Levomilnacipran Extended-Release Treatment in Patients With Major Depressive Disorder: Improvements in Functional Impairment Categories

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ABSTRACT

Objective: In this post hoc analysis, improvement in functional impairment in patients with major depressive disorder (MDD) treated with levomilnacipran extended release (ER) was evaluated by assessing shifts from more severe to less severe functional impairment categories on individual Sheehan Disability Scale (SDS) subscales.

Method: SDS data were pooled from 5 phase II/III studies conducted between December 2006 and March 2012 of levomilnacipran ER versus placebo in adult patients with MDD (*DSM-IV-TR* criteria). Proportions of patients shifting from moderate-extreme baseline impairment (score ≥ 4) to mild-no impairment (score ≤ 3) at end of treatment were assessed for each SDS subscale. Proportions of patients shifting from marked-extreme (score ≥ 7) baseline impairment to moderate-no (score ≤ 6) or mild-no impairment (score ≤ 3) at end of treatment, and shifts in which patients worsened from moderate-no to marked-extreme impairment, were also evaluated.

Results: A significantly higher proportion of patients treated with levomilnacipran ER than placebo-treated patients improved from more severe categories of functional impairment at baseline to less severe impairment categories across all SDS subscales: work/school, social life, and family life/home responsibilities ($P < .01$). Depending on the SDS subscale, 48%–55% of levomilnacipran ER–treated patients with moderate-extreme impairment at baseline improved to mild or no impairment, compared with no more than 40% of placebo patients on any subscale. Almost half (42%–47%) of levomilnacipran ER–treated patients versus only about one-third (29%–34%) of placebo patients improved from marked-extreme to mild or no impairment across functional domains.

Conclusions: These results suggest that functional improvement was observed across the SDS functional domains. To our knowledge, this is the first such categorical analysis of functional improvement, as measured by the SDS, for an antidepressant.

Trial Registration: ClinicalTrials.gov identifiers: NCT00969709, NCT01377194, NCT00969150, and NCT01034462 and EudraCT identifier: 2006–002404-34

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Symptoms of major depressive disorder (MDD) often lead to decreased quality of life, social isolation, and disability.[1–6] Many patients who respond to antidepressant therapy and experience improvement in depressive symptoms will continue to experience functional impairment.[7–15] Residual functional impairment is associated with an increased risk of depression relapse and continued or increased long-term disability.[6,12,16–18] From a patient's perspective, return to his/her previous level of functioning can be as important as symptom resolution.[1,19] Therefore, improving functional impairment is an essential goal of antidepressant therapy, and medications that improve functional impairment are an important tool in the management of depression.

In clinical research, rating scales such as the Montgomery-Asberg Depression Rating Scale (MADRS)[20] and the Sheehan Disability Scale (SDS)[21] are used to evaluate antidepressant efficacy by assessing depressive symptoms and functional impairment, respectively. Clinical trial results are usually presented quantitatively as mean score changes for the overall treatment group and not as individual patient outcomes. While these assessment tools are known to effectively demonstrate therapeutic efficacy in the research setting, they are not routinely used in clinical practice settings. Thus, it can be difficult for practitioners to interpret quantitative trial results and translate them into qualitative results that apply to "real-world" clinical settings. Novel analytic approaches that characterize symptomatic and functional improvements at the patient level may enhance our understanding of depression treatment outcomes.

Levomilnacipran extended release (ER) is US Food and Drug Administration approved for the treatment of MDD in adults. Levomilnacipran, a serotonin-norepinephrine reuptake inhibitor (SNRI), differs from other SNRIs (duloxetine, venlafaxine, and desvenlafaxine) in that it shows greater potency in vitro for inhibiting norepinephrine relative to serotonin reuptake.[22] Reduced norepinephrine neurotransmission has been associated with low energy, problems concentrating, and functional impairment; therefore, antidepressants with significant noradrenergic effects may be effective in improving functional impairment in depressed patients.[23,24] A previous analysis[25] of pooled SDS data from 5 phase II/III studies of levomilnacipran ER in patients with MDD[26–30] found significantly greater mean improvements in functional impairment for levomilnacipran ER versus placebo on the SDS average total score and on all 3 SDS subscales, representing domains of work/school, social life, and family life/home responsibilities.

Clinical Points

- This post hoc analysis, which utilizes a novel method to assess individual patient changes in functional impairment as categorical shifts, may help clinicians to establish expectations for improving functional impairment during MDD treatment.
- Improving functional impairment and reducing disability are critical to optimizing outcomes and achieving long-term wellness in MDD patients; therefore, antidepressants that are effective in improving functional impairment are valuable treatment options.
- A significantly higher proportion of levomilnacipran ER–treated than placebo-treated patients improved from more severe functional impairment categories at baseline to less severe impairment categories across the SDS functional domains of work/school, social life, and family life/home responsibilities.

In this post hoc analysis of the same 5 studies,[26–30] the treatment effect of levomilnacipran ER versus placebo on functional domains was evaluated by assessing the number of individual patients that improved from more severe to less severe impairment categories on each SDS subscale. Rather than evaluating group mean score changes, functional improvement was evaluated by assessing the percentage of patients who shifted from a baseline category of more severe functional impairment to a category of less severe impairment after treatment. To our knowledge, this is the first analysis to evaluate functional improvement in patients with MDD by studying categorical shifts among individual patients across SDS functional domains. This qualitative characterization of individual patient functional impairment outcomes may be more meaningful to practicing clinicians in the management of MDD.

METHOD

Clinical Study Design

Data were pooled from 5 randomized, double-blind, placebo-controlled trials conducted between December 2006 and March 2012 of levomilnacipran ER in MDD patients 18–80 years of age (4 US studies, ClinicalTrials.gov: NCT00969709,[26] NCT01377194,[27] NCT00969150,[28] NCT01034462[29]; and 1 non-US study, EudraCT: 2006–002404-34[30]). The US studies were 8 weeks' duration and had a fixed-dose (40, 80, and 120 mg/d[26] or 40 and 80 mg/d[27]) or flexible-dose (40–120 mg/d[28,29]) design. Patients in the US studies met *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[31] criteria for MDD and had a MADRS score ≥ 30[26,28,29] or a MADRS score ≥ 26 and a Clinical Global Impressions–Severity (CGI-S) score ≥ 4.[27] The non-US study[30] was 10 weeks' duration with a flexible-dose (75–100 mg/d) design and included patients who met *DSM-IV-TR* criteria for MDD and had a 17-item Hamilton Depression Rating Scale (HDRS-17)[32] score > 22, an SDS total score ≥ 10, and at least 1 SDS subscale score ≥ 6.

In all 5 of the pooled studies, patients were excluded if they had *DSM-IV-TR* Axis I disorders other than MDD (comorbid generalized anxiety disorder, social anxiety disorder, and/or specific phobias were acceptable), lifetime history of nonresponse to ≥ 2 antidepressants after adequate treatment trials, or current risk of suicide. Studies were in full compliance with guidelines for Good Clinical Practice and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent, and study protocols were approved by each study center's institutional review board. The primary efficacy measure was change from baseline to endpoint in MADRS total score; SDS total score change from baseline to endpoint was a prospectively defined secondary outcome (endpoint was either 8 weeks or 10 weeks, depending on study duration). The SDS scores were assessed at weeks 0, 4, 6, and 8 in the 8-week studies[25–27,29] and at weeks 0, 2, 4, 6, 8, and 10 in the 10-week study.[30]

Post Hoc Analyses: Categorical Improvement in Functional Impairment

The SDS assesses functional impairment in 3 subscales: work/school, social life, and family life/home responsibilities.[21] The SDS subscale impairment categories are numerically based using a discan metric, with descriptors representing a range of severity scores from 0 to 10: 0 = no impairment, 1–3 = mild impairment, 4–6 = moderate impairment, 7–9 = marked impairment, and 10 = extreme impairment.[21] Categorical improvement in functional impairment was analyzed by comparing the percentage of patients treated with levomilnacipran ER versus placebo that shifted from a more severe baseline SDS subscale category to a less severe category at the end of treatment.

In this analysis, proportions of patients that shifted from moderate-extreme baseline impairment (score ≥ 4) to mild-no impairment (score ≤ 3) at end of treatment (week 8 or 10 depending on study duration) were assessed for each SDS subscale. Proportions of patients shifting from marked-extreme (score ≥ 7) at baseline to moderate-no impairment (score ≤ 6) or mild-no impairment (score ≤ 3) at end of treatment and shifts in which patients worsened from moderate-no baseline impairment to marked-extreme impairment at end of treatment were also evaluated. As an indicator of overall functional impairment, an SDS "average total score" was calculated as the mean of any available SDS subscale score(s) at baseline and any available subscale score(s) at end of treatment. These category shifts were retrospectively determined as part of this post hoc analysis.

Statistical Analyses

The intent-to-treat (ITT) population comprised all patients who received ≥ 1 dose of study drug and had ≥ 1 postbaseline MADRS total score assessment (Table 1). The completer population, comprising ITT patients who had at least 1 postbaseline assessment in the given SDS subscale and completed either 8[26–29] or 10[30] weeks of double-blind treatment, was used for descriptive analyses of SDS subscales

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Table 1. Baseline Characteristics in Pooled Patient Population (ITT)

Characteristic	Placebo		Levomilnacipran ER	
	N[a]	Value	N[a]	Value
Women, n (%)	1,032	660 (64.0)	1,566	997 (63.7)
White, n (%)	1,031	846 (82.1)	1,566	1,228 (78.4)
Age, mean (SD), y	1,032	43.5 (12.7)	1,566	42.7 (12.9)
Duration of MDD, mean SD, y	1,030	11.4 (11.0)	1,565	11.3 (10.8)
Patients with recurrent MDD, n (%)	949	772 (81.3)	1,503	1,186 (78.9)
Baseline MADRS total score, mean (SD)	1,032	33.3 (4.6)	1,566	33.8 (4.5)
Baseline SDS total score, mean (SD)[b]	887	20.1 (5.1)	1,308	20.4 (5.3)

[a]N = number of ITT patients with available data.
[b]Only ITT patients with valid responses at baseline on all 3 SDS subscales, and at least 1 postbaseline SDS assessment, were included in SDS analyses. In this table, SDS total score is the sum of all 3 subscale scores.
Abbreviations: ER = extended release, ITT = intent to treat, MADRS = clinician-rated Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder.

of the baseline population, as well as for the categorical shift analyses. As per SDS instructions for administration, patients who did not work and were not in school for reasons unrelated to the disorder did not receive baseline scores on the work/school subscale; these patients were not included in the work/school subscale analyses.[21]

Descriptive statistics were used to analyze baseline demographics and baseline functional impairment severity category for each SDS item. For the SDS categorical shift analyses, the comparison between levomilnacipran ER and placebo and the corresponding odds ratio (OR) was estimated using a logistic model, with treatment as factor and baseline subscale as covariate.

RESULTS

Patient Population

Mean MADRS and SDS total scores indicated that patients in the pooled population were functionally impaired[21] and had moderate to severe symptoms of depression[20,33] at baseline (Table 1). Patients were distributed at baseline across all categories of functional impairment severity for all 3 SDS subscores (Figure 1A–C and Appendix I) and for SDS average total score (Figure 1D), with the majority of patients (> 80%) categorized as having moderate or marked impairment at baseline.

SDS Categorical Shifts

A significantly greater percentage of levomilnacipran ER–treated (55%) than placebo-treated (40%) patients with moderate-extreme functional impairment (SDS score ≥ 4) at baseline on the SDS work/school subscale improved to mild-no impairment (≤ 3) by end of treatment (OR = 2.0, $P < .0001$ (Figure 2A and Appendix I). This was also true for improvement from marked-extreme impairment (≥ 7) at baseline to moderate-no impairment (≤ 6) at end of treatment (73% vs 64%, respectively, OR = 1.8, $P < .0001$) and improvement from marked-extreme (≥ 7) to mild-no work impairment (≤ 3) (47% vs 33%, respectively, OR = 1.9, $P < .0001$). A significantly greater percentage of placebo patients relative to levomilnacipran ER patients worsened from moderate-no impairment at baseline to marked-extreme impairment at end of treatment (13% vs 6%, respectively, OR = 0.4, $P < .01$).

On the social life subscale, a significantly greater percentage of levomilnacipran ER (48%) than placebo (37%) patients improved from moderate-extreme baseline impairment to mild-no impairment at end of treatment (OR = 1.7, $P < .0001$, Figure 2B and Appendix I). Similarly, a greater proportion of levomilnacipran ER patients relative to placebo shifted from marked-extreme baseline social impairment to moderate-no impairment (68% vs 59%, respectively, OR = 1.6, $P < .0001$) or mild-no impairment (42% vs 29%, OR = 1.9, $P < .0001$) at end of treatment. A numerically greater percentage of placebo versus levomilnacipran ER patients worsened from moderate-no impairment at baseline to marked-extreme impairment; the difference between treatment groups did not reach statistical significance (12% vs 8%, OR = 0.6, $P = .0783$).

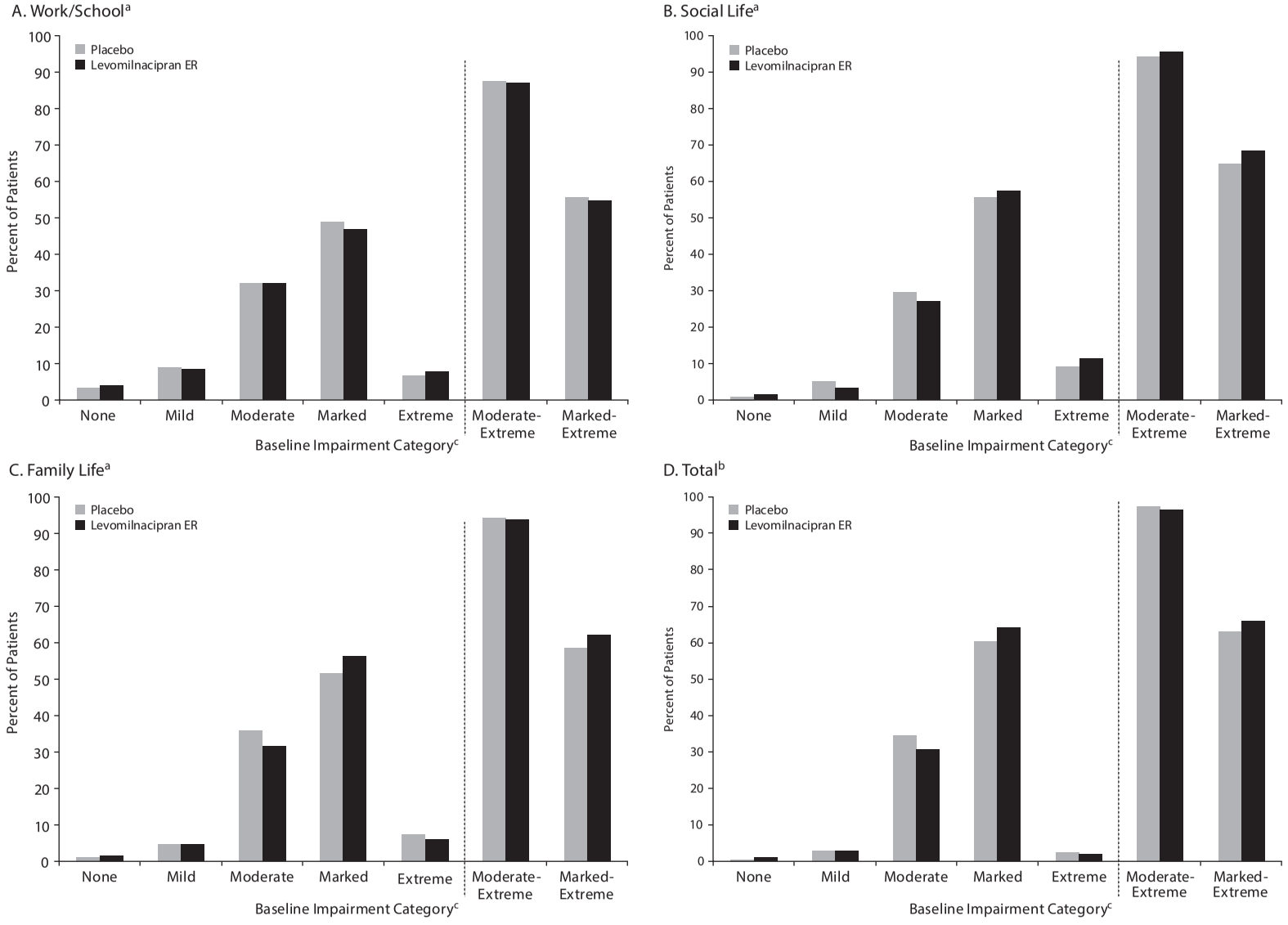
Levomilnacipran ER treatment was associated with a significantly higher percentage of patients relative to placebo that shifted from moderate-extreme baseline impairment on the family life/home responsibilities subscale to mild-no impairment at end of treatment (51% vs 39%, respectively, OR = 1.7, $P < .0001$, Figure 2C and Appendix I). This was also true for improvement from marked-extreme family/home impairment at baseline to moderate-no impairment (73% vs 65%, respectively, OR = 1.5, $P < .01$) and from the marked-extreme family/home impairment category at baseline to mild-no impairment at the end of treatment (45% vs 34%, respectively, OR = 1.6, $P < .001$). Only a small percentage of placebo or levomilnacipran ER patients worsened from moderate-no to marked-extreme impairment; the difference between treatment groups was not significant (12% vs 9%, respectively, OR = 0.7, $P = .1271$).

Category shift analyses for SDS average total score were similar to those obtained in the subscale analyses (Figure 2D). Significantly higher proportions of levomilnacipran ER than placebo patients shifted from more severe baseline impairment categories on SDS average total score to less severe impairment categories at the end of treatment (moderate-extreme to mild-no, 48% vs 37%, OR = 1.6, $P < .0001$; marked-extreme to moderate-no, 74% vs 63%, OR = 1.7, $P < .0001$; marked-extreme to mild-no, 42% vs 31%, OR = 1.7, $P < .0001$).

DISCUSSION

The 2010 Global Burden of Disease Study ranked unipolar depressive disorders as the second leading cause of years lived with disability worldwide; disability-adjusted life-years (a combined measure of years lived with disability and years of life lost) for depressive disorders increased by 38% from 1990 to 2010 and are predicted to continue increasing steadily.[34–36] Depression-related disability is associated with reduced quality of life, considerable economic burden, and increased health care costs.[37,38] Functional impairment and depression

Figure 1. Patient Distribution by Baseline Functional Impairment Severity on the SDS Scores (completer population)



[a]For SDS subscales, analyses only include patients who had a valid assessment at baseline with at least 1 corresponding postbaseline assessment and who completed treatment (work/school: placebo, n = 744 and levomilnacipran ER, n = 1,055; social life and family life/home responsibilities: placebo, n = 832 and levomilnacipran ER, n = 1,178).
[b]For SDS average total scores, analysis is based on the mean of any available SDS subscale score(s) in patients who completed treatment (placebo: n = 806, levomilnacipran ER: n = 1,129).
[c]SDS scores for impairment categories: none = 0, mild = 1–3, moderate = 4–6, marked = 7–9, extreme = 10, moderate-extreme = 4–10, marked-extreme = 7–10.
Abbreviation: ER = extended release.

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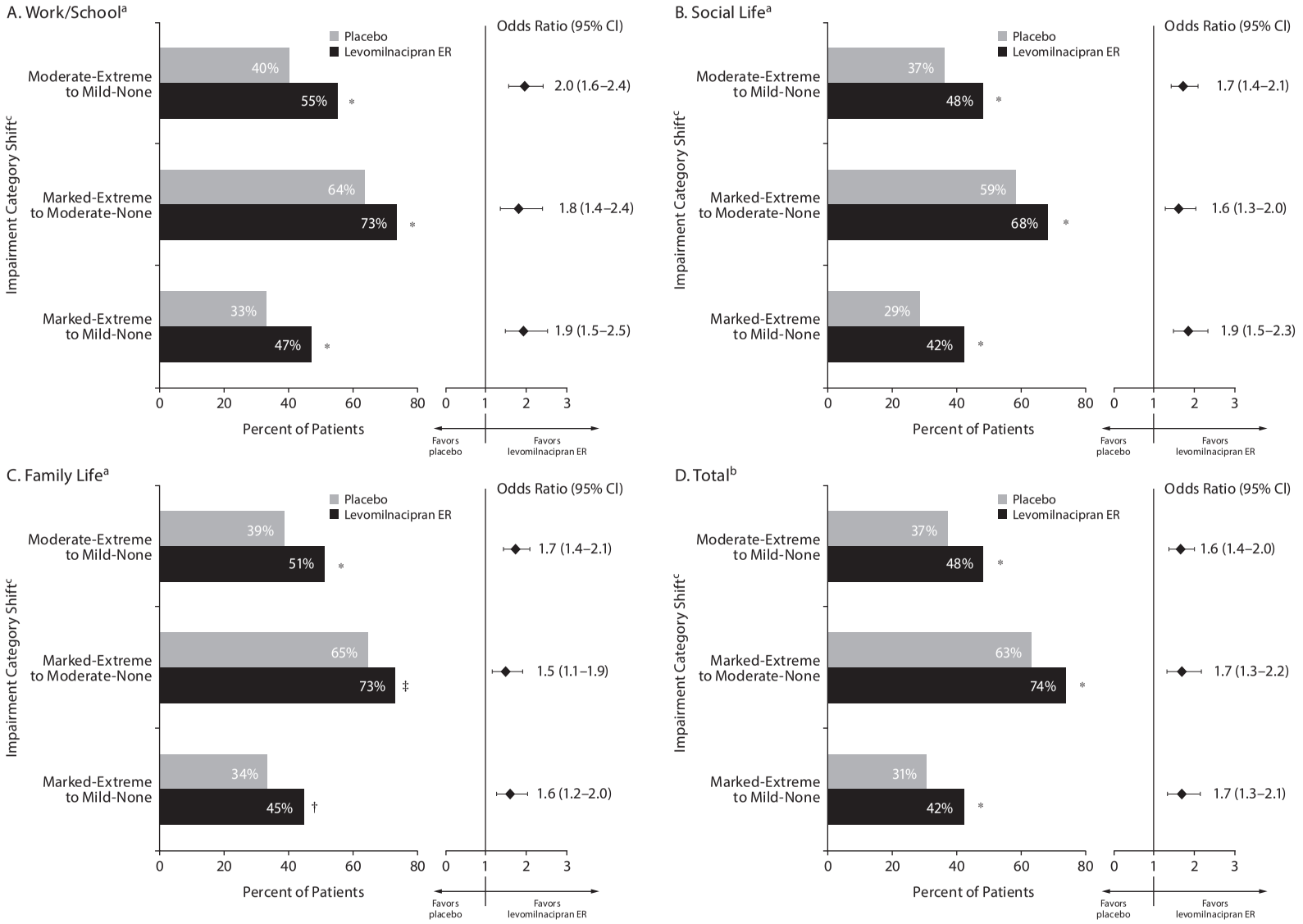
Figure 2. Categorical Shifts in Functional Impairment Severity (completer population)



[a]For SDS subscales, analyses only include patients who had a valid assessment at baseline with at least 1 corresponding postbaseline assessment and who completed treatment.
[b]For SDS average total scores, analysis is based on the mean of any available SDS subscale score(s) in patients who completed treatment.
[c]SDS scores for impairment categories: moderate-extreme = 4–10, marked-extreme = 7–10, moderate-none = 6–0, mild-none = 3–0.
*$P < .0001$. †$P < .001$. ‡$P < .01$.
Abbreviation: ER = extended release.

may be bidirectional, with depressive symptoms decreasing patient functioning and impaired function causing stressors (eg, problems with family/social relationships and/or at work) that intensify depressive symptoms and increase risk of relapse.[14,16] Conversely, improvements in employment and social and family relationships may attenuate external stressors and reduce risk of depression relapse.[16] Improving functional impairment and reducing depression-associated disability are critical for optimizing patient outcomes and achieving long-term wellness; therefore, antidepressants that have been shown to be effective in improving functional impairment are valuable options for the treatment of MDD.

A previous study of the same pooled population used in this analysis showed that functional outcomes were significantly improved overall in patients treated with levomilnacipran ER relative to placebo, regardless of age, sex, and severity of depressive symptoms or functional impairment at baseline.[25] In that study, improvements on the SDS total score, and on SDS work/school, social life, and family life/home responsibilities subscales, were demonstrated by statistically significant differences in mean scores and rates of functional response and remission in the levomilnacipran ER group compared with the placebo group.[25]

Mean change in SDS scores represents the overall outcome of a patient group, but may not fully characterize individual patient functional impairment outcomes. Conversely, SDS response and remission rates evaluate the percent of patients that meet specific clinical outcomes, but do not account for baseline severity of functional impairment or heterogeneous improvement across specific functional domains, which may limit the interpretation and clinical utility of results. This study utilizes a novel method to analyze improvements in functional impairment as categorical shifts from more severe impairment at baseline to less severe impairment at end of treatment. This type of qualitative assessment of individual patient outcomes may help clinicians to evaluate clinically meaningful changes and establish functional impairment improvement expectations during treatment (eg, the likelihood and extent to which a given patient's functional impairment will improve during treatment) and to determine if therapy needs to be modified (eg, switch to a different antidepressant or augment current treatment).

Similar analyses have been performed using pooled MADRS data from clinical studies of vilazodone in MDD to compare categorical improvement in individual symptoms of depression (MADRS single items),[39] supporting the utility of this approach. The SDS is particularly amenable to this approach, as the SDS anchors are intuitively understood (ie, mild, moderate, marked, severe, and extreme impairment). Additionally, the SDS has demonstrated construct and face validity and internal consistency and reliability.[40]

Our post hoc SDS category shift analyses show that a significantly higher proportion of levomilnacipran ER patients than placebo patients improved from more severe categories of functional impairment at baseline to less severe impairment categories at end of study across all 3 SDS domains of work/school, social life, and family life/home responsibilities. Depending on the individual SDS subscale, 48%–55% of levomilnacipran ER–treated patients with moderate-extreme impairment at baseline improved to mild or no impairment, compared with no more than 40% of placebo patients on any subscale. Almost half of levomilnacipran ER patients (42%–47%) versus only about one-third of placebo patients (29%–34%) improved from marked-extreme to mild or no impairment across functional domains. These results suggest that functional improvement was observed across all 3 functional domains measured by the SDS. Further, the high percentage of patients that improved to mild or no functional impairment, including those with high levels of baseline disability, is encouraging given that residual disability is associated with a poor long-term prognosis.[6,12,16–18]

The high percentage of patients with mild-no impairment at end of treatment (SDS score 0–3) is consistent with SDS subscale criteria for response (score ≤ 4)[40]; it is likely that many of these patients also meet subscale criteria for functional remission (≤ 2),[41] although the exact percentage was not calculated for these analyses. The current results are also consistent with findings from a previous post hoc analysis of the same patient population,[25] which showed that patients in the levomilnacipran ER group had significantly higher rates than placebo for response (SDS total score ≤ 12 and all subscale scores ≤ 4, 46.9% vs 36.1%, respectively) and remission (SDS total score ≤ 6 and all subscale scores ≤ 2, 26.7% vs 20.0%, respectively). These findings are important to note, as recent studies have correlated improved functional outcome with greater improvements in depressive symptom severity and higher rates of symptom remission.[18,40–42]

Only a small proportion of patients experienced worsening of functional impairment during this study, with numerically (or statistically significantly in the case of the work/school subscale) more placebo than levomilnacipran ER patients shifting from moderate-no impairment at baseline to marked-extreme impairment at end of treatment. The relatively small difference between the placebo and levomilnacipran ER groups is likely due to the low number of patients in either group that showed decreased functioning (no more than 13% of placebo and 9% of levomilnacipran ER patients worsened from moderate-no to marked-extreme impairment in any SDS subscale).

The greater improvement in functional impairment of levomilnacipran ER patients compared with placebo patients was seen in a relatively short timeframe (8–10 weeks) and accompanied the improvement of depressive symptoms. This finding is important given that previous antidepressant studies have found that improvement in functional impairment tends to lag behind improvement in depressive symptoms.[43] It is not clear if this finding is specific to levomilnacipran ER or to these particular studies. Further studies may be warranted to assess the timing and relationship between categorical improvement in functional impairment and improvements in depressive symptoms with levomilnacipran ER versus other antidepressants.

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Additionally, longer-term studies would be useful to investigate the relationship between functional impairment and depression relapse/recurrence.

Pooling the populations from several similarly designed studies provides increased statistical and analytic power to more precisely assess the effects of levomilnacipran ER on functional impairment. However, limitations of these analyses include their post hoc, retrospective nature and lack of correction for multiple comparisons. The inclusion/exclusion criteria in the primary studies may limit generalizability of these results, and the lack of an active comparator limits comparisons with other antidepressants. Treatment duration may not have been adequate to fully evaluate improvement in functional impairment, so the completer population (rather than ITT) was used for the shift analyses because it was likely to be more representative of patients who had adequate treatment duration. Though the SDS has been validated and is known to correlate with depressive symptom severity,[40] patient-based subjective ratings of disability may not accurately reflect objective functional measures (eg, employment status, work/school days missed, reports from family/friends, etc).

Recent studies have focused on assessing MDD-associated functional impairment as an important outcome of antidepressant treatment,[1,19,40,43–45] but none to date have qualitatively assessed improvement in individual SDS subscales. The current study used a unique impairment severity category shift analysis to show that patients treated with levomilnacipran ER experience improvement across the 3 broad functional domains of the SDS (work/school, social life, family life/home responsibilities). This post hoc pooled analysis supports previous results demonstrating that levomilnacipran ER treatment is associated with reduction in symptoms of MDD and depression-associated functional impairment.

Drug names: desvenlafaxine (Pristiq), duloxetine (Cymbalta), levomilnacipran (Fetzima), venlafaxine (Effexor and others).

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

THE PRIMARY CARE COMPANION
FOR CNS DISORDERS

Supplementary Material

Article Title: Levomilnacipran Extended-Release Treatment in Patients With Major Depressive Disorder: Improvements in Functional Impairment Categories

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List of Supplementary Material for the article

1. **Supplemental Appendix 1** Patient Distribution by SDS Subscale Severity Category at Baseline and End of Treatment (Completer Population[a])

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix I. Patient Distribution by SDS Subscale Severity Category at Baseline and End of Treatment (Completer Population[a])

		Severity Category at End of Treatment, n									
		None		Mild		Moderate		Marked		Extreme	
	Baseline Severity Category (n)	PBO	LVM	PBO	LVM	PBO	LVM	PBO	LVM	PBO	LVM
Work/School	None (PBO=25, LVM=47)	18	26	2	14	3	5	2	1	0	1
	Mild (PBO=66, LVM=97)	20	33	27	44	11	16	8	4	0	0
	Moderate (PBO=243, LVM=348)	51	88	75	148	84	88	30	23	3	1
	Marked (PBO=363, LVM=492)	41	90	86	153	116	133	111	102	9	14
	Extreme (PBO=47, LVM=71)	6	8	4	15	8	14	12	20	17	14
Social Life	None (PBO=6, LVM=16)	4	3	2	7	0	4	0	2	0	0
	Mild (PBO=42, LVM=38)	11	15	16	14	12	8	3	1	0	0
	Moderate (PBO=246, LVM=318)	52	61	79	141	84	91	30	22	1	3
	Marked (PBO=462, LVM=674)	55	118	79	185	144	194	168	161	16	16
	Extreme (PBO=76, LVM=133)	10	22	11	17	17	16	25	59	13	19
Family Life/ Home Responsibilities	None (PBO=8, LVM=17)	3	5	5	6	0	4	0	1	0	1
	Mild (PBO=38, LVM=55)	17	19	9	27	9	6	2	3	1	0
	Moderate (PBO=297, LVM=373)	45	86	96	153	118	101	37	32	1	1
	Marked (PBO=429, LVM=665)	49	99	100	205	140	195	132	152	8	14
	Extreme (PBO=60, LVM=69)	7	12	8	11	12	14	24	25	9	7

[a]Only patients with valid baseline scores and at least one corresponding post-baseline assessment in the given SDS Subscale are included.

LVM, levomilnacipran extended-release; PBO, placebo