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# Self-reported obstructive sleep apnea is associated with nonresponse to antidepressant pharmacotherapy in late-life depression

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## Abstract

**Background—**Obstructive sleep apnea (OSA) is frequently comorbid with late-life depression. The purpose of this project was to determine, using a sample of older adults with major depressive disorder, whether patient-reported diagnosis of OSA was associated with rate of response to venlafaxine.

**Methods—**Participants from this multisite study were adults ≥60 years old ($n$ = 468) with major depressive disorder and a Montgomery Asberg Depression Rating Scale (MADRS) score of ≥15. Depression response was the outcome variable, defined as a MADRS score of ≤10 for two consecutive assessments at the end of 12 weeks of open-label treatment with venlafaxine 300 mg/day. To assess OSA, participants were asked if they had been diagnosed with OSA using polysomnography.

**Results—**Eighty participants (17.1%) reported a diagnosis of OSA prior to baseline. Participants with OSA were more likely to be male, report greater impairment on measures of health, experience a longer duration of the index episode, and receive an adequate antidepressant trial prior to entering the study. During the 12 weeks of treatment, 40.8% responded to treatment with venlafaxine (43.6%, $n$ = 169/388 of the no OSA group, and 27.5%, $n$ = 22/80 of the OSA group). Participants without OSA were 1.79 times more likely to respond to treatment (HR: 1.79 [95%CI: 1.13–2.86], $P$ < .05) compared to those with OSA.

**Conclusions—**OSA may impair response to antidepressant pharmacotherapy in depressed older adults. Future studies of antidepressant response rates among depressed older adults with OSA should both prospectively diagnose OSA and monitor adherence to treatments such as continuous positive airway pressure.

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**Keywords**

antidepressant; depression; geriatrics; obstructive sleep apnea; response

## 1 | INTRODUCTION

Older adults often respond to antidepressant pharmacotherapy more slowly than younger patients (Alexopoulos et al., 1996). Complicating the treatment of late-life depression is the relatively high prevalence of medical comorbidities in this population (Lin et al., 2003). Obstructive sleep apnea (OSA) is a frequent medical "co-traveler" of late-life depression (Ejaz et al., 2011). In addition to obesity (Ong et al., 2009), age is one of the most significant risk factors for OSA, as the prevalence increases throughout life until the sixth or seventh decade (Young, Skatrud, & Peppard, 1993), where it can affect more than half of adults over 65 (Ancoli-Israel et al., 1991; Schroder & O'Hara, 2005). Besides leading to an increase or worsening of physical conditions and depression, OSA is related to excessive daytime sleepiness and cognitive impairment (Aloia et al., 2005; Ejaz et al., 2011).

Because it has been shown that middle-aged depressed patients with OSA may experience more severe and difficult to treat depression (Ejaz et al., 2011), the comorbidity of late-life depression and OSA has become a growing concern, as 17–22% of older adults in community samples, and 28–41% in clinical samples, live with both conditions (Bajpai et al., 2014). While there is some evidence that treating OSA may improve antidepressant response in middle-aged patients (Habukawa et al., 2010), it is not known if OSA in older adults affects treatment response in this vulnerable population. Thus, the aim of this project was to test, using a sample of older adults with major depressive disorder, whether patient-reported diagnosis of OSA (based on previously completed polysomnography [PSG]) was associated with response to antidepressant pharmacotherapy with venlafaxine. We hypothesized that older adults with OSA would have a decreased rate of response with venlafaxine pharmacotherapy compared to those with no reported diagnosis of OSA.

## 2 | METHODS

### 2.1 | Participants

Participants from the parent study (Lenze et al., 2015) were recruited from three sites: University of Pittsburgh, University of Toronto, and Washington University in St. Louis. Potential subjects were referred to the study by a health professional or were self-referred in response to print and radio advertisements and research registries. All patients were at least 60 years old, had a diagnosis of major depressive disorder (MDD; single or recurrent) as diagnosed by the SCID-IV, and a baseline Montgomery-Asberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979) score of ≥15. Exclusion criteria included dementia (defined as Mini Mental State Examination (MMSE) (Folstein et al., 1975) <24 and clinical symptoms of dementia), lifetime diagnosis of bipolar or psychotic spectrum disorder, abuse or dependence on alcohol or other substances within the past 3 months, high risk for suicide that was considered too challenging to manage safely within the confines of a clinical trial, or contraindication to venlafaxine XR. Participants were cleared by their

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primary care physician and all comorbid medical conditions were deemed to be under stable control prior to study entry. The methods and results of the project have been described in detail previously (Lenze et al., 2015) and are summarized below. The Institutional Review Boards from each of the three sites granted approval for the study, and all participants provided written informed consent.

## 2.2 | Assessments

**2.2.1 | Obstructive sleep apnea (OSA)—**To assess apnea, participants were asked whether they had been diagnosed with OSA using polysomnography. This information was elicited during the screening phase and was documented on the respiratory system item of the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992). Participants were also asked if they had been prescribed and/or were compliant with Continuous Positive Airway Pressure (CPAP) (or Bilevel Positive Airway Pressure (BiPAP); however, the manner in which this was assessed and recorded was not consistent across sites. No other treatments for OSA were assessed, such as position training, oral appliances, or airway surgery, and adherence to CPAP/BiPAP was not tracked during the course of the study.

**2.2.2 | Depression—**We assessed depression severity with the MADRS (Montgomery & Asberg, 1979). Assessments were administered by a trained rater and regular intersite sessions were conducted to maintain interrater reliability (intraclass correlation coefficient [ICC] = 0.997). Depression response was the outcome variable for this analysis. Response was defined as a MADRS score of ≤10 for two consecutive assessments at the end of the open-label treatment phase. Depression severity was also assessed at baseline with the 17-item Hamilton Rating Scale for Depression (HRSD-17) (Hamilton, 1960) to allow comparison of our data with data from other trials and to calculate the insomnia index (see below). Suicidal ideation was assessed with the 21-item Scale for Suicide Ideation (SSI) (Beck, Kovacs, & Weissman, 1979); a score of ≥1 indicated current suicidal ideation.

**2.2.3 | Insomnia—**The Hamilton Rating Scale for Depression (HRSD; 17-item (Hamilton, 1960)) was administered prior to treatment. The initial, middle, and delayed insomnia questions were summed to calculate an insomnia index. The possible total score range is 0 = 6. (Manber et al., 2005; Park et al., 2013).

**2.2.4 | Baseline descriptors—**Medical comorbidity was quantified with the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) (Miller et al., 1992), which rates each organ system from 0 (no problem) to 4 (end organ failure or severe functional impairment). The possible total score range is 0–52. Quality of life was measured with the 36-item Short-Form Health Survey from the Medical Outcomes Study (SF-36) (Ware & Gandek, 1998). Functioning and disability were assessed with the Late Life Function and Disability Instrument (LLFDI) (Sayers et al., 2004). The Antidepressant Treatment History Form (Oquendo et al., 2003) was used to assess the adequacy of previous trials of antidepressants or electroconvulsive therapy on a scale of 0–5, with a score ≥3 representing an adequate trial.

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The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph et al., 1998) was used to evaluate global cognitive functioning as well as delayed memory ability. Executive functioning was evaluated with the combined mean Scaled Scores of two tests (Color-Word Interference and Trail Making) on the Delis-Kaplan Executive Function System (D-KEFS) (Delis, Kaplan, & Kramer, 2001). All scores were age normed. Current or past anxiety disorders and drug or alcohol use were evaluated with the SCID.

Other pretreatment assessments focused on basic demographic information (age, sex, race, and education) and clinical variables (age at onset of first lifetime depressive episode, duration of current episode, history of substance abuse, plasma glucose, vital signs, and body mass index [BMI]).

### 2.3 | Intervention

Venlafaxine extended-release was initiated at 37.5 mg per day and titrated (in 37.5 mg increments separated by at least 3 days) to a target dose of 150 mg per day. At the end of week 6, nonresponders had their dose increased further (in 37.5 to 75 mg increments separated by at least 3 days) to a target dose of up to 300 mg/day. The dose could be reduced at any time if participants experienced adverse effects. Lorazepam (up to 2 mg/day) could be prescribed for sleep or anxiety. Participants were permitted to use other medications for sleep (zolpidem, trazodone, and low-dose nortriptyline or amitriptyline) or participate in outside psychotherapy if it had started prior to study entry and could not be discontinued. Participants were encouraged to reduce and to discontinue use of alcoholic beverages. Throughout the study, pharmacotherapy was embedded in a model of depression care management that did not incorporate any depression-specific psychotherapy (Reynolds et al., 2010). During regularly scheduled visits, the research team assessed depressive symptoms (MADRS), suicidal ideation (SSI), vital signs, and adverse effects (UKU side-effect rating scale (Lingjaerde et al., 1987)).

### 2.4 | Analysis

All data were examined for normality and transformations were used where necessary. To compare baseline characteristics of patients with and without a diagnosis of OSA, we used the multivariate analyses of variance (MANOVA) test for continuous variables and logistic regression for categorical variables. Analyses controlled for multiple comparisons and site differences. If the rate of occurrence was low for any of the categorical variables, exact logistic regression was used. For the age-normed cognitive measures, we also controlled for participant sex, education, medical burden, and depression severity.

To test the main hypothesis that obstructive sleep apnea would negatively affect response to venlafaxine treatment, formal inference was made between the apnea and no-apnea groups using Cox Proportional Hazard models controlling for site, participant sex, body mass index, medical illness (CIRS-G without the respiratory items), and depression severity (HRSD total score). Additional Cox Proportional Hazard models were examined separating the HRSD total into two components: insomnia index (sum of initial, middle, and delayed insomnia questions) and depression (sum of items without the three insomnia questions) as separate predictors because insomnia is thought to predict delayed and nonresponse to

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antidepressants. For all analyses, *P* values smaller than .05 were considered to be statistically significant. All analyses were performed using SPSS, version 24.0.

## 3 | RESULTS

Across the three sites, 1,081 potential participants were screened; 473 were excluded because of failure to satisfy exclusion/inclusion criteria; 608 provided informed consent. Of the 608, 140 participants dropped out before initiating venlafaxine treatment. Of the 468 participants who began treatment, 96 withdrew after beginning venlafaxine treatment, leaving 372 patients who completed the 12-week trial. Of the 468 participants who began venlafaxine treatment, 80 (17.1%) self-reported having received a diagnosis of OSA at some time prior to study entry, while 388 (82.9%) did not. Table 1 shows the prevalence rates across the three recruitment sites. Prevalence rates of OSA at the Pittsburgh location were significantly higher than Toronto. Washington University did not significantly differ from the other two sites.

Table 2 compares the demographic, physical, mental, and cognitive health of those with and without a baseline diagnosis of OSA Participants with OSA were more likely to be male and report greater impairment on a variety of physical health assessments. Compared to patients without OSA, those with OSA were more likely to have an elevated body mass index, higher plasma glucose levels, more medical comorbidity, and hypertension. Few differences between the groups emerged on the assessments of depression. However, those with OSA were more likely to report a longer duration of their current depressive episode, and they reported receiving an adequate antidepressant trial for their current episode of depression before entering the study. The cognitive assessments did not significantly differ between the two groups.

Table 3 shows the regression model that tested the effect of OSA status on response to treatment with venlafaxine. After 12 weeks of treatment, 40.8% ($n$ = 191/468) of patients responded to treatment with venlafaxine; 43.6% ($n$ = 169/388) of patients without OSA responded while 27.5% ($n$ = 22/80) of patients with OSA responded. Controlling for recruitment site, patient sex, body mass index, medical comorbidity (CIRS-G without respiratory item), and depressive symptoms (HRSD total score), there was a significant difference in the likelihood of response between the OSA groups. Patients without OSA were almost two times more likely to respond compared to those with OSA (HR: 1.79 [95% CI: 1.11–2.76], P < .05). Men and patients with less depressive symptom burden at baseline were also more likely to respond after 12 weeks of treatment. A second model (controlling for the same variables mentioned above) tested whether the insomnia index (three sleep items from the HRSD) was associated with response. Insomnia was not significantly associated with response (HR = 0.97 [95% CI: 0.89–1.05], $P$ = .52). A third model showed that the HRSD minus the insomnia items was significantly associated with response (HR = 0.92 [95% CI: 0.88–0.95], $P$ < .001).

Finally, we explored treatment-related side effects between the participants with and without OSA. We compared UKU scores between the two groups at week 6 (when patients had been on venlafaxine 150 mg/day for approximately 4 weeks) and at week 12 (when patients had

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been on venlafaxine 300 mg/day for approximately 4 weeks). No significant differences emerged between the groups at week 6 ($F$[1,464] = 3.22, $P$ = .07) or week 12 ($F$[1,393] = 0.45, $P$ =.51).

## 4 | DISCUSSION

In this multicenter, open-label study we observed a significant difference in older adults' antidepressant treatment response between those with and without a self-reported history of OSA. Those with a prior diagnosis of OSA were less likely to respond to 12 weeks of treatment with venlafaxine than those without a diagnosis of OSA. This finding is consistent with another study, which found that OSA may be linked with worse response to treatment with serotonin reuptake inhibitors in a mixed age population (Roest et al., 2012).

Frequent covariates of OSA that are diagnosed in mid-life include male gender, obesity, and greater medical multimorbidity (Ejaz et al., 2011). This is consistent with our observation that older participants with OSA were more likely to have hypertension, higher levels of fasting plasma glucose, and higher medical multimorbidity scores measured with the CIRS-G. The gender effect is also consistent with previous studies, with males consistently being diagnosed with OSA at higher rates than women (Young et al., 2004). This gender-related disparity, however, often diminishes with advancing age, and may reflect underreporting among women (Punjabi, 2008). While we controlled for comorbid medical burden with the CIRS-G (minus the respiratory item), gender, and depression (HRSD total score), we may not be able to attribute delayed treatment response causality to the OSA because of the high covariance among OSA and cardiovascular and metabolic comorbidities. Indeed, there are likely other related but unmeasured medical and physiologic differences which contribute to treatment nonresponse. OSA may be understood as one of several related conditions that are a marker of treatment nonresponse in late-life depression.

Other studies have described a strong association between OSA and diabetes (Ehrhardt et al., 2014; Seetho & Wilding, 2014) and cardiovascular disease (Kendzerska et al., 2014). While there was no statistically significant difference in rates of diabetes between those with and without an apnea diagnosis, this may be due to the established relationship between major depressive disorder and type 2 diabetes mellitus (Anderson et al., 2001). Because OSA is linked with these metabolic and cardiovascular conditions (Seetho & Wilding, 2014), in addition to depression, clinical care may be improved if physicians screen for OSA, especially because treatment of sleep-disordered breathing may improve management of other medical conditions such as hypertension (Denker & Cohen, 2014).

We observed that depressed older adults with comorbid OSA were more likely to experience longer episodes of depression and have been exposed to more treatments during the index episode of depression than those without OSA. Patients with OSA may have had more treatments because some of their symptoms were attributable to OSA, which may not respond to antidepressant pharmacotherapy. We did not observe a significant difference in either of the neurocognitive test scores between the apnea and no apnea groups. While there is evidence that patients with OSA have deficits in attention, memory, learning, executive functioning, and language (Andreou, Vlachos, & Makanikas, 2014), contrasting evidence

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does not support an association (Pierobon et al., 2008). Moreover, because all participants in this study were depressed, and depression in late life is associated with substantial impairments in cognition (Butters et al., 2004; Koenig et al., 2015), we may not have observed worse cognition in the OSA group because the effect of depression likely overwhelmed the effect of OSA. A more comprehensive cognitive battery that included measures of inductive and deductive reasoning and learning may have revealed cognitive differences between patients with and without OSA (Lai, Strange, & Bachman, 2012). Despite our not finding an association, it is relevant to note that Yaffe et al. (2015) recently reported an association between OSA and increased beta amyloid deposition; OSA may be both a risk factor for dementia as well as a consequence of it, just as depression can be both a risk factor for and consequence of dementia.

In addition to the likelihood of comorbid medical and physiologic conditions as well as unmeasured related medical parameters having an effect on outcome, another limitation to this project is that the data are from a larger study where the focus was not on OSA. Because the classification of OSA was dependent on patient self-report of a previous diagnosis by polysomnography, it is likely that OSA was underdiagnosed. Conducting polysomnography in study participants would likely have identified a much larger number with OSA, and could plausibly have led to even better discrimination of nonresponders. Despite this limitation, we still observed a difference in rate of response. Again, considering many patients are likely unaware of their nighttime arousals and thus do not report this to their physician (especially for those without a bed partner), they may not be appropriately referred to a sleep specialist for diagnosis. However, the prevalence rates of OSA in this sample is similar to the rates of other community samples with depression (18%) (Ohayon, 2003). Other limitations include a lack of information about: (1) how long since OSA was diagnosed; (2) adequacy or objective adherence to treatment; and (3) directional or temporal effects. For example, while it is logical to believe that those with OSA have more difficult-to-treat MDD, it is also possible that the most treatment-resistant patients are more likely to have been evaluated for OSA because their physicians are looking for any treatable comorbid diagnosis that may improve depression outcomes. This limitation could have led to an overestimation of the effect of OSA. Future studies of antidepressant response rates among patients with laboratory-confirmed diagnosis of OSA at time of study entry are needed in addition to ongoing, rigorous adherence to CPAP. There is no evidence to suggest that this is a medication class effect, or that other classes of antidepressant medications would result in superior outcomes in older patients with OSA (Brownell et al, 1982; Hanzel, Proia, & Hudgel, 1991; Veasey, 2003).

Despite these limitations, the results may still inform clinical care. If a depressed older adult reports a diagnosis of OSA based on polysomnography, the physician should consider the presence or inadequate treatment of OSA as a possible contributor to nonresponse. It may also be worth considering evaluation for OSA among depression treatment nonresponders. Physicians should not simply view sleep disturbances or excessive daytime sleepiness as a symptom of depression, but as a coexisting medical condition that requires treatment.

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## Abbreviations

| | |
|---|---|
| **BiPAP** | bilevel positive airway pressure |
| **CIRS-G** | Cumulative Illness Rating Scale for Geriatrics |
| **CPAP** | continuous positive airway pressure |
| **MADRS** | Montgomery Asberg Depression Rating Scale |
| **MDD** | major depressive disorder |
| **MMSE** | Mini Mental State Examination |
| **OSA** | obstructive sleep apnea |
| **PSG** | polysomnography |
| **SSI** | Scale for Suicide Ideation |

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**TABLE 1**

Prevalence by recruitment site

| Site | Total cohort *N* = 468 | No apnea *N* = 388 | Apnea *N* = 80 | Prevalence (%) | Significance test (controlling for site) |
|---|---|---|---|---|---|
| University of Pittsburgh | 43.0 (*n* = 201) | 40.5 (*n* = 157) | 55.0 (*n* = 44) | 21.90 | $\chi^2$ (2) = 6.2, *P* = .045 (Pittsburgh > Toronto) |
| University of Toronto | 27.1 (*n* = 127) | 28.9 (*n* = 112) | 18.8 (*n* = 15) | 11.80 | |
| Washington University | 29.9 (*n* = 140) | 30.7 (*n* = 119) | 26.3 (*n* = 21) | 15.00 | |

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## TABLE 2

Demographic and clinical characteristics of 468 participants with and without obstructive sleep apnea at baseline

| Variable | Total cohort *N* = 468 | No apnea *N* = 388 | Apnea *N* = 80 | Significance test (controlling for site) |
|---|---|---|---|---|
| Sociodemographics | | | | |
| Age (years), mean (SD) | 68.89 (7.10) | 69.10 (7.32) | 67.87 (5.92) | F(1,452) = 3.06, *P* = .08 |
| Women, no. (%) | 304 (65.0) | 260 (67.0) | 44 (55.0) | $\chi^2$ = 4.64, *P* =. 03 |
| Race, No. (%) | | | | |
| American Indian | 1 (0.21) | 1 (0.26) | 0 (0.0) | $\chi^2$ = 0.04, *P* =.84 (white vs. other) |
| Asian Pacific | 8 (1.71) | 6 (1.55) | 2 (2.50) | |
| Black | 47 (10.04) | 39 (10.05) | 8 (10.00) | |
| White | 412 (88.03) | 342 (88.14) | 70 (87.50) | |
| Education (years), mean (SD) | 14.40 (2.85) | 14.43 (2.85) | 14.22 (2.87) | F(1,452) = 0.27, *P* = .60 |
| Physical health | | | | |
| Body mass index (BMI) | 29.84 (6.87) | 28.97 (6.32) | 34.10 (7.84) | F(l, 452) = 38.24, *P* <.001 |
| BMI ≥ 30, no.(%) | 195/434 (42.03) | 137/384 (35.68) | 58 (72.50) | $\chi^2$ = 31.16, *P*<. 001 |
| Glucose ≥ 110 mmol/L, no. (%) | 134/467 (28.69) | 102/387 (26.36) | 32 (40.00) | $\chi^2$ = 4.35, *P*<.05 |
| QTC, mean (SD) | 423.65 (25.73) | 422.55 (24.88) | 428.97 (29.09) | F(1,452) = 6.24, *P*<.05 |
| QTC ≥ 480, no. (%) | 13 (2.78) | 9 (2.32) | 4 (5.06) | Exact *P* = 0.24 |
| Diabetes, no. (%) | 64/250 (14.22) | 50/370 (13.51) | 14 (17.50) | $\chi^2$ =0.28, *P* = .60 |
| Hypertension, no. (%) | 239/450 (53.11) | 179/370 (48.38) | 60 (75.00) | $\chi^2$ = 16.23, *P*<. 001 |
| CIRS-G, mean (SD) | | | | |
| Total | 9.87 (4.45) | 9.41 (4.40) | 12.08 (4.04) | F(l, 452) = 22.73, *P*<.001 |
| Count | 6.16 (2.35) | 5.90 (2.32) | 7.43 (2.11) | F(l, 452) = 25.94, *P*<.001 |
| Total minus respiratory item | 8.85 (4.16) | 8.47 (4.07) | 10.71 (4.13) | F(l, 452) = 17.91, *P*<.001 |
| Medical Outcomes Survey, mean (SD) | | | | |
| Physical scale | 42.69 (11.59) | 43.31 (11.46) | 39.67 (11.81) | F(1,452) = 6.65, *P*<.05 |
| Mental scale | 27.30 (8.87) | 27.11 (9.00) | 28.23 (8.19) | F(1,452) = 1.08, *P* = .30 |
| Depression | | | | |
| MADRS, mean (SD) | 26.72 (5.74) | 26.60 (5.81) | 27.29 (5.41) | F(1,452) = 1.55, *P* = .21 |
| HRSD-17, mean(SD) | 20.05 (4.97) | 19.99 (5.14) | 20.32 (4.06) | F(1,452) = 0.07, *P* = .79 |
| HRSD sleep items, mean (SD) | 3.08 (1.80) | 3.08 (1.80) | 2.06 (1.77) | F(1,452) = 0.00, *P* = .98 |
| Recurrent depression, no. (%) | 332 (70.84) | 279 (71.91) | 53 (66.25) | $\chi^2$ = 0.20, *P* = .66 |
| Age at first episode, mean (SD) | 41.95 (21.29) | 42.06 (21.57) | 41.42 (19.97) | F(1,452) = 0.61, *P* = .43 |
| Duration of index episode of depression | 295.13 (616.51) | 260.06 (566.06) | 466.40 (802.27) | F(1,452) = 6.83, *P* <.01 |
| Adequate depression treatment (%) ATHF ≥ 3 | 284/464 (61.21) | 228/386 (59.07) | 56/78 (71.79) | $\chi^2$ = 5.51, *P* =.02 |
| BSI anxiety subscale, mean (SD) | 1.50(0.93) | 1.52 (0.93) | 1.38 (0.89) | F(1,452) = 1.58, *P* =.21 |

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| Variable | Total cohort *N* = 468 | No apnea *N* = 388 | Apnea *N* = 80 | Significance test (controlling for site) |
|---|---|---|---|---|
| Cognitive status[a] | | | | |
| RBANS, mean (SD) | | | | |
| Language | 98.13 (12.24) | 98.18 (12.13) | 97.93 (12.86) | F(1,422) = 0.19, *P* = .66 |
| Visuospatial/constructional | 92.66 (17.10) | 92.39 (17.11) | 93.95 (17.13) | F(1,422) = 0.05, *P* = .82 |
| Attention | 99.27 (16.75) | 99.52 (16.88) | 98.11 (16.20) | F(1,422) = 0.39, *P* = .53 |
| Immediate memory | 97.79 (17.64) | 98.25 (17.65) | 95.67 (17.54) | F(1,422) = 1.18, *P* = .28 |
| Delayed memory | 97.10 (15.00) | 96.94 (15.43) | 97.86 (12.30) | F(1,422) = 0.25, *P* = .88 |
| Total | 95.75 (15.38) | 95.84 (15.31) | 95.37 (15.80) | F(1,422) = 0.23, *P* = .64 |
| DKEFS, mean (SD) | | | | |
| Color-word test | 10.27 (2.99) | 10.36 (3.00) | 9.84 (2.87) | F(1,422) = 1.34, *P* = .25 |
| Trail making test | 8.37 (3.58) | 8.27 (3.61) | 8.84 (3.45) | F(1,422) = 0.61, *P* = .44 |
| Executive Domain | 9.32 (2.66) | 9.32 (2.68) | 9.34 (2.55) | F(1,422) = 0.02, *P* = .89 |
| Medication, no. (%) | | | | |
| Lorazepam | 109 (59.9) | 87 (56.9) | 22 (75.9) | |
| Clonazepam | 29 (15.9) | 27 (17.6) | 2 (6.9) | |
| Trazodone | 28 (15.4) | 24 (15.7) | 4 (13.8) | $\chi^2$ = 4.52, *P* = .48 |
| Nortriptyline | 2 (1.1) | 2 (1.3) | 0 (0.0) | |
| Amitriptyline | 1 (0.5) | 1 (0.7) | 0 (0.0) | |
| Zolpidem | 13 (7.1) | 12 (7.8) | 1 (3.4) | |

Notes:

[a]Analyses controlled for participant sex, education, medical burden (CIRS-G) and depression severity (MADRS).

QTC, QT interval, corrected; CIRS-G, Cumulative Illness Rating Scale – Geriatrics; MADRS, Montgomery Asberg Depression Rating Scale; HRSD, Hamilton Rating Scale for Depression; BSI, Brief Symptom Inventory; RBANS, Repeatable Battery for the Assessment of Neuropsychological Function; DKEFS, Delis Kaplan Executive Function Test; used with permission from Pearson, Inc.

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**TABLE 3**

Regression model examining the effect of obstructive sleep apnea on time to depression response

| Variable | *B* | SE(B) | HR | 95% CI | *P*-value |
|---|---|---|---|---|---|
| Site: Toronto[a] | 0.62 | 0.18 | 1.87 | 1.31–2.66 | <.01 |
| Site: Washington[a] | 0.27 | 0.21 | 1.31 | 0.86–1.99 | .21 |
| Male sex | 0.34 | 0.17 | 1.41 | 1.02–1.95 | <.05 |
| Body mass index | 0.00 | 0.01 | 1.00 | 0.98–1.13 | .80 |
| Medical comorbidity[b] | −0.14 | 0.02 | 0.99 | 0.95–1.02 | .45 |
| Depressive symptoms[c] | −0.07 | 0.02 | 0.94 | 0.91–0.97 | <.001 |
| No obstructive sleep apnea[d] | 0.58 | 0.24 | 1.79 | 1.13–2.86 | <.05 |

Notes

[a]Pittsburgh site served as the referent group.

[b]measured with the Cumulative Illness Rating Scale-Geriatrics (CIRS-G).

[c]measured with the Hamilton Rating Scale for Depression (HRSD-17).

[d]Obstructive sleep apnea served as the referent group.