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Research report

Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. III. Pharmacotherapy

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ABSTRACT

Background: In 2001, the Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT) partnered to produce evidence-based clinical guidelines for the treatment of depressive disorders. A revision of these guidelines was undertaken by CANMAT in 2008–2009 to reflect advances in the field.
Methods: The CANMAT guidelines are based on a question–answer format to enhance accessibility to clinicians. An evidence-based format was used with updated systematic reviews of the literature and recommendations were graded according to Level of Evidence using pre-defined criteria. Lines of Treatment were identified based on criteria that included Levels of Evidence and expert clinical support. This section on "Pharmacotherapy" is one of 5 guideline articles.
Results: Despite emerging data on efficacy and tolerability differences amongst newer antidepressants, variability in patient response precludes identification of specific first choice medications for all patients. All second-generation antidepressants have Level 1 evidence to support efficacy and tolerability and most are considered first-line treatments for MDD. First-generation tricyclic and monoamine oxidase inhibitor antidepressants are not the focus of these guidelines but generally are considered second- or third-line treatments. For inadequate or incomplete response, there is Level 1 evidence for switching strategies and for add-on strategies including lithium and atypical antipsychotics.
Limitations: Most of the evidence is based on trials for registration and may not reflect real-world effectiveness.
Conclusions: Second-generation antidepressants are safe, effective and well tolerated treatments for MDD in adults. Evidence-based switching and add-on strategies can be used to optimize response in MDD that is inadequately responsive to monotherapy.

Introduction

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, collaborated on the publication in 2001 of evidence-based clinical guidelines for the treatment of depressive disorders (Kennedy and Lam, 2001). A revision of these guidelines was undertaken by CANMAT in 2008–2009 to update the recommendations based on new evidence. The scope of these guidelines encompasses the management of adults with unipolar major depressive disorder (MDD). This section on Pharmacotherapy is one of 5 guideline articles. There are separate CANMAT guidelines for bipolar disorder (Yatham et al., 2009).

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Pharmacotherapy remains the most studied and best evidenced treatment for MDD. Since 2000, at least 225 RCTs, 145 meta-analyses and 3 major systematic reports have been published on antidepressant medications for MDD. Despite this proliferation of data, it is widely recognized that the methodology of RCTs for antidepressants (including strict inclusion/exclusion criteria, intensive and frequent contact, short study duration, etc.), which are primarily conducted by pharmaceutical companies for registration of new medications, may not reflect real world clinical practice (Kennedy and Lam, 2001). While the past few years have also seen the emergence of larger scale effectiveness trials to address real-world generalizability, such as the U.S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush et al., 2004), these trials are still limited by many methodological deficiencies and some of the most important clinical questions remain unanswered. Hence, 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 described elsewhere (Kennedy et al., 2009b) but, in summary, relevant English language studies published from January 1, 2000 to December 31, 2008 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. The question–answer format of the previous guidelines has been retained based on feedback from clinicians. Recommendations include the Level of Evidence for each graded Line of Treatment, using specified criteria (Table 1). Note that this article does not provide comprehensive citations or references, but the evidence tables are posted on the CANMAT web site (www.canmat.org).

Because of the large number of RCTs, this Pharmacotherapy section will focus on systematic reviews and meta-analyses when these are available. However, the increasing number of meta-analyses also highlights the fact that meta-analyses, like RCTs, can arrive at different conclusions depending on the quality of the review and the criteria for study selection (Lieberman et al., 2005). Newer meta-analytic methods, such as network meta-analysis in which both direct and indirect comparisons of treatments are summarized (Cipriani et al., 2009), may overcome some of these limitations.

Differentiating and selecting antidepressants

3.1. What are the principles of pharmacotherapy management?

General principles of treatment with pharmacotherapy are similar to those for other treatment modalities for depression (Patten et al., 2009). Table 2 summarizes these principles, as adapted for pharmacotherapy. Adherence deserves special attention because early discontinuation rates of antidepressants are high. Although clinical practice guidelines recommend that the minimum duration of antidepressant treatment for MDD should be 6–12 months, about 30% of patients discontinue medications within 30 days and more than 40% discontinue within 90 days (Olfson et al., 2006). The main reasons cited for early discontinuation are lack of response, stigma associated with having a psychiatric illness, and side effects (Hodgkin et al., 2007). There is some evidence that extensive metabolizers of antidepressants are less likely to discontinue early due to side effects than poor metabolizers (Bijl et al., 2008).

Given these high discontinuation rates, it is important to optimize adherence to treatment when prescribing antidepressants. Strategies for enhancing adherence include the use of education and self-management by patients and collaborative

Table 1
Criteria for level of evidence [a] and line of treatment. [b]

	Criteria
Level of Evidence	
1	• At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
2	• At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals.
3	• Non-randomized, 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 [c]
Second-line	• Level 3 evidence or higher, plus clinical support [c]
Third line	• Level 4 evidence or higher, plus clinical support [c]

[a] Levels of evidence do not assume positive or negative or equivocal results; they merely represent the quality and nature of the studies that have been conducted. Note that Levels 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, 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.

[b] A first-line treatment represents a balance of efficacy, tolerability and clinical support. Second-line and third-line treatments are reserved for situations where first-line treatments are not indicated or cannot be used, or when first-line treatments have not worked.

[c] Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are realistic and applicable for clinical practice, in order to enhance the utility of the guidance for clinicians. 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.

Table 2
Principles of pharmacotherapy management.

Recommendations
• A thorough diagnostic assessment should be conducted, paying specific attention to suicidality, bipolarity, comorbidity, concomitant medications, and special features (psychosis, atypical features, seasonality).
• When clinically indicated, a laboratory assessment should be performed, including liver function tests and a metabolic workup.
• The use of antidepressants should be accompanied by clinical management, including patient education, attention to adherence issues, and self-management techniques.
• Patients should be carefully monitored every 1–2 weeks at the onset of pharmacotherapy, as this is the period of greatest risk. Depending on severity and response, follow up can then be decreased to visits every 2–4 weeks or longer.
• Monitoring should include the routine use of validated outcome scales.
• The selection of an antidepressant should be individualized based on clinical factors including symptom profile, comorbidity, tolerability profile, previous response, potential drug–drug interactions, patient preference, and cost.