# Sleep Quality After Quetiapine Augmentation in Patients With Treatment-Resistant Depression and Personality Disorders

*Christophe Moderie, MD, MSc,[1] Jacob D. King, MD,[2] Nicolas Nuñez, MD, MSc,[1] Stefano Comai, PhD,[1,3,4] and Gabriella Gobbi, MD, PhD[1,5]*



**Abstract:**

**Purpose/Background:** Quetiapine is a first-line augmenting agent for treatment-resistant depression (TRD) and is used off-label in insomnia. Quetiapine and its active metabolite norquetiapine act mostly on 5-$HT_{2A}$, 5-$HT_{2C}$, $H_1$, and $D_2$ as antagonists and on 5-$HT_{1A}$ as partial agonists. Patients with TRD often have comorbid personality disorder (PD), and evidence suggests an association between sleep disturbance and recovery among patients with PD. Here, we aimed to evaluate the effects of quetiapine on sleep in TRD patients with and without PD (PD+/PD−).

**Methods/Procedures:** We reviewed health records of 38 patients with TRD (20 TRD/PD+) who had been treated with a pharmacotherapy regimen including quetiapine. Clinical outcomes were determined by comparing changes in sleep items of the Hamilton Depression Rating Scale at the beginning (T0) and after 3 months of an unchanged treatment (T3).

**Findings/Results:** Patients with TRD/PD+ and TRD/PD− taking quetiapine showed significant improvement in sleep items from T0 to T3 ($P < 0.001$, $\eta_p^2 \geq 0.19$). There was a significant personality × time interaction for sleep-maintenance insomnia ($P = 0.006$, $\eta_p^2 = 0.23$), with TRD/PD+ showing a greater improvement at T3 compared with TRD/PD− ($P = 0.01$). While exploring other sleep items, no personality × time interaction was found. In the TRD/PD− group, improvement in sleep items was associated with an overall improvement in depressive symptoms ($r = 0.55$, $P = 0.02$).

**Implications/Conclusions:** Quetiapine induced greater improvements in sleep-maintenance insomnia among TRD/PD+ patients than TRD/PD−. These findings suggest quetiapine could have a therapeutic role for insomnia in PD underscoring a distinct underlying neurobiological mechanism of sleep disturbance in people living with PD.

**Key Words:** antidepressants, antipsychotics, insomnia, major depressive disorder, mood stabilizers, personality disorder, sleep, treatment-resistant depression

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Quetiapine, a 5-$HT_{2A}$, 5-$HT_{2C}$, $H_1$, and $D_2$ antagonist,[1] is a first-line augmentation agent for treatment-resistant depression (TRD).[2] Quetiapine's antidepressant activity is mediated, at least in part, by its active metabolite norquetiapine, which selectively inhibits NET reuptake, and acts as an antagonist at presynaptic $\alpha_2$, 5-$HT_{2C}$, and 5-$HT_7$ receptors.[3] Quetiapine has shown efficacy in treating insomnia symptoms/insomnia disorder comorbid to mood disorders due to its sedative effects, mostly acting via central histamine $H_1$ receptor blockade.[1,4] Improving sleep symptoms has shown a substantial benefit to depressive outcomes, although it can be challenging in patients with comorbid TRD and personality disorder (PD).[5–9] Despite a number of similarities with the pattern of sleep disturbance seen in depressive disorders and in PD,[10] several studies underscored specific cognitive and behavioral processes typical of PD, which may contribute to a disturbed sleep pattern.[11,12] Consequently, treatment approaches cannot be assumed to translate in the presence or absence of PD comorbidity.

Disturbed sleep is independently associated with a number of core symptoms of borderline PD such as emotional dysregulation,[13] impulsivity,[14] self-injurious behaviors,[15] and drug use,[16] as well as having an impact on quality of life.[17] These factors have been associated with overall poor outcomes and reduced recovery from PD over time.[18] Despite an emerging literature emphasizing the importance of improving the sleep quality of people with PD, very few studies have characterized its effect on treatment outcomes. The evidence on whether antipsychotic or mood-stabilizing medications do improve the quality of sleep of people with PD seems limited to a single positive experimental study of carbamazepine with a very short follow-up period.[19] A small pool of studies has studied the effects of other agents, including doxazosin[20] and clonidine,[21] on sleep outcomes in PD, but to date, no study has explored whether changes in sleep quality with these agents can be explained by improvement in comorbid mental health disorders. Our previous study in the same population suggests the benefits to insomnia associated with quetiapine augmentation in patients with TRD.[22] This present analysis therefore aims to test whether (i) quetiapine augmentation for TRD improves sleep quality in patients with comorbid PD and (ii) if the improvement in sleep quality for patients with PD is independent of improvements in depressive symptoms.

## METHODS

This retrospective study was approved by the institutional review board of the Research Institute of the McGill University Health Center (institutional review board no. 2020-6323) and was conducted from 2015 to 2020, in accordance with the Declaration of Helsinki and ICH Good Clinical Practice. Data were retrieved from a research database containing information systematically collected on patients followed at the Mood Disorders Clinic of the McGill University Health Center for ≥2 years (mean, 7.5 years). Written informed consent was not required as data were obtained by chart review. Diagnoses of major depressive disorder (MDD) and comorbidities were confirmed by the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*), as well as thorough clinical interviews by experienced mood disorder specialists and research coordinators. Personality disorders were diagnosed based exclusively on clinical interviews under *DSM-IV* criteria.[23] To align with the

From the [1]Department of Psychiatry, McGill University, Montreal, Quebec, Canada; [2]Division of Psychiatry, Imperial College, London, United Kingdom; Departments of [3]Pharmaceutical and Pharmacological Sciences; [4]Biomedical Sciences, University of Padova, Padova, Italy; and [5]McGill University Health Center, Montreal, Quebec, Canada.

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Address correspondence to: Gabriella Gobbi, MD, PhD, Neurobiological Psychiatry Unit, Room 220, 1033 Pine Ave West, McGill University, Montreal, Quebec, Canada H3A 1A1 (e-mail: gabriella.gobbi@mcgill.ca).

N.N. is now with the Department of Psychiatry and Psychology, Mayo Clinic, Rochester, MN.

C.M. and J.D.K. have contributed equally to this study.

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*International Classification of Diseases, Eleventh Revision* criteria, patients in the study were classified as having a PD (PD+) or not (PD−).[24] Patients with a mixed episode or with a neurological/developmental disorder and/or a mood disorder secondary to a medical condition were excluded. The Maudsley Staging Method was used to establish the severity of the TRD patients.[25] Some of the patients had been included in previous studies.[26–28]

## Patients

Charts of 206 patients meeting the *DSM-IV* criteria for a major depressive episode for ≥2 months were reviewed.[23] Seventy-six patients met the criteria for TRD, defined as a failure of ≥2 pharmacological trials with different antidepressants in monotherapy or combination therapy at an adequate dose for ≥3 weeks.[29] Of those, 38 patients were subsequently augmented with quetiapine. All patients had a mild to severe major depressive episode, suggested by a score of ≥13 on the Hamilton Rating Scale for Depression (HAMD-17) and a score of ≥20 on the Montgomery-Åsberg Depression Rating Scale (MADRS) based on cutoff values proposed by Zimmerman et al.[30] Patients were treated with augmentation strategies, which included antidepressants with mood stabilizers, antipsychotics, or both.

## Clinical Evaluation

Chart analysis was performed by 2 authors (N.A.N. and G. G.) and evaluated at baseline, before the beginning (T0), and after at least 3 months of an unchanged pharmacological treatment (T3). At T0 and T3, patients were assessed on the following behavioral scales: HAMD-17,[31] MADRS,[32] the Quick Inventory of Depressive Symptomatology[33] (QIDS-C16), and the Clinical Global Impression—Severity of Illness[33] (CGI-S). Response was defined as a ≥50% reduction from the pretreatment in the HAMD-17 score. Remission was defined as a score <7 of the HAMD-17 at the end point (T3). Our primary outcome of interest was sleep quality as measured by the 3 sleep items of the clinician-rated HAMD-17 relating to early, middle, and late-night insomnia symptoms each scored between 0 and 2, where 0 represents no disturbance. This approach has demonstrated a strong correlation with sleep diaries.[34] We also combined these scores in an additive manner and calculated the Total Sleep Score (TSS).[35] Our secondary outcome was sleep quality as measured by the 4 sleep items of the QIDS-C16.

## Reliability and Interrater Agreement for Psychometric Scales

The internal consistency was previously assessed utilizing Cronbach $\alpha$, and an acceptable reliability was found for all scales (HAMD-17: $\alpha = 0.82$, QIDS-C16: $\alpha = 0.77$).[26] Interrater reliability was previously assessed using Cohen $\kappa$[27,36] on a sample of 140 patients[26] with a moderate to good agreement for all behavioral scales (HAMD-17: $\kappa = 0.58$, QIDS-C16: $\kappa = 0.61$, CGI-S: $\kappa = 0.72$).

## Sample Size

In our sample of 76 patients meeting the criteria for TRD, we wished to assess the effects of psychotropic drugs on sleep in the presence or absence of PD. We thus performed a sample size calculation to estimate the numbers needed to detect a clinically meaningful difference in sleep quality. A drop in a score by 1 point on the TSS (a summation of 3 sleep items from the HAMD) equated to an individual who had complained of difficulty in falling to sleep every night, subsequently reporting only occasional difficulty. A sample size of 36 would give us power to detect a difference of 1 point on the 6-point TSS between the 2 groups. Only augmentation with quetiapine met this number of participants, as 38 patients were augmented with quetiapine.

## Statistical Analyses

Group comparisons on patients' demographics were computed through the Pearson $\chi^2$ test or by Fisher exact test (if n ≤ 5 in each subgroup). Changes in scales were analyzed using repeated-measures analysis of variance (ANOVA) with the presence of PD as a between-subject factor and time as a within-subject factor, followed by Tukey post hoc analyses. Effect sizes are reported for ANOVA (partial $\eta^2$ [$\eta^2_p$]). Small, medium, and large effect sizes were taken as 0.01, 0.06, and 0.14 for $\eta^2_p$, respectively.[37] Correlations between scales were computed with Pearson test; weak correlation was taken as $r < 0.4$, moderate as <0.7, and strong correlation ≥0.7.[37] Analyses were performed using R Statistical Software.[38] Significance was set at $P < 0.05$. Data are presented as mean ± SD, except when specified otherwise.

# RESULTS

## Participants

Thirty-eight patients were included in the study (aged 50.24 ± 11.84 years; Table 1). Personality disorder was present in a majority (n = 20 [53%]) of our cohort of patients with TRD. Pharmacotherapies are detailed in Table 2. At T0, TRD/PD+ and TRD/PD− had a moderate/severe depression (HAMD-17: 23.6 ± 6.2 and 22.4 ± 6.1, respectively). On average, patients with TRD/PD+ received higher doses of quetiapine compared with TRD/PD− patients, although this difference was not statistically significant ($P = 0.50$). Further characteristics of this sample are reported in previous studies.[22,26,27]

## Response and Remission

Response and remission rates of TRD/PD+ and TRD/PD− did not differ significantly between the 2 groups ($P \geq 0.28$; Table 3). Of note, no suicide attempt or suicidal behavior occurred during the 3-month follow-up of the patients.

## Clinical Outcomes in TRD/PD+ Versus TRD/PD−

For the HAMD-17, 2-way repeated-measures ANOVA indicated a significant main effect of time ($F_{1,32} = 86.30$, $P < 0.001$, $\eta^2_p = 0.73$). There was no main effect of PD ($F_{1,36} = 0.01$, $P = 0.96$, $\eta^2_p = 0.01$) or PD × time interaction ($F_{1,32} = 2.66$, $P = 0.11$, $\eta^2_p = 0.08$). For the MADRS, 2-way repeated-measures ANOVA indicated a significant main effect of time ($F_{1,32} = 85.72$, $P < 0.001$, $\eta^2_p = 0.73$). There was no main effect of PD ($F_{1,36} = 0.79$, $P = 0.38$, $\eta^2_p = 0.02$) or PD × time interaction ($F_{1,32} = 0.42$, $P = 0.51$, $\eta^2_p = 0.08$).

## Improvement in Sleep Items of the HAMD-17 in TRD/PD+ Versus TRD/PD−

At T0, the TSSs of TRD/PD+ and TRD/PD− were comparable. In Figure 1, we compared 3-month changes in sleep items of the HAMD-17 in TRD/PD+ and TRD/PD−. Two-way repeated-measures ANOVA indicated a significant main effect of time for TSS ($F_{1,32} = 24.61$, $P < 0.001$, $\eta^2_p = 0.45$) and a significant PD × time interaction ($F_{1,32} = 4.07$, $P = 0.05$, $\eta^2_p = 0.12$). Tukey post hoc analyses revealed group differences were marginal at T3 ($P = 0.07$). The main effect of group also approached significance ($F_{1,33} = 3.18$, $P = 0.08$, $\eta^2_p = 0.09$). As shown in Supplementary Figure 1 (http://links.lww.com/JCP/A884), the observed differences in the effects of quetiapine on sleep seem to be independent of the dose of quetiapine. Observed differences in the effects of quetiapine on

**TABLE 1.** Demographic and Psychiatric Measures of People With TRD/PD– and TRD/PD+ at T0

| Characteristics | Overall (N = 38)* | TRD/PD− (n = 18)* | TRD/PD+ (n = 20)* | $P^{\dagger}$ |
|---|---|---|---|---|
| Age | 50 (±12) | 51 (±13) | 50 (±11) | 0.6 |
| Sex | | | | 0.3 |
| Men | 18 (47%) | 10 (56%) | 8 (40%) | |
| Women | 20 (53%) | 8 (44%) | 12 (60%) | |
| Born in Canada | 23 (61%) | 11 (61%) | 12 (60%) | >0.9 |
| Duration of illness, y | 15 (±14) | 16 (±16) | 15 (±13) | 0.7 |
| PD‡ | | | | N/A |
| Cluster A | 2 (5%) | 0 | 2 (10%) | |
| Cluster B | 10 (26%) | 0 | 10 (50%) | |
| Cluster C | 10 (26%) | 0 | 10 (50%) | |
| No. of suicide attempts | 0.39 (±0.68) | 0.33 (±0.69) | 0.45 (±0.69) | 0.5 |
| Comorbid substance-use disorder | 7 (18%) | 3 (17%) | 4 (20%) | >0.9 |
| Comorbid anxiety disorder | 23 (61%) | 10 (56%) | 13 (65%) | 0.6 |
| Cognitive behavioral therapy | 7 (41%) | 3 (50%) | 4 (36%) | 0.6 |
| No. of medications | 4.81 (±2.40) | 5.00 (±1.66) | 4.65 (±2.92) | 0.2 |
| Quetiapine dose, mg | 124 (±151) | 81 (±69) | 163 (±192) | 0.5 |
| HAMD-17 | 23.0 (±6.1) | 22.4 (±6.1) | 23.6 (±6.2) | 0.6 |
| TSS | 3.29 (±1.52) | 3.39 (±1.75) | 3.20 (±1.32) | 0.5 |
| Sleep onset insomnia | 1.37 (±0.59) | 1.33 (±0.69) | 1.40 (±0.50) | >0.9 |
| Midnocturnal insomnia | 1.34 (±0.58) | 1.33 (±0.69) | 1.35 (±0.49) | >0.9 |
| Early morning insomnia | 0.58 (±0.68) | 0.72 (±0.67) | 0.45 (±0.69) | 0.2 |
| MADRS | 30 (±9) | 29 (±8) | 31 (±9) | 0.3 |
| CGI-S | 5.03 (±1.17) | 4.94 (±1.16) | 5.10 (±1.21) | 0.8 |
| QIDS-C16 | 14.2 (±3.9) | 13.7 (±3.7) | 14.7 (±4.1) | 0.6 |
| Sleep onset insomnia | 1.29 (±0.98) | 1.20 (±0.83) | 1.39 (±1.14) | 0.7 |
| Midnocturnal insomnia | 1.37 (±1.08) | 1.45 (±1.00) | 1.28 (±1.18) | 0.6 |
| Early morning insomnia | 0.79 (±0.93) | 0.80 (±0.89) | 0.78 (±1.00) | 0.8 |
| Hypersomnia | 0.05 (±0.23) | 0.10 (±0.31) | 0.00 (±0.00) | 0.2 |

*Mean (±SD); n (%).

†Wilcoxon rank sum test, Pearson $\chi^2$ test, Fisher exact test.

‡Some participants had multiple PD diagnoses.

sleep also appear independent of the type of PD. Although our study was not powered to perform statistical analyses on those subgroups, on average, changes in TSS were similar between cluster A/C PD (1.67 ± 1.37) and cluster B PD (1.75 ± 1.58).

We then analyzed separately the 3 sleep items of the clinician-rated HAMD-17 and found that, for sleep-onset insomnia, there was a significant main effect of time ($F_{1,32}$ = 19.80, $P < 0.001$, $\eta^2_p = 0.40$), but PD × time interaction ($F_{1,30}$ = 1.88, $P = 0.18$, $\eta^2_p = 0.06$) and the main effect ($F_{1,30} = 0.18$, $P = 0.66$, $\eta^2_p = 0.06$) of groups were not significant.

Two-way repeated-measures ANOVA indicated a significant main effect of time for sleep-maintenance insomnia ($F_{1,32} = 19.50$, $P < 0.001$, $\eta^2_p = 0.41$) and a significant PD × time interaction ($F_{1,32} = 8.65$, $P = 0.006$, $\eta^2_p = 0.23$). Tukey post hoc analyses revealed significant group differences at T3 ($P = 0.01$), and the main effect of group was marginal ($F_{1,33} = 3.90$, $P = 0.08$, $\eta^2_p = 0.11$).

Concerning the early morning awakening item, 2-way repeated-measures ANOVA indicated a significant main effect of time ($F_{1,32} = 8.06$, $P = 0.007$, $\eta^2_p = 0.19$). The main effect of group approached significance ($F_{1,33}$ = 3.87, $P$ = 0.056, $\eta^2_p = 0.09$). Personality disorder × time interaction was not significant ($F_{1,32} = 0.27$, $P = 0.060$, $\eta^2_p = 0.01$).

Finally, there was a moderately positive relationship between improvements in sleep quality and depressive symptoms among those in the TRD/PD− group ($r$ = 0.55 for HAMD-17, and $r = 0.53$ for MADRS; Table 4), but this correlation was not present in TRD/PD+. Of note, quetiapine dose was not associated with improvement in TSS in both groups ($P > 0.05$).

## Improvement in Sleep Items of the QIDS-C16 in TRD/PD+ Versus TRD/PD–

At T0, the QIDS items of TRD/PD+ and TRD/PD− were comparable. In Figure 2, we compared 3-month changes in individual sleep items of the QIDS-C16 in TRD/PD+ and TRD/PD−.

For sleep-onset insomnia, there was a significant main effect of time ($F_{1,32} = 23.18$, $P < 0.001$, $\eta^2_p = 0.42$), but PD × time interaction ($F_{1,30}$ = 0.51, $P$ = 0.47, $\eta^2_p$ = 0.02) and the main effect ($F_{1,30} = 1.01$, $P = 0.30$ $\eta^2_p = 0.03$) of groups were not significant.

Two-way repeated-measures ANOVA indicated a significant main effect of time for sleep-maintenance insomnia ($F_{1,32} = 6.54$, $P = 0.02$, $\eta^2_p = 0.16$) and a PD × time interaction approaching significance ($F_{1,32} = 3.72$, $P = 0.06$, $\eta^2_p = 0.10$). The main effect of group was not significant ($F_{1,33} = 0.33$, $P = 0.56$, $\eta^2_p < 0.001$).

Concerning the early morning awakening item, 2-way repeated-measures ANOVA indicated a significant main effect of time ($F_{1,32} = 11.54$, $P = 0.001$, $\eta^2_p = 0.27$). Personality disorder × time interaction ($F_{1,32} = 1.05$, $P = 0.31$, $\eta^2_p = 0.03$) and the

**TABLE 2.** Pharmacotherapy of the Included Patients (N = 38)

TRD/PD− (n = 18)
Bupropion 300 mg + quetiapine 50 mg + lamotrigine 200 mg
Bupropion 150 mg + quetiapine 50 mg + lamotrigine 25 mg
Citalopram 20 mg + quetiapine 150 mg
Clomipramine 25 mg + quetiapine 100 mg
Duloxetine 30 mg + quetiapine 150 mg + valproic acid 250 mg
Duloxetine 60 mg + quetiapine 50 mg + topiramate 25 mg
Duloxetine 60 mg + quetiapine 75 mg
Escitalopram 20 mg + mirtazapine 30 mg + quetiapine 25 mg
Escitalopram 10 mg + clomipramine 25 mg + quetiapine 150 mg
Escitalopram 10 mg + quetiapine 50 mg + lamotrigine 100 mg + lithium 300 mg + valproic acid 500 mg
Mirtazapine 30 mg + quetiapine 50 mg
Sertraline 75 mg + trazodone 100 mg + quetiapine 50 mg
Sertraline 100 mg + quetiapine 50 mg + gabapentin 600 mg
Sertraline 150 mg + bupropion 150 mg + quetiapine 25 mg
Venlafaxine 37.5 mg + quetiapine 25 mg
Venlafaxine 75 mg + olanzapine 5 mg + quetiapine 300 mg + lithium 300 mg
Venlafaxine 150 mg + quetiapine 50 mg
Venlafaxine 187.5 mg + bupropion 150 mg + quetiapine 50 mg

TRD/PD+ (n = 20)
Bupropion 150 mg + quetiapine 300 mg + gabapentin 300 mg + valproic acid 125 mg
Citalopram 20 mg + mirtazapine 30 mg + quetiapine 100 mg
Citalopram 20 mg + mirtazapine 60 mg + quetiapine 100 mg
Citalopram 20 mg + quetiapine 50 mg + valproic acid 250 mg
Citalopram 10 mg + quetiapine 25 mg + valproic acid 1000 mg
Desvenlafaxine 50 mg + bupropion 300 mg + quetiapine 150 mg
Duloxetine 60 mg + quetiapine 100 mg + valproic acid 250 mg
Escitalopram 10 mg + quetiapine 50 mg + gabapentin 300 mg
Fluoxetine 20 mg + bupropion 150 mg + mirtazapine 15 mg + aripiprazole 2 mg + quetiapine 25 mg
Fluvoxamine 50 mg + venlafaxine 75 mg + quetiapine 200 mg
Sertraline 200 mg + quetiapine 50 mg
Venlafaxine 225 mg + quetiapine 650 mg
Venlafaxine 262.5 mg + amitriptyline 125 mg + mirtazapine 15 mg + quetiapine 400 mg + risperidone 1 mg
Venlafaxine 300 mg + aripiprazole 2 mg + quetiapine 50 mg + valproic acid 250 mg
Venlafaxine 300 mg + quetiapine 600 mg + gabapentin 900 mg
Venlafaxine 37.5 mg + quetiapine 25 mg
Venlafaxine 150 mg + bupropion 300 mg + quetiapine 50 mg
Venlafaxine 150 mg + bupropion 150 mg + quetiapine 300 mg
Venlafaxine 150 mg + quetiapine 12.5 mg + topiramate 25 mg + valproic acid 125 mg
Venlafaxine 150 mg + quetiapine 25 mg

Antidepressants, antipsychotics, and mood stabilizers prescribed to patients.

**TABLE 3.** Response and Remission Rates of Patients With and Without PD

| Scale | | Overall (N = 38)* | TRD/PD− (n = 18)* | TRD/PD+ (n = 20)* | $P^{\dagger}$ |
|---|---|---|---|---|---|
| HAMD-17 | Response | 8 (21%) | 4 (22%) | 4 (20%) | >0.9 |
| | Remission | 3 (7.9%) | 2 (11%) | 1 (5.0%) | 0.6 |
| MADRS | Response | 11 (29%) | 7 (39%) | 4 (20%) | 0.2 |
| | Remission | 3 (7.9%) | 1 (5.6%) | 2 (10%) | >0.9 |

*n (%).
†Fisher exact test, Pearson $\chi^2$ test.

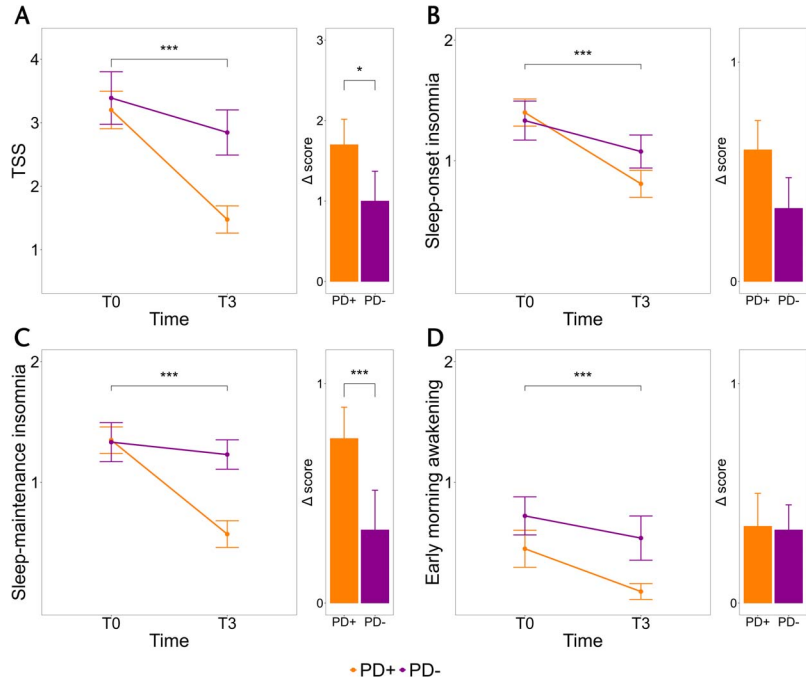


**FIGURE 1.** Changes in sleep items of the HAMD-17 in patients with TRD/PD+ (n = 20) versus TRD/PD– (n = 18) treated with quetiapine. Two-way ANOVAs with PD as between-subject factor and time as a within-subject factor, followed by Tukey post hoc analyses. Δ Scores are reported for TRD/PD+ and TRD/PD– (mean within-group change from T0 to T3). *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. TSS= Total Sleep Score.

main effect of group were not significant ($F_{1,33} = 0.23$, $P = 0.62$, $\eta_p^2 < 0.001$).

Concerning the hypersomnolence item, 2-way repeated-measures ANOVA indicated a trend

PD × time interaction ($F_{1,32} = 3.46$, $P = 0.07$, $\eta_p^2 = 0.05$). The main effects of time ($F_{1,32} = 0.16$, $P = 0.70$, $\eta_p^2 < 0.001$) and group were not significant ($F_{1,33} = 0.15$, $P = 0.70$, $\eta_p^2 < 0.001$).

## DISCUSSION

This is the first study to our knowledge to examine the differential benefits of quetiapine on the sleep quality of depressed patients with and without PD. In TRD patients augmented with quetiapine, there were greater improvements in sleep quality among TRD/PD+ patients compared with TRD/PD− patients, mostly explained by greater improvements in sleep maintenance. Furthermore, changes in sleep quality were moderately associated with changes in depressive scores in TRD/PD−, but not associated in TRD/PD+. These results might suggest alternative mechanisms of benefit from quetiapine on sleep quality depending on the presence of PD comorbidity. Our results are unlikely to be solely explained by the variability of the dosage as (1) we did not find an association between quetiapine dose and changes in TSS; (2) although TRD/PD+ patients received on average higher doses of quetiapine, there was a trend for more hypersomnia in TRD/PD− patients; (3) low doses of quetiapine are known to be sufficient to impact sleep[39–41]; and (4) a recent meta-analysis found no dose-response pattern of quetiapine for sleep improvement.[42]

Quetiapine is the most used off-label drug for insomnia treatment.[42] Most studies evaluating the effects of quetiapine on sleep seem to be based on the obsolete nomenclature separating primary insomnia from secondary insomnia, such as insomnia comorbid with depression. A systematic review[43] found only 1 randomized clinical trial of quetiapine for primary insomnia[44] and concluded that there was very low-quality evidence that quetiapine does not improve sleep parameters compared with placebo. However, in a pooled analysis of 4 randomized studies, Trivedi et al[45] found that quetiapine XR (50–300 mg/d) monotherapy improved symptoms of sleep disturbance versus placebo in patients with MDD. Some evidence also points toward the effectiveness of augmenting antidepressant medications with quetiapine to treat insomnia symptoms. As emphasized in a recent meta-analysis, low doses of quetiapine are generally sufficient to improve sleep, and a rapid onset of action is generally observed.[42] The combination of quetiapine (25–100 mg) and fluoxetine improved sleep over fluoxetine alone in 114 patients with MDD.[46] Likewise, in a randomized clinical trial evaluating the effects of adjunct quetiapine in patients with MDD and an inadequate response to ongoing antidepressant therapy, Bauer et al[35] found adjunct quetiapine XR (150–300 mg) improved sleep disturbance and quality compared with placebo. In a 20-week open trial with quetiapine (315 ± 109 mg, flexible dose), 14 patients with TRD

**TABLE 4.** Correlations (*R*) Between Age, Quetiapine Dose, and Changes (Δ) in TSS, HAMD, and MADRS Scores From T0 to T3

| | Δ HAMD-17 | Δ MADRS | Age | Quetiapine Dose |
|---|---|---|---|---|
| TRD/PD+ | | | | |
| Δ TSS | 0.37 | 0.40 | −0.41 | −0.29 |
| Δ HAMD-17 | — | 0.90* | 0.12 | −0.22 |
| Δ MADRS | — | — | 0.06 | −0.23 |
| TRD/PD− | | | | |
| Δ TSS | 0.55† | 0.53† | 0.14 | 0.02 |
| Δ HAMD-17 | — | 0.91* | 0.21 | 0.05 |
| Δ MADRS | — | — | 0.16 | 0.01 |

*$P < 0.001$.
†$P < 0.05$.

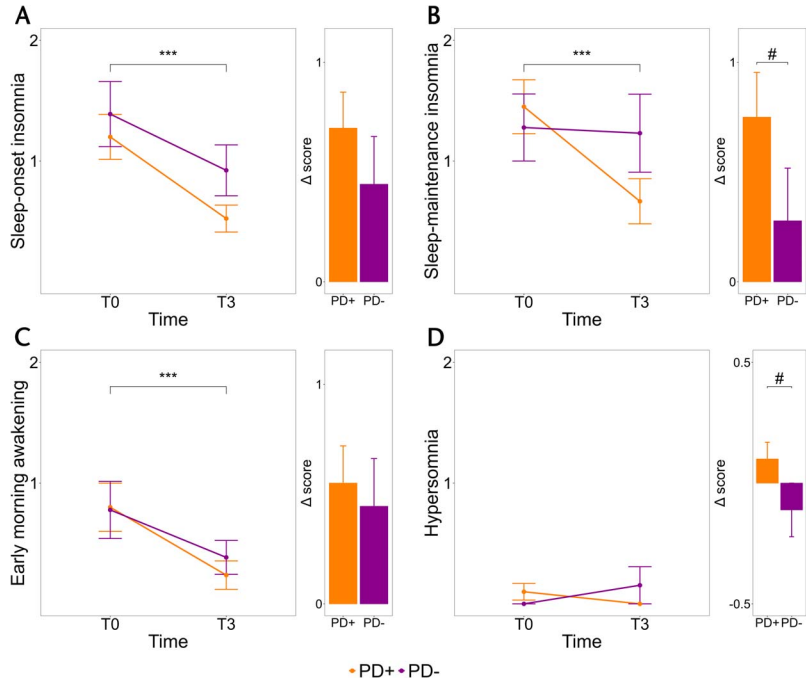


**FIGURE 2.** Changes in sleep items of the QIDS-C16 in patients with TRD/PD+ (n = 20) versus TRD/PD– (n = 18) treated with quetiapine. Two-way ANOVAs with PD as between-subject factor and time as a within-subject factor, followed by Tukey post hoc analyses. Δ Scores are reported for TRD/PD+ and TRD/PD– (mean within-group change from T0 to T3). #$P < 0.1$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

showed a decrease of more than 4 points on the TSS at their first time of measurement (eg, after only 2 weeks of treatment).[47] Although PD is among the most common comorbid psychiatric conditions in TRD, none of these studies reported on participants with both TRD and PD.[48–50] Our study supports previous studies showing that a pharmacotherapy including quetiapine can improve subjective sleep in TRD independently of the presence of PD or not.

However, we found a greater improvement of sleep quality in TRD/PD+ compared with TRD/PD− treated with a pharmacotherapy, which included quetiapine. We hypothesize that the greater improvement of sleep quality in TRD/PD+ may be due to the modulation of emotional dysregulation by quetiapine in PD. Indeed, emotional and cognitive arousal contributes to the pathophysiology of insomnia in PD,[16] and a bidirectional relationship between sleep deprivation and emotional dysregulation is well established.[16,51] In parallel, some evidence suggests that quetiapine can decrease emotional dysregulation in PD, as it was shown to reduce self-harm,[52] psychological distress,[53] and the overall severity of borderline PD symptoms.[54] Reducing emotional dysregulation could therefore improve sleep preferentially in the presence of comorbid PD. In addition to its sedative antihistaminergic properties, quetiapine is an antagonist of 5-$HT_{2A}$, 5-$HT_{2C}$, and $D_2$.[1] Moreover, the active metabolite norquetiapine selectively inhibits NET reuptake, is a partial 5-$HT_{1A}$ receptor agonist, and acts as an antagonist at presynaptic $\alpha_2$, 5-$HT_{2C}$, and 5-$HT_7$ receptors.[3] Activation of these particular receptors may also be the neurobiological explanation on the effects of quetiapine not only in major depression but also in the regulation of emotions and sleep in PD. Indeed, 5-$HT_{2A}$ dysfunction has been identified in PD,[55,56] including increased receptor binding in the hippocampus[55,57] and increased number of platelet receptors in PD compared with controls.[58] Genetic studies also suggested 5-$HT_{2C}$ may play a role in the susceptibility to PD,[59] which supports findings in animal models for impulsivity.[60] 5-$HT_{1A}$ receptors play a critical role not only in the pathogenesis of depression and its treatment,[61] but also in PD, where a low 5-$HT_{1A}$ sensitivity was found after the flesinoxan challenge,[62] along with the 5-$HT_{1A}$ genetic polymorphism.[63] Other contributing factors of norquetiapine to the PD regulation could relate to the antagonism over the 5-$HT_7$ receptor, highly implicated in emotional regulations and impulsivity,[64] as well as the norepinephrine reuptake, which is known to regulate rapid eye movement sleep, cognition,[65] and impulsivity.[66]

Sleep disturbances specific to PD were previously reported in the literature, and a study found that sleep disturbances are mediated by the presence of PD, even while controlling for substance dependence and depression.[67] Polysomnographic (PSG) studies also point toward neurobiological differences between TRD/PD+ and TRD/PD−. De la Fuente et al[68] showed sleep architecture differences between patients with MDD (PD−) and PD (MDD−), including increased rapid eye movement and decreased slow wave sleep in the PD compared with the MDD group. The same group found that PD patients had less slow wave activity than patients with MDD and suggested PD might have a biological substrate that is different from those having a depressive disorder without comorbid PD.[69] Another PSG study showed no differences between MDD patients with or without PD, but medication use was not reported and might have mitigated differences between the groups.[70] Development of tailored interventions for insomnia in PD is needed, given the differences in biopsychosocial factors predisposing, precipitating, and perpetuating the insomnia complaints.[71]

Another finding indirectly supporting differences in the etiology of insomnia in PD is the differential association between depressive symptoms and sleep disturbances between groups. There was a significant association between the improvement of the TSS and other depression items in TRD/PD−, which is in line with the antidepressant-augmenting properties of quetiapine. Such association was not found in TRD/PD+ and suggests that the effects on sleep could be mediated by another factor, such as emotional

regulation. The existence of a differential effect of quetiapine based on the subtype of PD remains to be eluted. Nonetheless, we did not obtain a clear signal that a specific cluster of PD was benefiting more than others. Our findings also emphasize the specific challenges associated with the management of insomnia in patients with TRD/PD−. Although there was a statistically significant improvement of sleep disturbance from T0 to T3 in the TRD/PD− group, the clinical improvement remained marginal. Our results align with the current paradigm that the pharmacological treatment of insomnia is separated from that of treating depression. Accordingly, insomnia symptoms persisted in most participants achieving remission of depression in the STAR*D trial.[6]

Although we found a distinct clinical improvement on the severity of sleep disturbances according to the presence of PD, we did not observe overall difference in their response or remission rates between groups. Such outcomes should be viewed considering the long period required to achieve remission in TRD.[72] The observed low rates of remission indeed reflect the refractory nature of patients included in this study. However, no suicide or suicide attempts were reported during the study follow-up underscoring that, even if the pharmacological combinations did not lead to remission within 3 months, they may be significant in certain depressive domains such as preventing suicidal behaviors.

Interestingly, the sleep improvement in TRD/PD+ was significant after 3 months, compared with TRD/PD−. Sleep is regulated by a homeostatic mechanism, which is rapidly regulated by hypnotics, but also by a circadian rhythm regulation.[1] It is possible that the impaired circadian regulation of sleep requires longer time to recover, especially in PDs. In confirmation of this hypothesis, recent evidence suggests that circadian rhythm disturbance is a common unaddressed feature of borderline PD, and circadian rhythm restoration may be a target for the therapeutics of PDs.[73]

## Limitations

Several limitations should be considered while interpreting these findings. First, we did not collect information on other potentially mediating factors associated with both PD presence and sleep quality, including nightmares and other environmental factors, which might have changed over time. Second, we did not match the sample of TRD/PD+ and TRD/PD− patients according to single pharmacological agents or dosages (including quetiapine), nor to depressive severity. Third, this study lacks objective measures of sleep (such as PSG or actigraphy), and our assessment of subjective sleep was limited to the HAMD and QIDS items. However, these items have shown in a previous study a significant correlation with sleep diaries.[34] There was no measure of daytime sleepiness, which was previously reported to be improved by quetiapine in a similar sample.[74] Fourth, the nonblinded retrospective outcome assessments should be considered, as well as the limitations of a naturalistic design study. Nevertheless, these findings may reflect real-world interactions of clinically selected pharmacotherapies, as clinical treatment was individualized and adjusted to tolerability to favor patients' preference and positive clinical outcomes.[2,75] The long follow-up of patients at the clinic also prevents the inclusion of undiagnosed bipolar affective disorder patients in our sample.[76]

## CONCLUSIONS

In this clinical sample of patients with TRD, augmentation with quetiapine induced a greater reduction of sleep-maintenance insomnia in comorbid PD compared with people with TRD alone. Moreover, the sleep of patients with TRD improved instep with their recovery from depressive symptomatology; this was not found among people with co-occurring PD. Altogether, these findings underscore differences in the biological mechanism and pathophysiology, which perpetuate disturbed sleep among people with a PD. Further work on this topic is likely to improve the understanding of the factors associated with sleep disturbance among patients with affective disorders and PD. Our results emphasize the need to evaluate and potentially adapt or rethink sleep interventions specific to patients with PD, depressive symptoms, and insomnia.

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## AUTHOR DISCLOSURE INFORMATION

*The authors declare no conflicts of interest.*

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