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ORIGINAL RESEARCH

Efficacy and safety of multiple doses of levomilnacipran extended-release for the treatment of major depressive disorder

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Objective: The aim of this meta-analysis was to evaluate the efficacy and safety of levomilnacipran extended-release (ER) in the treatment of major depressive disorder (MDD).

Methods: Randomized controlled trials were searched by electronic databases. Unpublished data were also searched by the relevant websites. Weighted mean difference (WMD) and risk ratio (RR) with 95% confidence interval (CI) were calculated and pooled using fixed-effects model or random-effects model.

Results: Five randomized placebo-controlled trials including 2,637 patients were analyzed. Compared with placebo, levomilnacipran ER had a greater reduction in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score and Sheehan Disability Scale (SDS) total score (MADRS: WMD −3.49 [95% CI −4.28, −2.70; $P<0.00001$]; SDS: WMD −2.41 [95% CI −3.05, −1.77; $P<0.00001$]). Significantly more patients in levomilnacipran ER achieved MADRS response rate (RR 1.35 [95% CI 1.23, 1.47; $P<0.00001$]) and MADRS remission rate (RR 1.30 [95% CI 1.06, 1.59; $P=0.01$]). In terms of safety, more patients discontinued due to adverse events (AEs) in levomilnacipran ER compared with placebo (RR 3.15 [95% CI 2.26, 4.39; $P<0.00001$]), but it was generally well tolerated in each eligible trial. The most common AEs were nausea, delay in ejaculation, erectile dysfunction, tachycardia, headache and increase in heart rate.

Conclusion: Levomilnacipran ER is a safe and effective short-term treatment for MDD (≤10 weeks). Long-term and head-to-head trials comparing levomilnacipran ER with other antidepressants are needed to confirm the conclusion.

Keywords: levomilnacipran ER, SNRI, major depressive disorder, meta-analysis

Introduction

Major depressive disorder (MDD) is one of the most prevalent mental disorder and is estimated to be the fourth leading cause of disease burden worldwide.[1,2] Pharmacotherapy is the primary choice for MDD. However, most antidepressants lacked efficacy and tolerability for patients with MDD, and adverse effects were the leading reasons of discontinuation during the treatment.[3,4] Therefore, new antidepressants that can offer a greater advantage in efficacy and tolerability are needed. In this regard, levomilnacipran, which has a unique pharmacological activity compared with currently marketed serotonin–norepinephrine reuptake inhibitors (SNRIs), may prove to be an appealing alternative.

Levomilnacipran (1*S*, 2*R*-milnacipran) extended-release (ER), as the fourth SNRI, was approved by the US Food and Drug Administration (FDA) in July 2013 with doses of 40–120 mg capsule once daily.[5] In vitro studies have shown that levomilnacipran

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ER has twofold greater potency for norepinephrine compared with serotonin reuptake inhibition.[6] Compared with duloxetine, desvenlafaxine, or venlafaxine, levomilnacipran ER showed 10-fold greater selectivity for inhibiting norepinephrine reuptake.[7]

The efficacy and safety of levomilnacipran ER have been evaluated in several clinical studies, but the evaluation results were not completely consistent. A recent review had pooled the efficacy of levomilnacipran ER for MDD, using Cohen's *d* and number-needed-to-treat (NNT) as effect sizes,[8] which did not evaluate the safety of levomilnacipran ER and the effect on Sheehan Disability Scale (SDS). However, a significant improvement in SDS may demonstrate efficacy in treating functional impairment.[9] Thus, the aims of this article were to systematically review the existing published data regarding the treatment of MDD comparing levomilnacipran ER and placebo (including Montgomery–Åsberg Depression Rating Scale [MADRS] total score, SDS total score, response rate, remission rate, adverse effects, and cardiovascular effects) and to evaluate the efficacy and safety of levomilnacipran ER.

Methods

Data sources and search strategy

We searched PubMed, Embase, Medline, Ovid, the Cochrane Collaboration Library, Scopus and ScienceDirect, PsycInfo, and International Pharmaceutical Abstracts from inception to March 2016, without restriction of language. Potentially relevant unpublished data were searched by ClinicalTrials.gov, FDA website, European Union Drug Regulating Authorities Clinical Trials and the World Health Organization International Clinical Trials Registry Platform. We used the following terms: "levomilnacipran", "LVM", "fetzlma", "F2695", "major depressive disorder", "depression or major depression", and "MDD". These terms were adjusted to comply with the relevant rules in each database.

Study election

Two investigators (QH and XZ) independently reviewed the title and abstract and selected randomized controlled trials of levomilnacipran ER for the treatment of MDD. All the studies met the following criteria:

1. All patients (18–80 years of age) were diagnosed for MDD by the *Diagnostic and Statistical Manual of Mental Disorder*, fourth edition, text revision and confirmed by the Mini International Neuropsychiatric Interview.
2. All patients were required to have baseline MADRS total score ≥26.
3. MADRS total score was used as the primary outcome in eligible studies.
4. Studies included one or more of the secondary outcomes: SDS total score, MADRS remission rate (total score ≤10), MADRS response rate (≥50% improvement from baseline), adverse events (AEs), and cardiovascular effects.

Full-text articles were retrieved independently by two investigators (QH and XZ). If they had a disagreement, the third investigator (YH) was used to solve the disagreement when necessary.

Data extraction

Data were extracted by two investigators (QH and XZ), and any discrepancies were resolved by consensus. For each study, two investigators (QH and XZ) extracted information on study characteristics, participants' baseline characteristics, interventions of the trial, end points, and findings.

Quality assessment

Two investigators (QH and XZ) assessed the quality of included studies by using the risk of bias tool.[10] The predefined key domains included random sequence generation, allocation concealment, blinding, and other items (ie, efficacy analysis, lost to follow-up, intention-to-treat analysis, and statistical analysis).

Statistical analysis

All outcomes were pooled by using RevMan 5.3 software (Nordiac Cochrane Center, Copenhagen, Denmark; http://www.cochrane.org/). For dichotomous data, risk ratio (RR) was calculated with 95% confidence intervals (CIs). On the other hand, in case of continuous data, we used weighted mean difference (WMD) with 95% CIs. We calculated the I^2 statistic to estimate heterogeneity. If I^2 was <50%, we chose fixed-effect model with the analyses of the Mantel–Haenszel method; otherwise, the random-effect model was adopted.

Results

Literature search and study characteristics

A total of 859 records were identified by our initial search. According to title and abstract, we excluded 825 records (irrelevant, annual meeting, animal, duplicates). Finally, we excluded 29 records and confirmed five studies that met the inclusion criteria by two investigators screening full-text articles. The flow of study search and selection is shown in Figure 1.

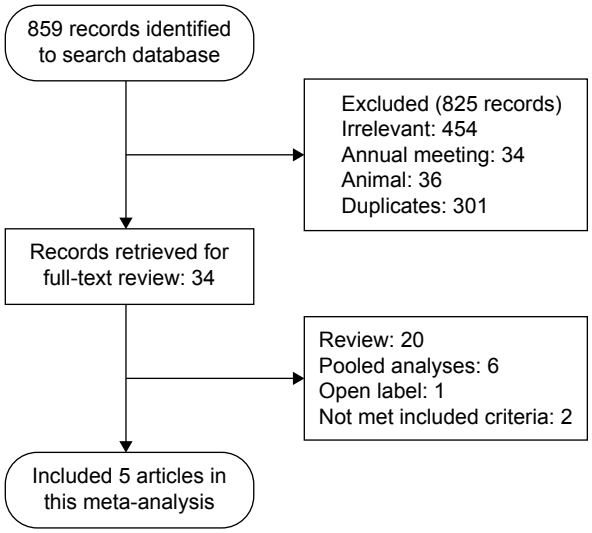

Figure 1 The flow of the study search and selection.

Five studies were randomized, double-blind, placebo-controlled trials. These included two fixed-dose trials[11,12] and three flexible-dose trials.[13–15] Trial durations ranged from 8 to 10 weeks. A total of 2,637 patients were randomized to the levomilnacipran ER group and placebo group, 2,623 patients were used for safety analyses and 2,598 patients were used for modified intent-to-treat and efficacy analyses (1,032 were randomized to placebo and 1,566 to the levomilnacipran ER group). The basic characteristics of the study are listed in Table 1.

Quality assessment

All eligible studies described the generation of the randomization sequence. However, allocation concealment was unclear in one study.[14] All studies were at least double blind. Five studies reported adequate intention-to-treat analysis.[11–15] Loss to follow-up was minimal and balanced in the five trials. Details of risk of bias assessment are shown in Table 2.

MADRS total score

Compared with placebo, a statistically significant reduction in the MADRS total score was observed in the levomilnacipran ER group (WMD −3.49 [95% CI −4.28, −2.70; $P<0.00001$]; Figure 2). The subgroup analysis results were WMD −3.26 (95% CI −4.95, −1.57; $P=0.0002$) for 40 mg, WMD −3.45 (95% CI −5.14, −1.75; $P<0.0001$) for 80 mg, WMD −4.90 (95% CI −7.66, −2.14; $P=0.0005$) for 120 mg, and WMD −3.37 (95% CI −4.50, −2.24; $P<0.00001$) for 40–120 mg (Figure 2).

In a sensitivity analysis, pooling the data on MADRS showed that the overall estimate was not impacted by excluding a phase II study[15] (WMD −3.24 [95% CI −4.16, −2.33; $P<0.00001$]).

SDS total score

The pooled effects estimate of the SDS total score was −2.41 (95% CI −3.05, −1.77; $P<0.00001$). The results of the subgroup analysis also demonstrated that levomilnacipran ER was superior to placebo on the SDS total score (40 mg: WMD −1.68 [95% CI −3.06, −0.30; $P=0.02$], 80 mg: WMD −2.67 [95% CI −4.05, −1.29; $P=0.0001$], 120 mg: WMD −2.5 [95% CI −4.61, −0.39; $P=0.02$], and 40–120 mg: WMD −2.35 [95% CI −3.88, −0.82; $P=0.003$]; Figure 3).

Response rate and remission rate

Levomilnacipran ER had a greater improvement in the MADRS response rate compared with placebo (40 mg: RR

Table 1 The basic characteristics of randomized controlled trials (mean ± SD)

Study	Duration of intervention (wk)	Interventions (n)	Age (years)	Weight (kg)	Baseline MADRS score	Outcomes
Asnis et al[11]	8	LVM 40 mg/d (178)	41.6±13.1	79.5±17.1	35.6±4.5	MADRS, SDS: response, remission
		LVM 80 mg/d (179)	41.0±12.8	83.0±17.3	36.0±4.1	
		LVM 120 mg/d (180)	40.3±11.9	84.2±18.6	36.1±3.9	
		Placebo (176)	41.3±11.3	83.8±19.3	36.0±3.9	
Bakish et al[12]	8	LVM 40 mg/d (188)	42.9±13.4	81.3±17.0	30.8±3.4	MADRS, SDS: response, remission
		LVM 80 mg/d (188)	43.1±12.8	81.7±17.5	31.2±3.5	
		Placebo (186)	42.3±13.2	81.6±17.7	31.0±3.8	
Gommoll et al[13]	8	LVM flexible dose (175)	42.8±12.9	82.4±18.1	35.9±4.1	MADRS, SDS: response, remission
		Placebo (182)	43.7±13.3	82.9±18.0	35.5±4.0	
Sambunaris et al[14]	8	LVM flexible dose (222)	45.0±13.2	84.4±18.9	35.0±3.6	MADRS, SDS: response, remission
		Placebo (220)	44.6±13.9	84.5±18.1	35.2±3.8	
Montgomery et al[15]	10	LVM flexible dose (282)	45	N/R	30.9±4.1	MADRS, SDS: response, remission
		Placebo (281)	44	N/R	30.5±3.7	

Abbreviations: wk, week; MADRS, Montgomery–Åsberg Depression Rating Scale; LVM, levomilnacipran; d, day; SDS, Sheehan Disability Scale; N/R, not reported; SD, standard deviation.

Table 2 Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding	Efficacy analysis	Lost to follow-up	ITT	Statistical analysis
Asnis et al[11]	Y	Y	Y	MMRM	Y	Y	ANCOVA
Bakish et al[12]	Y	Y	Y	MMRM	Y	Y	ANCOVA
Gommoll et al[13]	Y	Y	Y	MMRM	Y	Y	ANCOVA
Sambunaris et al[14]	Y	U	Y	FAS	Y	N	ANCOVA
Montgomery et al[15]	Y	Y	Y	MMRM	Y	Y	ANCOVA

Abbreviations: ITT, intention to treat; Y, yes; MMRM, mixed-model for repeated measures; ANCOVA, analysis of covariance; U, unclear; FAS, full analysis set; N, no.

1.36 [95% CI 1.12, 1.64; *P*=0.002], 80 mg: RR 1.34 [95% CI 1.10, 1.62; *P*=0.003], 120 mg: RR 1.42 [95% CI 1.06, 1.90; *P*=0.02], and 40–120 mg: RR 1.33 [95% CI 1.17, 1.51; *P*<0.0001]). The overall RR was 1.35 (95% CI 1.23, 1.47; *P*<0.00001; Figure 4).

The overall RR for the MADRS remission rate was 1.30 (95% CI 1.06, 1.59; *P*=0.01). The subgroup analysis results were RR 1.38 (95% CI 0.91, 2.10; *P*=0.12) for 40 mg, RR 1.40 (95% CI 0.85, 2.32; *P*=0.19) for 80 mg, RR 1.05 (95% CI 0.69, 1.60; *P*=0.81) for 120 mg, and RR 1.24 (95% CI 0.81, 1.91; *P*=0.31; Figure 5) for 40–120 mg.

Safety and tolerability

Compared with placebo, the overall rate of discontinuation and discontinuation due to AEs was higher for levomilnacipran ER (Table 3). Incidences of AEs (erectile dysfunction, delay in ejaculation, tachycardia, nausea, hedache, dry mouth, increase in heart rate) were higher for levomilnacipran ER (Table 3). The incidences of suicidal ideation and suicidal behavior were similar between the two groups (Table 3).

Compared with placebo, levomilnacipran ER showed greater increase in the pulse rate (WMD 7.56 [95% CI 6.81, 8.31; *P*<0.00001]), systolic blood pressure (WMD 3.14 [95% CI 2.37, 3.90; *P*<0.00001]), diastolic blood pressure (WMD 3.45 [95% CI 2.86, 4.05; *P*<0.00001]), and Bazett formula (QTcB; Table 4). In the five eligible studies, based on the Fridericia correction (QTcF), there was no QTc prolongation. None of the patients met potentially clinically significant criteria for PR (≥250 milliseconds), QTcB (>500 milliseconds), or QTcF (>500 milliseconds) interval.

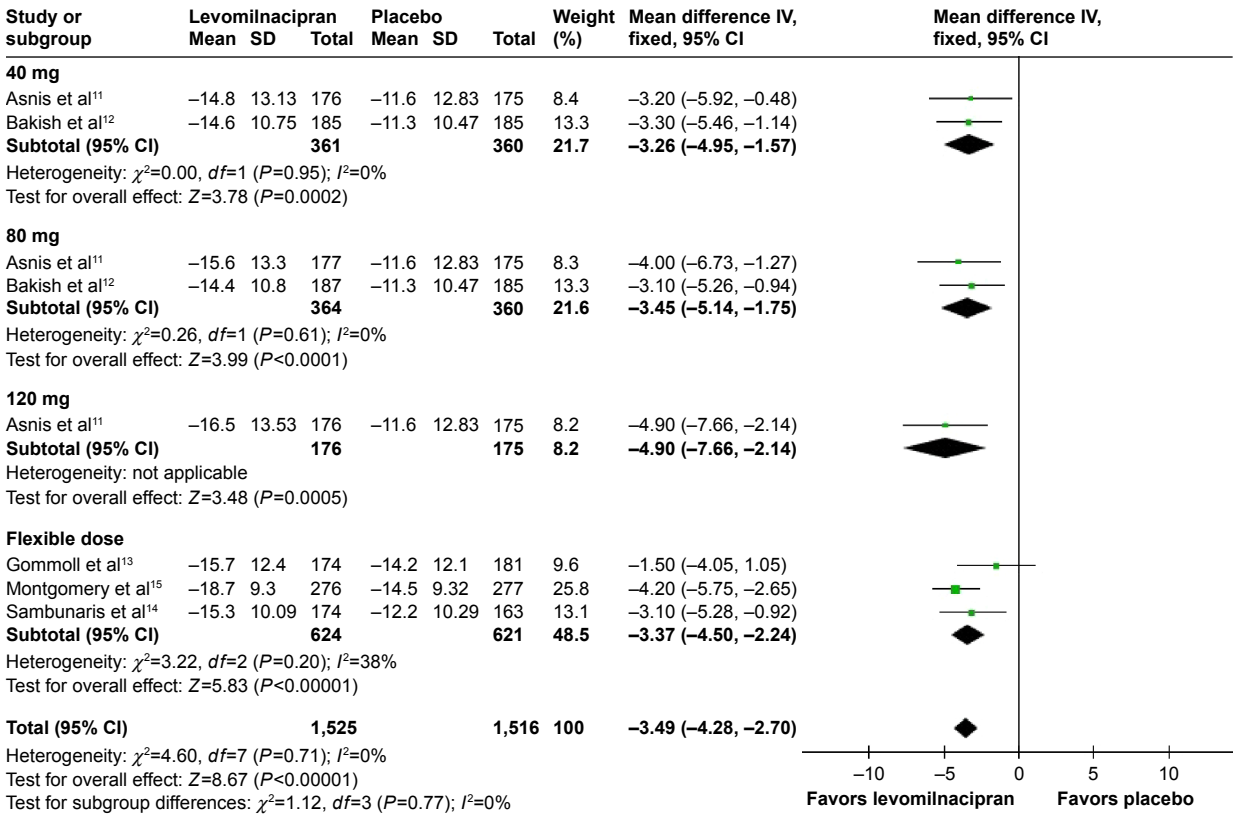

Figure 2 Meta-analysis for change in the MADRS total score from baseline, levomilnacipran ER versus placebo.
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; ER, extended-release; IV, inverse variance; CI, confidence interval; SD, standard deviation.

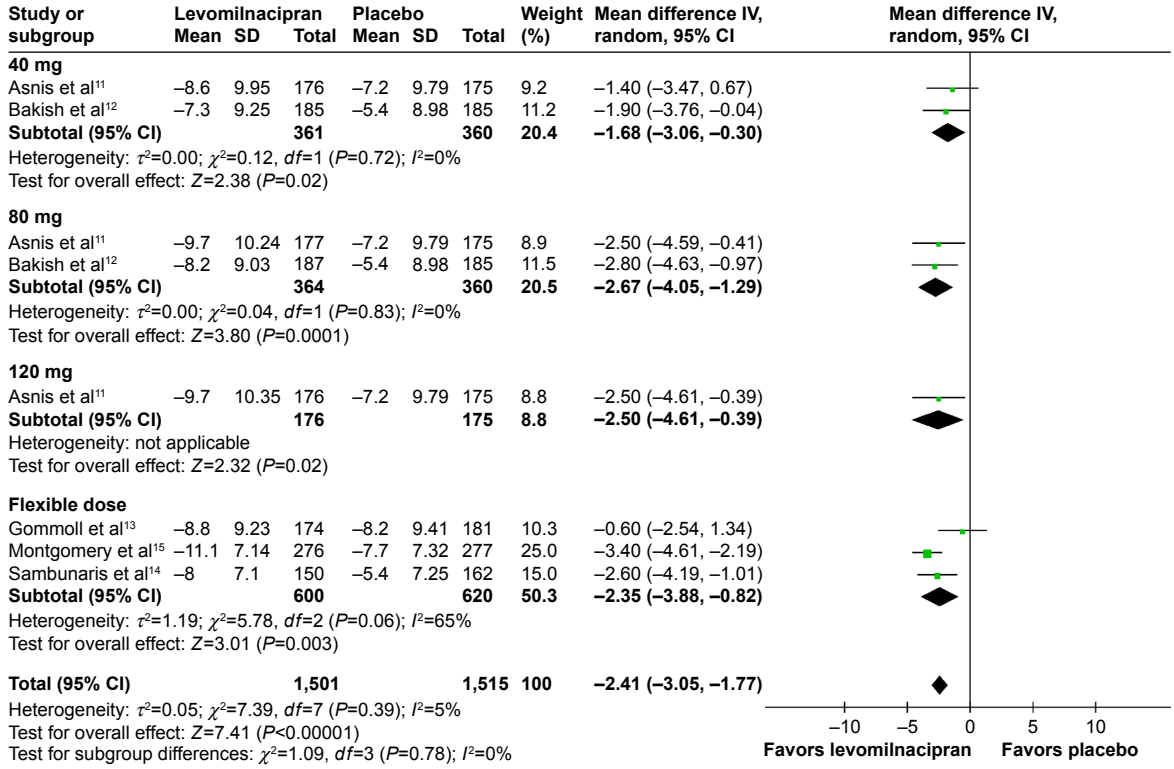

Figure 3 Meta-analysis for change in the SDS total score from baseline, levomilnacipran ER versus placebo.
Abbreviations: SDS, Sheehan Disability Scale; ER, extended-release; IV, inverse variance; CI, confidence interval.

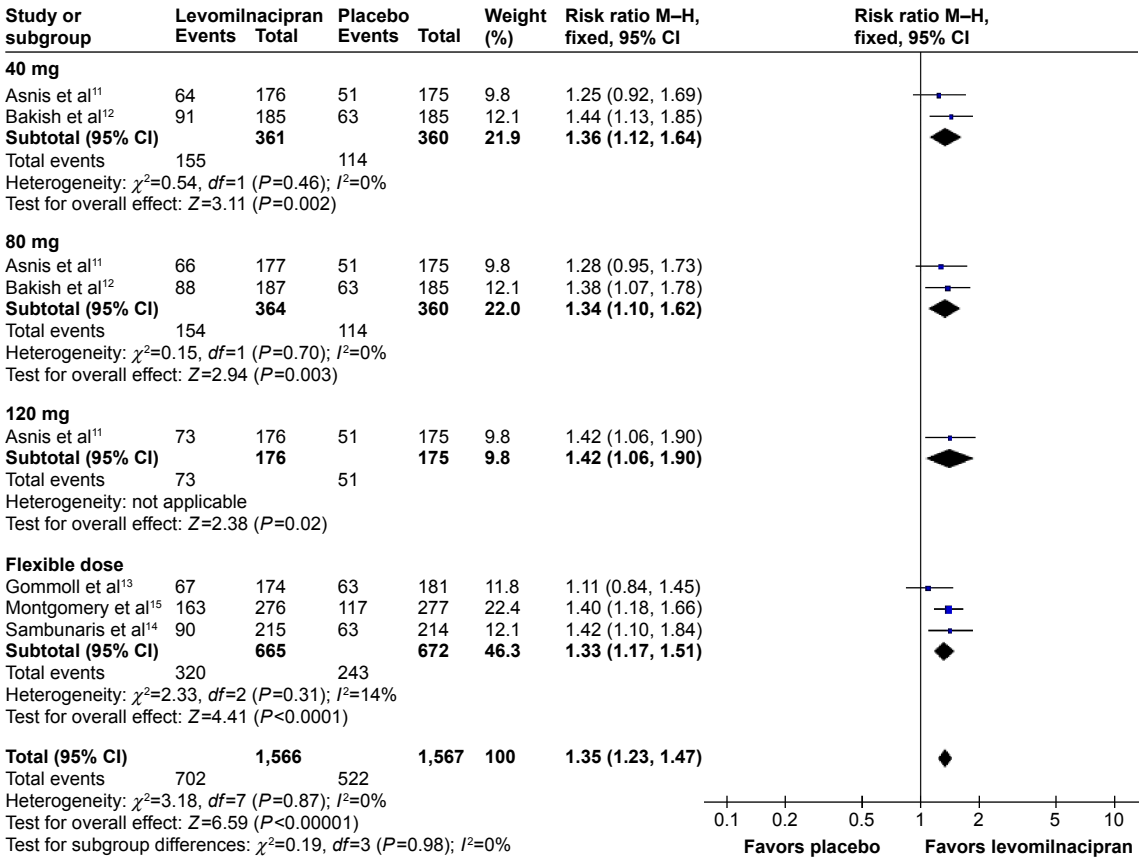

Figure 4 Meta-analysis for MADRS response rate (≥50% improvement from baseline), levomilnacipran ER versus placebo.
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; ER, extended-release; M–H, Mantel–Haenszel; CI, confidence interval.

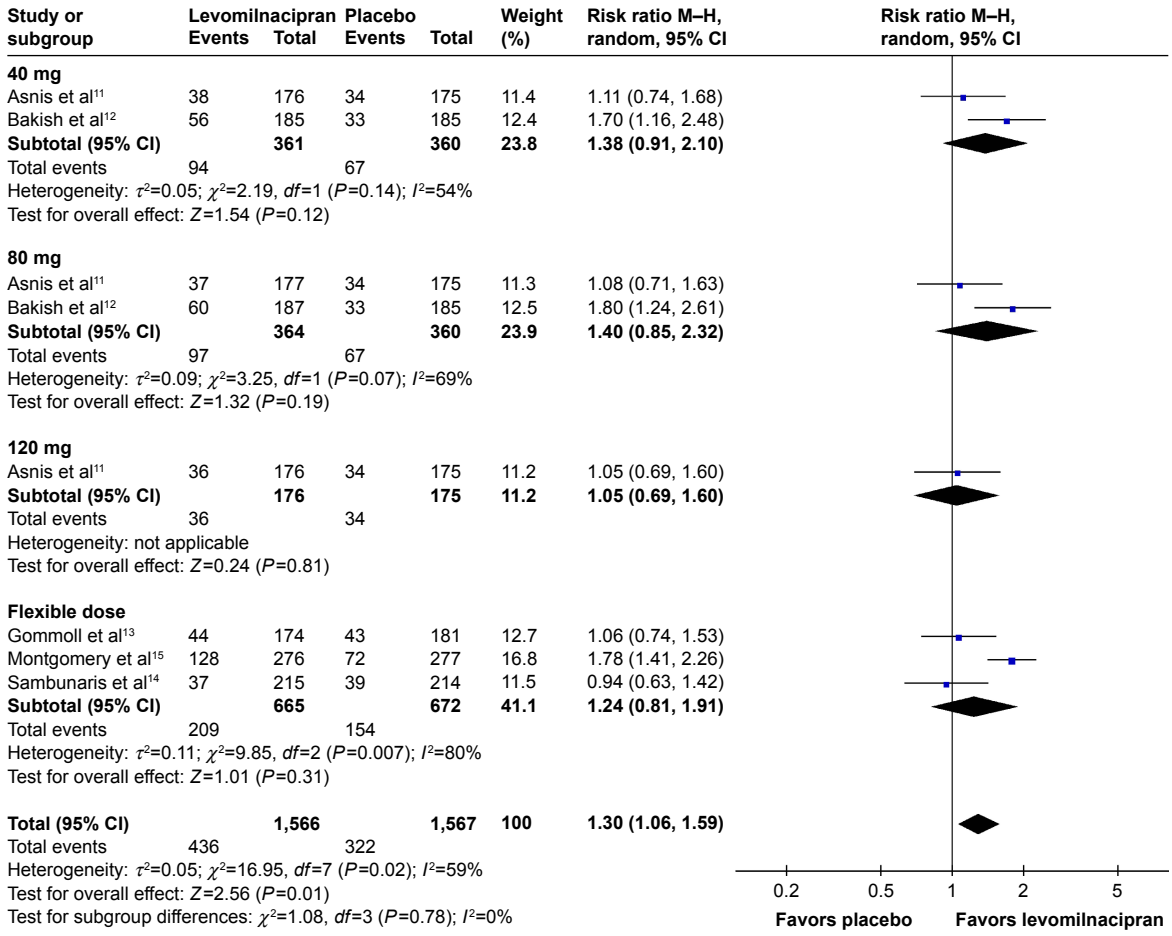

Figure 5 Meta-analysis for MADRS remission rate (total score ≤10), levomilnacipran ER versus placebo.
Abbreviations: MADRS, Montgomery–Åsberg Depression Rating Scale; ER, extended-release; M–H, Mantel–Haenszel; CI, confidence interval.

Discussion

In our systematic review and meta-analysis, levomilnacipran ER resulted in reduction in the MADRS total score and SDS total score compared with placebo. Levomilnacipran ER has a unique pharmacological activity and is relatively more selective for norepinephrine reuptake inhibition than serotonin reuptake inhibition.[6] The strong noradrenergic component of antidepressant may be especially effective in improving symptoms related to functioning.[16,17] Symptomatic and functional improvements are both critical components

Table 3 Meta-analysis for the safety outcomes (dichotomous data)

Outcome	Levomilnacipran (n/N)	Placebo (n/N)	Effect estimate (95% CI)	I^2 (%)	*P*-value
Discontinuation due to all reasons[a]	405/1,583	324/1,040	1.24 (1.09, 1.42)	42	**0.008**
Discontinuation due to AE	139/1,583	44/1,040	3.15 (2.26, 4.39)	41	**<0.00001**
Erectile dysfunction[b]	29/406	9/204	3.26 (1.56, 6.81)	0	**0.002**
Ejaculation delayed[b]	16/351	0/208	10.96 (2.09, 57.56)	0	**0.005**
Tachycardia	74/1,408	15/858	3.12 (1.50, 6.47)	43	**0.002**
Nausea	272/1,583	60/1,040	3.80 (2.47, 5.83)	62	**<0.00001**
Headache	262/1,583	136/1,040	1.40 (1.18, 1.66)	0	**0.0001**
Dry mouth	160/1,583	73/1,040	1.40 (1.11, 1.76)	25	**0.004**
Insomnia	67/1,207	41/854	1.22 (0.86, 1.73)	0	0.26
Heart rate increase	98/1,088	13/544	0.06 (0.04, 0.09)	33	**<0.00001**
Suicidal ideation	316/1,573	172/1,037	1.03 (0.89, 1.19)	9	0.72
Suicidal behavior	5/573	1/390	2.17 (0.49, 9.62)	0	0.31

Notes: [a]Discontinuation due to AEs, insufficient therapeutic response, protocol violation, loss to follow-up and other reasons. [b]Based on the number of men in the safety population. Bold numbers are considered statistically significant.
Abbreviations: CI, confidence interval; AE, adverse event.

Table 4 Meta-analysis for the safety outcomes (continuous data)

Outcome	Studies (n)	Participants analyzed (n)		WMD (95% CI)	I^2 (%)	*P*-value
		Levomilnacipran	Placebo			
Pulse rate	4	1,298	756	7.56 (6.81, 8.31)	20	<0.00001
SBP	4	1,300	756	3.14 (2.37, 3.90)	0	<0.00001
DPB	4	1,300	756	3.45 (2.86, 4.05)	0	<0.00001
QTcB	3	1,171	631	8.59 (6.97, 10.20)	0	<0.00001

Abbreviations: WMD, weighted mean difference; CI, confidence interval; SBP, systolic blood pressure; DPB, diastolic blood pressure.

of recovery from MDD. Symptomatic improvement may provide an early sign of treatment response, and functional improvement may be a better indicator of meaningful change.[18] The MADRS total score >2 points for the test group versus placebo, which suggests that symptomatic improvement is clinically relevant.[19] A significant improvement in SDS means that function is improved.[9] In our study, the MADRS score exceeded 3.36 points for levomilnacipran ER compared with placebo. In addition, a significant difference in favor of levomilnacipran ER was also observed in the SDS total score. These observations may indicate that levomilnacipran ER might provide both symptomatic and functional efficacies.

If the response rate far exceeds the 10% average advantage for drug versus placebo, it is generally regarded as sufficient to establish antidepressant treatment advantage.[20] In our results, the rate of MADRS response was significantly greater for levomilnacipran ER versus placebo.

Most likely due to levomilnacipran ER related to the twofold greater potency for norepinephrine reuptake inhibition compared with serotonin reuptake inhibition,[6] levomilnacipran ER was generally well tolerated in the five eligible studies, which was consistent with the results of 48-week open-label study and the 39-week relapse prevention study.[21,22] However, compared with placebo, most incidences of AEs were higher for levomilnacipran ER. The five eligible studies showed that the common AEs were nausea, delay in ejaculation, erectile dysfunction, tachycardia, headache, and increase in heart rate. Pulse rate and blood pressure increases were greater for levomilnacipran ER versus placebo. Greater increase in QTcB was observed in the levomilnacipran ER group compared with placebo, which was consistent with increases in heart rate. The mean QTcF changes were small in both groups. In suicidal ideation and suicidal behavior, levomilnacipran ER and placebo patients had similar numbers.

Milnacipran was approved for the management of fibromyalgia in the US and for the treatment of MDD in many countries outside the US.[23,24] A earlier systematic review had shown that there was no difference in the overall effectiveness and tolerability between milnacipran and other antidepressants (selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs]). Additionally, it has some advantages over TCAs in terms of discontinuation due to AEs and the rates of AEs.[25] Levomilnacipran is the levo enantiomer of milnacipran. Regulatory guidelines in the US and Europe recommend development of the enantiomers over racemates where appropriate.[26] Given the favorable pharmacokinetic and pharmacodynamic characteristics of enantiomeric formulation, levomilnacipran ER may be more effective than milnacipran. However, head-to-head trials with levomilnacipran ER and milnacipran have not been performed.

Limitations

There were also limitations in this meta-analysis. First, our analysis highlighted the overall short-term safety and efficacy of levomilnacipran ER; the extended period is needed to understand the long-term benefits and risks. Second, agomelatine is another novel antidepressant that does not induce 5-HT2A stimulation, having a more favorable adverse-effect profile compared with the common SSRIs.[27] However, the lack of head-to-head trials limited the ability to compare levomilnacipran ER with agomelatine or other antidepressants. Future studies will be needed to compare levomilnacipran ER with other antidepressants. Third, strict inclusion and exclusion criteria might have limited these findings to a smaller population. Future larger studies designed to evaluate patients with recurrent or treatment-resistant depression are necessary. Fourth, levomilnacipran ER appears to display greater noradrenergic activity at a lower dose and increasing effects on serotonergic neurotransmission as the dose increases.[28] However, our study did not detect dose–response effects, since most of the clinical studies used flexible dosing.

Conclusion

This meta-analysis indicated that levomilnacipran ER might be safe and effective for short-term treatment of MDD. However, large, multicenter, randomized controlled trials

are still needed to assess the safety and efficacy of levomilnacipran ER. Furthermore, head-to-head trials comparing levomilnacipran ER with other antidepressants are needed to confirm the conclusion.

Disclosure

The authors report no conflicts of interest in this work.

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