

# A Review of Antidepressant Therapy in Primary Care: Current Practices and Future Directions

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## ABSTRACT

**Objective:** To provide general practitioners with a comparison of major depressive disorder treatments received in primary care and psychiatric clinic settings, a focus on treatment outcomes related to currently prescribed antidepressants, and a review of new and emerging therapeutic strategies.

**Data Sources:** English-language evidence-based guidelines and peer-reviewed literature published between January 1, 2005, and December 31, 2011, were identified using PubMed, MEDLINE, and EMBASE. All searches contained the terms *major depressive disorder* and *unipolar depression*, and excluded the terms *bipolar disorder/manic depressive disorder*. The following search terms were also included: *naturalistic study, antidepressant, relapse, recurrence, residual symptoms, response, remission, sequential medication trials, and treatment-resistant depression*.

**Study Selection:** Meta-analyses, systematic reviews, and practice guidelines were included. Bibliographies were used to identify additional articles of interest.

**Data Extraction:** Abstracts and articles were screened for relevance to primary care practice. Population-based studies and those involving patients treated in primary care were used whenever possible.

**Data Synthesis:** Achieving remission from a major depressive episode is important to improve functional outcomes and to reduce relapse and recurrence. Despite the availability of numerous antidepressants, as many as 50% of patients require treatment modifications beyond first-line therapy. Among remitters, 90% report residual symptoms that may interfere with function. Patients treated in primary care often have chronic depression (symptom duration  $\geq 24$  months at presentation) and medical comorbidities. These are clinical predictors of worse outcomes and require individualized attention when treatment is initiated. Antidepressants differ in efficacy, tolerability, and side effects—factors that may affect adherence to treatment.

**Conclusions:** Major depressive disorder is highly prevalent in primary care and is among the most common causes of loss of disability-adjusted life-years worldwide. There are few differences in clinical profiles between depressed patients in primary care and those in specialist clinics, although differences in symptoms and comorbid conditions among individual depressed patients present a challenge for the physician providing individualized treatment. The goal of treatment is remission with good functional and psychosocial outcomes. Physicians in primary care should have expertise in working with a number of current antidepressant approaches and an awareness of new and emerging treatments.

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Unipolar depression or major depressive disorder (MDD) is one of the leading causes of disability worldwide, ranking fourth among the global causes of disease burden<sup>1</sup> and accounting for 65.5 million disability-adjusted life-years worldwide.<sup>2</sup> The chronic and episodic nature of MDD, along with poor psychosocial functioning,<sup>3</sup> are important drivers of disability and economic burden.<sup>4-6</sup>

The National Comorbidity Replication Survey reported a 12-month MDD prevalence of 6.7%, with a lifetime prevalence of 16% among adults in the United States.<sup>7</sup> Subsequent data from the National Health and Nutrition Examination Survey<sup>8</sup> yielded a prevalence of 20% in the previous 12 months on the basis of a score  $\geq 5$  on the 9-item Patient Health Questionnaire (PHQ-9).<sup>9</sup> In the same analysis,<sup>8</sup> only 25% of patients with severe symptoms (PHQ-9 score  $> 20$ ) were receiving evidence-based care, and 37% were not receiving an antidepressant or any form of psychotherapy. Moreover, the majority of adults (60%) under the age of 64 years who received antidepressant therapy had discontinued treatment in the first 6 months.<sup>10</sup> This lack of consistent treatment is a likely contributor to depression chronicity and episode recurrence.

The Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) study, a large-scale effectiveness trial, demonstrated that as many as 50% of patients required treatment beyond the first-line therapy, and approximately 30% of patients failed to remit even after 4 sequential therapies,<sup>11</sup> emphasizing the high prevalence of treatment resistance. In another population-based US study,<sup>4</sup> 15% of patients failed to remit and 35% had multiple episodes over 23 years of follow-up. Recurrence rates ranged from 40%<sup>12</sup> to 85%.<sup>13</sup> These results are of particular importance to clinicians, because individuals who are not treated to remission are at higher risk of recurrence.<sup>14,15</sup> Further complications in depression treatment arise from the occurrence of residual symptoms in a substantial percentage of patients who do achieve remission.<sup>16</sup>

The purpose of this article is to review the clinical and demographic characteristics as well as treatment outcomes with current antidepressants in patients treated in primary care and psychiatric settings and to highlight best treatment practices. The relationship between symptom profiles and functional outcomes will also be considered and the potential for individualized diagnostic strategies and treatment selection will be addressed.

- Symptom presentation, level of severity, and response to antidepressants are equivalent between patients treated in primary care and specialty psychiatric clinics.
- There should be some evidence of improvement of symptoms after 2 weeks; if not, then dose adjustment or other interventions should be considered to achieve virtual absence of all symptoms; evidence supporting add-on therapies is inconclusive, and they may increase side effects.
- New research to find biomarkers of depression subtypes may help to select specific targets for new and existing antidepressants; the novel antidepressant vortioxetine may provide favorable outcomes as a monotherapy for a wider range of depressed patients.

## METHOD

English-language evidence-based guidelines and peer-reviewed literature published between January 1, 2005, and December 31, 2011, were identified using PubMed, MEDLINE, and EMBASE. All searches contained the terms *major depressive disorder* and *unipolar depression* and excluded the terms *bipolar disorder/manic depressive disorder*. The following search terms were also included: *naturalistic study, antidepressant, relapse, recurrence, residual symptoms, response, remission, sequential medication trials, and treatment-resistant depression*. Meta-analyses, systematic reviews, and practice guidelines were included. Bibliographies were used to identify additional articles of interest.

Abstracts and articles were screened for relevance to primary care practice. Population-based studies and those involving patients treated in primary care were used whenever possible. Most studies of MDD conducted in primary care practices identified in the searches evaluated process rather than the safety and efficacy of pharmacologic therapies. For that reason, results from a multiple-treatment meta-analysis of 12 new-generation antidepressants<sup>17</sup> and the STAR\*D “real-world” effectiveness study,<sup>18</sup> in which approximately one-third of patients were treated in primary care practices, are emphasized.

## RESULTS

### Depression in Primary Care Versus Psychiatric Clinics

It is often assumed that depressed patients in primary care settings are less severely depressed, have a milder course of illness, and are more likely to present with fatigue or other somatic symptoms compared to patients at psychiatry clinics.<sup>19–21</sup> However, there were few differences in demographics or symptom profiles between primary care and psychiatric clinic patients as demonstrated in the STAR\*D study, wherein 42% of patients were evaluated and treated in a primary care setting.<sup>22</sup> Sociodemographic risk factors for poor outcomes were older age, female gender, African American or Hispanic ethnicity, and receiving Medicare or Medicaid. Only 2 core symptoms—psychomotor agitation

and decreased concentration—occurred significantly more often in specialty care settings.<sup>22</sup>

Baseline severity is also predictive of treatment outcome. In a prospective cohort study of over 1,300 consecutive primary care patients treated in Europe and Chile, 17% had a chronic course of depression, and 40% had at least 1 recurrence.<sup>23</sup> Depression severity based on PHQ-9 total score was also inversely correlated with the likelihood of achieving a sustained remission.<sup>23</sup> Symptom severity at presentation as well as response and remission rates were similar in both primary and specialty settings.<sup>18,22</sup> Lower remission rates were associated with chronic depression (symptom duration >24 months at presentation), as well as medical and psychiatric comorbidities.<sup>18</sup> Difficulty stabilizing symptoms and residual symptoms were also predictive of relapse.<sup>24,25</sup> Response and remission rates were similar in the 2 treatment settings.<sup>22</sup> These results emphasize that effective treatment for moderate to severe depression can be provided in the primary care setting with the use of evidence-based care.

### Guidelines for Evidence-Based Care

The primary goal of acute treatment is to achieve symptom remission, which is typically defined in clinical trials as a score  $\leq 7$  on the 17-item Hamilton Depression Rating Scale<sup>26</sup> or  $\leq 10$  on the Montgomery-Asberg Depression Rating Scale.<sup>27</sup> Beyond remission, there is robust evidence that antidepressants prevent relapse<sup>28,29</sup> and should be prescribed for at least 1 year after a patient achieves remission<sup>30</sup> (Table 1 and Figure 1).

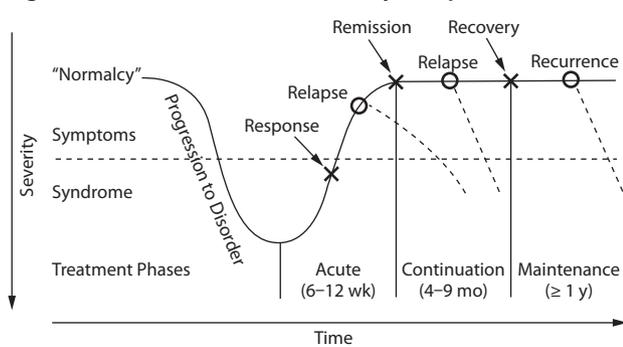
A number of international guidelines such as those of the National Institute for Health and Clinical Excellence,<sup>32</sup> American Psychiatric Association,<sup>33</sup> Canadian Network for Mood and Anxiety Treatments,<sup>34</sup> and British Association for Psychopharmacology<sup>35</sup> address the management of MDD across the treatment phases (Table 2). Although there are differences in recommendations based on depression severity, there is considerable agreement on treatment of an acute major depressive episode. All guidelines recommend psychotherapy (cognitive-behavioral therapy [CBT] or interpersonal therapy) as an option in mild-to-moderate depression. However, lack of immediate access tends to result in pharmacotherapy being the first choice of treatment for a major depressive episode. Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and bupropion are all first-line agents for treating patients with an acute major depressive episode.

In the absence of at least a modest improvement in symptom severity, defined as a reduction of  $\geq 20\%$  in total Hamilton Depression Rating Scale<sup>26</sup> score, optimizing acute treatment by increasing the dose of the first-line medication is usually the first strategy. Switching to another drug within the same class or to a different class or adopting an “add-on strategy,” typically with an augmentation agent (eg, lithium or an atypical antipsychotic) or with a second antidepressant, are also recommended.

**Table 1. Management of Patients With Major Depressive Disorder<sup>a</sup>**

Treatment Phase	Duration	Goals	Activities
Acute and continuation	0–6 mo	Remission of symptoms Restore function	Establish therapeutic alliance Educate Select and use treatment(s) Monitor progress
Maintenance	≥ 6–24 mo	Prevention of recurrence Return to full function	Educate Rehabilitate Treat comorbidities Monitor for recurrence

<sup>a</sup>Adapted with permission from Patten et al.<sup>30</sup>

**Figure 1. Phases of Treatment for Major Depressive Disorder<sup>a</sup>**

<sup>a</sup>Reprinted with permission from Kupfer et al.<sup>31</sup>

Once remission is achieved, treatment should be maintained at the same dose for at least 1 year. Maintenance therapy with drug treatment and/or evidence-based psychotherapies is recommended for a longer duration (24–48 months) for individuals who have  $\geq 3$  risk factors for recurrence (Table 3).<sup>34</sup> During follow-up visits, physicians should ask about residual symptoms, drug-related side effects, and treatment adherence as well as functional and psychosocial outcomes.

### Efficacy and Effectiveness Across Antidepressants

**Evidence from efficacy trials.** There is considerable controversy as to whether current first-line antidepressants have similar efficacy and safety/tolerability profiles. In a large meta-analysis of almost 26,000 patients in 117 antidepressant trials, antidepressants differed in both efficacy (measured as response rates) and tolerability (measured as discontinuation rates)<sup>17</sup> (Figure 2). Response rates after acute treatment for 8 weeks were 25% to 40% higher with mirtazapine, escitalopram, venlafaxine, or sertraline compared with duloxetine, fluoxetine, fluvoxamine, paroxetine, or reboxetine.<sup>17</sup> Escitalopram and sertraline, both SSRIs, had significantly lower discontinuation rates than duloxetine, fluvoxamine, paroxetine, reboxetine (not available in the United States or Canada), and venlafaxine.<sup>17</sup> On the basis of these findings, escitalopram and sertraline provided the best balance between efficacy and tolerability. In addition, the authors of a recently updated Agency for Health Care Research and Quality report concluded that there were no clinically significant differences among antidepressants in acute, continuation, or maintenance phases of MDD

treatment but identified individual differences in head-to-head comparisons, including superiority of escitalopram over citalopram and sertraline over fluoxetine.<sup>36</sup>

**Evidence from effectiveness trials.** The STAR\*D trial evaluated effectiveness in a 4-phase sequential approach (Figure 3) to treating patients in both psychiatric outpatient and primary care clinics. During the first phase of treatment with citalopram,<sup>18,25,38</sup> the response rate was 47% and the remission rate was 33% based on the Quick Inventory of Depressive Symptomatology. Options for nonremitters in step 2 were switching to another SSRI (sertraline), an SNRI (venlafaxine), or bupropion. Regardless of the option selected, the remission and response rates were similar.<sup>38,39</sup> Patients could also switch to CBT monotherapy or augment the citalopram regimen with CBT. Switching to CBT achieved a similar remission rate as switching to a different drug therapy, although it took a longer time to reach remission with CBT augmentation compared to drug augmentation.<sup>40</sup> In summary, switching within the SSRI class (citalopram to sertraline) was no less effective than switching to a different class of antidepressant (citalopram to venlafaxine or bupropion), and there were no significant differences in response or remission rates for patients who progressed to step 3, which involved augmenting step 2 therapy with either bupropion sustained release or buspirone. Overall, the treatments were well tolerated, although approximately 20% of patients discontinued treatment at each step. There were no significant differences in rates of adverse events across the pharmacologic treatment options except when buspirone add-on therapy was associated with a higher incidence of intolerance than bupropion (29% vs 13%, respectively).<sup>39</sup> This trial reaffirmed the importance of treating to remission in the acute phase, as nonremitters and partial remitters (regardless of treatment) were more likely to relapse, and relapses occurred sooner in nonremitters than in remitters.

### Concurrent Combination Therapies

In contrast to the STAR\*D approach involving sequential combination strategies, several investigators have evaluated the benefits of coinitiating treatment with 2 antidepressants from the outset rather than waiting to add a second agent if the first treatment fails. In a relatively small proof-of-concept trial,<sup>41</sup> 2 types of concurrent combined antidepressant therapy were compared with SSRI monotherapy. Although response rates did not differ among the groups, remission rates were significantly higher for mirtazapine plus fluoxetine (52%)

**Table 2. Comparison of International Guidelines in Major Depressive Disorder<sup>a</sup>**

Variable	NICE	CANMAT	APA	BAP
Mild	Guided self-help (cognitive therapy), psychotherapy	CBT/IPT or antidepressant	Psychotherapy ± antidepressant	CBT/BT/AS/IPT
Moderate	Antidepressant ± CBT or IPT	CBT/IPT or antidepressant	Antidepressant	Antidepressant or CBT/BT/AS/IPT
Severe	Antidepressant with individual CBT	Combination therapies Greater emphasis on treatment-resistant depression	Antidepressant or ECT	Antidepressant ± CBT/BT/AS
Severe with psychotic features	ECT/antidepressant + antipsychotic	ECT/antidepressant + antipsychotic	ECT/antidepressant + antipsychotic	ECT/antidepressant + antipsychotic
Relapse prevention	Antidepressant continued at acute treatment dose after remission for at least 2 y	Antidepressant continued at acute treatment dose after remission for at least 2 y	Antidepressant continued at acute treatment dose after remission; up to lifetime in some patients	Antidepressant continued at acute treatment dose after remission for 6–9 mo; up to 2 y for patients at risk for relapse

<sup>a</sup>Based on National Institute for Health and Clinical Excellence (NICE),<sup>32</sup> Canadian Network for Mood and Anxiety Treatments (CANMAT),<sup>34</sup> American Psychiatric Association (APA),<sup>33</sup> and British Association for Psychopharmacology (BAP).<sup>35</sup> Abbreviations: AS = activity scheduling, BT = behavioral therapy, CBT = cognitive-behavioral therapy, CT = cognitive therapy, ECT = electroconvulsive therapy, IPT = interpersonal therapy.

**Table 3. Risk Factors Supporting Long-Term (2-year to lifetime) Maintenance Therapy<sup>a</sup>**

Risk Factor
Older age
≥ 3 Depressive episodes
Chronic episodes
Psychotic episodes
Severe episodes
Difficult-to-treat episodes
Psychiatric or medical comorbidity
Residual symptoms (lack of remission) during current episode
History of recurrence during discontinuation of antidepressants

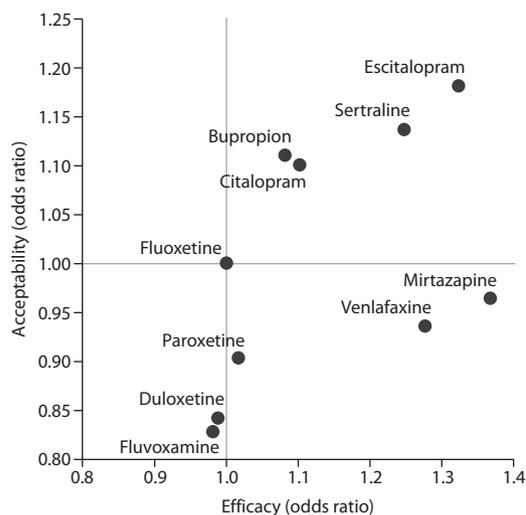
<sup>a</sup>Reprinted with permission from Lam et al.<sup>34</sup>

and mirtazapine plus venlafaxine (58%) compared with fluoxetine alone (25%). When placebo was substituted for one of the paired agents during a double-blind discontinuation phase, relapse occurred in approximately 40% of patients. In a previous 6-week trial, the same group reported remission rates of 19% with mirtazapine alone, 26% with paroxetine alone, and 43% with the combination.<sup>42</sup> However, the Combining Medications to Enhance Depression Outcomes trial<sup>38</sup> did not confirm an advantage for concurrent combined antidepressant therapy. The investigators evaluated outcomes with escitalopram plus placebo, escitalopram plus bupropion, and venlafaxine plus mirtazapine and found no difference in response or remission rates in acute or continuation phases of the treatment.<sup>38</sup> The reasons for these disparities are not yet understood but warrant investigation.

**Residual Symptoms**

The presence and importance of residual symptoms, even in remitted patients, are frequently overlooked. In a study of patients who attained remission while taking fluoxetine, more than 90% had residual symptoms.<sup>43</sup> Sleep disturbance, fatigue, and anhedonia were the most prevalent residual symptoms, which affect neurocognition and function. In the STAR\*D trial, a similar proportion of patients who remitted while taking citalopram (90%) had at least 1 residual symptom—most frequently sleep or appetite/weight

**Figure 2. Comparing Efficacy and Acceptability of Newer Antidepressants Versus Fluoxetine<sup>a</sup>**

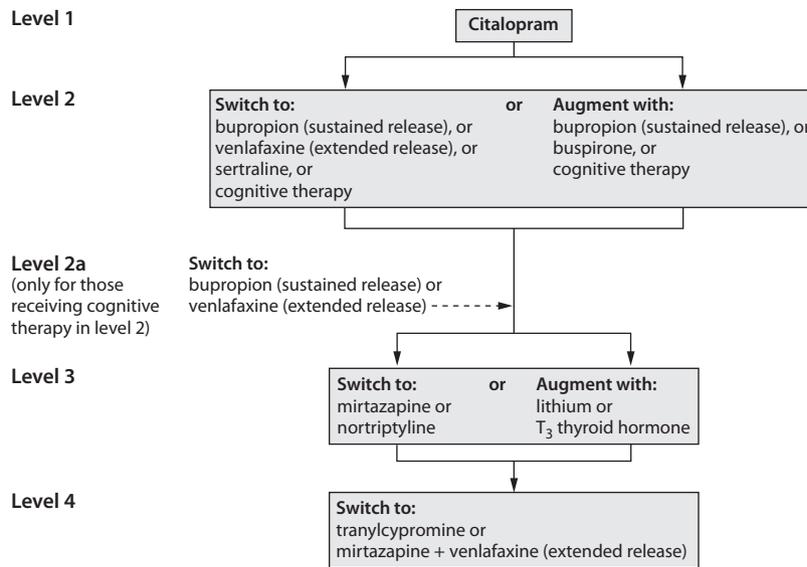


<sup>a</sup>Adapted with permission from Cipriani et al.<sup>17</sup>

<sup>b</sup>Milnacipran and reboxetine were omitted by the authors of the original analysis because they were not available in North America.

disturbance.<sup>44</sup> In contrast to the previously cited fluoxetine study,<sup>43</sup> residual symptoms were predictive of relapse.<sup>44</sup>

**Neurocognition.** There is considerable debate as to whether neurocognitive impairment in depression precedes depressive episodes or whether recurrent episodes are associated with a neurodegenerative process. Neuroimaging studies suggest that repeated episodes are associated with hippocampal volume reduction and neuropsychological impairment,<sup>45</sup> particularly impaired memory, psychomotor, and executive functions, as well as fatigue. These symptoms are common in patients with MDD and frequently persist after mood symptoms remit.<sup>46</sup> In a meta-analysis of antidepressant effects in neurocognitive function, it was concluded that current first-line antidepressants in general do not impair neurocognition, but methodological shortcomings, including small sample sizes in most studies,

**Figure 3. Sequenced Treatment Alternatives to Relieve Depression Treatment Levels<sup>a</sup>**

<sup>a</sup>Reprinted with permission from Gaynes et al.<sup>37</sup>

**Table 4. Single-Item Global Measures of Severity of Depression, Psychosocial Functioning, and Quality of Life<sup>a</sup>**

<b>Depression</b>	
	Rate the current level of severity of your symptoms of depression during the past week
	0 None
	1 Minimal
	2 Mild
	3 Moderate
	4 Severe
<b>Psychosocial functioning</b>	
	Overall, how much have symptoms of depression interfered with or caused difficulties in your life during the past week?
	0 Not at all
	1 A little bit
	2 A moderate amount
	3 Quite a bit
	4 Extremely
<b>Quality of life</b>	
	In general, how would you rate your overall quality of life during the past week?
	0 Very good; my life could hardly be better
	1 Pretty good; most things are going well
	2 The good and bad parts are about equal
	3 Pretty bad; most things are going poorly
	4 Very bad; my life could hardly be worse

<sup>a</sup>Reprinted with permission from Zimmerman et al.<sup>54</sup>

limit conclusions.<sup>47</sup> In contrast, there were residual deficits in sustained and selective attention, memory, and executive function in a subsequent meta-analytic study of remitted patients with MDD,<sup>48</sup> and in a 3-year prospective study of depressed patients in primary care, cognitive symptoms, lack of energy, and sleep disturbances were present 39% to 44% of the time during remission.<sup>49</sup>

**Functional outcomes.** Although functional impairment is implicit in the criteria for a major depressive episode, relatively few clinical trials report changes in functional outcomes despite the availability of several brief validated scales.<sup>50</sup> The Sheehan Disability Scale<sup>51</sup> is a brief 3-item self-report

instrument designed to evaluate the impact of depression on an individual's work, leisure, and family life. Several studies comparing antidepressants show differences in functional outcomes despite equivalent efficacy on symptom scales. For example, in a comparison of escitalopram and duloxetine over 24 weeks,<sup>52</sup> remission rates were comparable (73% and 70%, respectively), but there were significant differences in favor of escitalopram on the Sheehan Disability Scale.

The relationship between treating to remission and restoring quality of life is illustrated in a study of primary care patients receiving antidepressant treatment.<sup>53</sup> After 56 days of treatment, remitters (Montgomery-Asberg Depression Rating Scale score  $\leq 12$ ) had significantly better Euro Quality of Life 5-D scores than responders who did not remit and nonresponders. Results of the STAR\*D trial showed similar correspondence between remission and improved health-related quality of life.<sup>18</sup> These results have particular relevance to the emerging literature on patient self-report outcomes that emphasize the restoration of function and positive affect (Table 4).

### Relapse Prevention

There is robust evidence that antidepressant maintenance treatment prevents relapse. Typically, relapse prevention trials involve treating patients to remission and randomizing half to stay on the antidepressant while the other half receives placebo. Most trials evaluate the percentage of survivors who remain in remission over 6 to 24 months. In a meta-analysis of more than 30 randomized trials,<sup>28</sup> continuing treatment with an antidepressant reduced the odds of relapse by 70%. The relapse rate was 41% among patients receiving placebo and 18% among those who continued to receive an antidepressant.<sup>28</sup> These findings were confirmed in an updated meta-analysis of relapse prevention antidepressant trials.<sup>29</sup>

Other relapse prevention trials with venlafaxine,<sup>55</sup> duloxetine,<sup>56</sup> and escitalopram<sup>57</sup> have demonstrated significantly reduced relapse rates and low discontinuation rates due to adverse events. Another analysis from the extended Prevention of Recurrent Episodes of Depression with Venlafaxine Extended Release for Two Years trial demonstrated similar relapse prevention and discontinuation rates between venlafaxine extended release and fluoxetine,<sup>58</sup> and superiority of venlafaxine extended release over placebo after 1 and 2 years.<sup>55</sup>

### Treatment-Resistant Depression

The current definition of treatment-resistant depression requires that 2 or more first-line antidepressants prescribed at adequate doses for an adequate duration fail to produce a response. When treatment-resistant depression is suspected, misdiagnosis (eg, bipolar disorder), comorbid diagnoses (eg, substance abuse disorder), and nonadherence should first be ruled out.<sup>58</sup> There is no consensus on optimal next steps, although augmentation and combination strategies are routinely used.<sup>34</sup> Lithium is an established first-line augmentation strategy<sup>59</sup> despite limited information about its efficacy and safety in combination with SSRIs or SNRIs. Triiodothyronine (T<sub>3</sub>) appears to have similar efficacy to lithium with better tolerability.<sup>60</sup> Adjunctive methylphenidate improved apathy and fatigue in patients with treatment-resistant MDD but did not significantly reduce depression scores over 5 weeks.<sup>61</sup> Nevertheless, a systematic review of 32 trials found limited and inconsistent results for most strategies.<sup>62</sup> The most convincing evidence for augmentation strategies comes from several atypical antipsychotic studies.<sup>63</sup> Aripiprazole is now indicated in the United States as an adjunctive treatment for MDD on the basis of superiority to placebo with low rates of adverse event discontinuation (<10%),<sup>64</sup> and olanzapine in combination with fluoxetine is approved for treatment-resistant depression.<sup>65</sup> However, the improvement in depressive symptoms comes at the cost of potentially severe neuroendocrine, metabolic, and extrapyramidal side effects.<sup>63</sup>

### Adherence and Side Effects

In a review of adherence and persistence in patients prescribed branded and generic SSRIs and SNRIs, 30% of patients had discontinued treatment regardless of the drug prescribed within the first month.<sup>66</sup> At 12 months, adherence rates were 25% for SSRIs, 34% for venlafaxine extended release, and 38.1% for duloxetine, and persistence ranged from 129.1 days to 158.5 days.<sup>66</sup> These findings are consistent with an analysis performed in Quebec, Canada, wherein more than 60% of patients were found to be nonpersistent with antidepressants after 6 months.<sup>10</sup>

The reasons for nonadherence and nonpersistence can be diverse; however, physicians may underestimate the incidence of side effects and their impact on a patient's adherence to treatment.<sup>67</sup> One approach to increasing patient-reported side effects is to use a patient checklist.

In a recent trial, patients endorsed 20 times more side effects than were recorded on physician clinical notes, and about half described at least 1 side effect as very or extremely troubling.<sup>67</sup> By understanding the patient view of side effects, treatment choices can better meet the needs of individual patients.

Weight gain and sexual dysfunction are most concerning to patients during antidepressant maintenance therapy.<sup>68</sup> Although weight gain during SSRI or SNRI treatment is moderate overall, excessive weight gain is most likely to occur with mirtazapine and paroxetine.<sup>69,70</sup> Rates of sexual side effects associated with SSRIs and SNRIs range from 25% to 73%, although lower rates in the range of 10% to 25% are associated with bupropion and trazodone.<sup>71,72</sup> For bupropion, the difference is thought to be related to higher available dopamine levels, and trazodone blocks the activation of serotonin 5-HT<sub>2</sub> receptors that are responsible for sexual side effects with SSRIs and SNRIs.<sup>73</sup> In general, agents that are 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> antagonists<sup>74-76</sup> and 5-HT<sub>1A</sub> agonists<sup>77</sup> have favorable sexual profiles.

### Individualizing Antidepressant Therapy: Future Directions

While the overall effect size for antidepressant response in the acute phase of treatment is modest,<sup>78</sup> there are several publications showing distinct response trajectories differentiating responders and nonresponders to a range of antidepressants.<sup>58,79</sup> The challenge for researchers and clinicians is to identify markers of response at the earliest possible stage of treatment.

Clinical subtypes (eg, melancholic vs atypical) or profiles (symptom severity, childhood trauma) have limited utility in individualizing treatment strategies. While research has demonstrated that depression with seasonal patterns responds to light therapy and psychotic depression benefits from the use of atypical antipsychotics, there are few other examples of how clinical subtypes have led to distinctive treatment pathways.

Biomarkers also have not been helpful at the individual patient level to identify diagnostic subgroups or to select specific treatments. Neuroimaging offers an opportunity to examine neural pathways in patients at rest and in association with emotional challenges (eg, positive or negatively valenced pictures, words, faces) and to identify differences in brain responses. McCabe et al<sup>80</sup> demonstrated differences in how brain circuits associated with pleasure react to pictures and the taste of chocolate with an SSRI or a norepinephrine-acting antidepressant. Furthermore, data arising from the fusion of structural and functional brain imaging in patients with recurrent episodes of depression support the role of certain regions (eg, hippocampus, orbitofrontal cortex, subgenual cingulate) in the pathophysiology of depression and risk of recurrence.<sup>45,81</sup>

Other advances have come from the field of molecular psychiatry, wherein a combination of biomarkers reflecting monoamine neurotransmitters, neurotrophic factors, and inflammatory markers is able to distinguish patients with

MDD from healthy controls.<sup>82</sup> Although it is unlikely that any one of these putative biomarkers will identify unique subpopulations or predict treatment response, integrated biomarkers involving neuroimaging, proteomic, and genomic data, as well as clinical profiles, may help to individualize treatment strategies.<sup>83</sup>

### Antidepressant Development

The discussion so far has focused on identifying and applying currently accepted approaches to the use of first-line antidepressants, specifically dose optimization and switching strategies. However, there is growing support to explore mechanisms that go beyond the classical serotonin transporter and/or norepinephrine transporter targets.<sup>84</sup> There is also evidence that genetic factors related to patient susceptibility to MDD may correlate with treatment response<sup>85</sup> and potentially improve prevention, diagnosis, and treatment. New therapeutic targets include brain regions regulating circadian rhythms, the immune system,<sup>86–88</sup> and neurotrophins.<sup>89–91</sup> In addition, *N*-methyl-*D*-aspartate antagonists to target stress-related perturbation of the hypothalamic pituitary axis are currently being explored.<sup>92–95</sup> Moreover, a serotonin reuptake stimulator (tianeptine) has shown efficacy in MDD and is currently marketed for that indication in Europe and Asia, although this drug appears to act primarily as a glutamatergic agent.<sup>96</sup>

New molecular entities that target multiple receptors are in development and potentially would obviate the need for using multiple agents. Lu AA21004 (vortioxetine) has an affinity for the 5-HT<sub>1A</sub>, 5-HT<sub>1B</sub>, 5-HT<sub>3</sub>, and 5-HT<sub>7</sub> receptors, as well as the serotonin transporter.<sup>97</sup> Preliminary data from pivotal trials have recently been published.<sup>98,99</sup> Triple reuptake inhibitors that act at serotonin, norepinephrine, and dopaminergic transporters also are being studied.<sup>100</sup>

### SUMMARY AND CONCLUSIONS

Depressed patients with MDD seen in primary care tend to have sociodemographic and clinical features placing them at high risk for incomplete response and recurrence or relapse. This risk can be reduced by ensuring adequate dosing of antidepressant treatment during acute and maintenance therapy. Patient-directed treatment goals should be geared to selecting appropriate treatment and achieving remission. Patients should not continue on any antidepressant at the same dose for more than 4 weeks if there is no evidence of at least partial symptomatic improvement. Primary care physicians should have experience prescribing several current first-line antidepressants and several add-on strategies. The emphasis during maintenance treatment is on adherence and psychosocial and functional rehabilitation, as well as maintaining symptom remission. To maximize remission in the real world, individualized patient treatment is an important research avenue to improve antidepressant selection. New antidepressant therapies with novel mechanisms that limit unwanted side effects will offer alternative therapeutic options to treat depressed patients in primary care as well as specialist settings.

**Drug names:** bupropion (Wellbutrin, Aplenzin, and others), buspirone (BuSpar and others), citalopram (Celexa and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), lithium (Lithobid and others), methylphenidate (Focalin, Daytrana, and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

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