OPEN

The Relationship of Early Sleep Improvement With Response to Pharmacotherapy in Unipolar Psychotic Depression

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Abstract:

Background: Since insomnia and depression are interrelated, improved sleep early in antidepressant pharmacotherapy may predict a positive treatment outcome. We investigated whether early insomnia improvement (EII) predicted treatment outcome in psychotic depression (PD) and examined if there was an interaction effect between EII and treatment type to assess if findings were treatment-specific.

Methods: This study is a secondary analysis of a randomized trial comparing 7 weeks treatment with the antidepressants venlafaxine, imipramine and venlafaxine plus the antipsychotic quetiapine in PD (n = 114). Early insomnia improvement, defined as ≥20% reduced insomnia after 2 weeks, was assessed by the Hamilton Rating Scale for Depression (HAM-D-17). Associations between EII and treatment outcome were examined using logistic regressions. Subsequently, we added interaction terms between EII and treatment type to assess interaction effects. The predictive value of EII was compared with early response on overall depression (≥20% reduced HAM-D-17 score after 2 weeks).

Results: EII was associated with response (odds ratio [OR], 7.9; 95% confidence interval [CI], 2.7–23.4; P = <0.001), remission of depression (OR, 6.1; 95% CI, 1.6–22.3; P = 0.009), and remission of psychosis (OR, 4.1; 95% CI, 1.6–10.9; P = 0.004). We found no interaction effects between EII and treatment type on depression outcome. Early insomnia improvement and early response on overall depression had a comparable predictive ability for treatment outcome.

Conclusions: Early insomnia improvement was associated with a positive outcome in pharmacotherapy of PD, regardless of the medication type. Future studies are needed to confirm our findings and to examine the generalizability of EII as predictor in treatment of depression.

Key Words: psychotic depression, insomnia, early antidepressant response, antidepressant medication

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Insomnia, defined as difficulty initiating sleep or staying asleep, is one of the most prominent symptoms of unipolar major depressive disorder (MDD).[1–4] Approximately 90% of MDD patients have insomnia symptoms.[1–3,5] Insomnia and depression are bidirectionally related.[1] Insomnia is an important risk factor for the onset of first and recurrent episodes of depression and mood symptoms contribute to sleep disruption.[1,6,7] Higher insomnia severity in MDD is associated with higher levels of depression, anxiety and suicidality.[8–12]

The role of insomnia in the treatment of MDD is clinically relevant. Although the majority of studies could not demonstrate a significant association between pretreatment insomnia and the effect of antidepressants,[13–16] a systematic review found that treatment of insomnia improves mood-specific symptoms in MDD.[17] It has been suggested that early insomnia improvement (EII) within the first weeks of treatment with antidepressants predicts a positive outcome regarding overall depressive symptoms.[18–20] A study evaluating the effects of the antidepressant vortioxetine on sleep found that EII after 2 weeks was associated with response on depressive symptoms after 8 weeks.[18] Other studies reported associations between improved sleep after 6 or 12 weeks of combined pharmacotherapy and cognitive behavioral therapy (CBT) with treatment response after 16 weeks and 6 months, respectively.[16,20]

So far, the clinical utility of EII as predictor for outcome to antidepressant pharmacotherapy remains unclear. First, none of the previous studies examined its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for treatment outcome. Second, associations between EII and treatment outcome have only been investigated for vortioxetine and ketamine, 2 antidepressants with robust sleep-improving effects,[21,22] leaving unclear whether EII also predicts a positive outcome in treatment with other antidepressants.[21–23] Third, previous studies examined the prognostic significance of EII at different time intervals varying from 1 day until 12 weeks after treatment initiation. Based on a number of meta-analytic studies showing that early response on overall depression assessed after 2 weeks of treatment is associated with a positive outcome to antidepressants,[24–27] we investigated the predictive value of EII after 2 weeks.

We conducted this study specifically in unipolar MDD with psychotic features, ie, psychotic depression (PD), which is a subtype of MDD with additional hallucinations and delusions. Compared with nonpsychotic MDD, PD is associated with a higher severity of depressive and insomnia symptoms and a lower response to antidepressants and placebo.[28–32] Therefore, we consider PD an interesting condition to investigate the predictive value of EII for outcome to antidepressants.

The primary aim of the current study was to examine whether EII predicts response and remission of PD and if there was an interaction effect between EII and the type of treatment on the outcome measures. The secondary objective was to compare EII with early response on overall depression in predicting response and remission of PD. If EII predicts response to pharmacotherapy in PD this could potentially be used as an easily accessible prognostic marker in treatment of PD. Furthermore, this may address the importance

of treating sleep problems and achieving EII in PD, which may differ between medication types.

MATERIALS AND METHODS

Study Design

This study was a secondary analysis of the Dutch University Depression Group (DUDG)-study (protocol number: ISRCTN36607067).[33] The DUDG study was a double-blind randomized controlled trial comparing treatment outcome of the serotonin-noradrenaline reuptake inhibitor (SNRI) venlafaxine, the tricyclic antidepressant (TCA) imipramine and the combination of venlafaxine with the second-generation antipsychotic quetiapine in PD. Ethical approval was obtained from the medical ethical review board of the UMC Utrecht and the local review boards. All patients gave their written informed consent.

Participants

Patients (n = 122) were aged 18 to 65 years and had a diagnosis of PD according to DSM-IV-TR criteria. An inclusion criterium was a score of ≥18 on the Hamilton Rating Scale for Depression (HAM-D-17), indicating severe depression. Exclusion criteria were an acute indication for electroconvulsive therapy (ECT), mental disability (IQ <80), alcohol or substance use disorder within 3 months from enrollment, any serious somatic illness or somatic medication potentially affecting mood symptoms, contra-indications for study medication or previous treatment with imipramine (≥4 weeks with adequate plasma levels) or venlafaxine (≥4 weeks ≥300 mg/d) during the current depressive episode. For the present analysis, patients who did not initiate study medication or discontinued study medication during the first 2 weeks of treatment were excluded. Furthermore, patients without any insomnia symptoms at baseline were excluded, since for these patients improvement of insomnia symptoms after 2 weeks was not possible.

Study Treatment

Patients were randomized to 7 weeks double blind treatment with venlafaxine (maximum [max], 375 mg/d), imipramine (steady-state plasma concentrations, 200–300 μg/L) or venlafaxine plus quetiapine (max, 375 mg/d and max, 600 mg/d, respectively). Venlafaxine was started at 75 mg/d (first 2 days), followed by 150 mg/d (days 3–5), 225 mg/d (days 6–9), 300 mg/d (days 10–16) and 375 mg/d (rest of the study). Imipramine was initiated at 75 mg/d (first 2 days), followed by 150 mg/d (days 3 to 8), after which it was dosed guided by therapeutic drug monitoring. Quetiapine was initiated at 100 mg/d (first 2 days), followed by 200 mg/d (days 3–5), 400 mg/d (days 6–9), and 600 mg/d (rest of the study). Before initiation of study medication patients were free of psychotropic medication for at least 4 days except for benzodiazepines, which were allowed to an equivalent of maximum 3 mg lorazepam per day during conduct of the study.[34] Severity of depressive symptoms was scored weekly using the HAM-D-17.[35] Psychotic symptoms were assessed weekly on the basis of clinical impression and were scored dichotomously (present or absent).

Early Insomnia Improvement

The definition of EII used in this study was ≥20% reduction of insomnia severity after 2 weeks of treatment compared with baseline. Insomnia symptoms were assessed based on items of the HAM-D-17.[35] Insomnia severity was measured as the sum score of the 3 sleep-related HAM-D-17 items, ranging from 0 to 6.[15,36] The 3 sleep-related HAM-D-17 items are: difficulty falling asleep (item 4), waking during the night (item 5) and early morning waking (item 6).[35] The maximum score for each of these items is 2: 0 if absent, 1 if present during 1 or 2 of the past 3 nights and 2 if present each of the last 3 nights.

Early Response on Overall Depression

Early response on overall depression was defined as ≥20% reduction of the HAM-D-17 score after 2 weeks, in accordance with previous studies.[25,27,37,38] The sum score of the HAM-D-17 ranges from 0 to 52.

Outcome Measures

The primary outcome measure was response on overall depression, defined as ≥50% reduction of the HAM-D-17 score after 7 weeks of treatment in accordance with the literature.[39] With regard to the association between EII and response on depression we additionally defined response as >50% reduction on the HAM-D-17 scale excluding the 3 insomnia items. Secondary outcome measures were remission of depression, defined as a HAM-D-17 score of <8 after 7 weeks of treatment,[39] and remission of psychotic symptoms, defined as absence of hallucinations and delusions after 7 weeks.

Statistical Analysis

Baseline characteristics were compared between patients with and without EII using χ^2 tests or independent t tests as appropriate. Multivariate associations between EII and the outcome measures, ie, response on depression, remission of depression and remission of psychotic symptoms, were analyzed by conducting logistic regression models. Regression analyses were adjusted for gender, age, medication types, co-use of benzodiazepines (mean lorazepam equivalent [mg/d]) during conduct of the study,[34] pretreatment insomnia and pretreatment depression severity (HAM-D-17 score). Interaction effects between EII and medication types were analyzed after adding interaction terms, computed as the products of EII and venlafaxine, imipramine and venlafaxine plus quetiapine respectively, to the regression models. P values were 2-tailed and values <0.05 were considered significant. Regarding drop-outs, the last observation carried forward (LOCF) approach was applied in line with the original study.[33]

Subsequently, a similar procedure was conducted to investigate the association between early response on overall depression with the outcome measures. Logistic regressions models using early response on overall depression as independent variable were adjusted for gender, age, medication types, co-use of benzodiazepines and pretreatment depression severity. Finally, we compared the predictive value of EII for the outcome measures with early response on overall depression with regard to area under the curve (AUC) values yielded by receiver operating characteristic (ROC) curves, sensitivity, specificity, PPV and NPV. All statistical analyses were conducted in SPSS version 28 (IBM Corp., Armonk, NY).

RESULTS

Baseline Characteristics and Early Response

From the 122 patients in the original study, 4 patients were excluded since they did not start study medication and 1 patient was excluded as a drop-out within the first 2 weeks. Three patients were excluded as they had no insomnia symptoms at baseline. As a result, analyses were conducted for 114 patients: 37 in the venlafaxine (33%), 38 in the imipramine (33%) and 39 in the venlafaxine plus quetiapine group (34%). 17 (15%) patients had missing data due to drop-out at week 3 (n = 4), 4 (n = 2),

TABLE 1. Comparison of Baseline Characteristics Between Patients With EII to Patients Without EII

	Total (N = 114)	EII (n = 84)	No EII (n = 30)	*P*
Gender				0.53
Female, *n* (%)	59 (52)	42 (50)	17 (57)	
Male, *n* (%)	55 (48)	42 (50)	13 (43)	
Age: mean (SD), y	51.2 (10.6)	52.3 (9.8)	48.3 (12.3)	0.11
Insomnia*, mean (SD)	4.6 (1.5)	4.7 (1.4)	4.4 (1.7)	0.41
Other depressive symptoms†, mean (SD)	27.3 (4.6)	27.3 (4.2)	27.1 (5.5)	0.83
HAM-D-17 score at baseline, mean (SD)	31.9 (5.0)	32.0 (4.7)	31.5 (5.7)	0.64
Study treatment				0.056
Venlafaxine, n (%)	37 (32)	22 (26)	15 (50)	
Imipramine, n (%)	38 (33)	31 (37)	8 (27)	
Venlafaxine plus quetiapine, n (%)	39 (34)	31 (37)	7 (23)	
Co-use of benzodiazepines (mg/d)‡, mean (SD)	1.3 (1.0)	1.4 (1.0)	1.0 (1.0)	0.089

* Sum score of the 3 sleep-related HAM-D-17 items.

† Sum score of the 14 other HAM-D-17 items.

‡ Mean co-use of benzodiazepines during conduct of the study (mg of lorazepam per day). For patients using other benzodiazepines than lorazepam an equivalent dose (lorazepam, mg/d) was computed. Gender and study treatment were compared using χ^2 tests and other characteristics using independent *t* tests.

5 (n = 3), 6 (n = 5), and 7 (n = 3). As shown in Table 1, at baseline there were no significant differences between patients with and without EII concerning gender, age, co-use of benzodiazepines, depression severity (HAM-D-17 score) and insomnia severity.

We observed a different pattern regarding response on insomnia and other depressive symptoms over the course of treatment, as shown in Figure 1. After 2 weeks, average reduction of insomnia symptoms was significantly greater than on other depressive symptoms (see Fig. 1). In accordance, EII was achieved in 84 (74%) patients and early response on overall depression in 76 (67%) patients. After 7 weeks, the mean reduction of insomnia and other depressive symptoms was comparable. Trajectories of mean insomnia severity, other depressive symptoms and overall depression (HAM-D-17 score) per treatment group are shown in Figure S1, Supplemental Digital Content, http://links.lww.com/JCP/A875.

Associations Between Early Response and Treatment Outcome

After 7 weeks, response on overall depression was achieved in 65 (57%) patients, remission of depression in 36 (32%) patients and remission of psychotic symptoms in 76 (67%) patients. In logistic regression models we examined multivariate associations between EII and treatment outcome. As presented in Table 2, we found that EII was significantly associated with response on overall depression (Odds Ratio (OR) 7.9, 95% Confidence Interval (CI) 2.7 to 23.4, $P = <0.001$). Subsequent addition of interaction terms between EII and medication types was not associated with a significant change in explained variance (Nagelkerke R^2) (from 0.33 to 0.36, χ^2 (2) = 2.2, $P = 0.33$). In addition, we found that EII was also significantly associated with response on depression (HAM-D score) excluding the 3 insomnia items (OR, 6.3; 95% CI, 2.2–18.3; $P = <0.001$).

With regard to the secondary outcome measures, we observed that EII was significantly associated with remission of depression (OR, 6.1; 95% CI, 1.6–23.3; $P = 0.009$) and remission of psychotic symptoms (OR, 4.1; 95% CI, 1.6–10.9; $P = 0.004$). Subsequent addition of interaction terms between EII and medication types to the regressions was not associated with a significant change in explained variance (Nagelkerke R^2) concerning remission (from 0.22 to 0.24: χ^2 (2) = 1.7; $P = 0.43$) of depression. In contrast, addition of interaction terms increased the explained

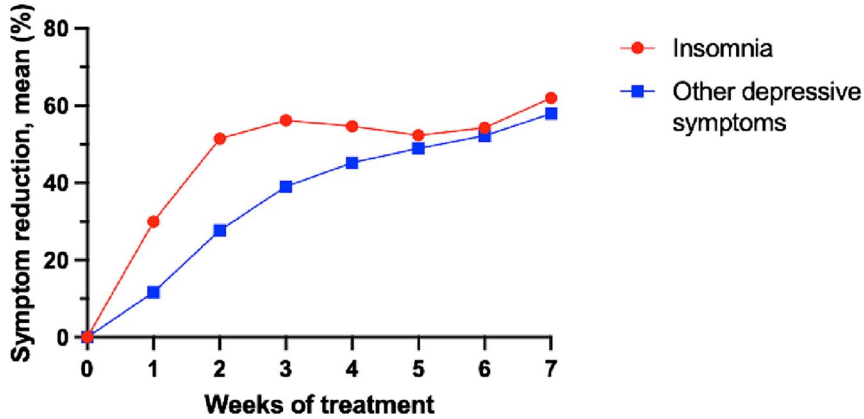

FIGURE 1. Mean reduction of insomnia (the sum score of HAM-D-17 items 4, 5, and 6) compared with other depressive symptoms (the sum score for the other 14 items of the HAM-D-17) during 7 weeks of pharmacotherapy. After 2 weeks average reduction of insomnia (52%) was significantly higher compared with other depressive symptoms (28%), independent *t* test, t(226) = 5.1, $P = <0.001$, n = 114. After 7 weeks the mean reduction of insomnia (62%) and other depressive symptoms (60%) was comparable, independent t-test, t(148) = 0.7, $P = 0.51$, n = 97.

TABLE 2. Multivariate Associations Between EII and Outcome to 7 Weeks of Pharmacotherapy (n = 114)

	HAM-D-17 Response		HAM-D-17 Remission		Psychosis Remission	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
EII	7.9 (2.7–23.4)	<0.001*	6.1 (1.6–23.3)	0.009†	4.1 (1.6–10.9)	0.004†

Logistic regression models were adjusted for gender, age, type of study medication, co-use of benzodiazepines, insomnia severity, and depression severity (HAM-D-17 score) at baseline.

*$P < 0.001$, †$P < 0.05$ (2-tailed).

variance significantly regarding remission of psychotic symptoms (Nagelkerke R^2, from 0.23 to 0.30, χ^2 (2) = 6.5, $P = 0.024$).

As for EII, we found significant multivariate associations between early response on overall depression with response on depression (OR, 6.0; 95% CI, 2.3–15.7; $P = <0.001$), remission of depression (OR, 3.2; 95% CI, 1.2–8.9; $P = 0.03$) and remission of psychotic symptoms (OR 5.3, 95% CI 2.1 to 13.5, $P = <0.001$) after 7 weeks. The ORs for early response on overall depression were relatively lower compared with EII for response and remission of depression; however, confidence intervals were overlapping.

Comparison Between EII and Early Response on Overall Depression as Predictor

We compared the predictive value of EII with early response on overall depression, as shown in Table 3. From the 84 patients with EII, 59 (70%) achieved response on depression compared with 6 of 30 (20%) without EII. Remission of depression was reached in 33 (39%) patients with EII and in 3 (10%) without EII. Remission of psychotic symptoms was achieved in 64 (76%) patients with EII and in 12 (40%) without EII. From the 76 patients with early response on overall depression, 53 (70%) patients attained response on depressive symptoms relative to 12 of 38 (32%) without early response, 29 (38%) patients achieved remission of depression compared with 7 (18%) without early response and 59 (78%) patients reached remission of psychosis compared with 17 (45%) without early response.

We observed that EII had a relatively higher sensitivity and NPV than early response on overall depression for all outcome measures (see Table 3). Area under the curve values and PPV of EII and early response on overall depression were similar while specificity of both predictors was modest. Post hoc, we compared the predictive ability of EII to early response on other depressive symptoms, ie, ≥20% reduction on the HAM-D-17 excluding the 3 insomnia-related items after 2 weeks of pharmacotherapy, presented in Table S1, Supplemental Digital Content, http://links.lww.com/JCP/A875. With regard to early response on other depressive symptoms, EII had a higher sensitivity and NPV for all outcome measures.

DISCUSSION

This is the first study investigating EII as predictor for treatment outcome in PD. EII was associated with response on depression, remission of depression and remission of psychotic symptoms after 7 weeks. There were no significant interactions between EII and medication types on depression outcome. Insomnia symptoms improved especially within the first weeks of pharmacotherapy, whereas response on overall depression occurred more gradually. Relative to early response on overall depression, EII had a similar predictive ability for treatment outcome, although EII had a relatively higher sensitivity and NPV for response and remission of depression after 7 weeks.

The finding that insomnia improved relatively faster than other depressive symptoms suggests that EII contributes importantly to early improvement of overall depression. Our findings are in line with studies in nonpsychotic MDD.[16,18–20,40,41] Previously, EII assessed after 2 weeks has only been examined in an open label study with vortioxetine ($n = 92$).[18] In this study EII was associated with treatment response after 8 weeks. Studies with Selective Serotonin Reuptake Inhibitors (SSRIs) and SNRIs found associations between sleep improvement after 6 or 12 weeks and a positive depression outcome after 16 weeks or 6 months, respectively.[16,20,40] We consider the predictive value of sleep improvement after 6 or 12 weeks less relevant for clinical practice because response to antidepressants is usually evaluated 6 to 8 weeks after treatment initiation.[42,43] Using EII after 2 weeks as a predictor for treatment outcome could reduce the time of ineffective treatment in nonresponders by at least 4 weeks. This is highly relevant given the tremendous burden of severe depression and the common occurrence of nonresponse to antidepressants medications, in particular in PD.[30,39,44]

TABLE 3. Comparison Between the Predictive Ability of EII and Early Response on Overall Depression (D) for Treatment Outcome After 7 Weeks ($n = 114$)

	HAM-D-17 Response		HAM-D-17 Remission		Psychosis Remission	
	EII	D*	EII	D	EII	D
AUC (95% CI)	0.70 (0.60–0.80)	0.69 (0.59–0.80)	0.63 (0.53–0.74)	0.60 (0.49–0.71)	0.66 (0.55–0.77)	0.66 (0.56–0.77)
Sensitivity (95% CI)	0.91 (0.91–0.91)	0.82 (0.81–0.82)	0.92 (0.91–0.92)	0.81 (0.80–0.81)	0.84 (0.84–0.84)	0.78 (0.77–0.78)
Specificity (95% CI)	0.49 (0.49–0.49)	0.53 (0.53–0.54)	0.35 (0.34–0.35)	0.40 (0.39–0.40)	0.47 (0.47–0.48)	0.55 (0.55–0.56)
PPV (95% CI)	0.70 (0.70–0.71)	0.70 (0.69–0.70)	0.39 (0.39–0.40)	0.38 (0.38–0.39)	0.76 (0.76–0.76)	0.78 (0.77–0.78)
NPV (95% CI)	0.80 (0.80–0.80)	0.68 (0.68–0.69)	0.90 (0.90–0.90)	0.82 (0.81–0.82)	0.60 (0.59–0.61)	0.55 (0.55–0.56)

* D, early response on overall depression (HAM-D-17).

So far, EII has not been investigated as predictor for remission of psychotic symptoms in MDD. Several studies identified insomnia as risk factor for hallucinations and delusions in psychotic disorders and in the general population.[1,45–47] A large study in students with insomnia (n = 3755), with or without depression and psychosis, found that improved sleep after 3 weeks of CBT or usual care mediates efficacy on psychotic symptoms after 10 weeks, which supports our findings in PD.[36]

A number of reviews reported that early response on overall depression predicts a positive outcome to pharmacotherapy in non-psychotic MDD, although sensitivity and specificity are modest.[24–27,48] For early response on overall depression we found AUCs of 0.69 regarding response and 0.60 concerning remission of depression. These values are within the ranges of values reported previously and slightly lower compared with EII in our study: response AUC, 0.70 and remission of depression AUC, 0.63.[25,27,38] In contrast to these AUC values, which do not promote the use of early response as a predictor in in clinical practice, the NPV of EII might potentially be more useful if replicated in other cohorts. In our study EII had a high NPV for response (0.80) and remission of depression (0.90), indicating that in our study patients without EII only 20% achieve response and only 10% remission of depression after 7 weeks.

In our study, insomnia improved the most with venlafaxine plus quetiapine and the least with venlafaxine, although no interaction effects between EII and medication types on depression outcome were observed. These findings are in line with several reviews showing variable effects of venlafaxine, imipramine and quetiapine on insomnia.[21–23,49,50] Quetiapine is the most hypnotic agent among the study medications and is frequently used in treatment of insomnia.[51–53] In contrast, venlafaxine has frequently been associated with insomnia.[21–23,54] For imipramine and its active metabolite desipramine mixed effects have been reported.[21,23] The interaction between EII and medication types on remission of psychosis remains unexplained but might be influenced by a low number of patients achieving EII and remission of psychosis in the venlafaxine group.

Early insomnia improvement may also be of guidance in pharmacotherapy of nonpsychotic MDD. This is supported by the common practice to treat MDD with sleep disruption with hypnotic antidepressants,[53,55–57] which presumably results more often in EII and in treatment response in MDD with insomnia. Nonetheless, the generalizability of EII as predictor for response to antidepressants in nonpsychotic MDD requires further research. So far, the mediating mechanisms of sleep improvement in recovery from depression are not fully clarified. Sleep has an important role in homeostasis, synaptic function and plasticity.[53,58,59] It has been speculated that restored sleep normalizes synaptic plasticity, which might play a pivotal role in sustained antidepressant effects.[58,60]

An important strength of our study is that it has been conducted in a homogeneous sample of PD patients. Depression severity was measured weekly. Patients were free of psychotropic medications, except for benzodiazepines at a low maximum dose of 3 mg lorazepam per day or equivalents. Most patients used benzodiazepines during conduct of the study, for which we adjusted in multivariate analyses, although we were not able to adjust for prestudy use of benzodiazepines since data on this were not available. Another limitation is that only the venlafaxine plus quetiapine group was treated in accordance with current guidelines (an antidepressant plus an antipsychotic),[61,62] although the association between EII and treatment outcome in all medication groups suggests that EII can be used in PD regardless of the treatment type. Further, insomnia was assessed by the 3 sleep-related HAM-D-17 items and not by a specific insomnia scale, such as the insomnia severity index.[63] The HAM-D-17 is not designed to assess insomnia. Nevertheless, the 3 sleep-related items have been considered a good global measure of insomnia severity.[64–66] Finally, we could only research EII in patients with at least one point on the sleep-related HAM-D-17 items. Although only 3 patients were excluded because of absence of insomnia symptoms, EII cannot be used in patients without any sleep-related symptoms before commencement of pharmacotherapy.

Taken together, we found that EII was associated with a higher response on depressive and psychotic symptoms in PD. Prospective studies are needed to further examine the role of EII in the improvement of depression, investigate the causality of the observed relationships and explore mechanistic underpinnings before clinical implementation can be recommended.

AUTHOR DISCLOSURE INFORMATION

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Data availability statement: The data sets used and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and patient consent statement: The study was approved by the ethical review board of the University Medical Center Utrecht and local review boards of participating centers and was conducted in accordance with the rules of Good Clinical Practice (GCP) (protocol number: ISRCTN36607067). Written informed consent was obtained from all participants or their legal representatives.

Authorship: C.F.V. and J.G.E.J. initiated the idea for the study and conducted the statistical analyses. C.F.V. was the primary author of the manuscript, to which T.K.B., W.A.N., W.W.vdB., S.E.tH., A.F.A.S., R.-J.V., and J.G.E.J. made important contributions. All authors read and approved the final manuscript.

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