

# Effects of levomilnacipran ER on fatigue symptoms associated with major depressive disorder

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The aim of this study was to evaluate the effects of levomilnacipran extended-release (ER) on depression-related fatigue in adults with major depressive disorder. Post-hoc analyses of five phase III trials were carried out, with evaluation of fatigue symptoms based on score changes in four items: Montgomery-Åsberg Depression Rating Scale (MADRS) item 7 (lassitude), and 17-item Hamilton Depression Rating Scale (HAMD<sub>17</sub>) items 7 (work/activities), 8 (retardation), and 13 (somatic symptoms). Symptom remission was analyzed on the basis of score shifts from baseline to end of treatment: MADRS item 7 and HAMD<sub>17</sub> item 7 (from  $\geq 2$  to  $\leq 1$ ); HAMD<sub>17</sub> items 8 and 13 (from  $\geq 1$  to 0). The mean change in MADRS total score was analyzed in patients with low and high fatigue (MADRS item 7 baseline score  $< 4$  and  $\geq 4$ , respectively). Patients receiving levomilnacipran ER had significantly greater mean improvements and symptom remission (no/minimal residual fatigue) on all fatigue-related items: lassitude (35 vs. 28%), work/activities (43 vs. 35%), retardation (46 vs. 39%), somatic symptoms (26 vs. 18%; all  $P$ s  $< 0.01$  versus placebo). The mean change in MADRS total score was

significantly greater with levomilnacipran ER versus placebo in both low (least squares mean difference =  $-2.8$ ,  $P = 0.0018$ ) and high (least squares mean difference =  $-3.1$ ,  $P < 0.0001$ ) fatigue subgroups. Levomilnacipran ER treatment was effective in reducing depression-related fatigue in adult patients with major depressive disorder and was associated with remission of fatigue symptoms. *Int Clin Psychopharmacol* 31:100–109 Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.

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## Introduction

Major depressive disorder (MDD) is a common yet heterogeneous disorder, and identifying variables that may predict response to specific treatments is an important public health concern (Leuchter *et al.*, 2009). Medications are often selected on the basis of predominant symptoms, although this is not always an evidence-based practice. Fatigue is one such symptom, and daily fatigue or loss of energy is recognized as one of the diagnostic criteria for MDD (American Psychiatric Association, 2013). In addition to the physical manifestations of fatigue (tiredness, low energy, weakness, heaviness, slowness), there are associated cognitive (decreased concentration or attention, slowed thinking) and emotional (decreased motivation, loss of interest, feelings of boredom, aversion to effort) symptoms that require focused treatment (Arnold, 2008).

Fatigue can negatively affect daily functioning. For example, in a clinic-based study of 164 consecutive

patients with MDD among whom greater than 90% had fatigue-related symptoms (Lam *et al.*, 2012) the majority reported that lack of motivation (59%), low energy (58%), and feeling physically slowed down (52%) substantially interfered with their ability to work. Similar findings were reported in a post-hoc analysis of data from the much larger Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) clinical trial, which found that greater than 90% of 2868 patients had substantial fatigue at baseline (Ferguson *et al.*, 2014). The STAR\*D study also showed that moderate-to-severe functional impairment was more common in patients with severe fatigue (59.5%) than in patients with moderate or mild fatigue (37.4 and 28.8%, respectively) and that higher levels of baseline fatigue significantly reduced the likelihood of remission (Ferguson *et al.*, 2014). These findings support the need for MDD treatments that address fatigue in addition to other symptoms of depression.

Another important finding of the STAR\*D trial was that 60.8% of patients had residual fatigue after receiving up to 14 weeks of treatment with a selective serotonin reuptake inhibitor (SSRI; Ferguson *et al.*, 2014). Compared with patients with remitted fatigue symptoms,

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patients with residual fatigue had significantly worse outcomes in mental and physical functioning, as well as a reduced likelihood of remission of MDD. These results were consistent with findings from an earlier study that found residual fatigue in 48.8% of patients who had responded to antidepressant treatment and were in full or partial remission; notably, 8.6% had residual fatigue that was considered moderate to severe (Fava *et al.*, 2006). Other studies have shown that fatigue may be difficult to treat, with slow response to medication or psychotherapy and low rates of clinically significant changes (Demyttenaere *et al.*, 2005). Few studies have been published that evaluate residual fatigue in patients with MDD, and continued efforts are needed to better address this important facet of depression (Fava *et al.*, 2013).

Current research indicates that the neurobiology of fatigue is complex (Harrington, 2012), which may explain why SSRIs alone may not adequately resolve fatigue in patients with MDD (Arnold, 2008; Fava *et al.*, 2013). Neuroimaging studies in patients with disease-related fatigue have shown atrophy or other damage in the striatum and cortex (Harrington, 2012). Ascending pathways that control arousal and motivation are also believed to play a key role in the clinical manifestation of fatigue. These pathways include projections from serotonergic neurons in the raphé nuclei, noradrenergic neurons in the locus coeruleus, dopaminergic neurons in the periaqueductal gray, histaminergic neurons in the tuberomammillary nucleus, and cholinergic neurons in the pedunculo-pontine and tuberomammillary nuclei. Inflammatory factors may contribute to the neurobiology of disease, including the negative effects of cytokines and glial activation on the synthesis and bioavailability of serotonin, norepinephrine, and dopamine (Dantzer *et al.*, 2014).

From a therapeutic standpoint, several studies have evaluated the effects of antidepressants on fatigue with varying results, including a few that examined the augmentation of SSRIs with bupropion or atomoxetine, which may increase noradrenergic and dopaminergic activity, or with modafinil, which may increase hypothalamic histaminergic activity (Arnold, 2008; Fava *et al.*, 2013). However, this area of clinical research is still lacking, and more studies are needed to identify medications with multiple mechanisms of action that may benefit patients with depression-related fatigue. To that end, a post-hoc analysis was carried out using pooled data from five clinical trials with levomilnacipran extended release (ER), a serotonin and norepinephrine reuptake inhibitor (SNRI) that is approved for the treatment of MDD in adults (Forest Laboratories, 2014). Other post-hoc analyses of these trials have shown that levomilnacipran ER significantly improves symptoms of depression (Montgomery *et al.*, 2014) and associated functional impairment (Sambunaris *et al.*, 2014b; Cutler *et al.*, 2015). As an SNRI, this medication may also target some of the MDD symptoms associated with reduced noradrenergic

activity, such as reduced motivation and energy, loss of interest, and decreased pleasure or enjoyment (Nutt *et al.*, 2007). Therefore, the goals of this post-hoc analysis were to identify and characterize patients with MDD who had high levels of fatigue, to evaluate the effects of levomilnacipran ER on depression-related fatigue symptoms, and to assess the effects of treatment in patients who had high and low levels of fatigue at baseline.

## Methods

### Study designs

Post-hoc analyses were carried out using data from 2598 patients who participated in five randomized, double-blind, placebo-controlled studies of 40–120 mg/day levomilnacipran ER for the treatment of MDD (Asnis *et al.*, 2013; Montgomery *et al.*, 2013; Bakish *et al.*, 2014; Gommoll *et al.*, 2014; Sambunaris *et al.*, 2014a). These included four US-based studies with 8 weeks of double-blind treatment, two of which evaluated fixed doses of levomilnacipran ER (Asnis *et al.*, 2013; Bakish *et al.*, 2014) and two of which used flexible dosing (Gommoll *et al.*, 2014; Sambunaris *et al.*, 2014a), and one non-US study with 10 weeks of double-blind treatment and flexible dosing (Montgomery *et al.*, 2013).

Detailed methodology for all five studies has been published previously. In brief, the studies included female and male patients, between 18 and 80 years of age, who met MDD diagnostic criteria and had a current major depressive episode. Other key inclusion and exclusion criteria are listed in Table 1. The primary endpoint in all studies was defined as the mean change from baseline in the Montgomery–Åsberg Depression Rating Scale (MADRS) total score. All levomilnacipran ER dose groups were pooled for the current analysis.

### Efficacy measures

The effect of levomilnacipran ER on fatigue symptoms was analyzed on the basis of measures that have been used to evaluate fatigue in other MDD studies (Demyttenaere *et al.*, 2005): MADRS item 7 (lassitude), 17-Item Hamilton Depression Rating Scale (HAMD<sub>17</sub>) item 7 (work/activities), HAMD<sub>17</sub> item 8 (retardation), and HAMD<sub>17</sub> item 13 (general somatic symptoms; Table 2). Least squares mean (LSM) changes from baseline to the end of double-blind treatment in fatigue-related items were analyzed for the overall pooled population and in patients categorized by sex (men and women), age (<60 and ≥60 years), and BMI (nonobese, <30 kg/m<sup>2</sup> and obese, ≥30 kg/m<sup>2</sup>). Analyses were also carried out to assess differences between premenopausal and postmenopausal women, which were approximated by categorizing women by age (<50 and ≥50 years) using the National Institute on Aging average age of menopause (51 years) as a guideline (National Institute on Aging, 2011), as menopause status was not obtained in the studies specifically. In addition, the percentage of

**Table 1 Levomilnacipran extended release clinical trials**

	Design	Treatment groups <sup>b</sup>	Eligibility criteria <sup>c</sup>
US study 1 <sup>a</sup> NCT00969709 (Asnis <i>et al.</i> , 2013)	1 week: single-blind, placebo run-in period 8 weeks: randomized, double-blind, fixed-dose treatment 2 weeks: double-blind taper	Placebo, <i>n</i> = 179 Levomilnacipran ER 40 mg, <i>n</i> = 181 80 mg, <i>n</i> = 181 120 mg, <i>n</i> = 183	Men and women, ages 18–65 years MDD diagnosis (DSM-IV-TR criteria) Current depressive episode ≥ 8 weeks MADRS total score ≥ 30 MADRS-SR total score ≥ 26 BMI 18–40 kg/m <sup>2</sup>
US study 2 <sup>a</sup> NCT01377194 (Bakish <i>et al.</i> , 2014)	1 week: single-blind, placebo run-in period 8 weeks: randomized, double-blind, fixed-dose treatment 1 week: double-blind taper	Placebo, <i>n</i> = 189 Levomilnacipran ER 40 mg, <i>n</i> = 190 80 mg, <i>n</i> = 189	Men and women, ages 18–75 years MDD diagnosis (DSM-IV-TR criteria) Recurrent episodes (2–5 in past 5 years) Current depressive episode ≥ 6 weeks MADRS total score ≥ 26 CGI-S score ≥ 4 BMI 18–40 kg/m <sup>2</sup>
US study 3 <sup>a</sup> NCT01034462 (Sambunaris <i>et al.</i> , 2014a)	1 week: single-blind, placebo run-in period 8 weeks: randomized, double-blind, flexible-dose treatment 2 weeks: double-blind taper	Placebo, <i>n</i> = 220 Levomilnacipran ER 40–120 mg, <i>n</i> = 222	Men and women, ages 18–80 years MDD diagnosis (DSM-IV-TR criteria) Current depressive episode ≥ 4 weeks MADRS total score ≥ 30 MADRS-SR total score ≥ 26 BMI 18–40 kg/m <sup>2</sup>
US study 4 NCT00969150 (Gommoll <i>et al.</i> , 2014)	1 week: single-blind, placebo run-in period 8 weeks: randomized, double-blind, flexible-dose treatment 2 weeks: double-blind taper	Placebo, <i>n</i> = 184 Levomilnacipran ER 40–120 mg, <i>n</i> = 178	Men and women, ages 18–80 years MDD diagnosis (DSM-IV-TR criteria) Current depressive episode ≥ 4 weeks MADRS total score ≥ 30 BMI 18–40 kg/m <sup>2</sup>
Non-US study EudraCT: 2006-002404-34 (Montgomery <i>et al.</i> , 2013)	10 weeks: randomized, double-blind, flexible-dose treatment 1 week: double-blind taper	Placebo, <i>n</i> = 281 Levomilnacipran ER 75–100 mg, <i>n</i> = 282	Men and women, 18–70 years MDD diagnosis (DSM-IV-TR criteria) Current depressive episode ≥ 4 weeks HAMD <sub>17</sub> total score > 22 SDS total score ≥ 10 Any SDS subscale score ≥ 6

CGI-S, Clinician Global Impression of Severity; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision; ER, extended release; HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; SDS, Sheehan Disability Scale; SR, self-reported.

<sup>a</sup>Pivotal study used for approval in the USA.

<sup>b</sup>*n*-Values represent the number of randomized patients.

<sup>c</sup>Eligibility assessed at screening. Key exclusion criteria for all of studies included: primary Axis I disorder other than MDD; other significant psychiatric disorders or medical conditions; suicide risk based on investigator judgment or structured interview; nonresponse to ≥ 2 prior antidepressants after adequate treatment.

**Table 2 Items reflecting depression-related fatigue symptoms**

Items <sup>a</sup>	Description	Scoring
MADRS item 7	Lassitude (difficulty or slowness in initiating and/or performing daily activities)	0 <sup>b</sup> : Hardly any difficulty in getting started; no sluggishness <sup>b</sup> 1 <sup>b</sup> : – 2: Difficulties in starting activities 3: – 4: Difficulties in starting simple routine activities which are then carried out with effort 5: – 6: Complete lassitude; unable to do anything without help
HAMD <sub>17</sub> item 7	Work and activities	0 <sup>b</sup> : No difficulty 1 <sup>b</sup> : Thoughts and feelings of incapacity; fatigue or weakness related to activities, work, or hobbies 2: Loss of interest in activities, hobbies, or work; reported directly or indirectly (listlessness, indecision, vacillation – patient feels that he/she must push self to engage in work or other activities) 3: Decrease in actual time spent in daily activities or decrease in productivity 4: Has stopped working because of illness
HAMD <sub>17</sub> item 8	Retardation (slowness of thought and speech; impaired ability to concentrate; decreased motor activity)	0 <sup>b</sup> : Normal speech and thought 1: Slight retardation at interview 2: Obvious retardation at interview 3: Difficult interview 4: Complete stupor
HAMD <sub>17</sub> item 13	General somatic symptoms	0 <sup>b</sup> : None 1: Heaviness in limbs, back, or head; backaches, headache, muscle aches; loss of energy or fatigability 2: Any clear-cut somatic symptom

HAMD<sub>17</sub>, 17-item Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale.

<sup>a</sup>Adapted with permission from Montgomery and Åsberg, 1979 and Hamilton, 1960.

<sup>b</sup>Scores used to define no/minimal residual fatigue symptoms after treatment.

patients who had fatigue symptoms before treatment and no/minimal residual symptoms after double-blind treatment were analyzed on the basis of the following score shifts: MADRS item 7 and HAMD<sub>17</sub> item 7 (from  $\geq 2$  to  $\leq 1$ ); HAMD<sub>17</sub> items 8 and 13 (from  $\geq 1$  to 0) after treatment (Table 2).

To identify and characterize patients with high levels of fatigue before treatment, patients were categorized into two subgroups on the basis of their MADRS item 7 (lassitude) baseline score: patients with high fatigue levels (score  $\geq 4$ ) and those with low fatigue levels (score  $< 4$ ). In each fatigue subgroup, LSM changes from baseline to the end of Week 8 (or Week 10 for the non-US study) were analyzed on the basis of measures used in the individual levomilnacipran ER studies to evaluate depression symptoms (MADRS and HAMD<sub>17</sub> total scores), functional impairment [Sheehan Disability Scale (SDS) total score], and overall disease severity [Clinical Global Impression of Severity (CGI-S) score]. The percentages of patients with a treatment response, an early response, or a sustained response were also analyzed in the low-fatigue and high-fatigue subgroups. These outcomes, all based on MADRS total scores, were defined as follows: response, 50% or higher improvement from baseline to the end of double-blind treatment; early response, 20% or higher improvement from baseline to the end of Week 2; early and sustained response, 20% or higher improvement at the end of week 1 or 2 and 50% or higher improvement at the final two study visits.

### Statistical analyses

The overall population in this report included all randomized patients who received one or more doses of the study drug and had an available baseline assessments, along with one or more postbaseline assessments, depending on the type of analysis being conducted (MADRS total or item 7; HAMD<sub>17</sub> total or items 7, 8, 13; SDS total; CGI-S). The LSM change from baseline to the end of treatment in fatigue-related items was analyzed using an analysis of covariance model, with study, pooled study sites, and treatment as factors, and baseline item scores as covariates; missing values were handled using the last observation carried forward approach. Cohen's effect sizes were estimated on the basis of the LSM difference between levomilnacipran ER and placebo.

In the fatigue subgroups, LSM changes from baseline to the end of Week 8/10 in MADRS total, HAMD<sub>17</sub> total, SDS total, and CGI-S scores were analyzed using a mixed-model for repeated measures, with pooled site, visit, treatment, baseline fatigue (MADRS item 7, score  $< 4$  or  $\geq 4$ ), fatigue-by-treatment, treatment-by-visit, fatigue-by-visit, and fatigue-by-treatment-by-visit as factors, and baseline and baseline-by-visit as covariates. A regression analysis was used to test for interactions between baseline fatigue levels (high or low) and MADRS, HAMD, SDS, and CGI-S score changes.

For assessment of score shifts in fatigue-related items, patients were required to have an available baseline score and one or more postbaseline scores for the MADRS or HAMD<sub>17</sub> items being analyzed. For the responder analyses, the patients were required to have a baseline MADRS total score and one or more postbaseline scores (for overall response), a score at the end of Week 2 (for early response), and scores at the end of Week 1 or 2 and at two or more consecutive visits after Week 2 (for early and sustained responses). Odds ratios and 95% confidence intervals were analyzed using a logistic regression model with treatment group and baseline score as explanatory variables.

## Results

### Patients

As reported elsewhere for this pooled study population, demographics and baseline characteristics were similar between treatment groups (Montgomery *et al.*, 2014). The majority of patients [73.8% (1917/2598)] had high levels of fatigue, as defined by a baseline score of 4 or higher on MADRS item 7 (Table 3). As in the overall population, more than 60% of patients in each subgroup were women, and  $\sim 80\%$  were white. The mean age in each fatigue subgroup was 43.0 years, with  $\sim 90\%$  of patients aged less than 60 years. As estimated on the basis of age ( $< 50$  years), 65% of the women in each subgroup were likely to be premenopausal. The mean baseline scores for MADRS total scores were higher in the subgroup with high baseline fatigue compared with the subgroup with no/low fatigue, which was expected, as MADRS item 7 had been used to classify the subgroups. Other mean baseline scores (HAMD<sub>17</sub> total and items, SDS total, and CGI-S) were comparable between the fatigue subgroups. No statistical testing between the fatigue subgroups was conducted.

### Improvements in fatigue symptoms

Greater improvements with levomilnacipran ER versus placebo were found in fatigue-related symptoms, as indicated by a significant LSM difference between the treatment groups for each MADRS and HAMD<sub>17</sub> item included in this analysis (Table 4). Drug-placebo differences were significant in the overall study population, as well as among women, men, patients less than 60 years, and patients 60 years or older (except for general somatic symptoms).

For some fatigue-related items, treatment effect sizes were larger in men than in women (work/activities, general somatic symptoms) and in older compared with younger patients (retardation). In women, treatment effect sizes for retardation and general somatic symptoms were notably larger in the premenopausal group (women  $< 50$  years) compared with the group aged 50 years or older, which approximated the postmenopausal group. No statistically significant differences between levomilnacipran ER and

**Table 3 Demographics and baseline characteristics**

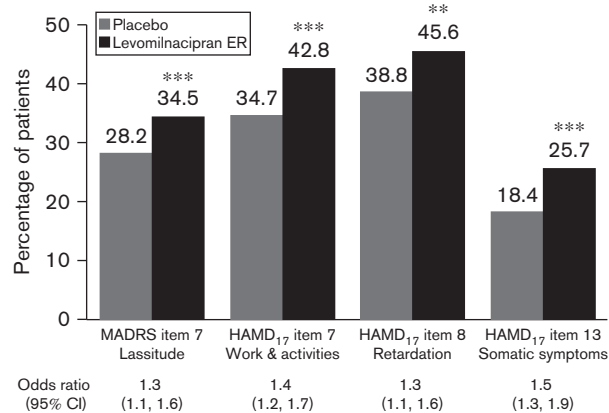
	Overall population (N = 2598)	With low baseline fatigue (n = 681) <sup>a</sup>	With high baseline fatigue (n = 1917) <sup>a</sup>
Age (years)			
Mean (SD)	43.0 (12.8)	43.0 (12.8)	43.0 (12.8)
< 60 years [n (%)]	2332 (89.8)	608 (89.3)	1724 (89.9)
≥ 60 years [n (%)]	266 (10.2)	73 (10.7)	193 (10.1)
Sex [n (%)]			
Men	941 (36.2)	268 (39.4)	673 (35.1)
Women	1657 (63.8)	413 (60.6)	1244 (64.9)
Women by age [n (%)]			
< 50 years	1078 (65.1)	270 (65.4)	808 (65.0)
≥ 50 years	579 (34.9)	143 (34.6)	436 (35.0)
Race [n (%)]			
White	2074 (79.9)	541 (79.4)	1533 (80.0)
Black/African-American	364 (14.0)	84 (12.3)	280 (14.6)
Other	159 (6.1)	56 (8.2)	103 (5.4)
BMI (kg/m <sup>2</sup> )			
Mean (SD)	28.2 (5.6)	27.4 (5.2)	28.4 (5.7)
< 30 kg/m <sup>2</sup> [n (%)]	1684 (64.8)	485 (71.2)	1199 (62.6)
≥ 30 kg/m <sup>2</sup> [n (%)]	913 (35.2)	196 (28.8)	717 (37.4)
MDD duration [mean (SD)] (years)	11.3 (10.9)	10.8 (10.7)	11.5 (10.9)
With recurrent episodes, n (%) <sup>b</sup>	1958 (79.9)	500 (81.2)	1458 (79.4)
Number of episodes [mean (SD)] <sup>b</sup>	4.2 (5.2)	3.7 (3.9)	4.3 (5.6)
Baseline scores [mean (SD)]			
MADRS total	33.6 (4.5)	30.8 (3.6)	34.6 (4.4)
MADRS item 7 (lassitude)	3.8 (0.8)	2.7 (0.6)	4.2 (0.4)
HAMD <sub>17</sub> total	24.1 (4.0)	23.2 (3.8)	24.4 (4.1)
HAMD <sub>17</sub> item 7 (work/activities)	2.9 (0.5)	2.7 (0.6)	3.0 (0.4)
HAMD <sub>17</sub> item 8 (retardation)	1.2 (0.8)	1.1 (0.8)	1.3 (0.8)
HAMD <sub>17</sub> item 13 (general somatic symptoms)	1.7 (0.5)	1.6 (0.5)	1.8 (0.5)
SDS total	20.3 (5.2)	18.7 (5.2)	20.8 (5.1)
CGI-S	4.7 (0.6)	4.5 (0.6)	4.8 (0.6)

CGI-S, Clinician Global Impression of Severity; HAMD<sub>17</sub>, 17-Item Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SDS, Sheehan Disability Scale.

<sup>a</sup>Low and high fatigue defined as MADRS item 7 baseline scores of less than 4 and 4 or higher, respectively.

<sup>b</sup>In patients with available data (N = 2452).

**Fig. 1**



\*\*P < 0.01; \*\*\*P < 0.001 versus placebo

Percentage of patients with fatigue symptoms at baseline and no/minimal residual symptoms after double-blind treatment (LOCF). Analyses based on score shifts from baseline to the end of treatment, defined as follows: MADRS item 7 and HAMD<sub>17</sub> item 7 (from ≥ 2 to ≤ 1); HAMD<sub>17</sub> item 8 and item 13 (from ≥ 1 to 0). CI, confidence interval; ER, extended release; HAMD<sub>17</sub>, 17-Item Hamilton Depression Rating Scale; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale.

placebo were detected in obese patients, defined by a BMI of 30 kg/m<sup>2</sup> or higher; moreover, treatment effects in this subgroup were generally smaller than the effects observed in nonobese patients.

For all fatigue-related MADRS and HAMD<sub>17</sub> items, the percentage of patients in the overall study population with remission of fatigue symptoms (no/minimal residual symptoms) at end of treatment was significantly greater with levomilnacipran ER compared with placebo (Fig. 1). Odds ratios for remission ranged from 1.3 (lassitude, retardation) to 1.5 (general somatic symptoms).

**Table 4 Effects of levomilnacipran extended release on fatigue-related symptoms (LOCF)**

	MADRS item 7 (lassitude)		HAMD <sub>17</sub> item 7 (work/activities)		HAMD <sub>17</sub> item 8 (retardation)		HAMD <sub>17</sub> item 13 (somatic symptoms)	
	LSMD (95% CI) <sup>a</sup>	Effect size	LSMD (95% CI) <sup>a</sup>	Effect size	LSMD (95% CI) <sup>a</sup>	Effect size	LSMD (95% CI) <sup>a</sup>	Effect size
Total	-0.3 (-0.5, -0.2) <sup>b</sup>	0.18	-0.3 (-0.3, -0.2) <sup>b</sup>	0.21	-0.1 (-0.2, -0.1) <sup>b</sup>	0.09	-0.1 (-0.2, -0.1) <sup>b</sup>	0.14
Sex								
Female	-0.3 (-0.4, -0.1) <sup>b</sup>	0.21	-0.2 (-0.3, -0.1) <sup>b</sup>	0.20	-0.1 (-0.2, -0.0) <sup>b</sup>	0.18	-0.1 (-0.2, -0.0) <sup>b</sup>	0.19
Male	-0.5 (-0.7, -0.3) <sup>b</sup>	0.24	-0.4 (-0.5, -0.2) <sup>b</sup>	0.30	-0.1 (-0.2, -0.1) <sup>b</sup>	0.16	-0.2 (-0.3, -0.1) <sup>b</sup>	0.24
Age								
< 60 years	-0.3 (-0.5, -0.2) <sup>b</sup>	0.22	-0.3 (-0.3, -0.2) <sup>b</sup>	0.23	-0.1 (-0.2, -0.0) <sup>b</sup>	0.14	-0.1 (-0.2, -0.1) <sup>b</sup>	0.21
≥ 60 years	-0.4 (-0.8, -0.1) <sup>b</sup>	0.22	-0.3 (-0.6, -0.0) <sup>b</sup>	0.27	-0.2 (-0.4, -0.0) <sup>b</sup>	0.22	-0.1 (-0.3, 0.1)	0.20
Women by age								
< 50 years	-0.3 (-0.5, -0.1) <sup>b</sup>	0.20	-0.2 (-0.3, -0.0) <sup>b</sup>	0.20	-0.1 (-0.2, 0.0)	0.12	-0.1 (-0.2, 0.0)	0.16
≥ 50 years	-0.3 (-0.5, -0.0)	0.23	-0.2 (-0.4, -0.0) <sup>b</sup>	0.23	-0.1 (-0.2, 0.0)	0.30	-0.2 (-0.3, -0.0) <sup>b</sup>	0.30
Baseline BMI								
< 30 kg/m <sup>2</sup>	-0.4 (-0.6, -0.3) <sup>b</sup>	0.29	-0.3 (-0.4, -0.2) <sup>b</sup>	0.30	-0.1 (-0.2, -0.1) <sup>b</sup>	0.16	-0.2 (-0.3, -0.1) <sup>b</sup>	0.25
≥ 30 kg/m <sup>2</sup>	-0.2 (-0.4, 0.0)	0.12	-0.1 (-0.3, 0.0)	0.13	-0.1 (-0.2, 0.0)	0.15	-0.0 (-0.2, 0.1)	0.11

CI, confidence interval; ER, extended release; HAMD<sub>17</sub>, 17-Item Hamilton Depression Rating Scale; LSMD, least squares mean difference; MADRS, Montgomery-Åsberg Depression Rating Scale.

<sup>a</sup>Difference between treatment groups (levomilnacipran ER—placebo) on the basis of the least squares mean score change from baseline to the end of treatment, defined as the last available assessment during double-blind treatment.

<sup>b</sup>P < 0.05, levomilnacipran ER versus placebo.

**Effects of baseline fatigue on treatment outcomes**

Regardless of the baseline fatigue level (MADRS item 7, score <4 or ≥4), the change from baseline in MADRS total, HAMD<sub>17</sub> total, SDS total, and CGI-S scores was significantly greater with levomilnacipran ER than with placebo (Fig. 2). Regression analyses carried out to test the effects of baseline fatigue on these treatment outcomes did not indicate any significant interaction ( $P > 0.05$  for all outcomes in both fatigue subgroups), suggesting similar efficacies of levomilnacipran ER in patients with and without high levels of fatigue.

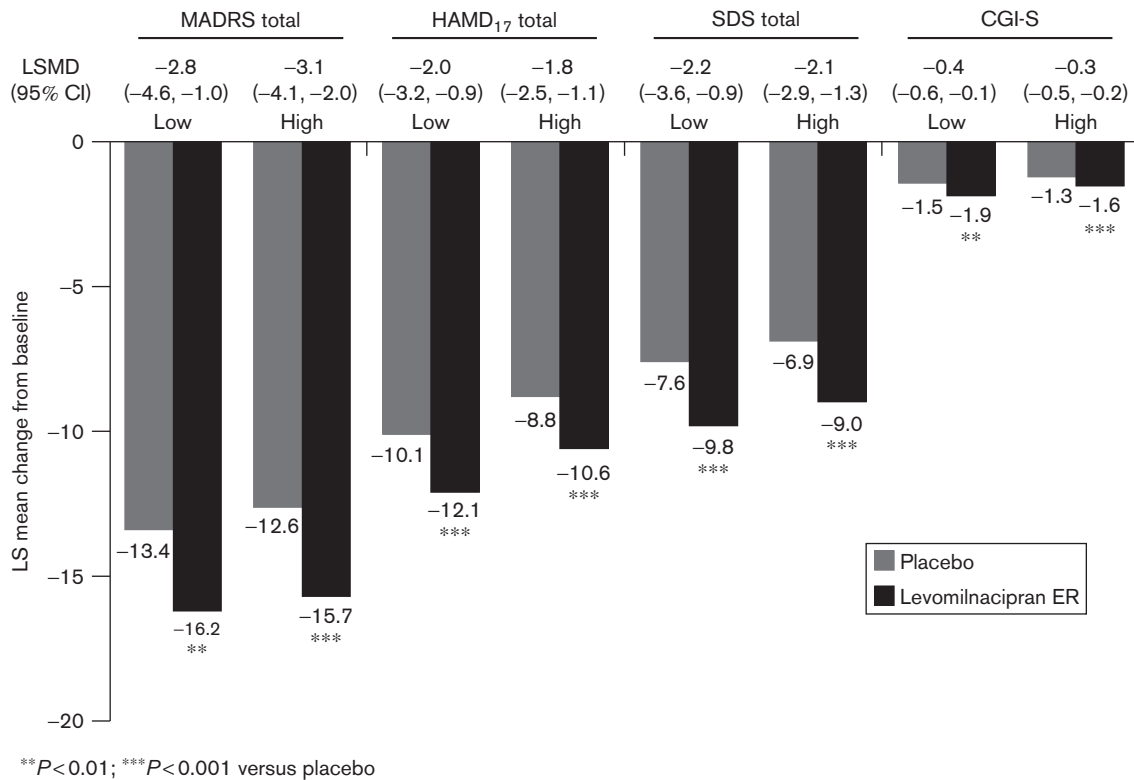
In all of the responder analyses, the percentage of patients meeting the response criteria was greater with levomilnacipran ER than with placebo regardless of the baseline fatigue level (Fig. 3). For overall treatment response, an odds ratio of 1.6 favoring levomilnacipran ER over placebo was found in both the low and the high fatigue subgroups. Almost 50% of levomilnacipran ER-treated patients in both fatigue subgroups had an early response, and ~30% of patients receiving levomilnacipran ER had an early and sustained response.

**Discussion**

The efficacy of levomilnacipran ER in MDD was evaluated in five randomized, double-blind, placebo-controlled trials that defined the mean change from baseline in MADRS total score as the primary outcome. With the exception of one flexible-dose trial (Gommoll *et al.*, 2014), these studies demonstrated clinically meaningful and statistically significant improvement in MADRS total score (Asnis *et al.*, 2013; Montgomery *et al.*, 2013; Bakish *et al.*, 2014; Sambunaris *et al.*, 2014a), indicating favorable treatment effects on overall depressive symptomatology. However, as some antidepressants can relieve mood and affective symptoms without improving fatigue (Demyttenaere *et al.*, 2005; Fava *et al.*, 2006; Ferguson *et al.*, 2014), post-hoc analyses of pooled data from all five trials were carried out to evaluate the effects of levomilnacipran ER on fatigue and to explore treatment outcomes in patients with low and high levels of fatigue at baseline.

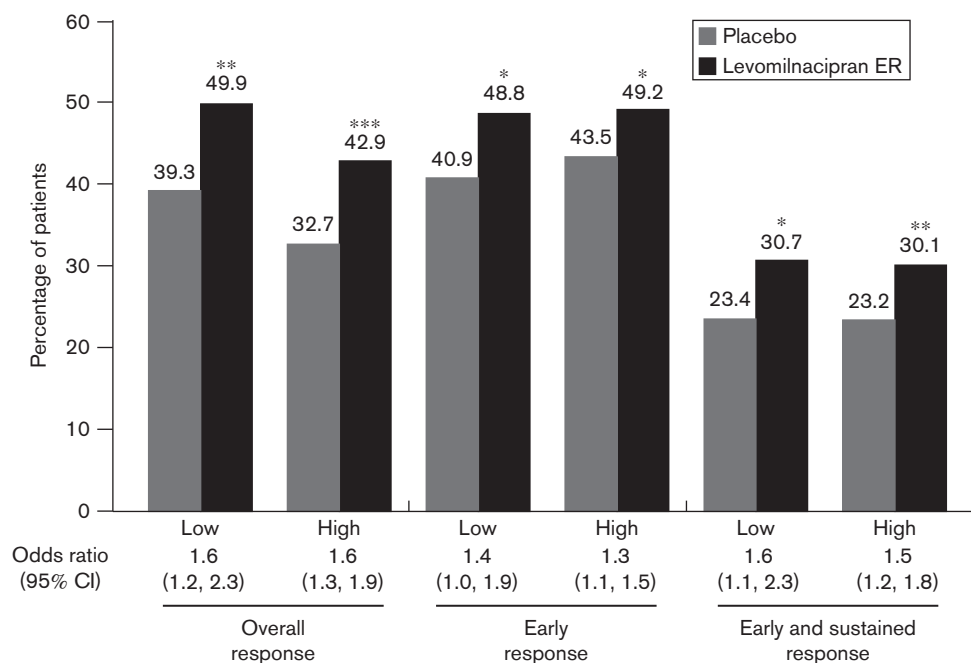
In the overall population, 73.4% of patients had high levels of fatigue before treatment, defined by a minimum baseline score of 4 on item 7 (lassitude) of MADRS

**Fig. 2**



Mean changes in efficacy measures in patients with low and high levels of fatigue at baseline (MMRM). Low and high fatigue were defined as MADRS item 7 (lassitude) baseline scores of less than 4 and 4 or higher, respectively. CGI-S, Clinical Global Impression of Severity; CI, confidence interval; ER, extended release; HAMD<sub>17</sub>, 17-Item Hamilton Depression Rating Scale; LSM, least squares mean; LSMD, least squares mean difference between treatment groups; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; SDS, Sheehan Disability Scale.

Fig. 3



\* $P < 0.05$ ; \*\* $P < 0.01$ ; \*\*\* $P < 0.001$  versus placebo

Treatment responses in patients with low and high levels of fatigue at baseline. Low and high fatigue were defined as MADRS item 7 (lassitude) baseline scores of less than 4 and 4 or higher, respectively. Responses were based on MADRS total scores and defined as follows: overall ( $\geq 50\%$  improvement from baseline); early ( $\geq 20\%$  improvement at end of Week 2); early and sustained ( $\geq 20\%$  improvement by end of Week 2 and  $\geq 50\%$  improvement at the last two visits). CI, confidence interval; ER, extended release; MADRS, Montgomery-Åsberg Depression Rating Scale.

(difficulties in starting simple routine activities that are carried out with effort). Relative to the low-fatigue subgroup, the high-fatigue subgroup had a greater proportion of women (64.9 vs. 60.6%) and obese patients (37.4 vs. 28.8%), more prior episodes (mean 4.3 vs. 3.7), and a greater mean MADRS total score (34.6 vs. 30.8). Although these analyses are preliminary, they suggest that there might be clusters of fatigue-related symptoms and patient characteristics that may help clinicians take a more individualized and symptom-based approach to the management of depression (Lin and Stevens, 2014).

The mean baseline MADRS total scores were greater in the high-fatigue subgroup, which was somewhat expected as the MADRS item 7 score had been used to stratify patients by fatigue severity. However, the mean baseline HAMD<sub>17</sub> total score, which also measures overall depression and includes somatic symptoms of depression, was similar between the high-fatigue and low-fatigue subgroups, as were the mean baseline SDS total and CGI-S scores. These results suggest that, although fatigue severity may be related to overall depression severity, fatigue might also involve neurobiological and psychosocial factors that are independent from other symptoms of depression (Arnold, 2008).

Statistically significant treatment effects with levomilnacipran ER versus placebo were found on fatigue-related MADRS and HAMD<sub>17</sub> items in the overall study population, as well as in subgroups of patients classified by sex and age (Table 4). As stand-alone parameters derived from a mathematical formula, and in the absence of Cohen's  $d$  estimates from other fatigue studies in patients with MDD, these effect sizes are somewhat difficult to interpret in terms of clinical relevance. However, they are similar to the effect sizes for overall depression in patients with mild to severe symptoms, as reported in a meta-analysis of clinical trials with antidepressants that have been approved by the US Food and Drug Administration (Fournier *et al.*, 2010). In this report, the main purpose for showing effect sizes was to provide a way to compare results between different subgroups of patients and across outcome measures that had different score ranges (i.e. MADRS and HAMD<sub>17</sub> items). No statistical testing was conducted between demographic subgroups, but the treatment effect sizes for a few of the MADRS and HAMD<sub>17</sub> fatigue-related items were greater in men versus women (work/activities, general somatic symptoms), in older versus younger patients (retardation), and in women 50 years or older versus those younger than 50 years (retardation, general somatic symptoms). The relatively larger treatment effects in postmenopausal women (as estimated by age) and in older

patients may reflect some overlapping data and are therefore difficult to interpret in this context. However, it is possible that, as premenopausal women experience cyclic changes in gonadotropins, unlike men and postmenopausal women, there may be hormonal factors that mediate the response to fatigue-related symptoms of depression (Freeman *et al.*, 2014).

Body weight was a factor that appeared to have a consistent impact on fatigue symptoms. In comparison with nonobese patients, patients with a BMI of 30 kg/m<sup>2</sup> or higher had smaller treatment effect sizes and no significant difference between levomilnacipran ER and placebo on any of the fatigue-related measures. These results are consistent with the findings of other studies that have shown slowed or decreased response to antidepressant treatment in obese patients (Papakostas *et al.*, 2005; Kloiber *et al.*, 2007). These blunted responses to treatment may be related to leptin levels or other hormonal factors, as suggested by a recent study of patients with treatment-resistant depression that showed no drug–placebo differences in the obese group despite significant treatment effects in the nonobese group (Fava *et al.*, 2015). Such findings with levomilnacipran ER and other antidepressants suggest that there may be additional challenges in treating depression-related fatigue symptoms in patients with high BMI and/or metabolic disorders. For these patients, more comprehensive or aggressive treatment paradigms may be required, including initiation of exercise programs, adjunctive medication, and/or psychotherapy.

In addition to evaluating the effects of levomilnacipran ER on fatigue symptoms in the overall population, as well as in patients stratified by age, sex, and BMI, a primary aim of this post-hoc analysis was to explore the effects of baseline fatigue on treatment outcomes. In contrast to studies that have found fatigue to be associated with poorer antidepressant response and decreased functioning (Demyttenaere *et al.*, 2005; Fava *et al.*, 2013), the current analyses showed that treatment with levomilnacipran ER improved depression symptoms (MADRS and HAMD<sub>17</sub> total), functional impairment (SDS total), and overall symptom severity (CGI-S) in patients with and without high baseline fatigue levels (Fig. 2). These results were further supported by statistically greater treatment responses found with levomilnacipran ER versus placebo regardless of baseline fatigue severity (Fig. 3), as indicated by a clinically meaningful number needed to treat 10 for overall response (calculated as the inverse of the rate difference between treatment groups) in both the low-fatigue and the high-fatigue subgroups (Thase, 2008). The significant results with levomilnacipran ER for early response and for early and sustained responses indicated that even among patients with high fatigue, ~50% showed early response to levomilnacipran ER and that

the majority of these patients maintained treatment response.

Fatigue symptoms in patients with MDD can be challenging to treat, and residual fatigue has been associated with greater functional impairment and lower rates of remission (Demyttenaere *et al.*, 2005). Several important studies have brought attention to the problem of residual fatigue (Nierenberg *et al.*, 1999; Greco *et al.*, 2004; Fava *et al.*, 2006; Ferguson *et al.*, 2014), but they have generally been limited to SSRI treatments and have used open-label or naturalistic study designs. To augment the existing literature on residual fatigue, the post-hoc analyses presented in this report were carried out to evaluate the effects of an SNRI on fatigue symptoms using data from five double-blind, placebo-controlled studies. These analyses indicated that after 8 or 10 weeks of double-blind treatment, a significantly greater percentage of levomilnacipran ER-treated patients compared with placebo-treated patients had remission of fatigue-related symptoms (i.e. no/minimal residual symptoms; Fig. 1). Although remission rates of fatigue symptoms with levomilnacipran ER ranged from 25.7% (general somatic symptoms) to 45.6% (retardation), the odds ratios favoring levomilnacipran ER over placebo were very similar across all four fatigue-related items (range, 1.3–1.5; all *P*'s < 0.01 vs. placebo). It should be noted that treatment-emergent fatigue, which is also an important concern when choosing an antidepressant therapy (Baldwin and Papakostas, 2006), occurred infrequently with both placebo and levomilnacipran ER in these studies (1.9 and 2.0%, respectively; data on file).

Current research evaluating the differential effects of noradrenergic and serotonergic medications on fatigue symptoms is limited and the findings are inconsistent (Fava *et al.*, 2013). However, the analyses presented here suggest that SNRIs with stronger noradrenergic activity, such as levomilnacipran ER, may be appropriate treatment choices for managing depression-related fatigue (Nutt, 2008). Given the prevalence and burden of fatigue in patients with MDD, more studies are needed to better understand how patients with various types of fatigue (physical, mental, emotional) respond to different antidepressants and the effects of these medications on the functional impairments associated with fatigue. Such efforts might include direct comparison studies that have multiple treatment arms with different antidepressant classes and predefined fatigue outcomes. Meta-analyses of published antidepressant trials that included fatigue-related measures could also be conducted, but differences in study design and patient populations would need to be considered.

Although this post-hoc analysis of data from five levomilnacipran ER trials provided an opportunity to explore the problem of fatigue in a large population of patients with MDD, several limitations should be noted. First,



there was no predefined fatigue measure used in any of the studies. Although the MADRS and HAMD<sub>17</sub> items used in this analysis were chosen on the basis of analyses from other MDD studies (Demyttenaere *et al.*, 2005), the items have not been specifically validated for this type of use. Second, this study population may not be representative of a more general clinical population. Because of eligibility criteria, for example, the majority of patients in the levomilnacipran ER studies had notable depression symptom severity at baseline (MADRS total score  $\geq 30$ ), which may have affected the percentage of patients classified with high levels of baseline fatigue. Third, the individual levomilnacipran ER studies implemented either a fixed-dose or flexible-dose design. As all of these dose groups were pooled for the current post-hoc analysis, no conclusion can be drawn with regard to the effects of specific dosages on fatigue-related symptoms in patients with MDD. Finally, no conclusion can be drawn with regard to the effect of levomilnacipran ER on fatigue relative to other antidepressants, as none of the clinical trials in this post-hoc analysis included an active control.

### Conclusion

Fatigue is highly prevalent in patients with MDD, and the physical, mental, and emotional difficulties associated with depression-related fatigue can interfere with a patient's ability to perform normal daily functions. Fatigue may be difficult to treat and residual fatigue after antidepressant treatment is associated with continued functional impairment. Therefore, identifying treatment options is an important clinical concern for patients with MDD who have prominent fatigue symptoms.

This exploratory post-hoc analysis of five clinical trials suggests that levomilnacipran ER may be effective in reducing fatigue symptoms in adults with MDD regardless of age or sex. Severity of baseline fatigue did not appear to have any substantial effects on treatment outcomes; patients in both the low-fatigue and the high-fatigue subgroups had significantly greater improvements with levomilnacipran ER relative placebo in depression symptoms, functional impairment, and overall disease severity. Response rates in both fatigue subgroups were also significantly higher with levomilnacipran ER relative to placebo. As has been seen in other MDD studies (Fava *et al.*, 2013), the majority of patients in this study population had some residual fatigue symptoms; however, patients treated with levomilnacipran ER did have a greater odds of fatigue symptom remission than those who received placebo. As with any post-hoc analysis, caution should be taken when drawing conclusions from the results presented here. When considered as a whole, however, these findings generally suggest that levomilnacipran ER may be an effective treatment option for reducing fatigue symptoms in adults with MDD.

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### Conflicts of interest

Marlene P. Freeman has received research support from GlaxoSmithKline and Takeda, has served on advisory boards for Takeda/Lundbeck, Otsuka, Genentech, and Johnson and Johnson, has served as consultant for JDS Therapeutics, and has performed medical editing for DSM Nutritionals and GOED Omega-3. Maurizio Fava's disclosures are as follows.

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