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Prevalence of obstructive sleep apnea in suicidal patients with major depressive disorder

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ABSTRACT

In this paper, we report the rate of previously undiagnosed obstructive sleep apnea (OSA) in a randomized clinical trial (RCT) of suicidal patients with major depressive disorder (MDD). One hundred and twenty-five suicidal adults with MDD were recruited into a RCT. None were suspected to have OSA. Fourteen percent met diagnostic criteria for OSA. The Apnea Hypopnea Index (AHI) was predicted by increasing age, male sex, and higher Body Mass Index. However, neither the degree of daytime sleepiness nor the degree of insomnia predicted AHI severity. A high degree of suspicion is warranted for OSA in suicidal patients with MDD, and for patients with treatment-resistant depression.

ClinicalTrials.gov identifier: NCT01689909

1. Introduction

The failure of major depressive disorder (MDD) to respond to at least two adequate therapeutic trials of an antidepressant medication is deemed treatment resistant depression (TRD)(Murphy et al., 2017). As many as 50% of persons with MDD demonstrate TRD(Murphy et al., 2017; Nierenberg et al., 2001). Some authors have defined the degree of TRD by "Stage"; Stage 1 represents failure to respond to one adequate antidepressant trial, Stage 2 is failing 2 trials, Stage 3 is Stage 2 plus failure to respond to an augmentation strategy, Stage 4 is failure of a second augmentation strategy, and Stage 5 is failure to respond to ECT(Thase et al., 1997). In some cases, TRD is not due to a resistance to the treatment, but rather due to non-adherence to treatment, or an error in the primary diagnosis (e.g., bipolar disorder or substance abuse instead of MDD), or a failure to detect an underlying medical comorbidity (Kornstein et al., 2001). This situation is instead termed "pseudoresistance." Although the rates of pseudoresistance due to medical illness in the outpatient setting are unknown, the rate of undetected medical illness contributing to psychiatric inpatient admissions has been estimated at 50%(Kornstein and Schneider, 2001).

The list of medical illnesses which could potentially contribute to pseudoresistance in the outpatient setting is long, with endocrine disorders being among the best described(Kornstein and Schneider, 2001). Other examples include coronary artery disease, HIV, cancer, syphilis, vitamin deficiencies, and medication effects(Bschor et al., 2014). Assessment for primary sleep disorders, in particular obstructive sleep apnea (OSA), is notably absent from most recommendations of the medical work-up of TRD(Bschor and Bauer, 2014).

While depression symptoms have been widely described in patients with known OSA(Ejaz et al., 2011; Harris et al., 2009; LaGrotte et al., 2016; Pan et al., 2016), relatively little is known regarding rates of undetected OSA in MDD patients. Severity of OSA is determined by the apnea-hypopnea index (AHI), with an AHI of 5–14 considered to be mild, AHI of 15–29 moderate, and AHI of 30 or greater severe disease (Young et al., 2002). In a prior study of 73 depressed insomniac outpatients believed to be at low pretest probability for OSA, we reported that 6 participants (8.2%) had an apnea-hypopnea index (AHI) ≥ 15(McCall et al., 2009). Drawing from a convenience sample of 703 depressed adults, Hein et al. found an OSA prevalence of 14% in MDD patients, where OSA was defined as an AHI ≥ 15(Hein et al.,

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2017). In a study that included 23 healthy elderly controls and 17 depressed elderly, Reynolds et al. found a rate of OSA of 4.3% in controls and 17.6% in depressed patients, where OSA was defined as AHI > 5(Reynolds et al., 1985). Similarly, Waterman et al. found that 17.1% of 468 older depressed patients reported a pre-existing diagnosis of OSA(Waterman et al., 2016), while Ohayon reported a 17.7% rate of OSA symptoms in adults with MDD drawn from a community sample of adults(Ohayon, 2003).

Herein we report the results of OSA testing in a sample of suicidal, depressed insomniacs (n = 125) who were believed to have a low pre-test probability for OSA and were being evaluated for participation in a randomized controlled trial (RCT). The goal of this paper was to provide estimates of the rate of unsuspected OSA in suicidal MDD patients, and to evaluate traditional risk factors for OSA (age, gender, Body Mass Index (BMI)) in this sample.

2. Materials and methods

The multi-site, RCT "Reducing Suicidal Ideation through Insomnia Treatment (REST-IT)" was designed to test whether the addition of a hypnotic to an antidepressant had an advantage in reducing suicidality (McCall et al., 2015). For safety, patients with clinically significant OSA were excluded from participation. Potential participants aged 18–65 years old were solicited through advertising and routine clinic flow. Inclusion criteria required the presence of MDD diagnosed per the Structured Clinical Interview for Diagnosis for DSM IV(First et al., 1996), insomnia (Insomnia Severity Index (ISI) > 7)(Bastien et al., 2001), and suicidality. Participants were excluded for (1) BMI > 50, (2) a history of any prior diagnosis of OSA or periodic limb movement disorder that had been confirmed with sleep testing, (3) restless legs syndrome, or (4) respiratory conditions.

Participants who satisfied these requirements underwent a test for OSA, either with one night of home portable testing (N = 60), measuring airflow, respiratory effort, and pulse oximetry, or one night of in-lab polysomnography that included EEG in addition to the respiratory measures (N = 65). The choice of sleep testing technology was driven by resources at each of the three recruiting sites, with Medical College of Georgia using portable testing, while Duke and University of Wisconsin used in-lab testing. Most participants were recruited from routine clinical referral to either psychiatric clinics or sleep clinics. Apneas and hypopneas were scored using standard criteria(Iber et al., 2007), and the AHI was calculated from the home test with 'time in bed' as the denominator for AHI, while the in-lab PSG used 'EEG total sleep time' as the denominator for AHI. Our review of the literature revealed variability in the definition of OSA, ranging from AHI > 5 to AHI > 15, but for the purposes of this study an AHI > 10 was a basis for exclusion from further participation in the RCT. The Epworth Sleepiness Scale (ESS) was collected on all participants at screening, before testing for sleep apnea(Johns, 1991), but was not used for inclusion or exclusion. The study was approved by the IRB of each recruiting site, written informed consent was obtained, and the study was registered at ClinicaTrials.gov (identifier: NCT01689909). Participants who tested positive for OSA were referred for treatment of OSA.

2.1. Statistical approach

Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables were used to assess differences in those patients with and without OSA. Multivariable logistic regression was used to determine which characteristics were jointly associated with OSA-diagnosis and multivariable linear regression was used to determine which characteristics were jointly associated with AHI. A log transformation was used on (AHI + 0.5) due to the skewed distribution. The offset of 0.5 was used since several of the AHI values were zero.

Table 1
Summary statistics for baseline characteristics by OSA Diagnosis.

	AHI ≤10			AHI > 10			p-value*
	N	Mean	SD	N	Mean	SD	
Age – years	108	40.6	13.2	17	48.7	11.0	.015
BMI	108	28.0	6.0	16	30.9	7.0	.132
Insomnia Severity Index	107	20.8	4.2	16	20.9	4.5	.812
Epworth Sleep Scale	103	8.4	4.9	15	9.9	4.9	.233
AHI	108	2.2	2.5	17	25.3	14.4	–
	N	(%)		N	(%)		
Sex							.687
Male	39	(36%)		7	(41%)		
Female	69	(64%)		10	(59%)		
Race							.453
Nonwhite	42	(39%)		5	(29%)		
White	66	(61%)		12	(71%)		
Fail Anti-depressant Trial							.294
No	60	(58%)		6	(43%)		
Yes	44	(42%)		8	(57%)		

* Wilcoxon rank-sum test for continuous variables and chi-square test for categorical variables.
BMI: Body Mass Index.
AHI: Apnea Hypopnea Index.

3. Results

One thousand three hundred and forty-eight persons completed an initial telephone screen for participation, but 56 (4%) were excluded over the telephone on basis of a self-reported history of sleep apnea. Of those that passed all other screening, 125 participants completed testing for OSA. Seventeen of these (14%) had AHI values greater than 10 and were excluded from REST-IT, including 4 persons (3%) with severe OSA (AHI > 30). Fifty-two of the participants had failed at least one adequate trial of an antidepressant. Table 1 shows the number and percentage of patients who were newly diagnosed with OSA by sex and race and Stage 1 TRD status. Those with OSA were significantly older than those without OSA, but otherwise those who met or did not meet our definition of an OSA diagnosis were similar based on gender, race, BMI, ISI, ESS, and Stage 1 TRD status.

Logistic regression was used to assess the unadjusted and adjusted association between baseline covariates and the diagnosis of OSA. Only age was significantly associated with OSA diagnosis, unadjusted (OR = 1.06, 95% CI: 1.01, 1.10) or adjusted (OR = 1.06, 95% CI: 1.00, 1.13) for other covariates.

Linear regression was used to assess the unadjusted and adjusted association between baseline covariates and AHI score. A log transformation was used for AHI score due to the skewness. Results are summarized in Table 2. Sex and age were both significantly associated with AHI score, unadjusted and adjusted for other covariates. Male sex and older age were associated with higher AHI score. After adjustment for other covariates, male sex, older age and greater BMI were associated with higher AHI score.

4. Discussion

In this sample of suicidal MDD outpatients with insomnia, we found a rate of 14% for unsuspected OSA, quite similar to the rates of 14%, 17.6%, 17.1%, and 17.1% reported by Hein, Reynolds, Waterman, and Ohayon, respectively.(Hein et al., 2017; Ohayon, 2003; Reynolds et al.,

Table 2
Unadjusted and adjusted associations between baseline characteristics and AHI.

	Unadjusted			Adjusted		
Covariate	Beta	SE	p-value	Beta	SE	p-value
Male Sex	0.63	0.23	.008	0.48	0.23	.034
Non-White	−0.42	0.23	.074	−0.18	0.22	.431
Failed trial	0.14	0.23	.554	0.00	0.22	.999
Age per year	0.03	0.01	< .001	0.03	0.01	.001
BMI	0.03	0.02	.064	0.04	0.02	.045
ISI	0.00	0.03	.929	0.00	0.03	.892
ESS	0.04	0.02	.065	0.03	0.02	.237

AHI: Apnea Hypopneas Index.
BMI: Body Mass Index.
ISI: Insomnia Severity Index.
ESS: Epworth Sleepiness Scale.

1985) This report relied upon portable OSA testing and calculated the AHI with 'Time in Bed' as the denominator in about half of the participants. Also, we excluded patients with pre-existing respiratory conditions. These factors may have led to an underestimation of the rate of unsuspected OSA in MDD. Hence, the actual rate of OSA in our sample may be somewhat higher than 14%. For example, a more lenient definition of OSA with AHI > 5 produces a prevalence of 21.6% in this sample.

Regardless, these data suggest that the rate of unsuspected OSA in adults with MDD is significant, especially in older, overweight men. (Partinen et al., 1992; Young et al., 2002) High rates of OSA in MDD patients are relevant to our understanding of TRD, as MDD patients *without* OSA may respond differently to treatments; for example, they are more likely to respond to venlafaxine as compared to patients *with* OSA (OR = 1.79, CI 1.13–2.86, p < 0.05)(Waterman et al., 2016). It is sobering to note that the presence of an OSA diagnosis could not be predicted from the degree of the insomnia complaint or the degree of reported sleepiness. For example, while OSA is often characterized as a disease of older, overweight men, we discovered 6 non-obese women (BMI < 30) who tested positive among our 79 women who were tested. These findings suggest a high degree of suspicion for OSA in MDD patients is warranted.

Apart from any potential impact on depression symptoms, treatment of OSA in MDD patients would be expected to confer the known benefits of risk reduction for accidents and cardiovascular disease(Feldstein, 2016; Tregear et al., 2010). Further, OSA may warrant treatment from a psychiatric standpoint, as a RCT of CPAP versus 'no CPAP' showed superior effect of CPAP on depression symptoms(Balcan et al., 2019). This finding is further supported by numerous uncontrolled trials of CPAP also showing benefit on depression symptoms in OSA patients(El-Sherbini et al., 2011; Gupta et al., 2016; Habukawa et al., 2010; Lee et al., 2017; Murphy et al., 2017; Schwartz et al., 2005, 2007).

Thus far, a recommendation for sleep apnea screening or testing has not appeared in routine recommendations for the management of MDD. Kirstein et al. suggested that a complete blood count, comprehensive metabolic testing, a thyroid stimulating hormone level and C-reactive protein should be considered as part of the preliminary evaluation of MDD through Stage 1 TRD(Kornstein and Schneider, 2001). They further suggest that anatomic imaging of the brain, carotid artery dopplers, HIV testing, serum vitamin levels, EEG, and cerebrospinal fluid (CSF) analyses should be considered when MDD reaches Stage 2 TRD.

We agree with Kornstein that additional evaluation is indicated at Stage 2, for the sake of not only relieving suffering and avoiding wasted time, but also to assure rationale allocation of resources. For example, a single failed adequate trial of an antidepressant might be viewed as an indication for consideration of a course of repetitive transcranial magnetic stimulation (TMS)(Tillman, 2014). Embarking upon rTMS might seem a costly diversion of resources if the TRD patient in fact had a treatable underlying medical condition contributing to treatment resistance.

Some of the recommendations of Kornstein et al. for the evaluation of TRD are relatively low cost, non-invasive, and high yield. For example, subclinical thyroid disease, as reflected in TSH levels, may be seen in more than 29% of TRD, a rate that is higher than the 8–17% rate seen in unselected cases of MDD(Howland, 1993). Further, treatment of hypothyroidism may improve symptoms of MDD(Gold et al., 1981). In contrast, the recommendation for CSF analysis is invasive and likely to be of low yield. The clinical yield and practicality of OSA testing for Stage 2 TRD is likely to fall intermediate between TSH testing and CSF analysis, and the testing is noninvasive with a moderately high likelihood of revealing clinically meaningful results.

The present study has several limitations. First, the sample was of moderate size. Second, while the entire sample was suicidal and highly acute, the rate of Stage 1 TRD was modest (44%). Third, the estimated rate of OSA in our sample was conservative, as the half of the AHI values were estimated from a ratio that included the less precise "Time in bed" in the denominator.

In summary, rates of unsuspected and undetected OSA occur at a clinically relevant level in undifferentiated samples of MDD, including suicidal patients. Treatment of OSA may improve symptoms of depression. Comprehensive screening and testing for OSA should be considered in TRD. Future research should examine the relative rates of OSA in never-treated MDD versus TRD, and consider RCTs of CPAP in TRD with comorbid OSA.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2019.06.015.

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