Introduction

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

Sidney H. Kennedy [a],*, Raymond W. Lam [b], Sagar V. Parikh [a], Scott B. Patten [c], Arun V. Ravindran [a]

[a] University of Toronto, Canada
[b] University of British Columbia, Canada
[c] University of Calgary, Canada

ARTICLE INFO

A working committee of the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, met in 2008 to discuss the process and structure for revising the 2001 Canadian Guidelines for the Management of Depressive Disorders that was originally co-sponsored by CANMAT and the Canadian Psychiatric Association (Kennedy and Lam, 2001). The question–answer format of the guidelines was retained owing to ease-of-use by busy clinicians. The committee updated the original list of questions to include progress in the field. The draft question list was circulated amongst groups of practitioners (psychiatrists and family physicians) for further suggestions.

A systematic literature search was conducted to identify relevant studies for each question via a computerized search, using appropriate key words, of electronic databases (PubMed, PsychInfo, Cochrane Library of Systematic Reviews and Clinical Trials). Studies were also identified by cross-referencing of bibliographies, review of other major reports and guidelines, and feedback from experts. Published studies in English from January 1, 2000 to December 31, 2008 were considered, with an emphasis on randomized controlled trials (RCTs) and meta-analyses. Information from the studies was extracted and summary evidence tables created. These evidence tables are available on the CANMAT web site (www.canmat.org).

Levels of evidence were specified for recommendations, based on criteria from the 2001 guidelines and revised to reflect

* Corresponding author.
 E-mail address: sidney.kennedy@uhn.on.ca (S.H. Kennedy).

consensus opinions about quantitative reviews (Lieberman et al., 2005) (Table 1). It is important to note that these 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.

In addition, recommendations were graded according to Line of Treatment, based on the criteria used for the 2001 guidelines (Table 2). A first-line treatment represents a balance of efficacy, tolerability and clinical support. 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. 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.

Manuscript drafts were circulated amongst committee members for discussion and consensus. Later drafts were then reviewed by external content experts. Final manuscripts were approved by all co-authors. The guidelines process and distribution were funded entirely by internal CANMAT funds; no external support was sought or received. All guidelines committee members disclosed potential conflicts of interest.

Table 1
Criteria for Level of Evidence.

Level	Criteria
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.

Table 2
Criteria for Lines of Treatment.

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

[a] 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.

The revised guidelines are comprised of 5 sections: 1) Classification, burden and principles of management; 2) Psychotherapy alone or in combination with antidepressant medication; 3) Pharmacotherapy; 4) Neurostimulation therapies; and 5) Complementary and alternative medicine treatments. The scope of these guidelines encompasses the management of adults with unipolar major depressive disorder (MDD). Guidelines for bipolar depression are included in the CANMAT guidelines for bipolar disorder (Yatham et al., 2009). Some questions include information and summary recommendations for other special populations (children and adolescents, older age, pregnant women, medical comorbidity) but there are full guidelines available that address those groups.

CANMAT recognizes that much of the evidence is based on studies using strict inclusion/exclusion criteria, intensive and frequent follow up, short duration of treatment, etc., and therefore may not be applicable to the average patient seen by clinicians. Hence, there are few absolute recommendations and these guidelines should be viewed as guidance that must be tailored to an individual patient, and not as standards of care.

To be comprehensive, these guidelines encompass a variety of treatments including psychotherapy, pharmacotherapy, neurostimulation and complementary and alternative medicine (CAM) treatments. There is, on balance, greater evidence and clinical experience with traditional treatments (psychotherapy and pharmacotherapy) and few studies directly comparing these with neurostimulation or CAM treatments. Therefore, first-line psychotherapy or pharmacotherapy recommendations usually should be considered before neurostimulation or CAM treatments.

As these guidelines are primarily addressed to specialists (psychiatrists and other mental health professionals), the level of detail may be greater than needed for primary care practitioners; a shorter summary of these guidelines will be made available for this group. The value of these guidelines to help define the best possible care for people with MDD will ultimately be determined by the clinicians and patients who use them.

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Commentary

CANMAT Guidelines for depression: Clear and user-friendly

Ian M. Anderson [a,*], Peter M. Haddad [b]

[a] Professor of Psychiatry and Honorary Consultant Psychiatrist, School of Community Based Medicine, Neuroscience and Psychiatry Unit, University of Manchester, M13 9PT, UK
[b] Consultant Psychiatrist and Honorary Senior Lecturer, Greater Manchester West Mental Health NHS Foundation Trust, Manchester, UK

Major depression in a common and disabling condition across the world. It presents many treatment challenges, not least the high proportion of sufferers who do not present to health professionals or receive no treatment. Even when treatment is received many individuals fail to achieve adequate response or subsequently relapse. Enabling access to, and optimising, treatment is therefore important and guidelines provide one resource in trying to achieve this. The new guidelines for the Management of Depressive Disorder in Adults from the Canadian Network for Mood and Anxiety Treatments (CANMAT) updates the network's previous guidance published in 2001. The revised guidelines are presented as five stand-alone sections; 1) Classification, burden and principles of management; 2) Psychotherapy alone or in combination with antidepressant medication; 3) Pharmacotherapy; 4) Neurostimulation therapies; and 5) Complementary and alternative medicine treatments (CANMAT, 2009). Each of the five sections has a brief abstract that includes a summary of the main results. The guidance primarily deals with adults but brief information is also provided on treating several special populations including children and adolescents, the elderly, pregnant women and those with medical comorbidity.

There are now a considerable number of guidelines available for the treatment of depression and many of these, like those from CANMAT, are now in their second or third revisions/updates. Most guidelines now share key features including attempts to systematically review the evidence, the involvement of a guideline development group or consensus meeting, the use of operationalised levels of evidence and a review process prior to finalisation. The CANMAT guidelines have been developed by professionals and experts in the field without explicit user or carer involvement (as is the usual pattern for guidelines from professional bodies) and addressed to specialists (psychiatrists and other mental

health professionals). There is the promise of a less detailed summary for primary care to follow. The lack of a universally accepted evidence grading system means that guidelines generally adopt their own version; evidence grading is seductively simple in principle but difficult in practice. The CANMAT version of the 'Level of Evidence', referring to the availability, not outcome, of evidence, does not specify placebo treatment as the comparator for assessment of primary efficacy. The matching of evidence to first, second and third line recommendations for treatment is then largely dependent on expert opinion.

A major problem for depression treatment guidelines is the amount of evidence to synthesise. The increasing fashion for meta-analysis is therefore a blessing for guideline developers, but one that requires a health warning. The quality of meta-analyses vary widely and vagaries of the primary data, decision about inclusion criteria for studies together with the interpretation of equivocal results reminds us that that in the end it is a very human process—as much art as science going into the final picture. Without going back to original data much depends on the quality of meta-analyses in the literature and it is possible to reach different conclusions. To illustrate this, the CANMAT guidelines propose light therapy as a first line treatment for seasonal affective disorder based on published meta-analysis, whereas the consultation draft to update the National Institute for Health and Clinical Excellence (NICE) depression guidelines, after going back to the primary data, concluded that there were was insufficient evidence to recommend light therapy once poorer quality studies had been excluded (NICE, 2009).

For the clinician consulting these guidelines perhaps the most obvious feature is in their presentation. The CANMAT guidance uses a question-and-answer format with each of the five sections posing between 12 and 26 key questions followed by a succinct answer, often in terms of first-, second- and third-line treatment alternatives. In contrast other guidelines, such as those from the British Association for Psychopharmacology (BAP, Anderson et al. 2008) and NICE guidance (NICE, 2009), have a narrative structure with sub-

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* Corresponding author.
  E-mail address: ian.anderson@manchester.ac.uk (I.M. Anderson).

sections. Each format has its advantages and disadvantages. CANMAT's question-and-answer format is attractive for busy clinicians who want to 'dip in' for an answer to a specific clinical question. On the other hand a narrative structure may be better suited to addressing clinical context, such as using a stepped care approach or choice between treatments. Deciding what questions to include in a question–and–answer format is a matter of opinion and will be influenced by the intended audience. CANMAT's review of evidence is brief and readable, but at times at the expense of being clear about problems with the quality of evidence and the uncertainties in the data. An example is Section 3.3 that discusses the comparative efficacy of antidepressants but without adequately addressing the question of clinical importance, potential sponsorship influence and methodology, all of which muddy the waters.

It is helpful that the CANMAT guidelines take a clinical usefulness approach to some terminology, for example dispensing with the differentiation between relapse and recurrence on the basis that they cannot be reliably distinguished. Consequently it considers two phases for the treatment of depression, acute and maintenance, in contrast to the traditional three-phase Kupfer model (acute, continuation and maintenance treatment). Other useful simplifications of terminology are to use the general term 'add-on' treatments instead of 'augmentation' and 'combination' (because of difficulties distinguishing between additions with and without intrinsic antidepressant activity) and an emphasis on considering strategies for non- or incomplete response rather than 'treatment resistance'. It is perhaps a shame that there isn't a more dimensional approach to depression and more tailoring of treatments to the level of severity, or consideration of persistent milder/subthreshold depression.

What about the details of the guidance itself? It is reassuring that there are few surprises when comparing these to other available guidelines. The CANMAT guidance has the current advantage of being amongst the most up-to-date and is probably the first guideline to consider the evidence for the atypical antipsychotic, quetiapine, as a monotherapy for unipolar depression, in addition to an add-on treatment. It is also always good to discover something new (at least to us) such as the use of the term 'nutriceuticals' (in fact coined in

1989) to describe natural nutritional substances used as drugs and that there is Level 2 evidence for yoga as a treatment for depression, even though this is probably through non-specific mechanisms.

Overall the CANMAT guideline for depression is a welcome addition. Its modular design and question-and-answer format make the guideline user-friendly. The downside is that these features make it more difficult to integrate treatments from different therapy areas and may reduce their usefulness when applied in a clinical context. Nevertheless clinicians should find it relatively easy to find key information. The broad scope and avoidance of unnecessary jargon are further attractions. Given the move to develop different, and hopefully more appealing, guideline formats (e.g. Malhi and Adams, 2009), a useful research question would be to what extent the format of guidelines makes it more likely that clinicians read and apply them.

Declaration of interests

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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. I. Classification, Burden and Principles of Management

Scott B. Patten [a],*, Sidney H. Kennedy [b], Raymond W. Lam [c], Claire O'Donovan [d], Marie J. Filteau [e], Sagar V. Parikh [b], Arun V. Ravindran [b]

[a] University of Calgary, Canada
[b] University of Toronto, Canada
[c] University of British Columbia, Canada
[d] Dalhousie University, Canada
[e] Université Laval, Canada

ABSTRACT

Background: Major depressive disorder (MDD) is one of the most burdensome illnesses in Canada. The purpose of this introductory section of the 2009 revised CANMAT guidelines is to provide definitions of the depressive disorders (with an emphasis on MDD), summarize Canadian data concerning their epidemiology and describe overarching principles of managing these conditions. This section on "Classification, Burden and Principles of Management" is one of 5 guideline articles in the 2009 CANMAT guidelines.
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 the Level of Evidence using pre-defined criteria. Lines of Treatment were identified based on criteria that included evidence and expert clinical support.
Results: Epidemiologic data indicate that MDD afflicts 11% of Canadians at some time in their lives, and approximately 4% during any given year. MDD has a detrimental impact on overall health, role functioning and quality of life. Detection of MDD, accurate diagnosis and provision of evidence-based treatment are challenging tasks for both clinicians and for the health systems in which they work.
Limitations: Epidemiologic and clinical data cannot be seamlessly linked due to heterogeneity of syndromes within the population.
Conclusions: In the eight years since the last CANMAT Guidelines for Treatment of Depressive Disorders were published, progress has been made in understanding the epidemiology and treatment of these disorders. Evidence supporting specific therapeutic interventions is summarized and evaluated in subsequent sections.

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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 Canadian 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 classification, burden and

principles of treatment is one of 5 guideline articles. There are separate CANMAT guidelines for Bipolar Disorder (Yatham et al., 2009).

The current classification of depressive disorders is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 2000) or "Recurrent Depressive Episodes" in the ICD-10 Classification of Mental and Behavioral Disorders (http://www.who.int/classifications/icd/en/). In neither case are these diagnoses linked to etiopathology. MDD is associated with a substantial health, psychosocial and financial burden and is increasingly recognized as a target for chronic disease management. While standardized diagnostic criteria are available, clinical assessment must extend beyond application of these criteria. It is important to consider the short term and long-term components of management and these will be expanded upon in subsequent sections of the guidelines, dealing with psychotherapies, pharmacotherapies, neurostimulation therapies and complementary and alternative medicines. The 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 described elsewhere (Kennedy et al, 2009-this issue) but, in summary, relevant English language publications 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 previous question–answer format has been retained based on feedback from clinicians. Recommendations for each Line of Treatment are based on the Level of Evidence and clinical support (Table 1).

1.1. What is a depressive disorder?

The DSM-IV provides a general definition for mental disorder: "a clinically significant behavioral or psychological syndrome or pattern that occurs in an individual and that is associated with present distress or disability or with a significantly increased risk of suffering death, pain, disability, or an important loss of freedom." In keeping with this definition, depressive disorders are mental disorders that are characterized predominantly by depressive features.

The DSM-IV concept of a depressive disorder adds considerable specificity to otherwise non-specific terminology such as "depression" which might otherwise imply a depressed (or lowered) mood, a normal response to loss (i.e. bereavement) or a maladaptive reaction to stress (i.e. an adjustment disorder with depressed mood). Depression can also be conceptualized as a dimension of symptom expression quantifiable using symptom rating scales. In clinical practice, depressive symptom ratings have an important role to play in case-finding (screening) and in monitoring outcomes.

1.2. How are depressive disorders classified?

The two most important depressive disorders are MDD and Dysthymic Disorder. The essential feature of MDD is the occurrence of one or more Major Depressive Episodes. In turn, Major Depressive Episodes are defined as periods lasting at least 2 weeks characterized either by depressed mood (most of the day, nearly every day) and/or markedly diminished interest or pleasure in all, or almost all, activities (most of the day, nearly every day). In total, during the same 2-week period, there must be five or more symptoms drawn from the list presented in Table 2. Major Depressive Episodes are also the predominant form of mood disturbance in Bipolar Disorder. These disorders are not discussed further here because CANMAT has produced separate Canadian guidelines for Bipolar Disorders (Yatham et al., 2009). Dysthymic Disorder is characterized by a chronically depressed mood that occurs most of the day, more days than not, for at least 2 years. While depressed mood is present there must be at least two additional depressive symptoms. Treatment of Dysthymic Disorder is not a focus of these guidelines. In addition to MDD, Bipolar Disorder and Dysthymic Disorder, DSM-IV contains a category for depressive episodes caused by the use of, or withdrawal from, a drug: Substance-Induced Mood Disorder, with Depressive Features. DSM-IV also recognizes depression caused by the direct physiological consequences of a general medical condition: Mood Disorder Due to a General Medical Condition, with Depressive Features. Finally, DSM-IV contains a residual category called Depressive Disorder Not Otherwise Specified.

1.3. What are the important subtypes of major depressive disorder and Dysthymic Disorder?

DSM-IV includes subtypes (specifiers) that can be used to further describe the course and characteristics of MDD. If there is

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

Level	Criteria
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	Criteria
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] 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, 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 in 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.

Table 2
DSM-IV criteria for a 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 depressed mood or markedly diminished interest or pleasure.

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) 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 made by others). Additional criteria are derived from the following symptoms:
(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.

DSM-IV (American Psychiatric Association, 2000).

a current episode, these specifiers refer to this episode. Otherwise, they are applied to the most recent episode. Some of the specifiers refer to severity: major depressive episodes can be classified as mild, moderate or severe. Within the severe category, the disorder may or may not be characterized by psychotic symptoms. Additional specifiers refer to clinical features, as presented in Table 3. Specifiers can also be used to describe partial or full remission of symptoms. Course specifiers

Table 3
DSM-IV-TR subtypes of MDD (Lam and Mok, 2008).

Subtype	DSM-IV-TR specifier	Key features
Melancholic depression	With melancholic features	Non-reactive mood, anhedonia, weight loss, guilt, psychomotor retardation or agitation, morning worsening of mood, early morning awakening and excessive or inappropriate guilt.
Atypical depression	With atypical features	Reactive mood, over-sleeping, over-eating, 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)
Chronic depression	Chronic pattern	Two years or more with full criteria for MDE
Seasonal affective disorder (SAD)	Seasonal pattern	Regular onset and remission of depressive episodes during a particular season (usually fall/winter onset)
Postpartum depression (PPD)	Postpartum pattern	Onset of depressive episode within 4 weeks postpartum

for Dysthymic Disorder refer to early onset (before age 21), late onset, and the presence of atypical features.

1.4. How common are depressive disorders?

The prevalence of depressive disorders is usually reported on a lifetime or annual basis. Lifetime prevalence is the proportion of the population meeting diagnostic criteria for a disorder at any time during their lives prior to the time of assessment. Annual prevalence is the proportion meeting diagnostic criteria during the preceding year. One month prevalence is less commonly reported and represents the proportion meeting diagnostic criteria during the month preceding an assessment interview. Lifetime prevalence estimates should be interpreted with caution. Measurement of lifetime prevalence using typical epidemiologic research instruments requires respondents to recall specific symptoms that may have occurred many years prior to the actual assessment interview. Long-term follow-up studies suggest that such symptoms are often not recalled so that diagnostic instruments may fail to detect prior episodes (Andrews et al., 1999). For this reason, available estimates of lifetime prevalence are probably underestimates (Andrews et al., 2005).

While prevalence reflects the frequency of depressive disorders in a population, it does not reflect the risk of developing a disorder: incidence. Assessment of incidence requires that a population at risk be identified (i.e. those who

Table 4
Prevalence studies of MDD in general populations.

Location (study)	Criteria	Current/1 month	12 months	Lifetime
Canada	DSM-IV	1.3	4.0	10.8
Europe (ESEMeD)	DSM-IV		3.9	12.8
Germany	DSM-IV	5.6	10.7	17.1
Netherland (NEMESIS)	DSM-III-R	2.7	5.8	15.4
UK (NSPM)	ICD-10	2.1		
USA (NCS-R)	DSM-IV		6.6	16.2
USA (NCS)	DSM-III-R	4.9		17.1
Australia	DSM-IV	3.2		
Australia	ICD-10	3.3		
Japan	DSM-III-R		1.2	2.9

Prevalence (%)

Modified from Lam and Mok (2008).

do not already have a depressive disorder), and that new cases emerging over a defined time interval be identified. Also, prevalence estimates do not fully reflect the burden of depressive disorders in the population. Disease burden depends not only on prevalence, but also on the amount of time spent in the depressed state, the extent of associated disability and the associated risk of premature mortality. Burden of disease is most often quantified using composite parameters that combine information about prevalence, course, impairment and premature mortality, for example the Disability Adjusted Life Year, or DALY used in the World Health Organization Global Burden of Disease Project (Ayuso-Mateos, 2003; Murray and Lopez, 1996).

Early estimates of depressive disorder prevalence in Canada were derived from studies conducted in Edmonton (Bland et al., 1988a,b) and in the province of Ontario (Offord et al., 1996). National estimates became available in 1994 with the first interview cycle of the National Population Health Survey (NPHS) (Beaudet, 1996). The NPHS included a brief version of the major depression module of the Composite International Diagnostic Interview (CIDI) (Kessler et al., 1998). As a longitudinal study, the NPHS also provided national incidence estimates (Beaudet, 1999; Patten, 2000; Patten and Lee, 2004). The first national estimates of prevalence based on the full version of the CIDI interview were produced by the Canadian Community Health Survey, Mental Health and Wellbeing (CCHS 1.2) conducted by Statistics Canada in 2002 (Gravel and Béland, 2005). Table 4 presents a summary of international prevalence estimates.

According to the CCHS 1.2, the lifetime prevalence of MDD in Canada is 10.8%. Annual and one month prevalence estimates arising from this survey were 4.0% and 1.3% respectively (Patten et al., 2005b). These estimates are lower than in the US where estimates of 16.2% lifetime and 6.6% annual prevalence were reported by Kessler et al. (2003). Canadian estimates more closely resemble recent European prevalence rates of 12.8% lifetime and 3.9% annual (Alonso et al., 2004). However, a telephone survey conducted jointly in Canada and the US did not find a difference in prevalence between the two countries (Vasiliadis et al., 2007). MDD has a higher prevalence in women and in younger age groups, although this sex difference diminishes with increasing age in Canada (Patten et al., 2005a,b), a pattern that was previously reported in the United Kingdom (Bebbington et al., 1998). According to NPHS data, the overall annual incidence of major depressive episodes is 3.1% (Patten and Lee, 2004). However, the incidence is higher in women and also tends to decline with age (Patten, 2000).

The CCHS 1.2 did not assess the prevalence of Dysthymic Disorder, so national Canadian prevalence estimates are not available. The Edmonton study, which used DSM-III diagnostic criteria, reported 3.7% lifetime prevalence (Bland et al., 1988a,b), closely resembling recent European estimates based on DSM-IV criteria, 4.1% lifetime (Alonso et al., 2004). Notably, the annual European prevalence was 1.1%, which also resembled the 0.8% annual prevalence estimate from the Mental Health Supplement of the Ontario Health Survey, based on DSM-III-R criteria (Offord et al., 1996).

1.5. What is the long-term course of MDD?

In the CCHS 1.2, the reported duration of initial Major Depressive Episodes was 2 weeks in 16% of episodes and one

month or less in 30% of episodes (Patten, 2006). At the other extreme, 13.7% of the subjects reported that their first episode lasted 5 years or longer. The percentage of respondents according to episode duration among those experiencing a past year major depressive episode is shown in Table 5. Mathematical modeling studies provide an explanation for these results: the probability of recovery appears to decline with increasing episode duration (Patten and Lee, 2004). Mean episode duration in the NPHS was 17 weeks (Patten and Lee, 2004), but the mean duration obscures both the brief nature of some episodes and the protracted nature of others. Prevalence is a product of incidence and duration, such that reducing the duration of episodes (for example, through treatment), in the absence of other changes, will reduce the prevalence in the population. Unfortunately, despite recent increases in treatment provision (Patten and Beck, 2004), a reduction in prevalence has not yet been discernable in those countries where before–after comparisons have been feasible (Brugha et al., 2004; Kessler et al., 2005). Many new-onset episodes occurring in the general population are brief, but longer episodes accumulate to a greater extent and predominate as prevalent cases in the population (Patten, 2006; Patten, 2007).

The Netherlands Mental Health Survey and Incidence Study (NEMESIS) provides important data on the longitudinal course of DSM-III-R defined MDD. This study retrospectively assessed episode duration in community residents with new-onset episodes. Consistent with Canadian data, a sizable proportion of episodes were brief: 50% of episodes recovered within 3 months. However, the recovery rate flattened over time, and the authors estimated that approximately 20% would have chronic episodes persisting longer than 24 months (Spijker et al., 2002).

MDD is often a recurrent condition. In the CCHS 1.2, respondents with lifetime MDD reported a single episode 56.0% of the time, 2 episodes 28.6% of the time and 3 or more lifetime episodes 15.4% of the time (CCHS 1.2, Public Use Microdata File). Given the potential role of recall bias (see above), it is likely that these are underestimates of the frequency of recurrent episodes.

1.6. What is the impact of depressive disorders on population health?

6.1. How substantial is the disease burden associated with MDD?

According to the Global Burden of Disease Study, MDD is one of the world's leading causes of disability (Murray and Lopez, 1996; The World Health Report 2001, 2001). Because cognitive symptoms are prominent, the ongoing transition to a knowledge-based economy is expected to further magnify the impact of MDD on occupational functioning (The Standing Senate Committee on Social Affairs Science and Technology, 2006). Depressive disorders impact society partially by increasing suicide risk. In a study of 102 suicides in New Brunswick,

Table 5
Number of weeks depressed (past year) in CCHS 1.2 respondents with past-year Major Depressive Episodes.

< 6 weeks	22.1%
7 to 12 weeks	20.8%
13 to 26 weeks	29.2%
27 to 52 weeks	27.9%

Canadian Community Health Survey 1.2, Public Use Microdata File.

almost 70% of victims had an affective disorder, usually comorbid with addictive or personality disorders (Seguin et al., 2006). Data from NEMESIS demonstrated that comorbid anxiety disorders amplify the risk of suicide attempt in individuals with mood disorders (Sareen et al., 2005). Depressive disorders also have a major impact on quality of life (QOL). In a study of QOL impairment in depressive and anxiety disorders, 63% of respondents with MDD had severe impairment in QOL, while 85% of those with double depression (MDD and Dysthymic Disorder) and 56% of those with Dysthymic Disorder had QOL impairment in the severe range (Rapaport et al., 2005).

1.7. What is the occupational impact?

Depression profoundly affects occupational functioning, both through absenteeism and presenteeism (loss of productivity while attending work when unwell) (Sanderson et al., 2007). A longitudinal study found that depressed workers had significantly greater performance deficits than control workers (who had rheumatoid arthritis) with regard to performing mental interpersonal tasks, time management, output tasks and physical tasks (Adler et al., 2006). Even after 18 months of follow-up, clinical improvement did not result in full recovery of job performance.

In a comparison of 6 'depressed-at work' and 'depressed-not at work' populations, the depressed workers were more likely to be young, better educated, white collar and of better overall health status than the non-working depressed group (Elinson et al., 2004). Depressed employees are also more likely to become unemployed or miss time at work than physically ill employees (Hoge et al., 2002). When depressed workers were compared to controls and workers with rheumatoid arthritis, the depressed employees became unemployed five times more frequently than the other 2 groups (Lerner et al., 2004).

1.8. What is the impact of MDD on other functional domains?

While occupational impairment has received the most attention, depressive disorders also negatively affect functioning in non-occupational tasks. In fact, the National Comorbidity Survey Replication study in the US found that role impairment in people with MDD was lowest in the occupational domain and highest in the social domain (Kessler et al., 2003). In this survey, 59.3% of respondents with past-year major depressive episodes reported severe or very severe role impairment. Depression in women may also have a negative effect on the development of their children and on family dynamics (Toney, 2007). Treatment of maternal depression to remission in the STAR*D child study was associated with decreased psychiatric symptoms and improved functioning in the offspring (Pilowsky et al., 2008). There is also evidence of increased consultation for developmental and behavioral problems in the children of fathers who meet criteria for major depressive disorder (Dave et al., 2009). Such intergenerational effects may magnify the impact of depression on population health (Ramchandani and Stein, 2003).

1.9. What is the impact of MDD on physical health?

MDD or depressive symptoms can negatively affect physical health by reducing adherence to medical treatment (Ciechanowski et al., 2000), reducing participation in preventive activities (Aro et al., 1999), and altering risk factors such as obesity (McIntyre et al., 2006), smoking (Murphy et al., 2003) and sedentary lifestyles (van Gool et al., 2003). Depressed patients with or without diabetes have a higher incidence of obesity, metabolic disorders, higher insulin resistance, decreased heart rate variability and arteriosclerosis (Lin et al., 2004). There is evidence from Saskatchewan Health data, that depressive disorders increase the risk of Type II diabetes (Brown et al., 2005). A growing body of evidence suggests that MDD is also associated with immune dysfunction (Corcos et al., 2002; Kop et al., 2002; Musselman et al., 2001; Penninx et al., 2003), and, in the case of recurrent MDD, with coronary and aortic calcification in middle aged women (Agatisa et al., 2005). Depression is increasingly recognized as an independent risk factor for cardiovascular disease and an independent predictor of mortality (Kop, 2003; Taylor et al., 2005; Wassertheil-Smoller et al., 2004; Writing committee for the ENRICHED investigators, 2003). Statistics Canada recently reported MDD to be predictive of new-onset heart disease in the Canadian general population (Gilmour, 2008) and a Science Advisory Statement by the American Heart Association (endorsed by the American Psychiatric Association) recommended routine screening for depression in patients with coronary heart disease (Lichtman et al., 2008). In addition to these specific examples, MDD appears to be associated with a general increase in chronic disease incidence (Patten et al., 2008) and there is a joint effect of depression and these chronic diseases on functional disability (Schmitz et al., 2007).

While there has been much interest in the relationship between MDD and chronic medical conditions such as heart disease and diabetes, the conditions most strongly associated with MDD in the Canadian population are neurological conditions and conditions related to pain and inflammation (Table 6).

1.10. How do patients with MDD typically present in clinical practice?

Depressive disorders, as currently defined by DSM-IV, are largely symptom-based diagnostic entities. These disorders are associated with a very broad range of clinical presentations, which must be understood in a biopsychosocial context. MDD can present at any age but the peak prevalence occurs in those between the ages of 15 and 45 years (Patten et al., 2005b). Consequently, MDD has a disproportionately large impact on education, work productivity, relationships and

Table 6
Medical conditions strongly associated with MDD in the Canadian population.

Medical condition	Odds ratio	Medical condition	Odds ratio
Emphysema/COPD	2.7	Asthma	1.9
Migraine	2.6	Stroke	1.7
Multiple sclerosis	2.3	Thyroid disease	1.4
Back problems	2.3	Diabetes	1.4
Cancer	2.3	Heart disease	1.4
Epilepsy	2.0		

Estimates derive from the Canadian Community.
Health Survey 1.1, Patten et al. (2005a).

parenting, all of which may appear to be the presenting problem. While many of those with depression never present to their primary care physician, up to 50% who do visit the office are not recognized as depressed and as many as two thirds present with somatic symptoms only (Cepoiu et al., 2008). Clinician training in communication and emotive skills may improve detection and management of depression in primary care (Gask et al., 1988; Roter et al., 1995).

The simplest approach to case-finding in clinical practice is a 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?" (Kroenke et al., 2003). This 2-question screening approach is recommended for routine practice by the US Preventive Services Task Force in settings where resources exist to confirm diagnoses and provide effective treatment and follow-up (US Preventive Services Task Force, 2002). An answer of "yes" to either question requires a more detailed assessment and consideration of other possible causes of depressive symptoms (Whooley et al., 1997). Despite the Task Force recommendations, the value of screening remains controversial (Palmer and Coyne, 2003) and available evidence does not confirm that screening activities in isolation lead to better outcomes (Gilbody et al., 2005). One concern is the low predictive value of screening instruments and approaches. This can be increased by restricting screening to high risk groups identified either using clinical groups or symptom presentations (Table 7).

1.11. What are the basic principles of clinical assessment?

DSM-IV provides valuable sets of diagnostic criteria but the nosology is not intended to supplant clinical judgment. Successful treatment depends on an accurate diagnosis, but an accurate diagnosis does not provide a sufficient basis for clinical management. The diagnosis of MDD is always a provisional diagnosis since the occurrence of hypomanic, manic or mixed episodes trigger a revision of the diagnosis (Blacker and Tsuang, 1992). As such, working diagnoses may evolve over time. Nevertheless, an accurate diagnosis is the most important starting point for clinical management. The goals of assessment include: assessment of safety, establishment of rapport and a therapeutic alliance, assessment of comorbidity, patient education, and obtaining informed consent to proceed with treatment.

Table 7
High risk groups and symptomatic presentation of MDD.

High risk clinical groups	High risk symptom presentations
Past history of depression	Unexplained physical symptoms
Family history of depression	Pain, including chronic pain
Psychosocial adversity	Fatigue
High users of the medical system	Insomnia
Chronic medical conditions (especially cardiovascular disease, diabetes, conditions involving chronic pain and neurological disorders)	Anxiety
Other psychiatric conditions	Substance abuse
Times of hormonal challenge (e.g. postpartum)	

Table 8
Case-finding and monitoring instruments for depression.

Instrument name	Number of items
Brief Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001)	9
Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR) (Rush et al, 2003)	16 (only 9 scored)
Beck Depression Inventory (BDI-I or BDI-II) (Beck et al., 1961)	7–21 [a]
Zung Self-Rating Depression Scale (Zung, 1965)	20
Center for Epidemiologic Studies Depression Rating Scale (CES-D) (Radloff, 1977)	20

[a] The BDI-II has 21 items.

In situations where clinicians choose to use a measurement instrument for case-finding, screening or monitoring, several tools are available (see Table 8), and there were no major differences between these (and other) instruments in a comparative study (Williams et al., 2002). However, many clinicians find the PHQ-9 or the QIDS-SR to be attractive options because of their brevity and strong alignment with DSM-IV.

In the assessment of depressed patients, clinicians should evaluate suicide risk. Suicide risk is an important consideration in determining the need for hospitalization. Clinicians should ensure that patients are aware of locally available sources of help and patients should be advised to seek help if their situation deteriorates. Physical health, psychosocial status (including social and interpersonal relationships) and psychiatric comorbidity should also be assessed. Assessment of past response to treatment can provide valuable guidance for treatment decisions. Information from supplemental sources such as health records and knowledgeable informants is often a key component of assessment.

The spectrum of depressive morbidity encountered by primary care physicians is broad. As such, "stepped care" strategies have an important role. In primary care, the range of interventions offered may extend from close monitoring of mild episodes without immediate treatment (so-called "watchful waiting"), through guided self-management (Bilsker et al., 2007), brief psychological or behavioral interventions, pharmacological management and, if needed, referral to more specialized services or hospital admission. A decision about where to start on this continuum is initially made, and a lack of response leads to stepped-up care. A stepped care approach is advocated by the NICE guidelines in the UK (National Institute for Health and Clinical Excellence, 2004), and is an intrinsic component of most disease management approaches for MDD. The stepped care approach has implications for assessment of patients presenting with depression — a clinician must form a judgment not only about the correct diagnosis, but also about where a particular patient falls on the continuum of care.

There has been a shift towards a conceptualization of MDD as a chronic disease (Andrews, 2001), resulting in the emergence of disease management strategies resembling those employed for other chronic medical conditions such as diabetes and congestive heart failure. Disease management for depression typically includes several elements: (1) active efforts to detect depression using screening questions or rating scales, (2) delivery of evidence-based care, including

both antidepressant medications and psychotherapy, (3) case-management in a collaborative context with "stepped" care options, (4) patient education about depression and self-management of depression and (5) process measurement such as monitoring of the timeliness and quality of care in addition to measurement of symptomatic outcome in patients (Kates and Mach, 2007). A systematic review of 10 high quality randomized controlled trials found robust evidence of the effectiveness of disease management for depression (Neumeyer-Gromen et al., 2004).

In the Canadian context, most treatment for depressive disorders occurs in fee for service primary care practices, where disease management strategies are challenging to implement. For example, fee for service funding arrangements do not generally provide support for case-management, which is a component of most disease management strategies. This situation may change in the future as primary care reform leads to a greater emphasis on chronic disease management. Nevertheless, collaborative care models have been a focus of interest in Canada for many years (Kates, 2002). When shared or collaborative care arrangements are in place, the professionals involved must maintain a clear awareness of their responsibilities within those arrangements.

1.12. What are the phases of treatment?

For heuristic purposes, the treatment of MDD can be divided into two phases: acute and maintenance (Table 9). The aim of acute treatment is to eliminate symptoms of depression and restore psychosocial functioning. The aim of maintenance treatment is to ensure a return to baseline function and quality of life and to prevent recurrence of symptoms.

1.13. What are the basic principles of treatment?

Although approaches to management differ depending on the context of care delivery, many of the basic principles remain the same. Trends in collaborative MDD management that incorporate "stepped care" and disease management have common elements, most of which (the exception being case-management) are applicable to other treatment settings (see Table 10). These elements include systematic monitoring

Table 9
Phases of treatment for MDD.

Treatment phase	Duration	Goals	Activities
Acute	8–12 weeks	• Remission of symptoms • Restore function	• Establish therapeutic alliance • Educate • Select and use treatment(s) • Monitor progress
Maintenance	6–24 months, or longer	• Return to full function and quality of life • Prevention of recurrence	• Educate • Rehabilitate • Treat comorbidities • Monitor for recurrence

Table 10
Chronic disease management strategies [a] for MDD.

Active efforts to detect depression
Delivery of evidence-based care
Patient education about depression
Process measurement and systematic outcome assessment

[a] Adapted from Kates and Mach, 2007.

of patient outcomes, treatment decisions that are evidence-based and responsive to therapeutic goals. The systematic progression through available treatment options is consistent with the CANMAT concept of "Lines of Treatment" which are elaborated in subsequent sections of these guidelines. Because MDD in itself may reduce treatment adherence, this should be discussed at an early stage and should be monitored frequently during treatment in an open manner (Trivedi et al., 2007).

1.14. What are the goals of acute treatment?

The target goal for acute treatment should be remission: a resolution of depressive symptoms. "Response" to treatment (a reduction in symptom levels) is not an adequate outcome because residual depressive symptoms are risk factors for relapse and negative predictors of long-term outcome (McIntyre and O'Donovan, 2004). Monitoring of symptom levels during treatment is an essential metric of outcome. Outcome assessment can be conducted using validated interviewer-rated scales, e.g., the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960) or the Montgomery Åsberg Depression Rating Scale (MADRS, Montgomery and Åsberg, 1979). A seven-item version of the HDRS is a suitable tool for clinical practice because of its brevity and validity (McIntyre et al., 2002). Busy clinicians also may find that the self-report scales listed in Table 8 are efficient tools to monitor progress and outcome. Response is usually defined as >50% reduction in scores on these scales, while remission is defined as a score within the normal range.

1.15. What are the goals of maintenance treatment?

The terms relapse (return of symptoms during a current episode) and recurrence (return of symptoms owing to a new episode) are not functionally useful because there are no methods to determine when an episode ends. Hence, once patients are treated in the acute phase and are well (i.e., in symptom remission), the critical questions are: how can they stay well and how long do treatments need to be maintained? The goals of this maintenance phase include resolving any residual symptoms, treating comorbid conditions, returning to full pre-morbid functioning and preventing return of symptoms (Table 10), Clinicians should focus on healthy life strategies, personality vulnerabilities, long-term self-management and clinical strategies to reduce recurrence (Rafanelli et al., 2007). Continued pharmacologic and non-pharmacologic treatments have a role in the prevention of recurrence: supporting evidence is evaluated in subsequent sections of these guidelines.

3. Conclusion

Depressive disorders are among the most common and burdensome conditions afflicting the Canadian population. Evidence-based management can reduce their burden in afflicted individuals and ultimately in society as a whole. By summarizing an updated evidence base, the aim of these revised CANMAT guidelines is to link the best available evidence to the best possible care of depressed patients.

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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. II. Psychotherapy alone or in combination with antidepressant medication

Sagar V. Parikh [a,*], Zindel V. Segal [a], Sophie Grigoriadis [a], Arun V. Ravindran [a], Sidney H. Kennedy [a], Raymond W. Lam [b], Scott B. Patten [c]

[a] University of Toronto, Canada
[b] University of British Columbia, Canada
[c] University of Calgary, Canada

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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. This article, one of five in the series, reviews new studies of psychotherapy in the acute and maintenance phase of MDD, including computer-based and telephone-delivered psychotherapy.
Methods: The CANMAT guidelines are based on a question–answer format to enhance accessibility to clinicians. Evidence-based responses are based on updated systematic reviews of the literature and recommendations are graded according to the Level of Evidence, using pre-defined criteria. Lines of Treatment are identified based on criteria that included evidence and expert clinical support.
Results: Cognitive-Behavioural Therapy (CBT) and Interpersonal Therapy (IPT) continue to have the most evidence for efficacy, both in acute and maintenance phases of MDD, and have been studied in combination with antidepressants. CBT is well studied in conjunction with computer-delivered methods and bibliotherapy. Behavioural Activation and Cognitive-Behavioural Analysis System of Psychotherapy have significant evidence, but need replication. Newer psychotherapies including Acceptance and Commitment Therapy, Motivational Interviewing, and Mindfulness-Based Cognitive Therapy do not yet have significant evidence as acute treatments; nor does psychodynamic therapy.
Limitations: Although many forms of psychotherapy have been studied, relatively few types have been evaluated for MDD in randomized controlled trials. Evidence about the combination of different types of psychotherapy and antidepressant medication is also limited despite widespread use of these therapies concomitantly.
Conclusions: CBT and IPT are the only first-line treatment recommendations for acute MDD and remain highly recommended for maintenance. Both computer-based and telephone-delivered psychotherapy—primarily studied with CBT and IPT—are useful second-line recommendations. Where feasible, combined antidepressant and CBT or IPT are recommended as first-line treatments for acute MDD.

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Introduction

The Canadian Psychiatric Association and the Canadian Network for Mood and Anxiety Treatments (CANMAT), a not-for-profit scientific and educational organization, collaborated

* Corresponding author.
E-mail addresses: sagar.parikh@uhn.on.ca (S.V. Parikh).

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 reviews psychotherapy, alone and in combination with medication, while a series of 4 companion sections review other aspects of MDD. There are separate CANMAT guidelines for Bipolar Disorder (Yatham et al., 2009).

Psychotherapy refers to the 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. Historically this required the establishment of a professional relationship between a patient and a therapist; with the advent of computer, internet, self-help, and to a lesser extent telephone therapies, the relationship is more explicitly between the patient and the psychological model, with an implicit link to the 'therapist' who designed the therapy.

Psychotherapy predates somatic therapies and includes a host of models, several of which have been rigorously tested, specifically for MDD. This review summarizes depression-specific psychotherapies as well as newer therapies which are promising, and seeks to clarify the evidence and usefulness of each major psychotherapy. While most psychotherapies share many common elements, the major treatments for MDD may be characterized by a number of key components: (a) the goal of treatment is alleviation of the core symptoms of depression, (b) there is careful attention to a specific method to deliver the therapy (typically a manual), (c) the psychotherapy focuses on the current problems of the patient, (d) high levels of activity are expected both of the therapist and the patient (who frequently has 'homework'), (e) careful symptom monitoring, preferably with rating scales, is expected, (f) psychoeducation about the illness is a universal component, and (g) 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, and the choice of either psychotherapy or pharmacotherapy alone or in combination are reviewed in a number of the following questions. 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., 2009) but, in summary, relevant English language publications 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 previous question–answer format has been retained based on feedback from clinicians. Recommendations for each Line of Treatment are based on the Level of Evidence and clinical support (Table 1). 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 have not worked.

CANMAT recognizes that much of the evidence is based on studies using strict inclusion/exclusion criteria with intensive and frequent follow up for a short duration of treatment, and therefore may not be applicable to the average patient seen by clinicians. Hence, there are few absolute recommendations and these guidelines should be viewed as guidance that must be tailored to an individual patient, and not as standards of care.

2.1. When is psychotherapy indicated for treatment?

Many factors influence the decision of when and where to employ psychotherapy. Employing a broad perspective, there are patient, provider, and (health) system issues that each play a role. Among the patient factors are adequacy of clinical evidence for a specific patient population (e.g. women during pregnancy); medication contraindications; patient preference; and the ability of a patient to engage in treatment. Patient preferences may in turn be influenced by social or cultural convictions regarding the efficacy of particular non-medical therapies, and the fear of potential medication side

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

Level	Criteria
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	Criteria
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] 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 in 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.

effects. Provider factors include the ability to provide the chosen psychotherapy of sufficient quality and in sufficient quantity to meet patient needs, as well as the capacity to engage the patient. System factors include ease of availability and if applicable, cost. System factors also play a role in which therapies are provided: some systems provide paid coverage for traditional psychotherapies such as psychodynamic methods for historical reasons, while other systems facilitate treatments that can be provided by specific professional groups within the health care system—for instance, the provision of CBT by specially trained counselors.

For the clinician using these guidelines, it would be reasonable to begin by identifying the first-line psychological treatments recommended for MDD, clarifying if there are any particular recommendations for a special subpopulation, and evaluating how the evidence and availability for these treatments compare to the evidence and availability of somatic therapies. Severity is another overarching issue in considering whether to recommend psychotherapy: for the most severe depressions, the efficacy and speed of somatic therapy over psychotherapy is a consideration.

Safety and relative contraindications should also be considered; it would be unwise to recommend monotherapy with psychotherapy in a severely suicidal patient, and the presence of psychotic depression would be an instance where psychotherapy alone would be contraindicated. While it is intuitive to assume that the combination of psychotherapy and pharmacotherapy may be better than either treatment alone, the strength of evidence varies across therapies, and availability issues often preclude combined treatments. Table 2 summarizes the treatment recommendations for psychotherapy for MDD. Since many psychotherapies exist, only those specifically studied for MDD are included, along with selected other forms which have significant prominence (e.g. Motivational Interviewing).

2.2. What is Cognitive-Behavioural Therapy (CBT)?

CBT for depression is an intensive, time-limited, symptom focused psychotherapy built on the premise that distorted beliefs about the self, the world, and the future maintain depressive affect. Once patients learn to recognize these automatic thinking patterns, they are taught more adaptive ways of responding. Behavioural interventions in CBT are

especially effective for symptoms of social withdrawal and anhedonia, and focus on activating patients' engagement in their environment as well as increasing their feelings of mastery and pleasure. These skills, when accompanied by affective arousal and practiced in the context of extra therapy assignments, are important engines of symptom change. As with other brief therapies, coverage of didactic content combined with case supervision is necessary to achieve competence in this approach. Further information can be obtained through the Academy of Cognitive Therapy's website (www.academyofct.org).

2.3. How effective is CBT in acute MDD?

Evidence from 85 randomized controlled trials (RCTs) since 1977 provides empirical support for CBT's efficacy in treating MDD (mild to moderate in severity), with the modal finding being one of relative equivalence to antidepressant medication (effect size 0.38) for the acute phase episode and superiority over control conditions (effect size 0.82 against placebo and wait-list controls) (Gloaguen et al., 1998). An important extension of this work involves the treatment of more severely (but non-psychotic) depressed patients, with two studies finding no difference between CBT and antidepressant medication (DeRubeis et al., 2005; Luty et al., 2007). Further evidence for the comparability of CBT to pharmacotherapy is found in the results from the STAR*D project, where CBT was one of several second level options for outpatients who failed to achieve remission with citalopram. For patients who switched to CBT there were no significant differences in remission rates and fewer side effects compared to switching to a different antidepressant, although the mean time to remission was approximately 3 weeks longer with CBT than with medication (Thase et al., 2007).

Additional extensions include recent evidence of the effectiveness of CBT in treating specific subgroups, for instance low income, young minority women (Miranda et al., 2003). A final factor influencing effectiveness of treatments is comorbidity, which is common in MDD. There is inconsistent evidence about the influence of comorbid personality disorders on psychiatric outcomes. With respect to patient selection, Joyce et al. (2007) compared CBT and IPT outcomes in depressed patients with comorbid personality disorder (PD) or traits and found that the presence of PD did not diminish clinical outcomes. In summary, there is Level 1 evidence for CBT in acute MDD, and it is a first-line treatment.

2.4. How effective is CBT in the maintenance phase of MDD?

This question deals with prevention of relapse following a successful acute treatment, and the ability of 'maintenance' or 'continuation' CBT to confer added benefits. A recent meta-analysis of 28 studies suggests that CBT prophylaxis endures beyond treatment cessation; if both CBT and medication are stopped after successful acute treatment of several months, patients who initially received CBT have lower rates of relapse (Vittengl et al., 2007). However, stopping acute phase CBT results in a relapse rate of 54% within 2 years (Vittengl et al., 2007); therefore, meta-analysis also examined the impact of maintenance CBT, using those who had already responded to CBT. The meta-analysis

Table 2
Recommendations for individual psychotherapies for acute MDD.

First-line treatments	Cognitive-Behavioural Therapy [CBT; Level 1] Interpersonal Therapy [IPT; Level 1]
Second-line treatments	Bibliotherapy [Level 1] Behavioural Activation [Level 2] Cognitive-Behavioural Analysis System of Psychotherapy [CBASP; Level 2 evidence for chronic MDD with acute episode] Computer-assisted CBT [Level 2] Telephone-delivered CBT and IPT [Level 2]
Third-line treatments	Acceptance and Commitment Therapy [ACT; Level 3] Motivational Interviewing [Level 4] Psychodynamic therapy [Level 2] Emotion-Focused Therapy [Level 2]

used an "enriched design" by looking only at full responders, much like medication studies, but nonetheless revealed that maintenance CBT (often at a dose of one session per month) provided further protection against relapse, comparable to pharmacotherapy. There is also evidence that CBT provides continued protection against relapse after maintenance CBT is stopped: the relapse rate was 31% over the subsequent 12 months for patients who received acute CBT plus up to 3 maintenance sessions compared to a 76% relapse rate following medication withdrawal in remitted patients. However, if the medication patients received ongoing pharmacotherapy, relapse rates were similar (Hollon et al., 2005). Paykel et al. (2005) reported that the benefits of CBT prophylaxis in the context of combination treatment of residual depression continued for 4.5 years post CBT. What is not known is whether these effects are due to changes in the causal processes that contribute to relapse risk, or to the incorporation of compensatory strategies that neutralize their effects on mood regulation. Overall, there is Level 1 evidence, and CBT is recommended as a first-line treatment for the maintenance phase of MDD.

2.5. What is Interpersonal Therapy (IPT)?

Interpersonal Psychotherapy (IPT) is a time-limited, manua-lized psychotherapy, that was first developed in the 1970's for the outpatient treatment of individuals with MDD. Much like the adaptation of CBT to treat other disorders, IPT has been modified for the treatment of Eating Disorders, Dysthymia, Bipolar Disorder, Substance Use Disorder, Panic Disorder, Social Anxiety Disorder, Body Dysmorphic Disorder, Somatization and Border-line Personality Disorder. IPT deals with current interpersonal relationships and focuses on the immediate social context. The original IPT format involved 16 sessions with three phases and a focus on one or more areas including role transitions, inter-personal role disputes, grief or interpersonal deficits; these foci have been modified for application in special populations. Numerous training options exist and information can be obtained on the International Society for Interpersonal Psychotherapy website (isIPT, www.interpersonalpsychotherapy.org).

2.6. How effective is IPT in MDD?

Among the many meta-analyses and reviews of IPT, two provide more specific overviews of the precise targeting of MDD (Markowitz, 2008; Parker et al., 2006). Although one meta-analysis did find IPT superior to CBT (deMello et al., 2005) and another reported modest superiority of antidepressant

medications over IPT (effect size 0,15) (Kotova, 2005), the weight of evidence does not support the superiority or inferiority of IPT compared to CBT or pharmacotherapy. Combination treatment with IPT and medication has not been found to be superior to either alone (Barkham and Hardy, 2001; Kotova, 2005; deMello et al., 2005). Important extensions of IPT include studies of acute and maintenance treatment of elderly patients, acute treatment for adolescents, several group studies with heterogeneous populations, and in prevention of MDD in high risk groups (Roth and Fonagy, 2005). There is Level 1 evidence for IPT as a first-line treatment recommendation for acute MDD, and Level 2 evidence for IPT as a second-line treatment recommendation for the maintenance phase of MDD (see Table 3).

2.7. What is psychodynamic therapy?

Psychodynamic psychotherapy is based on psychoanalytic principles (Bond, 2006). At its core is the assumption that conscious or unconscious emotions and defence mechanisms can contribute to the development of negative emotional and cognitive states, including those associated with MDD and anxiety disorders. By developing insight into these factors, i.e. recognizing them and understanding their source and influence on behaviour as well as physical and mental symptoms, psychological healing can take place. The ther-apeutic relationship plays a key role in the process.

2.8. How effective is psychodynamic psychotherapy?

Complicating factors in the evaluation of efficacy include combination of both short-term and long-term interventions under a single umbrella of psychodynamic therapy and the inclusion of broadly defined patient groups—often having a mix of significant depressive and anxiety symptoms—rather than definite MDD. Furthermore, psychodynamic therapy studies often lack the specific symptom measures established as valid outcome measures for almost all other treatments; this weakens the ability to support psychodynamic therapy as evidence-based. As noted in the previous guidelines (CANMAT, 2001), a meta-analysis found brief psychodynamic psychother-apy superior to no treatment in MDD, but inferior to alternate therapies like CBT (Svartberg and Stiles, 1991). However, these authors included IPT as a psychodynamic psychotherapy. Since 2001, psychodynamic psychotherapy has been evaluated in mild to severe MDD (with or without comorbid personality disorders), dysthymia, "double depression" and post parti depression (e.g. Burnand et al., 2002; Cooper et al., 2003;

Table 3
Recommendations for major psychotherapies for MDD.

Comparison of evidence for CBT and IPT and other major psychotherapies				
	CBT	IPT	Psychodynamic psychotherapy	Behavioural activation
Acute MDD	First-line treatment [Level 1]	First-line treatment [Level 1]	Third-line treatment [Level 2]	Second-line treatment [Level 2]
Maintenance	First-line treatment [Level 1]	Second-line treatment [Level 2]	Lack of specific findings with respect to MDD do not allow for recommendation	Second-line treatment [Level 2]
Combination with medications	Second-line treatment [Level 1]	Second-line treatment [Level 1]	Insufficient evidence	Insufficient evidence

Trowell et al., 2007; Wilson et al., 2008). The inclusion of diverse patient populations and treatment models (e.g. short psychodynamic supportive psychotherapy, brief/short-term psychodynamic therapy) further limits conclusions about the effectiveness of psychodynamic psychotherapy.

Formal meta-analyses comparing psychodynamic therapy to cognitive-behavioural or behavioural interventions (CBT/BT) have yielded mixed results, with two reporting that psychodynamic therapy is as effective as CBT/BT (Leichsenring, 2001; Wilson et al., 2008 in older adults), and one reporting that CBT is superior (Pinquart et al., 2007, in older adults). However, the Leichsenring study (2001) found only six suitable trials for inclusion, and noted that there were "no two studies of independent research groups demonstrating equal effectiveness of the same form of short-term psychodynamic psychotherapy (STPP) compared to CBT/BT in the treatment of depression." Given the heterogeneity of treatment models, durations, and types of populations, even under the rubric of 'short-term' psychodynamic psychotherapy, these studies provide Level 2 evidence and are recommended as third-line interventions (Anderson and Lambert, 1995). In patients with complicated comorbidities including personality disorders, however, there is Level 2 evidence to recommend psychodynamic therapy as a second-line treatment (Kool et al., 2003; Abbas, 2008; Bond and Perry, 2006).

2.9. How effective is psychodynamic psychotherapy in the maintenance phase of MDD?

There are only preliminary systematic outcome data on the long-term benefits of psychodynamic psychotherapy. Although one meta-analysis evaluated treatments longer than 1 year for a variety of disorders that included MDD and found benefit in general, it did not specify findings explicitly for MDD alone. As a result, the lack of evidence does not allow for recommendation of the value of psychodynamic psychotherapy for prevention of relapse of MDD (Leichsenring and Rabung, 2008).

2.10. Does psychotherapy prevent relapse in MDD?

The goals for any therapeutic intervention encompass both acute phase remission and maintenance phase prevention of relapse/recurrence. This has bolstered the use of

Table 4
Recommendations for individual psychotherapies for maintenance phase of MDD.

First-line treatments	CBT [Level 1]
Second-line treatments	Behavioural Activation [Level 2]
	CBASP [Level 2]
	IPT [Level 2]
	MBCT [Level 2]
Third-line treatments	None with evidence
Insufficient evidence to make a recommendation	ACT
	Motivational Interviewing
	Psychodynamic therapy
	Emotion-Focused Therapy
	Bibliotherapy
	Computer-assisted
	Telephone-delivered

psychotherapy as a continuation or maintenance treatment, as summarized in Table 4. Additionally, issues with non-adherence and other barriers to continuation therapy with antidepressants support the role of psychotherapy to prevent relapse. Furthermore, even continuation pharmacotherapy does not prevent all relapses of MDD, reinforcing a possible role for psychotherapy. Overall, data from depression-specific psychotherapies support their utility in preventing episode return; too few studies exist to evaluate similar benefits from long term psychodynamic treatments. Rates of relapse following acute phase CBT are similar to those for patients continuing on antidepressants (Hollon et al., 2005), while remitted patients receiving maintenance IPT (M-IPT) or CBASP (Klein et al., 2004) during remission benefit more than those who receive clinical management. Monthly M-IPT was as effective as weekly or biweekly sessions in patients who remitted with IPT alone, but less effective for patients who required SSRI augmentation to achieve remission (Frank et al., 2007; Browne et al., 2002). Psychological strategies have also been applied to enhance medication adherence (Dotoli et al., 2006) with fewer relapses following fluvoxamine and group psychoeducation compared to patients treated with fluvoxamine alone; however, a comprehensive review by Vergouwen et al. (2003) noted that improved antidepressant adherence in primary care was not achieved by psychoeducational interventions alone, but was achieved when multifaceted interventions including psychoeducation were provided.

Beyond enhancement of adherence and the continuation of acute depression psychotherapy into the maintenance phase, specific psychotherapy approaches have been designed to be sequenced with pharmacologically-induced remission. Fava et al. (2004) developed a modified CBT to include a "Well Being" focus on lifestyle management as well as affective symptoms (CBT-WB). Recurrent depressed patients who were treated to remission pharmacologically and withdrawn had a 90% relapse rate over 6 years, compared to a rate of 40% for patients who received CBT-WB following drug discontinuation. Similarly, Mindfulness-Based Cognitive Therapy (MBCT), a group intervention that targets dysphoria-activated depressogenic thinking has been evaluated in remitted, recurrently depressed patients. Controlled clinical outcomes for MBCT indicate increased relapse-free survival time by 50% in unmedicated patients, compared to patients receiving treatment as usual. In addition, depressed patients who remitted with pharmacotherapy and who were discontinued onto MBCT had the same rate of relapses as patients who continued antidepressant medication (Kuyken et al., 2008). These results provide additional evidence that several psychotherapy approaches may reduce relapse in MDD. While the presence of several RCTs provide Level 1 evidence, the diversity of psychotherapy models and small number of study participants indicate a second-line treatment recommendation.

2.11. What is Motivational Interviewing?

Motivational Interviewing (MI) was originally developed by Miller (1996) as a strategy for engaging and treating patients with substance use disorders (SUDs). MI incorporates the levels of motivation outlined in Prochaska and DiClemente's (1986) stages-of-change model. MI is a person-centred clinical method

to help patients resolve ambivalence and move ahead with change. Although it has been applied as a preparation for treatment and a freestanding brief intervention for SUDs, the term has also been used to describe a clinical style, and a default approach when motivational obstacles are encountered in treatment. MI approaches have been found to be equivalent to other active treatments for substance related disorders and have yielded moderate effects (0.25–0.57) compared to no treatment or placebo (Burke et al., 2003). MI has been incorporated into evidence-based therapy such as CBT for depression for those who are ambivalent about change and about taking necessary actions to bring about change.

2.12. How effective is Motivational Interviewing for MDD?

No published trials were identified using MI alone in patients with a primary diagnosis of MDD. Five MI trials involving subjects with a primary SUD also included some subjects with either depressive symptoms or full MDD, and found reductions in both substance misuse and depressive symptoms. For example, Baker et al. (2006) randomized 65 subjects with substance abuse and a psychotic disorder to a 10 session intervention which consisted of MI and CBT and compared them to 65 subjects who received routine treatment; the intervention showed short-term improvement in depression scores. Individuals with more severe depression benefited from more sessions (Baker et al., 2005). The general strategies of MI appear to increase the chances of successful treatment for the SUD and may also maximize the dual diagnosis patient's participation in treatment, and improve outcome. Thus, it is unclear if the improvement in substance abuse is a result of the impact of MI on the depression or independent of it. In the absence of specific MDD studies, evidence is at Level 4 (expert opinion) and MI receives a third-line recommendation.

2.13. What is Cognitive-Behavioural Analysis System of Psychotherapy (CBASP)?

CBASP is a form of psychotherapy that was developed specifically for the treatment of chronic depression (Arnow, 2005; McCullough, 2003; Swan and Hull, 2007). 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. These outcomes include negative relationship patterns, which are seen as a particular difficulty for chronically depressed patients. The therapeutic relationship serves as a medium for negative interpersonal behaviours to be changed.

2.14. How effective is CBASP for acute MDD?

Although there have been 11 publications on the efficacy of CBASP in chronic depression since 2000, they all relate to the same large multi-centre clinical trial, first reported by Keller et al. (2000) that was referenced in the previous guidelines (CANMAT, 2001). In this study, combination therapy was significantly superior to either treatment alone in improving symptoms and psychosocial functioning. The combination was also associated with significantly less attrition and significantly greater maintenance of gains during continuation treatment,

though the individual treatments were also effective (Arnow et al., 2007; Hirschfeld et al., 2002; Keller et al., 2000; Kocsis et al., 2003; Rush et al., 2005). However, nefazodone and combination therapy were superior to CBASP in improving sleep and sexual functioning (Manber et al., 2003; Thase et al., 2002; Zajecka et al., 2002). Regarding attrition, overall, CBASP and nefazodone had similar drop-out rates (Arnow et al., 2007), but when only monotherapy non-responders were considered, CBASP was associated with significantly lower attrition (Schatzberg et al., 2005). Finally, there was a significant advantage of CBASP, in monotherapy or combined with medication, compared to medication alone in a subset of patients who had experienced early childhood trauma (Nemeroff et al., 2003). In summary, there is Level 2 evidence to support CBASP as second-line monotherapy or "add-on" to antidepressants in the acute treatment of chronic MDD, with evidence of sustained benefit.

2.15. How effective is CBASP for maintenance therapy in MDD?

The evidence is derived from the extension phase of the previously described large scale acute treatment trial (Keller et al., 2000). In this continuation trial, CBASP alone and CBASP/nefazodone groups received 6 sessions of CBASP over 16 weeks and the combination group continued to demonstrate superior outcomes (Kocsis et al., 2003).

There was also a 1 year monotherapy treatment phase in which CBASP was found to be significantly superior for relapse prevention (Klein et al., 2004). Thus, Level 2 evidence also supports CBASP as second-line monotherapy or "add-on" to antidepressants in continuation and maintenance phases of treatment.

2.16. What is Acceptance and Commitment Therapy (ACT) and its efficacy?

ACT; Hayes et al., 2006) is a new model of psychotherapy stemming from CBT that is commonly referred to as a "third generation behaviour therapy" (along with Dialectical Behaviour Therapy and Mindfulness-Based Stress Reduction). ACT shares with CBT the grounding in empiricism and working within an active collaborative therapeutic relationship. ACT is based in a contextual theory of language and cognition (relational frame theory) (Barnes-Holmes et al., 2001). Many of the strategies used in ACT are borrowed from other models (use of metaphors and stories to communicate treatment concepts, behavioural exercises) that have been further refined and developed. Psychopathology is theorized to result largely from "experiential avoidance." The aim is to increase acceptance of the full range of subjective experiences, including distressing thoughts, beliefs, sensations and feelings, and subsequently cultivate a mindful outlook (i.e., awareness of mental events as products of the mind rather than literal truths). Strategies are used in an effort to promote desired behaviour change and ultimately quality of life. The concept of committed action towards one's goals is promoted in the context of experiential acceptance.

ACT has been applied in such conditions as workplace stress, psychosis, test anxiety, trichotillomania, epilepsy, obsessive–compulsive disorder, social anxiety, chronic pain, smoking cessation, diabetes, and substance abuse (summarized in a meta-analysis by Hayes et al., 2006). There is only one published

RCT involving MDD patients among heterogeneous outpatients with depressive, anxiety and adjustment disorders who were randomly assigned to CT or ACT (mean 15 sessions for CT and 16 sessions of ACT). Although this trial lacked a placebo condition, both treatment groups showed a significant reduction in depressive symptoms but the mechanisms of action were found to differ (Forman et al., 2007). With Level 3 evidence, ACT is recommended as third-line treatment for MDD.

2.17. What is Behavioural Activation (BA) for depression and its efficacy?

Behavioural Activation Therapy (BA) is based on the premise that depression is a consequence of compromised environmental sources of positive reinforcement. Treatment involves increasing patient activity and access to rewarding experiences, evaluating the consequences of depressive versus non-depressive behaviours and de-emphasizing particular cognitions or mood states as necessary for re-engaging with one's environment. This approach is well suited to address the inertia, avoidance and social withdrawal faced by many depressed patients and it has been suggested that the narrower focus on activation strategies may aid its dissemination. In the first of two RCTs of MDD, three arms involved BA, CBT, and an "Automatic Thought" arm that involved BA plus some but not all aspects of classic CBT. That study randomized 150 subjects but did not have a control group; all three treatments were equivalent in the acute phase as well as in relapse prevention (Jacobson et al., 1996; Gortner et al., 1998). A subsequent RCT (Dimidjian et al., 2006) randomized 241 subjects to four conditions: CBT, BA, pharmacotherapy, and control, with a double blind phase for 8 weeks followed by open treatment for another 8 weeks. The authors identified "severe depression" as HAM-D > 19 and reported that both BA and medications outperformed CBT and placebo in this subpopulation. In a follow up to this study, treatment responders were divided into three groups: (i) those who had originally received BA or CBT (ii) subjects discontinued from antidepressants and (iii) subjects maintained on antidepressants. BA and CBT were comparable in preventing relapse, and equal to continuing medication; these three groups in turn had longer time to relapse than those in the medication discontinuation arm (Dobson et al., 2008). Together, this body of evidence supports the efficacy of BA in both acute treatment and relapse prevention, as a second-line treatment with Level 2 evidence (based on the relatively small number of subjects and the fact that substantially the same investigators conducted all the trials).

2.18. What is Emotion-Focused Therapy (EFT) and its efficacy?

Emotion-Focused Therapy is a relatively new short-term psychotherapy, with an MDD intervention that involves sixteen to twenty individual sessions (Greenberg, 2002). The goal of EFT is to help the individual express emotions more easily by promoting emotional processing that brings emotional memory into consciousness. For MDD, this entails changing the emotionally based organization of the self through a number of techniques including focusing on an unclear bodily felt sense, dialogue with one critical internal voice, and "empty-chair dialogue" with a significant other regarding unresolved issues. Several small RCTs have been conducted using this technique, with various control conditions. One trial compared EFT to CBT and found equivalent improvement in acute MDD, while another found slight superiority to Client-Centred care (Watson et al., 2003; Goldman et al., 2006). In view of the trials emanating from substantially the same investigators and the small number of subjects, evidence is at Level 2 and the recommendation for EFT is as a third-line treatment.

2.19. What is bibliotherapy and its efficacy?

Bibliotherapy, the reading of self-help materials for psychological treatment, has numerous advantages over other treatments. It is self-paced, more convenient, less costly, and does not carry the stigma associated with attending a mental-health professional. On the other hand, the low motivation and energy experienced by depressed patients may compromise adherence. Nevertheless, bibliotherapy has received increasing attention, either as a stand-alone or combination treatment for a broad spectrum of mental heath problems. Individuals opting for bibliotherapy assume greater responsibility for treatment and outcome, and thus have a greater sense of control; this is seen as a key feature of the management of chronic diseases like depression.

In an early meta-analysis of bibliotherapy for depression, summarizing RCTs where the control condition was usually assignment to a waiting list for treatment, a large overall effect size of 0.83 was found (Cuijpers, 1997). Research comparing bibliotherapy that uses cognitive techniques with bibliotherapy that uses behavioural techniques indicates no differences between treatments, with superior outcomes in both groups compared to control conditions (Scogin et al., 1989), echoing the research findings about BA and CBT delivered by a therapist. Looking strictly at books, a meta-analysis by Anderson et al. (2005) identified 11 RCTs testing efficacy. While many self-help books on MDD exist, eight of the trials utilized "Feeling Good" (Burns, 1980). The meta-analysis concluded that all of the RCTs were small and had other limitations, and hence claimed the efficacy overall was weak. A subsequent meta-analysis of 34 studies (Gellatly et al., 2007) found bibliotherapy still effective, but noted clinical heterogeneity in study participants, from subclinical to clinical MDD. Studies using subjects with lesser severity, and particularly those in trials with a wait list control, showed more effect. This review also noted significant benefit if the self-help strategy was augmented by a clinician providing guidance and encouragement. These findings and limitations in studies suggest a second-line recommendation for bibliotherapy, with encouragement of use of bibliotherapy as an adjunct to formal psychotherapy or medication.

2.20. How effective is computer-based/internet delivery of psychotherapy for MDD?

Four meta-analyses of computer-based psychotherapies have been published involving 20–73 different studies across various psychiatric disorders. More specifically, 8 RCTs have been published, mostly for patients with depressive symptoms rather than a diagnosis of MDD. A confounding factor is that some studies involve only internet therapy, some involve

accessing psychotherapy via a computer in a clinic, and some involve computer-based exercises with brief coaching from clinicians, either live or via email. As reviewed by Spek et al. (2007), a meta-analysis of 4 RCTs involving depressive symptoms identified small effect sizes for MDD but large effect sizes in a separate analysis of internet CBT for anxiety disorders. Key factors hindering evaluation of internet CBT involve the inclusion of mixed groups of individuals with depressive symptoms ranging from subclinical to full episode MDD, and outcome measures that show reduction in symptoms without reporting of remission or response rates in MDD. Furthermore, limited information is provided on participant satisfaction, although retention rates are noted to be low. Such findings need to be balanced by the remarkable accessibility and reach of such interventions, particularly in a climate of massive use of the internet for health and disease information (Marks et al., 2003). Andersson et al. (2005) reported results of an RCT with two arms: the active intervention consisted of internet-delivered CBT with minimal therapist contact and a moderated online discussion group, compared to a control group which received only a separate online discussion group. This study specifically targeted MDD, and showed a moderate effect size between intervention and control. In addition, several studies of purely computer-based CBT delivery systems used in doctors' offices provide further evidence. Proudfoot et al. (2004) conducted an RCT with 274 patients with symptoms of anxiety and/or depression, randomly allocated to receive computerized CBT, with or without medication, or treatment as usual, with follow up assessment at 6 months. The computerized therapy improved depression symptoms, negative attributional style, work and social adjustment, without interaction with drug treatment, duration of pre-existing illness or severity of existing illness. Together, these studies provide Level 2 evidence and a second-line recommendation for computer-based psychological interventions.

2.21. How effective is telephone administered psychotherapy for MDD?

Telephone-based interventions for depression may be divided into two broad categories: telephone disease management and telephone psychotherapy. A large number of chronic disease management studies treating both depressive symptoms below MDD criteria and full MDD have used an element of telephone outreach to patients or providers; and in at least one study by Datto et al. (2003), telephone management was effective as the primary intervention. Advantages include immediacy of help, a degree of anonymity, low cost and ease of access.

In an RCT involving 600 MDD patients in primary care, Simon et al. (2004) evaluated three interventions: usual care, telephone care management (involving 3 phone calls to the patient, care coordination, and feedback to the physician) and telephone care management coupled with 8 sessions of CBT by phone. Those in the telephone CBT group showed significant improvement in depressive symptoms compared to those in usual care. The telephone management group did not demonstrate significant improvement in depressive symptoms, but patient self report of improvement and satisfaction with treatment were superior to usual care. Another RCT

involving MDD in individuals with Multiple Sclerosis (Mohr et al., 2005) showed the efficacy of a 16 session telephone CBT intervention. Several other studies have shown the acceptability and efficacy of telephone therapy (Bee et al., 2008). However, the studies are small and the types of therapy vary— IPT, CBT, supportive therapy —which make definitive conclusions difficult. In summary, while telephone-based interventions for depression are promising, they need to be studied further under more rigorous conditions; there is Level 2 evidence and clinical recommendation for their inclusion as second-line treatments.

2.22. Is combined treatment with psychotherapy and medication superior to psychotherapy alone?

Combination treatment for MDD can be either sequential (e.g., acute medication for 8 weeks, followed by psychotherapy) or concurrent (starting both treatments at the outset), and is summarized in Table 4. Evaluating outcomes of concurrent therapy is complicated by varying modes of delivery, including the use of single versus dual treatment providers. Perhaps because of these variations, results of initial meta-analyses were inconsistent and failed to provide evidence of superiority for combined treatment. However, a subsequent meta-analysis combining 18 studies with over 1800 subjects concluded that concurrent medication and psychotherapy was superior to psychotherapy alone, with a small to moderate effect size of 0.35 (Cuijpers et al., 2009). Most studies involved either CBT or IPT. Interestingly, when concurrent therapy is evaluated in more focal populations like the elderly, its superiority increases (Cuijpers et al., 2009).

2.23. Is combined treatment with psychotherapy and medication superior to medication alone?

Combination treatment for depression has also been compared to medication alone. Most studies are small, so meta-analyses and systematic reviews of the area involve relatively small number of subjects. Furthermore, the issue is complicated by differing approaches to combined treatment— in particular, more studies involve a sequential rather than strictly concurrent treatment approach, and variability exists in treatment delivery: sometimes one therapist provides both treatments, sometimes separate providers deliver psychotherapy and medication. In a meta-analysis (Pampallona et al., 2004), sixteen studies assigned 932 patients to combined concurrent therapy versus 910 to medications alone; clear superiority was seen with combined concurrent therapy in terms of symptom reduction, and in studies longer than 12 weeks, patient drop-out rates were significantly reduced in the combined treatment group. These researchers were unable to clarify if simple enhanced medication adherence might have been the active ingredient of the psychotherapy. Another study with less conclusive demonstration of benefit of the dual therapy show striking preference of the patients for combined treatment (de Jonghe et al., 2004); since patient preference is a major concern in psychiatric treatment, this too needs consideration in treatment recommendations.

In conclusion, the evidence suggests that combined treatment is superior to pharmacotherapy alone, and these effects

Table 5
Considerations for combining psychotherapy and medication.

Concurrent combined treatment	• Combined pharmacotherapy and CBT or IPT is superior to either modality alone, but the superiority is most evident in special populations such as the elderly or women. [Level 1] • Practical concerns including cost and availability may outweigh the additional benefit of concurrent combined treatment. • Both bibliotherapy and computer-assisted psychotherapy have evidence for efficacy, and may be particularly useful in combination with pharmacotherapy.
Sequential combined treatment (start pharmacotherapy, add psychotherapy later)	• Addition of psychotherapy (CBT or IPT) to partial responders to pharmacotherapy in the acute phase of MDD. [Level 2]
Crossover treatment (acute pharmacotherapy followed by switch to psychotherapy when well for maintenance)	• Discontinuing successful pharmacotherapy and crossing over to psychotherapy has never been shown to be superior to continuing pharmacotherapy. • Crossover to CBT, MBCT, or IPT in the absence of medication has been shown to provide significant benefit, with relapse prevention generally comparable to continuation of the pharmacotherapy. [Level 2]

are more pronounced in relapse prevention than in symptom relief in acute treatment (6–8 weeks), as reviewed below. This Level 2 evidence, coupled with patient (and often provider) preference for combined treatment, suggest that combined treatment could be a first-line recommendation for MDD; however, issues including practicality, cost, and availability relegate this to a second-line treatment recommendation.

2.24. Is sequential treatment (pharmacotherapy followed by psychotherapy) superior to monotherapy ?

No meta-analysis specifically explored this question, perhaps since few studies specifically address this issue. This issue is complicated by different approaches to sequential treatment; in some cases, patients are treated to response or remission with pharmacotherapy before receiving psychotherapy as a maintenance phase intervention, primarily to prevent relapse; in others, only those patients who fail to respond to pharmacotherapy receive the addition of psychotherapy(Table 5). There is evidence that MBCT has efficacy in relapse prevention among patients with 3 or more previous episodes; however, the overall number of subjects was small and not all had pharmacotherapy in the acute phase (Coelho et al., 2007). A broader review of the role of psychotherapy in prevention of relapse is summarized in Question 10, but that review combines studies with and without pharmacotherapy. Paykel et al. (1999) examined the value of CBT delivered to patients with residual symptoms after pharmacotherapy and found that those who received CBT had further reduction of acute symptoms and reduced rates of relapse. Based on a review by Rafanelli et al. (2007), there is Level 2 evidence to support sequential treatment (pharmacotherapy followed by psychotherapy) of MDD, and this is considered a second-line recommendation.

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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

Raymond W. Lam [a],*, Sidney H. Kennedy [b], Sophie Grigoriadis [b], Roger S. McIntyre [b], Roumen Milev [c], Rajamannar Ramasubbu [d], Sagar V. Parikh [b], Scott B. Patten [d], Arun V. Ravindran [b]

[a] University of British Columbia, Canada
[b] University of Toronto, Canada
[c] Queen's University, Canada
[d] University of Calgary, Canada

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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.

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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).

* Corresponding author.
E-mail address: r.lam@ubc.ca (R.W. Lam).

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

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.

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 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.

care systems by practitioners (Trivedi et al., 2007). For example, patients should be aware of the time lag to antidepressant effect, course of response, common and serious adverse events, and the need to continue medications even when feeling better.

3.2. What are first-line antidepressants?

The previous guidelines (Kennedy et al., 2001) noted that the selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and newer agents were first-line medications because they have better safety and tolerability profiles than older medications like tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors. This remains true, and hence this revision focuses on the comparative use of these first-line antidepressants.

Three major systematic reports published since 2001 did not find unequivocal efficacy or tolerability differences among the various second-generation antidepressants, all of which have Level 1 evidence to support efficacy (Gartlehner et al., 2007; National Institute for Clinical Excellence, 2004; Sartorius et al., 2007). In addition, there are no identified consistent predictors of outcome. Therefore, most of the second-generation antidepressants can be considered first-line medications for MDD (Table 3).

TCAs are recommended as second-line antidepressants because of tolerability and safety issues and MAO inhibitors are recommended as third-line because of tolerability and safety issues and dietary and drug restrictions. Trazodone is also considered a second-line antidepressant because it is very sedating at therapeutic doses. The selective MAO-B inhibitor, selegiline transdermal, has a better tolerability profile than the older MAO inhibitors, but because both dietary (at doses higher than 6 mg) and drug restrictions are required, it is recommended as a second-line antidepressant. Although the evidence for these guidelines is limited to published reports, there are numerous published abstracts of RCTs demonstrating efficacy of the atypical antipsychotic, quetiapine XR, as monotherapy for unipolar, non-psychotic MDD (e.g., (Datto et al., 2008; Cutler et al., 2009). Given the strength of this Level 1 evidence, quetiapine is included as an efficacious antidepressant. However, given its tolerability profile and relative lack of comparative data with SSRIs and newer agents, quetiapine XR is recommended as a second-line antidepressant.

In general terms, the choice of first-line medication still depends on individual assessment and matching of clinical factors including tolerability, patient preference, and cost. However, subsequent sections will describe the evidence for small but clinically relevant differences among the agents in efficacy, tolerability and other factors that may affect this decision (see Table 9 for summary).

3.3. What is the comparative efficacy among the SSRIs and newer agents?

Most RCTs are designed to evaluate efficacy against placebo and thus are not powered to detect smaller, but still clinically important differences between two active agents. Meta-analyses can provide some comparative information but are not substitutes for high-quality RCTs. Important factors that must be weighed in comparative efficacy studies include

Table 3
Summary information for antidepressants.

Antidepressant [brand name(s)]	Mechanism	Dose range
First-line recommendations		
• Agomelatine* [Valdoxan]	MT$_1$ and MT$_2$ agonist; 5-HT$_2$ antagonist	25–50 mg
• Bupropion [Wellbutrin] [a]	NDRI	150–300 mg
• Citalopram [Celexa, Cipramil]	SSRI	20–60 mg
• Desvenlafaxine [Pristiq]	SNRI	50–100 mg
• Duloxetine [Cymbalta]	SNRI	60–120 mg
• Escitalopram [Cipralex, Lexapro]	ASRI	10–20 mg
• Fluoxetine [Prozac]	SSRI	20–80 mg
• Fluvoxamine [Luvox]	SSRI	100–300 mg
• Mianserin* [Tolvon]	α$_2$-adrenergic agonist; 5-HT$_2$ antagonist	60–120 mg
• Milnacipran* [Ixel]	SNRI	100–200 mg
• Mirtazapine [Remeron] [b]	α$_2$-adrenergic agonist; 5-HT$_2$ antagonist	30–60 mg
• Moclobemide [Manerix]	Reversible inhibitor of MAO-A	300–600 mg
• Paroxetine [Paxil] [c]	SSRI	20–60 mg 25–50 mg for CR version
• Reboxetine* [Edronax]	Noradrenaline reuptake inhibitor	8–12 mg
• Sertraline [Zoloft]	SSRI	50–200 mg
• Tianeptine* [Stablon, Coaxil]	Serotonin reuptake enhancer	25–50 mg
• Venlafaxine [Effexor] [d]	SNRI	75–375 mg
Second-line recommendations		
• Amitriptyline, clomipramine and others	TCA	Various
• Quetiapine [Seroquel] [d]	Atypical antipsychotic	150–300 mg
• Selegiline transdermal* [Emsam]	Irreversible MAO-B inhibitor	6–12 mg daily transdermal
• Trazodone [Desyrel]	Serotonin reuptake inhibitor; 5-HT$_2$ antagonist	150–300 mg
Third-line recommendations		
• Phenelzine [Nardil]	Irreversible MAO inhibitors	45–90 mg
• Tranylcypromine [Parnate]		30–60 mg

5-HT = 5-hydroxytryptamine (serotonin); ASRI = allosteric serotonin reuptake inhibitor; 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.
* Not available in Canada.
[a] Available as sustained release (SR) and extended release (XL) versions.
[b] Available as rapid dissolving (RD) version.
[c] Available as controlled release (CR) version.
[d] Available as extended release (XR) version.

dosing, sample sizes, inclusion/exclusion criteria, duration of trials, and clinically meaningful outcomes (Lieberman et al., 2005). Comparisons of efficacy should specify the comparator drugs; superiority against an individual drug should not be assumed to hold true against other drugs in the same class.

Recent meta-analyses have not shown evidence for substantive differences among classical agents (TCAs, MAOIs) and SSRIs. Some meta-analyses have shown small differences in efficacy between newer antidepressants (e.g., venlafaxine over SSRIs [Nemeroff et al., 2008]; escitalopram over comparators [Kennedy et al., 2009a]) while others have not (National Institute for Clinical Excellence, 2004; Gartlehner et al., 2007). One research group has been systematically conducting comparative

meta-analyses for individual agents, and concluded that only sertraline had evidence for superior efficacy in some outcomes compared to other antidepressants (Cipriani et al., 2008). However, these meta-analyses combined all studies at all doses and severity ranges. A multiple comparisons network meta-analysis (in which both direct and indirect comparisons are analyzed) compared 12 second-generation antidepressants and identified a small superiority in response rates for escitalopram, mirtazapine, sertraline and venlafaxine compared to the others (Cipriani et al., 2009). Reboxetine was the only antidepressant in the network meta-analysis to show a significantly lower response rate than the other agents.

Other attempts to define superiority using RCT evidence and pre-defined criteria have also shown some differences among the newer antidepressants. An international expert consensus panel reviewed the head-to-head RCTs of antidepressants and concluded that clomipramine, escitalopram and venlafaxine had definite evidence (defined as two or more good quality RCTs and supportive meta-analyses) of superiority while duloxetine, milnacipran and mirtazapine had probable evidence (at least 2 RCTs and/or supportive meta-analysis) against SSRI comparators (most commonly, fluoxetine) (Montgomery et al., 2007). Table 4 summarizes the antidepressants with at least probable evidence for superior efficacy.

3.4. Are antidepressants associated with emergent suicidality?

The past few years have seen considerable public and professional concern about emergent suicidality (defined as worsening or emergent suicidal ideas and attempts) associated with the newer antidepressants, leading to the "black box warnings" in Canada, the U.S. and elsewhere. This has been chronicled in many reviews (e.g., Moller et al., 2008).

While placebo-controlled RCTs are the best way to evaluate any emergent adverse event, the limitations of the RCT evidence base (spontaneous reports, lack of power to detect rare occurrences, exclusion of actively suicidal patients) preclude a definitive conclusion (Lam and Kennedy, 2004; Moller, 2006). The results from RCTs must be supplemented by data from other sources, including naturalistic treatment studies (e.g., using pharmacy and administrative databases), forensic studies (e.g., toxicology studies of people who die by suicide) and pharmacoepidemiology studies.

To summarize the evidence in adults, meta-analyses of RCTs have not shown any increased risk of completed suicide (Hammad et al., 2006b) or increased suicidality with SSRIs

and newer antidepressants (Gunnell et al., 2005). In one age-stratified analysis, the young adult group (18–24 years) showed a small trend for increased suicidality (as per the paediatric data) which did not reach statistical significance, while in older age groups there was a trend for a protective effect. Nonetheless, the black box warning was extended to include the young adult group (Friedman and Leon, 2007). Naturalistic prescription and research databases have found no support for increased suicidality with antidepressant use in adults. Similarly, the forensic database and pharmacoepidemiology studies do not show any evidence for an increase in suicide associated with antidepressants (Lam and Kennedy, 2004; Moller, 2006). Systematic reviews of observational studies have also showed reduced risk and protective effects of SSRIs on suicide attempts and completions in adults (Barbui et al., 2009).

In summary, there is no clear indication that SSRIs and newer antidepressants are associated with emergent suicidality in young or older adults. The situation in children and adolescents is less clear and is discussed in Question 3.21.

3.5. What are other serious adverse effects of antidepressants?

Several uncommon but serious adverse effects of antidepressants have been reported during long term use of antidepressants. Serotonin syndrome or neuroleptic malignant syndrome-like events have occurred rarely when SSRIs/SNRIs are co-prescribed with MAO inhibitors or other serotonergic agents. Recent meta-analyses suggest that SSRIs are associated with increased risk of upper gastrointestinal tract bleeding, especially in combination with nonsteroidal anti-inflammatory drugs (NSAIDs) (Loke et al., 2008) and with osteoporosis and fractures in the elderly (Takkouche et al., 2007). Hyponatremia and agranulocytosis are also reported in a small but measurable percentage of patients (Mago et al., 2008). Risk estimates for seizures associated with antidepressants vary according to the sample population (Montgomery, 2005). The risk for seizures with SSRIs and the newer agents is similar to the risk in the general population (approximately 0.0–0.4%), although TCAs at therapeutic doses have higher risk (0.4–1.2%). The seizure rate associated with bupropion is dose-dependent but does not exceed the risk with other second-generation agents when prescribed within the recommended dose range. In overdose, venlafaxine was found to have significantly greater cardiotoxicity than SSRI agents (Deshauer, 2007).

3.6. What are the differences in tolerability across antidepressants?

Side effects, also known as treatment-emergent adverse events, affect tolerability and adherence to treatment. Commonly encountered side effects associated with the use of antidepressants depend primarily upon the class of antidepressant agent chosen. In terms of overall tolerability, meta-analyses have shown that fluvoxamine has poorer tolerability compared to other SSRIs (Anderson, 2001) while escitalopram and sertraline have better acceptability, based on overall withdrawal rates, compared to other antidepressants (Cipriani et al., 2009).

Meta-analyses have also identified some differences in individual side effects among the antidepressants (Brambilla et al., 2005; Gartlehner et al., 2008). For example, within the

Table 4
First-line antidepressants with evidence for superior efficacy against comparators.

Antidepressant	Comparators
Duloxetine [Level 2]	Paroxetine; pooled SSRIs
Escitalopram [Level 1]	Citalopram; duloxetine; paroxetine; pooled SSRIs
Milnacipran [Level 2]	Fluvoxamine; pooled SSRIs
Mirtazapine [Level 2]	Trazodone
Sertraline [Level 1]	Fluoxetine; pooled SSRIs
Venlafaxine [Level 1]	Duloxetine; fluoxetine; pooled SSRIs

SSRI class, fluoxetine has higher rates of gastrointestinal (GI) side effects including nausea, vomiting and diarrhea, fluvoxamine has higher rates of nausea, paroxetine has more sweating and sedation, and sertraline has higher rates of diarrhea. Duloxetine and venlafaxine have higher rates of nausea and vomiting than SSRIs. Mirtazapine and paroxetine have higher rates of weight gain, while mirtazapine and trazodone have higher rates of sedation.

Meta-analyses, however, may not adequately differentiate side effect profiles among antidepressants. Other methods can be used to compare relative side effects across individual agents. For example, Table 5 summarizes the unadjusted frequency of adverse events as reported in product monographs. While these rates are not adjusted for placebo and cannot take into account differences among the various studies, it does allow for a standard reporting format.

When patients achieve a response or remission on an antidepressant but continue to have troublesome side effects, it may be appropriate to manage the side effects so that they can stay on the medication. A number of strategies have been suggested to manage side effects, although few of these have been subject to controlled studies (Anderson et al., 2008). The potential benefits of using adjunctive medications to treat side effects must be weighed against the risk of increasing the side effect burden.

Several reviews have highlighted the main differences in side effect profiles across classes and agents (Anderson et al., 2008; Gartlehner et al., 2008; Hansen et al., 2005; Sartorius et al., 2007). To summarize, the rate of GI side effects, such as nausea and diarrhea, associated with SSRIs/SNRIs is higher than with antidepressants which do not primarily inhibit the serotonin reuptake transporter (e.g., agomelatine, bupropion, mirtazapine, moclobemide). The incidence of nausea with extended release formulations (e.g., paroxetine-CR, venlafaxine-XR) is lower when compared to the immediate release preparations. Treatment-emergent nausea is usually most severe in the first two weeks of therapy with tolerance developing thereafter. Symptomatic treatment of GI side effects can be helpful during this time. Co-administration with food, once daily dosing at night, and use of gastric motility agents may also reduce nausea.

Central nervous system (CNS) side effects including headaches, insomnia, sedation, nervousness and tremor also commonly occur with antidepressants. Headaches often respond to symptomatic treatment. Many antidepressants cause or worsen insomnia, although several are sleep promoting (e.g., agomelatine, mirtazapine, trazodone). Conversely, some sleep-promoting antidepressants (mirtazapine, trazodone) are associated with high rates of daytime somnolence. Short term use of benzodiazepine or non-benzodiazepine hypnotics (e.g., eszopiclone, zopiclone, zolpidem) in carefully selected patients may improve both sleep and depression outcomes (Fava et al., 2006). The judicious short term use of benzodiazepines also may reduce the nervousness and activation associated with the initiation of SSRI/SNRI antidepressants.

Metabolic adverse events include appetite stimulation, weight gain, disturbances in the lipid milieu and glucose homeostasis (McIntyre et al., 2006). Most short term and maintenance studies suggest that SSRIs and newer agents are generally "weight neutral", but mirtazapine and paroxetine are associated with weight gain during longer term treatment.

Other adverse events associated with antidepressant use include alterations in heart rate, systolic and diastolic blood pressure (higher rates are associated with agents that block noradrenaline reuptake), and elevation of liver enzymes, but these effects are usually not clinically relevant. Discontinuation (withdrawal) symptoms are associated with abrupt cessation, dose reduction, or tapering of some antidepressants, especially paroxetine and venlafaxine (Baldwin et al., 2007; Schatzberg et al., 2006).

3.7. What are the differences in treatment-emergent sexual dysfunction?

Although symptoms of MDD include reduced libido and sexual dysfunction, many antidepressants also disturb sexual function across various domains (i.e., desire, arousal, erectile ability, orgasm and ejaculation). The rate of treatment-emergent sexual dysfunction in RCTs is markedly underestimated because of spontaneous reporting; studies using more systematic assessment of sexual function report rates up to 50% with SSRIs and slightly lower rates with SNRIs (Taylor et al., 2005). Evidence suggests that the frequency of sexual dysfunction within the SSRIs may be greater for fluoxetine and paroxetine, and lower for citalopram/escitalopram (Table 6). Agomelatine, bupropion, mirtazapine, moclobemide, and selegiline transdermal exhibit placebo-level rates of sexual dysfunction.

There is usually little or no spontaneous remission of antidepressant-induced sexual dysfunction and there is only a limited evidence base for management strategies (Taylor et al., 2005). Dose reduction, if possible, is sometimes beneficial. Many pharmacological antidotes have been proposed but relatively few have demonstrated efficacy. Adjunctive bupropion and sildenafil (for antidepressant-induced erectile dysfunction) have the best evidence (Taylor et al., 2005); combination treatment with mirtazapine is also sometimes beneficial. Many patients will require a switch to another antidepressant with less propensity for sexual dysfunction (Table 6).

3.8. What are the differences in potential for drug–drug interactions?

The concurrent use of several medications (polypharmacy) is common in patients with MDD owing to the long course of depressive illness and antidepressant treatment, high prevalence of medical comorbidities and limited response to antidepressant monotherapy. Therefore, drug interactions with antidepressants are an important clinical issue. Although fatal drug interactions are rare, clinically significant increases in side effects and loss of efficacy can result from antidepressant drug interactions (Preskorn et al., 2006). However, there is only a limited evidence base about these drug interactions (Nieuwstraten et al., 2006).

Most of the drug interactions with antidepressants involve the cytochrome P450 (CYP) enzyme metabolic pathway (Ereshefsky et al., 2005) or p-glycoprotein, a membrane transporter (Weiss et al., 2003). Since most first-line antidepressants are metabolized through several CYP pathways, there are usually no significant interactions with other drugs that act as CYP inhibitors or inducers. Rifampicin induces several CYP isoenzyme pathways (2C9, 2C19, 2D6) responsible

Table 5

Unadjusted [a] frequency of common adverse events as reported in product monographs of some second-generation antidepressants.

	Central nervous system				Anticholinergic				Cardiovascular			Gastrointestinal					Body as a whole		
	Drowsiness, sedation, somnolence	Insomnia	Headache	Tremor	Dry mouth	Blurred vision	Sweating	Delayed micturition	Dizziness/ orthostatic hypotension	Hypertension	Tachycardia, palpitation	GI pain/ distress	Nausea	Vomiting	Diarrhea	Constipation	Nervousness/ anxiety	Fatigue/ aesthenia	Dermatitis, rash
Citalopram	B	*	*	A	B	*	B	*	*	*	*	A	B	A	A	*	A	A	*
Escitalopram	A	A	*	*	A	*	A	*	A	*	*	A	B	*	A	A	A	A	*
Fluoxetine	B	B	*	B	B	*	A	*	*	*	*	A	B	*	*	*	B	*	A
Fluvoxamine	C	B	C	B	B	*	B	A	B	*	*	A	C	*	A	B	C	A	*
Paroxetine	B	B	B	A	B	A	B	A	B	*	*	A	B	A	B	B	A	*	A
Sertraline	B	B	C	B	B	A	A	A	B	*	A	A	C	A	B	A	B	B	A
Agomelatine	A	A	A	*	*	*	A	*	A	*	*	A	A	*	A	A	A	A	*
Bupropion	*	B	*	A	B	A	A	*	A	A	A	A	B	A	*	B	A	*	A
Desvenlafaxine	A	B	B	A	B	A	B	A	B	A	A	*	B	A	B	A	A	A	A
Duloxetine	A	B	A	A	B	A	A	A	A	A	A	A	C	A	A	B	A	A	*
Mianserin [b]																			
Milnacipran [b]																			
Mirtazapine	D	*	*	A	B	*	*	*	A	*	*	*	*	*	*	B	*	A	*
Moclobemide	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Reboxetine [b]																			
Quetiapine [b]																			
Selegiline td	A	B	B	*	A	A	*	*	B	A	A	A	*	*	A	*	A	A	C
Tianeptine [b]																			
Trazodone	C	A	A	A	B	A	*	A	B	*	A	B	*	*	*	A	*	B	A
Venlafaxine	B	B	B	A	B	A	B	A	B	A	A	A	C	A	A	B	B	*	A

Controlled release formulations are not listed—frequency of adverse events may be lower for those formulations.

A = 9% or lower, B = 10–29%, C = 30–49%, D = 50% or higher.

* = Lower than the threshold rate for reporting in monograph (usually 5% or less).

[a] Some rates may be equal to, or less than, those reported for placebo.

[b] At the time of publication, product monographs were not available for these agents—an updated table is available at www.canmat.org.

Table 6
Frequency of treatment-emergent sexual dysfunction, using best available evidence, with first-line antidepressants.

Frequency of sexual dysfunction	Antidepressant
<10%	• Agomelatine • Bupropion • Mirtazapine • Moclobemide • Reboxetine • Selegiline transdermal
10–30%	• Citalopram • Duloxetine • Escitalopram • Milnacipran • Venlafaxine
>30%	• Fluoxetine • Fluvoxamine • Paroxetine • Sertraline

Modified from Kennedy et al. (2007), with permission.

Table 7
Some clinically significant drug interactions resulting from inhibition of cytochrome P450 (CYP) isoenzymes.

Cytochrome P450 (CYP) action	Increases serum levels of:	
• CYP 1A2 inhibition	• Agomelatine • Caffeine • Clozapine • Duloxetine • Mexiletine	• Naproxen • Tacrine • Theophylline • Warfarin
• CYP 2C19 inhibition	• Antiarrhythmics • Antiepileptics (diazepam, phenytoin, phenobarbital) • Indomethacin	• Omeprazole • Primidone • Propanolol • Warfarin
• CYP 2D6 inhibition	• TCAs • Beta blockers (metoprolol, propranolol) • Codeine and other opioids (reduces effect)	• Olanzapine • Risperidone • Tamoxifen • Tramadol
• CYP 3A4 inhibition	• Amiodarone • Antiarrhythmics (quinidine) • Antihistamines (astemizole, chlorpheniramine) • Calcium channel antagonists (e.g., diltiazem, verapamil) • Haloperidol • HIV protease inhibitors • Statins	• Immune modulators (ciclosporin, tacrolimus) • Macrolide antibacterials (clarithromycin, erythromycin) • Methadone • Phenothiazines • Quetiapine • Sildenafil • Tamoxifen

This is only a limited selection of interactions. For more comprehensive lists, see references in the text.

for metabolising antidepressants, so loss of antidepressant efficacy may result from co-administration. Agomelatine and duloxetine are extensively metabolized through the 1A2 pathway and should not be co-administered with drugs that potently inhibit CYP 1A2 (e.g., cimetidine, ciprofloxacin and other fluoroquinolone antimicrobials, ticlopidine) and hence increase the antidepressant levels.

Several antidepressants act as inhibitors of specific CYP isoenzymes, which can result in increased levels of co-administered drugs that are metabolized primarily through those isoenzymes (Tables 7 and 8). For example, fluoxetine and paroxetine are potent inhibitors of CYP 2D6, which can result in increased serum levels of co-administered drugs such as TCAs and beta-blockers. Conversely, co-administered codeine is less effective because CYP 2D6 metabolizes codeine to morphine. Bupropion and duloxetine are moderate inhibitors of CYP 2D6 so the risk for drug interactions with these agents is usually only at higher doses. Fluvoxamine is a potent inhibitor of CYP 1A2, 2C19 and 3A4, and therefore interacts with many other drugs (Table 7). For example, fluvoxamine co-administration can increase serum levels of warfarin (INR needs to be carefully monitored) and statins (which can lead to rhabdomyolysis). Other antidepressants (Table 8) have few effects on the CYP enzyme system and carry low risk for drug interactions.

Variations in CYP genes may explain individual differences in the metabolism of antidepressants and subsequent adverse events or clinical response (Ereshefsky et al., 2005). However, there is insufficient evidence to support routine use of genotyping to guide antidepressant selection (Thakur et al., 2007).

P-glycoprotein is an important component of the blood brain barrier and the intestinal barrier, and is responsible for the efflux of several antidepressants, anticancer and cardiac medications (Weiss et al., 2003). Paroxetine and sertraline are potent inhibitors of p-glycoprotein and may increase the levels of substrates including digoxin, cyclosporine, calcium channel blockers and some anticancer agents.

Although the reversible MAO-A (moclobemide) and irreversible MAO-B (selegiline transdermal) inhibitors carry fewer risks from dietary tyramine compared to older MAOI inhibitors, they have similar precautions for potentially fatal drug–drug interactions. Therefore, other antidepressants and serotonergic (e.g., meperidine) or sympathomimetic (e.g., pseudoephedrine, stimulants) medications should not be co-administered. Of note, linezolid [Zyvoxam], a novel antibiotic used in methicillin-resistant *Staphylococcus aureus* (MRSA)

Table 8
Potential for drug–drug interactions among first-line antidepressants (cytochrome P450 isoenzyme or p-glycoprotein inhibition noted in brackets).

Minimal or low potential	• Citalopram • Desvenlafaxine • Escitalopram • Mirtazapine • Venlafaxine
Moderate potential	• Agomelatine (1A2 substrate [a]) • Bupropion (2D6) • Duloxetine (2D6; 1A2 substrate [a])
Higher potential	• Fluoxetine (2D6, 2C19) • Fluvoxamine (1A2, 2C19, 3A4) • Moclobemide (MAO inhibitor precautions [b]) • Paroxetine (2D6; p-glycoprotein) • Selegiline (MAO inhibitor precautions [b]) • Sertraline (2D6; p-glycoprotein)

[a] Co-administration with CYP 1A2 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] Precautions similar to those of older MAO inhibitors. Avoid co-administration of other antidepressants, serotonergic drugs (e.g., meperidine), and sympathomimetic drugs (e.g., pseudoephedrine, stimulants).

infections, is also a reversible, non-selective MAO inhibitor (Sola et al., 2006); therefore, it carries the same drug restrictions as the other MAO inhibitors and should not be co-administered with antidepressants.

Other antidepressant drug interactions are less common. The combined use of serotonergic antidepressants with other serotonin enhancing drugs may result in serotonin syndrome (Boyer and Shannon, 2005). The bleeding risk with SSRIs increases with concomitant use of anticoagulants (e.g., aspirin, warfarin) and NSAIDs (Loke et al., 2008).

3.9. What other factors influence selection of antidepressant?

Patient factors and therapeutic factors should be considered in the selection of an antidepressant (Table 9). Historically, antidepressant selection had been influenced by subtype of depression (e.g., with atypical, melancholic, or psychotic features, or with seasonal pattern). However, there is limited evidence to support differences in outcome among first-line antidepressants for MDD with atypical or melancholic features. In contrast, there is Level 1 evidence to recommend an antidepressant combined with an antipsychotic agent for MDD with psychotic features (Dannon et al., 2006), although a Cochrane systematic review concluded that the combination was superior to antipsychotic monotherapy but not to anti-depressant monotherapy (Wijkstra et al., 2006). Given that the latter comparison was based on only 2 RCTs, the combination treatment is still recommended, unless there are specific reasons to avoid antipsychotics. In the treatment of seasonal MDD, there is Level 1 evidence for bupropion for prevention of winter depressive episodes (Modell et al., 2005).

Comorbid anxiety and substance use disorders are frequently associated with MDD, although there is also substantial overlap with eating disorders and attention deficit hyperactivity disorder. While these comorbidities do not substantially alter treatment selection, in general, there are lower rates of response and remission in patients with comorbid conditions (Howland et al., 2009).

There is some evidence that younger adults may respond preferentially to serotonergic rather than noradrenergic anti-depressants, while older populations show no differential response (Mulder et al., 2003). The evidence for differential response to antidepressants between men and women is inconsistent. In the STAR*D study, women had higher remission rates to citalopram than men (Young et al., 2008), while some meta-analyses found conflicting results in remission rates between men and women (Grigoriadis et al., 2007; Khan et al., 2005). Other meta-analyses found that response rates did not

differ between men and women in comparisons of venlafaxine and SSRIs (Entsuah et al., 2001), of bupropion and SSRIs (Papakostas et al., 2007a), and in response to duloxetine (Kornstein et al., 2006).

With regards to severity of symptoms, several antidepressants show significant superiority against placebo in severely depressed subgroups using pooled analyses of RCTs, including agomelatine, duloxetine, escitalopram, paroxetine-CR and ven-lafaxine. However, only escitalopram has been studied in RCTs involving patients with higher depression severity at baseline; it was found to be superior to fluoxetine and paroxetine (Montgomery et al., 2007).

There are conflicting results about genetic polymorphisms and antidepressant response. Patients carrying the short allele of the serotonin transporter gene appear to be more vulnerable to depression following adverse life events and in European studies had a worse response to SSRIs (Seretti et al., 2007; Kato et al., 2008). However, variations in the gene that encodes for the 5HT2A receptor was most predictive of response to citalopram in the STAR*D database, the largest pharmacogenetic study so far reported (McMahon et al., 2006). Despite some promising results, there is still insufficient evidence to consider routine use of biomarkers to guide antidepressant selection (Table 10).

Managing non-response or incomplete response

3.10. How long do you wait for a clinical response?

Most clinical trials define "clinical response" as ≥50% reduction in the score on a depression rating scale and "clinical remission" as a score within the "normal range" of the scale. Clinical lore states that the lag time for antidepressant therapeutic effects may be 2–4 weeks or longer. However, recent studies have shown an earlier onset of action, especially in those patients who eventually respond. Several recent meta-analyses concluded that onset of antidepressant effect can occur within 1–2 weeks of initiation (Papakostas et al., 2006; Posternak and Zimmerman,

Table 9
Clinical factors that influence antidepressant selection.

Patient factors	Therapeutic factors
• Age and sex	• Efficacy/tolerability/safety
• Severity	• Real world effectiveness
• Diagnostic subtype	• Potential for drug–drug interactions
• Comorbid disorders	• Simplicity of use
• Past response	• Discontinuation syndrome
• Sensitivity to side effects	• Cost
• Potential of biomarkers	• Branded vs. generic formulation

Table 10
Summary recommendations for pharmacotherapy.

Recommendations
• Appropriate assessment and monitoring of suicide risk is an important part of the management of MDD, however, concerns about antidepressant-induced suicidality should not discourage initiation of treatment in adults. [Level 1]
• The side-effect profile of individual antidepressants should be considered when choosing between specific medications. [Level 2]
• Uncommon but serious adverse events should be taken into consideration when choosing an antidepressant medication for patients at elevated risk of those events. [Level 2]
• For patients at risk of drug–drug interactions, the effects of specific antidepressants on CYP isoenzymes and p-glycoprotein should be considered when choosing an antidepressant. [Level 3]
• Sexual side effects and metabolic indices should be monitored in patients being treated with antidepressants. [Level 2]
• If side effects remain troublesome in circumstances of response or remission, strategies for managing those side effects, including dose reduction, pharmacological antidotes and switching options, should be considered. [Level 3]
• For MDD with psychotic features, antidepressants should be combined with an antipsychotic medication. [Level 1]

2005; Taylor et al., 2006), that subsequent weeks show decreasing rates of response (Taylor et al., 2006), and that early improvement can be an indicator of eventual remission (Wade and Friis, 2006). This suggests that patients who show little improvement (e.g., <20% improvement in scores on a depression rating scale) after 2 weeks of antidepressant use should have a change in treatment, such as a dose increase.

In real-world samples, response and remission may take longer. The STAR*D effectiveness trial showed that, of patients who ultimately showed clinical response when treated with open-label citalopram for 12 weeks, 56% first achieved response after 8 or more weeks, while 40% of patients who ultimately remitted first achieved remission after 8 or more weeks (Trivedi et al., 2006b). This suggests that patients showing more than minimal improvement (e.g., ≥20% improvement in scores on a depression rating scale) after 4–6 weeks should continue on the antidepressant for another 2–4 weeks before considering additional strategies.

3.11. What do you do when a patient does not respond?

Achieving and sustaining symptomatic remission is an essential first step toward functional recovery, but naturalistic treatment studies show that up to 2/3 of patients will not experience full remission with the first antidepressant (Trivedi et al., 2006b). When there has been no improvement following an optimized (i.e., increased) dose of an antidepressant, the first step should be to re-evaluate diagnostic issues (e.g., bipolarity, depressive subtype, comorbidity including substance abuse) and treatment issues (e.g., adherence, side effects, suicidality). Using validated rating scales to measure response and side effects can help in the clinical decision-making process (Trivedi et al., 2007).

Most of the studies examining pharmacological strategies for limited response have focused on treatment-resistant depression (TRD). While there is no consensus definition of TRD, the one most commonly used is failure (i.e., lack of improvement, or <20% reduction in depression scores) following adequate trials of two or more antidepressants. The evidence base is limited by this definition, since it does not account for previous trials of augmentation/combination strategies or situations where there is some improvement (but not to remission) with an antidepressant.

Treatment options for TRD include adding an evidence-based psychotherapy (Parikh et al., 2009), switching to a neurostimulation treatment such as electroconvulsive therapy or transcranial magnetic stimulation (Kennedy et al., 2009c), and continuing with pharmacological strategies. Pharmacological strategies include switching to a different antidepressant monotherapy, or adding another agent to the first antidepressant (Table 11; Fig. 1). The term "augmentation" has been used to describe adding a medication that is not considered an antidepressant (e.g., lithium or thyroid hormone), while "combination" refers to adding a second antidepressant to the first. While the evidence for these strategies is initially presented using these terms, henceforth we will refer to them as "add-on" treatments because of blurring of these definitions. For example, some medications that were previously considered as augmentation agents (e.g., quetiapine) may be effective antidepressants in monotherapy.

Table 11
Recommendations for non-response and incomplete response to an initial antidepressant.

• First-line	• Switch to an agent with evidence for superiority	• Duloxetine [Level 2] • Escitalopram [Level 1] • Milnacipran [Level 2] • Mirtazapine [Level 2] • Sertraline [Level 1] • Venlafaxine [Level 1]
	• Add-on another agent	• Aripiprazole [Level 1] • Lithium [Level 1] • Olanzapine [Level 1] • Risperidone [Level 2]
• Second-line	• Add-on another agent	• Bupropion [Level 2] • Mirtazapine/mianserin [Level 2] • Quetiapine [Level 2] • Triiodothyronine [Level 2] • Other antidepressant [Level 3]
	• Switch to an agent with evidence for superiority, but with side effect limitations	• Amitriptyline [Level 2] • Clomipramine [Level 2] • MAO Inhibitors [Level 2]
• Third-line	• Add-on another agent	• Buspirone [Level 2] • Modafinil [Level 2] • Stimulants [Level 3] • Ziprasidone [Level 3]

3.12. How effective is the strategy of switching to a different antidepressant?

"Switching" has been investigated in many open studies and several RCTs. Open label studies have reported good response and remission rates when switching for both non-response and intolerability reasons. Intuitively, it seems reasonable to switch to an agent with a different mechanism of action, but several RCTs and meta-analyses have shown no differences in outcomes when switching within a class (i.e., from one SSRI to another) compared to out of class (i.e., from an SSRI to a non-SSRI agent). For example, in the STAR*D effectiveness trial, there were no differences in response or remission rates when non-remitters to citalopram were switched to another SSRI (sertraline) or to non-SSRI agents (bupropion-SR or venlafaxine-XR) (Rush et al., 2006). Similarly, a meta-analysis of 8 RCTs also found no overall differences in outcomes with the type of switch after initial failure of an SSRI, although a subanalysis of 3 RCTs found a superior response when switching to venlafaxine compared to another SSRI (Ruhe et al., 2006). In contrast, another meta-analysis of 4 RCTs found a small but significant effect in remission rates, but no difference in response rates, when switching to a non-SSRI compared to another SSRI (Papakostas et al., 2008).

Overall, there is no conclusive evidence to support switching out of class over switching within the class, for SSRI non-responders. The small differences in outcome reported in some switching studies may simply be a result of enhanced efficacy of some antidepressants, regardless of mechanism of action (see Table 4).
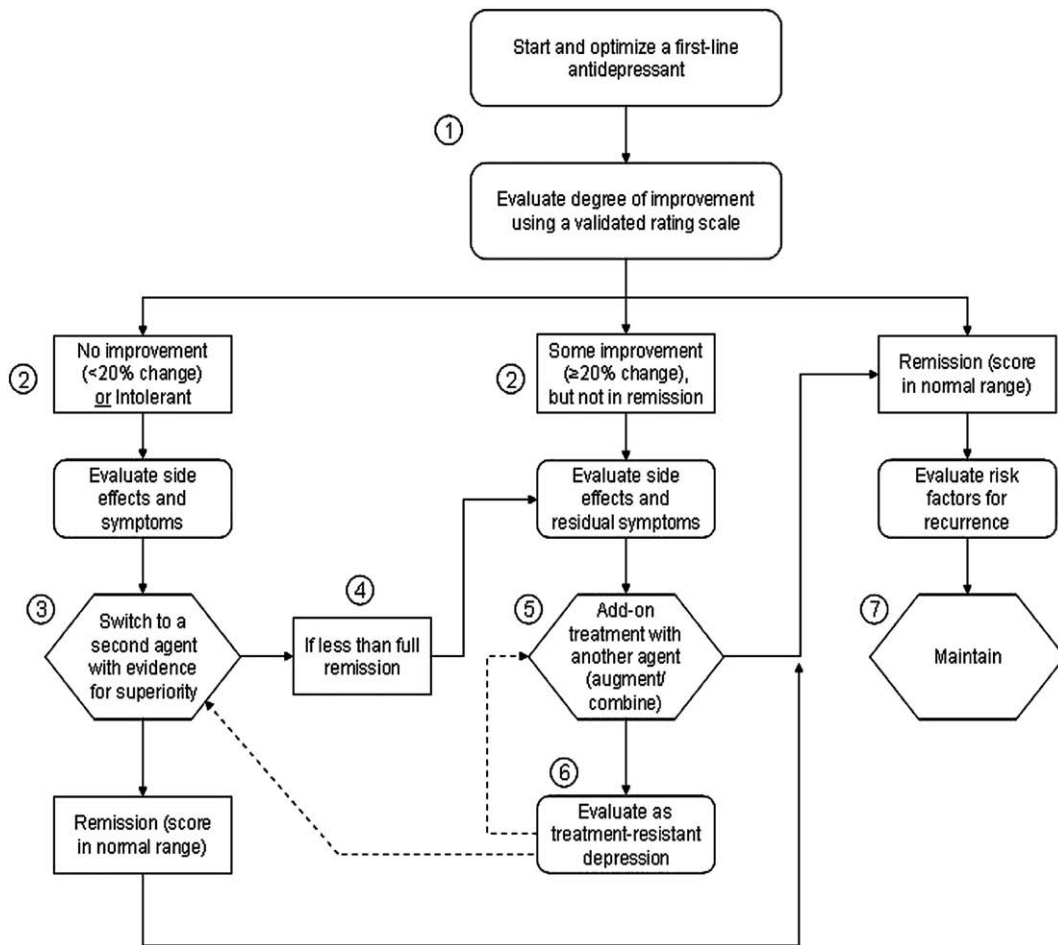
Fig. 1. Algorithm for managing limited improvement with a first-line antidepressant. 1) Initial improvement (defined as ≥20% reduction in symptom score) to a first-line antidepressant should be apparent within 1–4 weeks of achieving a therapeutic dose. If there is not at least an initial improvement within this time frame, and the drug is well tolerated, the dose should be increased. If there is still limited improvement, there should be a reassessment of diagnosis (especially comorbidity), degree of improvement (such as number and type of residual symptoms), adherence and tolerability. 2) At any step, depending on severity and patient preference, adding an evidence-based, non-pharmacological treatment (e.g., cognitive behavioural therapy, exercise, light therapy, etc.) or switching to a neurostimulation treatment (such as electroconvulsive therapy or transcranial magnetic stimulation) can be considered. 3) If there is no improvement (defined as <20% reduction in symptom score), switch to another antidepressant with evidence for superior efficacy (Table 4). If tolerability is an issue, switch to an antidepressant with a different side effect profile. 4) If there is no or limited improvement with the second monotherapy, an add-on treatment is recommended. 5) If there is some improvement but remission has not been achieved with the first-line antidepressant, and depending on tolerability, use an add-on treatment (adding another agent to the index antidepressant, Table 11). The selection of medication for add-on treatment should be individualized depending on efficacy, side effect burden, and residual symptoms. 6) If there is limited response to add-on treatment, consider strategies for treatment-resistant depression (TRD). The pharmacotherapy options include using another add-on agent, or switching to another first-line antidepressant with some evidence for superiority, or to second and third-line antidepressants including TCAs (especially clomipramine), quetiapine, or MAO inhibitors. 7) After achieving full symptom remission, patients should be maintained on antidepressants for at least 6–9 months before stopping. Patients with risk factors for recurrence (Table 12) should have a personalized assessment for maintenance treatment. Most should be maintained on their antidepressant for at least 2 years and some may require lifetime maintenance. The dose of antidepressant for maintenance treatment should be the same as that required for acute treatment.

3.13. How effective is the strategy of adding an "augmentation" agent?

Augmentation add-on strategies are among the best validated pharmacological treatments for TRD. However, conclusions are still limited by small sample sizes and lack of placebo controls. There are also few direct comparisons of different augmentation strategies and little information about the optimal duration of add-on strategies.

There is Level 1 evidence to support lithium augmentation. The most recent meta-analysis (10 RCTs, $N = 269$ participants) found it significantly superior to placebo in augmentation of antidepressants, including TCAs and SSRIs (Crossley and Bauer, 2007). Two RCTs found superiority of lithium over placebo in augmentation of SSRIs and in an RCT of relapse prevention following open-label augmentation of various antidepressants (including SSRIs) (Bauer et al., 2000), although another placebo-controlled RCT involving lithium augmentation of nortriptyline showed negative results (Nierenberg et al., 2003). Lithium is recommended at dosages of greater than 750 mg daily, or at a dose that achieves serum levels in the therapeutic range (0.5–1.0 meq/L). A suggested dosage schedule is 600 mg daily for 1 week, increasing to 900 mg daily for 1 week, and then titrating to adequate serum

levels. If there is no response after 3 to 4 weeks, then alternate strategies should be considered. Lithium augmentation is associated with the usual side effects of lithium use.

There is also Level 1 evidence to support add-on treatment with atypical antipsychotics for TRD. Two good-quality placebo-controlled RCTs reported efficacy of aripiprazole augmentation of SSRIs/SNRIs (Berman et al., 2007; Marcus et al., 2008). Aripiprazole is now approved in the United States as an adjunctive therapy to antidepressants. There are 4 placebo-controlled RCTs of the olanzapine-fluoxetine combination showing evidence for efficacy in TRD among antidepressant non-responders (e.g., Thase et al., 2007). Although a placebo-controlled RCT found risperidone efficacious as an augmentation to antidepressants, including SSRIs (Mahmoud et al., 2007), other RCTs noted no difference between risperidone and placebo to prevent relapse after 4–6 weeks of open-label augmentation of citalopram (Alexopoulos et al., 2008; Rapaport et al., 2006). Open studies and small, placebo-controlled RCTs suggest benefits for augmentation with quetiapine and ziprasidone. In addition, a meta-analysis (10 RCTs, $N = 1500$ participants) concluded that augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine and risperidone) was significantly superior to placebo in both response and remission rates (Papakostas et al., 2007c). The doses of atypical antipsychotics used as add-on treatment for MDD are usually lower than used for mania or schizophrenia. The side effects of these agents, especially weight gain, the potential for metabolic syndrome and small risk of extrapyramidal side effects, must be considered in the risk-benefit assessment, particularly in the context of long term therapy.

Triiodothyronine (T3, liothyronine) has shown benefit in many open trials and some RCTs, although earlier studies involved augmentation of TCAs. A recent systematic review, however, showed equivocal support for T3 augmentation of SSRIs (Cooper-Kazaz and Lerer, 2008). A STAR*D RCT of non-remitters after 2 treatment steps compared lithium to T3 and found comparable but modest remission rates of 15.9% vs. 24.7%, respectively (Nierenberg et al., 2006). The difference was not statistically significant but a Type II error is possible since the medium sized sample ($N = 142$) was underpowered to detect a 10% difference in outcomes. Treatment with T3 is usually initiated at a dose of 25 mcg daily and increased to 50 mcg after 1 week, if necessary. If there is no response after 2 weeks at the higher dose, another strategy should be considered. T3 is generally well tolerated, but long term effects at the higher doses are not well studied.

Other strategies have been evaluated in SSRI non-responders. Buspirone, a partial post-synaptic 5-HT1A agonist, was effective in a number of open-label studies, but placebo-controlled RCTs have been negative (Appelberg et al., 2001). Buspirone add-on to citalopram also had less favourable outcomes than the bupropion–citalopram combination in the STAR*D effectiveness trial (Trivedi et al., 2006a). Similarly, placebo-controlled RCTs of SSRI augmentation with pindolol, a beta-blocking drug that, in low doses, acts as a specific antagonist of the 5-HT1A pre-synaptic autoreceptor, were negative (Perry et al., 2004).

Two RCTs of augmentation with the CNS stimulant, methylphenidate, failed to detect differences in outcomes from placebo (Patkar et al., 2006; Ravindran et al., 2008) and a Cochrane systematic review found equivocal results for psychostimulants

Table 12
Risk factors supporting long term (2 years to lifetime) antidepressant maintenance.

Risk factors
• Older age
• Recurrent episodes (3 or more)
• Chronic episodes
• Psychotic episodes
• Severe episodes
• Difficult to treat episodes
• Significant comorbidity (psychiatric or medical)
• Residual symptoms (lack of remission) during current episode
• History of recurrence during discontinuation of antidepressants

as augmentation to antidepressants (Candy et al., 2008). As an add-on treatment in open studies, modafinil, a novel stimulant agent, showed benefit for treatment of residual symptoms of fatigue and sleepiness. Two subsequent placebo-controlled RCTs were negative, although a pooled analysis of these trials ($N = 348$ participants) did show significant benefit (Fava et al., 2007).

In summary, there is Level 1 evidence to support add-on treatment with lithium and atypical antipsychotics for TRD, and Level 2 support for T3 (Table 12). There is Level 3 evidence but also negative studies with buspirone, methylphenidate, modafinil and pindolol, so these agents are not recommended as first or second-line treatments.

3.14. How effective is the strategy of "combining" two antidepressants?

According to practitioner surveys, combining two (or more) antidepressants to enhance therapeutic effects or to treat side effects is common practice in many countries, (de la Gandara et al., 2005; Horgan et al., 2007; Mischoulon et al., 2000). Nevertheless, in contrast to augmentation strategies, there is a much smaller evidence base to show efficacy of antidepressant combinations.

Several placebo-controlled RCTs of antidepressant non-responders have shown efficacy when adding on mianserin (Ferreri et al., 2001) or mirtazapine (Carpenter et al., 2002) to the first antidepressant. However, in a large placebo-controlled RCT, there was no benefit when combining mianserin with sertraline compared to continuing sertraline monotherapy, although in the same study increasing the dose of sertraline from 100 mg to 200 mg resulted in worse outcomes (Licht and Qvitzau, 2002). In the STAR*D effectiveness trial, after non-remission to 3 treatment steps, the combination of mirtazapine with venlafaxine had similar outcomes (although Type II error may have obscured some possible superior outcomes) to tranylcypromine monotherapy, but the combination was better tolerated (McGrath et al., 2006).

Adding on bupropion in SSRI non-responders is also a popular combination, with many open and non-randomized cohort studies showing benefit, but there are no placebo-controlled RCTs (Dodd et al., 2005). However, in the STAR*D effectiveness trial after non-remission with citalopram, the addition of bupropion-SR to citalopram resulted in superior outcomes on some measures and was better tolerated than buspirone augmentation (Trivedi et al., 2006a).

Older studies suggested that combining fluoxetine and low-dose desipramine was efficacious in TRD, although subsequent

RCTs did not find any superiority of the combination compared to either higher dose fluoxetine alone or to fluoxetine augmented with low-dose lithium (Fava et al., 2002).

In summary, there is only Level 2 evidence to support efficacy of antidepressant combinations in non-responders to monotherapy (Table 11). The best available evidence is for add-on treatment with mirtazapine/mianserin or bupropion.

3.15. What are the relative benefits of switching versus add-on treatment?

Given the lack of trials comparing these strategies, most of these factors are speculative. Switching to another monotherapy offers simplicity, in that there is no concern about drug interactions or additive side effects. With add-on medications, especially another antidepressant, one can never be sure that the combination is necessary because any benefit may be due solely to the second agent. However, advantages of an add-on strategy include faster onset of response (for some augmentations) and the potential of a second agent to address specific residual symptoms and/or side effects. In addition, for some patients there may be a psychological advantage to adding a second agent to "boost" the effect of the first, rather than switching and "giving up" on the first agent. Finally, it is well recognized that a small percentage of patients are late responders, requiring 8 weeks or longer for initial response. It is very difficult for patients to continue taking a single agent for such a long time without any response, but adding a second agent allows a patient to continue longer on the first.

Since there are few comparative data available on the merits of each of these strategies, it remains a clinical decision weighing factors including the patient's past history and degree of response, side effects to the index antidepressant, and the potential side effects of a new medication (Kennedy et al., 2001).

3.16. What is a rational, sequential approach for non-response or incomplete response to a first-line antidepressant?

While there is considerable evidence to support the efficacy of switch and add-on strategies, there is still little information on how these strategies compare against each other and how they should be sequenced. It should also be noted that most switch and add-on studies focus on TRD, which is usually defined as treatment failure (<20% reduction in depression scores) after two or more adequate antidepressant trials. There is very little information about effective strategies for partial response (i.e., 20–49% reduction) or for residual symptoms (>50% reduction, but not in remission). While the objective of the STAR*D effectiveness study was to examine sequencing of treatments, the focus on non-remission did not allow differentiation between partial and non-responders and, beyond the second treatment step, there was inadequate power to detect small but clinically meaningful differences between treatments.

For these reasons, the recommended sequences are based primarily on expert opinion. Fig. 1 provides an algorithm for sequencing of treatments when there is inadequate response to a first-line antidepressant. At each decision stage, it is useful to evaluate the degree of improvement and side effect burden with validated rating scales in order to tailor subsequent treatments.

3.17. How long do you keep patients on an antidepressant once they are better?

Many RCTs and meta-analyses have shown that maintenance medication effectively prevents recurrence of symptoms with effects lasting from 6 months through 5 years. Two meta-analyses have examined predictors of the maintenance effect, and both had similar results: the effect size was not dependent on the risk factors for relapse (as well as could be determined), the duration of antidepressant treatment prior to randomization, nor the time of the randomized follow up period (Geddes et al., 2003; Hansen et al., 2008). One meta-analysis confirmed that maintenance doses should be the same as the dose that got people better, as those randomized to dose reduction had higher relapse/recurrence rates than those continuing on the same dose (Papakostas et al., 2007b). Only 1 RCT involving newer agents has prospectively examined the length of time for maintenance. The PREVENT trial entered patients with recurrent depression (defined as 3 or more episodes, two of which were in the past 5 years) who were treated to remission with venlafaxine for 6 months. They were then randomized to maintenance venlafaxine or placebo for 12 months, after which sustained remitters in the venlafaxine arm were re-randomized for another 12 months (Keller et al., 2007). The recurrence rate was significantly lower in the venlafaxine-treated patients compared to placebo after both follow up periods, indicating that maintenance treatment for at least 2 years is beneficial for recurrent depression [Level 2].

3.18. Who should be maintained longer on an antidepressant?

It is difficult to make specific recommendations for long term antidepressant treatment. Personalized approaches with individualized application of available evidence, careful evaluation of the benefits (prevention of recurrence) and the risks of continuing medication (e.g., side effects, cost) in each patient will be clinically more relevant than general recommendations. Patients with risk factors (Table 12) require longer term treatment for a minimum of 2 years and, for some, lifetime [Level 3] (Geddes et al., 2003; Hansen et al., 2008; Reynolds et al., 2006). Although empirical evidence is lacking, longer maintenance treatment should also be considered for patients with depression vulnerability factors including early onset depression, psychosocial adversity, and chronic medical illnesses [Level 4]. MDD with other psychiatric comorbidities including obsessive compulsive disorder or borderline personality disorder also may require long term treatment [Level 4].

In addition to clinical and demographic factors, certain biological (e.g., short allele of serotonin transporter gene promoter region polymorphism) and psychological (e.g., neuroticism, cognitive vulnerability) markers have been identified as possible risk factors for recurrence of MDD in the context of stress (Caspi et al., 2003). Longitudinal controlled studies are needed to establish the role of these markers in optimizing the length of antidepressant treatment. Besides antidepressants, cognitive behavioural therapy (CBT) has long-term effects in preventing relapses and recurrences (Parikh et al., 2009). Hence, integrating CBT with antidepressant treatment may shorten the term of antidepressant maintenance.

If the decision is made to discontinue an antidepressant, it should be tapered off gradually to avoid discontinuation symptoms [Level 3] (Schatzberg et al., 2006). The high risk patient should be monitored regularly for early signs of recurrence after discontinuation of antidepressants.

Special populations

3.19. Which antidepressants can be used during pregnancy?

Since the previous guidelines in 2001, there have been no RCTs evaluating the safety and efficacy of antidepressants during pregnancy. The evidence remains limited to small studies or case control/cohort designs, often with many confounding variables and conflicting results. For example, comparison groups usually include women who are not using antidepressants but who are not necessarily depressed, so potential adverse effects associated with depression itself are not taken into account (Table 13).

At least 7 meta-analyses examining safety of antidepressants during pregnancy have been published since 2000. Some concluded that SSRIs and newer antidepressants had no associated risks of major (Einarson and Einarson, 2005; Rahimi et al., 2006) or minor (Rahimi et al., 2006) malformations, but one found evidence that SSRI use late in pregnancy was associated with subtle adverse effects (serotonergic overstimulation, withdrawal syndromes, long term neurobehavioural effects) in newborns (Lattimore et al., 2005). The newer antidepressants are associated with an increased risk of spontaneous abortions, although an effect of depression could not be ruled out (Hemels et al., 2005; Rahimi et al., 2006). The use of SSRIs during late pregnancy also has been associated with persistent pulmonary hypertension in newborns in some studies (Chambers et al., 2006) but not in others (Andrade et al., 2009); meta-analyses are not currently available.

For individual drugs, first trimester use of fluoxetine was not associated with teratogenicity (Addis and Koren, 2000) while first trimester use of paroxetine was associated with an increased risk for cardiac malformation in one meta-analysis (Bar-Oz et al., 2007) but not in another (O'Brien et al., 2008). The authors of the first study acknowledged that detection bias may have affected the results (Bar-Oz et al., 2007). In summary, antidepressants do not appear to be major teratogens but they may be associated with neonatal complications, usually described as transient reactions. Further study is required of longer term neurobehavioural effects in children exposed *in utero* to these medications.

3.20. How should antidepressants be used postpartum and during lactation?

Women with postpartum depression respond to antidepressants, although trials have not been done comparing treatment during postpartum episodes to depressive episodes at other times (Table 13). Small-sample RCTs have examined antidepressant use in postpartum depression. In one trial there was no difference in outcomes when paroxetine alone was compared to paroxetine with CBT (Misri et al., 2004), while another found that paroxetine was superior to placebo in achieving remission (Yonkers et al., 2008). In another study, sertraline was comparable to nortriptyline (Wisner et al., 2006).

In two small RCTs designed to study prevention, non-depressed women with a history of postpartum depression were randomized to antidepressant or placebo immediately after childbirth; sertraline (Wisner et al., 2004) showed a preventative effect compared to placebo, but nortriptyline did not (Wisner et al., 2001).

Data on antidepressant use during lactation are also limited, especially on infant outcomes during long term follow up (Eberhard-Gran et al., 2006). Most studies of mother–infant pairs show that antidepressants are excreted into breast milk in varying and, usually, small amounts. In a pooled analysis of 57 studies, infant serum levels of nortriptyline, sertraline and paroxetine were usually not detectable, while infants exposed to fluoxetine had higher risk of having elevated serum levels (Weissman et al., 2004). Although the pooled analysis also suggested that infants exposed to citalopram may be at higher risk, especially if the mother's citalopram dose was high, subsequent prospective case series showed very low or undetectable infant serum levels (Berle et al., 2004; Heikkinen et al., 2002). One study followed infants who had been exposed to antidepressant medication during lactation and reported no effects on infant weight up to 18 months postpartum (Hendrick et al., 2003).

3.21. Which antidepressants can be used for children and/or adolescents?

Pharmacotherapy in youth (children and adolescents under age 18) with MDD has been a controversial topic because the benefits of antidepressants are less evident and the risks include increased suicidality (defined as worsening suicidal thoughts and self-harm behaviours) in this age group (Table 14). A previous meta-analysis of 12 RCTs assessing the efficacy of TCAs in youth did not demonstrate efficacy and therefore TCAs are not recommended in this age group (Hazell et al., 1995). Subsequent meta-analyses have shown favourable evidence of efficacy of SSRIs in youth with MDD (Tsapakis et al., 2008), especially with fluoxetine and citalopram (Usala et al., 2008; Wallace et al., 2006), but the effect sizes of antidepressants are modest, with a number needed to treat (NNT) of 10 for clinical response (Bridge et al., 2007).

In adolescents who did not respond to a first SSRI, there were no differences in effectiveness or safety when switching to another SSRI (citalopram, fluoxetine or paroxetine) compared to venlafaxine, although the SSRI switch led to fewer adverse events (Brent et al., 2008). However, the combination of medication and CBT resulted in the best outcomes.

Table 13
Recommendations for pharmacotherapy of MDD in pregnancy and postpartum.

Recommendation
• In pregnant women, the small risk of exposing the fetus or neonate to an antidepressant must be balanced against the benefits in treating MDD. [Level 2]
• During pregnancy, fluoxetine and other SSRIs are first-line antidepressants, but paroxetine may have a higher risk for cardiac malformations. [Level 2]
• In nursing mothers, first-line antidepressants include citalopram, nortriptyline, sertraline, and paroxetine because these medications in therapeutic doses are associated with low to undetectable serum concentrations in breast-fed babies. [Level 3]

Table 14
Recommendations for pharmacotherapy in youth with MDD.

Recommendation
• In youth (children and adolescents) with moderate to severe MDD, there is a modest benefit of antidepressants, with an NNT of 10 for clinical response. There is also a small risk for increased suicidality (suicidal ideation/ behaviours), with an NNH of 143. Therefore, the benefits of antidepressants must be balanced against the harms of antidepressants and of untreated MDD. [Level 1]
• Fluoxetine and citalopram are first-line antidepressants with the best benefit-risk evidence, especially in children. [Level 1]
• Other SSRIs can be considered as second-line agents. Paroxetine may have a higher side effect burden than other SSRIs. [Level 1]
• Venlafaxine has a higher risk estimate for suicidality and is a third-line antidepressant in this age group. [Level 2]
• The best outcomes generally have resulted from combining antidepressants with CBT. [Level 2]

In regards to risks, independent meta-analyses (Bridge et al., 2007; Dubicka et al., 2006; Hetrick et al., 2007) have replicated the meta-analyses from the U.S. Food and Drug Administration (FDA) (Hammad et al., 2006a; Mosholder and Willy, 2006) showing a 1.5 to 2 fold risk of increasing suicidal thoughts/ behaviours associated with newer antidepressants compared to placebo. Of note, there were no completed suicides in the clinical trial database. The absolute risks are quite small, however, with a recent estimated risk difference of 0.7%, corresponding to a number needed to harm (NNH) of 143 (Bridge et al., 2007). The only individual antidepressant associated with a significantly higher risk estimate is venlafaxine (Bridge et al., 2007; Hammad et al., 2006a). Some trials have shown that CBT can reduce the risk of suicidality associated with SSRIs (Emslie et al., 2006) while others have not (Goodyer et al., 2007). In addition, results of meta-analyses should be supplemented by real-world evidence, such as that from pharmacoepidemiology studies and forensic toxicology studies (Bridge and Axelson, 2008). These studies have shown only mixed evidence that suicidality is associated with antidepressant use in youth.

In part because of the meta-analysis data, in 2003 the U.S. FDA, Health Canada, the U.K. MHRA and other regulatory agencies warned against the use of SSRIs in children and adolescents and, since 2004, a "black box warning" about potential suicidality in the paediatric age group was added to all antidepressant monographs. This warning was also extended to young adults (age 18–24) despite the fact that no statistically significant increase in suicidality was demonstrated (Friedman and Leon, 2007). Studies in the U.S., Canada and the U.K. have shown a marked reduction of antidepressant prescriptions in the youth age group following these warnings (Gibbons et al., 2007; Kurdyak et al., 2007; Libby et al., 2007; Murray et al., 2005). Unfortunately, the lower rate of use of antidepressants does not seem to be offset by increased use of psychotherapy or mental health services; in Canada, the number of ambulatory visits for youth and young adults decreased following the warnings (Katz et al., 2008). A more serious finding was that the suicide rate in these age groups in the 2 years following the warnings showed reversal of a previously declining trend, i.e., an increase in suicide rate, in Canada (Katz et al., 2008) and the U.S.(Gibbons et al., 2007), but not in the U.K. (Wheeler et al., 2008). Although causality cannot be proven, these results suggest that some youth may not be receiving appropriate antidepressant treatment because of the black box warnings.

In summary, there is Level 1 evidence to support modest efficacy of SSRI and SNRI antidepressants in this age group, with most evidence for fluoxetine and citalopram, and only a very small risk of increased suicidality (Table 14). Regardless, close monitoring is required when using antidepressants in youth and young adults.

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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. IV. Neurostimulation therapies

Sidney H. Kennedy [a,*], Roumen Milev [b], Peter Giacobbe [a], Rajamannar Ramasubbu [c], Raymond W. Lam [d], Sagar V. Parikh [a], Scott B. Patten [c], Arun V. Ravindran [a]

[a] University of Toronto, Canada
[b] Queen's University, Canada
[c] University of Calgary, Canada
[d] University of British Columbia, Canada

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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. There is renewed interest in refined approaches to brain stimulation, particularly for treatment resistant major depressive disorder (MDD).
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 evidence and expert clinical support. This section on "Neurostimulation Therapies" is one of 5 guidelines articles.
Results: Among the four forms of neurostimulation reviewed in this section, electroconvulsive therapy (ECT) has the most extensive evidence, spanning seven decades. Repetitive transcranial magnetic (rTMS) and vagus nerve stimulation (VNS) have been approved to treat depressed adults in both Canada and the United States with a much smaller evidence base. There is also emerging evidence that deep brain stimulation (DBS) is effective for otherwise treatment resistant depression, but this is an investigational approach in 2009.
Limitations: Compared to other modalities for the treatment of MDD, the data based is limited by the relatively small numbers of randomized controlled trials (RCTs) and small sample sizes.
Conclusions: There is most evidence to support ECT as a first-line treatment under specific circumstances and rTMS as a second-line treatment. Evidence to support VNS is less robust and DBS remains an investigational treatment.

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1. 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 et al., 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 Neurostimulation is one of 5 guidelines articles. There are separate CANMAT guidelines for Bipolar Disorder (Yatham et al., 2009).

Neurostimulation involves the delivery of a physical intervention either through electric current or a magnetic

field to target selective or generalized brain regions. ECT represents the prototypic form of neurostimulation, that has been used since the 1930s although it only received the Food and Drug Administration's (FDA) approval in 1979. Despite favourable rates of outcome, failure to sustain antidepressant response and adverse cognitive effects have been the main limitations of ECT. rTMS relies on electromagnetic induction to generate a superficial current in the dorsolateral prefrontal cortex (DLPFC) which may be of high intensity or low intensity. This treatment is devoid of adverse neurocognitive effects and continues to be refined in the treatment of MDD. VNS and DBS are more invasive forms of neurostimulation that have been approved for the treatment of neurological disorders prior to being investigated for treatment resistant depression (TRD). The VNS device received approval for adjunctive long-term use for chronic or recurrent MDD and relays a mild electrical pulsed stimulus to the left vagus nerve which activates limbic structures. The efficacy of this procedure is still being evaluated, although it has a good safety profile. DBS is the most invasive form of neurostimulation and requires direct neurosurgical implantation of electrodes to targeted brain regions. In both VNS and DBS, patients require an implantable pulse generator (IPG), usually inserted subclavicularly to maintain pulsatile or continuous current. Although early reports suggest promising results in open-label trials, DBS requires RCT evidence before it can be recommended in routine clinical practice. A summary of evidence and recommendations is contained in Table 1. However, 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., 2009) but, in summary, relevant studies of English language publications 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 previous question–answer format has been retained based on feedback from clinicians. Recommendations for each Line of

Table 1
Summary of recommendations for neurostimulation therapies.

Neurostimulation	Overall recommendation	Acute efficacy	Relapse prevention	Safety and tolerability
ECT	First-line under specific circumstances (see Table 4) Second-line for otherwise treatment resistant or medication intolerant populations	Level 1	Level 1	Level 1
rTMS	Second-line	Level 1	Level 3	Level 1
VNS	Third-line	Level 3	Level 2	Level 2
DBS	Investigational	Level 3	Level 3	Level 3

Table 2
Criteria for Level of Evidence [a] and Line of Treatment. [b]

Level	Criteria
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	Criteria
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] 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, 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 in 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.

Treatment are based on the Level of Evidence and clinical support (Table 2).

3. Electroconvulsive therapy (ECT)

4.1. What is ECT and how is it delivered?

ECT involves the induction of a convulsion (seizure) by the application of electrical current to the brain. The stimulus parameters are: current (usually 500 to 800 mA); frequency (20 to 120 Hz); pulse width (0.25 to 2 ms) and duration (0.5 to 8 or more seconds). The charge of electricity delivered is measured in millicoulombs (below 600 mC for machines sold in Canada and USA but somewhat higher for other markets) and the energy is measured in joules. The minimum charge to induce a seizure is known as the seizure threshold. The electrodes can be placed bilaterally (either bitemporal or bifrontal) or unilaterally (typically, on the right side — RUL). Markedly suprathreshold ECT is the goal for unilateral placement and entails applying a stimulus dose up to 6 times above seizure threshold. In contrast, moderately suprathreshold ECT is the goal for bilateral placement, which implies 1.5 to 2.5 times threshold. Barely suprathreshold brief-pulse unilateral ECT is remarkably ineffective (Sackeim et al., 1987). Response rates of 80% or higher have been reported with ECT although there are very few comparisons between ECT and first-line antidepressants.

There is consistent evidence that the antidepressant efficacy of ECT is related to its stimulation parameters. Bitemporal placement is generally regarded as faster in improving depressive symptoms and more effective than unilateral, at a lower dose of electrical stimulus. However, bitemporal placement is associated with more cognitive side effects (Stoppe et al., 2006). There is evidence that the right unilateral stimulus at suprathreshold dose is as effective as bilateral stimulation

and is associated with fewer side effects (Sackeim et al., 1993, 2000). Meta-analyses suggest that ECT delivered bitemporally is associated with greater acute cognitive side effects compared to RUL (The UK ECT Review Group, 2003). There is also evidence that the less frequently evaluated, bifrontal placement of electrodes is as effective as bitemporal or right unilateral, and is also associated with fewer cognitive side effects (Bailine et al., 2000; Eschweiler et al., 2007). In addition, shorter pulse width and lower pulse frequency may have lower seizure thresholds (Kotresh et al., 2004; Sackeim, 2004; Sackeim et al., 2008).

4.2. What is the recommended frequency and duration of a course of ECT?

ECT is typically delivered two or three times per week under monitored conditions. The need for a rapid onset of antidepressant effects must be weighed against the deleterious effects of more frequent ECT treatments. Some studies (Shapira et al., 2000), but not all (The UK ECT Review Group, 2003), support a faster onset of action when patients receive the treatment 3 times per week. On the other hand, patients receiving a twice weekly regimen have decreased frequency and intensity of cognitive side effects compared to those on a three times weekly schedule (The UK ECT Review Group, 2003) (Table 3).

4.3. How effective is ECT as an acute antidepressant therapy?

When ECT is prescribed as a first-line treatment (Table 4) or in individuals with a history of antidepressant medication trials of inadequate dose or duration, response rates in the 80%–90% range have been reported (Petrides et al., 2001). Several meta-analyses have concluded that ECT is a superior acute antidepressant compared to pharmacotherapy (Kho et al., 2003; Pagnin et al., 2004; The UK ECT Review Group, 2003), although there are very few direct comparisons between ECT and the first-line antidepressants as monotherapies used alone or in combination. In most countries the use of ECT is reserved for a major depressive episode that has proved "treatment resistant" to adequate trials of two or more pharmacotherapies, including combination medications and/ or cognitive therapy. When used in patients who have failed to respond to one or more adequate antidepressant medication trials, ECT response rates have traditionally been estimated to be 50–60% (Prudic et al., 1996).

4.4. How effective is ECT as a relapse prevention therapy?

Although the antidepressant benefits of ECT tend to be acute, they may not persist without some form of maintenance treatment. Results from two large multi-site collaborations —

Table 3
Recommendations for delivery of ECT.

• Start with either high dose (e.g., 6 times seizure threshold) right unilateral or low dose (e.g., 2 times seizure threshold) bitemporal treatment [Level 1].
• If improvement (at least 20% reduction in a standardized rating scale) after 4–6 sessions, continue to 8–10 sessions [Level 3].
• If no response after 6 treatments, switch to bitemporal treatment up to 12 sessions (bifrontal placement represents an alternative option) [Level 3].

Table 4
Indications for ECT as a first-line treatment.

Indications	
• Acute suicidal ideation [Level 1]	• Repeated medication intolerance [Level 3]
• *MDE with psychotic features [Level 1]	• Rapidly deteriorating physical status [Level 3]
• Treatment resistant depression [Level 1]	• During pregnancy, for any of the above indications [Level 3]
• Catatonia [Level 3]	• Patient choice [Level 4]
• Prior favourable response [Level 3]	

*MDE = Major Depressive Disorder.

the Consortium for Research in ECT (CORE) (Kellner et al., 2006) and Columbia University Consortium (CUC) (Sackeim et al., 2001a,b,c) support the combination of nortriptyline plus lithium for relapse prevention in patients who responded to ECT. The CORE study reported that both continuation pharmacotherapy and maintenance ECT were equally effective for relapse prevention during the first 6 months after responding to ECT (Kellner et al., 2006). Maintenance ECT ranging from one per week to one per month is associated with low rates of cognitive side effects (Vothnecht et al., 2003). However, there is insufficient evidence to recommend one frequency over another for maintenance ECT. Maintenance treatments should be reviewed every 6 months.

4.5. Which patients respond best to ECT?

ECT is a first-line treatment under certain clinical circumstances (see Table 4). Evidence exists that ECT is effective for all subtypes of MDD, including atypical depression (Husain et al., 2008), and bipolar depression (Grunhaus et al., 2002), but may be especially effective for psychotic depression (Petrides et al., 2001) and depression with prominent suicidal ideation (Kellner et al., 2005). A recent report from the Consortium for Research in ECT (CORE) concluded that antidepressant medication treatment failure does not predict lower remission with ECT (Rasmussen et al., 2007).

4.6. What are the adverse effects associated with ECT?

ECT is a safe procedure with a very low mortality rate (0.2 per 100,000 treatments), approximating the risk of general anaesthesia (Kramer, 1999). Patients who have myocardial ischemia, cardiac arrhythmias, or abdominal aortic aneurysms carry higher morbidity and mortality risks.

The most frequently reported short-term side effects are nausea, headache, muscle pain, oral lacerations, dental injuries, and persistent myalgia (Wijeratne et al., 1999). Although improvements in depression-related cognitive dysfunction have been reported with ECT (Stoudemire et al., 1998), cognitive side effects are of most concern to patients and their families, particularly acute confusional states, anterograde and retrograde amnesia, word finding difficulties, and deficits in autobiographical memory. There is evidence to show impairment in verbal learning after three treatments (Porter et al., 2008), although this did not correlate with long-term memory function. In addition, there were no differences in retrograde memory loss between patients who received unilateral followed by bilateral stimulation, compared to those who received

only unilateral stimulation (O'Connor et al., 2008). Others have found persistent retrograde amnesia at 2 months post-ECT for bilateral ECT compared to unilateral ECT (Lisanby et al., 2000).

Reducing the frequency of treatments (from 3 to 2 per week), the use of brief pulse rather than sine wave ECT machines, right unilateral or bifrontal positioning of the electrodes (instead of bitemporal) and lower dose stimuli should reduce the frequency and intensity of cognitive side effects (Sackeim et al., 2007).

Claims that ECT may result in structural brain damage are unsubstantiated (Devanand et al., 1994; Zachrisson et al., 2000). In fact, consistent with evidence about various antidepressant treatments, ECT stimulates neurotrophic growth factors including brain derived neurotrophic factor (BDNF), causing migration and growth of new neurons in the hippocampus (Marano et al., 2007), and this may contribute to the antidepressant effect.

4.7. Should ECT be combined with other antidepressant treatments?

Although it has been generally accepted that combining ECT and antidepressant medication does not increase therapeutic effects (Flint and Rifat, 1998), there is recent evidence to suggest that continuation of nortriptyline during ECT increases the remission rate compared to ECT plus placebo (Sackeim et al., 2009) [Level 2]. If replicated, these results have the potential to alter clinical practice.

Because of reports that lithium may increase post-ictal confusion and delirium, many practitioners omit one or two doses prior to each ECT session. The use of benzodiazepines and anticonvulsants may interfere with the seizure duration and are best avoided (Rabheru and Persad, 1997) [Level 3]. In practice, patients who are receiving ECT and taking anticonvulsants/mood stabilizers are generally required to avoid medication on the days of treatment.

4. Repetitive transcranial magnetic stimulation (rTMS)

4.8. What is rTMS and how is it delivered?

Repetitive transcranial magnetic stimulation (rTMS) involves a non-invasive, superficial, powerful magnetic stimulation of the brain. A magnetic field (1.5–2.5 T), generated when current is passed through a coil (electromagnetic induction), is delivered through the skull. In the brain, the magnetic field induces electric currents affecting neuronal function (see George et al., 2007 for a detailed review).

The TMS coil is usually round or figure-eight (butterfly) in shape. The latter produces a stronger and more focal field than the circular coil, and is widely used to deliver repetitive (rTMS) stimuli. There are two types: (i) low-frequency rTMS (at or below 5 Hz) which appears to produce a transient reduction in cortical excitability and (ii) high-frequency rTMS (usually over 5 Hz) which seems to increase excitability (Fitzgerald et al., 2006a). Almost all studies have applied a standard procedure to position the coil, identifying the motor cortical site for optimal stimulation of abductor pollicis brevis, and measuring 5 cm anteriorly along the skull surface and in a parasagittal line. An alternative method of MRI based neuronavigation to target the left DLPFC between BA 9 and BA 46 has also been evaluated (Fitzgerald et al., 2009).

rTMS is delivered in trains, lasting several seconds, followed by inter-train intervals. Several trains can be delivered per session and usually five sessions are delivered per week. Early reports evaluated the effect of rTMS over 2 weeks (10 sessions), but subsequent trials have been 4–6 weeks in duration (O'Reardon et al., 2007). Variations in the frequency of sessions range from two sessions per day (Loo et al., 2006), to one session every second or every third day (Schutter, 2008).

The intensity of the stimulus is based on the individual motor threshold (the minimal intensity required to produce muscle twitches), and usually is between 90% and 120% of this threshold. Target areas to be stimulated are left or right DLPFC. There is most evidence to support high-frequency rTMS applied to the left DLPFC, but positive results have also been reported with low-frequency right DLPFC (Fitzgerald et al., 2006b), simultaneous combined high-frequency left DLPFC with low-frequency right-DLPFC stimulation, and sequential low frequency to the right hemisphere followed by high frequency to the left (Fitzgerald et al., 2006b) (Table 5).

4.9. How effective is rTMS as an acute antidepressant therapy?

rTMS has been approved for use in Canada since 2002, and received approval in the United States in 2008 to treat depressed adults who failed to respond to at least one antidepressant. Since the first case reports in 1993 (Hoflich et al., 1993), there have been many open label and RCTs, evaluating the effect of rTMS for the treatment of depression (O'Reardon et al., 2007). Direct comparisons among rTMS studies are limited by variations in study design, dosing and frequency parameters, and site of stimulation. The authors of two meta-analyses (Couturier, 2005; Martin et al., 2003) concluded that there was insufficient evidence to support claims that high-frequency left sided rTMS was superior to low-frequency right sided rTMS. Subsequent reports (Schutter, 2008) have reached the opposite conclusion. A meta-analysis in 2007 concluded that the efficacy of rTMS was higher in studies published after 2005 (Gross et al., 2007). The best support for rTMS to date is an RCT involving 301 medication free patients showing the active TMS was significantly better than sham, but only after a post hoc correction for inequality of baseline severity between groups (O'Reardon et al., 2007). This study accounts for one third of the entire sample reviewed in a subsequent meta-analysis (Daskalakis et al., 2008).

A meta-analysis of rTMS for TRD reported response and remission rates, respectively, of 25% and 17% for active treatment compared to 9% and 6% for sham treatment. Although these rates are lower than those reported in studies of other interventions for TRD, the differences between active and sham treatments were significant for both response and remission rates (Lam et al., 2008). Enhanced response to

Table 5
Recommendations for delivery of rTMS.

• Start with high-frequency rTMS to the left DLPFC. [Level 1]
• Superior outcome for 20 vs 10 sessions. [Level 2]
• Minimal evidence for maintenance and relapse prevention effect. [Level 3]

rTMS has been reported when an MRI based neuro-navigation technique is used to target the specific site on the DLPFC for administration (Fitzgerald et al., 2009).

There is no evidence to support superiority of rTMS over ECT. In fact, comparisons suggest either equal efficacy (Rosa et al., 2006) or some advantage for ECT (Eranti et al., 2007), although rTMS and ECT are equally cost-effective (Knapp et al., 2008).

4.10. How effective is rTMS as a relapse prevention therapy?

To date, there is only one open-label case series supporting maintenance rTMS to left DLPFC at 100% motor threshold delivered on average 1 to 2 times per week for up to 6 years (O'Reardon et al., 2005). This is a major gap in the evidence base for rTMS.

4.11. Which patients respond best to rTMS?

There is inadequate evidence to characterize a prototypic responder to rTMS although this procedure has been evaluated for the treatment of major depressive episodes in both MDD and bipolar disorder. Predictors of positive treatment outcomes with high-frequency left-DLPFC rTMS include shorter duration of current depressive episode, and the absence of anxiety disorder comorbidity (Lisanby et al., 2009). The majority of evidence supports the superiority of ECT compared to rTMS in depressed patients with psychotic symptoms (Gershon et al., 2003), although there are conflicting data regarding the efficacy of rTMS in TRD (Brakemeier et al., 2007; Lisanby et al., 2009; Loo et al., 2008). Superior efficacy has also been reported in more severe depression (Fitzgerald and Daskalakis, 2008).

There are also preliminary reports that rTMS is effective in various medical populations with comorbid MDD, including patients who have comorbid Parkinson's Disease (PD) (Fregni et al., 2006), vascular depression (Jorge et al., 2008) and pain in the context of depression (Avery et al., 2007). Results from a Canadian open trial and large case series suggest efficacy in late-life depression (Abraham et al., 2007; Milev et al., 2009), contrary to earlier findings (Mosimann et al., 2004). A preliminary report suggests that the response to rTMS correlates with serotonergic gene polymorphisms (Zanardi et al., 2007).

4.12. What are the adverse effects associated with rTMS?

In general, rTMS is a safe and well-tolerated treatment. Common short-term side effects include headaches and scalp pain usually responding well to symptomatic treatments. Because of concerns about hearing loss (due to the clicking noise of the apparatus), both patients and staff should use ear plugs with 30 dB protection during the treatment process. rTMS does not involve general anaesthesia or seizure induction and is not associated with adverse cognitive effects.

There is no evidence of cognitive impairment with rTMS. In a sham-controlled rTMS study, patients who received active rTMS displayed improvements in measures of executive functioning (Moser et al., 2002). In a head to head comparison of rTMS vs ECT, cognitive performance remained constant or improved and memory complaints were alleviated in the rTMS group (Schulze-Rauschenbach et al., 2005).

There have been 12 case reports of seizures occurring during rTMS (Loo et al., 2008) [Level 3]. In the majority of cases, pre-existing neurological disorders or sleep deprivation were noted. Patients should be screened for these conditions before they receive rTMS (Keel et al., 2000). The effects of rTMS on the fetus are not known at this stage, so this treatment is not recommended during pregnancy.

To date, there have been no systematic long-term safety evaluations of rTMS, although open-label reports on maintenance rTMS suggest that it is safe in the long term (O'Reardon et al., 2005) [Level 3].

Absolute contraindications include seizures, the presence of ferromagnetic material anywhere in the head (excluding the mouth) such as cochlear implants, brain stimulators or electrodes, aneurysm clips, plates, etc. Cardiac pacemakers are also a contraindication. Increased intracranial pressure, severe cardiovascular disease, epilepsy and other serious medical conditions are also contraindications (Nahas et al., 2008).

4.13. Should rTMS be combined with other antidepressant treatments?

There is growing evidence that the combined use of rTMS with antidepressant medication accelerates response under sham-controlled conditions (Bretlau et al., 2008; Rossini et al., 2005; Rumi et al., 2005), although initial advantages are not always sustained (Poulet et al., 2004; Rossini et al., 2005) [Level 1]. Adding open-label mirtazapine also increased the response to rTMS monotherapy (Schule et al., 2003) [Level 3].

Vagus nerve stimulation (VNS)

4.14. What is VNS and how is it delivered?

VNS is an approved treatment in the USA and Canada for refractory epilepsy. The clinical observation of mood improvement during VNS therapy for epilepsy provided the rationale to evaluate its potential use in TRD. The US FDA approved the use of the VNS for refractory depression in 2005 and Health Canada approved its use for TRD in 2001.

VNS involves implantation of a bipolar electrode around the left vagus nerve, accessed through a small incision in the lower neck. This wire is connected to a subclavicular pulse generator, which delivers intermittent electrical signals to the left vagus nerve. Signal frequency and intensity can be controlled remotely using a telemetric wand linked to a palmtop computer. The left vagus nerve is chosen for VNS due to its limited cardiac effects. The most commonly used stimulation parameters are: a frequency of 20–30 Hz, an intensity 0.25 mA, and a pulse width of 250–500 ms with a cycle of 30 s of stimulation every 5 min. Battery life of the device is 6–8 years: hence its status needs to be checked during the course of clinical follow-up until it is ultimately replaced (Rado and Janicak, 2007).

The mechanism of action of VNS is not fully understood although emerging data suggest that VNS therapy modulates the function of neural structures implicated in depression and also influences monoaminergic neurotransmission (Nemeroff et al., 2006).

4.15. How effective is VNS as an acute antidepressant therapy?

In a randomized sham-controlled trial, VNS only showed a modest effect with a response rate of 15% compared to 10% with sham treatment (implantation but device not activated) during a 10 week trial and thus failed to demonstrate significant acute antidepressant effects (Rush et al., 2005a). Results from four open-label studies showed a response rate of 30% and remission rate of 15% during 10–12 weeks of adjunctive VNS therapy (Rush et al., 2000; Sackeim et al., 2001c; Corcoran et al., 2006; Schlaepfer et al., 2008b).

4.16. How effective is VNS during extended therapy?

When patients were followed for 1–2 year extension phases, response rates ranged from 27% to 46% and remission rates from 16% to 29% (Marangell et al., 2002; George et al., 2005; Nahas et al., 2005; Rush et al., 2005a,b; Nierenberg et al., 2008). In one of these studies, a parallel non-randomized design was used to compare VNS plus treatment as usual with treatment as usual only and response rates at 12 months were 27% for VNS and 13% for treatment as usual (George et al., 2005). One explanation is that VNS may deliver a delayed antidepressant effect with an increasing clinical improvement over time, although changes in concurrent antidepressant medications during the extension trials cannot be excluded as an explanation for the increased rates of response and remission. Given the lack of substantial evidence for short-term and long-term efficacies in acute severe depression, the appropriate place of VNS in the treatment algorithm for TRD remains to be determined.

4.17. How effective is VNS as a relapse prevention therapy?

Given the evidence of a slowly progressive therapeutic effect in extension studies, adjunctive VNS therapy may have a role in long-term maintenance treatment for less severe TRD [Level 3], although further RCT evidence is required.

4.18. Which patients respond best to VNS?

Results from an acute phase pilot study of 59 TRD participants suggest that patients with chronic or recurrent, TRD may show long-term benefit when treated with VNS (Nahas et al., 2005). In practice, it would be reasonable to consider patients who have failed at least 4 prior treatments at adequate dose and duration for the current episode. Failure to respond to ECT is not a prerequisite.

4.19. What are the adverse effects associated with VNS?

Overall, VNS has a favourable side effect profile, however, the common acute side effects are voice alteration, neck pain, headache, cough, dysphagia and dyspnoea (Table 6). They are related to the stimulation parameters and can be minimized by reducing the intensity of the stimulation being delivered. The rate of psychiatric adverse events have been reported as follows: hypomania (3.3%), mania (1.2%), and suicide attempt (3.5%). No cognitive side effects have been reported (Sackeim et al., 2001b).

4.20. Should VNS be combined with other antidepressant treatments?

As with other neurostimulation treatments, most patients in VNS trials have continued on their pre-trial antidepressant medications. Evidence of greater antidepressant effects accruing over time with concurrent medication changes in patients receiving VNS suggests that these two antidepressant modalities may work synergistically [Level 3]. However, there is insufficient evidence to recommend any specific combination of VNS and antidepressant medication.

Deep brain stimulation (DBS)

4.21. What is DBS and how is it delivered?

DBS involves the stereotactic neurosurgical implantation of electrodes under MRI guidance to distinct brain regions. These electrodes are connected to a stimulator implanted in the chest wall (similar to VNS) that provides continuous electrical stimulation. After several decades of evaluation as a treatment for Parkinson's Disease, where stimulation of the subthalamic nucleus results in acute and sustained relief of tremor and rigidity, there is emerging evidence to support DBS as an experimental intervention for patients with treatment-refractory depression.

There is no consensus on the most effective target brain region for implantation, although three regions have been explored. To date, the subcallosal cingulate gyrus (SCG) (approximately Brodmann Area 25) has been evaluated most (Lozano et al., 2008; Mayberg et al., 2005; Neimat et al., 2008). The rationale for this site comes from evidence that healthy volunteers experiencing sadness during functional neuroimaging display increased activity in BA 25 and depressed patients responding to antidepressant medications demonstrate a reduction (Mayberg, 2003). Two additional sites in close proximity to one another have also been examined: the nucleus accumbens (Schlaepfer et al., 2008a) and the ventral caudate/ventral striatum region (Malone et al., 2009), on the basis that anhedonia, a core depressive symptom, is modulated through dopaminergic pathways involving these regions.

Following surgery, which may be carried out in the awake state, patients wait approximately 7–14 days before the device is switched on. This allows localized edema to resolve and inspection of both the scalp and subclavicular wound sites. Typical settings within a range of 3.5–5.0 V, 130 Hz and 90 ms have been reported (Lozano et al., 2008).

4.22. How effective is DBS as an acute antidepressant therapy?

To date, there are no large RCTs, on which to judge efficacy. In the largest open trial reported so far, 20 patients with

Table 6
Profile of adverse events with VNS.

Side effect	Range
Hoarseness 54%–68% [Level 2]	Neck pain 13–21% [Level 2]
Cough 6–29% [Level 2]	Headache 4–22% [Level 2]
Dyspnoea 15–23% [Level 2]	Dysphagia 4–21% [Level 2]

Modified from O'Reardon et al. (2006).

treatment resistant MDD were followed for one year after surgery (Lozano et al., 2008). Six months post-surgery, 60% of patients met response criteria and 35% achieved remission. The improvements in depressive symptomatology remained stable for the remainder of the 12 month period, with 55% of patients (13/20) meeting criteria for response: results similar to those in the original report on 6 patients with TRD (Mayberg et al., 2005) and in a more recent report that noted a 50% response rate (Malone et al., 2009).

4.23. How effective is DBS as a relapse prevention therapy?

Patients who responded early to SCG DBS were more likely to maintain their response, although late responders (response after 6 months of DBS) were also observed. There are currently no relapse prevention studies, but anecdotal case reports suggest relapse when the device has been inadvertently switched off or the battery has failed, with a return to symptom improvement when the device is reactivated.

4.24. Which patients respond best to DBS?

To date, no demographic factors or illness characteristics have been identified to predict response to DBS. Larger sample sizes are required to establish definition of factors associated with antidepressant response with DBS.

4.25. What are the adverse effects associated with DBS?

Post-operative pain, or discomfort, intracranial or subcutaneous hemorrhage, and wound infection at the intracranial or subclavicular site, have been reported in some depressed patients who have received DBS (Lozano et al., 2008). Emergent symptoms of hypomania have been reported in a limited number of patients, including those with and without a history of bipolar disorder (Malone et al., 2009). Follow-up of 6 patients with neuropsychological testing revealed no evidence of cognitive impairment after 12 months of SCG DBS (McNeely et al., 2008) [Level 3]. Adverse events associated with DBS for PD, essential tremor and dystonia have been reported in a meta-analysis of ten years experience (Appleby et al., 2007). These authors conclude that the prevalence of depression was lower (2–4%) than in PD patients who have not received DBS, but that the rate of completed suicide appears to be elevated compared to both the general population and PD patients who did not received DBS (Appleby et al., 2007). While the adverse events reported in the small number of TRD patients compare favourably to those reported in the much larger sample included in this ten year meta-analysis among DBS-PD patients, and may be explained by the different anatomical sites for stimulation and the neurodegenerative nature of PD, caution is required at this early stage in the evaluation of DBS for TRD.

4.26. Should DBS be combined with other antidepressant treatments?

To date, the open-label studies of DBS for TRD have aimed to minimize concurrent changes to antidepressant medications. There is no published evidence on the relative effec-

tiveness of DBS with or without concurrent antidepressant medications. In the largest study of DBS for TRD to date, it was noted that one year post-DBS, antidepressant medications were either decreased in dose or discontinued in half of the patients (Lozano et al., 2008). Therefore, there is insufficient evidence to recommend DBS in the absence of concurrent antidepressant medication [Level 3].

7. Conclusion

There have been important advances in neuromodulation techniques since the previous CANMAT guideline publication for MDD in 2001. These changes reflect advances in theoretical models for depression, paired with emerging technologies to deliver continuous or intermittent electrical stimulation and experience from the application of these techniques in other disease states. At this stage, only ECT has a robust evidence base for its recommendation.

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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. V. Complementary and alternative medicine treatments

Arun V. Ravindran [a,*], Raymond W. Lam [b], Marie J. Filteau [c], François Lespérance [d], Sidney H. Kennedy [a], Sagar V. Parikh [a], Scott B. Patten [e]

[a] University of Toronto, Canada
[b] University of British Columbia, Canada
[c] Université Laval, Canada
[d] Université de Montréal, Canada
[e] University of Calgary, Canada

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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. There is widespread interest in complementary and alternative medicine (CAM) therapies in the treatment of major depressive disorder (MDD).
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 evidence and expert clinical support. This section on "Complementary and Alternative Medicine Treatments" is one of 5 guideline articles.
Results: There is Level 1 evidence to support light therapy in seasonal MDD and St. John's wort in mild to moderate MDD. There is also some evidence for the use of exercise, yoga and sleep deprivation, as well as for omega-3 fatty acids and SAM-e . Support for other natural health products and therapies is still limited.
Limitations: The evidence base remains limited and studies often have methodological problems, including small samples, variability in dose, short duration of treatment, unknown quality of the agent and limited long-term data. Safety data are also sparse with little information about drug interactions.
Conclusions: Some CAM treatments have evidence of benefit in MDD. However, problems with standardization and safety concerns may limit their applicability in clinical practice.

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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 et al., 2001).

A revision of these guidelines was undertaken by CANMAT in 2008–2009 to update the recommendations based on new evidence. The scope of this guideline encompasses the management of adults with unipolar major depressive disorder (MDD). Guidelines for bipolar depression are included in the CANMAT guidelines for bipolar disorder (Yatham et al., 2009).

Complementary and alternative medicine (CAM) treatments (such as light therapy, acupuncture, yoga, dietary and herbal supplements, etc.) are commonly used by people with depression and other psychiatric conditions, in part because of a

* Corresponding author.
E-mail address: arun_ravindran@camh.net (A.V. Ravindran).

prevalent belief that "natural is better" (Tindle et al., 2005). There are also intuitive reasons to support the use of light, sleep deprivation and exercise in the treatment of MDD. In a survey of primary care patients, about 11% of people with depression and anxiety reported using a CAM therapy (Roy-Byrne et al., 2005), which is similar to the proportion of people with MDD who use antidepressants (Mojtabai and Olfson, 2008). There is also a bias towards certain forms of CAM in different parts of the world, e.g., yoga in India, and St. John's wort in Germany and other parts of Europe. In this section, guidance is provided for the use of physical therapies and natural health products for MDD. As with all guidelines, recommendations must be customized within the context of an individual patient and should not be considered as standards of care.

Due to the large number of publications in this area, these guidelines are restricted to the more common and more evidence-based therapies. As such, certain other CAMs, including aromatherapy, qi gong and massage therapy, have not been reviewed.

Methods

The full methods have been described elsewhere (Kennedy et al., 2009) 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 reviews 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).

5.1. What are general caveats and limitations to the evaluation and clinical use of CAM treatments?

Because CAM therapies are not regulated like pharmaceuticals, the evidence supporting many of these therapies is often anecdotal. Nutraceuticals and herbal remedies (called dietary supplements in the U.S. and other countries) are regulated by Health Canada under the Natural Health Product Regulations, which stipulate a pre-market approval process that includes the review of evidence of both safety and efficacy, albeit with lower rigor for efficacy in conjunction with the claims. Licensed products are assigned a natural product number and only products with such a number are recommended for use.

There are an increasing number of randomized controlled trials (RCTs) for CAM treatments. The quality of many RCTs remains an issue, with variability in diagnostic criteria, small sample sizes, limitations of blinding and placebo controls, and few systematic evaluations of side effects. Even for those treatments with reasonable evidence of efficacy, there are variations and lack of standardization in dosage, potency, and concentration, all of which make it difficult for clinicians and patients to be confident they are using the same doses as described in clinical studies. There is, on balance, greater evidence and clinical experience with traditional treatments (pharmacotherapy and psychotherapy) and few studies directly compare these with novel treatments like neurostimulation or CAM.

Because of these issues, first-line psychotherapy (Parikh et al., 2009) or pharmacotherapy (Lam et al., 2009) recommendations should usually be considered before CAM treatment, especially as monotherapy. Adjunctive use of CAM therapies as an add-on treatment to evidence-based psychotherapy or pharmacotherapy can be considered, but clinicians must still be cautious because there is very little information about interactions of CAM therapies with medications.

Physical Therapies

5.2. What is light therapy? Is it effective in treating depression?

Light therapy consists of daily exposure to bright light, usually administered at home with a fluorescent light box. The standard "dose" of light is 10,000 lux (intensity) for 30 min per day given in the early morning. Response usually occurs within 1–3 weeks. Other light devices that have shown efficacy, in small studies, include those using light-emitting diodes (LEDs) (Desan et al., 2007; Glickman et al., 2006). The mechanism of action of light therapy is still under debate, with correction of disturbed circadian rhythms and modulation of serotonin and catecholamine systems being among the theories proposed (Sohn and Lam, 2005).

Table 1
Criteria for Levels of Evidence [a] and Lines of Treatment. [b]

Level of Evidence	Criteria
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	Criteria
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.
[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.

The previous Canadian guidelines noted the considerable RCT evidence for light therapy in the acute treatment of seasonal MDD (Kennedy et al., 2001). Subsequent systematic reviews and meta-analyses have confirmed the efficacy of bright light therapy versus credible placebo controls (Golden et al., 2005; Thompson, 2001). There are few studies comparing light therapy to antidepressants, but one RCT found comparable effectiveness between a standard course of light therapy and fluoxetine 20 mg (Lam et al., 2006). No studies have examined the combination of light therapy and antidepressants in the treatment of seasonal MDD. Similarly, there are few studies comparing light therapy to other non-drug treatments. One RCT found that cognitive behavioural therapy modified for seasonal MDD was as effective as bright light therapy or the combination treatment (Rohan et al., 2007). Although seasonal MDD, by definition, is a recurrent condition, there are few studies of maintenance or preventative treatment with light therapy.

Systematic reviews of light therapy for non-seasonal MDD have reported the efficacy of bright light against placebo conditions, but most studies had small numbers, inadequate control conditions and were short-term (2–5 weeks) (Even et al., 2008; Golden et al., 2005; Tuunainen et al., 2004). A recent RCT in patients with chronic non-seasonal MDD found that bright light and high-density negative ions as monotherapy were both superior to placebo low-density negative ions (Goel et al., 2005). Also in non-seasonal MDD, the combination of sertraline and bright light (10,000 lux × 60 min) was superior to sertraline and a dim light control over 5 weeks of treatment (Martiny et al., 2005).

The side effects of bright light therapy include headache, eye strain, nausea, and agitation, but these are generally mild and rarely lead to treatment discontinuation. Bright light exposure may trigger hypomanic or manic episodes, particularly in susceptible individuals such as those with bipolar disorder.

In summary, there is Level 1 evidence for the efficacy of light therapy in (Table 2) seasonal MDD, and as such it is recommended as a first-line treatment (Table 2). There is also Level 2 evidence for its use as an adjunctive treatment in mild to moderate non-seasonal MDD, and thus, is recommended as a second-line treatment (Table 2).

5.3. What efficacy has sleep deprivation shown in depression?

Sleep deprivation involves patients being kept awake for varying periods of time, ranging from total sleep deprivation (awake for up to 40 h) to partial sleep deprivation (3–4 h of sleep allowed per night) (Eichhammer et al., 2002; Giedke et al., 2003). Sleep deprivation results in rapid improvement in mood but its main limitation is that relapse usually occurs after a recovery sleep. The sequential use of total sleep deprivation may prevent this relapse. Each occasion of sleep deprivation followed by recovery sleep is termed a "cycle". Treatment is administered for 1–6 cycles over a period of up to 4 weeks (e.g. Caliyurt and Guducu, 2005; Reynolds et al., 2005). The therapeutic benefit of sleep deprivation is proposed to be mediated by its effects on hypothalamic–pituitary axis activity and on circadian rhythms (Parekh et al., 1998; Vgontzas et al., 1999).

The previous guidelines provided preliminary support for the benefit of sleep deprivation in depressive disorders (Kennedy et al., 2001). Subsequently, two open trials in MDD found the combination of sleep deprivation and medication

superior to either treatment alone (Caliyurt and Guducu, 2005; Wiegand et al., 2001). An RCT found sleep deprivation comparable to SSRIs or the combination (Reynolds et al., 2005), while another RCT found total sleep deprivation superior to partial sleep deprivation in drug-free patients (Giedke et al., 2003). Of comparisons to non-drug therapies, an RCT found CBT alone as effective as CBT combined with sleep deprivation in medication-free patients (Kundermann et al., 2008). Another RCT found sleep deprivation with exercise superior to sleep deprivation with light therapy or light therapy alone or exercise alone in drug-free patients (Putilov et al., 2005).

In seasonal MDD, one RCT found no difference between sleep deprivation alone and sleep deprivation combined with melatonin treatment (Danilenko and Putilov, 2005), while another RCT found that monotherapy with exercise or light therapy was superior to the combination with sleep deprivation (Putilov and Danilenko, 2005). In pregnancy-onset and postpartum MDD, monotherapy with sleep deprivation was beneficial in drug-free patients in a small RCT (Parry et al., 2000). A small sample RCT in a dysthymic population found sleep deprivation combined with exercise superior to sleep deprivation with light therapy or light therapy or exercise alone (Putilov et al., 2005).

There are no long-term reports on sleep deprivation as even partial sleep deprivation is difficult for patients to maintain for more than a few days. Safety data are also limited. Another drawback of this treatment is the occurrence of rebound depressive symptoms after cessation of treatment (Kennedy et al., 2001). Also, some reports indicate that the therapeutic effect is highest with the first cycle and tends to diminish with subsequent cycles, suggesting little benefit to extended application (Giedke et al., 2003). However, this was not substantiated by others (Caliyurt and Guducu, 2005; Kundermann et al., 2008).

In summary, there is Level 2 evidence for sleep deprivation as adjunctive treatment in the acute management of mild to moderate MDD, and some limited support for its use in seasonal, antepartum and postpartum MDD, (Table 2). However, it is recommended as third-line due to the practical difficulties associated with sustaining treatment.

5.4. What benefits does exercise have for depression?

In studies of exercise, control conditions have been difficult to establish due to the challenges of blinding. As a result, comparative studies tend to use medication/placebo, non-exercise, or varying frequencies and intensities of exercise as alternate conditions. In most studies, exercise has been administered for 8–20 weeks (average of 12 weeks), usually three times a week for 30–60 min per session. However, two studies did note significant improvement in depressive symptoms with as little as 7–10 days of daily exercise (Knubben et al., 2007; Pinchasov et al., 2000). Comparisons of high versus low frequency (e.g. Dunn et al., 2005; Legrand and Heuze, 2007) have had mixed results and a meta-analysis found no difference in benefit between high and low intensity exercise (Larun et al., 2006).

The previous guidelines (Kennedy et al., 2001) noted that a meta-analysis did not find clear evidence of benefit for exercise versus no treatment (Lawlor and Hopker, 2001). In two subsequent meta-analyses, one found exercise superior to no treatment and equivalent to psychological interventions in children and young adults (Larun et al., 2006), and the

other found psychological interventions superior, but exercise also effective (Pinquart et al., 2007). More recently, a large review concluded that methodological deficiencies in the majority of studies confined recommendation of exercise to an augmentation strategy only (Daley, 2008). Furthermore, a recent meta-analysis noted that when only well-designed studies were evaluated, exercise did not show any superiority over treatment as usual, no treatment or placebo (Mead et al., 2008).

Recent studies have evaluated exercise against medication. Two RCTs found no difference between exercise, SSRIs or placebo, suggesting that patient expectancy of improvement may play a significant role (Blumenthal et al., 2007; Brenes et al., 2007). The evidence for exercise in combination with antidepressant medication is more robust. Babyak et al. (2000) found medication, exercise and the combination equally effective. Two other RCTs and an open trial supported the superiority of the combination over medication alone even in severe or refractory cases (Knubben et al., 2007; Mather et al., 2002; Trivedi et al., 2006).

Long-term efficacy data for exercise are limited. Of the few studies involving follow-up, one found that the treatment gains associated with exercise persisted up to two years post-treatment (Singh et al., 2001) and another study noted superior maintenance of gains with exercise versus medication or combination six months post-treatment, with continued exercise predicting lower depression (Babyak et al., 2000). Prevention-wise, a 10-year cohort study noted that physical activity was associated with lower recurrence of depression and better tolerance of life stressors (Harris et al., 2006).

In summary, there is Level 2 evidence for the benefit of exercise as adjunct to medications in mild to moderate MDD, but not as monotherapy (Table 2).

5.5. What is yoga? Is it useful for depression?

Yoga is a discipline that integrates physical postures, breath control and meditation. The duration of yoga in most reports was between four to eight weeks, with an average frequency of four times a week for 45–60 min per session. Only one RCT offered yoga for a considerably longer period of 24 weeks (Krishnamurthy and Telles, 2007). There are no studies comparing types of yoga or the effect of the frequency or intensity of yoga.

A recent review noted the possible benefits of yoga as monotherapy for MDD, but methodological variations, including the forms of yoga used, study details reported and severity of illness, were limitations (Pilkington et al., 2005). Since then, two RCTs have found monotherapy with yoga significantly superior to no treatment in improving mild to moderate depressive symptoms in MDD (Krishnamurthy and Telles, 2007; Oretzky, 2007). However, few trials have compared yoga to pharmacotherapy and in the RCTs, the nature of the therapies prevented blinding, with resulting risk of bias. In the only comparative (unblinded) RCT available, Janakiramaiah et al. (2000) found yoga as effective as TCAs in severe MDD. Another RCT noted that augmentation of antidepressants with yoga significantly improved depressive symptoms over antidepressants alone (Sharma et al., 2005). Long-term data are limited; only one study reported a duration of treatment of longer than 5 weeks. In dysthymia, one RCT (Butler et al., 2008) and four open trials

(Janakiramaiah et al., 1998; Lavey et al., 2005; Naga Venkatesha Murthy et al., 1997, 1998) have found yoga useful as monotherapy or augmentation.

In summary, there is Level 2 evidence to support the use of yoga, but the quality of trials makes it difficult to interpret these results (Table 2). As with all group treatments, the non-specific benefits of group dynamics cannot be entirely separated from the benefits of yoga. Thus, yoga may be considered a second-line adjunctive treatment in mild to moderate MDD, if available.

5.6. How effective is acupuncture for depression?

Acupuncture requires special needles which are used to pierce the skin surface at specific body points in order to produce particular therapeutic effects. In most studies, the acupuncture performed was described according to the Standards for Reporting Interventions in Controlled Studies of Acupuncture (STRICTA) (MacPherson and Schroer, 2007). The usual duration of treatment was 4 to 8 weeks. The number of needles used (2 to 16) and number of acupuncture sessions varied between studies.

Research into the benefits of acupuncture for depression is limited. Systematic reviews highlight the difficulty in evaluating available results due to poor quality, small sample size, and unclear description of enrolment criteria, randomization or blinding, and forms of acupuncture used (Leo and Ligot, 2007; Mukaino et al., 2005; Smith and Hay, 2004). This review has only considered published literature in English, while acknowledging that there have been clinical trials conducted and published in China.

A recent meta-analysis found that acupuncture significantly improved depressive symptoms, but the difference was small in clinical terms and the studies analyzed had many methodological deficiencies, limiting the impact of their results (Wang et al., 2008). In individual trials, there have been mixed results when active acupuncture was compared to sham. One RCT found no difference (Allen et al., 2006) while another found active acupuncture superior (Quah-Smith et al., 2005). In the only RCT comparison against medication, there was no difference between active acupuncture, sham acupuncture and fluoxetine (Song et al., 2007).

Acupuncture is generally a well-tolerated intervention when performed by an adequately trained practitioner. Adverse effects include syncope and skin irritation, transient bleeding and bruising at needle insertion site.

In summary, the current evidence does not support the use of acupuncture for the management of MDD (Table 2).

Nutraceutical therapies

5.7. What are nutraceuticals?

Nutraceuticals are one class of natural health products available in Canada. They are non-prescription products that are usually concentrated forms of naturally occurring substances, such as vitamins and minerals. They are used alone or in combination to support good nutrition and general physical and mental well-being. Among those reviewed in this section, the following have been approved by Health Canada: omega-3 fatty acids, tryptophan, S-adenosyl-L-methionine (SAM-e), folic acid,

Table 2
Summary of recommendations for physical therapies.

Therapy	Indication	Evidence	Recommendation	Comment
Light	Seasonal (winter) MDD	Level 1	First-line	Monotherapy
	MDD (mild-moderate severity)	Level 2	Second-line	Adjunctive therapy
Sleep deprivation	MDD (mild-moderate severity)	Level 2	Third-line	Adjunctive therapy
	Seasonal (winter) MDD	Level 2	Third-line	Adjunctive therapy
	MDD in pregnancy or postpartum	Level 2	Third-line	Adjunctive therapy
Exercise	MDD (mild-moderate severity)	Level 2	Second-line	Adjunctive therapy
Yoga	MDD (mild-moderate severity)	Level 2	Second-line	Adjunctive therapy
Acupuncture	MDD	Insufficient evidence for recommendation		

Note: Much of the evidence for physical therapies is limited by small sample sizes, problems with blinding, and short durations. Unlike pharmaceutical agents or evidence-based psychotherapies, in most countries there is limited standardization of physical therapies and practices. Clinicians must be aware that techniques of practitioners may not reflect those used in clinical studies.

inositol, amino acids, and alpha-lactabumin (as an ingredient in approved compounds). Dehydroepiandrosterone (DHEA) and acetyl-L-carnitine are not currently licensed in Canada.

5.8. What are omega-3 fatty acids? How effective are they in treating depression?

Omega-3 fatty acids are polyunsaturated fatty acids integrated in multiple biological systems and considered essential nutrients for physical health. Their mechanisms of action are not yet understood. They have been studied in different doses and formulations in the treatment of depression. Formulations include highly purified estyl esters of eicosapentanoic acid (EPA) or docosahexaenoic acid (DHA) or a combination of both. In individual formulations, 1–2 g of EPA has been found to be effective (Nemets et al., 2002; Peet and Horrobin, 2002). In the combined formulation, results varied depending on the concentration of each component. While formulations with higher levels of EPA were superior to placebo, those with higher levels of DHA were not (Grenyer et al., 2007; Silvers et al., 2005; Su et al., 2003, 2008). Duration of treatment ranged from 4–16 weeks.

Three meta-analyses have been published on the use of omega-3 fatty acids in depression (Appleton et al., 2006; Freeman et al., 2006; Lin and Su, 2007). One reported negative results which, were attributed to heterogeneity of the included studies (Appleton et al., 2006), while the other two found significant benefit for omega-3 fatty acids in mood disorders as both monotherapy and augmentation to antidepressants, but included bipolar depression in their analyses (Freeman et al., 2006; Lin and Su, 2007). Subsequent studies have been published, with mixed results (Freeman et al., 2008; Jazayerim et al., 2008; Mischoulon et al., 2008; Rogers et al., 2008; Su et al., 2008).

The omega-3 supplements are usually well tolerated, with mild side effects, such as diarrhoea, nausea and a fishy aftertaste, which rarely cause discontinuation. Monitoring of increased bleeding tendencies among patients prescribed with the anticoagulant coumadin (warfarin) and anti-platelet medications (acetylsalicyclic acid, clopidogrel) has been suggested (Freeman et al., 2006). However, results from a very large RCT suggest that 1000 mg daily of omega-3 fatty acids may be cardioprotective (GISSI investigators, 1999). A few cases of drug-induced hypomania have been reported, although RCTs conducted in bipolar depression did not report increased risk of hypomanic switch (Osher et al., 2006; Parker et al., 2006).

In summary, there is Level 1 evidence from published studies for the efficacy of omega-3 fatty acids as an augmentation in mild to moderate MDD (Table 3). However, it is recommended as a second-line adjunctive treatment due to the lack of systematic use and lack of clinical support.

5.9. What is SAM-e? How effective is it for depression?

SAM-e is a synthetic form of a dietary amino acid. It is thought to function as a methyl donor in many biological processes involving neurotransmitters. In Europe, SAM-e is available as a prescription drug but in the US and Canada, oral dosage forms are licensed as over-the-counter natural health products, while injectable forms have to be approved under national drug regulations. Many studies used injectable (intravenous, intramuscular) formulations of SAM-e at doses of 200–400 mg. Oral preparations contain higher doses, ranging from 800 to 1600 mg/d, usually given in divided doses with meals. Length of treatment ranged from 2 to 8 weeks.

Since 2009, there have been 6 published systematic reviews of SAM-e (Echols et al, 2000; Fetrow and Avila, 2001; Hardy et al, 2003; Mischoulon and Fava, 2002; Papakostas et al, 2003; Williams et al., 2005); three of these also included results from previously published meta-analyses (Fetrow and Avila, 2001; Hardy et al., 2003; Williams et al., 2005). All concurred that for mild to moderate depression, SAM-e shows superior efficacy compared to placebo, and similar efficacy to tricyclic antidepressants (TCAs, usually imipramine). All the controlled trials of SAM-e are short-term (8 weeks or less), so there are no data on long-term use or for relapse prevention.

SAM-e is well tolerated with few adverse events, which include headaches, insomnia, jitteriness, and loose stools. Available information on drug interactions and safety suggests the risk of serotonin syndrome when it is added to first-line antidepressants, and induction of manic episodes in vulnerable patients (Natural Medicines, 2009b).

In summary, there is Level 1 evidence for SAM-e as monotherapy in mild to moderate MDD (Table 3). However, due to limited clinical support and lack of widespread clinical experience, it is recommended as a second-line treatment. There is no evidence for its use as an augmenting agent and its use as such should be considered carefully given the possibility of serotonin syndrome.

5.10. What is DHEA? Is it useful for depression?

DHEA (dehydroepiandrosterone) is a natural steroid produced by the adrenal glands, which is then converted into testosterone and estrogen in the body. It is frequently used as an anti-aging nutritional supplement, but with poorly established benefits in this area (Bhagra et al., 2008). In studies of depression, dosages of DHEA varied widely from 30 mg/day to 450 mg/day. Treatment duration was generally 6–8 weeks.

A recent small meta-analysis of antiglucocorticoids in depression found benefits in non-psychotic major depression, but not in psychotic depression (Gallagher et al., 2008). However, varying compounds were used in the studies, limiting generalizability. Also, only one study utilized DHEA (Wolkowitz et al., 1999).

In MDD, one RCT found DHEA monotherapy to be significantly superior to placebo (Schmidt et al, 2005) and another found it superior to placebo as both monotherapy and augmentation (Wolkowitz et al., 1999). A pilot RCT also found DHEA monotherapy more effective than placebo in dysthymia (Bloch et al., 1999). An RCT in subsyndromal depression in the medically ill also found DHEA monotherapy beneficial (Rabkin et al., 2006).

Since DHEA is a precursor of more potent sex hormones, side effects include acne and hirsutism, and some trials have excluded patients with symptomatic prostatism or family history of breast cancer (Bloch et al, 1999; Schmidt et al, 2005). Safety data suggests potential effects of DHEA on blood clotting and liver damage, induction of mania in vulnerable individuals, and increased risk of adverse effects at higher doses (Natural Medicines, 2009a; Natural Standard, 2009).

In summary, there is Level 2 evidence for the use of DHEA as monotherapy in mild to moderate MDD, and Level 3 for its benefit as an augmentation agent (Table 3). However, due to its adverse effects and the lack of clinical support, it is recommended as a third-line treatment.

5.11. What is tryptophan? Does it have benefits in depression?

Tryptophan is a dietary amino acid that is converted to 5-hydroxytryptophan (5-HTP) and then into serotonin (5-HT) centrally and peripherally (Shaw et al. 2002). It is a prescription drug in Canada, and recently was reintroduced in the US. Tryptophan has mostly been studied in the short-term (up to 12 weeks). The dose of tryptophan has tended to vary between 2 g to 4 g daily (Shaw et al., 2002; Turner et al., 2006).

In MDD, one early RCT found tryptophan monotherapy superior to placebo in severely depressed patients (Van Praag et al., 1972). However, most other studies have evaluated tryptophan as an augmenting agent. Early open trials reported benefits but RCTs have generally had negative results with tryptophan augmentation of SSRIs or TCAs (Levitan et al., 2000; Turner et al., 2006). In the only positive RCT (but with small sample size), Shaw et al. (2002) found amitriptyline, tryptophan, or tryptophan combined with amitriptyline, to be superior to placebo. The only long-term study included tryptophan as part of a combination of dietary supplements taken by the subjects for 5–8 years and did not find any benefit of the regimen (Hakkarainen et al., 2003).

Side effects reported with tryptophan include drowsiness, dry mouth, nausea, and other gastrointestinal symptoms, but not serotonin syndrome (Levitan et al., 2000; Shaw et al., 2002). Tryptophan ingestion was associated with an outbreak of Eosinophilia–Myalgia Syndrome in 1989, with significant mortality, but was attributed to a contaminated batch from a single manufacturer (Shaw et al., 2002).

In summary, there is insufficient evidence to confirm the benefits of tryptophan in depression (Table 3).

5.12. What other nutraceuticals have been evaluated in depression?

In MDD, a meta-analysis of two studies noted the efficacy of folic acid or folate, which is a form of Vitamin B9, as adjunctive treatment to antidepressants (Taylor et al., 2004a). However, it was unclear whether this benefit would be seen both in those with folate deficiency and those with normal folate levels. In a small RCT, an individualized amino acid mixture, as adjunct to mirtazapine, (Ille et al., 2007). Results for other nutraceuticals have been negative. Alpha-lactalbumin, a tryptophan-rich protein fraction, was no better than placebo in one RCT (Merens et al., 2005), and a meta-analysis found no clear benefit for inositol, a carbocylic polyol, as monotherapy or augmentation (Taylor et al., 2004b). In a large RCT involving patients with dysthymia, acetyl-L-carnitine (a form of the amino acid, L-carnitine) was found effective as monotherapy versus the atypical antipsychotic, amisulpiride (Zanardi and Smeraldi, 2006). The compounds were found to be safe and tolerable in these studies.

Table 3
Summary of recommendations for nutraceutical therapies.

Therapy	Indication	Evidence	Recommendation	Comment
Omega-3	MDD (mild to moderate severity)	Level 1	Second-line	Monotherapy and adjunctive therapy
SAM-e	MDD (mild-moderate severity)	Level 1	Second-line	Monotherapy
DHEA	MDD (mild to moderate severity)	Level 2	Third-line	Monotherapy
Tryptophan	MDD	Insufficient evidence for recommendation		
Folic acid	MDD (mild to moderate severity)	Level 2	Third-line	Adjunctive therapy

Note: Much of the evidence for CAM therapies is limited by small sample sizes, problems with blinding, and short durations. Unlike pharmaceutical agents, in most countries there is limited standardization of formulation and dose of nutraceutical and herbal preparations. Canada now has stricter quality standards than most countries because of the introduction of the Natural Health Product Regulations in 2004 (look for NPN — Natural Product Numbers — on bottles of approved products). Clinicians must be aware that labelled doses may not reflect those used in clinical studies and that there is very limited information on drug interactions with these preparations.

In summary, although there is Level 2 evidence for folic acid as augmentation in mild to moderate MDD, this comes from one small meta-analysis. Thus, it is listed as a third-line agent (Table 3). There is insufficient evidence to support the use of other nutriceuticals.

Herbal therapies

5.13. What are herbal remedies?

Herbal remedies are another sub-category of natural health products in Canada that are derived from plants and plant extracts, such as leaves, flowers, roots, bark and berries. They are regulated by Health Canada, though they are sold as non-prescription products. Among those reviewed in this section, St. John's wort, Crocus sativus, Lavandula angustifolia, Rhodiola rosea, Echium amoenum (as an ingredient in licensed compounds) and Gingko biloba, have been approved for use by Health Canada. The Japanese herbal compounds, Unkei-to, Rokumigan and Hachimijiogan, are not currently licensed in Canada.

5.14. What is St. John's wort and how is it used?

St. John's wort (*Hypericum Perforatum*) is a flowering plant and its extracts, which contain a number of components, including hypericin and hyperforin, are candidates for its active ingredient. In Germany, hypericum is available as a pharmaceutical formulation. Variations in formulations and dose ranges (generally 500 mg/day to 1800 mg/day) are noted in studies, with varying efficacy. St. John's wort has been studied mostly in the short-term (4–12 weeks). Its mechanism of action is unknown; serotonergic and dopaminergic effects have been proposed with no definitive conclusions.

5.15. How effective is St. John's wort in treating depression?

Early meta-analyses supported the superiority of St. John's wort over placebo and its equivalency to antidepressants in the short-term treatment of mild to moderate MDD (Gaster and Holroyd, 2000; Linde and Mulrow, 2000), but were criticized for methodological limitations in the included RCTs. A subsequent large placebo-controlled RCT that addressed these limitations found that St John's wort was no better than the placebo for the treatment of moderately severe MDD (Shelton et al., 2001). Since then, two meta-analyses showed that St. John's wort is superior to placebo and comparable to antidepressants (Kasper and Dienel, 2002; Whiskey et al., 2001), but two others reported minimal effects over placebo with decreasing effect size as sample sizes increased (Linde et al., 2005; Werneke et al., 2004). A more recent meta-analysis included many new large trials. This meta-analysis found that St. John's wort to be as effective as tri- or tetracyclic antidepressants and SSRIs in mild to moderate MDD (Linde et al., 2008). St. John's wort was also superior to placebo and more tolerable than the comparator medications. Of note, these results were particularly noticeable in the German literature, affecting generalizability. The overall data also suggest that the therapeutic benefit is much less evident in patients with more severe forms of depression.

Most studies evaluated the efficacy of St. John's wort in the short-term (4–12 weeks). Longer-term data are limited and have yielded inconsistent results, with three positive (Anghelescu et al., 2006; Brenner et al., 2002; Gastpar et al., 2005) and two negative RCTs (Gelenberg et al., 2004; Hypericum Depression Trial Study Group, 2002). On the other hand, the safety and tolerability data were consistent in all the studies, and a meta-analysis found St. John's wort almost as safe as the placebo (Trautmann-Sponsel and Dienel, 2004).

However, some cautions should be noted when considering the clinical use of this agent. In Canada, St. John's wort is regulated under the Natural Health Product Regulations which sets minimum quality standards. However, there is no regulation of dosage or quality for St. John's wort preparations in the US. Adverse effects include photosensitivity and drug interactions with immunoregulatory compounds, anticoagulants, anti-infective agents and oral contraceptives, attributed in part to its effect on cytochrome P450 enzymes (Golan et al., 2007). Serotonin syndrome, when it is added to antidepressants, and induction of hypomania have also been reported (Natural Medicines, 2009c). Therefore, combining St. John's wort with other medications, including antidepressants, should be done with caution.

In summary, there is Level 1 evidence to support the first-line use of St. John's wort as monotherapy in mild to moderate MDD (Table 4). In MDD of greater severity, St. John's wort has less evidence for efficacy but may be considered as second-line augmentation treatment (Table 4).

5.16. What other herbal remedies have been studied in depression? How effective are they?

Other herbal remedies studied in depression include Crocus sativus (saffron), Lavandula (lavender), Rhodiola rosea (roseroot), Echium amoenum (borage), Gingko biloba and different Japanese herbal formulations. Limited data restricts statements on standard dose regimens, though Crocus sativus was generally administered at 30 mg/day. Treatment was only studied in the short-term (4–8 weeks), with the exception of one cross-over study that lasted a year.

In MDD, Crocus sativus has been found to be significantly effective as monotherapy and as effective as SSRIs or TCAs in five RCTs from the same group of investigators (Akhondzadeh Basti et al., 2007; Akhondzadeh et al., 2004, 2005; Moshiri et al., 2006; Noorbala et al., 2005). Rhodiola rosea (1 medium-sized RCT) and Echium amoenum (1 small RCT) may also have benefits as monotherapy in MDD (Darbinyan et al., 2007; Sayyah et al., 2006). Small RCTs found augmentation of TCAs with Lavandula significantly superior to either treatment alone (Akhondzadeh et al., 2003), and augmentation of hormone replacement therapy with the Japanese herbal formula, Un-kei, effective for depression associated with menopause (Koike et al., 2004). Open trials have suggested benefits for Gingko biloba and the Japanese herbal formulations, Rokumigan and Hachimijiogan, as augmentation to antidepressants in MDD (Hemmeter et al., 2001; Yamada et al., 2005). As noted in a systematic review (Sarris, 2007), most of these RCTs had relatively small samples and there are no long-term efficacy and safety data.

In summary, although there is Level 2 evidence for Crocus sativus in mild to moderate MDD, given the lack of replications by other research centres and lack of documented clinical usage and support, it is suggested as a third-line agent (Table 4). There is insufficient evidence to recommend other herbal remedies.

Table 4
Summary of recommendations for herbal therapies.

Therapy	Indication	Evidence	Recommendation	Comment
St. John's wort	MDD (mild to moderate severity)	Level 1	First-line	Monotherapy
	MDD (moderate and higher severity)	Level 2	Second-line	Adjunctive therapy
Crocus Sativus	MDD (mild to moderate severity)	Level 2	Third-line	Monotherapy

Note: Much of the evidence for CAM therapies is limited by small sample sizes, problems with blinding, and short durations. Unlike pharmaceutical agents, in most countries there is limited standardization of formulation and dose of nutraceutical and herbal preparations. Canada now has stricter quality standards than most countries because of the introduction of the Natural Health Product Regulations in 2004 (look for NPN — Natural Product Numbers — on bottles of approved products). Clinicians must be aware that labelled doses may not reflect those used in clinical studies and that there is very limited information on drug interactions with these preparations.

Conclusions

Among the CAM therapies, the most robust evidence is for light therapy as monotherapy in seasonal MDD and for St. John's wort as monotherapy for mild to moderate MDD. There is reasonable evidence for the use of sleep deprivation, exercise, SAM-e and omega-3 fatty acids as adjunctive agents in the treatment of MDD. Some forms of physical, herbal and nutraceutical therapies have shown preliminary evidence of benefit in depressive disorders, but large, placebo-controlled RCTs of efficacy and safety are required to confirm these indications.

Several limitations to available results must be noted. Most studies involved patients with mild to moderate MDD, and treatment tended to be short-term. There are few RCTs and these often had methodological limitations, including variability in the dose and duration of treatment, as well as in the quality of the agents used. Further, little safety information is available, particularly on drug interactions. In addition, few studies have directly compared CAM therapies to pharmacotherapy or evidence-based psychotherapies. These limitations must be considered when contemplating clinical use of these therapies.

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