

SCIENTIFIC INVESTIGATIONS

Associations Between the Use of Common Medications and Sleep Architecture in Patients With Untreated Obstructive Sleep Apnea

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Study Objectives: Obstructive sleep apnea (OSA) is often associated with other disorders, which are usually treated with medications. Little is known about the extent to which medications are used in the OSA population or the effects of common prescription medications on the sleep architecture of patients with OSA. The aim of this study was to describe the frequency of use of medications by patients with untreated OSA and to examine the potential associations between specific, frequently used medication types and indexes of sleep architecture assessed through laboratory-based polysomnography.

Design: This study used a retrospective design with analyses of archival clinical data.

Setting: Tertiary public sleep disorders center in Brisbane, Australia.

Patients or Participants: Consecutive patients with a clinical diagnosis of OSA (N = 1779).

Interventions: None.

Measurements and Results: Of the patients with OSA, 77.1% were taking at least 1 medication; 12.4% were taking β -adrenergic receptor-blocking agents and 20.8% were taking antidepressant or anxiolytic medications. Analyses of covariance demonstrated reliable effects of

medication use on sleep architecture, after accounting for age, sex, and body mass index variables. Both tricyclic and selective serotonin reuptake inhibitor antidepressant or anxiolytic medications were associated with a lower percentage of rapid eye movement sleep and lower sleep-efficiency values in patients with OSA, compared with those not taking any medications. The use of β -adrenergic receptor-blocking agents and aspirin had no consistent associations with the indexes of sleep architecture.

Conclusions: Medication use was high within this sample of patients with OSA. Some common medications may be associated with differences in objective sleep quality in a large proportion of patients with OSA. The potential effects of classes of common medication on both the presentation and treatment of OSA need to be further assessed.

Keywords: Obstructive sleep apnea syndrome, sleep architecture, medication effects, antidepressants, anxiolytics

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Sleep involves a complex interaction between central neurophysiologic mechanisms and more peripheral cardiac and respiratory feedback mechanisms.¹ The pathophysiologic features associated with obstructive sleep apnea (OSA) and the use of common medications that target cardiopulmonary or central neurophysiologic mechanisms are likely to alter or disrupt normal sleep processes. Despite the frequent community use of prescription and nonprescription medications,^{2,3} there is a great deal of missing information on the effect that specific medications have on sleep architecture in populations with OSA, and, in fact, there are no available data for many medications. Psychotropic medications, including antidepressants, anxiolytics, sedatives/hypnotics, and antipsychotics, have been the medications most widely studied in clinical samples without OSA or in nonclinical samples.

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General disruption of sleep continuity is frequently observed in association with these medications,⁴ and there is substantial evidence of rapid eye movement (REM) sleep inhibition associated with the decrease of serotonergic tone caused by selective serotonin reuptake inhibitors (SSRI).⁵ Antihypertensives, particularly those affecting central adrenergic mechanisms, have also been associated with sleep disturbance, specifically increased wakefulness, increased or decreased REM sleep, and increased slow-wave sleep, in patients without OSA.⁶

Hypertension and depression commonly co-occur with OSA, and antihypertensive and antidepressant medication use is likely to be high among the OSA population.⁷ Further, it has been reported previously that the use of antihypertensive and antidepressant medication leads to a greater chance of being diagnosed with OSA.⁸ The pathophysiology of OSA involves an interaction between neurophysiologic and anatomic influences on upper-airway dilator muscle activity. While strong anatomic correlates of OSA have been determined,⁹⁻¹¹ ventilation is typically normal during wake, with a state change to sleep required to precipitate obstruction.¹²⁻¹⁴ For these reasons, pharmacologic interventions designed to augment upper-airway dilator muscle activity have been studied in an attempt to reduce the frequency of obstructive events while asleep.^{15,16} Two recent reviews of these studies have found limited support for the efficacy of SSRI in the treatment

of OSA.^{15,17} However, in clinical populations, patients with OSA are more typically prescribed SSRI to ameliorate mood after a diagnosis of clinical depression or clinical anxiety. The effects of antidepressants or anxiolytics on the sleep of nondepressed or nonanxious patients with OSA may not generalize to the sleep of patients with OSA taking the same medication to treat depression or anxiety. Similarly, the effects of antihypertensives (including β -adrenergic receptor-blocking agents) on the sleep of normal participants may not generalize directly to patients with OSA with comorbid hypertension.

Few studies have reported the effects of specific medications within OSA samples, and description of medication effects is typically restricted to effects on the respiratory disturbance index (RDI) alone.¹⁸⁻²² Some reports suggest that specific medications (particularly antiepileptics and β -adrenergic receptor-blocking agents) may exacerbate OSA.^{21,23,24} When medication effects on the sleep architecture of patients with OSA have been presented, they are often secondary to other areas of interest such as manipulation of the duration of slow-wave sleep or the RDI in an attempt to reduce the rate of apnea events.²⁵⁻²⁸ Other results have been reported from a single patient.²⁹ Thus, there is a lack of data on the effects that commonly used medications have on the sleep architecture of patients with OSA. The initial aim of this study was to describe the frequency with which various medication classes are used by patients with OSA in a representative Australian population. The major aim was to examine the effects of specific medication classes (particularly antihypertensive and antidepressant or anxiolytic medications) on indexes of sleep architecture in a natural study of patients with OSA.

METHODS

Participants

Participants consisted of a consecutive series of new patients attending a large public hospital-based sleep disorders clinic in Brisbane, Australia, between 2003 and 2004. The sleep service was accredited by the Thoracic Society of Australia and New Zealand and the Australasian Sleep Association. Participants had a clinical diagnosis of OSA provided by physicians accredited in sleep medicine by the Royal Australian College of Physicians. The clinical diagnosis conformed to the clinical criteria of the International Classification of Sleep Disorders Revised³⁰ and American Academy of Sleep Medicine Task Force³¹ research criteria for OSAS. The clinical diagnosis was confirmed by full-night diagnostic polysomnography (PSG). None of the patients had current or previous treatment with continuous positive airway pressure. Data were obtained from the records of 1270 men and 506 women (3 of unknown sex) with a mean age of 51.0 years (SD = 13.1) and 51.30 years (SD = 13.6), respectively. The mean body mass index for the sample was 33.3 (SD = 9.8) with RDIs in the range of 0 to 186.5 (mean = 28.3, SD = 25.5). One thousand three hundred fifty-nine patients (76%) reported comorbid medical disorders, most frequently depression, hypertension, hypothyroidism, diabetes, gastroesophageal reflux, and asthma. This study was approved by the Human Research Ethics Committees of the Prince Charles Hospital and the University of Queensland.

Design

The study design was retrospective, using de-identified archi-

val data collected as part of routine clinical care at a major sleep disorders center.

Sleep Architecture Variables

Clinical PSG evaluated the following physiologic and respiratory variables: central and occipital electroencephalogram, oblique electrooculogram, submental and tibialis electromyographic activity, electrocardiogram, nasal and oral airflow via nasal pressure transducer and thermistor, thoracic and abdominal excursions with piezoelectric belts, and continuous oxygen saturation. Sleep stage was scored by trained technicians using standard criteria.³² Apneas and hypopneas were scored using recommended guidelines by trained sleep scientists.³¹ Apnea-severity measures included the RDI and the percentage of total sleep time spent below 90% blood oxygenation during the overnight PSG ($\text{SaO}_2 < 90\%$). Measurements of height and weight were recorded and body mass index (BMI) was derived (kg/m^2).

Procedure

Patients reported their current medication regimen on the night of their PSG study to the nursing staff responsible for the patient during the overnight monitoring. The list of medications was crosschecked with previous outpatient letters and correspondence from referring doctors. The medications used by each patient were assigned to their respective classes and mechanisms of action using full medicine information.³³ Unidentified medications (i.e., no results from MIMS³³ search) and uncommon medications (only small number being used by the sample) were classed as miscellaneous. Three PSG indexes of sleep architecture were extracted from the center's clinical database: the percentage of REM sleep, the sleep efficiency, and the arousal index. The proportion of total sleep time with an SaO_2 below 90% saturation was also extracted as a proxy measure of OSA severity.

Data Analysis

To assess the pattern of medication use in this sample of patients with OSA, a frequency analysis was conducted. The frequency of use of each class of medication was tabulated from the 1779 patients' records. The results are presented in Table 1 (note that medication categories are not exclusive). As predicted, there was frequent medication use within the sample, with 77.1% of the sample using at least 1 medication. The use of cardiac medications was particularly high in this sample, with 43.7% of the sample taking any antihypertensive medication, 24.0% taking anticoagulants, 12.4% taking β -adrenergic receptor-blocking agents specifically, and 8.4% taking antiangina medications. Hyperacidity and reflux medications were also in frequent use (20.6%), as was the use of antidepressant or anxiolytic medications (20.8%). A subset of patients taking specific medications was selected for further analysis. Patients were excluded if they were taking more than 1 medication suspected to have an association with sleep architecture and if no age data were available for that patient. An a priori power analysis (α level .05, estimated power .80, 6 groups, 1-way F test design) estimated that a minimum sample size of 36 for each cell (medication type) was required to detect a medium effect.^{34,35} A subset of 5 medication classes was considered for further analyses based on these criteria. These classes included common antidepressant or anxiolytics (amitriptyline, paroxetine/

Table 1—Medication Usage by 1779 Patients With Untreated Obstructive Sleep Apnea

Medication	No.	%
Cardiac		
All antihypertensives	778	43.7
Anticoagulant	427	24.0
β-adrenergic receptor-blocker	220	12.4
Antiangina	150	8.4
Cardiac inotropic medication	50	2.8
Antiarrhythmic	38	2.1
Respiratory		
Bronchospasm relaxants	144	8.1
Preventative aerosols and inhalants	124	7.0
Topical nasopharyngeal medication	101	5.7
Bronchodilator	123	7.0
Adrenal steroid hormones	35	2.0
Other		
Hypolipidemic	404	22.7
All antidepressants	370	20.8
Hyperacidity/reflux	366	20.6
Nonsteroidal anti-inflammatory	239	13.4
Hypoglycemic	218	12.3
Other pain	191	10.7
Narcotic analgesics	128	7.2
Diuretic	200	11.2
Thyroid hormones	109	6.1
Gout	84	4.7
Anticonvulsants	73	4.1
Insulin	58	3.3
Antipsychotics	57	3.2
Antianxiety	49	2.8
Gonadal hormones	43	2.4
Sedatives hypnotics	43	2.4
Muscle relaxant	29	1.6
Immunomodifiers	17	1.0
Hormone replacement therapy	13	1.0
Nonprescription		
Supplements	117	6.6
Minerals	39	2.2
Laxatives	22	1.2
Antihistamines	19	1.1
Antidiarrheal	14	1.0
Miscellaneous	759	42.7

Sum of frequency estimates exceeds 100% because individual patients may have been on multiple medications.

fluoxetine, and sertraline) and common cardiac medications (β-adrenergic receptor-blocking agents and aspirin). Results from patients taking these medication classes were compared with those of patients not taking any of the medications included in the analysis and not on other medications known to affect sleep architecture (no medication). All β-adrenergic receptor-blocking agents used by the sample were combined to increase sample size, as were fluoxetine and paroxetine. Initial sample sizes for each of the medication classes were; no medication (217 cases), aspirin (199 cases), amitriptyline (22 cases), paroxetine/fluoxetine (50 cases), β-adrenergic receptor-blocking agents (81 cases), and sertraline (57 cases). Further analyses were limited to data from these 626 patients, with data from 470 men (mean age = 51.2 years, SD = 13.3) and 156 women (mean age = 52.7, SD = 13.3) with a mean BMI of 33.5 (SD = 6.9) and a mean RDI of 29.0 (SD = 23.8, range of 0-130.0).

To determine the potential effects of specific medication classes on sleep architecture variables, a series of 4 parallel 1-way analyses of covariance (ANCOVA) were conducted. Each of the sleep-architecture variables (percentage of REM sleep, percentage of non-REM [NREM] sleep, sleep efficiency, and apnea index) served as the dependent variables, and medication type, with 6 levels (no medication, aspirin, β-adrenergic receptor-blocking agents, paroxetine/fluoxetine, amitriptyline, and sertraline), was the independent variable. To equalize sample sizes for each medication class and avoid heterogeneity of variances, random samples of 50 cases were taken for each of medication classes (no medication, aspirin, paroxetine/fluoxetine, β-adrenergic receptor-blocking agents, and sertraline) from the 626 cases with existing age data. Because the sample size for amitriptyline was below that required for the ANCOVA to be likely to detect a medium effect and equal samples were required for the ANCOVA, amitriptyline was examined in a separate analysis with another equal random sample of no medication cases ($n = 22$). In the amitriptyline analysis, medication type with 2 levels (no medication and amitriptyline) was the independent variable, and each of the sleep architecture variables was the dependent variables. To test the validity of the resampling strategy, analyses were run with the full data set (i.e., unequal samples) and compared with the equal-samples results. Substantively similar trends in the data were observed, and the analyses were considered to be valid. Some slight non-normality was detected in each ANCOVA. When non-normality was detected, square root and logarithmic transformations were applied according to the procedures described in Howell.³⁶ Substantive trends in the data remained consistent with both transformed and untransformed data, so conservative results from untransformed data are presented. Outliers were observed for all variables, with 9 for percentage of REM sleep, 4 for sleep efficiency, and 8 for apnea index. All outliers were values within the possible clinical range of values. Substantive trends in the data remained consistent with the outlier values excluded; these data were therefore retained in the analyses. Missing data were observed only for analyses with sleep efficiency as the dependent variable (1 case), and this case was therefore excluded from the analysis ($n = 249$). The Levene test of homogeneity of variance revealed no heterogeneity at the .01 α level for the equal samples analyses. No other statistical assumptions were violated.

Equivalency of Groups

The groups were first examined to ensure that they were equivalent in terms of age, BMI, RDI, and sex. Separate 1-way ANOVAs were conducted on the equal-samples data, with age, BMI, and RDI as the dependent variables, and medication type as the independent variable. Missing data were observed for 1 case in each of the RDI and BMI analyses, so these cases were excluded from such analyses ($n = 249$). A significant effect was found only for age ($F_{4,245} = 15.05, p < .001$). RDI was not significant at the .05 level ($F_{4,244} = .42, p = .80$), nor was BMI ($F_{4,244} = 1.046, p = .38$). T tests were used to demonstrate equivalency of groups for the amitriptyline analysis. No significant differences were detected between the amitriptyline and no-medication groups for age ($t_{42} = -1.38, p = .18$), BMI ($t_{41} = -1.15, p = .148$), or RDI ($t_{41} = .32, p = .75$). Examination of the distribution of men and women between the medication classes also suggested differences between groups in terms of sex. The χ^2 analyses confirmed this for both the main

analysis ($\chi^2 = 20.94$, $p < .001$) and the amitriptyline analysis ($\chi^2_1 = 14.14$, $p < .001$). Therefore age and sex were included as the covariates for the main analysis, and sex was the covariate for the amitriptyline analysis.

RESULTS

Percentage of REM Sleep

Because percentage of REM sleep is the inverse of percentage of NREM sleep and statistics are equivalent (except for means), the results for the percentage of only REM sleep are reported. The 1-way ANCOVA were significant for the medication factor ($F_{4,243} = 3.95$, $p = .004$). Means and SD for each medication class and power and effect size estimates are reported in Table 2. ANCOVA pairwise comparisons (Bonferroni correction, $\alpha = .05$) and cell means revealed that paroxetine/fluoxetine ($P = .009$) and sertraline ($P = .007$) were both associated with a significantly lower percentage of REM sleep, compared with those patients not taking any medication. The use of β -adrenergic receptor-blocking agents and aspirin were not associated with a significantly different percentage of REM sleep when compared with the no-medication group. All other comparisons were nonsignificant. An effect size of $P\eta^2 = .06$ was observed with .91 observed power. Pooled within-cell correlations revealed that only sex was significantly associated with the dependent variable ($r = -.15$, $p = .02$). However, neither covariate uniquely adjusted the scores on the dependent variable after covariates were adjusted for other covariates and main effect. The amitriptyline ANCOVA also revealed a significant effect ($F_{1,141} = 8.91$, $p = .005$), with amitriptyline associated with a significantly lower percentage of REM sleep (mean = 10.94, SEM = 2.12) and an increased percentage of NREM sleep (mean = 89.01, SEM = 2.12) than was found in those subjects not taking any medications (mean = 20.71, SEM = 2.12 and mean = 79.29, SEM = 2.12, respectively). An effect size of $P\eta^2 = .18$ was observed with .83 observed power. Sex was not significantly associated with the dependent variable and did not make a unique adjustment on the dependent variable. It was therefore found that the use of paroxetine/fluoxetine, sertraline, and amitriptyline was each associated with a significantly lower percentage of REM sleep (and increased percentage of NREM sleep), after accounting for age, BMI, RDI, and sex.

Sleep Efficiency

A significant association between medication type and sleep efficiency was found after covarying for age and sex ($F_{4,242} = 3.61$, $p = .007$). The pairwise comparisons (Bonferroni correction) and adjusted means (see Table 2) indicated that those taking paroxetine/fluoxetine had significantly a lower sleep efficiency ($P = .017$), compared with those not taking any medications, with the association with sertraline approaching significance ($P = .053$). An effect size of $P\eta^2 = .06$ was observed with .87 observed power. The pooled within-cell correlations suggested that only age was significantly negatively associated with sleep efficiency ($r = -.32$, $p < .001$) and only age uniquely adjusted the sleep-efficiency scores ($F_{1,242} = 22.41$, $p < .001$), after adjusting for the other covariate and main effect. This suggests that only paroxetine/fluoxetine (and sertraline) was associated with significantly lower sleep-efficiency values after controlling for age, BMI, RDI, and sex. However, the amitriptyline ANCOVA was also significant ($F_{1,41}$

Table 2—Percentage of REM Sleep and Sleep Efficiency in 1779 Patients With Untreated Obstructive Sleep Apnea Based on Medication Usage

Medication	REM sleep, %		Sleep efficiency, %	
	Mean	SEM	Mean	SEM
None	19.8	1.5	72.0	2.4
Aspirin	16.1	1.4	67.0	2.3
Paroxetine/fluoxetine	13.1	1.4	61.8	2.2
β -adrenergic receptor-blocking agents	16.4	1.4	69.6	2.3
Sertraline	12.8	1.4	62.8	2.3
F	3.61	3.95		
p	.007	.004		
$P\eta^2$ *	0.06	0.06		
Observed power	0.90	0.87		

REM refers to rapid eye movement.

* $P\eta^2$ can be directly interpreted as the proportion of total variability attributable to a factor.

= 9.45, $p = .004$), with lower sleep efficiency found for those on amitriptyline (mean = 57.09, SEM = 4.15), compared with those on not on any medications (mean = 76.79, SEM = 4.15). An effect size of $P\eta^2 = .19$ was observed with .85 observed power. Sex did make a unique adjustment to the sleep-efficiency scores ($F_{1,41} = 6.27$, $p = .016$). Therefore, paroxetine/fluoxetine, sertraline, and amitriptyline were each associated with a significantly lower sleep efficiency.

Arousal Index

Medication type had no significant associations with arousal index ($F_{4,243} = 1.22$, $p = .30$) after age and sex were entered as covariates. The ANCOVA for amitriptyline compared to the group not taking any medication was also not significant ($F_{1,41} = .81$, $p = .37$). Small potential effect sizes were estimated ($P\eta^2 = .02$) for this parameter.

Total Sleep Time Spent with an SaO₂ Below 90%

A parallel ANCOVA analysis was conducted to assess the potential associations between medication type and SaO₂ < 90%, with SaO₂ < 90% providing a potential index of apnea severity. After adding age and sex as covariates, SaO₂ < 90% was not significantly associated with medication type ($F_{4,240} = 1.51$, $p = .20$). The ANCOVA for amitriptyline compared with the no-medication group, however, was also not significant ($F_{1,41} = .78$, $p = .38$). Again, a small potential effect size was estimated for this parameter ($P\eta^2 = 0.02-.03$).

DISCUSSION

As predicted, this study found that a large proportion of this sample of patients with OSA (77%) was using at least 1 medication at the time data were collected. These results are consistent with Otake et al's³⁷ findings, in which 83.4% of patients with OSA used at least 1 medication in the year before their diagnosis. Antihypertensives were the most frequently used medications within this sample (43.7% of the sample). This is consistent with the high association between OSA and comorbid hypertension that has previously been reported.⁷ Other cardiac medications (antiangina, antiarrhythmic, anticoagulant, and cardiac inotro-

Table 3—Summary of Specific Medication Effects on Sleep Architecture in 1779 Patients With Untreated Obstructive Sleep Apnea

Medication	REM Sleep, %	Sleep Efficiency, %	Apnea Index, no.
Aspirin	NS	NS	NS
Paroxetine			
/fluoxetine	↓ 6.7	↓ 10.3	NS
β-adrenergic receptor-blocking agents	NS	NS	NS
Sertraline	↓ 7	↓ 9.4	NS
Amitriptyline	↓ 9.8	↓ 19.7	NS

Change is in comparison with the no-medication group

pic agents) were used by approximately 50% of our sample. The proportion of cardiac medication is again consistent with findings from other populations of patients with undiagnosed OSA, in which 36.6% of cases have been found to be using medications for cardiovascular disease.³⁷ Antidepressants or anxiolytics were used by approximately 21% of our sample. This is also consistent with estimates of likely prevalence of comorbid depression in patients with OSA.⁷ Results from the current study therefore appear generally concordant with previous reports, including those that have suggested that use of both antidepressants and antihypertensives increases the likelihood of an OSA diagnosis.⁸ Importantly, this concordance suggests that the current sample of patients with OSA is representative of the wider OSA population in terms of their use of medications.

Consistent associations with sleep-architecture measures were found for SSRI (paroxetine/fluoxetine and sertraline) and a tricyclic (amitriptyline) antidepressants. A summary of the main findings is presented in Table 3. These effects were found after controlling for variables such as age, BMI, RDI, and sex. Specifically, an association between a lower percentage of REM sleep was found in patients who were taking paroxetine/fluoxetine or sertraline (about 7% lower) and in those taking amitriptyline (about 10% lower), compared with those not taking any medications. The finding of reduced REM sleep is concordant with the reported effects of such medications on REM sleep in depressed patients without OSA.^{4,38} Nicholson and Pascoe³⁹ have reported that fluoxetine decreased sleep efficiency and total sleep time and increased awakenings in healthy adults. The finding of a lower sleep efficiency in patients taking antidepressants is also consistent with previous reports that some SSRI antidepressant or anxiolytic medications can reduce sleep continuity.⁴ However, this finding is not consistent with other reports that amitriptyline can improve sleep continuity in both depressed and normal individuals.⁴ Instead, the results of this study suggest that, in these patients with OSA, tricyclic and SSRI antidepressants are both associated with a significantly lower sleep efficiency. In the current study, however, there was no increase in the number of arousals (nor in oxyhemoglobin desaturation) associated with the use of the antidepressant or anxiolytic medications examined. Increased initial sleep latency or longer time spent awake after an arousal might provide a mechanism that results in a lower sleep efficiency. Insomnia is sometimes reported as a side effect of the use of both SSRI and tricyclic antidepressants,^{33,40} and fluoxetine has been shown to increase wakefulness and decrease sleep duration.³⁹ Hence, sleep efficiency might be lower due to the reported alerting properties of such SSRI medications through serotonergic

arousal pathways.^{1,39}

The potential implications of these antidepressant or anxiolytic effects in patients with OSA are complex. Because apneas may be more likely to occur in REM sleep,²⁷ less REM sleep may provide a protective mechanism against respiratory-related arousals and associated oxyhemoglobin desaturation. Reported treatment of OSA with antidepressants has been based on this assumption.¹⁷ An early study by Hanzel et al²⁶ reported some improvement in OSA after treatment with protriptyline and fluoxetine. They found a reduced number of respiratory-related events and oxygen desaturations, along with a reduction in percentage of REM sleep for both medications. However, while Hanzel et al²⁶ found that the RDI was significantly reduced in NREM sleep, it was not significantly changed in REM sleep. Hence, the reduced RDI was not a direct result of the reduction in REM sleep, suggesting that other mechanisms of action were involved. Serotonin is also a ventilatory stimulant, and this may provide an explanation of such results.¹⁷ Even so, a therapeutic dose of fluoxetine, and in conjunction with other common medication combinations within this OSA sample, did not appear to have beneficial effects. The antidepressant or anxiolytic medications were not associated with a significant reduction in the arousal index or oxyhemoglobin desaturation in the current study. This is in contrast to Hanzel et al's²⁶ findings. In the current study, the use of SSRI and tricyclic antidepressant or anxiolytic medications seems to be associated with a shorter duration of REM sleep without providing protection against frequency of apneas. Clearly, there are likely differential effects of antidepressant or anxiolytic medications between patients who were initially depressed or anxious and those with OSA alone.

The current study did not find any reliable associations between the use of β-adrenergic receptor-blocking agents and sleep architecture in patients with OSA. This is not consistent with previous reports by Monti^{6,41} and Buysse,⁴² who found that the use of β-adrenergic receptor-blocking agents reduced REM sleep duration, sleep continuity, and total sleep time. Kostis and Rosen⁴³ have reported significantly more awakenings in participants (without OSA) taking metoprolol and propranolol, when compared with patients taking atenolol or a placebo. This result, and the findings in animal studies that have reported effects for metoprolol and propranolol but not atenolol, might help explain the null results in the current study. Associations with sleep architecture may have been attenuated in the current study due to combining all β-adrenergic receptor-blocking agents (propranolol, metoprolol, atenolol, and carvedilol) into the one group. Atenolol was the β-adrenergic receptor-blocking agent used most frequently within the β-adrenergic receptor-blocking medication class, and the null effects for atenolol may have dominated the current study's results. However, other reviews of the effects of β-adrenergic receptor-blocking agents on human sleep have also reported inconclusive findings.⁴⁴ Previous studies that have reported effects for β-adrenergic receptor-blocking agents have also not typically controlled for the known influences of age and RDI on sleep architecture.⁴³ A strength of the current study was that it controlled for variables that are known to impact upon sleep architecture. Although there were initially sufficient cases for metoprolol and propranolol to enter the analysis separately from other β-adrenergic receptor-blocking agents, the high use of aspirin in conjunction with propranolol and metoprolol saw the sample size drop substantially. An alternative strategy for future research could include cases

using both aspirin and metoprolol, as it appears this combination is common within this clinical sample. The issue of the effects of common or frequent medication combinations appears to be a prospect for future research.

This study was limited by the availability of detailed sleep-study data (particularly detailed sleep staging). Lower REM sleep duration and sleep-efficiency values were associated with use of the antidepressant or anxiolytic medications examined, with a corollary higher proportion of NREM sleep. It is not known, however, whether increases in slow-wave sleep or in Stage 1 or 2 sleep accounts for the increased proportion of NREM sleep. If slow-wave sleep had been increased, effects on daytime functioning might be minimal.⁴⁵ However, if it had been Stage 1 or 2 sleep durations that were greater, greater deficits in daytime functioning might be expected.⁴⁶ The use of aspirin and β -adrenergic receptor-blocking agents were not found to have any significant associations with any of the sleep-architecture variables measured. Previous studies have reported effects of these medications on sleep architecture in other samples, with aspirin reported to primarily affect Stage 2 and slow-wave sleep.⁴⁷ Therefore, associations may have been uncovered for the use of aspirin and β -adrenergic receptor-blocking agents had the different stages of NREM sleep been available separately. These issues could be addressed by a more-comprehensive assessment of individual medication regimes and by the inclusion of more-detailed PSG data, including analysis of electroencephalogram power spectra differences between medication classes. The strategy of matching medication groups by RDI also introduced a potential confound to the study. It was not possible with this strategy to assess the potential relationships between medication type and the frequency of apneic and hypopneic events as indexes of OSA severity. However, $\text{SaO}_2 < 90\%$ provided an alternative measure of OSA pathophysiologic severity, and very small potential associations between medication class and this measure were estimated. A further consideration is the issue of effects on sleep architecture due to medication use as distinct from effects due to the underlying medical conditions for which the medications were prescribed. This is a particular issue for depression or anxiety and the use of antidepressant or anxiolytic medications, as direct effects of mood on sleep architecture have been well demonstrated. For example, reduced latency to the first REM sleep episode of the night and increased REM density, with an associated reduction in slow-wave sleep duration, and increased arousals from sleep experienced as insomnia, are typically noted on PSG studies of patients with clinical depression.⁵ Inadequately treated depression could, for example, provide an explanation for differences in sleep efficiency between patients taking antidepressant medication and those who were not. Further, the REM disruptive effects of SSRI and tricyclic antidepressant medications in patients without OSA can vary with both the dose and length of time on the drug and may normalize over time.⁴⁸⁻⁵⁰ Longitudinal studies, in which the clinical diagnosis, level of mood, and adherence to medication are carefully described, are needed to better address this issue. The major limitation of this study is the inability to assign causality, which is inherent in the use of a cross-sectional design. As Stradling⁵¹ notes, "... cross-sectional studies are hypothesis generators, not proof of cause and effect. To demonstrate causal links requires controlled interventional studies." The potential relationship between sleep, depression, and the use of antidepressants in patients with OSA, therefore, requires exploration through prospective controlled trials.

Models of OSA pathophysiology do not generally incorporate the potential effects of medication, despite the frequent use of medication by patients with OSA. OSA involves a complex interplay of sleepwake neurophysiology and cardiorespiratory mechanisms. This study demonstrated that the use of antidepressants or anxiolytics (or depression and anxiety) in particular may have an association with such sleep-wake mechanisms in patients with OSA in the laboratory. Approximately 21% of the sample was using at least 1 antidepressant or anxiolytic medication, and the results of this study are therefore potentially relevant to a significant proportion of patients with OSA. It is yet to be demonstrated whether potential effects are due to medication or to the underlying disorders, what the mechanism of potential effects might be, and how such effects translate into either patients reports of daytime symptoms (particularly self-reported sleepiness) and well-being or to the outcomes of treatment of OSA. The results of this study nevertheless suggest potential implications for the use of common prescription medications in patients with OSA.

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