

## Update on New Therapies for Treating Major Depressive Disorder (MDD)

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Depressive disorders, including Major Depressive Disorder (MDD), are common mental health conditions thought to be related to imbalances in serotonin and norepinephrine. Medical management of depressive disorders include first-generation antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) and second generation antidepressants (selective serotonin reuptake inhibitors [SSRIs] and serotonin/norepinephrine reuptake inhibitors [SNRIs]). Recently, two antidepressants were approved for use in MDD, levomilnacipran (Fetzima<sup>®</sup>) and vortioxetine (Brintellix<sup>®</sup>).

### Comparative Efficacy

The FDA-accepted primary endpoint of trials evaluating antidepressants for efficacy is change in baseline in an administered depression scale, often the Montgomery-Asberg Depression Rating Scale (MADRS) or the Hamilton Rating Scale for Depression (HAM-D).<sup>1</sup> Response and remission rates are common outcomes by which antidepressants are clinically evaluated. Response refers to a clinically significant degree of depressive symptom reduction following treatment initiation (generally accepted as a 50% decrease in MADRS or HAM-D score).<sup>2,3</sup> Remission is the virtual absence of depressive symptoms (generally accepted as a MADRS score of <10 or HAM-D score of <7).<sup>2</sup> The period of remission may end with either relapse (a return of the index major depressive episode following the onset of remission) or recovery (recognized when the period of remission has been successfully sustained).<sup>2</sup>

Current evidence suggests that most antidepressants have similar efficacy for the treatment of MDD.<sup>4</sup> SSRIs are used first line because they have their favorable risk-benefit ratio;<sup>5</sup> at the same time, because most SSRIs are generic, they are inexpensive. An AHRQ comparative efficacy review shows that more patients reach response and remission with escitalopram than citalopram, that citalopram may have a faster onset of action than fluoxetine but no greater response or remission rates after 8 weeks, and more patients responded to sertraline than fluoxetine (NNT=14).<sup>4</sup>

### Optimal Treatment of First-Episode MDD

The American Psychiatric Association guidelines for depression recommend offering an antidepressant as an initial treatment choice for patients with mild to moderate MDD, and definitely providing an antidepressant to those with severe MDD.<sup>6</sup> After an adequate trial of an antidepressant dose (4-6 weeks), patients should be evaluated for response and antidepressant doses should be increased if a response is not seen.<sup>6</sup> If a patient does not achieve a response after 4-6 weeks on the maximum dose or is unable to tolerate side effects, the trial is considered failed and the patient should be switched to an alternative agent (another SSRI or non-SSRI antidepressant).<sup>6</sup> Once response is achieved, treatment should continue unmodified for 4-9 months before discontinuing therapy to prevent relapse in first episode MDD.<sup>6</sup>

### Preferred Antidepressants for Oregon Medicaid

Oregon law prohibits traditional methods of Preferred Drug List (PDL) enforcement for mental health drugs. The Oregon Health Plan (OHP) relies on prescribers to voluntarily choose high value antidepressants for Oregon Medicaid patients. Second generation antidepressants were reviewed for clinical efficacy and safety with specific agents chosen as clinically preferred (table 1). Prescribing preferred antidepressants eliminates patient copays. OHP patients are charged \$3 copays for non-preferred branded antidepressants and \$1 for non-preferred generic antidepressants (table 2).

Table 1. Current preferred agents on the Voluntary Mental Health PDL

Preferred Agents	
Amitriptyline Tablet	Imipramine Tablet
Bupropion HCl/SR Tablet	Mirtazapine Rapids/Tablet

Citalopram Tablet/Solution	Nortriptyline Capsule/Solution
Escitalopram	Paroxetine Tablet
Fluoxetine	Sertraline Oral Tablet/ Concentrate
Fluvoxamine	Venlafaxine Tablet/ER

Table 2. Current non-preferred agents on the Voluntary Mental Health PDL

Non-preferred Agents	
Bupropion XL /Bupropion HBr (APLENZIN <sup>®</sup> )	Levomilnacipran (FETZIMA <sup>®</sup> )
Clomipramine HCl	Nefazodone
Desvenlafaxine (PRISTIQ <sup>®</sup> , KHEDEZLA <sup>®</sup> )	Paroxetine HCl (PAXIL CR <sup>®</sup> ), Paroxetine Mesylate (PEXEVA <sup>®</sup> )
Duloxetine	Selegiline Patch (EMSAM <sup>®</sup> )
Escitalopram Solution	Vilazodone (VIIBRYD <sup>®</sup> )
Fluoxetine DR (PROZAC <sup>®</sup> Weekly)	Olanzapine/Fluoxetine (SYMBYAX <sup>®</sup> )
Fluvoxamine ER (LUVOX CR <sup>®</sup> )	Vortioxetine (BRINTELLIX <sup>®</sup> )

### Vortioxetine (Brintellix<sup>®</sup>)

Vortioxetine, a serotonin modulator and stimulator, was approved in October 2013 for treatment of MDD.<sup>7</sup> A total of 11 short-term studies evaluated the efficacy and safety of vortioxetine in MDD.<sup>8-18</sup> However, FDA approval was based on the results of six good- or fair-quality, randomized, placebo- and active-controlled positive efficacy studies that were conducted in both US and non-US populations.<sup>7</sup> Patients in these trials were mostly white, women, in their mid-40's, and a majority had moderate-to-severe MDD. Extensive exclusion criteria, including patients at risk of suicide, concurrent psychiatric disorders or medical illnesses and patients with treatment-resistant depression, make it hard to generalize findings to a broader population. In trials conducted exclusively in the US, only the 20 mg daily dose demonstrated statistically significant change in baseline score (measured by MADRS or HAM-D) over placebo and was therefore chosen as the target daily dose. Nonetheless, lower doses (5 mg and 10 mg) demonstrated improved efficacy compared to placebo in studies conducted in both non-US and US populations.<sup>7</sup>

Overall, response and remission was improved for those on vortioxetine compared to placebo and the effect does not appear to be dose-dependent. Henigsberg et al. studied three doses of vortioxetine and response rates were similar in all arms (relative risks (RR) of 1.9, 1.8, and 2.0 for 1 mg, 5 mg, and 10 mg, respectively).<sup>8</sup> Remission rates were also similar with RRs of 1.6, 1.7, and 1.6 for the 1-mg, 5-mg and 10-mg groups, respectively.<sup>8</sup> Three of the four studies including a vortioxetine 20-mg arm are unpublished, and two of these studies did not demonstrate that the 20-mg dose was statistically different than placebo, as measured by the MADRS scale (RRs of 1.1 [95% CI 0.9 to 1.5] and 1.4 [95% CI 1.0 to 1.9]). Thus one could question the designation of 20 mg as the target dose.

While vortioxetine is being promoted as having a novel mechanism of action, there is no evidence that it is more efficacious than, and some data suggesting it is inferior to, other available second-generation antidepressants. In studies comparing venlafaxine XR or duloxetine to vortioxetine, rates of response and remission were similar to the active comparator.<sup>9-13</sup> At low doses, there were no differences in response rates between vortioxetine and the active comparison, but when compared to 15 and 20 mg doses of vortioxetine, MADRS response rates were higher in the active control arms.<sup>9-13</sup> There were no differences in remission rates at any dose of vortioxetine compared to the active control. There is a need for more

head-to-head trials to truly understand vortioxetine's comparative effectiveness in this class.

The most common adverse events (occurring in >2% of patients and at least 2% greater than placebo) are nausea, diarrhea and dry mouth and the most common serious adverse events are serotonin syndrome, abnormal bruising or bleeding, hypomania, or hyponatremia.<sup>19</sup> It does not appear that side effects are dose-related; however there is an increase likelihood of discontinuation due to adverse events as the dose increases compared to placebo.

### Levomilnacipran (Fetzima®)

Levomilnacipran is the active enantiomer of milnacipran (Savella®), an SNRI approved for use in fibromyalgia<sup>20</sup> (but not depression). The approval of levomilnacipran was based on three fair-quality, 8-week randomized, placebo-controlled phase III clinical trials in adults with MDD.<sup>21–23</sup> There are four approved strengths, 20 mg, 40 mg, 80 mg and 120 mg. Dosage adjustment is necessary in moderate to severe renal impairment, and use is not recommended in end stage renal disease.<sup>20</sup>

MADRS response rates appear to be similar for all approved doses.<sup>21–23</sup>

MADRS response rates were similar between the two doses of levomilnacipran studied in the Bakish et al. study with RRs of 1.4 (95% CI 1.1–1.9) and 1.3 (95% CI 1.1–1.8) for the 40-mg and 80-mg groups, respectively.<sup>21</sup> MADRS remission RRs were 1.7 (95% CI 1.1–2.5) and 1.80 (95% CI 1.2–2.7) for the 40-mg and 80-mg groups, respectively.<sup>21</sup> In Asnis et al.,<sup>22</sup> which studied three doses of levomilnacipran (40 mg, 80 mg, and 120 mg), only the 120 mg group had a statistically significant MADRS response rate (RR 1.4; 95% CI 1.1–1.9), while no dose group was statistically significant for MADRS remission rates. A third short-term efficacy study titrated patients from levomilnacipran sustained-release 25 mg daily to either 75 mg or 100 mg daily based on tolerance; both MADRS response (RR 1.3; 95% CI 1.2–1.7) and MADRS remission (RR 1.8; 95% CI 1.4–2.3) outcomes were statistically significant.<sup>23</sup> No head-to-head trials or comparative studies have been published. There is low quality evidence of no difference in the response rates (around a 40% increase) of all studied doses compared to placebo, but further research is needed before we fully understand this drug's place in therapy and comparative effectiveness.

The most common adverse events (incidence >2% and at least twice the rate of placebo) seen in trials as compared to placebo were nausea, constipation, hyperhidrosis, tachycardia, erectile dysfunction, increased heart rate and vomiting. The two dose-related adverse reactions were urinary hesitation and erectile dysfunction.

### Summary

Vortioxetine and levomilnacipran appear to be safe and effective agents for the treatment of MDD based on short-term placebo-controlled trials. However, there is insufficient evidence to determine the most effective treatment dose of vortioxetine and there is a need for more head-to-head trials for both vortioxetine and levomilnacipran to fully understand their efficacy and safety and to determine their place in therapy relative to less expensive alternatives. These drugs may be useful when patients have failed current first- and second-line agents in the treatment of depression, but there is no evidence at this point to support widespread use.

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