

Levomilnacipran (Fetzima™) for the treatment of major depressive disorder

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ABSTRACT

Levomilnacipran (Fetzima™) was approved by the United States Food and Drug Administration (FDA) in July 2013 for the treatment of Major Depressive Disorder (MDD) in adults. Levomilnacipran is the (1S,2R) enantiomer of racemic milnacipran and represents one of the newest medications designed and marketed as an enantiomer of an already approved medication with hopes of improving efficacy and limiting side effects. This article reviews the evidence supporting the use of milnacipran for MDD, examines the clinical studies behind levomilnacipran's approval, and discusses practical considerations regarding the use of this new antidepressant medication.

KEYWORDS

Depression, serotonin norepinephrine reuptake inhibitor, milnacipran, levomilnacipran

BACKGROUND

Levomilnacipran (Fetzima™) is the newest serotonin-norepinephrine reuptake inhibitor (SNRI) approved by the United States Food and Drug Administration (FDA) for the treatment of major depressive disorder (MDD). Levomilnacipran is one of the latest medications designed and marketed as an enantiomer of an already approved medication with hopes of improving efficacy and limiting side effects. Levomilnacipran is the (1S, 2R) enantiomer of racemic milnacipran.¹ Milnacipran (Savella®) is an FDA approved agent for the treatment of fibromyalgia and has been used since 1996 for MDD under a variety of trade names in other countries.²⁻³

IS THERE EVIDENCE TO SUPPORT THE USE OF MILNACIPRAN IN MDD?

Despite not being approved for MDD by the FDA, milnacipran has evidence supporting its use for this indication. The largest placebo controlled trial of milnacipran for MDD was 8 weeks in duration and included 527 outpatients with a Hamilton Depression Rating Scale (HDRS) score of >22. Patients were randomized to receive placebo or one of three different doses of milnacipran (25, 50, or 100 mg BID). Both the 50 mg BID and 100 mg BID were statistically superior to placebo on change from baseline Montgomery-Asberg Depression Rating Scale (MADRS) scores (-11.5 for placebo, -16.6 at 50 mg BID, and -14.7 at 100 mg BID). Only the 50 mg BID was statistically superior to placebo on change from baseline HDRS scores (-9.9 for placebo and -13.2 at 50 mg BID).⁴ In addition to placebo controlled trials, milnacipran has been studied against a variety of medications (i.e., amitriptyline, clomipramine,

imipramine, fluvoxamine, fluoxetine, paroxetine, sertraline) and has demonstrated comparable efficacy.⁵

HOW DOES RECEPTOR BINDING DIFFER WITH LEVOMILNACIPRAN?

Levomilnacipran has been shown to be the more active enantiomer of milnacipran. Its affinity for the norepinephrine (Ki = 92.2 nM) and serotonin (Ki = 11.2 nM) transporters is over 10 times that of the (1R, 2S) enantiomer (>10⁴ and 290, respectively). Levomilnacipran potently inhibits norepinephrine (IC₅₀ = 11 nM) and serotonin (IC₅₀ = 16-19 nM) reuptake and lacks significant affinity for other receptors. Additionally, levomilnacipran's selectivity ratio (0.6) for norepinephrine reuptake relative to serotonin reuptake is over 10-fold higher than that of other SNRIs venlafaxine (Effexor®) (10) and duloxetine (Cymbalta®) (16).^{1,6}

HOW DID LEVOMILNACIPRAN PERFORM IN CLINICAL TRIALS? (TABLE 1)

Levomilnacipran was evaluated by the FDA through three manufacturer-sponsored, 8-week, randomized, double-blind, placebo-controlled trials in adult outpatients with MDD. In the first published study, subjects were randomized to receive fixed-dose levomilnacipran 40 mg (n = 181), 80 mg (n = 181), 120 mg (n = 183), or placebo (n = 179) once daily. For inclusion, patients were 18 - 65 years of age, with an ongoing major depressive episode (MDE) at least 8 weeks in duration, and a score of at least 30 on the clinician-rated MADRS (moderate depressive symptoms). Excluded patients were those with a primary Axis I diagnoses other than MDD; substance abuse/dependence within 6 months of the study, significant medical conditions, significant suicide risk,

Table 1. Summary of levomilnacipran clinical trial outcomes

Study	Population of outpatients with MDD	Randomized Groups	LSMD vs placebo endpoint MADRS	Response ($\geq 50\%$ change from baseline MADRS at endpoint)	Remission (endpoint MADRS ≤ 10)
Asnis et al. ⁷ 8-week DB, PC, randomized	18-65 yo	40 mg	-3.23*	36.4%	21.6%
	MDE ≥ 8 weeks	80 mg	-3.99*	37.3%	20.9%
	MADRS ≥ 30	120 mg	-4.86*	41.5%*	20.5%
	Excluded: All other Axis I, significant medical conditions, SI, non-response to meds, concomitant psychoactive meds	Placebo		29.1%	19.4%
Bakish et al. ⁸ 8-week DB, PC, randomized	18-75 yo	40 mg	-3.30*	49%*	30%*
	MDE ≥ 6 weeks but ≤ 12 months	80 mg	-3.14*	47%*	32%*
	MADRS ≥ 26	Placebo		34%	18%
	Excluded: All other Axis I (anxiety disorders and specific phobias allowed), significant medical conditions, SI, non-response to meds				
Sambunaris et al. ⁹ 8-week DB, PC, randomized	18-80 yo	40-120 mg	-3.10*	41.9%*	17.2%
	MDE ≥ 4 weeks	(mean = 73mg)		29.4%	18.2%
	MADRS ≥ 30	Placebo			
	Excluded: All other Axis I (comorbid GAD, SAD, and specific phobias allowed), significant medical conditions, SI, non-response to meds				
Montgomery et al. ¹⁰ 10-week DB, PC, randomized	18-70 yo	75-100 mg ⁺	-4.2*	59.1%*	46.4%*
	MDE ≥ 1 month	Placebo		42.2%	26%
	HDRS ₁₇ ≥ 23				
	Excluded: All other Axis I, significant medical conditions, SI, non-response to meds, starting or stopping psychotherapy, current ECT (last 3 months)				

DB = Double-blind, PC = Placebo-controlled, MDD = Major depressive disorder, yo = years old, MDE = Major depressive episode, MADRS = Montgomery-Asberg Depression Rating Scale, GAD = Generalized anxiety disorder, SAD = Social anxiety disorder, HDRS₁₇ = 17-item Hamilton Depression Rating Scale, ECT = Electroconvulsive therapy, LSMD = Least squares mean difference

⁺Target dose of 100 mg utilized if tolerated

*Statistically significant versus placebo

intolerance to SNRIs or selective serotonin reuptake inhibitors (SSRIs), and nonresponse to ≥ 2 adequate antidepressant trials. There was a one week placebo run-in period followed by a titration to the randomized dose. After week 8, patients were tapered off the medication over 2 weeks. The primary efficacy measure was MADRS total score change from baseline to week 8. All doses of levomilnacipran showed statistically significant differences from placebo by week 4 and had a statistically significant least squares mean difference (LSMD) from placebo at week 8 (-3.23 at 40 mg, -3.99 at 80 mg, and -4.86 at 120 mg). Despite reaching statistical significance in the primary outcome measure, statistical significance in response (defined as $\geq 50\%$ decrease in MADRS score from baseline) was only reached by the 120 mg group and no levomilnacipran group was statistically significant compared to placebo in remission rates (defined as MADRS score ≤ 10). The most common adverse events (\geq

10% incidence in any levomilnacipran group) were headache, nausea, constipation, dry mouth, increased heart rate, and hyperhidrosis. Additionally, among patients treated with levomilnacipran, there was a mean increase in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) relative to placebo of 0.5 U/L and 1.4 U/L, respectively. Seven patients (2 in the 40 mg group, 2 in the 80 mg group, and 3 in the 120 mg group) had post-baseline AST and/or ALT elevations ≥ 3 times the upper limit of normal.⁷ No additional information regarding these cases has been published to date.

In the second study, patients with MDD were randomized to receive fixed-dose levomilnacipran 40 mg (n = 188), 80 mg (n = 188), or placebo (n = 186) once daily. Patients were 18 – 75 years of age, with an ongoing major depressive episode of at least 6 weeks, and a score of at least 26 on the MADRS (moderate depressive symptoms). Additionally, patients were required to have recurrent

depression, defined as ≥ 2 MDEs separated by at least 2 months during which criteria for a MDE are not met. Patients were excluded if they had an Axis I disorder other than MDD (except comorbid anxiety disorders and/or specific phobias) in the past 6 months, substance abuse in the last 6 months, significant medical conditions, significant suicide risk, or nonresponse to ≥ 2 adequate antidepressant trials. The primary efficacy measure was MADRS total score change from baseline at week 8. Both levomilnacipran groups achieved statistically significant LSMD from placebo at week 8 (-3.30 at 40 mg and -3.14 at 80 mg). Additionally, both groups had statistically significant differences in response (34% placebo, 49% at 40 mg, and 47% at 80 mg) and remission (18% for placebo, 30% at 40 mg, and 32% at 80 mg) rates compared to placebo. The most common adverse events ($\geq 10\%$) in the levomilnacipran groups were nausea, headache, and dry mouth. Additionally, in the 80 mg group, testicular pain and erectile dysfunction were reported by 7.8% and 14.1% of males, respectively.⁸

The third study evaluated patients randomized to flexible dose levomilnacipran ($n = 222$) or placebo ($n = 220$) once daily. For inclusion, patients were 18 - 80 years of age with an ongoing major depressive episode of at least 4 weeks, with a score of ≥ 30 on the clinician-rated MADRS or ≥ 26 on the MADRS-Self Rated (moderate depressive symptoms). Patients were excluded for a primary Axis I diagnoses other than MDD in the past 6 months (except secondary diagnoses of comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias); substance abuse/dependence within 6 months of the study, significant medical conditions, significant suicide risk, intolerance to SNRIs or SSRIs, and nonresponse to ≥ 2 adequate antidepressant trials. The primary efficacy measure was change in MADRS score at week 8. Levomilnacipran treated patients were started at 20 mg on day 1, and increased to 40 mg on day 3. Doses could be further increased based on response and tolerability to 80 mg after week 1 or 2, and 120 mg at week 4. The mean daily dose of levomilnacipran was 73 mg. Similar to other studies, the LSMD for the levomilnacipran group was statistically significant compared to placebo (-3.10). Additionally, the levomilnacipran group had a statistically significant difference in patients achieving response (41.9% versus 29.4%), but not remission (MADRS score ≤ 10) rates, compared to placebo. The most common adverse events ($\geq 10\%$) in the levomilnacipran group were nausea, dizziness, and constipation. Levomilnacipran was associated with a mean increase in heart rate (8.5 beats per minute), systolic blood pressure (3.5 mmHg), and diastolic blood pressure (3.4 mmHg).⁹

An additional published support study from Europe was also randomized, double-blind, placebo-controlled, and flexible dose. Adult patients between 18 - 70 years of age with MDD were eligible for inclusion if they met criteria for a MDE at least one month in duration and had a 17-item Hamilton Depression Rating Scale (HDRS₁₇) score of at least 23 (moderate depressive symptoms). Exclusion criteria included history of a psychotic disorder or bipolar disorder, other current psychiatric or personality disorders, substance abuse (preceding 6 months), substance dependence (preceding 2 years), significant medical conditions, initiating or stopping psychotherapy (preceding 6 months), electroconvulsive therapy (preceding 3 months), moderate/severe suicide risk, and nonresponse to ≥ 2 antidepressant trials. Patients were randomized to receive either placebo ($n = 281$) or levomilnacipran ($n = 282$) once daily. Levomilnacipran treated patients were titrated from 25 mg on day 1 to 75 mg by day 8. If the 75 mg dose was tolerated, patients were then increased to the 100 mg target dose. Patients could be decreased from 100 mg to 75 mg for intolerance, but if the 75 mg dose was not tolerated at any point, patients were withdrawn from the study. The primary efficacy measure was MADRS total score change from baseline to week 10. After week 10, patients were then tapered off the medication over 7 days. The levomilnacipran treated group showed statistically significant difference on the primary endpoint by week 3 and had a statistically significant LSMD from placebo of -4.2 at week 10. Additionally, response (59.1% versus 42.2%) and remission (46.4% versus 26.0%) rates in the levomilnacipran group were statistically significant compared to placebo. The most common adverse events ($\geq 10\%$) in the levomilnacipran group were nausea, headache, dizziness, and hyperhidrosis. Among patients treated with levomilnacipran, there was a mean increase in AST and ALT relative to placebo of 1.2 U/L and 2.0 U/L, respectively.¹⁰

WHAT OTHER INFORMATION IS IMPORTANT ABOUT THIS NEW MEDICATION?

Levomilnacipran is supplied as extended release capsules (20, 40, 80, and 120 mg) for once daily administration. They should be swallowed whole and not crushed or chewed. It is recommended to start at 20 mg once daily for 2 days then increase to 40 mg once daily. After that, increase based on efficacy and tolerability in 40 mg increments, with a maximum daily dose of 120 mg. Dosing adjustments are required for moderate (maximum dose = 80 mg) to severe (maximum dose = 40 mg) renal impairment.

The primary metabolizing isozyme of levomilnacipran is CYP_{3A4}. When administered with strong inhibitors of CYP_{3A4}, it is recommended to not exceed 80 mg per day. Pharmacokinetic studies demonstrated an increase in area under the curve (AUC) and maximum concentration (C_{max}) when levomilnacipran was coadministered with ketoconazole. While the package insert states no dosage adjustment is needed when levomilnacipran is coadministered with a potent inducer of CYP_{3A4}, a 28.9% decrease in AUC and 26.4% decrease in C_{max} was found when coadministered with carbamazepine. Therefore, there may be clinical scenarios when dosing above the recommended daily max is necessary.¹¹ In clinical trials, dose related adverse effects included urinary hesitation and erectile dysfunction in men. When discontinuing this medication, gradual tapering is recommended.¹

WHAT PLACE DOES LEVOMILNACIPRAN HAVE IN THE TREATMENT OF MDD?

While levomilnacipran has demonstrated efficacy in the treatment of MDD versus placebo, its place in the treatment of MDD is still not certain. It has not been directly compared to alternative SNRIs or other evidence based treatments for MDD. Though its selectivity for norepinephrine reuptake may warrant investigation for the treatment of pain syndromes, none of the trials presented investigated any of these indications. The most common adverse effects of levomilnacipran are similar to other antidepressants (e.g., headache, nausea). However, the presence of other adverse effects including increases in heart rate and blood pressure warrant consideration prior to using levomilnacipran. Increases in AST and ALT found in two published studies suggest that monitoring of transaminases may be appropriate at baseline and within 1-3 months of starting therapy. Its availability as once daily dosing is certainly preferred to milnacipran's twice daily requirement. However, other SNRIs also provide this convenience. As both products are brand name only at this point, little cost difference would be expected between the two. Though levomilnacipran offers an additional option for treatment of MDD, its place in therapy is uncertain. Differences in receptor binding may provide theoretical basis for use but the clinical importance of this is questionable. Without studies containing generalizable patient populations demonstrating benefit over current evidence based options, its use should not be routinely recommended.

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