Effects of levomilnacipran extended-release on major depressive disorder patients with cognitive impairments: post-hoc analysis of a phase III study
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Performance-based cognitive data were collected using the Cognitive Drug Research System in a study of levomilnacipran extended-release (ER) 40–120 mg/day (NCT01034462) in adults with major depressive disorder. These data were analyzed post-hoc to explore the relationship between cognitive measures, depression symptoms (Montgomery–Åsberg Depression Rating Scale, MADRS), and self-reported psychosocial functioning (Sheehan Disability Scale; SDS). Changes from baseline were analyzed in the intent-to-treat population and subgroups with impaired attention, as indicated by baseline Cognitive Drug Research System scores for Power of Attention and Continuity of Attention. Path analyses evaluated the direct and indirect effects of levomilnacipran ER on SDS total score change. Significantly greater improvements were observed for levomilnacipran ER versus placebo for Power of Attention, Continuity of Attention, MADRS, and SDS score changes; the mean differences were larger in the impaired subgroups than in the overall intent-to-treat population. Path analyses showed that the majority of SDS total score improvement (>50%) was attributable to an indirect treatment effect through MADRS total score change; some direct effect of levomilnacipran ER on SDS total score improvement was also observed. In adults with major depressive disorder, levomilnacipran ER effectively improved measures of depression and cognition, which contributed toward reductions in self-reported functional impairment. \textit{Int Clin Psychopharmacol} 32:72–79 Copyright © 2017 Wolters Kluwer Health, Inc. All rights reserved.

Introduction
The diagnostic criteria for major depressive disorder (MDD) include cognitive symptoms such as diminished ability to concentrate or think, indecisiveness, and psychomotor retardation (American Psychiatric Association, 2013). The general prevalence of cognitive symptoms in MDD is not known (Trivedi and Greer, 2014), but results from a clinic-based study (Lam \textit{et al.}, 2012) and the STAR*D trial (Hollon \textit{et al.}, 2006) indicate that ~90% of patients report difficulties with concentration, memory, and/or decision making. Such impairments can negatively affect psychosocial functioning and the ability to work (Mcintyre \textit{et al.}, 2013; Evans \textit{et al.}, 2014). In a study of gainfully employed adults with MDD, cognitive dysfunction accounted for impairment in workplace productivity to an even greater extent than total depression severity (Mcintyre \textit{et al.}, 2015).

Multiple studies have reported persistent impairments in performance-based assessments of cognition after resolution of depression symptoms, and in patients with recurrent depressive episodes, cognitive impairments can become more severe with each subsequent episode (Neu \textit{et al.}, 2005; Baune and Renger, 2014; Trivedi and Greer, 2014; Papakostas, 2015; Maeshima \textit{et al.}, 2016). Such persistence suggests that cognitive impairment may be both a state marker and a trait marker of depression (Baune and Renger, 2014), and that depression itself may have a lasting impact on cognitive ability (Baune \textit{et al.}, 2010). The problems of residual and worsening cognitive symptoms highlight the importance of choosing medications that not only improve depression symptoms but also the cognitive impairments associated with MDD.

Widely varying methods have been used to evaluate the effects of antidepressants on cognition in patients with MDD. Meta-analyses of these studies indicate limited...
evidence for some medications over placebo in certain cognitive domains, such as the effects of duloxetine on processing speed and verbal memory or reboxetine on processing speed and continuity of attention (Keefe et al., 2014; Rosenblat et al., 2015). The most consistent effects have been found with vortioxetine (Al-Sukhni et al., 2015), which include results from double-blind, placebo-controlled studies in which objective tests of cognition were defined as the primary efficacy parameter (McIntyre et al., 2014; Mahableshwarkar et al., 2015). Path analyses in these studies showed vortioxetine to have direct treatment effects on cognition. In contrast to these newer antidepressants, some of the older pharmacotherapies, such as tricyclic antidepressants, can have anticholinergic or sedative effects that may interfere with cognitive function (Biringer et al., 2009).

Levomilnacipran extended-release (ER) is a serotonin and norepinephrine reuptake inhibitor currently approved in the USA for the treatment of MDD in adults (Forest, 2014). In one of the pivotal phase III studies (NCT01034462) that served as the basis for US approval (Sambunaris et al., 2014), cognition was evaluated using three computerized tests of attention from the Cognitive Drug Research (CDR) System (Keith et al., 1998; Ferguson et al., 2003; Vasudev et al., 2012). On the basis of predefined statistical analyses for the CDR System measures, the original trial report indicated a significantly greater improvement with levomilnacipran ER versus placebo on the Continuity of Attention (COA) score \( (P = 0.0036) \) and a trend toward statistical significance on the Power of Attention (POA) score \( (P = 0.0666) \). The current report includes additional analyses that were carried out to further investigate the effects of levomilnacipran ER on cognition and explore the relationship between changes in cognitive measures, mood symptoms, and functional impairments in adult MDD patients treated with levomilnacipran ER.

**Methods**

**Study design and participants**

Post-hoc analyses were carried out using data from an 8-week, randomized, double-blind, placebo-controlled, flexible-dose study of levomilnacipran ER 40–120 mg/day in adults with a *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) diagnosis of MDD (Sambunaris et al., 2014). The study was carried out in full compliance with Good Clinical Practice guidelines and Declaration of Helsinki principles. All patients provided written informed consent before any study procedures.

Details of eligibility and study design have been published previously (Sambunaris et al., 2014). Key criteria for inclusion were current depressive episode (duration ≥ 4 weeks) and clinician-rated Montgomery–Asberg Depression Rating Scale (MADRS) total score of 30 or more. Key exclusion criteria were as follows: any axis I disorder other than MDD within 6 months before screening; lifetime history of any other major psychiatric diagnosis; substance abuse or dependence within 6 months before screening; comorbid anxiety-related or phobia-related disorder; history of non-response to adequate treatment with two or more antidepressants; significant risk of suicide; and dementia, amnesia, or other cognitive disorder. The primary and secondary efficacy outcomes were defined as changes from baseline to week 8 in MADRS total score and Sheehan Disability Scale (SDS) total score, respectively.

**Cognitive assessments**

The cognitive assessments in this study comprised three CDR System tests of attention: digit vigilance, simple reaction time, and choice reaction time. Four validated composite scores (Wesnes et al., 2005) were derived from these tests as follows: (a) POA, which is based on the speed scores from all three tests and reflects the ability to temporarily focus attention and efficiently process information; (b) COA, which is based on measures of accuracy from the choice reaction time and digit vigilance tests and reflects the ability to sustain attention; (c) cognitive reaction time, which is the additional response time taken in the choice reaction time test over that from simple reaction time test and reflects central processing speed; and (d) reaction time variability, which is based on the coefficients of variation of the speed scores in the three tasks and reflects fluctuations in attention. Overall, these four measures incorporate all nine of the outcome measures from the three tasks. Self-ratings of mood and alertness were also measured using the three-factor scores from the Bond–Lader visual analog scales: alertness, calmness, and contentment (Bond and Lader, 1974).

Changes from baseline to week 8 in the four CDR System composite scores (POA, COA, cognitive reaction time, reaction time variability) and the three self-rated visual analog scale scores (alertness, calmness, contentment) were defined in the study as additional efficacy parameters.

**Post-hoc analyses**

The median POA and COA scores at baseline in the predefined intent-to-treat (ITT) population (i.e. all randomized patients who received ≥ 1 dose of double-blind study drug and had ≥ 1 postbaseline MADRS assessment) were used to categorize patients with ‘higher’ cognitive impairment (POA score ≥ 1303 or COA score < 92) and ‘lower’ cognitive impairment (POA score < 1303 or COA score ≥ 92). Median scores were selected as cutoffs to segregate the ITT population into two sets of similarly sized subgroups with different levels of cognitive impairment. These cutoffs are not intended to provide any information on cognitive impairment of the subgroups relative to healthy controls.

In the ITT population, changes from baseline to end of treatment in CDR System and Bond–Lader scores were
### Table 1 Demographics and baseline characteristics

| ITT population | Lower cognitive impairment subgroups* | Higher cognitive impairment subgroups* |
|----------------|---------------------------------------|----------------------------------------|
|                | POA < 1303 | COA ≥ 92 | POA < 1303 | COA < 92 |
|                | PBO (n = 214) | LVM-ER (n = 215) | PBO (n = 105) | LVM-ER (n = 108) | PBO (n = 122) | LVM-ER (n = 111) | PBO (n = 108) | LVM-ER (n = 107) | PBO (n = 92) | LVM-ER (n = 104) |
| Demographics and MDD history | | | | | | | | | | |
| Age (mean [SD] [years]) | 44.6 (13.8) | 44.9 (13.3) | 43.5 (12.6) | 41.0 (12.6) | 44.9 (12.6) | 43.5 (12.0) | 45.8 (14.8) | 49.9 (12.8) | 43.9 (15.2) | 46.4 (14.4) |
| Women [n (%)] | 141 (65.9) | 140 (65.1) | 63 (59.0) | 61 (56.3) | 83 (60.0) | 70 (63.1) | 77 (71.3) | 76 (72.8) | 60 (63.8) | 70 (67.3) |
| White race [n (%)] | 180 (84.1) | 174 (81.9) | 93 (88.6) | 91 (83.3) | 105 (86.1) | 87 (78.4) | 86 (79.6) | 86 (80.4) | 77 (81.9) | 89 (85.6) |
| BMI [mean (SD) [kg/m²]] | 29.6 (5.3) | 29.1 (5.4) | 30.1 (5.2) | 29.1 (5.8) | 29.8 (5.2) | 29.6 (5.6) | 29.2 (5.3) | 29.2 (5.1) | 29.3 (5.3) | 28.6 (5.2) |
| Recurrent episodes [n (%)] | 179 (82.5) | 176 (81.1) | 92 (87.6) | 91 (83.3) | 105 (86.1) | 84 (75.7) | 85 (78.7) | 86 (80.4) | 77 (81.9) | 89 (85.6) |
| MDD duration [mean (SD) [years]] | 14.2 (12.0) | 13.9 (13.2) | 15.8 (12.3) | 12.8 (12.7) | 16.0 (12.7) | 13.2 (12.4) | 12.7 (12.2) | 15.1 (13.7) | 11.5 (11.3) | 14.8 (14.1) |
| Baseline scores [mean (SD)] | | | | | | | | | | |
| POA composite | 1461.6 (498.1) | 1483.5 (645.0) | 1189.5 (71.6) | 1181.2 (70.4) | 1306.9 (191.5) | 1283.0 (206.6) | 1721.4 (586.7) | 1816.0 (851.8) | 1666.5 (684.2) | 1742.5 (909.7) |
| COA composite | 89.5 (7.5) | 89.2 (8.1) | 91.8 (3.0) | 92.0 (2.8) | 93.5 (1.0) | 93.6 (1.0) | 88.1 (9.0) | 86.3 (10.7) | 84.4 (9.2) | 84.3 (10.0) |
| MADRS total | 35.2 (3.8) | 35.0 (3.6) | 35.0 (4.0) | 35.1 (3.3) | 34.7 (3.6) | 35.1 (3.6) | 35.5 (3.6) | 35.5 (3.8) | 35.1 (3.6) | 34.9 (3.5) |
| SDS total | 19.7 (5.2) | 20.1 (5.0) | 19.1 (5.6) | 19.9 (5.0) | 19.5 (5.3) | 20.4 (4.7) | 20.4 (5.0) | 20.7 (5.3) | 20.1 (5.3) | 20.2 (5.2) |
| SDS work/school | 6.1 (2.4) | 6.1 (2.4) | 5.8 (2.6) | 6.0 (2.4) | 6.1 (2.5) | 6.2 (2.3) | 6.4 (2.4) | 6.4 (2.3) | 6.2 (2.5) | 6.2 (2.5) |
| SDS social life | 7.0 (1.9) | 7.3 (1.8) | 6.7 (2.0) | 7.4 (2.0) | 6.8 (1.9) | 7.5 (1.7) | 7.3 (1.8) | 7.4 (1.7) | 7.2 (1.9) | 7.3 (1.9) |
| SDS family/home | 6.6 (1.5) | 6.8 (1.3) | 6.2 (2.0) | 6.7 (2.1) | 6.6 (1.3) | 6.8 (1.8) | 6.7 (1.8) | 6.9 (1.8) | 6.7 (1.8) | 6.8 (2.0) |

BMI, body mass index; COA, Continuity of Attention; ITT, intent-to-treat; LVM-ER, levomilnacipran extended-release; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder; PBO, placebo; POA, Power of Attention; SDS, Sheehan Disability Scale.

*Subgroups were defined using the median POA and COA scores at baseline in patients with available POA and COA assessments at baseline.

In the safety population: PBO, n = 217; LVM-ER, n = 217.

The percentage of patients with previous major depressive episodes before the current episode and previous MDD history were generally similar between the treatment groups in the ITT population (Table 1). However, the percentage of patients with previous major depressive episodes (i.e., had a history of MDD) did not differ significantly between treatment groups. Therefore, we included these variables as factors in the statistical models. The primary outcome measure was change from baseline in MADRS total score, and MADRS total score was included in the models or other extraneous factors such as variance or measurement errors. Standardized scoring was imputed in all path analyses to adjust for the use of assessment scales that had very different possible score ranges.

Two path analyses were constructed using data from the POA and COA subgroups, but with subgroup category (POA ≥ 1303, COA ≥ 1303), treatment-by-category, and visit-by-category as factors. For the POA and COA subgroup analyses, the treatment-by-category interaction was tested at the 0.05 level of significance. All other statistical tests were performed at the 0.05 level of significance.
Effects of treatment on cognitive function

Significantly greater POA and COA score improvements were found with levomilnacipran ER versus placebo in the ITT population and in the higher cognitive impairment subgroups (POA ≥ 1303, COA < 92) (Fig. 1). Although the least-squares mean differences (LSMDs) for levomilnacipran ER versus placebo were greater in the higher cognitive impairment subgroups than in the lower cognitive impairment subgroups, no statistical differences between subgroups (P > 0.10) were detected, except for change in the COA score (POA ≥ 1303 vs. < 1303) (Fig. 1b).

Similarly greater mean improvements from baseline with levomilnacipran ER versus placebo were also found for reaction time variability in the ITT population and in the higher cognitive impairment subgroups, as well as for self-rated contentment in the POA ≥ 1303 subgroup (Table 2). No significant differences were found between levomilnacipran ER and placebo for cognitive reaction time, self-rated alertness, or self-rated contentment.

Effects of baseline cognitive impairment on treatment outcomes

In the ITT population, treatment with levomilnacipran ER versus placebo resulted in significantly greater mean improvements from baseline in both the MADRS total score (LSMD = −3.11; P = 0.0051) and the SDS total score (LSMD = −2.65; P = 0.0010) (Fig. 2), as well as in all three SDS subscale scores (Fig. 3).

Mean improvements in these outcome measures were also significantly greater with levomilnacipran ER versus placebo in the subgroups of patients with higher cognitive impairment. Although the LSMDs for levomilnacipran ER versus placebo in the higher cognitive impairment subgroups (POA ≥ 1303 and COA < 92 subgroups) were generally larger than those found in the ITT population and the lower cognitive impairment subgroups, the differences between the higher and the lower cognitive impairment subgroups were not significant (P > 0.10) for MADRS total, SDS total, and SDS work/school subscale score changes from baseline (Figs 2 and 3). However, significant differences (P < 0.10) in treatment effect (LSMDs for levomilnacipran ER vs. placebo) were found between higher and lower cognitive impairment groups for the SDS social life (POA ≥ 1303 vs. < 1303; COA < 92 vs. ≥ 92) and SDS family/home life (COA < 92 vs. ≥ 92) score changes from baseline (Fig. 3b).

Path analyses

In model 1, the direct treatment effect of levomilnacipran ER on SDS total score change was 11.1%; the indirect effects through MADRS total score change and POA score change were 80.9 and 8.0%, respectively. In model 2, the direct treatment effect of levomilnacipran ER on SDS total score change was 48.4%; the indirect effects through MADRS total score change and COA score change were 51.2 and 0.3%, respectively.

Discussion

The availability of CDR System data from a phase III trial of levomilnacipran ER in adults with MDD (Sambunaris et al., 2014) provided an opportunity to assess the effects of this medication on computer-based, composite measures of attention and to explore the relationship between changes in these cognitive measures and functional impairment. These post-hoc analyses indicate that relative to placebo, levomilnacipran ER significantly improved three of the four CDR System composite measures (POA, COA, reaction time variability) in the ITT population.

Cognitive declines were observed with placebo in the higher cognitive impairment subgroups (POA ≥ 1303 and COA < 92). As indicated by POA and COA score changes from baseline (Fig. 1), patients in the higher cognitive impairment subgroups worsened with placebo, whereas patients with lower impairment generally improved (or showed less worsening) with placebo. Consequently, larger treatment effects (i.e. LSMDs for levomilnacipran ER vs. placebo) on POA and COA score changes were observed in higher cognitive impairment subgroups. However, the difference in the magnitude of treatment effect between cognitive impairment subgroups was statistically significant for only 1 of the 4 comparisons (POA ≥ 1303 vs. POA < 1303 for COA score change from baseline). It is also worth noting that the placebo results for POA score change (decline in higher cognitive impairment subgroups, improvement in lower cognitive impairment subgroups) rule out ‘regression to the mean’ as a possible explanation for the POA score improvements that were observed with levomilnacipran ER in patients with higher levels of cognitive impairment at baseline (Fig. 1a).

Two validated measures, one rated by the investigator and the other self-reported by the patient (MADRS and SDS, respectively), were predefined in this trial as the primary and secondary efficacy measures, respectively. As reported previously for the ITT population (Sambunaris et al., 2014) and presented again here (Figs 2 and 3), treatment with levomilnacipran ER versus placebo resulted in significantly greater improvements in MADRS total, SDS total, and all three SDS subscale
scores. Treatment effects (i.e. LSMDs for levomilnacipran ER vs. placebo) were numerically larger in the higher cognitive impairment subgroups relative to the lower impairment subgroups, although the differences between subgroups were only statistically significant for two SDS subscales (social life, family/home life) (Fig. 3).

On the basis of the predefined efficacy analyses, it was already known that levomilnacipran ER significantly improved depression symptoms (MADRS total score) and self-reported functional impairment (SDS total score) relative to placebo in this trial (Sambunaris et al., 2014). It was not known, however, the degree to which levomilnacipran ER might have directly affected the change in the SDS total score relative to any indirect effects through changes in MADRS total score and POA or COA score. Two path analyses were carried out to explore this question, both of which indicated a limited indirect effect through POA score change (8.0%) or COA score change (0.3%). These results were not entirely unexpected as the SDS is a patient-reported measure, whereas POA and COA are objective measures, and subjective measures of functioning do not correlate as strongly with objective measures of cognition as they do with subjective measures of cognition (Naismith et al., 2007). Future investigations of the effects of cognitive improvements on functional impairment may need to take into consideration the types of measures being used. For example, path analyses that include objective measures of cognition, such as the POA or COA, may be more informative if they also include an objective measure of functioning, such as the rating of functional disability by an informant who knows the patient well (e.g. caregiver or high-contact clinician). In contrast to self-reported measures of functional impairment, this type of functional evaluation has been found to correlate with cognitive performance (Harvey and Keefe, 2015).

Results from the two path analyses differed in terms of the direct treatment effect and the indirect treatment effect through MADRS total score change. In model 1 (which included POA score change in addition to MADRS total score change as factors for estimating

![Fig. 1](image)

Mean changes from baseline in POA (a) and COA (b) scores. Subgroups were defined using the median POA and COA scores at baseline. For interaction analyses, *significance at the 0.1 level; **P < 0.05; ***P < 0.01; ****P < 0.001 for levomilnacipran ER versus placebo for score changes. COA, Continuity of Attention; ER, extended-release; ITT, intent-to-treat; n, number of patients with available assessments at baseline and end of treatment; LS, least squares; LSMD, least-squares mean difference between treatment groups; ns, not significant; POA, Power of Attention.

| Table 2  | Effects of treatment on additional cognition measures |
|---------|-----------------------------------------------------|
| CDR System composite scores [LSMD (95% CI)] | Lower cognitive impairment subgroups* | Higher cognitive impairment subgroups* |
| Cognitive reaction time | 12.13 (−12.89−37.15) | 5.02 (−30.49−40.53) | −0.13 (−33.69−33.43) | 17.37 (−18.16−52.90) | 29.36 (−8.44−67.16) |
| Reaction time variability | −0.01 (−0.02−0.00) | 0.00 (−0.01−0.02) | −0.01 (−0.02−0.01) | −0.03 (−0.04−0.01) | −0.02 (−0.04−0.01) |
| Self-rated Bond–Lader scores [LSMD (95% CI)] | Lower cognitive impairment subgroups* | Higher cognitive impairment subgroups* |
| Alertness | 3.17 (−0.25−6.59) | 2.09 (−2.81−6.98) | 2.23 (−2.39−6.86) | 4.29 (−0.53−9.11) | 4.58 (−0.53−9.69) |
| Calmness | 0.42 (−2.66−3.50) | 0.43 (−3.98−4.85) | −1.15 (−5.32−3.02) | 0.35 (−3.99−4.69) | 2.45 (−2.16−7.05) |
| Contentment | 3.68 (−0.31−7.67) | 1.61 (−4.08−7.30) | 2.77 (−2.62−8.15) | 5.76 (0.16−11.38) | 5.38 (0.57−11.32) |

CDR, Cognitive Drug Research; CI, confidence interval; COA, Continuity of Attention; ER, extended-release; ITT, intent-to-treat; LSMD, least-squares mean difference between treatment groups in the mean score change from baseline; POA, Power of Attention.

*Subgroups were defined using the median POA and COA scores at baseline.

**P < 0.05, levomilnacipran ER versus placebo.
indirect treatment effects), the effect of levomilnacipran ER on SDS total score was mostly indirect through MADRS total score change (80.9%). However, in model 2 (which included COA score change and MADRS total score change as factors), the indirect effect of levomilnacipran ER on SDS total score change through MADRS total score change (51.2%) was roughly equal to the direct treatment effect (48.4%). It is difficult to ascertain why one model had a negligible direct treatment effect whereas the other had ~50% direct treatment effect, although it is important to note that path analysis
results vary depending on the factors that are included in the model. Therefore, the path analyses in this report do not account for any factors (e.g. mental or physical fatigue, reduced motivation) that may have also contributed toward the effects of levomilnacipran ER on functional impairment. What both path analyses do suggest, however, is that improvement in the MADRS total score accounted for much (but probably not all) of the SDS total score improvement, which is consistent with numerous studies that have found the severity of depression to be associated with self-reported functional impairment in patients with MDD (Lam et al., 2011). What model 2 suggests is that some degree of functional improvement may have been attributable to a direct treatment effect with levomilnacipran ER.

More work is needed to better understand how improvements in depression symptoms, cognitive dysfunction, and functional impairment are interrelated. However, as it is already known that cognitive deficits can persist during periods of remission and that residual cognitive dysfunction can negatively impact occupational functioning (Fava, 2003; Woo et al., 2016), the first step is to establish whether an antidepressant can improve cognitive impairments in addition to reducing the core symptoms of depression. Whether such cognitive improvements directly or indirectly contribute toward diminished functional impairment and whether these effects are pseudospecific are also important questions that need to be examined concurrently with the clinical task of finding medications that can effectively treat cognitive impairments in patients with MDD who show such symptoms.

Limitations
Although CDR System score changes were predefined in the clinical trial as additional efficacy measures, the cognitive impairment subgroup definitions and the subsequent subgroup analyses were carried out post hoc. As such, some baseline characteristics (e.g. MDD duration and recurrent episodes) were not evenly distributed between treatment groups in cognitive impairment subgroups, which may have had some effect on the outcomes. Another potential limitation of these post-hoc analyses was that the study was not designed to provide sufficient statistical power in every subgroup, although differences between levomilnacipran ER and placebo were detected in many of the tested outcomes. Finally, the analyses presented in this report focused on POA and COA scores, which are primarily related to task-based attention. Therefore, no conclusions can be drawn on the effects of levomilnacipran ER on other types of cognitive impairment (e.g. memory, learning, executive functioning) or the relationship of such measures with overall psychosocial functioning. Moreover, as discussed earlier, future studies may need to include performance-based measures of everyday functional skills.

Conclusion
In addition to significantly greater improvements in depression symptoms (MADRS total score) and functional impairment (SDS total score), significantly greater improvements in two objective measures of attention were found with levomilnacipran ER versus placebo in adult MDD patients. Path analyses indicated that improvements in functional impairment during treatment with levomilnacipran ER were partly because of the direct effects of levomilnacipran ER and partly because of the improvements in MDD symptoms associated with levomilnacipran ER treatment.

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Conflicts of interest
At the time of the study, Keith Wesnes was an employee and stockholder in Bracket Inc., the company that supplied the CDR System for the study. Since February 2014, he has run his own company, Wesnes Cognition Ltd, which provides consultancy for Bracket as well as for pharmaceutical and nutraceutical companies. Angelo Sambunaris is an employee of the Institute for Advanced Medical Research and has received clinical research grant support from the Forest Research Institute (an Allergan affiliate), Alkermes, Cerecor, Daiichi-Sankyo, Indivior, Lundbeck, Merck, Otsuka, Palatin, Pfizer, and Tal Medical, as well as from Duke University School of Medicine. Roger S. McIntyre has received research grant support from Lundbeck, AstraZeneca, Pfizer, Shire, Otsuka, Bristol-Myers Squibb, National Institute of Mental Health, Stanley Medical Research Institute, Canadian Institutes for Health Research, and The Brain and Behavior Research Foundation. He has also received speaker/consultant fees from Lundbeck, Pfizer, AstraZeneca, Eli Lilly, Janssen Ortho, Sunovion, Takeda, Forest, Otsuka, Bristol-Myers Squibb, and Shire. Philip D. Harvey has been a consultant for Boehringer Ingelheim, Forest Laboratories (an Allergan affiliate), FORUM Pharmaceuticals, Genentech, Lundbeck, Otsuka, Hoffman-La Roche, Sanofi, Sunovion Pharmaceuticals, and Takeda Pharmaceutical Company. Carl Gommoll and Changzheng Chen are full-time employees of Allergan.

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