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# The Role of Levomilnacipran in the Management of Major Depressive Disorder: A Comprehensive Review

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**Abstract:** Levomilnacipran, the more active enantiomer of the serotonin and norepinephrine reuptake inhibitor (SNRI) milnacipran, was recently approved in the US for the treatment of major depressive disorder (MDD). The drug was developed as an extended release (ER) capsule formulation to allow for once-daily administration, thereby improving patient adherence. This agent differs from other available SNRIs in having a greater potency for inhibition of norepinephrine relative to serotonin reuptake. The efficacy of levomilnacipran ER has been evaluated in seven randomised, double-blind clinical trials (one Phase II and four Phase III trials, and two long-term efficacy studies). These studies documented that levomilnacipran is generally more effective than placebo for the treatment of MDD in the short-term, whereas no firm evidence exists on long-term efficacy for relapse prevention. Preliminary evidence suggests that levomilnacipran ER may be effective in improving not only depressive symptoms but also symptoms related to functioning (social life, work, and family life). Short-and longer-term studies found that the rate of withdrawal from levomilnacipran therapy due to adverse events was rather low. Moreover the drug appeared to be generally well tolerated. The most common adverse effects included nausea, hyperhidrosis, constipation, tachycardia, palpitations, erectile dysfunction and ejaculation disorder. As hypertension or orthostatic hypotension may occur in a few patients, the cardiovascular safety of levomilnacipran needs to be more extensively investigated especially on long-term treatment. Additional active comparator trials evaluating efficacy, tolerability and cost-effectiveness are required to better define the role of levomilnacipran ER in the treatment of MDD in relation to currently available antidepressants including other SNRIs.

**Keywords:** Antidepressants, efficacy, levomilnacipran extended release, major depressive disorder, safety, tolerability.

## INTRODUCTION

Major depressive disorder (MDD) is a serious and chronic disorder which is very common throughout the world. Its global point prevalence is estimated to be 4.7% [1]. MDD is associated with significant reductions in quality of life, impaired work productivity, reduced social functioning, poor physical health, disability and risk of death by suicide, and substantial direct and indirect economic costs.

Pharmacological management remains the cornerstone of treatment of MDD. Antidepressant medications are efficacious in acute, continuation and maintenance treatment for many patients with MDD. While short- and medium-term therapy with antidepressants is effective for acute episodes, longer-term antidepressant treatment is associated with reduced risk of relapse and recurrence [2]. However, currently available antidepressants have important limitations both in terms of efficacy and tolerability. It has been estimated that only 30-40% of antidepressant-treated patients achieve full remission after a single adequate course of antidepressants; a further third show a suboptimal response with residual symptoms which limit their social functioning and increase their risk of relapse [3,4]. For reasons that are barely understood, individual patients can be responder to one antidepressant but not to another, either within or outside the same class. Moreover, tolerability remains an important problem with antidepressants and adverse effects are one of the leading causes of discontinuation during the first few months of treatment [5]. Common side effects (which are often prominent in the weeks before any clinical response becomes evident) include weight gain, sexual dysfunction, nausea, headache, and sleep disturbances. Treatment adherence is a further problem with fewer than half of patients with MDD taking their antidepressants consistently and for the full recommended duration [6]. Therefore, the need to develop novel antidepressants with distinct mechanisms of action and improved side effect profiles remains critical.

Most antidepressant medications increase synaptic concentrations of serotonin (5-HT) and/or norepinephrine (NE) by blocking the reuptake of one or both of these neurotransmitters [7]. These treatments mainly include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs) and norepinephrine selective reuptake inhibitors (NRIs). Selective reuptake inhibitors (SSRIs, SNRIs, and NRIs) show better tolerability and safety profile than tricyclic antidepressants. In addition, there is some evidence

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suggesting the "dual action" of SNRIs may confer advantages over SSRIs or NRIs in treating MDD symptoms [7, 8].

Levomilnacipran hydrochloride extended release (Fetzima, Forest Laboratories) is a novel SNRI approved by the US FDA in July 2013 for treatment of MDD [9]. It is also currently under investigation for use in functional recovery of patients after acute ischemic stroke in Europe. Other members of this class used to treat MDD include duloxetine, venlafaxine, desvenlafaxine and milnacipran; however, only the first three are available in the US. Milnacipran is marketed as an antidepressant only in Europe and Japan, whereas it is available for the treatment of fibromyalgia in the US and Australia. Levomilnacipran (1S, 2R-milnacipran), previously known as F2695, is the more potent of the enantiomers found in racemic milnacipran compared with the F2696 (1R, 2S-milnacipran) [10]. Levomilnacipran (LVM) has been developed solely as an extended release formulation to allow for once-daily dosing. This is likely to improve patient adherence in comparison with milnacipran, which is dosed twice per day.

Several reviews have been recently published covering the pharmacological properties, clinical efficacy, tolerability and safety profile of LVM extended release for the treatment of MDD [11-19]. The aim of this article is to provide an updated and critical evaluation of the role of LVM extended release in the management of patients with MDD.

## REVIEW OF PHARMACOLOGY, MODE OF ACTION, PHARMACOKINETICS OF EXTENDED RELEASE LEVOMILNACIPRAN

### Pharmacology and Mode of Action

LVM is categorized as a SNRI. While the exact mechanism of action of SNRIs in MDD is as yet unknown, it is believed to be related to the enhancement of serotonin (5-HT) and norepinephrine (NE) activity in the central nervous system, *via* inhibition of reuptake at 5-HT and NE transporters [20]. SNRIs differ in their relative potency at NE and/or 5-HT transporters *in vitro* (and to some extent *in vivo*). *In vitro*, duloxetine, venlafaxine and desvenlafaxine preferentially inhibit 5-HT reuptake relative to NE reuptake [21-23], while milnacipran more potently inhibits NE reuptake relative to 5-HT reuptake by approximately 2-fold [22]. Like racemic milnacipran, also LVM appears to be a more potent inhibitor of NE versus 5-HT transporter [10].

The pharmacological profile of LVM has been characterized by a series of *in vitro* and *in vivo* experimental studies described by Auclair *et al*. [10]. Preliminary *in vitro* experiments have demonstrated that LVM is the pharmacologically more active enantiomer of milnacipran. In fact, in rat hypothalamic synaptosomes, LVM was 50 and 13 times more potent inhibitor of NE and 5-HT reuptake than the other enantiomer of milnacipran, F2696 [10]. *In vitro* experiments with human recombinant transporters have shown that LVM is a potent and selective inhibitor of NE [inhibition constant (Ki) 92.2 nmol/L] and 5-HT (Ki 11.2 nmol/L) transporters; corresponding Ki values for venlafaxine were $>10^4$ and 17.9 nmol/L, and for duloxetine were 8.9 and 0.2 nmol/L [10]. These data indicate that LVM has a greater absolute affinity for NE and 5-HT transporters than venlafaxine and a lower affinity as compared to duloxetine. On the other hand, in terms of relative affinity, LVM has a more balanced affinity for NE versus 5-HT transporters, while duloxetine and venlafaxine have a significant preference for 5-HT reuptake inhibition. *In vitro* studies utilizing Chinese hamster ovary cells stably expressing transfected human transporters have demonstrated that LVM inhibits the NE transporter with 2-fold higher potency than the 5-HT transporter, based on the half-maximal inhibitory concentration (IC50) of drug administered (IC50 = 10.5 nM [NE] and 19.0 nM [5-HT]; NE/5-HT ratio = 0.6) [10]. At the lowest effective dose (10 mg/kg), LVM exhibited greater activity for NE, and as the dosage increased to 20 and 40 mg/kg, it displayed equivalent activities for both NE and 5-HT. Thus, LVM appears to display greater noradrenergic activity at lower doses and increasing serotonergic selectivity at higher doses.

LVM had no significant affinity for 23 off-target receptors, such as dopaminergic, serotonergic, α- and β-adrenergic, muscarinic and histaminergic receptors [10].

*In vivo* microdialysis studies documented that LVM increases extracellular concentrations of NE and 5-HT in the rat prefrontal cortex [10]. In agreement with the *in vitro* data (see above), LVM had a greater impact on extracellular NE levels than 5-HT levels at lower doses, whereas at higher doses it increased NE and 5-HT concentrations with equal efficacy.

In mice models of depression and anxiety, such as forced swimming and tail suspension tests, intraperitoneal LVM was associated with a significantly reduced immobility time more potently than venlafaxine and duloxetine [10]. In particular, in the forced swimming test, which is an animal model used to predict antidepressant efficacy, LVM was 33 times more potent than its enantiomer F2696 [10].

### Pharmacokinetics

The pharmacokinetics of LVM extended-release were investigated in three randomized phase I studies in healthy volunteers aged 18-45 years [24]. Some of the available information results from abstracts and from the US FDA manifacturer's prescribing information [9].

After oral administration, LVM reaches peak concentration in 6 to 8 hours ($T_{max}$) [9]. LVM demonstrated dose-proportional increases in peak plasma concentration ($C_{max}$) and area under the plasma concentration-time curve (AUC) when dosed singly over the 25–120 mg dose range, and when given in multiple doses over the range of 25–300 mg once daily. LVM ER capsules have high bioavailability (92%) compared with the oral solution. Food does not interfere with absorption and biovailability of LVM. The extended release formulation allows for the convenience of once daily dosing. This is in contrast to the racemic milnacipran, which must be dosed twice daily [25].

LVM is rapidly and widely distributed in humans with an apparent volume of distribution ranging from 387 to 473 L and it is only 22% bound to plasma proteins [9]. Low protein

binding may be advantageous in patients with hepatic dysfunction and subsequent hypoalbuminemia, since it can reduce the possibility of drug-drug interactions by displacement of other highly plasma protein–bound agents.

Elimination of LVM occurs by hepatic biotransformation (42%) and by renal excretion (58%). LVM is metabolized *via* desmethylation, primarily catalyzed by cytochrome P450 (CYP) 3A4, with minor contribution of CYP2C8, CYP2C19, CYP2D6, and CYP2J2, forming N-desethyl LVM, and *via* hydroxylation, forming P-hydroxy-levomilnacipran. The two metabolites, which are pharmacologically inactive, are then conjugated with glucuronides. Interconversion between LVM and its stereoisomer does not occur in humans. LVM and its metabolites are primarily eliminated by renal excretion. Following oral administration of 14C-levomilnacipran solution, approximately 58% of the dose is excreted in urine as unchanged LVM. N-desethyl levomilnacipran is the major metabolite excreted in the urine and it accounts for approximately 18% of the dose. Following oral administration, the mean apparent total clearace of LVM is 21-29 L/h, while its elimination half-life is approximately 12 hours [9].

As renal excretion plays a major role in the elimination of LVM, patients with moderate or severe renal impairment should be prescribed adjusted dosages of LVM ER. On the other hand, based on the results a recent single-dose, open-label, parallel-group pharmacokinetic study in adults with mild, moderate, or severe hepatic impairment and normal controls receiving a 40 mg LVM ER capsule, no dose adjustment is recommended in patients with hepatic insufficiency [26]. Elderly patients may have increased exposure to LVM compared with younger patients. Considerations for adjustment of dosage should be made, taking into account the effects of renal drug clearance in this population [9].

### Drug Interactions

LVM has a relatively low potential for pharmacokinetic drug interactions. As the drug is not a clinically significant inducer or inhibitor of any prominent cytochrome P450 isoenzymes, it is not expected to cause clinically relevant metabolically-based drug interactions with other agents. LVM, however, is a substrate of CYP3A4 and, therefore, it is susceptible to the effects of potent inhibitors or inducers of this isoenzyme. In case of concomitant administration of LVM with potent CYP3A4 inhibitors such as ketoconazole and clarithromycin, it is recommended that dosage should not exceed 80 mg/d [9]. Likewise, *in vivo* studies have shown that coadministration of LVM with potent CYP3A4 inducers such as rifampicin or carbamazepine was associated with a decrease in serum LVM concentrations. In these cases, however, no specific dosage adjustment recommendations have been made [9].

Similarly to other agents in the SNRI class, LVM may be hypothetically involved in pharmacodynamic drug interactions. Thus, the combination of LVM with monoamine oxidase inhibitors (MAOIs) is contraindicated, due to the possible development of a potentially life-threatening serotonin syndrome. MAOIs, such as phenelzine, should be discontinued 14 days prior to initiation of LVM; conversely, LVM should be discontinued 7 days prior to initiation of a MAOI [9]. Serotonin syndrome may also occur when LVM is coadministered with other serotonergic agents such as triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone, linezolid, and St. John's wort. Therefore, concomitant treatment of LVM with these medications is not recommended. Like other antidepressants that inhibit 5-HT reuptake, LVM may increase the risk of bleeding events, particularly with concomitant use of other bleeding risk-increasing medications, such as nonsteroidal anti-inflammatory drugs, oral anticoagulants and antiplatelet drugs including low-dose aspirin [27].

## EFFICACY STUDIES, SAFETY AND TOLERABILITY

### Efficacy

The efficacy of LVM in patients with MDD has been evaluated in seven randomised, double-blind clinical trials, without considering results from smaller studies presented as case reports, posters, and proceedings of congresses (Table **1**). These studies included one Phase II trial [28], four Phase III trials [29-32], two long-term efficacy studies [33, 34], and four secondary and post-hoc analyses [35-38].

In the Phase II, randomized, placebo-controlled, multicenter study by Montgomery *et al*. [28], the full analysis set (FAS) was formed by 553 outpatients (placebo=277; levomilnacipran sustained release=276), who met the criteria for a major depressive episode. Results showed that levomilnacipran sustained release (SR) 75 mg/day or 100 mg/day was more effective than placebo on depressive and disability symptoms, as assessed by changes on MADRS (mixed-effects model for repeated measures; $P<0.05$), HDRS scores, and SDS scores at the end of the trial. Furthermore, significantly more levomilnacipran-treated patients than placebo patients ($P < 0.05$) achieved remission as defined by 'complete' (MADRS $\leq$ 5; 24 vs. 10%) and 'sustained' (MADRS $\leq$ 10 in Weeks 4-10; 16 vs. 10%) criteria. Regarding functional impairment, the proportion of patients who achieved remission (SDS total score $\leq$ 6 and each item score $\leq$ 2; 26 vs. 17%) and response (total score $\leq$ 12 and each item score $\leq$ 4; 52 vs. 35%) was significantly greater in levomilnacipran group than in placebo group.

The 8-week, randomized, double-blind study by Asnis *et al*. [29] evaluated in 713 outpatients with an ongoing major depressive episode $\geq$ 8 weeks' duration the efficacy and tolerability of fixed-dose levomilnacipran SR (40 mg: n = 181; 80 mg: n = 181; 120 mg: n = 183) versus placebo (n=179). Results evidenced that levomilnacipran SR at all doses was significantly more effective than placebo for reducing MADRS total score from baseline to the end of the trial (40 mg=-3.23, P =.0186; 80 mg= -3.99, P =.0038; 120 mg=-4.86, P =.0005). Regarding secondary and additional outcomes, best results were seen with the 80 and 120 mg/day doses of levomilnacipran SR versus placebo.

The multicenter, randomized, double-blind, placebo-controlled, fixed-dose study by Bakish *et al*. [30] evaluated the efficacy and tolerability of levomilnacipran ER 40 mg/day or 80 mg/day versus placebo in outpatients affected

**Table 1. Published efficacy trials of levomilnacipran extended-release (ER) in major depressive disorder.**

| Authors / Year of Publication | Study Design | Trial Duration | Number of Patients | Levomilnacipran Regimen | Principal Outcome Measures | Main Efficacy Results |
|---|---|---|---|---|---|---|
| ***Phase II Trial*** | | | | | | |
| Montgomery *et al*. (2013) [28] | Randomized, double-blind, placebo-controlled, flexible-dose. | 10 weeks | 553 outpatients (levomilnacipran SR=276; placebo=277) | 75-100 mg/day | MADRS HDRS17 SDS | LVM more effective than Pl on MADRS, HDRS17 and SDS total scores change from baseline to week 10. |
| ***Phase III Trials*** | | | | | | |
| Asnis *et al*., 2013 [29] | Randomized, double-blind, placebo-controlled, fixed-dose. | 8 weeks | 713 outpatients (levomilnacipran SR 40 mg =181; 80 mg =181; 120 mg=183; placebo=179) | 40-80-120 mg/day | MADRS HDRS17 SDS | LVM at all doses was significantly more effective than Pl for reducing MADRS total score from baseline to the end of the trial. |
| Bakish *et al*., 2014 [30] | Randomized, double-blind, placebo-controlled, fixed-dose. | 8 weeks | 557 outpatients (levomilnacipran ER 40 mg =185; 80 mg =187; placebo=185) | 40-80 mg/day | MADRS SDS | Both LVM doses were significantly superior than Pl on MADRS total score change from baseline to week 8. |
| Sambunaris *et al*., 2014 [31] | Randomized, double-blind, placebo-controlled, flexible-dose. | 8 weeks | 442 outpatients (levomilnacipran ER=222; placebo=220) | 40-120 mg/day | MADRS SDS | A statistically significant difference in MADRS total score change from baseline to week 8 was observed in favour of LVM over Pl. |
| Gommoll *et al*., 2014 [32] | Randomized, double-blind, placebo-controlled, flexible-dose. | 8 weeks | 357 outpatients (levomilnacipran ER=175; placebo=182) | 40-120 mg/day | MADRS HDRS17 SDS | No statistically significant differences between LVM and Pl on primary (MADRS) and secondary efficacy measures. |
| ***Long-term Trials*** | | | | | | |
| Mago *et al*., 2013 [33] | Multicenter, open-label, flexible-dose. | 48 weeks | 825 patients | 40–120 mg/day | MADRS | Decrease in MADRS score was seen from week 0 to week 48 of the extension trial; no inferential statistics were performed. |
| Shiovitz *et al*., 2014 [34] | Randomized, double-blind, placebo-controlled, fixed-dose. | 24 weeks | 348 outpatients (levomilnacipran ER=235; placebo=113) | 40-80-120 mg/day | MADRS SDS | Time to relapse was longer in the LVM group than in the Pl group, but the difference was not statistically significant. |

Abbreviations: ER, extended-release; SR, sustained-release; LVM, levomilnacipran; Pl, placebo; MADRS, Montgomery-Åsberg Depression Rating Scale; HDRS17, 17-item Hamilton Depression Rating Scale; SDS, Sheehan Disability Scale.

by recurrent MDD. Both levomilnacipran ER doses were significantly superior than placebo in improving clinical symptoms and functional impairment, as assessed by change in MADRS total score from baseline to the end of the trial. A greater proportion of patients in the levomilnacipran ER 40 mg/day (49%, $p = 0.004$) and 80 mg/day (47%, $p = 0.010$) groups than in the placebo group (34%) achieved MADRS response ($\geq$ 50% improvement). Moreover, a significantly greater percentage of patients assuming levomilnacipran ER 40 mg/day (30%, $p = 0.012$) and 80 mg/day (32%, $p = 0.002$) encountered remission criterion (MADRS $\leq$ 10) when compared to placebo group (18%).

A multicenter, randomized, double-blind, flexible-dose study comparing 40, 80 and 120 mg/day of levomilnacipran ER with placebo in outpatients with MDD showed that levomilnacipran ER was significantly superior to placebo in reducing clinical and functional symptoms, as documented

by changes in primary and additional efficacy measures from baseline to week 8 [31].

Negative results were reported by a randomized, double-blind, placebo-controlled, flexible doses (40-120 mg/day) study of levomilnacipran ER for MDD; although levomilnacipran ER-treated patients demonstrated greater reduction in MADRS total score from baseline endpoint compared to placebo group, the difference from placebo did not reach statistical significance [32].

Phase II and Phase III studies documented that LVM is generally more effective than placebo for the treatment of MDD in the short-term, whereas no firm evidence exists on long-term efficacy for relapse prevention. These results need to be confirmed by further studies, as no randomised evidence or head-to-head trials have compared LVM with any other antidepressant drugs; furthermore, the 8-week period chosen in the majority of trials seems too short for drawing definite indication on efficacy. Available evidence does not allow to fully gather enough information about the place of LVM within the class of antidepressant drugs.

Regarding the two available studies that have assessed the longer term efficacy of levomilnacipran [33, 34], the first one was an open-label, 48-week extension trial mainly focused on evaluating safety and tolerability of levomilnacipran in patients with MDD, although measure on efficacy were also collected, but no inferential statistics were performed; thus, the absence of a placebo or active- control group for comparison, makes it impossible to draw conclusion regarding the efficacy of levomilnacipran ER in long-term use [33].

The second, more recent study was a multicenter, randomized, double-blind, placebo-controlled trial in adult outpatients with MDD [34]. Following a 12-week open-label treatment period with flexible-dose levomilnacipran ER (40-120mg/day), fixed-dose levomilnacipran ER (40, 80, or 120mg/day) was compared with placebo in a 24-week double-blind treatment. Results showed that time to relapse during double-blind treatment was prolonged in the levomilnacipran ER group than in the placebo group (13.9% versus 20.5%, respectively); however, the treatment effect did not reach statistical significance. Post hoc analysis showed that greater severity of depression at baseline was correlated with greater reduction in risk of relapse for levomilnacipran-treated patients compared to placebo-treated group.

Concerning the secondary and post-hoc analyses on LVM, retrospective findings by Montgomery *et al*. [35] confirmed the efficacy of LVM compared with placebo on a range of clinical and functional depressive symptoms and domains, with significantly more LVM ER versus placebo patients ($P < .05$) achieving complete (MADRS$\leq$5; 24 vs. 10%) and sustained (MADRS$\leq$10; 16 vs. 10%) remission. Functional improvement, as demonstrated by changes from baseline in assessed by Sheehan Disability Scale (SDS) total and subscale scores (response: total score$\leq$12 and each item score$\leq$ 4; 52 vs. 35%; remission: total score$\leq$6 and each item score$\leq$2; 26 vs. 17%) was also observed.

Post-hoc analyses of pooled data of the five randomized, placebo-controlled, double-blind studies [36] supported the efficacy of LVM ER across various subgroups of adult MDD patients. As regards to efficacy, evaluated by MADRS least squares mean difference (LSMD) from baseline, LVM was found more effective than placebo (LSMD=-3.0, $P<.001$), and LVM-treated patients showed a significantly greater response rate (44.7% vs 34.5%, $P<.001$) and remission rate (27.7% vs 21.5%, $P<.05$) than placebo-treated subjects.

Functional impairment, measured by SDS scores change, was evaluated by post-hoc analyses on pooled data from the five short-term LVM studies [37]; results suggested a significant improvement in LVM group over placebo group in SDS total scores (Total scores= $P<.001$) as well as in each of the SDS subscales (Work/School = $P<.001$, Social Life = $P<.001$, and Family Life = $P<.001$).

Recently, prospective and post hoc analyses of the SF-36 Health Survey Mental and Physical Component Summaries (MCS, PCS) data by the 11-week Phase III study by Asnis *et al*. [29] were aimed to evaluate functional health and well-being in patients with MDD who were treated with 40-mg, 80-mg, or120-mg LVM ER. Results showed that LVM ER was significantly more effective than placebo for improving health-related functioning as documented by MCS change at Week 8 ($P=.0011$). In details, statistically significant ($P<.05$) improvement was seen at the following individual domains: General Health ($P=.0010$), Vitality ($P=.0307$), Social Functioning ($P=.0097$), Role-Emotional ($P=.0078$), and Mental Health ($P=.0005$) [38].

In summary, long-term trials, and post hoc and pooled analyses showed that LVM is effective in improving clinical symptoms and impaired functioning in MDD patients; nevertheless, limitations of these analyses include their post-hoc, retrospective nature and the lack of statistical adjustment/corrections for multiple comparisons. Further limitations concern the lack of comparisons with currently available antidepressants, and the inclusion and exclusion criteria in the primary studies that may limit the generalizability of the results. Thus, the results should be interpreted with caution.

**Safety and Tolerability**

As reported in the product monograph, the safety of levomilnacipran was evaluated in 2673 MDD patients aged from 18 to 78 years of age diagnosed with MDD recruited in clinical studies, representing 942 patient-years of exposure [9]. The most frequent adverse events (AEs) under levomilnacipran treatment, with a incidence at least 5% and twice that for placebo were nausea, hyperhidrosis, constipation, heart rate increased, erectile dysfunction and ejaculation disorders in males, urinary hesitation, vomiting, palpitations and tachycardia in females. Most AEs were from mild to moderate in intensity; nausea and headache generally occurred early during treatment and were transient. However, as further reported in the product labelling, data from the short-term trials showed that the presence of at least one AE, most frequently nausea (1.5%) was the main reason for leaving the treatment in 9% of the levomilnacipran patients (N=1583) versus 3% of those receiving placebo (N=1040) [9]. The incidence of AEs was not dose related for levomilnacipran doses between 40 and 120 mg/day, with the

only exception of erectile dysfunction and urinary hesitation; this latter AE, due to increased peripheral noradrenergic tone, was observed in up to 6% of levomilnacipran-treated patients versus none of the patients receiving placebo [9].

Regarding cardiovascular AEs, in short-term studies small mean changes in blood pressure (BP), sustained systolic or diastolic hypertension were greater for patients in the levomilnacipran ER group compared with placebo in short-term studies [29-32], and the presence of both sustained systolic and diastolic hypertension occurred in 0.3% of levomilnacipran patients versus 0.1% of the placebo patients; levomilnacipran-treated patients also exhibited orthostatic hypotension in higher percentage than patients on placebo (11.6% versus 9.7%, respectively) [9]. Heart rate resulted also increased during levomilnacipran treatment (7.4 b.p.m.) in contrast with a mean decrease of 0.3 b.p.m. in placebo-treated patients [9]. Treatment with levomilnacipran was not associated with clinically significant prolongation of QT interval corrected for heart rate according to Bazett's (QTcB) or Fridericia's (QTcF) formulas in short term studies; small dose-dependent mean increases in QTcB were reported, probably as a function of the increase in heart rate during levomilnacipran therapy [14].

In patients on levomilnacipran, laboratory tests showed mean increases in gamma-glutamyl transferase (GGT) [24], alkaline phosphatase [30], aspartate aminotransferase (AST) and alanine aminotransferase (ALT) [28-30]; in the study by Asnis *et al*. [29], AST and/or ALT levels three times above the upper limit of normal, thus considered as potentially clinically significant, were found in seven levomilnacipran-treated patients.

Regarding suicidality, short-term studies did not show differences between patients on levomilnacipran versus those on placebo; nevertheless, as pointed out by Mago *et al*. [14], the presence of recent suicidal behavior and/or significant suicidal ideation at baseline was considered as an exclusion criterion in the cited trials.

LVM has a neutral profile on body weight: four of the five short-term LVM trials [29-32] reported a mean weight change of -0.5 kg for LVM-treated patients and 0.1 kg for placebo-treated patients. In the 48-week, open-label study a -0.55 kg weight change by the end of treatment was observed [33], whereas the 24-week multicenter study reported a -0.5 kg weight change for LVM versus a 0.5 kg weight change for placebo [34].

In the 48-week open-label extension trial by Mago *et al*. [33] focused on the longer-term safety and tolerability of levomilnacipran, treatment-emergent AEs occurred in 86% of patients and most were mild to moderate in severity. The most common AEs were headache (22%), nausea (16%), upper respiratory tract infection (13%), hyperhidrosis (11%) and constipation (10%). Discontinuations due to any AEs occurred in 107 (13%) of patients, most commonly for nausea and hyperhidrosis. Serious AEs (angina pectoris, heart rate increased, tachycardia, supraventricular extrasystoles and/or ventricular extrasystoles, convulsions, encephalopathy) were reported in 36 (4%) patients and resulted in the discontinuation of 13 patients. Mean increases in systolic BP (3.9 mmHg), diastolic BP (3.1 mmHg) and heart rate (9.1 b.p.m.) were observed, whereas the incidence of sustained hypertension was 6%. Mean (SD) change in QTcB interval was +11.2 (20.7) ms and in QTcF interval was -1.1 (17.3) ms; no patient exhibited QTcF intervals greater than 500. AST and/or ALT levels three times above the upper limit of normal were found in five patients. Suicidal ideation occurred in 22% of patients, and suicidal four patients discontinued the study because of a suicide attempt.

In the 24-week study by Shiovitz *et al*. [34], nausea, headache, hyperhidrosis, dizziness, constipation, and dry mouth were the most frequent AEs. Erectile dysfunction was reported in 8.7% of male participants. Discontinuation rate due to AEs was 10.9; regarding serious AEs, only hypertension was considered to be related to active treatment. Levomilnacipran-treated patients compared with placebo-treated patients exhibited a greater mean increase in heart rate (12.3 vs 3.6 b.p.m.) and mean QTcB interval (10.5 vs 5.1 ms), whereas no differences were found on QTcF interval. No clinically meaningful changes in laboratory parameters were observed in patients throughout the study. During the double-blind treatment period, the incidence of suicidal ideation was higher in the levomilnacipran ER group than in the placebo group (4.8% versus 2.7%).

Overall, data from short-term and longer-term studies showed that the rate of withdrawal from levomilnacipran therapy due to adverse events was rather low; the drug appeared to be generally well tolerated. Nevertheless, levomilnacipran is associated with heart rate increase, hypertension, and orthostatic hypotension, thus additional controlled data may add further knowledge in estimating the total cardiovascular safety of levomilnacipran, especially on long-term treatment.

## FOCUS ON THE PATIENT RELATED OUTCOMES AND CONSIDERATIONS

Antidepressant drugs have shown efficacy in acute and maintenance treatment for MDD, and longer-term treatment may considerably reduce the risk of recurrence and/or relapses, substantially modifying the natural course of depressive illness. Nevertheless, still a significant proportion of patients show only partial response to AD treatment, or they do not obtain stable remission. Patients related outcomes (PROs) include symptoms, patient satisfaction with treatment, functional status, psychological well-being, and treatment adherence [39]. Incorporating PROs evaluations in the context of a clinical trial provides a subjective indicator of the impact of disease and of treatment efficacy, a more extensive knowledge of clinical outcomes and, finally, a core element in treatment decision making. Secondary and additional outcomes measures provide an opportunity for evaluating wider aspects of outcome; accordingly, clinical trials in MDD are increasingly providing disability and functional assessments beyond symptoms severity measures. The majority of available clinical studies have shown that levomilnacipran was generally superior to placebo for depressive symptoms as assessed by MADRS scores, and functional disability based

on SDS [28-30]. Symptomatic and functional improvements are essential component of stable recovery; partial response and residual symptoms are reliable predictors of MDD relapses, whereas achieving remission during AD treatment is associated with a reduced relapse risk [40]. Regarding response and remission, after pooling all five short-term trials [28-32], Citrome [11] found that number needed to treat (NNT) for levomilnacipran over the dose range of 40-120 mg/day vs. placebo for response was 10 (95% CI 8–16), and for remission, 16 (95% CI 11–33), thus indicating a significant advantage of levomilnacipran over placebo on the considered parameters. Nevertheless, although remission is the best outcome of antidepressant treatment, it is quite difficult to fully interpret significant differences in remission rates in 8-week treatment trials. In the long-term study by Shiovitz *et al*. [34], time to relapse in the levomilnacipran group was greater than in placebo group, although no statistically significant differences were found (p=0.165). In post hoc analyses, the hazard ratio (HR) for relapse in levomilnacipran-treated patients was lower than in placebo-treated patients, thus indicating a lower risk of relapse, as the severity of depressive symptoms at baseline increased. The only statistically significant difference was found in patients with baseline MADRS total score ≥ 36; however, this subgroup was too small (N=38) for providing useful insight.

Similarly to symptomatic improvement, significant treatment advantage on functional improvement and/or remission, fundamental components of PROs, were found across the domains of social life, work, and family life [31].

A main limitation of the cited trials lies in the selection of samples, as inclusion and exclusion criteria were almost restrictive, since patients with current comorbid substance use disorders, untreated medical conditions, suicidality, or concomitantly treated with other psychotropic agents were ordinarily excluded. Moreover, acknowledged non-responders to ADs are also usually excluded from participating in these trials. It derives that the recruited samples might be not representative of the depressed patients in real world settings, and the generalizability of findings is decreased.

## PATIENT FOCUSED PERSPECTIVES SUCH AS QUALITY OF LIFE, PATIENT SATISFACTION/ ACCEPTABILITY

Health-related quality of life (HRQL) and patients satisfaction and acceptability are important for understanding the impact of treatment on patient functioning and well-being [41, 42]. As the ultimate goal of antidepressant treatment is to achieve and maintain remission, both symptomatic and functional, a drug's therapeutic potential must be weighed against the potential for an increase in AEs which can lead to discontinuation [11]. Thus, tolerability remains an important issue in ADs treatment and AEs are one of the main causes of treatment. Levomilnacipran ER exhibited a generally good safety and tolerability profile; this favourable side effect profile, along with low incidence of drug-drug interactions, may be considered advantageous. As shown by pooled data from the short-term placebo-controlled studies, the main dose-related adverse AEs in levomilnacipran-treated patients were erectile dysfunction and urinary hesitation in men [28-32]. Similarly to other SNRIs, levomilnacipran has been associated with hypertension and increases in heart rate; thus, in order to substantially reduce cardiovascular risk, BP and heart rate should be measured prior to initiating treatment and periodically monitorized throughout treatment. It is also recommended that pre-existing hypertension, tachyarrhythmias and other cardiac illnesses should be controlled before initiating treatment with levomilnacipran. Treatment discontinuation or appropriate medical interventions may be required for those patients who exhibit a sustained increase in heart rate or BP during levomilnacipran therapy [9]. The potential of levomilnacipram to cause mydriasis should also be considered, and the drug should not be prescribed to patients with uncontrolled narrow angle glaucoma. Regarding special population, levomilnacipran has not been tested in children, adolescents, and in pregnant and lactating women.

Levomilnacipran ER has the advantage of once-daily dosing, therefore potentially improving patient adherence in comparison with other ADs, and has displayed the potential to improve motivation, functional impairment, energy, and acceptable long-term tolerability for up to 48 weeks [31, 33]. Patients assuming levomilnacipran should be provided with information regarding sexual dysfunctions, gastrointestinal AEs (nausea and vomiting), and instructed to regularly monitor BP and heart rate.

## CONCLUSIONS, PLACE IN THERAPY

Treatment of core symptoms of depression still remains a challenge, and several symptom clusters of depression may be particularly responsive to increases in the levels of neurotransmitters other than serotonin [43]. Across ADs classes, SNRIs appear to be to some extent more efficacious than SSRIs [8, 44]. Furthermore, patients who did not respond adequately to an SSRI may benefit of switching to an SNRI. In contrast to other available SNRIs, levomilnacipran ER is characterized by a greater potency at inhibiting NE reuptake at lower doses and increasing effects on serotonergic neurotransmission as the dose increases; this preferential inhibition of NE compared with serotonin is a peculiar feature of levomilnacipran when compared with other SNRIs [45]. The differences in relative receptor affinity of SNRIs towards NE and 5-HT receptors may have different clinical implications. The enhancement of noradrenergic transmission is thought to be associated with energy, social and motor activity, alertness, attention, arousal and with decreased pain in patients with MDD [46]. Based on its peculiar profile, it may be hypothesized that levomilnacipran could be effective in a subset of MDD patients in whom the above descripted symptomatic dimensions are prominent; accordingly, AD choice should be based on patient's features, individual tolerability, and on prior therapeutic response. Nevertheless, it should be emphasized that there is no clear evidence supporting the role of levomilnacipran in treating the above symptomatic dimensions. Although the overall results of clinical trials on levomilnacipran were positive, head-to-head studies directly comparing levomilnacipran ER to other antidepressants are still lacking.

Information on the efficacy and safety of levomilnacipran in potentially at-risk populations such as adolescents, elderly patients, and subjects with impaired organ function is still limited or lacking. At the present, it is difficult to define the place of levomilnacipran in the management of MDD in the next few years. Further independent and appropriately powered clinical studies, mainly direct "head-to-head" comparisons with other AD agents, are needed to clinically define the role of levomilnacipran in the treatment of depressive disorders, and to draw any definitive conclusions about any potential benefit for specific symptom clusters.

## DATA SOURCES

Articles for this review were obtained from a PubMed search using the keyword levomilnacipran. To retrieve all available information on LVM, neither limits nor inclusion/ exclusion criteria were applied. Data were also collected from the FDA-approved drug. Pertinent review articles were additionally scrutinized for use in this manuscript.

## CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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