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Research report

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

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ABSTRACT

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

Introduction

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

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Pharmacotherapy remains the most studied and best evidenced treatment for MDD. Since 2000, at least 225 RCTs, 145 meta-analyses and 3 major systematic reports have been published on antidepressant medications for MDD. Despite this proliferation of data, it is widely recognized that the methodology of RCTs for antidepressants (including strict inclusion/exclusion criteria, intensive and frequent contact, short study duration, etc.), which are primarily conducted by pharmaceutical companies for registration of new medications, may not reflect real world clinical practice (Kennedy and Lam, 2001). While the past few years have also seen the emergence of larger scale effectiveness trials to address real-world generalizability, such as the U.S. Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush et al., 2004), these trials are still limited by many methodological deficiencies and some of the most important clinical questions remain unanswered. Hence, the recommendations are presented as guidance for clinicians who should consider them in the context of individual patients, and not as standards of care.

Methods

The full methods have been described elsewhere (Kennedy et al., 2009b) but, in summary, relevant English language studies published from January 1, 2000 to December 31, 2008 were identified using computerized searches of electronic databases (PubMed, PsychInfo, Cochrane Register of Clinical Trials), inspection of bibliographies, and review of other guidelines and major reports. The question–answer format of the previous guidelines has been retained based on feedback from clinicians. Recommendations include the Level of Evidence for each graded Line of Treatment, using specified criteria (Table 1). Note that this article does not provide comprehensive citations or references, but the evidence tables are posted on the CANMAT web site (www.canmat.org).

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

Differentiating and selecting antidepressants

3.1. What are the principles of pharmacotherapy management?

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

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

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

	Criteria
Level of Evidence	
1	• At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
2	• At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals.
3	• Non-randomized, controlled prospective studies *or* case series *or* high-quality retrospective studies.
4	• Expert opinion/consensus.
Line of treatment	
First-line	• Level 1 or Level 2 evidence, plus clinical support [c]
Second-line	• Level 3 evidence or higher, plus clinical support [c]
Third line	• Level 4 evidence or higher, plus clinical support [c]

[a] Levels of evidence do not assume positive or negative or equivocal results; they merely represent the quality and nature of the studies that have been conducted. Note that Levels 1 and 2 evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, hence the highest Level of Evidence is usually Level 3. Higher order recommendations (e.g., principles of care) reflect higher level judgment of the strength of evidence from various data sources, and therefore are primarily Level 4 evidence.

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

[c] Clinical support refers to application of expert opinion of the CANMAT committees to ensure that evidence-supported interventions are realistic and applicable for clinical practice, in order to enhance the utility of the guidance for clinicians. Therefore, treatments with higher Levels of Evidence may be downgraded to lower Lines of Treatment due to clinical issues such as side effect or safety profile.

Table 2
Principles of pharmacotherapy management.

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

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).

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.

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 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.

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

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

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.

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 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.

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 antidepressant 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 antidepressants, 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 venlafaxine. 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).

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

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 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).

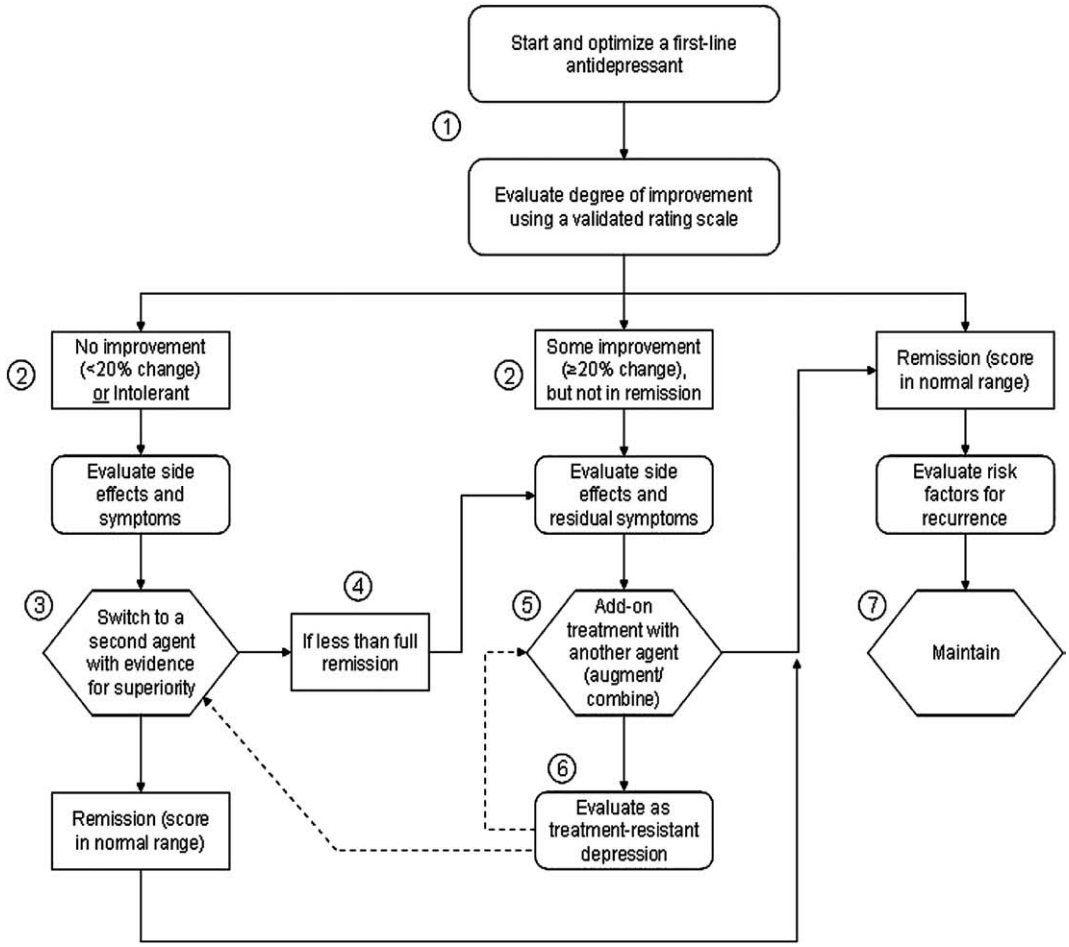

Fig. 1. Algorithm for managing limited improvement with a first-line antidepressant. 1) Initial improvement (defined as ≥20% reduction in symptom score) to a first-line antidepressant should be apparent within 1–4 weeks of achieving a therapeutic dose. If there is not at least an initial improvement 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 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.

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

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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References

Addis, A., Koren, G., 2000. Safety of fluoxetine during the first trimester of pregnancy: a meta-analytical review of epidemiological studies. Psychol. Med. 30, 89–94.

Alexopoulos, G.S., Canuso, C.M., Gharabawi, G.M., Bossie, C.A., Greenspan, A., Turkoz, I., Reynolds III, C., 2008. Placebo-controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression. Am. J. Geriatr. Psychiatry 16, 21–30.

Anderson, I.M., 2001. Meta-analytical studies on new antidepressants. Br. Med. Bull. 57, 161–178.

Anderson, I.M., Ferrier, I.N., Baldwin, R.C., Cowen, P.J., Howard, L., Lewis, G., Matthews, K., McAllister-Williams, R.H., Peveler, R.C., Scott, J., Tylee, A., 2008. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J. Psychopharmacol. 22, 343–396.

Andrade, S.E., McPhillips, H., Loren, D., Raebel, M.A., Lane, K., Livingston, J., Boudreau, D.M., Smith, D.H., Davis, R.L., Willy, M.E., Platt, R., 2009. Antidepressant medication use and risk of persistent pulmonary hypertension of the newborn. Pharmacoepidemiol. Drug Saf. 18, 246–252.

Appelberg, B.G., Syvalahti, E.K., Koskinen, T.E., Mehtonen, O.P., Muhonen, T.T., Naukkarinen, H.H., 2001. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. J. Clin. Psychiatry 62, 448–452.

Baldwin, D.S., Montgomery, S.A., Nil, R., Lader, M., 2007. Discontinuation symptoms in depression and anxiety disorders. Int. J. Neuropsychopharmacol. 10, 73–84.

Barbui, C., Esposito, E., Cipriani, A., 2009. Selective serotonin reuptake inhibitors and risk of suicide: a systematic review of observational studies. CMAJ 180, 291–297.

Bar-Oz, B., Einarson, T., Einarson, A., Boskovic, R., O'Brien, L., Malm, H., Berard, A., Koren, G., 2007. Paroxetine and congenital malformations: meta-analysis and consideration of potential confounding factors. Clin. Ther. 29, 918–926.

Bauer, M., Bschor, T., Kunz, D., Berghofer, A., Strohle, A., Muller-Oerlinghausen, B., 2000. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. Am. J. Psychiatry 157, 1429–1435.

Berle, J.O., Steen, V.M., Aamo, T.O., Breilid, H., Zahlsen, K., Spigset, O., 2004. Breastfeeding during maternal antidepressant treatment with serotonin reuptake inhibitors: infant exposure, clinical symptoms, and cytochrome p450 genotypes. J. Clin. Psychiatry 65, 1228–1234.

Berman, R.M., Marcus, R.N., Swanink, R., McQuade, R.D., Carson, W.H., Corey-Lisle, P.K., Khan, A., 2007. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 68, 843–853.

Bijl, M.J., Visser, L.E., Hofman, A., Vulto, A.G., van Gelder, T., Stricker, B.H., van Schaik, R.H., 2008. Influence of the CYP2D6*4 polymorphism on dose, switching and discontinuation of antidepressants. Br. J. Clin. Pharmacol. 65, 558–564.

Boyer, E.W., Shannon, M., 2005. The serotonin syndrome. N. Engl. J. Med. 352, 1112–1120.

Brambilla, P., Cipriani, A., Hotopf, M., Barbui, C., 2005. Side-effect profile of fluoxetine in comparison with other SSRIs, tricyclic and newer antidepressants: a meta-analysis of clinical trial data. Pharmacopsychiatry 38, 69–77.

Brent, D., Emslie, G., Clarke, G., Wagner, K.D., Asarnow, J.R., Keller, M., Vitiello, B., Ritz, L., Iyengar, S., Abebe, K., Birmaher, B., Ryan, N., Kennard, B., Hughes, C., Debar, L., McCracken, J., Strober, M., Suddath, R., Spirito, A., Leonard, H., Melhem, N., Porta, G., Onorato, M., Zelazny, J., 2008. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: the TORDIA randomized controlled trial. JAMA 299, 901–913.

Bridge, J.A., Axelson, D.A., 2008. The contribution of pharmacoepidemiology to the antidepressant-suicidality debate in children and adolescents. Int. Rev. Psychiatry 20, 209–214.

Bridge, J.A., Iyengar, S., Salary, C.B., Barbe, R.P., Birmaher, B., Pincus, H.A., Ren, L., Brent, D.A., 2007. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA 297, 1683–1696.

Candy, M., Jones, L., Williams, R., Tookman, A., King, M., 2008. Psychostimulants for depression. Cochrane Database Syst. Rev. 2, CD006722.

Carpenter, L.L., Yasmin, S., Price, L.H., 2002. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. Biol. Psychiatry 51, 183–188.

Caspi, A., Sugden, K., Moffitt, T.E., Taylor, A., Craig, I.W., Harrington, H., McClay, J., Mill, J., Martin, J., Braithwaite, A., Poulton, R., 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science 301, 386–389.

Chambers, C.D., Hernandez-Diaz, S., Van Marter, L.J., Werler, M.M., Louik, C., Jones, K.L., Mitchell, A.A., 2006. Selective serotonin-reuptake inhibitors and risk of persistent pulmonary hypertension of the newborn. N. Engl. J. Med. 354, 579–587.

Cipriani, A., Furukawa, T.A., Geddes, J.R., Malvini, L., Signoretti, A., McGuire, H., Churchill, R., Nakagawa, A., Barbui, C., MANGA Study Group, 2008. Does randomized evidence support sertraline as first-line antidepressant for adults with acute major depression? A systematic review and meta-analysis. J. Clin. Psychiatry 69, 1732–1742.

Cipriani, A., Furukawa, T.A., Salanti, G., Geddes, J.R., Higgins, J.P., Churchill, R., Watanabe, N., Nakagawa, A., Omori, I.M., McGuire, H., Tansella, M., Barbui, C., 2009. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 373, 746–758.

Cooper-Kazaz, R., Lerer, B., 2008. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. Int. J. Neuropsychopharmacol. 11, 685–699.

Crossley, N.A., Bauer, M., 2007. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J. Clin. Psychiatry 68, 935–940.

Cutler, A.J., Montgomery, S.A., Feifel, D., Lazarus, A., Astrom, M., Brecher, M., 2009. Extended release quetiapine fumerate monotherapy in major depressive disorder: a placebo- and duloxetine-controlled study. J. Clin. Psychiatry 70, 526–529.

Dannon, P.N., Lowengrub, K., Gonopolski, Y., Kotler, M., 2006. Current and emerging somatic treatment strategies in psychotic major depression. Expert. Rev. Neurother. 6, 73–80.

Datto, C., Lam, R.W., Lepola, U., et al., 2008. Double blind study of extended release quetiapine fumarate XR monotherapy for maintenance treatment of MDD (abstract). Program and abstracts of the American Psychiatric Association 161st Annual Meeting; May 3-8, 2008; Washington, DC, Abstract NR3-017.

de la Gandara, J., Aguera, L., Rojo, J.E., Ros, S., de Pedro, J.M., 2005. Use of antidepressant combinations: which, when and why? Results of a Spanish survey. Acta Psychiatr. Scand., Suppl. 428, 32–36.

Deshauer, D., 2007. Venlafaxine (Effexor): concerns about increased risk of fatal outcomes in overdose. CMAJ 176, 39–40.

Dodd, S., Horgan, D., Malhi, G.S., Berk, M., 2005. To combine or not to combine? A literature review of antidepressant combination therapy. J. Affect. Disord. 89, 1–11.

Dubicka, B., Hadley, S., Roberts, C., 2006. Suicidal behaviour in youths with depression treated with new-generation antidepressants: meta-analysis. Br. J. Psychiatry 189, 393–398.

Eberhard-Gran, M., Eskild, A., Opjordsmoen, S., 2006. Use of psychotropic medications in treating mood disorders during lactation: practical recommendations. CNS Drugs 20, 187–198.

Einarson, T.R., Einarson, A., 2005. Newer antidepressants in pregnancy and rates of major malformations: a meta-analysis of prospective comparative studies. Pharmacoepidemiol. Drug Saf. 14, 823–827.

Emslie, G., Kratochvil, C., Vitiello, B., Silva, S., Mayes, T., McNulty, S., Weller, E., Waslick, B., Casat, C., Walkup, J., Pathak, S., Rohde, P., Posner, K., March, J., 2006. Treatment for Adolescents with Depression Study (TADS): safety results. J. Am. Acad. Child Adolesc. Psych. 45, 1440–1455.

Entsuah, A.R., Huang, H., Thase, M.E., 2001. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitors, or placebo. J. Clin. Psychiatry 62, 869–877.

Ereshefsky, L., Jhee, S., Grothe, D., 2005. Antidepressant drug–drug interaction profile update. Drugs R & D 6, 323–336.

Fava, M., Alpert, J., Nierenberg, A., Lagomasino, I., Sonawalla, S., Tedlow, J., Worthington, J., Baer, L., Rosenbaum, J.F., 2002. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. J. Clin. Psychopharmacol. 22, 379–387.

Fava, M., McCall, W.V., Krystal, A., Wessel, T., Rubens, R., Caron, J., Amato, D., Roth, T., 2006. Eszopiclone co-administered with fluoxetine in patients with insomnia coexisting with major depressive disorder. Biol. Psychiatry 59, 1052–1060.

Fava, M., Thase, M.E., Debattista, C., Doghramji, K., Arora, S., Hughes, R.J., 2007. Modafinil augmentation of selective serotonin reuptake inhibitor therapy in MDD partial responders with persistent fatigue and sleepiness. Ann. Clin. Psychiatry 19, 153–159.

Ferreri, M., Lavergne, F., Berlin, I., Payan, C., Puech, A.J., 2001. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. Acta Psychiatr. Scand. 103, 66–72.

Friedman, R.A., Leon, A.C., 2007. Expanding the black box – depression, antidepressants, and the risk of suicide. N. Engl. J. Med. 356, 2343–2346.

Gartlehner, G., Hansen, R.A., Thieda, P., DeVeaugh-Geiss, A.M., Gaynes, B.N., Krebs, E.E., Lux, L.J., Morgan, L.C., Shumate, J.A., Monroe, L.G., Lohr, K.N., 2007. Comparative effectiveness of second-generation antidepressants in the pharmacologic treatment of adult depression. Agency for Healthcare Research and Quality, Rockville, MD.

Gartlehner, G., Thieda, P., Hansen, R.A., Gaynes, B.N., DeVeaugh-Geiss, A., Krebs, E.E., Lohr, K.N., 2008. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. Drug Safety 31, 851–865.

Geddes, J.R., Carney, S.M., Davies, C., Furukawa, T.A., Kupfer, D.J., Frank, E., Goodwin, G.M., 2003. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 361, 653–661.

Gibbons, R.D., Brown, C.H., Hur, K., Marcus, S.M., Bhaumik, D.K., Erkens, J.A., Herings, R.M., Mann, J.J., 2007. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am. J. Psychiatry 164, 1356–1363.

Goodyer, I., Dubicka, B., Wilkinson, P., Kelvin, R., Roberts, C., Byford, S., Breen, S., Ford, C., Barrett, B., Leech, A., Rothwell, J., White, L., Harrington, R., 2007. Selective serotonin reuptake inhibitors (SSRIs) and routine specialist care with and without cognitive behaviour therapy in adolescents with major depression: randomised controlled trial. BMJ 335, 142.

Grigoriadis, S., Konarski, J.Z., Kennedy, S.H., Mancini, D.A., McIntyre, R.S., 2007. Sex differences in antidepressant response in a Canadian primary-care sample. J. Clin. Psychopharmacol. 27, 95–98.

Gunnell, D., Saperia, J., Ashby, D., 2005. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 330, 385.

Hammad, T.A., Laughren, T., Racoosin, J., 2006a. Suicidality in pediatric patients treated with antidepressant drugs. Arch. Gen. Psychiatry 63, 332–339.

Hammad, T.A., Laughren, T.P., Racoosin, J.A., 2006b. Suicide rates in short-term randomized controlled trials of newer antidepressants. J. Clin. Psychopharmacol. 26, 203–207.

Hansen, R.A., Gartlehner, G., Lohr, K.N., Gaynes, B.N., Carey, T.S., 2005. Efficacy and safety of second-generation antidepressants in the treatment of major depressive disorder. Ann. Intern. Med. 143, 415–426.

Hansen, R., Gaynes, B., Thieda, P., Gartlehner, G., DeVeaugh-Geiss, A., Krebs, E., Lohr, K., 2008. Meta-analysis of major depressive disorder relapse and recurrence with second-generation antidepressants. Psychiatr. Serv. 59, 1121–1130.

Hazell, P., O'Connell, D., Heathcote, D., Robertson, J., Henry, D., 1995. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis [see comments]. BMJ 310, 897–901.

Heikkinen, T., Ekblad, U., Kero, P., Ekblad, S., Laine, K., 2002. Citalopram in pregnancy and lactation. Clin. Pharmacol. Ther. 72, 184–191.

Hemels, M.E., Einarson, A., Koren, G., Lanctot, K.L., Einarson, T.R., 2005. Antidepressant use during pregnancy and the rates of spontaneous abortions: a meta-analysis. Ann. Pharmacother. 39, 803–809.

Hendrick, V., Smith, L.M., Hwang, S., Altshuler, L.L., Haynes, D., 2003. Weight gain in breastfed infants of mothers taking antidepressant medications. J. Clin. Psychiatry 64, 410–412.

Hetrick, S., Merry, S., McKenzie, J., Sindahl, P., Proctor, M., 2007. Selective serotonin reuptake inhibitors (SSRIs) for depressive disorders in children and adolescents. Cochrane Database Syst. Rev. 3, CD004851.

Hodgkin, D., Volpe-Vartanian, J., Alegria, M., 2007. Discontinuation of antidepressant medication among Latinos in the USA. J Behav. Health Serv. Res. 34, 329–342.

Horgan, D., Dodd, S., Berk, M., 2007. A survey of combination antidepressant use in Australia. Australas. Psychiatry 15, 26–29.

Howland, R.H., John, R.A., Wisniewski, S.R., Trivedi, M.H., Warden, D., Fava, M., Davis, L.L., Balasubramani, G.K., McGrath, P.J., Berman, S.R., 2009. Concurrent anxiety and substance use disorders among outpatients with major depression: clinical features and effect on treatment outcome. Drug Alcohol Depend. 99, 248–260.

Kato, M., Fukuda, T., Serretti, A., Wakeno, M., Okugawa, G., Ikenaga, Y., Hosoi, Y., Takekita, Y., Mandelli, L., Azuma, J., Kinoshita, T., 2008. ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 398–404.

Katz, L.Y., Kozyrskyj, A.L., Prior, H.J., Enns, M.W., Cox, B.J., Sareen, J., 2008. Effect of regulatory warnings on antidepressant prescription rates, use of health services and outcomes among children, adolescents and young adults. CMAJ 178, 1005–1011.

Keller, M.B., Trivedi, M.H., Thase, M.E., Shelton, R.C., Kornstein, S.G., Nemeroff, C.B., Friedman, E.S., Gelenberg, A.J., Kocsis, J.H., Dunner, D.L., Hirschfeld, R.M., Rothschild, A.J., Ferguson, J.M., Schatzberg, A.F., Zajecka, J.M., Pedersen, R.D., Yan, B., Ahmed, S., Musgnung, J., Ninan, P.T., 2007. The prevention of recurrent episodes of depression with venlafaxine for two years (PREVENT) study: outcomes from the 2-year and combined maintenance phases. J. Clin. Psychiatry 68, 1246–1256.

Kennedy, S.H., Lam, R.W. (Eds.), 2001. Clinical guidelines for the treatment of depressive disorders: Can. J. Psychiatry, 46, pp. 1S–92S. Suppl 1.

Kennedy, S.H., Lam, R.W., Cohen, N.L., Ravindran, A.V., 2001b. Clinical guidelines for the treatment of depressive disorders. IV. Medications and other biological treatments. Can. J. Psychiatry 46, 38S–58S.

Kennedy, S.H., Lam, R.W., Nutt, D.J., Thase, M.E., 2007. Treating Depression Effectively, 2nd Edition. London, UK, Martin Dunitz.

Kennedy, S.H., Andersen, H.F., Thase, M.E., 2009a. Escitalopram in the treatment of major depressive disorder: a meta-analysis. Curr. Med. Res. Opin. 25, 161–175.

Kennedy, S.H., Lam, R.W., Parikh, S.V., Patten, S.B., Ravindran, A.V., 2009b. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the treatment of management of major depressive disorder in adults. J. Affect. Disord. 117, S1–S2.

Kennedy, S.H., Milev, R., Giacobbe, P., Ramasubbu, R., Lam, R.W., Parikh, S.V., Patten, S.B., Ravindran, A.V., 2009c. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. J. Affect. Disord. 117, S44–S53.

Khan, A., Brodhead, A.E., Schwartz, K.A., Kolts, R.L., Brown, W.A., 2005. Sex differences in antidepressant response in recent antidepressant clinical trials. J. Clin. Psychopharmacol. 25, 318–324.

Kornstein, S.G., Wohlreich, M.M., Mallinckrodt, C.H., Watkin, J.G., Stewart, D.E., 2006. Duloxetine efficacy for major depressive disorder in male vs. female patients: data from 7 randomized, double-blind, placebo-controlled trials. J. Clin. Psychiatry 67, 761–770.

Kurdyak, P.A., Juurlink, D.N., Mamdani, M.M., 2007. The effect of antidepressant warnings on prescribing trends in Ontario, Canada. Am. J. Public Health 97, 750–754.

Lam, R.W., Kennedy, S.H., 2004. Prescribing antidepressants for depression in 2005: recent concerns and recommendations. Can. J. Psychiatry 49, 1–6 Insert.

Lattimore, K.A., Donn, S.M., Kaciroti, N., Kemper, A.R., Neal Jr., C.R., Vazquez, D.M., 2005. Selective serotonin reuptake inhibitor (SSRI) use during pregnancy and effects on the fetus and newborn: a meta-analysis. J. Perinatol. 25, 595–604.

Libby, A.M., Brent, D.A., Morrato, E.H., Orton, H.D., Allen, R., Valuck, R.J., 2007. Decline in treatment of pediatric depression after FDA advisory on risk of suicidality with SSRIs. Am. J. Psychiatry 164, 884–891.

Licht, R.W., Qvitzau, S., 2002. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. Psychopharmacology (Berl) 161, 143–151.

Lieberman, J.A., Greenhouse, J., Hamer, R.M., Krishnan, K.R., Nemeroff, C.B., Sheehan, D.V., Thase, M.E., Keller, M.B., 2005. Comparing the effects of antidepressants: consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. Neuropsychopharmacology 30, 445–460.

Loke, Y.K., Trivedi, A.N., Singh, S., 2008. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. Aliment. Pharmacol. Ther. 27, 31–40.

Mago, R., Mahajan, R., Thase, M.E., 2008. Medically serious adverse effects of newer antidepressants. Curr. Psychiatry Rep. 10, 249–257.

Mahmoud, R.A., Pandina, G.J., Turkoz, I., Kosik-Gonzalez, C., Canuso, C.M., Kujawa, M.J., Gharabawi-Garibaldi, G.M., 2007. Risperidone for treatment-refractory major depressive disorder: a randomized trial. Ann. Intern. Med. 147, 593–602.

Marcus, R.N., McQuade, R.D., Carson, W.H., Hennicken, D., Fava, M., Simon, J.S., Trivedi, M.H., Thase, M.E., Berman, R.M., 2008. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. J. Clin. Psychopharmacol. 28, 156–165.

McGrath, P.J., Stewart, J.W., Fava, M., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Thase, M.E., Davis, L., Biggs, M.M., Shores-Wilson, K., Luther, J.F., Niederehe, G., Warden, D., Rush, A.J., 2006. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. Am. J. Psychiatry 163, 1531–1541.

McIntyre, R.S., Soczynska, J.K., Konarski, J.Z., Kennedy, S.H., 2006. The effect of antidepressants on lipid homeostasis: a cardiac safety concern? Expert Opin Drug Safety 5, 523–537.

McMahon, F.J., Buervenich, S., Charney, D., Lipsky, R., Rush, A.J., Wilson, A.F., Sorant, A.J., Papanicolaou, G.J., Laje, G., Fava, M., Trivedi, M.H., Wisniewski, S.R., Manji, H., 2006. Variation in the gene encoding the serotonin 2A receptor is associated with outcome of antidepressant treatment. Am. J. Hum. Genet. 78, 804–814.

Mischoulon, D., Nierenberg, A.A., Kizilbash, L., Rosenbaum, J.F., Fava, M., 2000. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. Can. J. Psychiatry 45, 476–481.

Misri, S., Reebye, P., Corral, M., Milis, L., 2004. The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. J. Clin. Psychiatry 65, 1236–1241.

Modell, J.G., Rosenthal, N.E., Harriett, A.E., Krishen, A., Asgharian, A., Foster, V.J., Metz, A., Rockett, C.B., Wightman, D.S., 2005. Seasonal affective disorder and its prevention by anticipatory treatment with bupropion XL. Biol. Psychiatry 58, 658–667.

Moller, H.J., 2006. Is there evidence for negative effects of antidepressants on suicidality in depressive patients? A systematic review. Eur. Arch. Psychiatry Clin. Neurosci. 256, 476–496.

Moller, H.J., Baldwin, D.S., Goodwin, G., Kasper, S., Okasha, A., Stein, D.J., Tandon, R., Versiani, M., 2008. Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: consensus statement. Eur. Arch. Psychiatry Clin. Neurosci. 258, 3–23.
Montgomery, S.A., 2005. Antidepressants and seizures: emphasis on newer agents and clinical implications. Int. J. Clin. Pract. 59, 1435–1440.
Montgomery, S.A., Baldwin, D.S., Blier, P., Fineberg, N.A., Kasper, S., Lader, M., Lam, R.W., Lepine, J.P., Moller, H.J., Nutt, D.J., Rouillon, F., Schatzberg, A.F., Thase, M.E., 2007. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int. Clin. Psychopharmacol. 22, 323–329.
Mosholder, A.D., Willy, M., 2006. Suicidal adverse events in pediatric randomized, controlled clinical trials of antidepressant drugs are associated with active drug treatment: a meta-analysis. J. Child Adolesc. Psychopharmacol. 16, 25–32.
Mulder, R.T., Watkins, W.G., Joyce, P.R., Luty, S.E., 2003. Age may affect response to antidepressants with serotonergic and noradrenergic actions. J. Affect. Disord. 76, 143–149.
Murray, M.L., Thompson, M., Santosh, P.J., Wong, I.C., 2005. Effects of the Committee on Safety of Medicines advice on antidepressant prescribing to children and adolescents in the UK. Drug Safety 28, 1151–1157.
National Institute for Clinical Excellence, 2004. Depression: management of depression in primary and secondary care. Clinical Guideline 23. London, NICE.
Nemeroff, C.B., Entsuah, R., Benattia, I., Demitrack, M., Sloan, D.M., Thase, M.E., 2008. Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol. Psychiatry 63, 424–434.
Nierenberg, A.A., Papakostas, G.I., Petersen, T., Montoya, H.D., Worthington, J.J., Tedlow, J., Alpert, J.E., Fava, M., 2003. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J. Clin. Psychopharmacol. 23, 92–95.
Nierenberg, A.A., Fava, M., Trivedi, M.H., Wisniewski, S.R., Thase, M.E., McGrath, P.J., Alpert, J.E., Warden, D., Luther, J.F., Niederehe, G., Lebowitz, B., Shores-Wilson, K., Rush, A.J., 2006. A comparison of lithium and T(3) augmentation following two failed medication treatments for depression: a STAR*D report. Am. J. Psychiatry 163, 1519–1530.
Nieuwstraten, C., Labiris, N.R., Holbrook, A., 2006. Systematic overview of drug interactions with antidepressant medications. Can. J. Psychiatry 51, 300–316.
O'Brien, L., Einarson, T.R., Sarkar, M., Einarson, A., Koren, G., 2008. Does paroxetine cause cardiac malformations? J. Obstet. Gynaecol. Can. 30, 696–701.
Olfson, M., Marcus, S.C., Tedeschi, M., Wan, G.J., 2006. Continuity of antidepressant treatment for adults with depression in the United States. Am. J. Psychiatry 163, 101–108.
Papakostas, G.I., Perlis, R.H., Scalia, M.J., Petersen, T.J., Fava, M., 2006. A meta-analysis of early sustained response rates between antidepressants and placebo for the treatment of major depressive disorder. J. Clin. Psychopharmacol. 26, 56–60.
Papakostas, G.I., Kornstein, S.G., Clayton, A.H., Soares, C.N., Hallett, L.A., Krishen, A., Tucker, V.L., 2007a. Relative antidepressant efficacy of bupropion and the selective serotonin reuptake inhibitors in major depressive disorder: gender-age interactions. Int. Clin. Psychopharmacol. 22, 226–229.
Papakostas, G.I., Perlis, R.H., Seifert, C., Fava, M., 2007b. Antidepressant dose reduction and the risk of relapse in major depressive disorder. Psychother. Psychosom. 76, 266–270.
Papakostas, G.I., Shelton, R.C., Smith, J., Fava, M., 2007c. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J. Clin. Psychiatry 68, 826–831.
Papakostas, G.I., Fava, M., Thase, M.E., 2008. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. Biol. Psychiatry 63, 699–704.
Parikh, S.V., Segal, Z.V., Grigoriadis, S., Ravindran, A.V., Kennedy, S.H., Lam, R.W., Patten, S.B., 2009. 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. J Affect Disord 117, S15–S25.
Patkar, A.A., Masand, P.S., Pae, C.U., Peindl, K., Hooper-Wood, C., Mannelli, P., Ciccone, P., 2006. A randomized, double-blind, placebo-controlled trial of augmentation with an extended release formulation of methylphenidate in outpatients with treatment-resistant depression. J. Clin. Psychopharmacol. 26, 653–656.
Patten, S.P., Kennedy, S.H., Lam, R.W., O'Donovan, C., Filteau, M.J., Parikh, S.V., Ravindran, A.V., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) clinical guidelines for the treatment of management of major depressive disorder in adults. I. Classification, burden and principles of management. J. Affect. Disord. 117, S5–S14.
Perry, E.B., Berman, R.M., Sanacora, G., Anand, A., Lynch-Colonese, K., Charney, D.S., 2004. Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. J. Clin. Psychiatry 65, 238–243.
Posternak, M.A., Zimmerman, M., 2005. Is there a delay in the antidepressant effect? A meta-analysis. J. Clin. Psychiatry 66, 148–158.
Preskorn, S.H., Borges-Gonzalez, S., Flockhart, D., 2006. Clinically relevant pharmacology of neuropsychiatric drugs approved over the last three years: Part II. J. Psychiatr. Pract. 12, 312–316.
Rahimi, R., Nikfar, S., Abdollahi, M., 2006. Pregnancy outcomes following exposure to serotonin reuptake inhibitors: a meta-analysis of clinical trials. Reprod. Toxicol. 22, 571–575.
Rapaport, M.H., Gharabawi, G.M., Canuso, C.M., Mahmoud, R.A., Keller, M.B., Bossie, C.A., Turkoz, I., Lasser, R.A., Loescher, A., Bouhours, P., Dunbar, F., Nemeroff, C.B., 2006. Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 31, 2505–2513.
Ravindran, A.V., Kennedy, S.H., O'Donovan, M.C., Fallu, A., Camacho, F., Binder, C.E., 2008. Osmotic-release oral system methylphenidate augmentation of antidepressant monotherapy in major depressive disorder: results of a double-blind, randomized, placebo-controlled trial. J. Clin. Psychiatry 69, 87–94.
Reynolds III, C.F., Dew, M.A., Pollock, B.G., Mulsant, B.H., Frank, E., Miller, M.D., Houck, P.R., Mazumdar, S., Butters, M.A., Stack, J.A., Schlernitzauer, M.A., Whyte, E.M., Gildengers, A., Karp, J., Lenze, E., Szanto, K., Bensasi, S., Kupfer, D.J., 2006. Maintenance treatment of major depression in old age. N. Engl. J. Med. 354, 1130–1138.
Ruhe, H.G., Huyser, J., Swinkels, J.A., Schene, A.H., 2006. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. J. Clin. Psychiatry 67, 1836–1855.
Rush, A.J., Fava, M., Wisniewski, S.R., Lavori, P.W., Trivedi, M.H., Sackeim, H.A., Thase, M.E., Nierenberg, A.A., Quitkin, F.M., Kashner, T.M., Kupfer, D.J., Rosenbaum, J.F., Alpert, J., Stewart, J.W., McGrath, P.J., Biggs, M.M., Shores-Wilson, K., Lebowitz, B.D., Ritz, L., Niederehe, G., 2004. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. Control. Clin. Trials 25, 119–142.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Stewart, J.W., Nierenberg, A.A., Thase, M.E., Ritz, L., Biggs, M.M., Warden, D., Luther, J.F., Shores-Wilson, K., Niederehe, G., Fava, M., 2006. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. N. Engl. J. Med. 354, 1231–1242.
Sartorius, N., Baghai, T.C., Baldwin, D.S., Barrett, B., Brand, U., Fleischhacker, W., Goodwin, G., Grunze, H., Knapp, M., Leonard, B.E., Lieberman, J., Nakane, Y., Pinder, R.M., Schatzberg, A.F., Svestka, J., Baumann, P., Ghalib, K., Markowitz, J.C., Padberg, F., Fink, M., Furukawa, T., Fountoulakis, K.N., Jensen, P., Kanba, S., Riecher-Rossler, A., 2007. Antidepressant medications and other treatments of depressive disorders: a CINP Task Force report based on a review of evidence. Int. J. Neuropsychopharmacol. 10, S1–207.
Schatzberg, A.F., Blier, P., Delgado, P.L., Fava, M., Haddad, P.M., Shelton, R.C., 2006. Antidepressant discontinuation syndrome: consensus panel recommendations for clinical management and additional research. J. Clin. Psychiatry 67, 27–30.
Serretti, A., Kato, M., De Ronchi, D., Kinoshita, T., 2007. Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol. Psychiatry 12, 247–257.
Sola, C.L., Bostwick, J.M., Hart, D.A., Lineberry, T.W., 2006. Anticipating potential linezolid–SSRI interactions in the general hospital setting: an MAOI in disguise. Mayo Clin. Proc. 81, 330–334.
Takkouche, B., Montes-Martinez, A., Gill, S.S., Etminan, M., 2007. Psychotropic medications and the risk of fracture: a meta-analysis. Drug Safety 30, 171–184.
Taylor, M.J., Rudkin, L., Hawton, K., 2005. Strategies for managing antidepressant-induced sexual dysfunction: systematic review of randomised controlled trials. J. Affect. Disord. 88, 241–254.
Taylor, M.J., Freemantle, N., Geddes, J.R., Bhagwagar, Z., 2006. Early onset of selective serotonin reuptake inhibitor antidepressant action: systematic review and meta-analysis. Arch. Gen. Psychiatry 63, 1217–1223.
Thakur, M., Grossman, I., McCrory, D.C., Orlando, L.A., Steffens, D.C., Cline, K.E., Gray, R.N., Farmer, J., DeJesus, G., O'Brien, C., Samsa, G., Goldstein, D.B., Matchar, D.B., 2007. Review of evidence for genetic testing for CYP450 polymorphisms in management of patients with nonpsychotic depression with selective serotonin reuptake inhibitors. Genet. Med. 9, 826–835.
Thase, M.E., Corya, S.A., Osuntokun, O., Case, M., Henley, D.B., Sanger, T.M., Watson, S.B., Dube, S., 2007. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. J. Clin. Psychiatry 68, 224–236.
Trivedi, M.H., Fava, M., Wisniewski, S.R., Thase, M.E., Quitkin, F., Warden, D., Ritz, L., Nierenberg, A.A., Lebowitz, B.D., Biggs, M.M., Luther, J.F., Shores-Wilson, K., Rush, A.J., 2006a. Medication augmentation after the failure of SSRIs for depression. N. Engl. J. Med. 354, 1243–1252.

Trivedi, M.H., Rush, A.J., Wisniewski, S.R., Nierenberg, A.A., Warden, D., Ritz, L., Norquist, G., Howland, R.H., Lebowitz, B., McGrath, P.J., Shores-Wilson, K., Biggs, M.M., Balasubramani, G.K., Fava, M., 2006b. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am. J. Psychiatry 163, 28–40.

Trivedi, M.H., Rush, A.J., Gaynes, B.N., Stewart, J.W., Wisniewski, S.R., Warden, D., Ritz, L., Luther, J.F., Stegman, D., DeVeaugh-Geiss, J., Howland, R., 2007. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR(*)D measurement-based care. Neuropsychopharmacology 32, 2479–2489.

Tsapakis, E.M., Soldani, F., Tondo, L., Baldessarini, R.J., 2008. Efficacy of antidepressants in juvenile depression: meta-analysis. Br. J. Psychiatry 193, 10–17.

Usala, T., Clavenna, A., Zuddas, A., Bonati, M., 2008. Randomised controlled trials of selective serotonin reuptake inhibitors in treating depression in children and adolescents: a systematic review and meta-analysis. Eur. Neuropsychopharmacol. 18, 62–73.

Wade, A., Friis, A.H., 2006. The onset of effect for escitalopram and its relevance for the clinical management of depression. Curr. Med. Res. Opin. 22, 2101–2110.

Wallace, A.E., Neily, J., Weeks, W.B., Friedman, M.J., 2006. A cumulative meta-analysis of selective serotonin reuptake inhibitors in pediatric depression: did unpublished studies influence the efficacy/safety debate? J. Child Adolesc. Psychopharmacol. 16, 37–58.

Weiss, J., Dormann, S.M., Martin-Facklam, M., Kerpen, C.J., Ketabi-Kiyanvash, N., Haefeli, W.E., 2003. Inhibition of P-glycoprotein by newer antidepressants. J. Pharmacol. Exp. Ther. 305, 197–204.

Weissman, A.M., Levy, B.T., Hartz, A.J., Bentler, S., Donohue, M., Ellingrod, V.L., Wisner, K.L., 2004. Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. Am. J. Psychiatry 161, 1066–1078.

Wheeler, B.W., Gunnell, D., Metcalfe, C., Stephens, P., Martin, R.M., 2008. The population impact on incidence of suicide and non-fatal self harm of regulatory action against the use of selective serotonin reuptake inhibitors in under 18s in the United Kingdom: ecological study. BMJ 336, 542–545.

Wijkstra, J., Lijmer, J., Balk, F.J., Geddes, J.R., Nolen, W.A., 2006. Pharmacological treatment for unipolar psychotic depression: systematic review and meta-analysis. Br. J. Psychiatry 188, 410–415.

Wisner, K.L., Perel, J.M., Peindl, K.S., Hanusa, B.H., Findling, R.L., Rapport, D., 2001. Prevention of recurrent postpartum depression: a randomized clinical trial. J. Clin. Psychiatry 62, 82–86.

Wisner, K.L., Perel, J.M., Peindl, K.S., Hanusa, B.H., Piontek, C.M., Findling, R.L., 2004. Prevention of postpartum depression: a pilot randomized clinical trial. Am. J. Psychiatry 161, 1290–1292.

Wisner, K.L., Hanusa, B.H., Perel, J.M., Peindl, K.S., Piontek, C.M., Sit, D.K., Findling, R.L., Moses-Kolko, E.L., 2006. Postpartum depression: a randomized trial of sertraline versus nortriptyline. J. Clin. Psychopharmacol. 26, 353–360.

Yatham, L.N., Kennedy, S.H., Schaffer, A., Parikh, S.V., Beaulieu, S., O'Donovan, C., MacQueen, G.M., McIntyre, R.S., Sharma, V., Ravindran, A., Young, L.T., Young, A.H., Alda, M., Milev, R., Vieta, E., Calabrese, J.R., Berk, M., Ha, K., Kapczinski, F., 2009. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: Update 2009. Bipolar Disord. 11, 225–255.

Yonkers, K.A., Lin, H., Howell, H.B., Heath, A.C., Cohen, L.S., 2008. Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. J. Clin. Psychiatry 69, 659–665.

Young, E.A., Kornstein, S.G., Marcus, S.M., Harvey, A.T., Warden, D., Wisniewski, S.R., Balasubramani, G.K., Fava, M., Trivedi, M.H., John, R.A., 2008. Sex differences in response to citalopram: a STAR *D report. J. Psychiatr., Res.