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Sleep apnea risk and clinical correlates in patients with bipolar disorder

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Abstract

Objective—Despite the high prevalence of risk factors for obstructive sleep apnea (OSA) among individuals with bipolar disorder, the presence of sleep-disordered breathing has not been systematically assessed in this population. In this study, we sought to determine the level of risk for OSA in a population of remitted individuals with a diagnosis of bipolar I disorder.

Methods—A total of 72 individuals with a diagnosis of bipolar I disorder, all of whom were overweight by the World Health Organization criteria, completed the Berlin Questionnaire, a self-assessment tool to establish risk for OSA.

Results—Over half of this study population (54.1%) was found to be in the high-risk category for OSA. Participants at high risk for OSA scored significantly higher on measures of both depression and mania, even when sleep items were not counted in the total scores.

Conclusions—Sleep apnea may be prevalent in patients with bipolar I disorder. Considering the substantial overlap of symptoms between OSA and depression and the potentially harmful effects of sleep disruption in patients with mood disorders, a systematic screening to assess prevalence and associated features of OSA in patients with bipolar disorder is warranted.

Keywords

bipolar disorder; cardiovascular risk factors; obstructive sleep apnea

Bipolar disorder (BD) is often associated with high levels of general medical burden, high rates of cardiovascular diseases and a high mortality rate from medical causes (1–5). In spite of the high prevalence of well-documented risk factors for obstructive sleep apnea (OSA) (6), the actual prevalence of sleep-related disordered breathing in BD has not been systematically investigated beyond small case series and anecdotal reports (7). The clinical presentation of OSA may overlap substantially with that of major depression, including report of poor sleep quality, daytime fatigue, difficulty concentrating, cognitive deficits and somatic symptoms such as headaches.

Since the depressive phase of BD is often chronic and difficult to treat, and undiagnosed underlying medical conditions may greatly contribute to its unfavorable outcome, it is reasonable to speculate that sleep-disordered breathing may play a role in this clinical picture. Indeed, the presence of medical comorbidities that constitute risk factors for OSA

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has been associated with a worse outcome of BD (8). For example, obesity has been linked to a higher number of lifetime depressive episodes and to a shorter time to recurrence (9). Abdominal obesity, particularly, is associated with increased suicidality (3). Part of the detrimental effect of these conditions on mood regulation may be ascribed to underlying sleep-related breathing problems. Patients who develop OSA as a result of cumulative risk factors may be over-represented among those who present a history of chronic and treatment-resistant depressive symptoms.

Therefore, we sought to determine the risk for OSA in a population of 72 patients with bipolar I disorder who were currently engaged in an outpatient maintenance treatment protocol. We asked participants to complete a validated instrument that determines risk for sleep apnea. We then compared the demographic and clinical characteristics of patients at high risk and low risk for sleep apnea. Our goal was to explore whether the age and gender distribution of the apnea risk would reflect the age and gender distribution reported in the general population. We also tested the hypothesis that being at high risk for sleep apnea would be associated with greater severity of the mood disorder, independent of sleep disturbance.

Methods

General procedures

The Institutional Review Board at the University of Pittsburgh (Pittsburgh, PA, USA) reviewed and approved all of the study procedures. Participants in this study were taking part in a National Institute of Mental Health-funded treatment study (MH081003, D.J. Kupfer, Principal Investigator) comparing standard of care with an integrated model of care for patients with bipolar I disorder in maintenance treatment. As part of the inclusion criteria for the parent study, participants were required to meet lifetime criteria for BD, type I [ascertained using the Semi-structured Clinical Interview for DSM–IV (SCID–IV)], be free of unstable or untreated medical conditions, have a body mass index (BMI) ≥ 25, and have rating scale scores consistent with remission [defined as a Hamilton Rating Scale for Depression (HAM-D) score ≤ 10 and a Young Mania Rating Scale (YMRS) score ≤ 8 for at least two weeks and have not been hospitalized in the previous year]. Patients were excluded if they had ultra-rapid cycling bipolar I disorder (more than eight episodes per year); had unstable medical conditions requiring immediate and intensive medical care; had antisocial personality disorder, current substance abuse or dependence, or an organic mental disorder; or were pregnant or breastfeeding. Mood symptom severity was assessed monthly using the HAM-D and YMRS. BMI and waist circumference were recorded at every clinic visit. At baseline, participants were also asked to complete the MOOD questionnaire self rating version (MOOD-SR), a measure of lifetime burden of mood symptoms, and complete the Pittsburgh Sleep Quality Index (PSQI). Participants for the parent study were recruited through media announcements in the community and through referral from primary care and specialty practices.

Sleep apnea risk was determined using the Berlin Questionnaire (10), a validated instrument that consists of ten questions in three categories which globally determine risk for OSA. In Category 1, high risk is defined as persistent symptoms reported in response to two or more questions about snoring. Category 2 assesses wake-time sleepiness, drowsy driving, or both, with persistent occurrences classified as high risk. Category 3 consists of the presence of hypertension or obesity. Individuals are considered at high risk of OSA if they meet high-risk criteria in two of three categories. The Berlin Questionnaire was validated in a study enrolling 744 adults who presented for unrelated problems at five primary care sites. One hundred of these patients underwent polysomnography. A finding of high risk on the Berlin Questionnaire predicted an Apnea–Hypopnea Index (AHI) score > 5, with 86% sensitivity

and 77% specificity, a positive predictive value (PPV) of 89%, and a positive likelihood ratio of 3.79 (10).

As the specific interest in sleep apnea risk began after the start of our ongoing study of medical burden, participants were asked to complete the Berlin Questionnaire at their next study visit. Depression and mania scores and BMI measured on the same visit at which they completed the Berlin questionnaire were used, as well as baseline depression and mania scores measured at entry in the parent study.

Statistical analysis

Statistical analyses were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA) and all data were reported as mean and standard deviation. Variable distribution was assessed for normality and differences between groups were assessed using *t*-test for continuous variables to determine the main effects of the Berlin questionnaire risk group category. The relationships between Berlin questionnaire risk group category and categorical variables were assessed using chi-square tests. Groups were compared for sociodemographic characteristics, symptom severity at the time they completed the Berlin Questionnaire and at the time they had entered the parent study (baseline), duration of illness, and lifetime mood symptom burden. Since the HAM-D and the YMRS also assess sleep disturbance as part of the depressive and manic syndromes, we carried out our analyses subtracting the sleep items from the HAM-D and YMRS total score.

One of our goals was to evaluate whether patients in the high-risk group have more severe psychiatric symptoms, independent of sleep disturbances. To this end, we executed two-step hierarchical regression analyses, entering the HAM-D and YMRS scores as the dependent variable and a set of covariates (age and sex). These covariates were selected based on the knowledge that they constitute independent risk factors for OSA in the general population (6) and also in patients with severe psychiatric disorders (11) and on the basis of their univariate association with outcome variable. As BMI was not associated with HAM-D or YMRS scores in our sample, it was not included as a covariate. The R^2 change was examined as an indicator of the percentage of variance in depressive and manic symptoms, explained by the risk group. One subject had an outlier HAM-D score and was therefore removed from the analyses. YMRS scores had a skewed distribution (as the majority of participants had scores of 0 or 1) and we therefore used the log-transformed scores for our analyses.

Results

Seventy-two participants completed the Berlin Questionnaire. Their demographic and clinical characteristics are shown in Table 1. Of this group, 39 (54.1%) fell in the high-risk category for OSA (Table 1). The high-risk group had a higher mean BMI and waist circumference, and higher HAM-D and YMRS scores both at baseline and at the time when the Berlin Questionnaire was completed; these scores remained significantly higher in the high-risk group when the sleep items were removed. The high-risk group included more women and participants that were receiving disability benefits. We also calculated Bonferroni-adjusted p-values for the 14 separate tests in Table 1 to provide a conservative approach to determining the significance of these univariate relationships. Only the '*mean HAM-D scor'* and '*HAM-D minus sleep items*' variables remained significant ($p = 0.0014$) after this adjustment. Duration of the mood disorder, lifetime burden of mood symptoms (as assessed by the MOOD-SR), and sleep quality were not significantly different between high-risk and low-risk groups (Table 1). Table 2 shows endorsement of each risk category.

The first regression model showed that the sleep apnea risk category accounted for nearly 15% of the HAM-D variance (Step 1: $R^2 = 0.202$; Step 2: $\Delta R^2 = 0.151$; adjusted $\Delta R^2 = 0.142$; F-change = 10.878, $p = 0.002$). The association between sleep apnea risk category and YMRS was not significant.

Discussion

In the present study, we found that over half of a cohort of overweight or obese individuals with bipolar I disorder can be considered at high risk of sleep apnea according to the Berlin Questionnaire. The Berlin Questionnaire has a positive predictive value of 89% of having an AHI score > 5 when falling in the high-risk group; therefore, it is expected that 35 participants (47%) in the present study would receive a formal diagnosis of OSA. Although all study participants were required to have rating scale scores consistent with remission at study entry, those in the high-risk group evidenced greater severity of mood symptoms both at study entry and at the point at which the Berlin Questionnaire was completed. Further studies should explore whether sleep apnea may independently worsen the course of BD. Interestingly, self-reported sleep quality, as measured by the PSQI, was not significantly different between the two risk groups, suggesting that the most frequently used clinical measures of sleep disturbances may not capture sleep apnea risk. Moreover, in the vast majority of cases, sleep apnea is asymptomatic, suggesting that any screening based solely on subjective sleep quality may not be sensitive to apnea risk.

Most patients with BD have multiple risk factors for developing OSA (3, 8, 9), including life-long medication management with mood stabilizers or other agents that may increase the risk of developing apnea through various mechanisms, including weight gain, decreased arousability during sleep, and upper airway muscle dysfunction (11). In spite of the recent increase in the prevalence of sleep apnea in the general population and the increased sensitivity of clinicians to the problem (12), apnea has been surprisingly neglected in patients with BD. Our results indicate that an evaluation of sleep apnea risk factors should be considered for patients with BD, particularly those who have chronic mood symptoms.

Limitations

Our study had limitations that need to be taken into account when interpreting our results. The first was the lack of a control group. We know from the literature that the prevalence of OSA among mid-life individuals that are overweight or obese ranges from 7% to 36% (13); however, we did not have a matched non-BD sample for direct comparison. All our participants were required to at least meet World Health Organization criteria for being overweight, so we cannot completely separate out the effects of factors related to BD *per se* and factors related to body weight. Further research should explore risk for sleep apnea in normal-weight patients with BD. Aspects related to the pathophysiology of BD, such as increased markers of inflammation and autonomic dysregulation that may increase the risk of OSA independent of BMI, should also be studied. The present study only included patients with bipolar I disorder who were at least overweight; this limits the generalizability of our results to other types of BD and to those with normal weight. The most important limitation of the present study was that we used a self-report screening tool for OSA, without a polysomnography diagnostic verification. Thus, we cannot confirm that those participants who scored in the high-risk range actually had OSA. Nonetheless, our finding of over half of patients being in the high risk range should be sufficient to sensitize clinicians and raise awareness concerning OSA in BD.

Finally, given the cross-sectional design of the study, we could not ascertain whether the onset of apnea risk followed or preceded the onset of BD. In our sample, participants were,

on average, diagnosed with BD in their late teens / early 20s. In the general population, rates of OSA in this age range are very low and it is therefore reasonable to infer that the mood disorder preceded the onset of apnea risk. Future research should address whether lifestyle and biological factors specific to BD are responsible for the increased risk for OSA. Moreover, given the evidence that patients at risk for sleep-disordered breathing have increased mood symptoms, longitudinal studies that investigate the probable reciprocal interaction between mood and OSA are needed.

In summary, considering the substantial overlap between symptoms of OSA and symptoms of depression and the potentially harmful effects of sleep disruption in patients with mood disorders, a systematic screening to assess the prevalence and associated features of OSA in patients with BD is clearly warranted.

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Table 1

Demographic and clinical characteristics of the bipolar I disorder sample (n = 72)

	High risk (n = 39)	Low risk (n = 33)	*F*	df	p-value
BMI	36.80 (7.69)	32.50 (6.56)	0.434	70	0.014
Age	45.30 (7.95)	43.80 (8.37)	0.228	61	0.477
Waist (inches)	42.80 (6.20)	39.10 (5.60)	0.586	56	0.027
Duration of illness	26.10 (11.17)	23.80 (8.80)	1.695	70	0.343
HAM-D score	13.10 (9.20)	6.30 (5.10)	12.390	70	0.000[a]
HAM-D minus sleep items	9.82 (7.19)	4.30 (3.86)	11.621	70	0.000[a]
YMRS score	3.10 (3.00)	1.50 (2.30)	3.041	70	0.022
YMRS minus sleep items	2.79 (2.80)	1.36 (2.07)	2.568	70	0.018
HAM-D at baseline	7.59 (2.81)	5.73 (4.27)	1.916	70	0.037
YMRS at baseline	1.95 (2.22)	1.27 (2.00)	0.542	70	0.179
PSQI	6.87 (3.55)	5.39 (3.81)	0.073	64	0.111
MOOD-SR	97.20 (27.5)	85.76 (37.7)	4.195	66	0.150
Male / female, n	12 / 26	18 / 16	4.157[b]	1	0.056
Employment status, n (%)					
Full time	5 (12.8)	13 (39.3)	13.211[b]	5	0.021
Part time	8 (20.5)	6 (18.1)			
Home maker	3 (7.6)	0 (0)			
Leave of absence	1 (2.5)	0 (0)			
Unemployed	8 (20.5)	10 (30.3)			
Disabled	14 (35.8)	4 (12.1)			

Values are reported as mean [standard deviation (SD)]. BMI = body mass index; HAM-D = Hamilton Rating Scale for Depression; MOOD-SR = MOOD questionnaire self rating version; PSQI = Pittsburgh Sleep Quality Index; YMRS = Young Mania Rating Scale.

[a]Remains significant (p = 0.0001 × 14 = 0.0014) after Bonferroni adjustment for 14 comparisons.

[b]Pearson's chi-square value.

Table 2

Prevalence of risk criteria for sleep apnea in patients with bipolar I disorder (n = 72)

Category	Description	High risk n (%)	Low risk n (%)	Total n (%)
1	Persistent symptoms reported in response to two or more questions about snoring	34 (47.2)	6 (8.0)	40 (55.5)
2	Wake-time sleepiness, drowsy driving, or both, with persistent occurrences	24 (33.3)	2 (2.0)	26 (36.1)
3	Presence of hypertension or obesity	37 (51.3)	18 (25.0)	55 (76.3)
Risk		39 (54.1)	33 (45.8)	72 (100)