Individualized antidepressant therapy in patients with major depressive disorder

Novel evidence-informed decision support tool

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Abstract

Objective To introduce a visual clinical decision support tool to assist with individualizing first-line antidepressant pharmacotherapy for adults with major depressive disorder (MDD) in a Canadian context.

Sources of information A literature review was conducted with Google Scholar, PubMed, the Cochrane Database of Systematic Reviews, and Trip Pro using the MeSH headings *depression*, *antidepressive agents*, *primary care*, *practice patterns*, *medication adherence*, and *decision making*, *shared*.

Main message Major depressive disorder affects about 4.7% of Canadians annually and is a prevalent condition encountered and diagnosed in primary care. Untreated depression is associated with decreased quality of life, increased risk of suicide, and worsening physical health outcomes when depression co-occurs with other chronic medical conditions. In a network meta-analysis, antidepressant medications (such as selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, bupropion, and vortioxetine) reduced depressive symptoms by 50% or more when compared with placebo in acute treatment of adults with moderate to severe MDD. Poor treatment adherence and high discontinuation rates limit MDD treatment success. Factors such as strong therapeutic alliances between patients and prescribers, collaborative care, patient education, and supportive self-management have been shown to enhance treatment adherence. The most recent Canadian Network for Mood and Anxiety Treatments depression treatment guidelines (published in 2016) suggest 15 different first-line antidepressant medication options for the treatment of MDD. There is a need for evidence-informed decision support aids to individualize antidepressant therapy to treat patients diagnosed with MDD.

Conclusion Recent studies on antidepressants have indicated no single antidepressant is superior to others in treating patients with MDD. This suggests there may be opportunities to enhance treatment adherence and success by tailoring antidepressant therapy to align with each patient's preferences. The Antidepressant Decision Support Tool was developed to help prescribers and adult patients engage in shared decision making to select an individualized and optimal first-line antidepressant for the treatment of acute MDD.

Major depressive disorder (MDD) affects about 1.5 million (4.7%) Canadians annually.[1] The Global Burden of Diseases, Injuries, and Risk Factors Study ranked depressive disorders as the most prevalent mental disorder causing disability, 13th overall in leading specific causes of global disability-adjusted life-years and second in specific noncommunicable causes of years living in disability.[2] Untreated depression is associated

Editor's key points

- While depression is a prevalent condition seen in primary care, primary care providers have limited guidance in tailoring depression therapy to patients.
- Antidepressive agents (eg, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, bupropion, vortioxetine) are effective in substantially reducing symptoms for select patients experiencing moderate to severe depression. Earlier treatment of major depressive disorder is associated with better outcomes.
- A clinical decision support tool for individualizing first-line antidepressants may be useful in primary care practices to help prescribers and patients collaborate in depression treatment.

with decreased quality of life,[3] increased risk of suicide,[4] and worsening physical health outcomes when depression co-occurs with chronic medical conditions.[5] Major depressive disorder is also associated with major productivity losses as a result of absenteeism and presenteeism.[1] Early intervention demonstrates improved treatment response and remission and better long-term outcomes in replicable prospective and retrospective studies.[6,7] In adults with moderate to severe MDD, antidepressants reduce greater than 50% of depressive symptoms (number needed to treat=4 to 7) when compared with placebo in acute treatment.[8] Antidepressant therapy also reduces relapse (by approximately 20%, number needed to treat=6) in those who have achieved remission for up to 1 year when compared with placebo.[9] Previous studies have shown that only a fraction of patients receive guideline-congruent treatment.[6] Poor treatment adherence and high discontinuation rates also limit success of MDD treatment.[1] Strong therapeutic alliances between patients and prescribers, collaborative care, patient education, and supportive self-management have been shown to enhance treatment adherence.[1]

Depression is a prevalent condition seen in primary care.[10] Quality-of-care studies for depression treatment at 65 Canadian primary care clinics found 52.1% of adult patients who met the criteria for a major depressive episode received minimally adequate treatment for depression based on quality indicators established from Canadian clinical practice guidelines and previous studies.[11] Clinics where most GPs were using treatment algorithms with individuals diagnosed with anxiety or depressive disorders had a greater association with providing adequate treatment of MDD than clinics that did not use treatment algorithms (odds ratio=1.46, 95% CI 1.06 to 2.02).[11] This article aims to provide primary care prescribers with a systematic and efficient clinical decision support tool to help individualize pharmacotherapy for depression.

Case descriptions

Case 1. J.M. is a 59-year-old man seen at your multidisciplinary primary care clinic. J.M. has been newly diagnosed with moderately severe MDD. He is interested in a trial of an antidepressant. J.M. has a history of hypertension, type 2 diabetes mellitus, dyslipidemia, peripheral neuropathy, and obesity. How would you determine the appropriate antidepressant to initiate for J.M.?

Case 2. C.P. is a healthy 32-year-old woman who has just been diagnosed with MDD. You believe that C.P. would benefit from an antidepressant, but C.P. seems unsure. C.P. shares that she has been having troubles with her libido. How would you decide which antidepressant would be most appropriate for C.P.?

Sources of information

A literature review was conducted using Google Scholar, PubMed, the Cochrane Database of Systematic Reviews, and Trip Pro using the following MeSH headings: *depression*, *antidepressive agents*, *primary care*, *practice patterns*, *medication adherence*, and *decision making*, *shared*. Abstracts of all papers were retrieved and those related to the management of depression in primary care, shared decision making in depression, or antidepressant prescribing patterns in primary care were included in this review. Relevant consensus guidelines or practice statements from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and the Canadian Task Force on Preventive Health Care (CTFPHC) were included. Relevant topics in tertiary databases, such as UpToDate, were retrieved and critiqued, and relevant citations were included in this clinical review.

Main message

Screening. The CTFPHC does not recommend routinely screening for depression in adults who present at primary care settings with no apparent symptoms of depression (weak recommendation).[12] The CTFPHC guideline does suggest that screening may be appropriate if patients present with signs or symptoms of depression or verbalize symptoms of depression.[12] This CTFPHC guideline does not apply to people with known depression, with a history of depression, or who are receiving treatment for depression.[12]

In a meta-analysis of screening instruments in primary care, the median sensitivity and specificity of instruments were 85% and 74%, respectively, with no significant differences in performance between instruments.[13] The Patient Health Questionnaire–9 (**Table 1**)[14] is the most commonly used tool for screening for depression in primary care and has been shown to have sensitivity and specificity for depression screening comparable to semistructured interviews in a variety of age ranges and cultures.[15,16] The Patient Health Questionnaire–9 has also been useful for monitoring patient response to treatment.[16,17]

Assessment. Diagnosis of MDD is established once a patient meets the criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (*DSM-5*; **Box 1**).[18] The *DSM-5* was introduced in 2013 without changing the MDD core symptoms and duration from the *DSM* 4th edition, text revision (*DSM-IV-TR*).[1,18] Notable changes in the *DSM-5* include removing the *bereavement exclusion* from the *DSM-IV-TR*, adding *persistent depressive disorder* as a new classification of chronic depression (formerly known as *chronic major depressive episode* and *dysthymic disorder* in the *DSM-IV-TR*), and adding 2 new depressive disorders: *disruptive mood dysregulation disorder* and *premenstrual dysphoric disorder*.[1,18]

Table 1. Patient Health Questionnaire–9 (PHQ-9)

OVER THE LAST 2 WEEKS, HOW OFTEN HAVE YOU BEEN BOTHERED BY ANY OF THE FOLLOWING PROBLEMS?	NOT AT ALL	SEVERAL DAYS	MORE THAN HALF THE DAYS	NEARLY EVERY DAY
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3
Total score =		+	+	+
Score interpretation: 5 to 9 = mild, 10 to 14 = moderate, 15 to 19 = moderately severe, 20 to 27 = severe				
If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult

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Management. Options for depression management include pharmacologic therapy, psychotherapy, neurostimulatory therapy, lifestyle modifications, complementary or alternative therapies, or a combination of various therapies.[1] This review focuses solely on pharmacologic therapy. The most recent CANMAT guidelines on MDD (published in 2016) recommend 15 different antidepressants as possible first-line therapy (**Table 2**).[19] A 2018 systematic review and network meta-analysis did not demonstrate statistically significant superiority of any particular first-line antidepressant.[8] The CANMAT depression guidelines provide a list of patient and medication factors to consider when selecting from the many antidepressant drugs recommended for MDD treatment.[19] Patient factors include clinical features and dimensions, comorbid conditions, response and side effects during previous use of antidepressants, and patient preference. Medication factors to consider include comparative efficacy, comparative tolerability, potential drug interactions, simplicity of use, cost, and availability.[19] There are limited tools and support available to help primary care prescribers tailor antidepressants based on medication and patient factors.[20]

Our proposed Antidepressant Decision Support Tool (**Figures 1A** and **1B**; references are provided in Appendix 1, available from **CFPlus***) was developed to assist prescribers and adult patients in selecting an individualized and optimal first-line antidepressant medication for acute MDD treatment. Once a patient is diagnosed with MDD and pharmacologic therapy is part of the elected treatment modality, prescribers can use the Antidepressant Decision Support Tool to select an antidepressant with their patient. The tool's algorithm starts in the top left-hand corner of **Figure 1A**. The prescriber determines whether the patient has any MDD specifiers as defined by the *DSM-5*.[18] If the patient is diagnosed with a MDD specifier, stage 1 of the tool guides the prescriber to a horizontal box labeled *Depression specifiers* at the top of **Figure 1A**. The *Depression specifiers* box contains summarized antidepressant recommendations from the most recent CANMAT guidelines for treatment of the respective MDD specifier. If the patient is not diagnosed with an MDD specifier, the Antidepressant Decision Support Tool stage 1 guides the prescriber to the box labeled *No depression specifiers*. On the left-hand side of **Figure 1A** in the *No depression specifiers* box, the tool starts with consideration of the patient's comorbidities; if the patient has no comorbidities, any first-line agent may be selected and prescribers can move to stage 2 (**Figure 1B**) of the Antidepressant Decision Support Tool to narrow down antidepressant choices. For patients with comorbidities, considerations are organized according to the affected system of the body. Antidepressants with published evidence supporting their use in association with a particular comorbidity are summarized in the *No depression specifiers* box (**Figure 1A**).

*__Appendix 1__ is available from **https://www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Box 1. Criteria for diagnosing major depressive disorder from the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning, and at least 1 of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

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

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Note: Criteria A to C represent a major depressive episode.
Note: Responses to a significant loss (eg, bereavement, financial ruin, losses from a natural disaster, a serious medical illness or disability) may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss noted in Criterion A, which may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered. This decision inevitably requires the exercise of clinical judgment based on the individual's history and the cultural norms for the expression of distress in the context of loss.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode. **Note:** This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

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Table 2. CANMAT depression guidelines: *Recommendations for first-line (level 1 evidence) antidepressants. Level 1 evidence includes meta-analysis with narrow confidence intervals or 2 or more randomized placebo-controlled trials with adequate sample size available to support use in depression treatment.*

CLASS	AGENT	DAILY DOSE
SSRI	Citalopram	20-40 mg
	Escitalopram	10-20 mg
	Fluoxetine	20-60 mg
	Fluvoxamine	100-300 mg
	Paroxetine	IR: 20-50 mg CR: 25-62.5 mg
	Sertraline	50-200 mg
SNRI	Desvenlafaxine	50-100 mg
	Duloxetine	60 mg
	Venlafaxine	75-225 mg
NDRI	Bupropion	150-300 mg
Other	Mirtazapine	15-45 mg
	Vortioxetine	10-20 mg
Not available in Canada	Agomelatine	25-50 mg
	Mianserin	60-120 mg
	Milnacipran	100 mg

CANMAT—Canadian Network for Mood and Anxiety Treatments, CR—controlled release, IR—immediate release, NDRI—norepinephrine-dopamine reuptake inhibitor, SNRI—serotonin-norepinephrine reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor.
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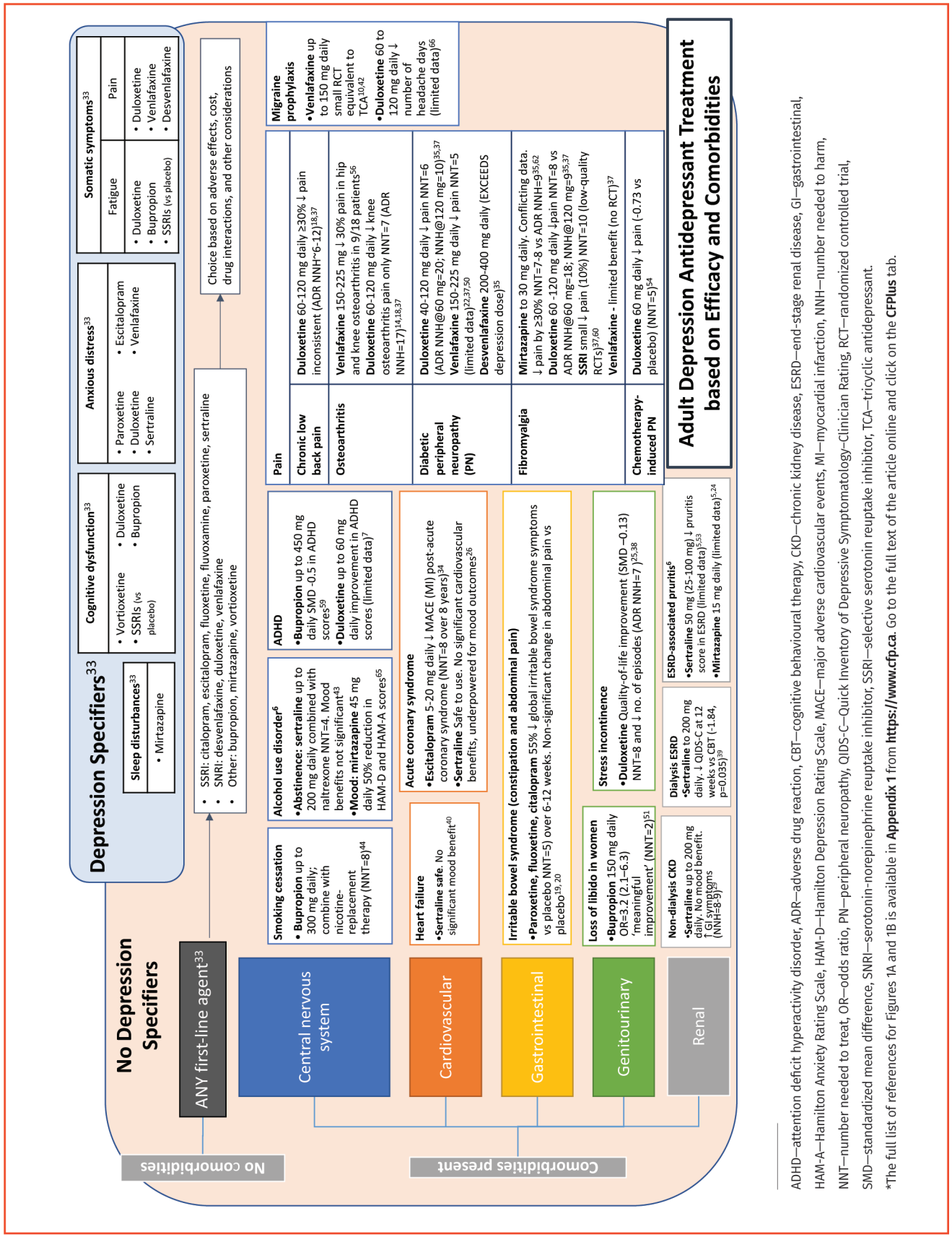
Figure 1A. Antidepressant Decision Support Tool: *Stage 1—adult depression antidepressant treatment based on efficacy and comorbidities.**



ADHD—attention deficit hyperactivity disorder, ADR—adverse drug reaction, CBT—cognitive behavioural therapy, CKD—chronic kidney disease, ESRD—end-stage renal disease, GI—gastrointestinal, HAM-A—Hamilton Anxiety Rating Scale, HAM-D—Hamilton Depression Rating Scale, MACE—major adverse cardiovascular events, MI—myocardial infarction, NNH—number needed to harm, NNT—number needed to treat, OR—odds ratio, PN—peripheral neuropathy, QIDS-C—Quick Inventory of Depressive Symptomatology–Clinician Rating, RCT—randomized controlled trial, SMD—standardized mean difference, SNRI—serotonin-norepinephrine reuptake inhibitor, SSRI—selective serotonin reuptake inhibitor, TCA—tricyclic antidepressant.

*The full list of references for Figures 1A and 1B is available in **Appendix 1** from **https://www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

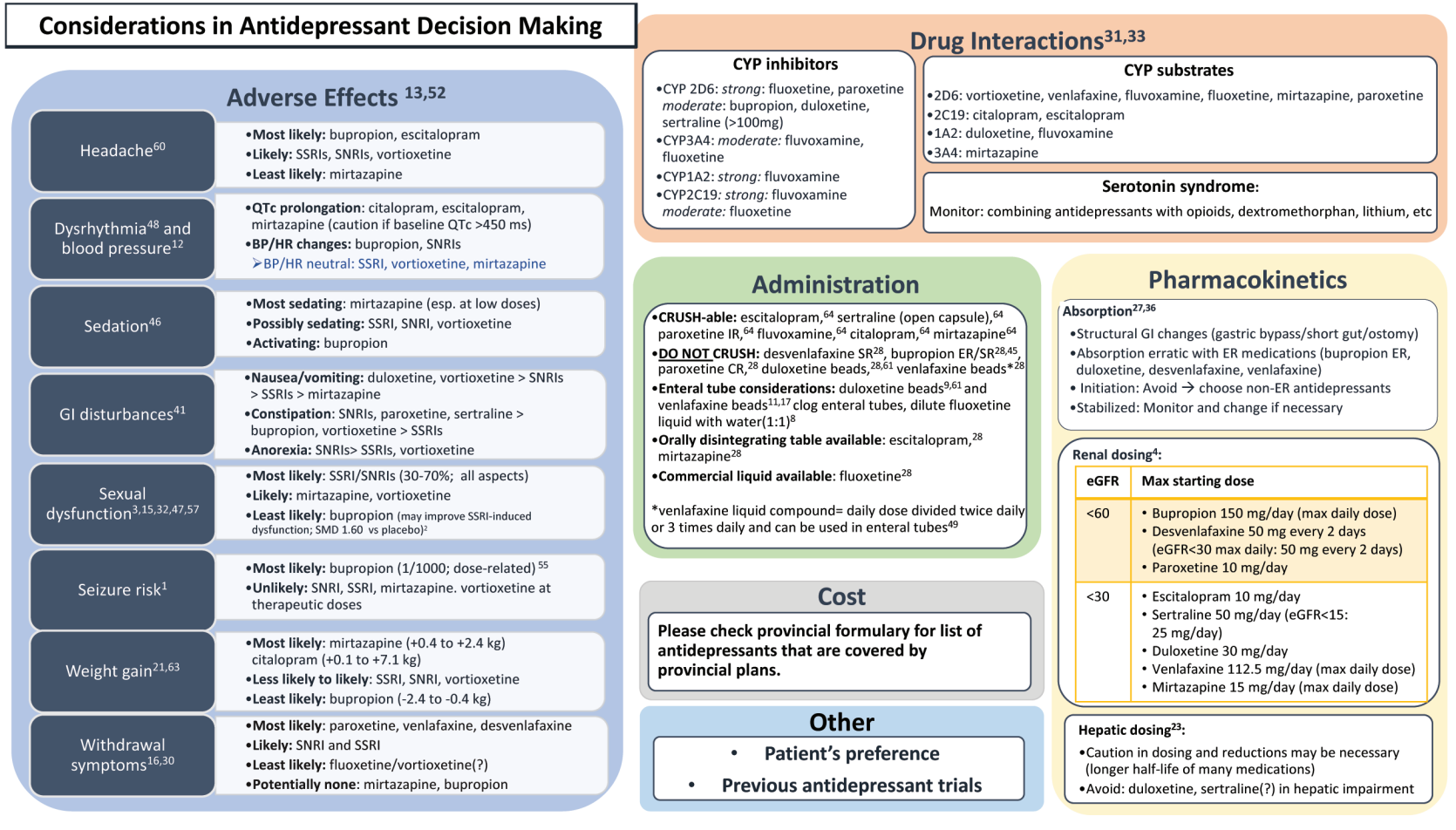


Figure 1B. Antidepressant Decision Support Tool: *Stage 2—considerations in antidepressant decision making.**

BP—blood pressure, CR—controlled-release, CYP—cytochrome P450 enzyme, eGFR—estimated glomerular filtration rate, ER—extended-release, GI—gastrointestinal, HR—heart rate, IR—immediate-release, QTc—corrected QT interval, SMD—standardized mean difference, SNRI—serotonin-norepinephrine reuptake inhibitor, SR—sustained-release, SSRI—selective serotonin reuptake inhibitor.

*The full list of references for Figures 1A and 1B is available in **Appendix 1** from **https://www.cfp.ca**. Go to the full text of the article online and click on the **CFPlus** tab.

Stage 2 of the tool further assists with individualizing antidepressant therapy. After using stage 1 of the Antidepressant Decision Support Tool, prescribers may have successfully narrowed down antidepressant options based on a patient's comorbidities but may not have definitively chosen which antidepressive agent to recommend. Stage 2 of the tool uses patient considerations—such as patient preference based on adverse effects, concomitant drug therapy, administration considerations, renal or liver dysfunction considerations, patient preference for specific antidepressants, the patient's previous antidepressant experiences, and cost considerations—to narrow down antidepressant options further. The ultimate goal of the tool is to support a thoughtful antidepressant choice through patient-prescriber collaboration.

Considering patient characteristics in antidepressant prescribing is not a novel idea. Prescribers already consider a patient's age, comorbidities, specific depression symptoms, and preferences prior to initiating antidepressant therapy. However, no systematic decision support tools have been published to date that assist prescribers in selecting an antidepressant individualized to the patient. The Antidepressant Decision Support Tool was not meant to replace a prescriber's clinical decision-making process; rather, it was developed to support prescribers in a comprehensive, evidence-based, and pragmatic evaluation of patient characteristics to tailor antidepressant therapy. The visual tool also allows patient engagement in their own care by giving the patient an opportunity to view and discuss the rationale of antidepressant selection with their prescriber. Shared decision making between clinicians and patients for antidepressant therapy has been shown to improve clinician and patient satisfaction and comfort with treatment decisions.[21]

There is a paucity of evidence demonstrating improved outcomes or improved patient adherence with individualized antidepressant therapy. Studies are currently being conducted to investigate whether individualizing antidepressant therapy improves depression outcomes.[22] Antidepressant therapy may not be the most appropriate treatment modality for all patients experiencing MDD. The pilot Antidepressant Decision Support Tool does not include an algorithm to assist patients and prescribers with decisions regarding treatment modality (psychotherapy, pharmacotherapy, lifestyle therapy, or a combination of various modalities); the tool assumes that the prescriber and patient have already decided to pursue pharmacotherapy.

The pilot Antidepressant Decision Support Tool focuses solely on pharmacologic management of depression in adults based on current evidence. Once the utility of the decision support tool is established, future projects include expanding evidence-based algorithms for switching antidepressants, adding details about using augmenting agents in conjunction with antidepressants, expanding the algorithm to include second- and third-line agents, and supporting pharmacologic selection in specific populations such as geriatric patients, women, and adolescents and young adults. To date, studies in these populations are limited and antidepressants are used with precautions in these populations.

Case resolutions

Case 1. J.M. is currently taking 5 mg of rosuvastatin daily, 5 mg of ramipril daily, 1000 mg of metformin twice daily with meals, and 5 mg of linagliptin daily. He has no history of renal or liver disease. You review J.M.'s laboratory results and investigations and find no substantial abnormalities. J.M. states that the peripheral neuropathy in his feet has been bothersome. You find out that J.M. had been diagnosed with depression previously (approximately 20 years ago) and had been prescribed amitriptyline, which caused intolerable side effects. J.M. also shares that he is concerned about weight gain because of his diabetes. J.M. is unemployed and receives social assistance; medication costs are a concern for him. Using the Antidepressant Decision Support Tool, you review the *Diabetic peripheral neuropathy* section under *Comorbidities present* in stage 1 (**Figure 1A**) of the tool and narrow down J.M.'s options to desvenlafaxine, duloxetine, or venlafaxine. Using stage 2 of the tool (**Figure 1B**), you discover that desvenlafaxine is not covered and may not be affordable for J.M. You and J.M. discuss the options of duloxetine or venlafaxine. J.M. decides he would like to initiate duloxetine. You write him a prescription to start 30 mg of duloxetine daily and to follow up in 1 week to reassess the dosage. J.M. agrees with this plan.

Case 2. C.P. is currently not taking any other medications and does not have any comorbidities. C.P. has never tried any antidepressant medications in the past. C.P. shares that she is most concerned about weight gain and loss of libido. She is employed as a dental hygienist and does not like dry mouth, but she is able to tolerate it. You believe C.P. would benefit from an antidepressant, but C.P. is worried about starting medications. You review the Antidepressant Decision Support Tool with C.P. and she notices that there may be benefit with bupropion to help with libido in women and it is least likely to cause weight gain. C.P. notes that bupropion may cause dry mouth. In discussion with you, she is agreeable to trying bupropion. You write a prescription for 150 mg of extended-release bupropion daily for C.P. and ask to follow up with her in a week.

Conclusion

Major depressive disorder is a commonly encountered mental health disorder in primary care that can have a substantial impact on a patient's quality of life and functioning. Earlier treatment of MDD is associated with better outcomes. Supportive therapeutic relationships, patient

education, and multidisciplinary collaborative care have positively affected patient adherence and engagement in MDD treatment. Recent studies on antidepressants have suggested there is no superiority of 1 antidepressant over others in MDD treatment. This review introduces a novel systematic approach to selecting antidepressant therapy through the use of a pilot Antidepressant Decision Support Tool designed to help prescribers individualize antidepressant therapy and encourage shared decision making between patients and prescribers.

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Contributors

All authors contributed to the literature review and interpretation, and to preparing the manuscript for submission.

Competing interests

Drs Tracy Chin, Trudy Huyghebaert, and **Clark Svrcek** have no conflicts of interest to report. **Dr Oloruntoba Oluboka** has worked with various pharmaceutical companies. **Dr Oluboka's** involvement with pharmaceutical companies had no effect or influence on the concept, planning, and writing of this manuscript.

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