Levomilnacipran: More of the Same?

Mohan Gautam, DO, MS[a,*]; Madhupreet Kaur, DO[b]; Pranav Jagtap, MD[a]; and Bassem Krayem, MD[a]

ABSTRACT

Objective: The primary objective of this narrative review is to provide clinicians an in-depth analysis of the mechanism of action, pharmacokinetics, toxicology, and efficacy of levomilnacipran. We propose that unlike selective serotonin reuptake inhibitors (SSRIs), or even their precursor serotonin-norepinephrine reuptake inhibitors (SNRIs), levomilnacipran demonstrates a potentially unique ability to alleviate the fatigue symptom cluster of major depressive disorder (MDD).

Data Sources: A literature review was completed in PubMed using the MeSH term *levomilnacipran*.

Study Selection: Inclusion criteria were English-language only, randomized controlled trials and systematic reviews published through March 2019. Analyses using product labels and anecdotal or uncontrolled reports of clinical applications were excluded. Only published data from short-term and long-term trials were analyzed. The search resulted in 73 articles. The evidence-based review comprises a total of 31 articles.

Data Synthesis: The data analyzed suggest that levomilnacipran has evidence in the treatment of MDD. More specifically, data suggest that levomilnacipran may be unique among SSRI and SNRI antidepressants in its ability to improve the fatigue symptom cluster in MDD.

Conclusions: Further investigations are warranted into levomilnacipran's potentially unique ability to alleviate the fatigue symptom cluster of MDD. Future head-to-head studies and studies that assess for clinically relevant improvements in fatigue are needed.

Prim Care Companion CNS Disord 2019;21(5):19nr02475

To cite: Gautam M, Kaur M, Jagtap P, et al. Levomilnacipran: more of the same? *Prim Care Companion CNS Disord.* 2019;21(5):19nr02475.

To share: https://doi.org/10.4088/PCC.19nr02475

[a]Department of Psychiatry, Henry Ford Health System/Wayne State University, Detroit, Michigan

[b]Internal Medicine, William Beaumont Hospital, Royal Oak, Michigan

**Corresponding author:* Mohan Gautam, DO, MS, Department of Psychiatry, Henry Ford System/Wayne State University, 2799 West Grand Blvd, Detroit, MI 48202 (mgautam1@hfhs.org).

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have significantly impacted the treatment of major depressive disorder (MDD). However, the available clinical data show that many patients' symptoms are not adequately addressed.[1] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[2] approximately 30% of patients achieved remission and 50% of patients had a clinical response to citalopram. Thus, there is a continued unmet need for antidepressants with alternative mechanisms of action to treat patients who continue to experience symptoms of MDD. In July 2013, the US Food and Drug Administration (FDA) approved levomilnacipran for the treatment of MDD.[3,4]

The purpose of this narrative review is to provide clinicians an in-depth analysis of the mechanism of action, pharmacokinetics, toxicology, and efficacy of levomilnacipran. We propose that levomilnacipran may be unique among SSRI and SNRI antidepressants in its ability to alleviate the fatigue symptom cluster of MDD and warrants further investigation.

METHODS

PubMed was searched using the MeSH term *levomilnacipran*. The inclusion criteria were English-language only, randomized controlled trials and systematic reviews published through March 2019. The search resulted in a total of 73 articles. Only published data from short-term and long-term trials were analyzed. Analyses using product labels and anecdotal or uncontrolled reports of clinical applications were excluded. Thirty-one articles[1,3,5–33] are included in this evidence-based review.

RESULTS

Mechanism of Action

The precursor of levomilnacipran was milnacipran, a racemic mixture of 2 enantiomers: (1S,2R) and (1R,2S).[3] Although milnacipran is approved in Europe and Japan for the treatment of MDD, in the United States it is only FDA approved for the management of fibromyalgia.[1,3]

Levomilnacipran, on the other hand, is composed entirely of the levorotary (1S,2R) enantiomer and does have FDA approval for the treatment of MDD.[3,4] This enantiomer is significantly more potent than the dextrorotary enantiomer and exhibits almost 10 times greater affinity for serotonin and norepinephrine transporters than the dextrorotary form.[5,7,8]

Furthermore, the SNRI precursors to levomilnacipran have significantly greater potency to inhibit serotonin reuptake over norepinephrine reuptake.[9] Levomilnacipran is unique because it

Clinical Points

- Many selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants demonstrate similarly limited efficacy in the treatment of major depressive disorder (MDD).
- Data suggest that levomilnacipran may be unique among SSRI and SNRI antidepressants in its potential to alleviate the fatigue symptom cluster of MDD and that future research is warranted to compare levomilnacipran with other antidepressants.

has twice as much affinity to inhibit norepinephrine reuptake as it does to inhibit serotonin reuptake. This property of levomilnacipran provides a striking juxtaposition to other SNRIs, which preferentially inhibit serotonin reuptake. The clinical relevance, as demonstrated by Chen and colleagues,[8] is that levomilnacipran would be expected to inhibit reuptake of norepinephrine by > 90% and serotonin by > 80% in dosages ≥ 40 mg. In comparison to other SNRIs (eg, venlafaxine), much higher relative doses such as 225 mg are required to significantly affect norepinephrine reuptake inhibition.[10] Indeed, in patients taking duloxetine 60 mg, plasma samples have demonstrated that serotonin reuptake was inhibited by 75% and norepinephrine reuptake by 60%.[11]

Pharmacokinetics

Levomilnacipran can be administered with or without food, as this does not appear to impact absorption. In human studies,[12] median time to reach maximum plasma concentration is 2.75 hours with a mean half-life of 10.4 hours. Other literature[7] estimates the half-life to be approximately 12 hours. Levomilnacipran is metabolized primarily through hepatic cytochrome P450 (CYP) 3A4 enzymes, with minor contributions from other CYP enzymes, into 2 inactive metabolites. The major metabolite is formed through desethylation into *N*-desethyl levomilnacipran, and the minor metabolite is formed through hydroxylation into p-hydroxy-levomilnacipran. Levomilnacipran is 22% bound to protein and primarily excreted by the kidneys with approximately 58% excreted unchanged in urine.[1,7]

Because levomilnacipran is so extensively metabolized by CYP3A4, caution is warranted when there is a need to administer other medications that also interact with CYP3A4. Coadministration of levomilnacipran with ketoconazole, a strong CYP3A4 inhibitor, increases levomilnacipran exposure (as measured by the area under the curve [AUC]) by 57%.[7] Therefore, we agree with the recommendation that levomilnacipran dose should not exceed 80 mg if coadministered with ketoconazole.[9] On the other hand, coadministration with drugs that are metabolized by CYP3A4 (eg, alprazolam) do not appear to alter the pharmacokinetic profile of levomilnacipran. Finally, coadministration with the CYP3A4 inducers such as carbamazepine causes a mild reduction of levomilnacipran exposure (as measured by AUC) of approximately 26%.[9]

Hepatic Impairment

In a pharmacokinetic analysis of single-dose levomilnacipran in patients with mild, moderate, or severe hepatic impairment, a single dose of levomilnacipran ER 40 mg was generally well tolerated. In a single-dose study[13] of levomilnacipran 40 mg, the AUC and Cmax were approximately 28% and 32%, respectively, in participants with severe hepatic dysfunction. Asnis and Henderson[1] argue that no dosage adjustments are necessary for mild, moderate, or even severe hepatic impairment. Longer-term studies on metabolism of levomilnacipran in patients with hepatic impairment are needed to provide further recommendations.

Renal Impairment

In mild, moderate, and severe renal impairment, levomilnacipran plasma levels were higher than those of healthy volunteers in terms of Cmax and AUC.[14] Furthermore, the half-life of levomilnacipran was prolonged in patients with renal impairment. Normal renal function was defined as creatinine clearance ≥ 80 mL/min, mild between 50 mL/min and 80 mL/min, moderate between 30 mL/min and 50 mL/min, and severe < 30 mL/min. In participants with normal renal function, approximately 50% of levomilnacipran was eliminated unchanged. In mild renal impairment, the AUC value was only 1.2 times higher than that present in normal renal function. However, moderate renal impairment produced a 2-fold increase in AUC, and severe renal impairment produced a 3-fold increase in AUC.[14] These data suggest that moderate or greater renal dysfunction would require down titration of the dose of levomilnacipran.

Toxicology

Levomilnacipran, like all SNRIs, carries a risk of withdrawal symptoms if suddenly discontinued.[15] Discontinuation symptoms are often related inversely to SNRI half-life. For example, venlafaxine, which has a half-life of 5 hours, is particularly prone to causing more severe discontinuation symptoms. Therefore, we recommend that patients should be monitored for discontinuation symptoms and a gradual dose reduction considered.[16] In 2018, Wagner and colleagues[17] completed a network meta-analysis of levomilnacipran, vilazodone, and vortioxetine and found similar efficacy and harm among these 3 medications.

Cardiovascular

SNRIs as a class have been associated with an overall increase in basal heart rate.[18] Data from short-term studies[1] (8–10 weeks) demonstrate that levomilnacipran is associated with a modest increase in heart rate (7.4 bpm) compared with placebo, which had a negligible increase in heart rate (0.3 BPM). Furthermore, short-term studies demonstrate that levomilnacipran also has a modest increase in systolic blood pressure (levomilnacipran: 3 mm Hg vs placebo: −0.04 mm Hg) and diastolic blood pressure (levomilnacipran: 3.2 mm Hg vs placebo: 0.0 mm Hg). Short-term studies[1]

demonstrated no dose-dependent relationship on blood pressure.

In a 39-week placebo-controlled study,[19] the levomilnacipran group had an increased heart rate of 12.3 bpm compared with 3.6 bpm in the placebo group. A second long-term 48-week open-label trial[20] also demonstrated a heart rate increase in patients taking levomilnacipran of 9.1 bpm. During the 48-week open-label trial,[20] there was an increase in systolic blood pressure of 3.9 bpm and an increase in diastolic blood pressure of 3.3 bpm. However, the 39-week placebo-controlled study[19] reported no clinically meaningful changes in vital signs in response to levomilnacipran.

The risk of QTc prolongation among the newest antidepressants, including levomilnacipran, remains low with therapeutic doses.[21] No patients in the short-term studies[1] developed a QTc > 500 ms. Even at doses 2.5 times the maximum recommended dose (300 mg), levomilnacipran did not elevate QTc to a clinically relevant degree.

Gastroenterology

Levomilnacipran has been shown to be weight neutral in all short-term studies[8,22–25] as well as in long-term studies.[19,20] In short-term studies,[1] the most commonly reported gastrointestinal adverse effects compared to placebo were nausea (17 vs 6), dry mouth (10 vs 7), constipation (9 vs 3), and vomiting (5 vs 1).

In short-term trials,[1,8,22–25] there were a few instances of mildly elevated liver enzymes. However, no patients developed alanine aminotransferase or aspartate aminotransferase levels ≥ 3 times the upper limit of normal or total bilirubin 2 times the upper limit of normal.[1,8,22–25]

Genitourinary

Short-term trials[1,8,22–25] of levomilnacipran have demonstrated a dose-dependent relationship with the development of urinary hesitancy and erectile dysfunction. Urinary hesitancy in placebo groups remained approximately 0% but developed in the levomilnacipran groups: 4% of participants taking 40 mg, 5% of participants taking 80 mg, and 6% of participants taking 120 mg. The development of erectile dysfunction appears to be more pronounced: 2% in the placebo group compared to 6% in the 40-mg levomilnacipran group, 8% in the 80-mg levomilnacipran group, and 10% in the 120-mg levomilnacipran group.[1,8,22–25]

The potential for levomilnacipran to cause urinary hesitancy is consistent with other medications that cause norepinephrine reuptake inhibition. Discontinuation of treatment or reduction of dose frequently alleviates this side effect. If there are significant benefits in symptom reduction with levomilnacipran, augmentation with an alpha-1 antagonist such as tamsulosin can be utilized to improve urinary hesitancy.[26]

Mortality

No deaths occurred during any of the levomilnacipran trials. There was no clear relationship between the emergence of suicidal ideation or suicidal behavior in any of the clinical trials. However, it should be noted that an exclusion criteria utilized in the screening processes were suicidal risk or prior suicide attempt in the past year or severe suicidal ideation.[1] Thase and colleagues[33] conducted a post hoc analysis on all 5 phase III clinical trials[8,22–25] and were unable to identify a relationship between levomilnacipran and suicidality, regardless of dosage or duration of treatment.

Efficacy

Prior to human studies, levomilnacipran demonstrated improvements in rodents in the forced swim test and the tail suspension test.[27] Short-term human trials (8–10 weeks) of levomilnacipran demonstrate improvements in depression as measured by the Montgomery-Asberg Depression Rating Scale (MADRS). However, the improvements are not necessarily consistent. Montgomery et al[25] demonstrated that at the conclusion of their 10-week trial, levomilnacipran showed a statistically significant response of 59% compared to 42% with placebo and remission of 46.4% compared to 26% with placebo. Asnis and colleagues[22] demonstrated that by the end of their 8-week trial, statistically significant changes in the MADRS were attained for all dosages compared to placebo. These changes were attained by the end of week 4 at the higher dosages of 80 mg and 120 mg. Although levomilnacipran produced strong response rates, there was no statistically significant difference in the remission rates for any dosage of levomilnacipran compared with placebo.[22] These findings were somewhat replicated by Bakish et al,[23] who found statistically significant differences in MADRS scores for the levomilnacipran 40-mg group and the levomilnacipran 80-mg group by the end of week 4 of treatment, which was also sustained through 8 weeks. Additionally, in this study,[23] remission was greater in the levomilnacipran 40-mg group (30%) and the levomilnacipran 80-mg group (32%) compared with the placebo group (18%).

However, response and remission using MADRS scores were more ambivalent in a study by Gommoll et al,[24] wherein a statistically significant response was achieved by 39% of the levomilnacipran group and 35% of the placebo group, and remission was achieved by 25% of the levomilnacipran group and 24% of the placebo group. Finally, Sambunaris et al[8] demonstrated a significantly greater response in MADRS scores in the levomilnacipran group (42%) compared with the placebo group (29%) but reported no statistically significant difference for remission between the 2 groups.

Two long-term clinical trials[19,20] with levomilnacipran have been conducted. In a 48-week open trial conducted by Mago et al,[19] the number of patients who met criteria for response at 48 weeks was high (last observation carried forward: 73%, original cases: 88%). The other long-term study was conducted by Shiovitz et al,[20] who analyzed time to relapse between patients who responded at the end of a 12-week open-label trial by randomizing them to placebo and levomilnacipran groups. The authors[20] found that

Table 1. Administration Guidelines for Levomilnacipran Extended Release (Fetzima)

Available capsules	20 mg, 40 mg, 80 mg, 120 mg
Initiation	20 mg/d orally for 2 days, then 40 mg/d; maximum: 120 mg/d
Administration	Food does not impact absorption
Time to reach peak plasma concentration	2.75 h
Primary metabolism	Hepatic cytochrome P450 3A4
Primary elimination, half-life	Urine, 10–12 h
Hepatic impairment	No dosage adjustments necessary; long-term studies are needed
Mild renal impairment (creatinine clearance > 50 mL/min)	No dosage adjustments necessary
Moderate-severe renal impairment (creatinine clearance ≤ 50 mL/min)	Down titration necessary
Pregnancy, children, geriatrics, cardiovascular comorbidities	Long-term studies are needed
Discontinuation	Sudden discontinuation can cause withdrawal symptoms; gradually reduce dose

time to relapse was longer for the levomilnacipran group compared with placebo but that treatment differences were not statistically significant.

Montgomery et al[28] conducted a proof-of-concept ad-hoc analysis on the results of their clinical trial and found that significantly more patients in the levomilnacipran group versus the placebo group achieved complete remission, defined as a MADRS score ≤ 5. Remission was achieved in 24% of the levomilnacipran group and 10% of the placebo group. Sustained remission, defined as a MADRS score ≤ 10 in weeks 4–10, was attained by 16% of the levomilnacipran group and 10% of the placebo group.[28]

Kornstein et al[29] conducted a post hoc analysis of the original 5 short-term clinical trials and found significant improvements in MADRS scores for patients treated with levomilnacipran versus placebo. In first-episode depression, this improvement was 45% in the levomilnacipran group and 35% in the placebo group; in the highly recurrent group, improvement was 44% in the levomilnacipran group and 34% in the placebo group; and in the chronic depression group, improvement was 37% in the levomilnacipran group and 22% in the placebo group.[29] These trends were corroborated by Wesnes et al[30] and suggested through expert opinion by Ragguett et al.[31]

Unique Benefit: Fatigue

Fatigue is a crucial component of MDD. The STAR*D trial[2] demonstrated that approximately 61% of patients treated with an SSRI continued to experience this symptom after 14 weeks of treatment, which was a negative prognostic indicator compared with another studies that showed greater fatigue improvement to correspond to a more positive prognosis in the treatment of MDD.[32] As a preferential norepinephrine reuptake inhibitor, we propose that levomilnacipran is an evidence-based recommendation for patients whose MDD-associated fatigue causes impairment.

Thase and colleagues[33] conducted a post hoc analysis of the study conducted by Sambunaris et al[8] using a validated short-form version of the Motivation and Energy Inventory. They demonstrated that the levomilnacipran treatment group had improved motivation and energy compared with the placebo group, especially in patients with lower baseline scores. They showed an effect size in the higher baseline energy/motivation group of 0.23 and an effect size of 0.32 in the lower baseline energy/motivation group.[33]

Freeman and colleagues[32] conducted a post hoc analysis of the 5 short-term clinical trials by focusing on specific items of the MADRS and Hamilton Depression Rating Scale (HDRS) consisting of symptoms associated with fatigue. The items analyzed were MADRS item 7: lassitude, HDRS item 7: work/activities, HDRS item 8: retardation, and HDRS item 13: somatic symptoms. In all these fatigue-related items, remission of fatigue symptoms was significantly greater for the levomilnacipran group compared with the placebo group. Interestingly, there were differences in subgroup response to levomilnacipran. For example, work/activities and general somatic symptom improvement was more prominent in men. Women aged < 50 years had greater improvements in retardation/general somatic symptoms compared with women aged > 50 years. Furthermore, treatment effect sizes in obese patients (body mass index > 30 kg/m^2) tended to be smaller than those of nonobese patients.[32]

CONCLUSION

The data analyzed in this review suggest that levomilnacipran has evidence in the treatment of MDD. Table 1 summarizes administration guidelines. More specifically, data suggest that levomilnacipran may be unique among SSRI and SNRI antidepressants in its ability to improve the fatigue symptom cluster in MDD. However, several limitations need to be addressed. All studies in this review compared levomilnacipran to placebo. Therefore, head-to-head studies are needed to truly label the potential impact of levomilnacipran on fatigue as a unique feature among these classes of antidepressants. Further, to determine whether these findings bear clinical relevance, future independent studies and reviews should examine if the impact of levomilnacipran on fatigue translates to quantifiable improvements in function. Significant considerations with regard to the utilization of levomilnacipran in certain subgroups require further investigation. For example, the safety and efficacy of levomilnacipran is unknown for pregnant patients, mothers who are breastfeeding, children and adolescents, and those patients with a cardiovascular comorbidity such as recent myocardial infarction. Long-term studies are also needed to determine the safety of levomilnacipran in hepatic impairment.

Submitted: April 29, 2019; accepted July 11, 2019.
Published online: September 5, 2019.
Potential conflicts of interest: None.
Funding/support: None.

REFERENCES

1. Asnis GM, Henderson MA. Levomilnacipran for the treatment of major depressive disorder: a review. *Neuropsychiatr Dis Treat*. 2015;11:125–135.
2. Warden D, Rush AJ, Trivedi MH, et al. The STAR*D Project results: a comprehensive review of findings. *Curr Psychiatry Rep*. 2007;9(6):449–459.
3. Citrome L. Levomilnacipran for major depressive disorder: a systematic review of the efficacy and safety profile for this newly approved antidepressant—what is the number needed to treat, number needed to harm and likelihood to be helped or harmed? *Int J Clin Pract*. 2013;67(11):1089–1104.
4. FETZIMA. Forest Pharmaceuticals, Inc. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204168s000lbl.pdf. Accessed August 9, 2019.
5. Auclair AL, Martel JC, Assié MB, et al. Levomilnacipran (F2695), a norepinephrine-preferring SNRI: profile in vitro and in models of depression and anxiety. *Neuropharmacology*. 2013;70:338–347.
6. Zadka Ł, Dziwota E, Olajossy M. Levomilnacipran—a successor of milnacipran with a higher noradrenergic selectivity. *Acta Pol Pharm*. 2016;73(2):285–289.
7. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. *Handb Exp Pharmacol*. 2019;250:145–180.
8. Sambunaris A, Bose A, Gommoll CP, et al. A phase III, double-blind, placebo-controlled, flexible-dose study of levomilnacipran extended-release in patients with major depressive disorder. *J Clin Psychopharmacol*. 2014;34(1):47–56.
9. Chen L, Boinpally R, Gad N, et al. Evaluation of cytochrome P450 (CYP) 3A4-based interactions of levomilnacipran with ketoconazole, carbamazepine or alprazolam in healthy subjects. *Clin Drug Investig*. 2015;35(10):601–612.
10. Spina E, Trifirò G, Caraci F. Clinically significant drug interactions with newer antidepressants. *CNS Drugs*. 2012;26(1):39–67.
11. Chen L, Greenberg WM, Gommoll C, et al. Levomilnacipran pharmacokinetics in healthy volunteers versus patients with major depressive disorder and implications for norepinephrine and serotonin reuptake inhibition. *Clin Ther*. 2015;37(9):2059–2070.
12. Brünner V, Maynadier B, Chen L, et al. Disposition and metabolism of [14C]-levomilnacipran, a serotonin and norepinephrine reuptake inhibitor, in humans, monkeys, and rats. *Drug Des Devel Ther*. 2015;9:3199–3215.
13. Chen L, Boinpally R, Greenberg WM, et al. Effect of hepatic impairment on the pharmacokinetics of levomilnacipran following a single oral dose of a levomilnacipran extended-release capsule in human participants. *Clin Drug Investig*. 2014;34(5):351–359.
14. Chen L, Greenberg WM, Brand-Schieber E, et al. Effect of renal impairment on the pharmacokinetics of levomilnacipran following a single oral dose of levomilnacipran extended-release capsule in humans. *Drug Des Devel Ther*. 2015;9:3293–3300.
15. Fava GA, Benasi G, Lucente M, et al. Withdrawal symptoms after serotonin-noradrenaline reuptake inhibitor discontinuation: systematic review. *Psychother Psychosom*. 2018;87(4):195–203.
16. McIntyre RS. The role of new antidepressants in clinical practice in Canada: a brief review of vortioxetine, levomilnacipran ER, and vilazodone. *Neuropsychiatr Dis Treat*. 2017;13:2913–2919.
17. Wagner G, Schultes MT, Titscher V, et al. Efficacy and safety of levomilnacipran, vilazodone and vortioxetine compared with other second-generation antidepressants for major depressive disorder in adults: a systematic review and network meta-analysis. *J Affect Disord*. 2018;228:1–12.
18. Carvalho AF, Sharma MS, Brunoni AR, et al. The safety, tolerability and risks associated with the use of newer generation antidepressant drugs: a critical review of the literature. *Psychother Psychosom*. 2016;85(5):270–288.
19. Mago R, Forero G, Greenberg WM, et al. Safety and tolerability of levomilnacipran ER in major depressive disorder: results from an open-label, 48-week extension study. *Clin Drug Investig*. 2013;33(10):761–771.
20. Shiovitz T, Greenberg WM, Chen C, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and safety of levomilnacipran ER 40–120 mg/day for prevention of relapse in patients with major depressive disorder. *Innov Clin Neurosci*. 2014;11(1–2):10–22.
21. Jasiak NM, Bostwick JR. Risk of QT/QTc prolongation among newer non-SSRI antidepressants. *Ann Pharmacother*. 2014;48(12):1620–1628.
22. Asnis GM, Bose A, Gommoll CP, et al. Efficacy and safety of levomilnacipran sustained release 40 mg, 80 mg, or 120 mg in major depressive disorder: a phase 3, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2013;74(3):242–248.
23. Bakish D, Bose A, Gommoll C, et al. Levomilnacipran ER 40 mg and 80 mg in patients with major depressive disorder: a phase III, randomized, double-blind, fixed-dose, placebo-controlled study. *J Psychiatry Neurosci*. 2014;39(1):40–49.
24. Gommoll CP, Greenberg WM, Chen C. A randomized, double-blind, placebo-controlled study of flexible doses of levomilnacipran ER (40–120 mg/day) in patients with major depressive disorder. *J Drug Assess*. 2014;3(1):10–19.
25. Montgomery SA, Mansuy L, Ruth A, et al. Efficacy and safety of levomilnacipran sustained release in moderate to severe major depressive disorder: a randomized, double-blind, placebo-controlled, proof-of-concept study. *J Clin Psychiatry*. 2013;74(4):363–369.
26. Asnis GM, Caneva E, Henderson MA. A review of antidepressant-induced urinary hesitancy: a focus on levomilnacipran ER including two case presentations (5633). *Expert Opin Drug Saf*. 2016;15(5):717–725.
27. Sansone RA, Sansone LA. Serotonin norepinephrine reuptake inhibitors: a pharmacological comparison. *Innov Clin Neurosci*. 2014;11(3–4):37–42.
28. Montgomery SA, Mansuy L, Ruth AC, et al. The efficacy of extended-release levomilnacipran in moderate to severe major depressive disorder: secondary and post-hoc analyses from a randomized, double-blind, placebo-controlled study. *Int Clin Psychopharmacol*. 2014;29(1):26–35.
29. Kornstein SG, Gommoll C, Chen C, et al. The effects of levomilnacipran ER in adult patients with first-episode, highly recurrent, or chronic MDD. *J Affect Disord*. 2016;193:137–143.
30. Wesnes KA, Gommoll C, Chen C, et al. Effects of levomilnacipran extended-release on major depressive disorder patients with cognitive impairments: post-hoc analysis of a phase III study. *Int Clin Psychopharmacol*. 2017;32(2):72–79.
31. Ragguett RM, Yim SJ, Ho PT, et al. Efficacy of levomilnacipran extended release in treating major depressive disorder. *Expert Opin Pharmacother*. 2017;18(18):2017–2024.
32. Freeman MP, Fava M, Gommoll C, et al. Effects of levomilnacipran ER on fatigue symptoms associated with major depressive disorder. *Int Clin Psychopharmacol*. 2016;31(2):100–109.
33. Thase ME, Gommoll C, Chen C, et al. Effects of levomilnacipran extended-release on motivation/energy and functioning in adults with major depressive disorder. *Int Clin Psychopharmacol*. 2016;31(6):332–340.