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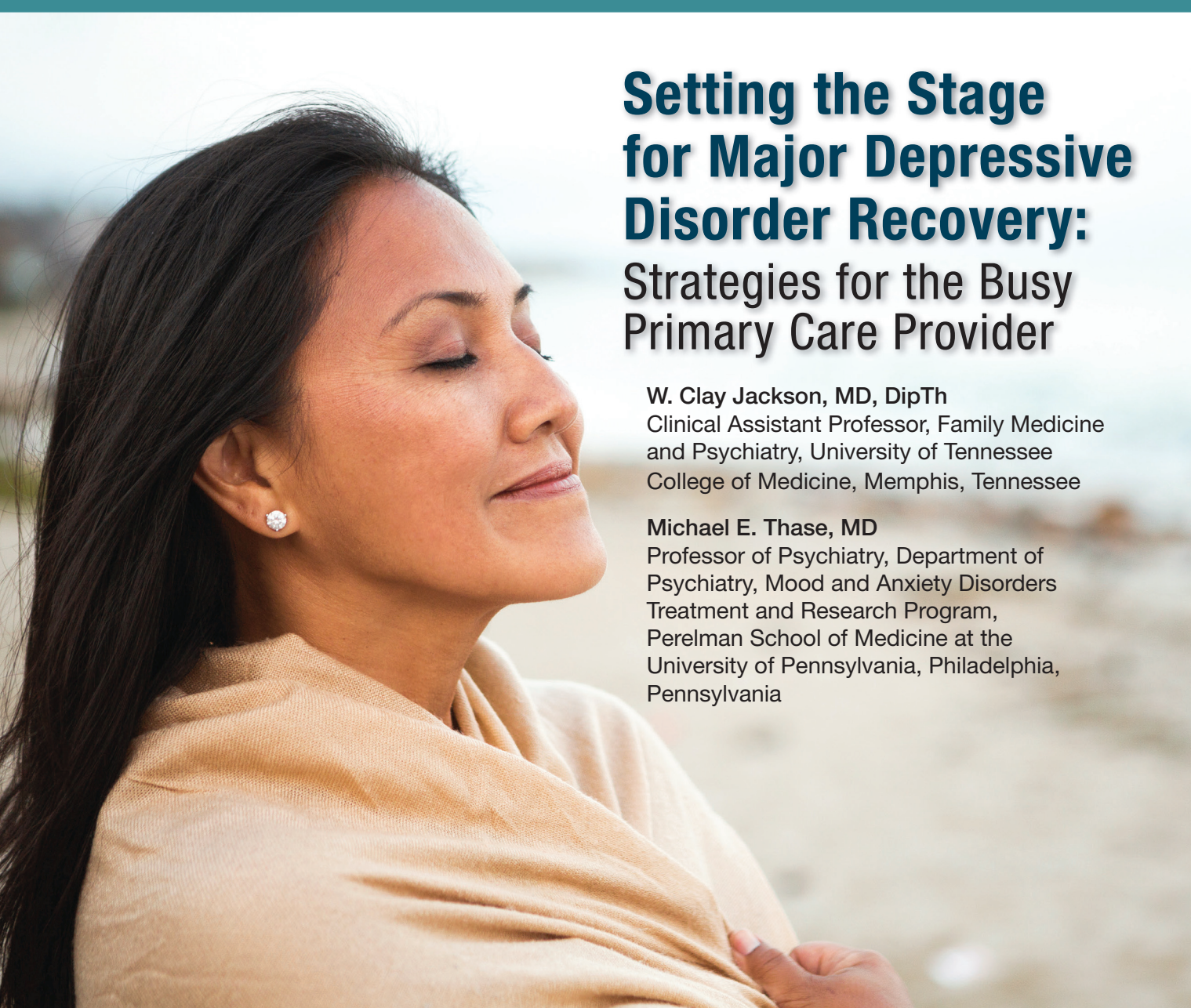


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## Setting the Stage for Major Depressive Disorder Recovery: Strategies for the Busy Primary Care Provider

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### **CME/CE INFORMATION**

After reviewing the learning objectives and reading the supplement, please complete the Activity Evaluation/Credit Request form online at [www.cmesurvey.site/MDDJFP](http://www.cmesurvey.site/MDDJFP). *AMA PRA Category 1 Credit*<sup>™</sup>, ANCC contact hours, and AAFP Prescribed credits are provided. This educational activity should take a maximum of 1.5 hours to complete.

### **TARGET AUDIENCE**

The audience for this educational initiative is primary care clinicians who care for patients with major depressive disorder (MDD).

### **ACTIVITY DESCRIPTION**

In the United States, most adults with MDD are treated by primary care providers (PCPs). Therefore, it is essential that PCPs are adept at using patient-centered care to set the stage for MDD recovery. In particular, PCPs must be prepared to detect and respond to 2 of the most common threats to recovery: residual MDD symptoms and intolerable adverse effects of antidepressants. In these articles, 2 expert faculty members discuss how busy PCPs can optimize MDD care by implementing shared decision-making; employing measurement-based care; identifying and managing MDD residual symptoms and antidepressant adverse effects; and switching patients to new antidepressants when necessary. Two patient cases illustrate evidence-based approaches to common clinical scenarios.

### **LEARNING OBJECTIVES**

On completion of this activity the learner will be better able to:

- Explain the practical benefits of incorporating shared decision-making and patient goals into MDD treatment plans
- Identify tools suited to measure MDD symptoms and patient wellness during a primary care office visit
- Demonstrate knowledge of evidence-based strategies for treating MDD residual symptoms
- Formulate an appropriate treatment plan for a patient experiencing adverse effect related to their antidepressant
- Analyze whether and how to switch a patient's MDD therapy

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# Using Patient-Centered Care to Improve Major Depressive Disorder Outcomes

W. Clay Jackson, MD, DipTh

Despite the availability of a variety of effective antidepressants,<sup>1</sup> the burden of inadequately treated major depressive disorder (MDD) in the United States remains deeply troubling. Nearly two-thirds of adults being treated for MDD report that they continue to experience symptoms that affect their ability to function at work, school, or home.<sup>2</sup> In fact, in a study of over 1500 patients being treated for MDD over a 6-month window, only roughly half achieved recovery.<sup>3</sup> Failure to reach remission compromises patients' quality of life and ability to function.<sup>4-7</sup> It also has important implications for metabolic outcomes,<sup>8,9</sup> contributing to the 80% higher risk of developing or dying from coronary heart disease that patients with MDD experience.<sup>10</sup>

Primary care providers (PCPs) have a key role to play in alleviating the burden of inadequately treated MDD, as studies have shown that roughly 10% of primary care patients meet the criteria for MDD.<sup>11</sup> PCPs' involvement in MDD care begins with diagnosis: They are often the healthcare providers who patients approach about feeling depressed or the ones who administer depression screenings that lead to the detection of MDD.<sup>12</sup> After diagnosis, their expertise is still needed: Over half of US adults living with MDD (57%) report that their PCP is their primary provider of MDD treatment.<sup>13</sup> Indeed, roughly 80% of antidepressants are prescribed by healthcare providers who are not psychiatrists.<sup>14</sup>

## US Preventive Services Task Force (USPSTF) Recommendation: Screening for Depression in Adults<sup>15</sup>

"The USPSTF recommends screening for depression in the general adult population, including pregnant and postpartum women. Screening should be implemented with adequate systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up." (B recommendation)

Ensuring that patients with MDD receive effective care can be a challenge for PCPs. Primary care offices are busy, office visits are short, and PCPs must provide high-quality care despite not having received extensive specialty training in mental health care. In particular, because roughly two-thirds of patients with MDD will not achieve remission on their first therapy,<sup>16</sup> it is critical that PCPs are able to recognize and manage inadequately treated MDD. In this article, we discuss practical strategies PCPs can use to make sure that their patients with MDD receive optimal treatment, focusing on patient-centered approaches that work in the real world.

## PATIENT-CENTERED CARE: DOES IT REALLY MAKE A DIFFERENCE?

The Institute of Medicine has identified "patient-centeredness" as one of 6 key areas in need of improvement in the US healthcare system.<sup>17</sup> MDD care is no exception; research has shown that patient-centered care has an important role to play in the treatment of this disorder specifically. In a recent study of 792 patients who were diagnosed with MDD and received new prescriptions for antidepressants from a PCP, a number of patient-centered measures (eg, PCPs soliciting patient preferences for care and questions or concerns, PCPs asking patients to complete a depression scale) were positively associated with depression remission.<sup>18</sup> Here, we explore further what patient-centered care for MDD looks like in a primary care office visit.

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Dr. Jackson discloses that he has received consulting fees from Abbvie, Inc/Allergan, Inc; Genentech, Inc; Otsuka Pharmaceutical Company, Ltd; and Sunovion Pharmaceuticals, Inc.

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## SHARED DECISION-MAKING IN MDD CARE

Shared decision-making (SDM) is a key component of patient-centered care (FIGURE). For many decisions in MDD treatment, evidence does not clearly identify one option as better than another; this scenario is ideal for SDM, as a patient's goals, values, and preferences can help guide decision-making. Moreover, by actively participating in decision-making, patients with MDD can begin to regain a sense of autonomy and personal agency.<sup>19</sup>

SDM is important because a patient's desires help determine the success of any treatment plan. Over a given 6-month period, nearly half of primary care patients (46%) who are prescribed antidepressants will be nonadherent to their treatment plan.<sup>20</sup> This is a major problem, as response and remission rates are significantly higher among adherent patients.<sup>21</sup> In general, participation in SDM improves a patient's adherence to their MDD treatment plan.<sup>22</sup> In addition, a randomized trial has shown that the strength of a patient's preference for their treatment plan is associated with a higher adherence rate.<sup>23</sup>

Not surprisingly, the improved patient engagement and adherence that accompany SDM lead to better MDD outcomes. Relative to usual care, treatment that incorporates SDM results in significantly better social functioning.<sup>24</sup> And in one study conducted among patients whose MDD was being managed by a PCP, involvement in SDM was associated with a higher probability of receiving quality care and improvement in symptoms over an 18-month period.<sup>25</sup>

Thus, it is critical to take into account a patient's preferences when selecting a treatment plan. Of note, the treatment options considered using SDM need not be limited to pharmacologic therapies. Evidence-based nonpharmacologic treatments such as psychological interventions (eg, cognitive behavioral ther-

## Patient Case Studies: Strategies for the Busy Primary Care Provider

**CASE 1:** Kimberly is a 38-year-old woman who has been receiving care for major depressive disorder (MDD) from her primary care provider (PCP) for the past 8 months. Since starting treatment with a selective serotonin reuptake inhibitor (SSRI), her mood has improved substantially. But at her most recent office visit, she reported that she still doesn't feel like herself. At work, she feels "foggy," and her supervisor has expressed frustration with her recent performance. She is also feeling abnormally tired. In the past, she had often enjoyed meeting coworkers for happy hour or inviting friends and family over for dinner. Now, on a typical day, she goes straight home from work, heats up a quick dinner, watches a little TV, and goes to bed early. She wants to know if this is her new normal.

After hearing about Kimberly's symptoms, her PCP administered the Patient Health Questionnaire (PHQ)-9. Her score confirmed that, overall, she was responding well to her antidepressant. Technically, she met the criteria for remission. But it was clear Kimberly had not achieved her treatment goals, which included getting back to being a top performer at work and having the energy to spend quality time with the people she cares about.

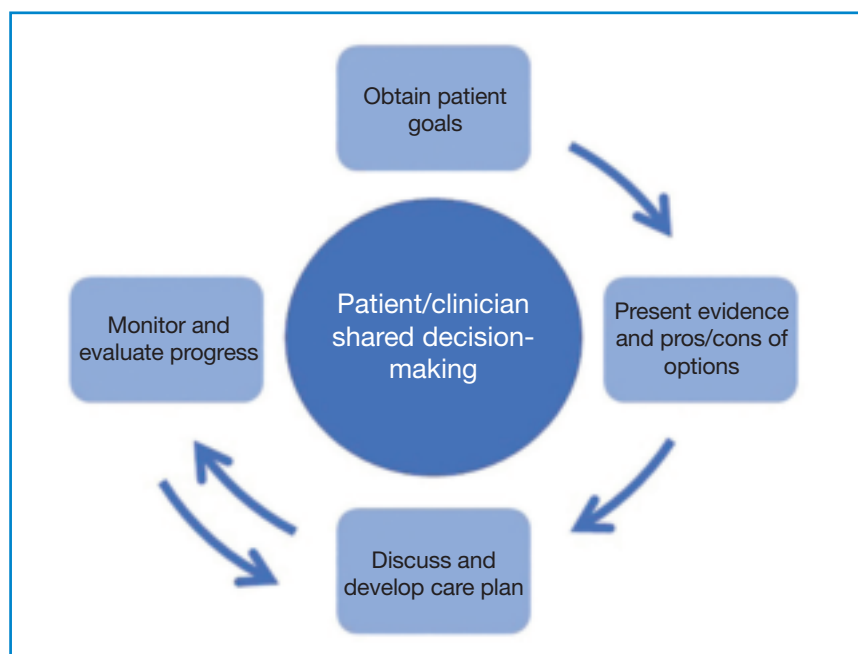
Unsure how to proceed, Kimberly's PCP set up a curbside consult with a psychiatrist with whom he had a good working relationship. After listening to the PCP's description of Kimberly's symptoms, the psychiatrist suggested administering the THINC-it cognition screening tool, which takes 10 to 15 minutes to complete and can be completed on a tablet or computer. At the next visit, Kimberly completed the THINC-it assessment and her results indicated that she was experiencing cognitive dysfunction, consistent with her descriptions of feeling "not herself" and "foggy," as well as with her performance problems at work.

**CASE 2:** Salvador is a 54-year-old man who recently began SSRI therapy for MDD under the care of his PCP. At his most recent office visit, his PCP reviewed his chart and noticed that he had missed his last 2 scheduled appointments. In addition, Salvador had not filled all of the prescriptions needed to supply him with daily doses of his antidepressant. When the PCP asked him about his recent mood, Salvador sounded noncommittal about noticing any improvement. When the PCP asked if he had experienced any trouble taking his medication, Salvador looked embarrassed and was reluctant to engage in conversation.

Salvador's PCP was aware that sexual adverse effects are common with antidepressants and that patients are often uncomfortable discussing this issue. She decided to ask Salvador directly if he was experiencing any sexual adverse effects, listing some of the most frequent ones. Salvador revealed that since starting his antidepressant, he had been troubled by delayed ejaculation and he was also sometimes unable to achieve orgasm. Dismayed by this unexpected adverse effect, he had experimented with taking drug holidays. Unfortunately, during these drug holidays, which had been growing longer and longer, his mood symptoms would often return. Salvador told his PCP he was unsure about whether he would prefer to deal with unmedicated MDD or accept the sexual adverse effects he was afraid were going to ruin his relationship.

CASE STUDIES CONTINUED ON PAGE S17

**FIGURE** The 4-step process for engaging patients in shared decision-making around major depressive disorder treatment plans



apy,<sup>26</sup> mindfulness-based cognitive behavioral therapy<sup>27</sup>) and exercise<sup>28</sup> may also be helpful. By discussing the full range of treatment options, every patient's treatment plan can be tailored to their needs, desires, and unique life circumstances.

This leaves the question of how best to implement SDM for MDD in primary care. From the beginning, PCPs can emphasize to patients that MDD treatment is a continual work in progress, one that is bound to have ups and downs. Research shows it is important to provide patients with hope for recovery,<sup>29</sup> but it is also important not to oversell the recovery process as quick or without challenges. Indeed, a realistic sense of hope helps patients adhere to the treatment plan, even before they experience the benefits of therapy.<sup>30</sup> When initiating MDD care, PCPs can explain that the patient and provider will work together as partners to identify when treatments are ineffective and to address any challenges that might lead to nonadherence. At every step of the MDD management process, PCPs can elicit patient feedback about treatment decisions, and at every visit, PCPs can ask patients about their recent experiences with regard to MDD symptoms, functioning, and their current therapy.

According to both clinicians and patients, the most

common barrier to engaging in patient-centered care activities such as SDM is time.<sup>31</sup> However, asking patients questions about their goals and experiences and listening to their answers need not necessarily take up large amounts of time. In addition, decision aids can help PCPs make efficient use of time by structuring the discussion of treatment options. Using decision aids in mental health care has also been shown to increase patients' knowledge and participation in decision-making, decrease conflict between provider and patient about treatment decisions, and enhance patients' satisfaction with care.<sup>32</sup>

One tool that can be used to support SDM in MDD care is the Depression Medication Choice Encounter Decision Aid, which can be accessed online or given as a printout (<https://depressiondecisionaid.mayoclinic.org/index>).<sup>33</sup> This series of 7 cards allows clinicians and patients to select

treatments together, improving both parties' level of comfort with treatment decisions, as well as patients' knowledge of and satisfaction with the treatment plan.<sup>33</sup> It is important to keep in mind that some of the newer antidepressants are not included in the aid and that costs may not be up to date, as medications continually become available in generic formulations. However, the aid does help patients evaluate key considerations including cost; effects on weight, sexual function, and sleep; and the discontinuation approach for various antidepressants.

## MEASUREMENT-BASED CARE FOR MDD

Put simply, measurement-based care entails working with patients to identify their treatment goals and then systematically measuring progress toward those goals.<sup>34,35</sup> Measurement-based care for MDD is efficient in that it quickly allows the PCP to determine whether a patient is making adequate progress toward their treatment goals.<sup>34</sup> Gaining this type of information in a timely manner is a crucial means of illuminating key decision points. In addition, measurement-based care allows patients to gain greater insight into their illness, including how their adherence affects their symptoms. For that reason, measurement-based care can be viewed as a practical tool for psychoeducation.

TABLE 1 Scales useful in the diagnosis and treatment of major depressive disorder (MDD)

MDD symptom scales	Wellness and functioning scales	Other useful scales
Pick 1 to administer every visit	Pick 1 to administer every visit	Use as needed during screening/ diagnosis or to track anxiety symptoms
<i>Patient Health Questionnaire (PHQ)-9</i> <a href="https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/218">https://www.uspreventiveservicestaskforce.org/Home/GetFileByID/218</a>	<i>World Health Organization (WHO)-5 Well-Being Index</i> <a href="https://www.psychiatri-regionh.dk/who-5/Documents/WHO-5%20questionnaire%20-%20English.pdf">https://www.psychiatri-regionh.dk/who-5/Documents/WHO-5%20questionnaire%20-%20English.pdf</a>	<i>Patient Health Questionnaire (PHQ)-2</i> <a href="https://cde.drugabuse.gov/sites/nida_cde/files/PatientHealthQuestionnaire-2_v1.0_2014Jul2.pdf">https://cde.drugabuse.gov/sites/nida_cde/files/PatientHealthQuestionnaire-2_v1.0_2014Jul2.pdf</a>
<i>Quick Inventory of Depressive Symptomatology (QIDS)</i> <a href="http://www.ids-qids.org/">http://www.ids-qids.org/</a>	<i>HERO Wellness Scale</i> <a href="https://static.helpjuice.com/helpjuice_production/uploads/upload/image/5745/direct/1584118888540-HERO%20Wellness%20Scale.pdf">https://static.helpjuice.com/helpjuice_production/uploads/upload/image/5745/direct/1584118888540-HERO%20Wellness%20Scale.pdf</a>	<i>Mood Disorder Questionnaire (MDQ)</i> <a href="https://www.ohsu.edu/sites/default/files/2019-06/cms-quality-bipolar_disorder_mdq_screener.pdf">https://www.ohsu.edu/sites/default/files/2019-06/cms-quality-bipolar_disorder_mdq_screener.pdf</a>
	<i>Sheehan Disability Scale</i> <a href="http://memorialparkpsychiatry.com/doc/sheehan_disability_scale.pdf">http://memorialparkpsychiatry.com/doc/sheehan_disability_scale.pdf</a>	<i>Rapid Mood Screener (RMS)</i> <a href="https://www.psychcongress.com/sites/psychcongress.com/files/2020-09/132-Depressive-Symptoms--Could-it-be-Bipolar-Depre.pdf">https://www.psychcongress.com/sites/psychcongress.com/files/2020-09/132-Depressive-Symptoms--Could-it-be-Bipolar-Depre.pdf</a>
		<i>General Anxiety Disorder (GAD)-7</i> <a href="https://med.dartmouth-hitchcock.org/documents/GAD-7-anxiety-screen.pdf">https://med.dartmouth-hitchcock.org/documents/GAD-7-anxiety-screen.pdf</a>

### IMPORTANCE OF A PATIENT'S EARLY RESPONSE TO ANTIDEPRESSANTS

Among patients who have not responded to an antidepressant by 2 weeks, only roughly 11% will display a stable response to that medication after 4 weeks.<sup>36</sup> Thus, if a less-than-20% response is noted after 3 weeks of treatment, experts recommend dose escalation or switching be considered to avoid leaving patients inadequately treated,<sup>37</sup> and augmentation might also be considered.<sup>38</sup>

Measurement-based care improves patient engagement and outcomes. In a survey of 200 individuals with MDD, 61% expressed the belief that a goal attainment approach based on SDM would be helpful.<sup>39</sup> And in a 6-month randomized study of 120 patients with MDD, patients who received measurement-based care (vs non-measurement-based care) were significantly more likely to exhibit a treatment response (87% vs 63%) and to achieve remission (74% vs 29%).<sup>40</sup> They also did so in a significantly shorter period of time than their peers who had not received measurement-based care: 6 vs 12 weeks for response and 10 vs 19 weeks for remission.

A variety of standardized rating scales can be used to screen for MDD, arrive at a diagnosis, and then track progress toward treatment goals (TABLE 1). In terms of

screening, the Patient Health Questionnaire (PHQ)-2 and PHQ-9 are the most frequently used tools in the primary care setting.<sup>41</sup> In the United States, MDD has an annual prevalence rate of 10% and a lifetime prevalence rate of 21%,<sup>42</sup> so screening patients at least once a year seems reasonable. A positive screening result can then be followed up with a more thorough assessment, to see if a patient meets the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* criteria for MDD.<sup>43</sup> During the diagnostic process, it is helpful to administer the Mood Disorder Questionnaire (MDQ)<sup>44</sup> or Rapid Mood Screener (RMS)<sup>45,46</sup> to screen for bipolar depression and the General Anxiety Disorder (GAD)-7 scale<sup>47</sup> to assess whether comorbid anxiety symptoms are present. Comorbid anxiety disorders have been shown to increase a patient's suicide risk and will need to be addressed during treatment.<sup>48,49</sup>

To track progress toward treatment goals, it is helpful to administer one MDD symptom scale and one function/wellness scale at each office visit (TABLE 1). In primary care, the PHQ-9 is the scale most often used to assess MDD remission,<sup>41</sup> defined as a score <5,<sup>50</sup> and to measure symptom amelioration. The Quick Inventory of Depressive Symptomatology (QIDS)<sup>51</sup> is another scale that can be used to monitor depressive symptoms. However, it is important to keep in mind that patients consider many domains of their lives important when



TABLE 2 World Health Organization (WHO)-5 Well-Being Index

**Instructions:** For each of the 5 statements, please indicate which is closest to how you have been feeling over the last 2 weeks. Note that higher numbers mean better well-being.

*Example:* If you have felt cheerful and in good spirits more than half of the time during the last 2 weeks, circle the number 3 in the first row.

Over the last 2 weeks:	All the time	Most of the time	More than half of the time	Less than half of the time	Some of the time	At no time
1. I have felt cheerful and in good spirits	5	4	3	2	1	0
2. I have felt calm and relaxed	5	4	3	2	1	0
3. I have felt active and vigorous	5	4	3	2	1	0
4. I woke up feeling fresh and rested	5	4	3	2	1	0
5. My daily life has been filled with things that interest me	5	4	3	2	1	0

**Scoring and Interpretation:** To calculate the raw score, total the 5 numbers selected. To calculate the percentage score, multiply the raw score by 4.

If a patient has a raw score below 13, or if they have selected 0 or 1 for any of the 5 items, a full assessment for MDD is recommended.

To monitor changes in well-being, the percentage score is used. A difference of 10% or greater indicates a significant change.

assessing treatment effectiveness. In addition to a reduction in mood-related symptoms, they typically value a return to functioning and a general sense of well-being and satisfaction with their lives.<sup>52</sup> For example, in a survey of 200 individuals with MDD, the most commonly reported treatment goals were in the areas of physical health, cognitive functioning, and social functioning.<sup>39</sup> Thus, the common symptom-based definition of MDD remission may not match patients' conceptions of what recovery looks like. For this reason, regularly administering scales that measure function and wellness can be helpful. The World Health Organization (WHO)-5 Well-Being Index (see TABLE 2),<sup>53</sup> the HERO Wellness scale,<sup>54</sup> and the Sheehan Disability scale<sup>55</sup> can all be used in the primary care setting. In addition, it can be helpful to simply ask patients, "How much do you think you have improved as a percentage since you started taking your medication?" or to rate the severity of their depression on a scale of 0 (depressed) to 10 (not depressed at all).<sup>37</sup>

Like SDM, measurement-based care need not take up an inordinate amount of a PCP's time if it is done strategically. Patients can complete self-report scales in the waiting room before an office visit or even online between appointments. And given the superior outcomes associated with measurement-based care, the consistent use of rating scales has a significant return on investment of clinician and patient time.

## MDD CARE IN THE COVID-19 ERA

Providing effective care for MDD is more important than ever during the COVID-19 pandemic. Patients are dealing with high levels of stress as they contend with anxiety about the virus; unemployment; feeling isolated from friends, family, and coworkers; adjusting to new routines at home and at work that may include greater responsibilities and fewer breaks; and the inability to engage in their normal activities and routines. Not surprisingly, with so many of us stuck at home, there is evidence that people are spending more time on social media, which is associated with elevated levels of depressive symptoms—especially if someone also reports experiencing symptoms of distress.<sup>56</sup>

As a result of these factors, the prevalence of depression in the United States is rising. One survey conducted in June 2020 found that 31% of US adults reported symptoms of anxiety disorder or depressive disorder, and 11% reported having seriously considered suicide in the 30 days prior.<sup>57</sup> Another study found that the prevalence of depressive symptoms in US adults is 3-fold higher now than it was prior to the pandemic.<sup>58</sup> In this study, individuals with lower access to economic resources and those with greater exposure to stressors such as job loss were at particularly high risk of developing depressive symptoms. The suicide rate is also projected to increase as a result of COVID-19-related unemployment and its ramifications.<sup>59,60</sup>

Given the multitude of novel stressors present in



the COVID-19 era, it is important for PCPs to be alert for depressive symptoms in patients who have not been diagnosed with MDD and for worsening symptoms in those who already have an MDD diagnosis. Screening for MDD may be especially valuable now, and existing MDD treatment plans may need to be modified given the unique circumstances in which patients are living.

## CONCLUSION

There is much room left to improve outcomes for patients with MDD. Currently, only 27% of individuals with MDD report that they are very or extremely satisfied with their lives overall, compared with 55% of the general public.<sup>13</sup> These numbers are real, preventable, and tragic, as they represent an enormous reservoir of unalleviated human suffering. As the frontline of defense against MDD, PCPs are uniquely positioned to help improve patients' lives by reducing the burden of inadequately treated MDD. This may seem like a great responsibility, and it is. But it is also important to keep in mind that large improvements in care don't necessarily require large amounts of time or effort. To the contrary, SDM and measurement-based care are strategies likely to help PCPs win back scarce time by helping them direct their energy and attention to productive channels. Some busy PCPs may be skeptical about whether patient-centered care strategies work as well in the real world as they work in clinical trials. But anyone who gives patient-centered care strategies a good faith effort is likely to find that they result in considerable gains for patients and their families. In addition, it is likely that gains will accrue to clinicians, who will experience a sense of personal and professional reward that derives from substantially improving human lives. It is also likely that many PCPs who experience these benefits will end up encouraging their colleagues to give patient-centered care a try. ●

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# Strategies for Optimizing the Treatment of Major Depressive Disorder

Michael E. Thase, MD

**P**rimarily care providers (PCPs) provide the first line of treatment for many patients with major depressive disorder (MDD).<sup>1,2</sup> As such, they are the health-care providers best positioned to detect common threats to recovery, such as bothersome residual symptoms or antidepressant adverse effects that reduce patients' quality of life. Detecting and solving these problems promptly is essential, as they frequently drive individuals with MDD to either take their antidepressants erratically or to abandon their treatment plans altogether.<sup>3-5</sup> Optimizing MDD treatment in the busy primary care setting can be challenging, however. Limited time for office visits can make holding sensitive discussions difficult. This is particularly true when patients are reluctant to bring up problems, either because they are embarrassed or because they do not realize that solutions exist.<sup>6</sup> In addition, PCPs must be able to troubleshoot a variety of potential barriers to MDD recovery without having received extensive specialized education in mental health. In this article, we describe evidence-based

approaches to optimizing MDD treatment in the primary care setting, including strategies for recognizing and managing residual symptoms and antidepressant adverse effects. We also discuss how to carry out a patient's switch to a new antidepressant, when indicated.

## PHARMACOLOGIC VS NONPHARMACOLOGIC MDD THERAPIES

Much of this article will focus on how to optimize antidepressant therapy. However, nonpharmacologic therapies are also important components of patients' overall treatment plans. A large body of research shows that cognitive behavioral therapy (CBT) and several other forms of psychotherapy are effective strategies for treating MDD.<sup>7-11</sup> The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines recommend that, when feasible, evidence-based psychological treatments such as CBT or interpersonal therapy be combined with antidepressant therapy, concluding that the evidence supports combination treatment over monotherapy.<sup>12</sup> The CANMAT guidelines also recommend exercise as first-line monotherapy for patients with mild to moderate episodes of MDD and as a second-line adjunct to pharmacotherapy for patients with moderate to severe MDD.<sup>13</sup> Indeed, one randomized controlled trial found that regardless of whether exercise was low intensity (such as yoga) or high intensity (such as aerobic training), it reduced depressive symptoms significantly more than treatment as usual.<sup>14</sup> Other CANMAT-recommended adjunctive therapies for mild to moderate MDD include yoga and acupuncture.<sup>13</sup> Adding such nonpharmacologic therapies to the treatment plan can be an excellent way to tailor MDD therapy to the individual patient.

## RESIDUAL MDD SYMPTOMS

Residual symptoms of MDD are extremely common, even among patients who experience a good overall response to antidepressant therapy (**FIGURE 1**).<sup>15</sup> One large study found that among patients who meet the criteria for MDD remission, 90% experience at least one residual symptom, the

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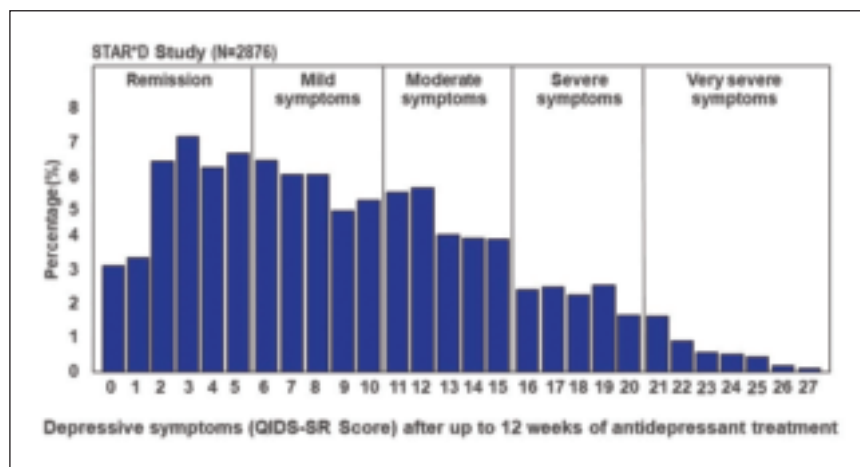
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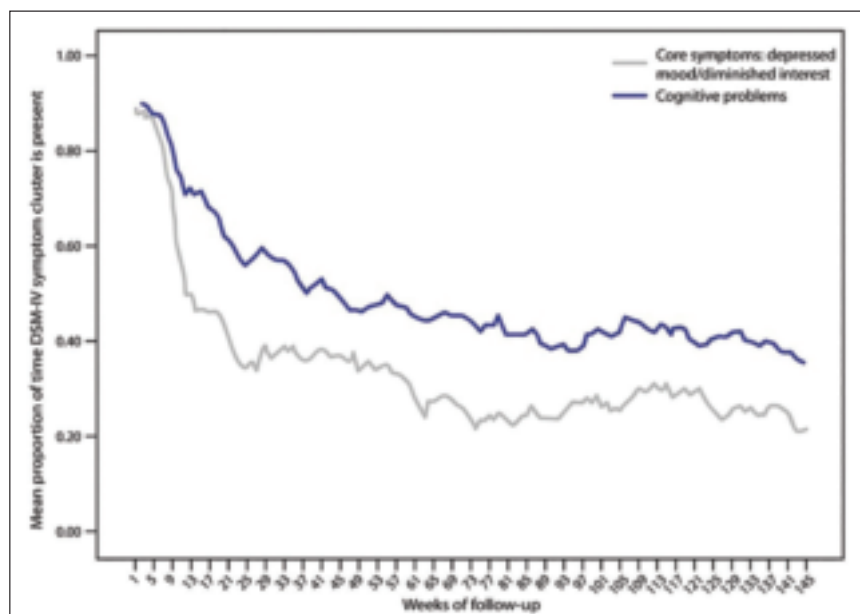
**FIGURE 1** Data from the Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study show that residual MDD symptoms are common following antidepressant therapy<sup>15</sup>



**Abbreviation:** QIDS-SR, Quick Inventory of Depressive Symptomatology, Self-Report.

Adapted from Trivedi MH, et al. *Am J Psychiatry*. 2006;163(1):28-40.

**FIGURE 2** Presence of core MDD symptoms and cognitive problems over a 3-year period in which 267 primary care patients with MDD were followed and their symptoms tracked<sup>19</sup>



Adapted from Conradi HJ, et al. *Psychol Med*. 2011;41(6):1165-1174.

most common being weight gain and insomnia.<sup>16</sup> These residual symptoms, along with other frequent residual symptoms, such as impaired concentration, anhedonia, pessimism, fatigue, or lack of motivation, have real con-

sequences for patients' ability to function and their quality of life.<sup>17</sup>

Residual cognitive symptoms were reported in 71% of antidepressant responders in one study of MDD<sup>18</sup> and were present for up to 44% of the time in a second study of MDD patients in remission (FIGURE 2).<sup>19</sup> A recent systematic review and meta-analysis found that deficits in selective attention, working memory, and long-term memory persist during MDD remission and worsen with repeated episodes.<sup>20</sup> These deficits affect patients' social, occupational, and global functioning, as well as their quality of life.<sup>21,22</sup> In practical terms, cognitive dysfunction caused by MDD is associated with reduced ability to function at work, school, and home.<sup>23</sup> Given the consequences of cognitive and other types of residual MDD symptoms for patients' lives, it is crucial they are detected and managed promptly.

Typically, PCPs will detect residual symptoms through conversations with their patients and by regularly administering the Patient Health Questionnaire (PHQ)-9. In some cases, a patient will share information that points toward residual symptoms that are not measured, or not measured well, by the PHQ-9. In these cases, PCPs may want to consider administering another standardized rating scale to better characterize the symptoms. For example, if residual anxiety symptoms are the major concern, the General Anxiety Disorder (GAD)-7 scale<sup>24</sup> may be helpful. If a patient seems troubled by cognitive symptoms, the THINC integrated tool (THINC-it)<sup>25</sup> may prove useful. In addition to helping the clinician gauge the severity of a patient's residual symptoms at baseline, scales such as these can help a PCP measure the effectiveness of any treatment

employed to address the symptoms.<sup>26,27</sup>

It is important to differentiate between the residual symptoms of MDD and the adverse effects of antidepressants. For example, insomnia is a potential adverse effect



of many antidepressants.<sup>28,29</sup> Identifying the root cause of insomnia is essential for responding appropriately, especially because experiencing this sleep problem during the maintenance phase of treatment is a significant predictor of MDD relapse.<sup>30</sup> If a patient's insomnia worsens after initiating antidepressant therapy, it is plausible that the medicine is responsible. The best approaches to managing insomnia caused by the activating effects of an antidepressant include lowering the dose of the medication, administering it well before bedtime, or switching to another agent with a more favorable insomnia profile.<sup>29</sup> By contrast, the best approach to managing insomnia caused by MDD is to ensure that the patient's antidepressant therapy is effective.

Once it is clear that a residual symptom is present, its potential causes must be considered in order to select an appropriate response. Residual symptoms can result from suboptimal doses of antidepressants, inadequate duration of treatment, or a lack of adherence to the treatment plan.<sup>31,32</sup> If one of these causes is responsible, a clinician may need to adjust the dose of the antidepressant, continue treatment for a longer period, or help patients identify solutions to adherence problems. If none of these potential causes appear to explain the residual symptom, however, the patient's current treatment may need to be switched or augmented.<sup>33</sup>

### ANTIDEPRESSANT ADVERSE EFFECTS

Like residual symptoms of MDD, antidepressant adverse effects are very common. These adverse effects have a major effect on patients' ability to adhere to the treatment plan. For example, in one survey of 316 individuals with MDD, roughly 44% reported that they had discontinued a therapy in the past because of weight gain and roughly 37% because of lethargy (**FIGURE 3**).<sup>34</sup> In another survey, this one of 430 individuals living with MDD, 26% reported that they had stopped taking an antidepressant because they didn't like its physical or sexual adverse effects.<sup>2</sup>

Indeed, sexual dysfunction is a particularly problematic adverse effect during antidepressant therapy. In one survey of over 700 patients taking antidepressants, approximately 46% of men and 52% of women reported experiencing treatment-associated sexual dysfunction.<sup>35</sup> Patients who reported sexual dysfunction also reported worse quality of life, self-esteem, mood, and relationships with partners than those who did not. Of note, sexual adverse effects often begin before or at about the same time therapeutic effects become evident.<sup>6</sup> This may dissuade some patients from continuing treatments that are beginning to show promising effects on depressive symptoms. Not surprisingly, sexual dysfunction is one of the

top reasons that patients discontinue taking antidepressants or are noncompliant with the treatment plan.<sup>36</sup>

Weight gain is another frequent adverse effect of antidepressants, one that tends to emerge later in treatment. Weight gain is especially concerning because, as most people know, it seems much easier to gain excess weight than to lose it.<sup>37</sup> Antidepressant-associated weight gain can be considerable: In one study that followed patients for 10 years after they initiated antidepressant therapy, an individual's risk of gaining  $\geq 5\%$  of their original body weight remained increased over the entire study period.<sup>37</sup> Indeed, researchers have expressed concern that this elevated risk of weight gain, paired with the high prevalence of antidepressant use, could result in problematic increases in weight (and associated health conditions) at the population level.<sup>37,38</sup> Finally, like sexual dysfunction, weight gain is one of the main reasons that patients discontinue their antidepressants or are noncompliant with their treatment plans.<sup>36</sup>

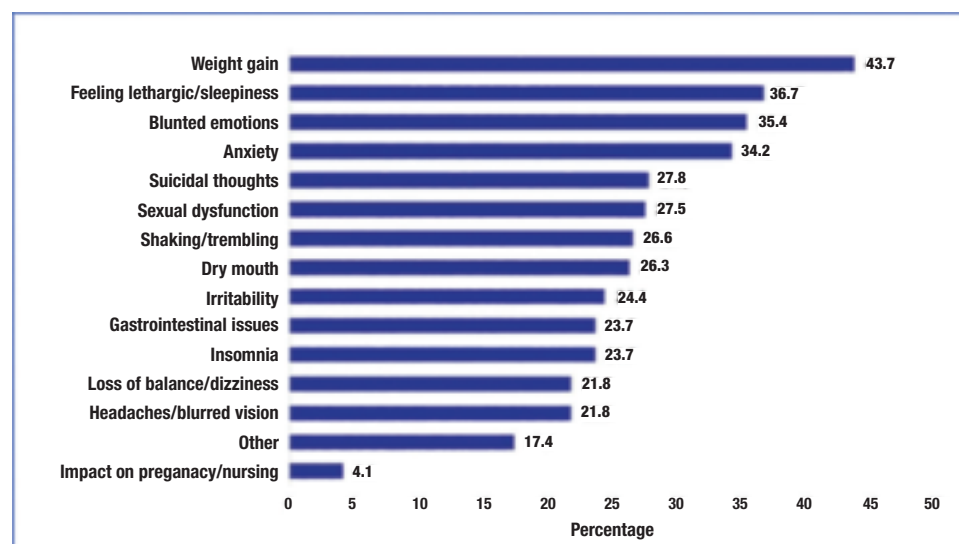
For these reasons, healthcare providers must be ever alert for the presence of antidepressant adverse effects. One of the best ways to detect adverse effects is simply to ask patients whether they are experiencing any and then listen to what they have to say. Patients say over and over that their healthcare providers don't ask them about adverse effects enough. In addition, patients may be reluctant to broach the topic of adverse effects on their own, especially if they find the topic embarrassing.<sup>6</sup> Therefore, discussion of potential adverse effects should begin when a PCP prescribes an antidepressant, so that patients can recognize adverse events when they occur and are aware that they can get help.<sup>6</sup> To aid in the detection and monitoring of adverse effects, key baseline data should be collected prior to antidepressant initiation, including a patient's weight and any information about sexual health or sleep concerns.

At follow-up visits, PCPs can regularly ask about adverse effects in a nonjudgmental manner, so that patients feel comfortable sharing information about sensitive topics such as sexual functioning.<sup>31</sup> For example, healthcare providers can ask whether patients have noticed any bothersome changes in their sexual function or sleep patterns. It is also important to carefully monitor changes in patients' weight as soon as treatment starts: A recent study found that weight gain within the first month of antidepressant treatment is associated with an elevated risk of developing metabolic syndrome.<sup>39</sup>

When an antidepressant adverse effect is detected, it can generally be managed using 3 basic steps:

1. For most adverse effects, clinicians can initially

**FIGURE 3 Percentage of 316 patients with MDD who reported discontinuing treatment in the past because of a given adverse effect<sup>34</sup>**



temporize, to see if they resolve on their own by the next visit.

2. If an adverse effect does not resolve on its own, the dose of a patient's antidepressant can be reduced.<sup>31</sup> Research shows that for the most commonly used second-generation antidepressants, doses at the lower licensed range tend to achieve an optimal balance between efficacy, tolerability, and acceptability.<sup>40</sup> However, lowering the dose of a patient's antidepressant does increase the risk of relapse.<sup>41</sup> Therefore, it is important to keep a close eye on symptom control when adjusting dosing.
3. If dose reduction does not ameliorate the adverse effect, the patient can be switched to a different antidepressant with a profile more conducive to managing the adverse effect in question.<sup>31</sup>

Although these 3 steps represent a basic framework for treatment, each patient's plan will need to be individualized. For example, patients experiencing weight gain may also benefit from counseling on diet and exercise,<sup>38</sup> and patients experiencing sexual dysfunction may also benefit from adjunctive medications.<sup>42,43</sup>

## SWITCHING ANTIDEPRESSANTS

Many people seeking treatment for MDD will need to switch antidepressants at some point. In a survey of 447 individuals with MDD, only 19% reported that they had only ever tried one medication.<sup>34</sup> In fact, research shows

that only roughly one-third of individuals with MDD achieve remission on their first antidepressant.<sup>44</sup> Thus, when a patient's current treatment regimen is not working for them, healthcare providers must be prepared to help them switch to a different antidepressant.

Over the past several decades, it has become increasingly clear that it is easier to predict who will not respond to an antidepressant than who will achieve full remission. For example, if a patient has obtained little to no symptom relief during the first 2 weeks of pharmacotherapy, they only have a

roughly 10% chance of experiencing a stable response to that medication after 2 more weeks of therapy.<sup>45</sup> Hence, the absence of early symptom improvement is a strong indicator that some additional action, whether dose escalation, switching antidepressants, or adding a proven adjunctive strategy, should be considered.<sup>32,33</sup> Unfortunately, this very pragmatic strategy has not yet been widely incorporated into everyday practice. In one recent study of MDD conducted in primary care practices, changes to treatment plans were rare, even after a number of weeks of nonresponse.<sup>46</sup> After a year of follow-up, 131 of 181 patients remained on the same unsuccessful antidepressant as when they started the study, and 103 of the 131 also remained on the same dose of that antidepressant.

Healthcare providers must feel comfortable with managing antidepressant switches, given their importance to treatment success. Specifically, switching a patient's antidepressant may be necessary when the current antidepressant is not effective or cannot be tolerated or when significant drug-drug interactions exist.<sup>33</sup> Determining whether a given antidepressant is not effective can be challenging. If a patient is not responding to their current therapy, it is important to first confirm that the dose of the drug is adequate and the patient has been adherent to the treatment plan.<sup>33</sup> If a patient has not yet received an adequate dose of one antidepressant, switching to another could just restart the waiting time for onset of action, prolonging the time until remission.<sup>47</sup> For this reason, escalation to the maximum acceptable

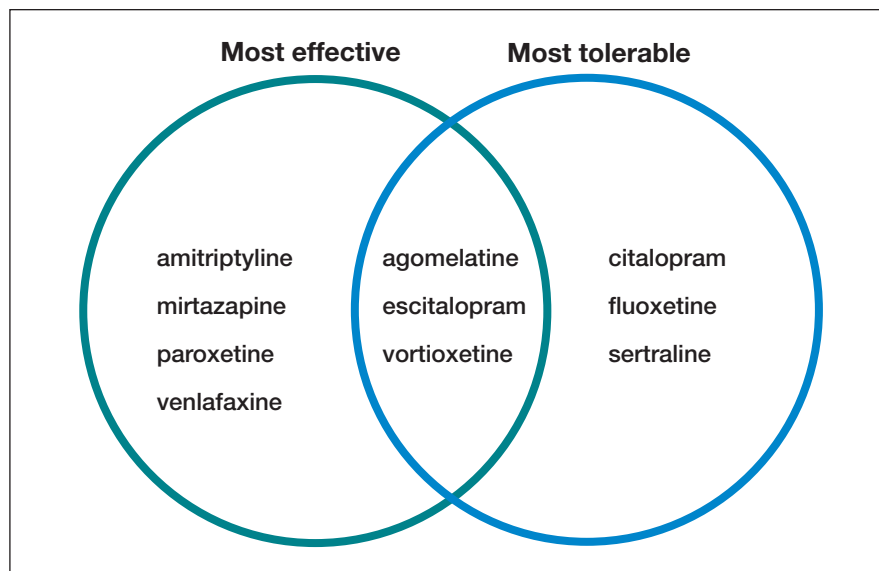
**TABLE Canadian Network for Mood and Anxiety Treatments (CANMAT)-recommended factors to consider when deciding whether to switch a patient to another antidepressant or add adjunctive medication<sup>32</sup>**

Consider switching to another antidepressant when:	Consider an adjunctive medication when:
It is the first antidepressant trial	There have been 2 or more antidepressant trials
There are poorly tolerated adverse effects to the initial antidepressant	The initial antidepressant is well tolerated
There is no response (<25% improvement) to the initial antidepressant <sup>a</sup>	There is partial response (>25% improvement) to the initial antidepressant
There is more time to wait for a response (MDD symptoms are less severe; there is less functional impairment)	There is less time to wait for a response (MDD symptoms are more severe; there is more functional impairment)
Patient prefers to switch to another antidepressant	Patient prefers to add on another medication
	There are specific residual symptoms or adverse effects to the initial antidepressant that can be targeted

**Abbreviation:** MDD, major depressive disorder.

<sup>a</sup> For the initial antidepressant trial. In subsequent trials, lack of response may not be a factor for choosing between switch and adjunctive strategies.

**FIGURE 4 Most effective and most tolerable antidepressants, as identified in a systematic review and network meta-analysis<sup>52</sup>**



dose of the first antidepressant makes sense. If, however, a patient's adherence is good and dose escalation is not successful, switching to another antidepressant, adding psychotherapy, or beginning an adjunctive medication should be considered.<sup>31,32</sup>

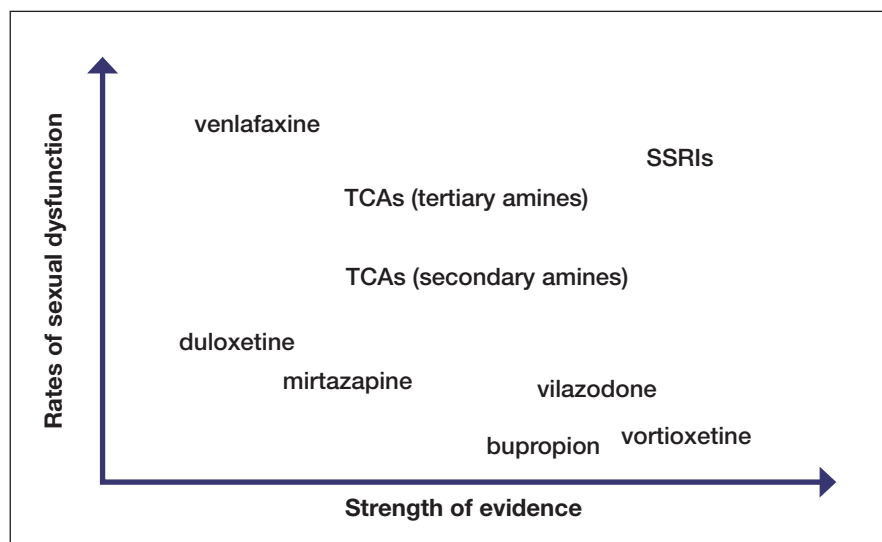
Given the limited evidence regarding antidepressant switching vs adjunctive therapy, CANMAT guidelines recommend that the decision be based on a patient's individual clinical factors (TABLE).<sup>32</sup> Adjunctive therapies may be helpful for some patients<sup>48,49</sup> but also come with their own set of concerns, including adverse effects.<sup>49</sup> CANMAT guidelines list atypical antipsychotics as first-line adjunctive

medications for patients with a partial response to antidepressant treatment.<sup>32</sup>

When a PCP determines an antidepressant switch is in order, the next decision is whether to switch within class or out of class and then which specific agent to switch to. Clinical tradition and common sense say that switching to a different antidepressant class makes sense when faced with a lack of response. Conversely, switching within class may be appropriate if the switch is motivated by adverse effects, unless an adverse effect is characteristic of an entire class of antidepressants.<sup>33</sup> It should be noted, however, that little evidence exists to recommend an out-of-class over a within-class switch

to address lack of response.<sup>33</sup> CANMAT guidelines recommend that, rather than focusing on class, healthcare providers focus on switching to an antidepressant with evidence of superior efficacy.<sup>32</sup> Indeed, some antidepressants appear to represent more successful medications than others, in terms of remission rates and adverse event profiles.<sup>50-52</sup> A recent analysis of head-to-head studies, for example, found that agomelatine (not currently available for use in the US), amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine were more effective than the other antidepressants considered (FIGURE 4).<sup>52</sup> In this study, the most effective antidepressant

FIGURE 5 Rates of sexual dysfunction for different antidepressants<sup>56</sup>



Abbreviations: SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Adapted from Clayton AH, et al. *Psychiatr Clin North Am*. 2016;39(3):427-463.

sants had efficacy odds ratios ranging from 1.19 to 1.96, whereas the least effective had odds ratios ranging from 0.51 to 0.84. In addition, some antidepressants have a superior ability to target specific types of MDD symptoms. For example, differences between classes and agents exist with regard to the amelioration of cognitive symptoms of MDD.<sup>53,54</sup>

In terms of adverse effects, the same study that analyzed head-to-head studies of antidepressant effectiveness found that vortioxetine, agomelatine, citalopram, escitalopram, fluoxetine, and sertraline are the most tolerable antidepressants, as determined by study drop-out rates (FIGURE 4).<sup>52</sup> In this study, the most tolerable antidepressants had drop-out odds ratios ranging from 0.43 to 0.77, whereas the least tolerable had odds ratios ranging from 1.30 to 2.32. And just as some antidepressants are more likely to address certain residual symptoms, some antidepressants are less likely to cause specific types of adverse effects. For example, certain antidepressants are associated with a lower rate of sexual dysfunction (FIGURE 5).<sup>6,55-57</sup> Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors, in particular, are associated with a relatively high risk of sexual dysfunction.<sup>57</sup> Similar differences between agents exist with regard to weight gain<sup>37</sup> and sleep problems.<sup>28,29</sup> In one study, the adjusted rate ratios associated with  $\geq 5\%$  weight gain ranged from 1.05 (95% CI: 1.00 to 1.10) for the most favorable antidepressant to 1.50 (95% CI: 1.45 to 1.56) for

the least favorable, the comparison group being individuals not taking antidepressants.<sup>37</sup>

When carrying out an antidepressant switch, major concerns should include avoiding drug-drug interactions, discontinuation symptoms, and relapse of depression.<sup>58</sup> One approach is to sequentially lower the dose of the old antidepressant until it is no longer being taken, start the new antidepressant at a low level, and then sequentially raise its dose.<sup>33,58</sup> Even with such tapering, patients should be warned that they may experience some withdrawal symptoms.<sup>33</sup> A second approach is to cross-taper the antidepressants, so that both medications are being taken simultaneously—doses of the old antidepressant are gradually low-

ered while doses of the new antidepressant are gradually increased.<sup>33,58</sup> Cross-tapering may work well for patients at high risk for relapse. There are some scenarios in which healthcare providers must be especially careful about selecting a switch strategy. For example, in the case of monoamine oxidase inhibitor (MAOI) antidepressants, a strict washout period between agents is necessary to minimize the risk of a patient developing serotonin syndrome.<sup>33</sup> Although serotonin syndrome is rare, occurring in 0.07% to 0.14% of patients using serotonergic agents in one recent study,<sup>59</sup> it is potentially lethal.

#### WHEN TO REFER PATIENTS TO A SPECIALIST

Referring patients with MDD for specialty treatment is often not feasible. Over 4000 regions of the United States are currently considered mental health professional shortage areas, making it difficult for residents to access specialty care.<sup>60</sup> Insurance issues can further complicate referrals to specialty care.<sup>60</sup> Fortunately, the scenarios in which a referral to a psychiatrist is necessary are relatively few for MDD. These scenarios include when patients are acutely suicidal; when other psychiatric disorders, such as anxiety or personality disorders, are present; when psychotic features are present; or when a patient's MDD is treatment resistant (typically defined as 2 prior treatment failures, when adequate dose and duration of the antidepressant have been confirmed).<sup>61-63</sup>



## Patient Case Studies (continued from S5)

**CASE 1:** Kimberly's PCP checked in with the psychiatrist again to share the results of Kimberly's THINC-it assessment. The psychiatrist suggested switching Kimberly to a different antidepressant.

Kimberly agreed to give the new antidepressant a try, and at her next office visit she reported feeling more like herself. Over the next few visits, her PHQ-9 scores showed that her MDD symptoms were responding to the antidepressant, and her results on the THINC-it assessment showed that her cognitive symptoms were improving. At Kimberly's most recent visit, she shared that her supervisor had recently asked her to head up a presentation for a key client—a new responsibility she was thrilled to be entrusted with.

**CASE 2:** Salvador's PCP assured him that sexual adverse effects of antidepressants are common, but she was hopeful they could find a solution. She suggested he switch to another antidepressant and, after reviewing the evidence base, selected one with a favorable profile regarding sexual function.

At Salvador's next follow-up visit, he reported that since starting the new antidepressant, his sexual adverse effects had disappeared—but he had been feeling more and more depressed. His PHQ-9 results revealed his response to the antidepressant was not adequate. His PCP tried increasing the dose of the antidepressant several times, but it still failed to control Salvador's mood symptoms well. After 2 months of this, Salvador was growing increasingly despondent about his chances of ever finding an MDD treatment plan that worked.

At this point, Salvador's PCP decided it was time to try another antidepressant. Again, she selected one with a favorable profile regarding sexual function. The third antidepressant, which belonged to a different class than the second antidepressant, was successful: It was able to control Salvador's MDD symptoms without causing sexual adverse effects. After finding an antidepressant that worked for him, Salvador began consistently filling his prescriptions. At his most recent follow-up visits, he has reported that he feels much better, and his PHQ-9 results indicate that he is on his way to remission.

## CONCLUSION

Because PCPs provide care to so many patients with MDD, they are uniquely positioned to ensure that those individuals receive effective, tolerable treatments. Research shows that PCPs who follow best practices, including evaluating

depressive symptoms and adverse effects at each visit, are capable of delivering MDD care that results in identical remission and response rates as care from mental healthcare specialists.<sup>64</sup> Providing this type of responsive care, which should include shared decision-making, can go a long way toward addressing the low adherence and persistence rates that plague antidepressant therapy and toward improving outcomes.<sup>65-68</sup> In short, by increasingly playing the role of mental healthcare providers, PCPs have already made MDD care more accessible to their patients. Now, PCPs have the opportunity to increase the quality of the MDD care they provide by optimizing these patients' treatment plans, further improving MDD outcomes in the United States. ●

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