e is relatively well tolerated, with the most common side effects being gastrointestinal upset, insomnia, sweating, headache, irritability, restlessness, anxiety, tachycardia, and fatigue.[11,81]

In summary, SAM-e is recommended as a second-line adjunctive treatment for use in mild to moderate MDD (Level 1 Evidence) (Table 3).

5.10. What Is DHEA? How Effective Is DHEA for the Treatment of MDD?

Dehydroepiandrosterone (DHEA) is a hormone produced by the adrenal cortex, which is subsequently converted to sex hormones in the body.[82] It plays a role in modulating neuroendocrine and immune homeostasis and influences monoaminergic and glutaminergic neurotransmission.[83] Dosage of DHEA commonly used in research ranges from 30 to

450 mg/day, with treatment lasting 6 to 8 weeks.[11] No new clinical trials have been conducted since 2009 that specifically evaluated the efficacy of DHEA in treating MDD, and therefore, there is no new evidence to assess.

Side effects of DHEA include hirsutism, acne, hypertension, liver damage, and manic induction.[84] Higher doses are also associated with more serious adverse effects, such as worsening of prostatitis and increased risk of breast cancer.[84]

DHEA remains recommended as a third-line treatment with Level 2 Evidence as monotherapy and Level 3 Evidence as adjunctive treatment (Table 3).

5.11. What Is Tryptophan? How Effective Is Tryptophan for the Treatment of MDD?

Tryptophan is a precursor of serotonin, which cannot be synthesized de novo and must be supplied through diet. It is hypothesized that adjunctive tryptophan may potentiate serotonergic neurotransmission, mediating antidepressant benefits by the process of 'precursor loading'.[85] The recommended dose in clinical practice is 2 to 4 g/day, with a suggested duration of 3 to 4 months.[85,86]

A systematic review[69] and 1 RCT[87] have been published since 2009, with no clear evidence to support an adjunctive role for tryptophan to treat MDD (Suppl. Table S9). Reported side effects of tryptophan are mild and most frequently include sedation, dry mouth, and gastrointestinal distress, but may also include serotonin syndrome and a potential to increase lithium toxicity when used in combination.[88]

Tryptophan is therefore not recommended for the treatment of MDD (Table 3).

5.12. What Other Natural Health Products Have Been Evaluated in the Treatment of MDD?

Several other natural health products have been evaluated as potential treatments for depression (Table 3). Only the evidence for relatively better evaluated agents (folate preparations, inositol, acetyl-L-carnitine, *C. sativus* [saffron], *Lavandula* [lavender], and *R. rosea* [roseroot]) was reviewed (Suppl. Table S10).

A meta-analysis (11 trials, $N = 2204$) of folic acid found no evidence to support its efficacy as a short-term adjunctive agent for antidepressants, although many subjects had medical and other psychiatric comorbidities.[89] However, 2 narrative reviews[90,91] and a retrospective analysis[92] support the use of folate preparations (particularly L-methylfolate) as monotherapy[90] or adjunct to antidepressants for MDD,[90-92] although small samples and the lack of double-blind, placebo-controlled trials are notable limitations. Genetic polymorphisms may also play a role in efficacy, and certain folate preparations may be better suited to specific genetic profiles.[90]

There was no evidence from a meta-analysis (9 trials, $N = 242$) to support the efficacy of inositol as monotherapy or adjunctive therapy in MDD.[93]

In contrast, a narrative review found that acetyl-L-carnitine was superior to placebo, and as effective as fluoxetine and amisulpride, as a monotherapy for mild to moderate depression.[94] It is generally well tolerated without significant side effects.[10,94]

The usual dose of *C. sativus* (saffron) is 20 to 30 mg/day over 6 to 8 weeks.[95,96] One new meta-analysis (5 trials, $N = 177$)[97] and 3 systematic reviews[96,98,99] further support its use as a monotherapy with comparable efficacy to antidepressants in mild to moderate MDD. Reported adverse effects of *C. sativus* are mild and include anxiety/nervousness, increased appetite, nausea, and headache.[96]

Lavandula (lavender) doses are recommended at 2 to 4.5 mL/day (alcoholic tincture 1:2) or 6 to 12 mL/day (alcoholic tincture 1:5).[100] It has only been studied as an acute intervention in the short term (4-8 weeks).[69] In 1 RCT, the combination of *Lavandula* and citalopram was significantly more effective than citalopram alone for moderate to severe depression.[101] Adverse effects of *Lavandula* include nausea, confusion, and mild headaches.[69,101]

Standard dose regimens for *R. rosea* (roseroot) are not available in the literature, with studies reporting a range of 100 to 680 mg/day. It, too, has only been studied in the short term (4-8 weeks).[102] One RCT of *R. rosea* monotherapy and sertraline in mild to moderate MDD found that neither condition was significantly different from placebo.[103] *R. rosea* has mild and infrequent side effects, including nervousness, dizziness, allergy, irritability, insomnia, fatigue, and unpleasant sensations.[102,103] Interactions with concomitant medications, such as theophylline and warfarin, have been reported.[104]

In summary, for mild to moderate MDD, acetyl-L-carnitine (Level 2 Evidence) is recommended as a third-line monotherapy and *C. sativus* as third-line monotherapy or adjunctive treatment (Level 2 Evidence) (Table 3). Folate (Level 2 Evidence) and *Lavandula* (Level 3 Evidence) are recommended as third-line adjunctive treatments. Inositol and *R. rosea* are not recommended for the treatment of MDD.

Conclusions

Overall, there are few substantial changes to the recommendations made in the previous CANMAT CAM treatment guidelines.[9] Across CAM treatments, exercise, St. John's wort, and LT (for seasonal depression) have the most robust evidence. For unipolar mild to moderate MDD, there is sufficient evidence and clinical support to recommend, as first- or second-line treatment, the use of exercise, LT, ω-3 fatty acids and St. John's wort as monotherapies, and exercise, LT, yoga, ω-3 fatty acids, and SAM-e as adjunctive treatments. For moderate to severe MDD, adjunctive use of exercise, St. John's wort, ω-3 fatty acids, SAM-e, and SD can be considered. Other physical and natural health products are not recommended as first- or second-line treatment but may be useful in specific clinical situations.

The evidence presented recognizes the strengths and limitations of various CAM treatments. Pharmacological and psychological treatments remain the first-line interventions for moderate to severe MDD because of a generally larger evidence base for efficacy and safety. However, the growing body of evidence in support of specific CAM treatments indicates that they are efficacious for milder forms of illness and/or when patient preference may affect adherence to other treatments. More physician education is needed on the benefits and application of CAM treatments to increase usage and to enhance evidence-based treatment options for patients.

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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 6. Special Populations: Youth, Women, and the Elderly

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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. This section on "Special Populations" is the sixth of six guidelines articles.

Results: Recent studies inform the treatment of MDD in children and adolescents, pregnant and breastfeeding women, women in perimenopause or menopause, and the elderly. Evidence for efficacy of treatments in these populations is more limited than for the general adult population, however, and risks of treatment in these groups are often poorly studied and reported.

Conclusions: Despite the limited evidence base, extant data and clinical experience suggest that each of these special populations can benefit from the systematic application of treatment guidelines for treatment of MDD.

Keywords

major depressive disorder, clinical practice guidelines, evidence-based medicine, meta-analysis, child and adolescent psychiatry, geriatric psychiatry, maternal health, perinatal, postpartum, systematic reviews

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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 mental health specialists. This section covers the treatment of depressive disorders in children and adolescents, women in the perinatal and menopausal stages, and the elderly, recognizing that these life stages carry distinct challenges for treatment. The section is 1 of 6 guidelines articles; other sections expand on principles of care and psychological, pharmacological, neurostimulation, and complementary and alternative medicine treatments. Treatment recommendations in this section will emphasize differences from the general guidelines for adults. These recommendations are presented as guidance for clinicians who should consider them in context of individual patients and not as standards of care.

Methods

The full methods have been previously described,[2] but in summary, relevant studies in English 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.

In special populations, consideration of harm becomes a more prominent concern than in general adult populations, because of the unique vulnerabilities of these developmental windows. The recommendations for various treatment approaches therefore reflect an attempt to balance treatment benefit and potential risks in a way that is acceptable to clinicians and patients. As studies examining harm in the treatment of MDD are often of low quality,[3] the confidence of the treatment recommendations in these groups may be lower than in sections focused on general adult populations. The following sections provide an overview of the treatment challenges and options for children and adolescents; pregnant, postpartum, and menopausal women; and the elderly.

Childhood and Adolescence: A Unique Neurodevelopmental Period

In 2014, 11.4% of American youth aged 12 to 17 years reported at least 1 major depressive episode (MDE) in the past year.[4] Canadian statistics are limited, but 2012 Statistics Canada data found that 8.2% of surveyed youth aged 15 to 24 years reported mood disorders.[5] Most of the randomized-controlled trials (RCTs) of youth assess antidepressant effectiveness in 12- to 18-year-old participants, despite the rapid maturational changes during this period and the fact that a 12-year-old is developmentally distinct from an 18-year-old.[6] Some studies also combine children (<12 years) and adolescents (12-18 years); when recommendations are intended for a specific age group (pediatric or adolescent), this is explicitly stated.

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.

6.1. What is the Initial Approach to a Child or Adolescent with Suspected Depression?

Use of standardized depression screening tools is recommended for assessing children and youth; different screening tools exist for these age groups.[7,8] When feasible, health care providers should use a semistructured approach to diagnostic assessment of children and adolescents who screen positive for MDD (e.g., Kiddie Schedule for Affective Disorders [K-SADS]). Given that a semistructured interview requires both time and training, this may be difficult in some settings but should be attempted (e.g., by appointing trained personnel for this purpose). Although diagnostic criteria for MDD are the same for children and adolescents, presenting symptoms may differ by age group; adolescents typically report more hypersomnia, fewer appetite and weight changes, and fewer psychotic symptoms than children.[9] As such, the patient's age should be taken into account when assessing

children/youth, selecting treatments, and tracking response.[10] Best clinical practice includes the use of various sources for diagnosis and symptom severity assessments, including a clinical interview and auxiliary information (i.e., from parents, teachers).

Supportive clinical care may be sufficient to reduce depression symptoms of a mild MDE. Supportive approaches include psychoeducation, active and empathetic listening, and lifestyle advice, including the benefits of good sleep hygiene, proper eating habits, and exercise.[11]

6.2. Is Psychotherapy an Effective Treatment for Depressed Children/Adolescents?

Previous meta-analyses found that psychotherapy, largely in the form of cognitive-behavioural therapy (CBT), confers modest antidepressant effects in depressed children/adolescents relative to comparison conditions (e.g., waitlist, minimally-treated, active placebo), with more evidence for its use in adolescents.[12,13] A recent review of psychotherapeutic interventions in children/adolescents (52 studies, $N = 3805$) found that interpersonal therapy (IPT) retained superiority over both the short and long term compared with control interventions (waitlist, no treatment, treatment as usual, psychological placebo).[14] However, both CBT and IPT retained superiority over the short term compared with control conditions.[14] When focusing on children (8-12 years), results are mixed; 1 meta-analysis (10 RCTs, $N = 523$) found CBT to be modestly superior to control conditions (largely waitlist controls), although outcome heterogeneity was sizable,[15] while another meta-analysis (7 RCTs) reported inconclusive evidence for the effectiveness of psychotherapy, mainly CBT, in depressed children (control: waitlist, no treatment, or medication).[16]

The effectiveness of Internet-based psychotherapeutic interventions in children/adolescents has also been explored. One meta-analysis found no significant benefit to Internet-based interventions in 7- to 25-year-olds on depression symptoms (although anxiety was reduced) compared with waitlist controls.[17] Others found that computer/Internet-based CBT in children and youth was more effective than comparison conditions (e.g., waitlist, no treatment) in alleviating depression symptoms, particularly in adolescents.[18,19] As such, these interventions may be a promising treatment alternative when in-person/face-to-face treatment is not feasible or available. Most Internet-based interventions have a considerable component of parental and/or teacher involvement, as well as guidance from a therapist. Therefore, Internet-based therapies may be better conceived as a piece within a therapeutic intervention strategy rather than a stand-alone approach.

A Cochrane meta-analysis (11 trials, $N = 1307$) evaluated the effectiveness of psychotherapy and antidepressant medication, alone and in combination, for treating MDD in 6- to 18-year-old participants.[20] There were no significant group differences on most outcome measures and limited evidence favouring pharmacotherapy or combination treatment (vs. pharmacotherapy) in achieving remission.[20] Similarly, another meta-analysis (5 trials) found that CBT conferred limited additional benefit to pharmacological treatment in depressed adolescents,[21] but the combination did reduce functional impairment in the short term,[21] which is consistent with previous work.[11] Another Cochrane meta-analysis (9 trials, $N = 882$) assessed the effectiveness of psychological and pharmacological interventions in preventing relapse or recurrence of depression after an initial episode in children and youth up to 25 years of age, and found no difference in outcomes with either approach.[22] Finally, CBT for suicide prevention combined with pharmacotherapy resulted in greatest improvements in depressed youth who had recently attempted suicide; these improvements appear comparable to those in nonsuicidal adolescents with MDD.[23]

Table 2 summarizes the treatment recommendations for MDD. In summary, as there is no clear comparative advantage for pharmacotherapy or psychotherapy in treating children/youth with non-treatment-resistant MDD, psychotherapy should be the first line of treatment in mild to moderate MDD. CBT and IPT should be considered ahead of other types of psychotherapies in treating depressed pediatric and adolescent populations.

Table 2. Treatment of Major Depressive Disorder in Children/Youth.

Recommendation	Treatment	Level of Evidence
First line	CBT or IPT	Level 1
	Internet-based psychotherapy (for milder severity, if in-person is not possible)	Level 1
Second line	Fluoxetine	Level 1
	Escitalopram, sertraline, citalopram[a]	Level 2
Third line	Venlafaxine,[b] TCA[b]	Level 2
Minimal or nonresponse		
First line	Add SSRI to psychotherapy	Level 1
Second line	Switch to another SSRI (if unresponsive to fluoxetine)	Level 2
Third line	Venlafaxine[b]	Level 2
	TCA[b]	Level 3
Treatment resistant		
First line	SSRI + psychotherapy	Level 2
Second line	Switch to another SSRI (if unresponsive to fluoxetine)	Level 2
Third line	Venlafaxine[b]	Level 2
	TCA[b]	Level 3
	Neurostimulation treatment (ECT[b] or rTMS[b])	Level 3

Suicide/adverse events must be monitored during SSRI treatment; weekly follow-ups recommended during first 4 weeks. CBT, cognitive-behavioural therapy; ECT, electroconvulsive therapy; IPT, interpersonal therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; rTMS, repetitive transcranial magnetic stimulation.

[a]Not recommended in those with congenital long QT syndrome, congenital heart disease, or hepatic impairment.

[b]Only recommended for adolescents (older than 12 years).

6.3. What Antidepressant Medication Should Be Used in Depressed Children/Adolescents?

Selective serotonin reuptake inhibitors (SSRIs) are the most extensively studied medications for the treatment of MDD in children/youth. A Cochrane review (19 trials, $N = 3335$) examined efficacy and adverse outcomes of newer generation antidepressants (SSRIs and others vs. placebo) in participants 6 to 18 years of age.[24] Overall, antidepressant-treated children/youth had lower depression severity scores and higher response/remission rates than placebo-treated individuals, although the effect size was small.[24] Fluoxetine is superior to placebo in pediatric/adolescent cohorts and is the recommended first-choice pharmacological treatment.[24,25] Some studies have demonstrated escitalopram superiority over placebo on functioning and depression scores,[24] although this may be more pronounced in adolescent cohorts rather than children.[26] Paroxetine has not shown efficacy in this age group.[24] There is some evidence that sertraline may be superior to placebo, but the effects are small; finally, there is little evidence for antidepressant effects of citalopram in children or adolescents, although remission rates tended to be higher compared with placebo.[24] Children/adolescents with congenital long QT syndrome should not be treated with citalopram; those with congenital heart disease or hepatic impairment should be treated with caution.[27]

Tricyclic antidepressants (TCAs) are not useful in treating depression in children, and there is only marginal evidence to support their use in adolescents.[28] Monoamine oxidase inhibitors (MAOIs) are not recommended for depressed children/youth because there has been limited assessment of MAOI effectiveness in this population and because of the side effect burden as well as potential for difficulties with the tyramine-free diet.

In summary, if psychotherapy is not accessible, acceptable, or effective, pharmacotherapy should be considered in youth with depressive episodes of moderate severity (Table 2). Pharmacotherapy should be considered as a first-line intervention in more severe cases of depression. Fluoxetine is considered a first-choice antidepressant in children/youth while escitalopram, sertraline, and, to a lesser extent, citalopram are generally considered second-choice antidepressants. Paroxetine is not recommended. TCAs and MAOIs should only be considered in treatment-resistant depression.

6.4. How Should Children/Adolescents Be Monitored following Initiation of Pharmacotherapy?

The United States Food and Drug Administration (FDA) recommends that patients be seen on a weekly basis during the first 4 weeks of treatment, followed by visits every 2 weeks for a month, and then after 12 weeks of treatment to monitor adverse events/suicidality.[29] This is especially true in more severely depressed patients, those with high suicidal ideation, and those experiencing family conflict.[30] The Canadian Psychiatric Association also recommends that appointments or telephone contacts should be scheduled at least weekly within the first month of treatment for children and adolescents.[31] When starting antidepressant pharmacotherapy in youth, the initial dose is generally at the low end of the therapeutic range and continues for a minimum of 4 weeks before a dose increase is considered. If the patient continues to show only a partial response after 12 weeks despite adequate dosing, a change in treatment is warranted.[8,9]

6.5. How Long Should Children/Adolescents Be Treated with Pharmacotherapy?

Relatively little is known about antidepressant maintenance strategies in children/adolescents. Based primarily on adult research, maintenance treatment for 1 year or more is recommended in children/youth with a history of at least 2 depressive episodes or 1 severe or chronic episode.[9] In individuals with no MDD history, maintenance strategies should persist for 6 to 12 months. Antidepressant discontinuation should consist of a slow taper and occur during a relatively stress-free time (e.g., summer months).

6.6. How Should Treatment-resistant Depression or Comorbidity Be Approached in Children or Adolescents?

If a child/adolescent is unresponsive to first-line treatment, the possibility of a misdiagnosis (e.g., undetected bipolar disorder, comorbid medical or psychiatric disorder) should be considered prior to a treatment switch. Treatment nonadherence should also be considered, as should psychosocial factors (e.g., bullying, sexual identity concerns, and family conflict).

Based largely on findings from the Treatment of Resistant Depression in Adolescents (TORDIA) study, following an adequate course with an initial SSRI, children/adolescents showing minimal response (<20% decrease in symptoms) should be switched to another SSRI. Although participants in the TORDIA trial were equally responsive to the serotonin and norepinephrine reuptake inhibitor (SNRI) venlafaxine as to another SSRI, venlafaxine was associated with a higher rate of self-harm events in those with higher suicidal ideation; venlafaxine is therefore less preferable than switching to another SSRI.[30] For youth with SSRI-resistant depression, combined treatment (antidepressant + psychotherapy) decreases the number of days with depression and may be cost-effective.[32]

There is limited evidence for the use of neurostimulation treatments and other modalities in treating depression in pediatric/adolescent populations. Repetitive transcranial magnetic stimulation (rTMS) may hold some promise,[33] although large-scale randomized, sham-treatment controlled studies are lacking. Similarly, RCTs of electroconvulsive therapy (ECT) in children/adolescents are lacking, although ECT parameters in adolescents exist.[34] Case series indicate that ECT is effective in alleviating depression symptoms in adolescents with treatment-resistant MDD, although some

individuals did report long-term cognitive/memory impairments.[35] Given the potential side effect profiles and lack of evidence, ECT is not recommended in children (<12 years of age) and is only recommended with extreme caution in adolescents with treatment-resistant and severe MDD (Table 2).

Finally, the presence of a comorbid psychiatric disorder may complicate treatment. There are sparse data to guide treatment of MDD in the context of psychiatric comorbidity in individuals younger than 18 years. Some limited evidence supports the use of fluoxetine in depressed youth with mild to moderate alcohol use disorders[36] and with oppositional symptoms.[37] In the TORDIA study, remission from depression, regardless of treatment, was associated with a greater reduction in measures of anxiety, attention-deficit/hyperactivity disorder (ADHD), and oppositional symptoms.[38] Although the evidence is limited, treating depression in children/adolescents may reduce comorbid disorder(s) symptoms.

6.7. What Are the Safety Concerns for Antidepressant Medications in Children/Adolescents?

Health Canada has not approved any antidepressant medications for use in individuals younger than 18 years. Fluoxetine is the only antidepressant approved by the FDA for preadolescents (8 years and older), but both fluoxetine and escitalopram are FDA-approved for children 12 years and older.

The FDA issued a black-box warning in 2003 on SSRI use in those younger than 24 years; other regulatory agencies, including Health Canada, followed suit. The Cochrane review of newer generation antidepressants (SSRIs and others) found that median baseline risk of suicide-related outcomes (behaviour and ideation) rose from 25/1000 to 40/1000.[24] These results were consistent with the FDA meta-analysis that showed an $\sim$1.5- to 2-fold risk of increased suicidal thoughts/behaviours (no suicide deaths reported) for newer antidepressants.[39] While epidemiological data do not demonstrate a relationship between prescriptions of antidepressants and suicide deaths in large populations of youth,[40] a systematic review of observational studies found a higher risk (odds ratio = 1.92) of suicidal acts (suicide and attempted suicide) with SSRI exposure in adolescents but a reduced risk in older age groups.[41] Given that these were observational studies, it is possible that the adolescents with SSRI exposure were more severely depressed and at higher risk of suicidality. While recognizing the risks associated with SSRI use, the consequence of untreated depression in children/adolescents is more likely to result in harm; therefore, treatment with SSRIs may be appropriate with careful monitoring.

Perinatal Depression

Unipolar MDEs occurring during pregnancy and in the first year postpartum are frequently referred to as *perinatal depression* and are among the most common morbidities of pregnancy and the postnatal period. The *DSM-5* defines the *peripartum onset specifier* as an MDE that emerges during pregnancy or in the first 4 weeks after delivery, an acknowledgement that up to 40% of postpartum MDEs begin during pregnancy.

Up to 7.5% of women will have a unipolar MDE during pregnancy, and 6.5% will experience one in the first 3 months postpartum. When cases of minor depressive disorder are considered, these rates increase to 18.4% and 19.2%, respectively.[42,43] If left untreated, MDEs can affect infant development, future depression risk, and family and vocational functioning. Timely treatment is therefore essential to optimizing outcomes for women and their families.

6.8. What Are the Principles of Management for Perinatal Depression?

Up to 50% of pregnancies are unplanned.[44] Discussions about a woman's intent to become pregnant and the safety of selected treatment strategies if a pregnancy (planned or unplanned) occurs should therefore comprise a part of the assessment and documentation of all depressed women of childbearing age.

The treatment of MDD during pregnancy and the postpartum period is marked by a number of unique challenges. These include the known risks of fetal and infant exposure to pharmacologic treatments during pregnancy and lactation, as well as those posed by untreated depression. Unfortunately, the evidence upon which our understanding of these risks is based remains limited. The *DSM-5* defines perinatal depression as a unitary diagnostic concept, but given these uncertainties and the unique risks posed by depression and its treatment during the perinatal period, we have developed separate sets of recommendations for pregnancy and the postpartum period, as well as for MDEs of mild to moderate severity, and for severe episodes. Severity of depressive episodes is defined according to the *DSM-5*.

6.9. How Should Depression during Pregnancy Be Treated?

Decision making around the treatment of depression during pregnancy must balance the risks associated with fetal medication exposure with those of untreated depression. Left untreated, MDEs during pregnancy are not only associated with poorer nutrition and prenatal medical care, smoking, and recreational substance misuse,[45,46] but also with significant suffering for women. Depression is linked to an increased risk of poor obstetrical outcomes,[47] small neonates for gestational age,[48] neonatal intensive care unit admission,[49] increased rates of neonatal complications,[50] impairments in mother-infant bonding, infant sleep difficulties,[51] mild developmental delays,[52] and cognitive, behavioural, and emotional problems in offspring.[53]

The recommendations for MDD in pregnancy are summarized in Table 3. The efficacy of first-line treatments for

Table 3. Treatment of Mild to Moderate Major Depressive Disorder during Pregnancy.

Recommendation	Treatment	Level of Evidence
First line	CBT (individual or group)	Level 1
	IPT (individual or group)	Level 1
Second line	Citalopram, escitalopram, sertraline	Level 3
Third line	Structured exercise, acupuncture (depression specific), bright-light therapy	Level 2
	Bupropion, desvenlafaxine, duloxetine fluoxetine, fluvoxamine, mirtazapine, TCAs (caution with clomipramine), venlafaxine	Level 3 or Level 4
	ECT (for severe, psychotic, or treatment-resistant depression)	Level 3
	Therapist-assisted Internet CBT, mindfulness-based CBT, supportive psychotherapy, couples therapy, psychodynamic psychotherapy, rTMS	Level 4
	Combination SSRI + CBT or IPT	Level 4

For severe major depressive disorder, pharmacotherapies each move up one recommendation line (e.g., second line becomes first line), despite a paucity of treatment trials in pregnant women. Psychotherapy and complementary and alternative medicine therapies as monotherapy are not recommended. ECT remains third line. CBT, cognitive-behavioural therapy; ECT, electroconvulsive therapy; IPT, interpersonal therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; rTMS, repetitive transcranial magnetic stimulation.

mild to moderate depression, including CBT and IPT delivered in either individual or group format, is supported by meta-analyses.[54,55] Given the established efficacy of SSRIs as first-line treatments in MDD outside of the perinatal period, citalopram, escitalopram and sertraline are recommended based on efficacy and safety; combination treatment with an SSRI and CBT or IPT can also be considered. Other SSRIs (except paroxetine) and newer antidepressants are less preferred options given the relative absence of reproductive data and limited antenatal clinical use. Despite increased risks of fetal cardiovascular (CV) malformations (outlined below), paroxetine and clomipramine may be discussed with women where there is a compelling reason to consider it, such as a previous good response or ongoing stability on the medication. Doxepin should be avoided during pregnancy given its high rate of passage into breast milk and accompanying complications. MAOIs are not recommended during pregnancy given their propensity to interact with certain analgesic and anaesthetic agents. When MAOIs must be used, early consultation with anaesthesia is recommended.

Other treatments, including neurostimulation and complementary and alternative medicine strategies, can also be considered as third-line recommendations.[56] Recognizing the need for rapid treatment during pregnancy, interventions that have previously been effective for that woman may be worth discussing as potential second-line strategies, as long as they are not contraindicated.

In keeping with recommendations in general population samples, the use of antidepressants in the perinatal period should continue until 6 to 12 months after remission in low-risk women, although treatment for longer periods of time should be considered in those at high risk of relapse.

6.10. What Is the Approach to Treating Severe Depression during Pregnancy?

For severe depression during pregnancy, pharmacotherapy with particular agents is a first-choice treatment, either alone or in combination with CBT or IPT. The remaining SSRIs (except paroxetine), newer generation antidepressants, and TCAs are second line. ECT can also be considered.[57] Combination pharmacotherapy (see Section 3)[58] may be cautiously considered, but little is known about short- and long-term risks to the fetus with this approach.

6.11. What Are the Risks of Using Antidepressant Medications in Pregnancy?

Unfortunately, studies examining the risks of antidepressants during pregnancy are limited by the presence of exposures (e.g., maternal depression, substance or prescription misuse, poor prenatal care, maternal physical health problems) that confound associations between antidepressants and these risks. Available studies cannot fully adjust for these factors, and so the magnitude and specific nature of the risks associated with antidepressants are not completely understood.[59]

Most antidepressants have not been linked to an increased risk of major congenital malformations. An increased risk of CV malformations (odds ratio $\sim$1.5) has been found with first-trimester paroxetine exposure,[59] although a number of these complications resolve spontaneously and do not pose significant functional impairment.[60] Reports have linked fluoxetine use early in pregnancy to a small increase in congenital malformations as well.[61] Significant evidence has not yet accrued that supports increased risks with the other SSRIs, bupropion, mirtazapine, SNRIs, or TCAs (except for clomipramine, which may be associated with an elevated risk of CV malformations). However, antidepressant risk is an active area of study, and discussions with patients should take into account the most recent data.

There may be a very modest link between gestational SSRI use and clinically recognized spontaneous abortion (odds ratio $\sim$1.5).[62] However, neither this nor the risk of malformations is in excess of the 2-fold increase in risk that is accepted as clinically significant in the field.[63] Studies have also linked SSRIs to a 4-day shortened gestational duration and reduced birth weight (74 grams).[62]

At delivery, fetuses exposed to SSRI antidepressants in the third trimester are at elevated risk of developing a syndrome of poor neonatal adaptation marked by jitteriness, irritability, tremor, respiratory distress, and excessive crying. Occurring

in 15% to 30% of infants, these symptoms are most often time-limited (typically resolving in 2-14 days), are not associated with an increased risk of mortality or longer-term neurodevelopmental problems, and resolve with supportive care.[64] This risk may be highest with paroxetine, venlafaxine, and fluoxetine.[64] Limited data also suggest that SSRIs taken late (but not early) in pregnancy may be associated with an increased risk of persistent pulmonary hypertension of the newborn (PPHN). The absolute risk is 2.9 to 3.5 per 1000 infants compared to a general population risk of 2 per 1000.[65]

The limited data on the longer-term postnatal effects of fetal intrauterine exposure to SSRIs report no lasting cognitive, language, emotional, or behavioural problems in offspring.[66] Finally, despite the fact that a small number of studies have suggested that fetal SSRI exposure may be associated with autism-spectrum disorder in offspring, these studies have significant methodological limitations, have wide confidence intervals, and require further replication before evidence-based recommendations can be made.[67]

6.12. How Is Depression Treated during the Postpartum Period?

The deleterious effects of untreated postpartum depression (PPD) on women and their families can be significant. PPD has been linked to impaired mother-infant attachment[68] and cognitive, emotional, and behavioural problems in offspring.[69] Successful treatment of maternal depression may reduce these risks.[70]

Breastfeeding is not contraindicated during treatment with an antidepressant medication. Concerns about breastfeeding during medication treatment include short-term adverse reactions and longer-term neurodevelopmental effects. Treatment recommendations for PPD are given for use in women who are breastfeeding. Women with PPD who are not breastfeeding should follow the general CANMAT guidelines.

For women with a mild to moderate PPD who are breastfeeding, first-line recommendations again include IPT and CBT[54,55] (Table 4). Second-line treatments include citalopram, escitalopram, and sertraline, which have data for effectiveness during the postpartum period, minimize risk during lactation, and pose the least known risk during the childbearing years.[70] Structured exercise and depression-specific acupuncture are complementary and alternative treatments that have some evidence in the postpartum period.[71-73] An increasing body of evidence also supports the use of therapist-assisted Internet-based behavioural activation and CBT, whereas the effectiveness of *unsupported* Internet-based psychotherapeutic interventions has not been established.[74-76] While not extensively studied in the postpartum period, mindfulness-based CBT and supportive, couples, and psychodynamic psychotherapy may have a role for selected women.

Despite the presence of RCT support for fluoxetine and paroxetine, they are recommended as third-line choices, the former because of its long half-life and slightly higher rates of minor adverse reactions in breastfed infants,[77] and the latter because of its association with CV malformations in subsequent pregnancies. Other second-generation antidepressants are categorized as third-line treatments because of limited evidence in lactating women. Among the TCAs, nortriptyline has the most evidence in the postpartum setting and a solid track record in lactation.[78] Doxepin should be avoided in the postpartum period because of reports of significant adverse reactions in infants with breastfeeding.[79,80] Finally, rTMS[79,81] and bright-light therapy[81,82] may be effective for mild to moderate PPD.

Table 4. Treatment of Mild to Moderate Postpartum Depression during Breastfeeding.

Recommendation	Treatment	Level of Evidence
First line	CBT (individual or group)	Level 1
	IPT (individual or group)	Level 1
Second line	Citalopram, escitalopram, sertraline	Level 2
	Combination SSRI + CBT or IPT	Level 2
Third line	Structured exercise, acupuncture (depression specific), therapist-assisted Internet CBT, or behavioural activation	Level 2
	Fluoxetine, fluvoxamine, paroxetine	Level 2
	TCAs (except doxepin)	
	Bupropion, desvenlafaxine, duloxetine, mirtazapine, venlafaxine, TMS, bright-light therapy	Level 3
	ECT (for severe, psychotic, or treatment-resistant depression)	Level 3
	Mindfulness-based CBT, supportive psychotherapy, couples therapy, psychodynamic psychotherapy	Level 4

For severe postpartum depression, pharmacotherapies each move up one recommendation line (e.g., second line becomes first line), despite a paucity of treatment trials in this population. Psychotherapy and complementary and alternative medicine treatments as monotherapy are not recommended. ECT remains third line. CBT, cognitive-behavioural therapy; ECT, electroconvulsive therapy; IPT, interpersonal therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TMS, transcranial magnetic stimulation.

6.13. What Is the Approach to Treating Severe PPD?

For severe PPD, pharmacotherapy should be used first line, with or without psychotherapy. First-choice medications are citalopram, escitalopram, and sertraline. Other antidepressants are second-choice treatments for women who are more severely depressed. ECT is also an effective treatment that is listed as third line because of its side effect profile, but it can be considered a first-choice treatment for severe depression, especially with psychosis; women can also continue to breastfeed during ECT.[83]

6.14. What Are the Risks of Antidepressants during Breastfeeding?

Exposure to antidepressants in breastfed infants is 5 to 10 times lower than exposure in utero. Serum levels in preterm

infants or those with liver and/or kidney impairment may be higher, and so consultation with a pediatrician should help guide decisions in these cases. Relative infant doses (RID) of medication <10% are generally safe, and all of the SSRIs and SNRIs tested to date appear to meet this criterion.[84] Sertraline, fluvoxamine, and paroxetine have the lowest RID and "milk-to-plasma" ratios. Minor reactions have been noted in case studies of over 200 infants with breastfeeding exposure to sertraline or paroxetine. Citalopram and fluoxetine have had higher rates of infant reactions (4%-5%), but these are reversible and generally limited to short-lived increases in irritability, restlessness, somnolence, or insomnia.[78] Given its relatively low relative infant dose, nortriptyline can be a good choice if women prefer or require treatment with a TCA. Unfortunately, next-to-no data exist on MAOIs during lactation. There is a paucity of data on the long-term neurodevelopmental outcomes of infants who receive antidepressants in breast milk, but there is currently no evidence of significant long-term neurodevelopmental effects.[77]

Table 5. Current Evidence for Treatment of Perimenopausal Depression.

Recommendation	Treatment	Level of Evidence
First line	Desvenlafaxine	Level 1
	CBT	Level 2
Second line	Transdermal estradiol[a]	Level 2
	Citalopram, duloxetine, escitalopram, mirtazapine, quetiapine XR, venlafaxine XR	Level 3
	Omega-3 fatty acids, fluoxetine, nortriptyline, paroxetine, sertraline	Level 4
Third line	Mindfulness-based CBT, supportive psychotherapy	Level 4

CBT, cognitive-behavioural therapy.
[a]Women with an intact uterus should also be prescribed concomitant progesterone.

Perimenopausal Depression

The transition to menopause (or perimenopause, the beginning of ovarian failure) starts when menstrual cycles become 7 days longer or shorter than usual and extends to the early postmenopausal years.[85] Perimenopause is a period of increased risk for depression compared to premenopausal years. Notably, in epidemiological studies, both increased depressive symptoms and diagnosis of an MDE occurred more frequently in perimenopausal relative to premenopausal women.[86-89] Perimenopause is associated with risk for both depressive recurrence and new-onset depression.[87,88] Along with increased rates of depression and anxiety, this period is also associated with emergence of menopausal symptoms such as hot flashes, night sweats, decreased libido, vaginal dryness, sleep disturbances, and memory complaints, all of which may negatively affect mood. Hot flashes and night sweats have been identified as independent predictors of perimenopausal depression.[90]

Table 5 summarizes the current evidence for treatment of MDD in perimenopausal women.

6.15. Is Antidepressant Medication Effective during Menopause?

Only desvenlafaxine has been specifically evaluated through randomized, placebo-controlled trials for antidepressant efficacy in peri- and postmenopausal depressed women; the 2 trials found that desvenlafaxine (50 mg daily, $N = 434$[91]; 100 mg and 200 mg daily, $N = 387$[92]) was superior to placebo. Importantly, a post-hoc analysis of these RCTs showed no differences in treatment response to desvenlafaxine between peri- and postmenopausal women.[93] Otherwise, small-sample, open-label studies have shown the benefit of citalopram, duloxetine, escitalopram, mirtazapine, quetiapine XR, and venlafaxine XR. There are no comparative studies of antidepressants in menopausal women. Based on these limited data, the recommendations for antidepressants in peri- or postmenopausal depression do not differ from those in the general adult population.

6.16. Are Hormonal Agents Effective as Monotherapy or Adjunctive Treatment with Antidepressants?

Transdermal estradiol has been evaluated as both monotherapy and adjunctive posttherapy to treat perimenopausal depression. In a comparative trial of 3 hormone replacement therapies as adjuncts to venlafaxine XR in postmenopausal women, methyltestosterone but not estradiol was superior to placebo.[94] In 2 other small RCTs, estrogen augmentation was superior to placebo in perimenopausal women,[95,96] while there was no difference between transdermal estradiol and placebo in late postmenopausal women.[97] Hormonal agents are recommended as second-line agents for women who understand the risks and have no contraindications to hormonal therapy.

6.17. Are There Effective Nonpharmacologic Treatments for Depression during Menopause?

Only 1 study ($N = 50$) investigated the use of CBT in perimenopausal women with depression.[98] Group CBT significantly decreased mean scores on the Beck Depression Inventory-II in both pre- and perimenopausal women with depression, but no change was observed in the waitlist control group. These results are consistent with a post-hoc analysis of a large open-label trial ($N = 353$) showing no differences in treatment response to cognitive therapy between premenopausal, perimenopausal, and postmenopausal women.[99]

In contrast, adjunctive acupuncture conferred no advantage when added to self-care versus self-care alone for the

treatment of hot flashes and depressive symptoms in postmenopausal women.[100]

Late-Life Depression

Late-life depression (LLD) can be defined as MDD occurring in adults 60 years and older. When discussing LLD, it is important to differentiate early adult-onset depression recurring in late life from late-onset depression. Compared to patients with earlier onset of MDD, late-onset depression has a worse prognosis, a more chronic course, a higher relapse rate, and higher levels of medical comorbidity, cognitive impairment, and mortality.[101] The vascular depression hypothesis posits that cerebrovascular disease predisposes, precipitates, or perpetuates some depressive syndromes in older age. This vascular burden affects fronto-striatal circuitry, resulting in depression and associated cognitive impairment, especially executive dysfunction.[102,103] Evidence also suggests that late-onset depression or depressive symptoms may be a prodrome for dementia; hence, monitoring of cognition at initial assessment and over time is warranted.[104,105]

6.18. What Is the Role of Nonpharmacological Treatments in LLD?

Meta-analyses have demonstrated efficacy for psychological treatments of depression in older adults,[106] with even higher effect sizes when minor depression and dysthymia were included.[107] Newer meta-analyses have addressed some methodological issues in earlier studies—namely, the need for randomization of treatment and the need to assess the effect of the type of control group on the magnitude of psychotherapy effects. A meta-analysis of 27 RCTs including 2245 participants demonstrated great variability in standardized mean differences of 0.05 to 1.36 depending on the control group.[108] In this meta-analysis, psychotherapies (including bibliotherapy) yielded large effects compared with waitlist and attention controls but small to moderate effects compared with supportive therapy or treatment as usual. The authors suggested that supportive therapy best controlled for the nonspecific elements of psychotherapy and should be used as the control for future studies and that problem-solving therapy (PST) has the strongest evidence base using supportive therapy as a control.[108] A recent meta-analysis assessed the efficacy of PST in MDD in older adults, demonstrating that PST significantly reduced depression rating scale scores and reduced disability. The authors also noted that PST is one of the few therapies studied in older people with cognitive impairment and executive dysfunction.[109]

6.19. What Are the Principles of Pharmacological Treatment of LLD?

The adage of "start low and go slow (and keep going)" is relevant in LLD. Divisions into young-old (<75 years) and old-old (≥75 years) can be helpful, with a greater degree of vigilance required in treating the old-old. Overall, there are pharmacokinetic changes with aging that may decrease the rate of absorption, modify bioavailability, increase half-life for lipid-soluble drugs, and increase relative concentration for water-soluble drugs and metabolites.[110] As comorbid medical burden and polypharmacy expand, the risk for pharmacokinetic and pharmacodynamic drug interactions increases (see Section 3).[58] In addition, rare antidepressant side effects in adults such as bone loss, serotonin syndrome, extrapyramidal side effects, and neuroleptic malignant syndrome are more common in the elderly.[111] Particular attention should be paid to falls, hyponatremia, and gastrointestinal bleeding, which are associated with SSRIs in general[112,113] and to QTc prolongation with citalopram.[114] Standard principles of conservative prescribing should be applied to minimize adverse drug outcomes.[115] Meta-analyses also suggest that longer antidepressant treatment trials (10-12 weeks) are required in LLD.[116]

6.20. What Is the Pharmacological Approach to LLD?

An inherent paradox in the treatment of LLD stems from the dissonance between routine clinical practice and RCT evidence. For example, while citalopram and escitalopram are generally considered by clinicians to be first-line treatments for LLD due to tolerability and fewer drug interactions,[117-119] none of the RCTs involving these drugs demonstrated superiority over placebo in the elderly,[120-122] with the exception of citalopram in a subset of old-old (>75 years) patients with severe depression (Hamilton Depression Rating Scale score > 24).[120] In fact, a meta-analysis of 7 studies demonstrated no difference between citalopram and other antidepressants for depression remission or trial withdrawal for adverse effects.[123] In contrast, geriatric clinicians are reluctant to prescribe paroxetine due to anticholinergic effects and fluoxetine due to drug interactions, yet these same SSRIs have positive RCT evidence in the treatment of LLD.[124,125] Thus, treatment recommendations for LLD have been evidence-informed, rather than evidence-based.[119]

Overall, recent systematic reviews and meta-analyses support the efficacy of antidepressants in LLD, with no difference between SSRI and SNRI classes,[126] and in adult-onset MDD where episodes recurred in LLD.[127] A subsequent meta-analysis, in adult and geriatric populations, demonstrated that antidepressants are efficacious for depression in adults 55+ years of age.[128] However, drug-placebo differences for studies with an entry criterion of 65+ years were modest and nonsignificant. Heterogeneity, small study number, physical comorbidity, and chronicity were all considered to affect the ability of a trial to separate drug from placebo effects.[128] A recent network meta-analysis, with response as an outcome (>50% reduction in depression score from baseline), demonstrated relative risks compared to placebo of greater than 1.2 for only 3 drugs: sertraline, paroxetine, and duloxetine.[129] A meta-analysis of moderators of

treatment response in LLD suggests older adults with longer illness duration and moderate to severe depression benefit from antidepressants compared to placebo, whereas short illness duration does not show antidepressant response.[130] Furthermore, executive dysfunction, especially in the subdomains of planning and organization, has been associated with poor antidepressant treatment response in LLD, which may be a factor in trial heterogeneity.[131] One can speculate that vascular depression, associated with executive dysfunction, may be more resistant to traditional pharmacotherapeutic approaches, and may be related to depressive syndromes that are in fact early manifestations of dementia. These are important considerations when assessing lack of response to initial treatment approaches. Among new antidepressants, vortioxetine and agomelatine have been evaluated in LLD. An RCT ($N = 453$) comparing vortioxetine, duloxetine, and placebo demonstrated significant reduction of depression scores with both comparators versus placebo in adults (aged 65+ years) with depression. Additionally, both medications improved verbal learning, with vortioxetine demonstrating an additional improvement in processing speed.[132] Agomelatine was associated with improved depressive symptoms and better treatment response than placebo but did not separate from placebo for remission.[133]

There is also evidence to support efficacy of continuation and maintenance treatment in LLD. A meta-analysis of 8 double-blind RCTs found antidepressants effective in preventing relapses and recurrences in the elderly, with similar tolerability for TCAs and SSRIs.[134]

6.21. Is There a Role for Atypical Antipsychotic Medication in LLD?

In a post-hoc analysis pooling clinical trial data of the 61- to 67-year age group, adjunctive aripiprazole and antidepressants showed a large effect size of 0.8 compared to placebo; the most common side effects were akathisia and dizziness.[135] A recent National Institute of Mental Health–funded RCT ($N = 181$) reported on aripiprazole augmentation (10-15 mg) in older adults (aged 60+ years) with late and early onset LLD who were nonremitters to venlafaxine XR monotherapy. For remission, aripiprazole was superior to placebo (40/91 [44%] vs. 25/90 [29%], respectively). The most common adverse events were akathisia (26%) and Parkinsonism (17%). Serious adverse events were reported in 4% of patients on aripiprazole and 2% on placebo, with 6% discontinuation on aripiprazole and 9% with placebo.[136]

An RCT ($N = 338$) of older adults (aged 65+ years) with MDD found that quetiapine XR monotherapy (median dose 158.7 mg) demonstrated efficacy versus placebo in depression scores, response, and remission rates.[137] However, subgroup analysis of participants aged 75+ years demonstrated only a trend-level significance for depression score reduction ($P = 0.068$). Dropout rates were 9.6% for quetiapine XR versus 4.1% for placebo.[137] Post-hoc analysis demonstrated efficacy for depressive symptoms irrespective of baseline sleep, anxiety, or pain.[138]

When prescribed for dementia, antipsychotic medications are associated with increased risk of all-cause mortality, with greater risks for typical than atypical antipsychotics; the risk is less well elucidated in cognitively intact elderly populations.[139] Antipsychotic medications may be considered in selected elderly individuals, recognizing that the risk profile in cognitively intact individuals has not been confirmed.

6.22. What Is the Recommended Sequential Approach to Pharmacological Treatment of LLD?

There is support for a stepwise approach to treatment of LLD in providing the best likelihood of achieving response and remission.[119] In 2 large studies, IMPACT[140,141] and PROSPECT,[142,143] elderly depressed patients randomized to a stepwise algorithmic approach were much more likely to improve than if they were randomized to usual care. Specifically, the odds ratio for IMPACT versus usual care was 3.45 (response rate 45% vs. 19%; $P < 0.001$), and for PROSPECT versus usual care, the odds ratio was 2.13 (likelihood of remission, 43% vs. 28%; $P < 0.05$).

A systematic review and meta-analysis of treatment-resistant depression (defined as failure to respond to at least 1 treatment) in adults aged >55 years identified a dearth of randomized trial data for this patient population. Half of the participants responded to a switch or augmentation strategy, with lithium augmentation demonstrating the most consistent data for all approaches.[144] Of all studies included in the analysis, a sequential treatment strategy provided the highest response rates.[145]

For LLD, RCT data generally only assess an individual step in an algorithmic or stepwise approach. Given the challenges in interpreting the evidence in LLD, therefore, an evidence-informed sequential treatment approach is recommended, rather than simply extrapolating from individual trials (Table 6). While good clinical judgement suggests choosing antidepressants to avoid mechanisms that may be harmful in the elderly (e.g., avoiding anticholinergic antidepressants to minimize confusion and delirium risk), there is yet little evidence over the long term to support ad-hoc tailoring of antidepressant choices to target symptom clusters or to leverage specific side effects for therapeutic benefit. For example, evidence does not necessarily support that using a sedating medication to optimize sleep in a depressed patient improves overall outcomes over the course of treatment or longer. It is possible, for example, that when depression has remitted and sleep has normalized that the ongoing sedating effects of medications contribute to noncompliance or lack of tolerability. Hence, use of medications in a consistent and algorithmic manner is suggested, leveraging the extensive evidence for this approach to optimize depression outcomes.[119]

Revised Table 6. Algorithmic Pharmacological Treatment of Late-life Depression (see text).

	Treatment	Level of Evidence*
First Step	Duloxetine.	Level 1
(use one or more agents in sequence)	Mirtazapine, sertraline, venlafaxine, vortioxetine.	Level 2
	Citalopram, desvenlafaxine, escitalopram.	Level 3/4
Second Step	*Switch to*	
(if multiple first-step treatments are not effective or not indicated)	Nortriptyline.	Level 1
	Fluoxetine, moclobemide, paroxetine, phenelzine, quetiapine, trazodone.	Level 2
	Bupropion.	Level 3
	Or combine with	
	Aripiprazole.	Level 1
	Methylphenidate.	Level 2
	Lithium.	Level 3
Third Step	*Switch to*	
(if multiple first- and second-step treatments are not effective or not indicated)	Amitriptyline, imipramine.	Level 2
	or	
	Combine SSRI or SNRI with bupropion.	Level 3

*Based on evidence in studies of late-life depression samples. SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

Summary

Depression is common across the life span. While special populations (children and youth, women in the perinatal or menopausal period, and older adults) bring unique challenges, the essential approach to depressive episodes is similar to that of the general adult population. Careful diagnosis, evidence-based evaluation of the risk-benefit ratios of specific treatment strategies, and careful monitoring of outcomes are universal elements of optimal treatment. Evidence for efficacy of treatments in these populations is often more limited than for the general population, and risks of treatment in these groups are often poorly studied and reported. Despite the limited evidence base, extant data and clinical experience suggest that each of these special populations can benefit from the systematic application of treatment guidelines for treatment of depression.

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The CANMAT guidelines are not officially endorsed by the Canadian Psychiatric Association.

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GMM has been on advisory boards or a speaker for Janssen, Lilly, Lundbeck, and Pfizer.

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MS has no financial conflicts to declare.

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