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[Category: Review]

New Treatment Options for Depression: A Primer for Internists

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### Clinical Significance

- Multiple new antidepressant and adjunctive medication options have been approved over the past decade for treatment of major depressive disorder.
- The therapies outlined should be considered for patients with treatment-resistant depression and adverse effects to first-line medications.

## Abstract

Depression continues to be a challenging condition to treat despite the myriad treatment options available. Primary care providers are increasingly tasked with providing second- and third-line treatments for major depressive disorder and, thus, should be familiar with newer medication therapies that are available. In this article, we aim to provide the general internist and other providers who treat depression in their practice with a succinct review of recent developments in the treatment of depression.

## Abbreviations

5-HT, serotonin

FDA, US Food and Drug Administration

MADRS, Montgomery-Asberg Depression Rating Scale

MTHFR, 5,10-methylenetetrahydrofolate reductase

NE, norepinephrine

SNRI, serotonin-norepinephrine reuptake inhibitor

SSRI, selective serotonin reuptake inhibitor

## Background

Major depressive disorder is a common condition, affecting 6.7% of adults in the United States in 2015<sup>1</sup>; 16.2% of Americans will experience a depressive episode during their lifetime,<sup>2</sup> and in 2010, depression resulted in 8 million ambulatory visits in the United States.<sup>3</sup> Antidepressants are the second most commonly prescribed drug class, with a peak prevalence of 26% in women aged 50 to 64 years.<sup>4</sup> Although a plethora of treatment options are available, most patients (56%-72.5%) will not respond to initial treatment with antidepressant monotherapy.<sup>5,6</sup> Thus, additional treatment options are needed for patients with inadequate response to first-line medications. In this article, we aim to familiarize

physicians with newer and adjunctive pharmacologic major depressive disorder treatments.

### **Antidepressants Approved in the Past 10 Years**

#### ***Desvenlafaxine***

Desvenlafaxine, the third serotonin-norepinephrine reuptake inhibitor (SNRI), was approved by the US Food and Drug Administration (FDA) in 2008 for major depressive disorder. Although it has been reported as safe and well-tolerated in children,<sup>7,8</sup> it is not currently approved for use in pediatric patients. Desvenlafaxine is a salt of the major active metabolite of venlafaxine. It binds serotonin (5-HT) and norepinephrine (NE) receptors, with inhibition of 5-HT uptake being approximately 10 times more potent than NE uptake.<sup>9</sup>

Desvenlafaxine was studied in 3 randomized controlled trials at doses of 100 to 400 mg/d. The first 2 trials showed improvements in depression rating scales compared with placebo,<sup>10,11</sup> but the third study did not show a significant benefit of desvenlafaxine over placebo at 8 weeks.<sup>12</sup> Because data from the initial studies showed increasing adverse effects with higher doses of desvenlafaxine, another study evaluated lower dosages and showed improvements in the primary end point, Hamilton Rating Scale for Depression score, with desvenlafaxine over placebo at the 50-mg but not the 100-mg dose.<sup>13</sup>

Despite the availability of 25-mg, 50-mg, and 100-mg desvenlafaxine tablets, 50 mg/d is the recommended starting and maintenance dosage, on the basis of the above trial data. Desvenlafaxine is generally safe and well tolerated at this dosage. Trial data indicate that doses higher than 50 mg offer no additional benefit<sup>14</sup> and are associated with increased adverse effects and discontinuation rates.<sup>9,15</sup> Because metabolism of desvenlafaxine is through hepatic conjugation and urinary excretion, dosing should be adjusted for those with hepatic and renal impairment (Table). For discontinuation, tapering over 2 to 4 weeks is suggested;

the 25-mg tablet should be used for this purpose.<sup>14</sup> Desvenlafaxine is only available as extended-release tablets, which should not be split.

Desvenlafaxine has minimal inhibitory and induction effects on cytochrome P450 and CYP2D6.<sup>17</sup> Thus, the risk of drug-drug interactions is lower for desvenlafaxine than for other SNRIs. The most common adverse effects include nausea, insomnia, dizziness, dry mouth, and decreased appetite, with nausea being the most common reason for discontinuation. Because blood pressure can be increased with use of desvenlafaxine, it should be monitored periodically during treatment. Desvenlafaxine has limited effects on sexual function and weight, which may also be benefits to consider.<sup>15</sup>

Desvenlafaxine has also been used off label for the treatment of menopausal hot flashes, with placebo-controlled trial data showing evidence of benefit at a dosage of 100 mg daily.<sup>18</sup> Unlike the case with other SNRIs, study outcomes do not support the use of desvenlafaxine for treatment of neuropathic pain.<sup>19, 20</sup> In summary, prescribers should consider the use of desvenlafaxine for patients who have concomitant postmenopausal vasomotor symptoms or those who are taking other medications metabolized through the cytochrome P450 and CYP2D6 pathways.

### ***Levomilnacipran***

Levomilnacipran is a novel SNRI that was FDA approved for the treatment of major depressive disorder in adults in 2013. It is not currently approved for use in children. It is the enantiomer of milnacipran, which is currently FDA approved for the treatment of fibromyalgia. Unlike the other SNRIs, levomilnacipran more potently inhibits NE reuptake relative to 5-HT reuptake by about 2-fold.<sup>21</sup>

Approval for levomilnacipran was based on a series of randomized, double-blind, placebo-controlled trials. Initial, short-term trials evaluated the drug

for 8 weeks at doses of 40 to 120 mg. In 3 trials,<sup>22-24</sup> levomilnacipran in all doses was significantly more effective than placebo in decreasing the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline to the end of the trial. Two longer-term trials evaluated the drug for 24 and for 48 weeks. The first showed a decrease in MADRS score from week 0 to week 48,<sup>25</sup> and the second showed a nonsignificantly longer time to depression relapse in the levomilnacipran group.<sup>26</sup>

Levomilnacipran is started at 20 mg once daily for 2 days and then increased on day 3 to 40 mg/d. It may then be increased by 40-mg increments every 2 days to a maximum dose of 120 mg/d. Because levomilnacipran is primarily renally excreted, patients with moderate-to-severe renal impairment should be prescribed adjusted doses ( $\leq 80$  mg/d). Gradual taper over at least several weeks is recommended for discontinuation. Levomilnacipran is available only as an extended-release capsule that cannot be split. A dose-titration pack is available for the initial 28 days of therapy (contains 2 20-mg and 26 40-mg capsules).

The most common adverse effects of levomilnacipran are headache, gastrointestinal tract symptoms (nausea, vomiting, constipation), hyperhidrosis, tachycardia, urinary hesitancy, and erectile dysfunction and ejaculatory disorders in men.<sup>22-27</sup> The incidence of these adverse effects is not dose related, with the exception of erectile dysfunction and urinary hesitancy due to increased peripheral NE tone. Short-term studies also showed small mean increases (3-4 mm Hg) in both systolic and diastolic blood pressure and mild increases in serum transaminase values in those taking levomilnacipran compared with placebo.<sup>22-24, 27</sup> Unlike many commonly used antidepressants, levomilnacipran has not been associated with weight gain or significant prolongation of QTc interval.<sup>22-24, 27</sup>

Because of levomilnacipran's chemical similarity to milnacipran, it would be a good choice for patients with concomitant fibromyalgia. Prescribers

should also consider levomilnacipran for patients with substantial negative symptoms of depression because the increased noradrenergic activity of levomilnacipran may improve these symptoms more effectively.

### ***Vilazodone***

Vilazodone is a novel antidepressant that was FDA approved in 2011 for the treatment of major depressive disorder. It has selective serotonin reuptake inhibitor (SSRI) effects plus postsynaptic 5-HT<sub>1A</sub> receptor partial effects, so it is regarded as a serotonin partial agonist-reuptake inhibitor.<sup>28-30</sup> Because of the 5-HT<sub>1A</sub> effects, vilazodone is hypothesized to have a more rapid onset of effect than other antidepressants,<sup>31</sup> although no head-to-head clinical trials have confirmed this.

Vilazodone was FDA approved for treatment of major depressive disorder on the basis of 8-week, randomized, double-blind, placebo-controlled trials. Vilazodone at a dosage of 40 mg/d showed superior efficacy over placebo in mean changes on several depression rating scales—MADRS, Hamilton Rating Scale for Depression, and Clinical Global Impressions scale.<sup>32,33</sup> In addition, significant differences on the MADRS were observed in week 1,<sup>30,32</sup> which supports the theory of a more rapid onset of therapeutic benefit for vilazodone. Furthermore, subsequent pooled-data studies showed significantly greater improvement in depressive symptoms that were apparent from week 1<sup>34</sup> and superior efficacy of vilazodone over placebo in cumulative response rates, also evident from week 1 ( $P < .001$ ).<sup>35</sup>

Vilazodone should be started at 10 mg/d and doubled every 7 days to a target of 40 mg/d. More gradual dose titration should be considered for patients with severe gastrointestinal adverse effects. Dosage adjustment to 20 mg/d is recommended if vilazodone is used in combination with a strong CYP3A4 inhibitor, but no adjustment is required for those with mild-to-moderate renal or

hepatic impairment. Vilazodone has not been studied for use in the setting of severe renal or hepatic dysfunction.<sup>31, 36</sup>

The most common adverse effects of vilazodone are diarrhea (28%), nausea (23.4%), insomnia (6%), headache (13.4%), dizziness (8.5%), and dry mouth (8.0%).<sup>31, 37</sup> One published randomized controlled trial showed comparable safety and tolerability between vilazodone and citalopram.<sup>38</sup> Insomnia is an important adverse effect to consider when selecting vilazodone. A study of 10 healthy men receiving 1 20-mg dose of vilazodone showed decreases in total sleep time, loss of rapid eye movement sleep, and more wakefulness in later portions of the night with vilazodone compared with placebo.<sup>31, 39</sup> Patients treated for 8 weeks with vilazodone did not have significant weight gain,<sup>32, 33</sup> and the mean weight increase in patients treated with vilazodone for 52 weeks was 1.7 kg.<sup>40</sup> Vilazodone is speculated to have a lower risk of treatment-related sexual adverse effects and to improve depression-related sexual dysfunction on the basis of its postsynaptic 5-HT<sub>1A</sub> receptor actions. Pooled data from placebo-controlled trials of vilazodone showed that 91% of patients had stable or improved sexual function at the end of treatment.<sup>41</sup> Only 8% of vilazodone-treated patients noted treatment-related sexual dysfunction (vs 0.9% with placebo),<sup>41</sup> which is much lower than rates seen with other common antidepressants.<sup>42</sup>

An 8-week randomized, double-blind, placebo-controlled trial of vilazodone for treatment of generalized anxiety disorder showed a significantly greater change in Hamilton Anxiety Rating Scale score in the vilazodone group ( $P < .001$ ).<sup>43</sup> Use of vilazodone for anxiety is currently off label, but vilazodone may be a good choice for patients with concurrent depression and anxiety. Prescribers should also consider vilazodone in patients with sexual dysfunction.

### ***Vortioxetine***

Vortioxetine is an SSRI that was FDA approved in 2013 for the treatment of major depressive disorder in adults. It is not currently approved for use in children. Originally branded as Brintellix, the brand name was changed to Trintellix (Takeda Pharmaceuticals) in 2016 because of confusion with the drug Brilinta (ticagrelor; AstraZeneca). Although vortioxetine is considered an SSRI, its precise mechanism of action is ambiguous because of multiple effects, including antagonism at 5-HT<sub>3</sub>, 5-HT<sub>1D</sub>, and 5-HT<sub>7</sub> receptors and agonism at 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors.<sup>44</sup>

Vortioxetine was studied in 11 short, randomized, placebo-controlled trials and 5 longer-duration open-label trials. Vortioxetine at fixed dosages of 15 mg/d and 20 mg/d was associated with statistically significant improvement ( $P < .001$ ) in MADRS score and major depressive disorder remission rates.<sup>45</sup>

Vortioxetine is available as 5-mg, 10-mg, and 20-mg tablets; 10 mg/d is the recommended starting dosage. Dosage adjustment is not required for persons with renal and mild-to-moderate hepatic impairment, and there are no data to advise its use with severe hepatic impairment. A maximum of 10-mg dosing is recommended for poor metabolizers of CYP2D6. If dosing is more than 15 mg/d, a reduction to 10 mg/d for 1 week is advised before discontinuation.

Vortioxetine is generally safe and better tolerated than other antidepressants.<sup>46, 47</sup> Common adverse effects of vortioxetine include dizziness, headache, and gastrointestinal upset.<sup>47-49</sup> Sexual dysfunction was increased mildly (1%-5%) in some studies<sup>48</sup> but not significantly increased in others.<sup>47</sup> Vortioxetine was not associated with significant increases in blood pressure, heart rate, QT interval, or weight.<sup>47, 48</sup>

Unlike other SSRIs, vortioxetine has unclear benefits in the treatment of generalized anxiety disorder. Some studies show small benefit and others show no benefit; meta-analyses of the available studies also show mixed results.<sup>50, 51</sup> Thus,

we recommend against the use of vortioxetine for major depressive disorder with concomitant anxiety because other available drugs have clear benefit in the treatment of both. The clinical role for vortioxetine would be for patients who do not tolerate antidepressant therapy because of adverse effects.

### **Augmentation Strategies**

#### ***Second-Generation Antipsychotics***

The second-generation antipsychotics are thought to be beneficial for treatment of depression through variable effects on several neurotransmitters, including the 5-HT<sub>2</sub>, 5-HT<sub>1A</sub>, and dopamine D<sub>2</sub> and D<sub>3</sub> receptors and the NE reuptake transporter.<sup>52</sup> The second-generation antipsychotic medications currently FDA approved for adjunctive treatment of depression are aripiprazole, olanzapine, quetiapine, and brexpiprazole. Augmentation with ziprasidone and risperidone has been described, although their use remains off label.<sup>53, 54</sup>

Aripiprazole is a second-generation antipsychotic that was the first of its class to be FDA approved, in 2008, for adjunctive therapy for major depressive disorder. Two industry-conducted, randomized, placebo-controlled studies of aripiprazole have demonstrated the efficacy of adjunctive aripiprazole added to standard antidepressant therapy (SSRIs or SNRIs) in improving depression symptom scores and remission rates in nonresponders to first-line antidepressant therapy alone. The rates of remission in the treatment group vs the placebo group were 26.0% vs 15.7% ( $P=.01$ ) in one study<sup>55</sup> and 25.4% vs 15.2% ( $P<.05$ ) in the other.<sup>56</sup> The dosage used in these studies was 5 mg/d, titrating upward by 5 mg per week, as needed, to a maximum dosage of 15 mg/d. The dosage was decreased to 2 mg/d if the patient had adverse effects at the 5-mg/d dosage.

Brexpiprazole was FDA approved in 2015 on the basis of industry-conducted, 6-week, randomized, placebo-controlled studies of patients who had inadequate response to standard antidepressant therapy. The 1-mg daily dosage did

not show significant benefit, but the 3-mg daily dosage showed improvement in the primary end point (MADRS score) compared with placebo.<sup>57</sup> A fixed 2-mg dose and showed improvements in MADRS score and Sheehan Disability Scale.<sup>58</sup> Brexpiprazole should be started at 0.5 to 1 mg/d and increased by 1 mg each week to a maximum of 3 mg/d.

The notable potential adverse effects of second-generation antipsychotics include extrapyramidal symptoms, hyperprolactinemia, anticholinergic effects, and weight gain/metabolic syndrome. More rare but serious adverse effects include tardive dyskinesia, neuroleptic malignant syndrome, seizures, and agranulocytosis. Dosages of the second-generation antipsychotics used for major depressive disorder treatment augmentation are typically lower than those used for other indications, so fewer adverse effects will most likely occur. Aripiprazole and brexpiprazole are associated with lower risks of metabolic disorders and anticholinergic adverse effects than many of the other second-generation antipsychotics and, thus, may be preferred over most of the other second-generation antipsychotics in this setting.<sup>59</sup> Additionally, brexpiprazole is associated with fewer extrapyramidal symptoms and akathisia, which may make it the preferable agent for augmentation, although aripiprazole may be cheaper (Table).

Augmentation with second-generation antipsychotics is favorable over combination antidepressant therapy or further antidepressant switching for patients with severe treatment-resistant depression, depression with psychotic features, substance-use disorders, and personality disorders.<sup>60</sup>

### ***Folic Acid Derivatives***

Folic acid was hypothesized to be beneficial in the treatment of depression after studies demonstrated a relationship between folate deficiency, depression, and treatment resistance to first-line antidepressants.<sup>61, 62</sup> Studies,

including small randomized placebo-controlled trials, of folic acid and methyltetrahydrofolate as adjunctive therapy to standard treatment with antidepressants have shown improvement in depression response rates with the addition of a folate derivative.<sup>63-65</sup> Dosages of folate used in these studies ranged from 200 to 500 mcg/d with 15 to 50 mg/d of methyltetrahydrofolate.<sup>65</sup>

Folic acid (supplemental form of folate) and dihydrofolate (food-derived form of folate) are both converted to L-methylfolate (the centrally active form of folate that crosses the blood-brain barrier) by 5,10-methylenetetrahydrofolate reductase (MTHFR). About 8% to 20% of white North Americans are homozygous and 40% to 50% are heterozygous for mutations in the *MTHFR* gene, which confer decreased enzymatic activity.<sup>62</sup> Persons with decreased MTHFR activity would be expected to have decreased response to folic acid—hence, the rationale for treatment with L-methylfolate, which bypasses the need for conversion by MTHFR.

One randomized, double-blind, placebo-controlled trial demonstrated that L-methylfolate, used as adjunctive therapy to SSRIs in patients not initially responding to SSRI therapy, increased response to treatment, from 14.6% in the placebo group to 32.3% in the treatment arm after 30 days of therapy.<sup>66</sup> This benefit was seen only at the 15-mg/d dosage. No substantial adverse effects were reported in the treatment group compared with placebo.

L-methylfolate is classified as a *medical food* (as opposed to folic acid, which is a supplement). Medical foods do not require FDA approval before marketing and are regulated like supplements, but the packaging appears similar to prescription products. Unlike supplements, medical foods can be labeled for treatment of specific medical conditions.<sup>67</sup> Since L-methylfolate is more expensive than folic acid (\$94 vs \$7 for a 30-day supply),<sup>16</sup> targeted *MTHFR* genotyping may be useful in patients for whom this therapy is being considered.

## Conclusion

This review has discussed recently approved medications for treatment of major depressive disorder. Given the frequency of depression in the general population, general internists and other primary care providers should keep themselves abreast of treatment options for this common and often chronic disease. Although several newer antidepressants and augmentation strategies are available, we recommend that providers consider these to be third- or fourth-line treatments after trials of antidepressants that are generically available, primarily because of cost. With the exception of desvenlafaxine and aripiprazole, the lack of generic availability may make these drugs cost-prohibitive for many patients, at hundreds of dollars per month if not covered by insurance. Prescribers may also want to consider the use of these agents for patients who have had adverse effects associated with first-line therapies.

Although this review has focused on pharmacologic therapy, physicians should also consider nonmedication treatment options for patients who do not respond to first-line medications. Psychotherapy (in-person and internet-based) has been well-described as both an alternative and adjunct to antidepressant medication.<sup>68,69</sup> Exercise, an inexpensive and well-tolerated intervention with additional health benefits, also has been systematically reviewed and provides moderate benefit.<sup>70</sup>

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**Table.** Comparison of Newer Antidepressant Drugs

<b>Drug</b>	<b>Mechanism of Action</b>	<b>Dosing</b>	<b>Notable Adverse Effects</b>	<b>Other Considerations</b>	<b>Cost for 30-day Supply (Dose)<sup>1</sup></b>
Monotherapy					
Desvenlafaxine	SNRI	Start at 50 mg/d Can increase, although additional benefit of dosages >50 mg is limited For moderate-severe hepatic impairment: maximum dosage is	Nausea, insomnia, dizziness, dry mouth, and decreased appetite Must monitor periodically for increased blood pressure	Improves menopausal hot flashes No benefit for neuropathic pain	\$150 (50 mg)

		100 mg/d			
		For CKD			
		stage 4 or			
		greater:			
		maximum			
		dosage is			
		50 mg/d			
Levomilnacipra	SNRI	Start at 20	Headache,	Consider with	\$340
n		mg/d for 2	nausea/vomitin	concomitant	(40
		days, then	g,	fibromyalgia	mg)
		increase to	hyperhidrosis,	Good for	
		40 mg/d	constipation,	patients with	
		Titrate	tachycardia,	negative	
		every 2+	urinary	symptoms of	
		days based	hesitancy,	depression	
		on	erectile	Weight neutral	
		response	dysfunction,	No QT	
		to	ejaculatory	prolongation	
		maximum	disorders		
		dosage of	May cause small		
		120 mg/d	increase in		
			blood pressure		
			(3-4 mm Hg)		
			and		
			transaminases		
Vilazodone	SPARI	Start at 10	GI symptoms,	Additional	\$220
		mg/d and	insomnia,	benefit for	(40

double headache, anxiety mg)  
 every 7 dizziness, dry May have  
 days to 40 mouth faster onset of  
 mg/d antidepressant  
 Limit effect  
 dosage to Less sexual  
 20 mg/d if dysfunction  
 used in Weight neutral  
 combinatio  
 n with  
 strong  
 CYP3A4  
 inhibitors  
 Has not  
 been  
 studied for  
 use with  
 severe  
 renal or  
 hepatic  
 dysfunctio  
 n

Vortioxetine	SSRI	Start at 10 mg/d Can increase to 20 mg/d if needed Do not exceed 10 mg/d for CYP2D6 poor metabolizers	GI symptoms, headache, dizziness	No increase in blood pressure, heart rate, QT interval Limited benefit for anxiety	\$330 (10 mg)
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## Adjunctive Therapy

Aripiprazole	Second-generation antipsychotic	Start at 2-5 mg/d Titrate every 7+ days based on response to maximum dosage of 15 mg/d	Headache, extrapyramidal symptoms, akathisia, sedation, insomnia, weight gain, metabolic syndrome, anticholinergic effects, tremor	Not for use as monotherapy	\$75 (5 mg)
Brexiprazole	Second-generation	Start at 0.5-1 mg/d	Akathisia, metabolic	Not for use as monotherapy	\$984 (2 mg)

	antipsychot ic	Titrate every 7+ days based on response to maximum dosage of 3 mg/d	syndrome, weight gain, headache, extrapyramidal symptoms, dizziness		
L-Methylfolate	Medical food	15 mg/d	No substantial known adverse effects	Not for use as monotherapy	\$143 (15 mg)

Abbreviations: CKD, chronic kidney disease; GI, gastrointestinal; SNRI, serotonin-norepinephrine reuptake inhibitor; SPARI, serotonin partial agonist-reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.