

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

^aNote 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.

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 guidelines¹ (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 network⁷ 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

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

^aClinical 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.

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.

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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 Depression¹² (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.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

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

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Supplementary Material

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

References

- Kennedy SH, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. Introduction. *J Affect Disord.* 2009;11(Suppl 1): S1-S2.
- Yatham LN, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2013. *Bipolar Disord.* 2013;15:1-44.
- McIntyre RS, Schaffer A, Beaulieu S. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid conditions. *Ann Clin Psychiatry.* 2012; 24:2-3.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med.* 2009;6:e1000097.
- Schulz KF, Altman DG, Moher D, et al. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *PLoS Med.* 2010;7:e1000251.
- Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol.* 2011;64:383-394.

7. Mills EJ, Thorlund K, Ioannidis JPA. Demystifying trial networks and network meta-analysis. *BMJ*. 2013;346:f2914.
8. Berlin JA, Golub RM. Meta-analysis as evidence: building a better pyramid. *JAMA*. 2014;312:603-605.
9. Lieberman JA, Greenhouse J, Hamer RM, et al. Comparing the effects of antidepressants: consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. *Neuropsychopharmacology*. 2005;30:445-460.
10. Yatham LN, Beaulieu S, Schaffer A, et al. Optimal duration of risperidone or olanzapine adjunctive therapy to mood stabilizer following remission of a manic episode: a CANMAT randomized double-blind trial. *Mol Psychiatry*. 2015 Oct 13. [Epub ahead of print]
11. Parikh SV, Zaretsky A, Beaulieu S, et al. A randomized controlled trial of psychoeducation or cognitive-behavioral therapy in bipolar disorder: a Canadian Network for Mood and Anxiety Treatments (CANMAT) study. *J Clin Psychiatry*. 2012;73:803-810.
12. Lam RW, Milev R, Rotzinger S, et al. Discovering biomarkers for antidepressant response: protocol from the Canadian biomarker integration network in depression (CAN-BIND) and clinical characteristics of the first patient cohort. *BMC Psychiatry*. 2016;16:105.