Schizophrenia, Obesity, and Obstructive Sleep Apnea

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Background: This study evaluated the risk factors for obstructive sleep apnea in psychiatric patients.

Method: The subjects were 364 patients referred to a sleep disorders consultation service from an inpatient psychiatric hospital. Seventy-eight percent underwent polysomnographic testing. Rates of obstructive sleep apnea in different diagnostic groups (established by clinical DSM-III-R diagnosis) were retrospectively assessed.

Results: Logistic regression demonstrated significant independent effects of age ($p = .046$), gender ($p = .002$), body mass index ($p < .001$), and chronic neuroleptic use ($p = .012$) on the presence of obstructive sleep apnea (defined as more than 20 instances of apnea and/or hypopnea per hour of sleep). Patients with schizophrenia were significantly heavier and had higher rates of sleep apnea than did other psychiatric patients.

Conclusion: Obesity, male gender, and chronic neuroleptic administration are risk factors for obstructive sleep apnea in psychiatric patients. Since patients with schizophrenia are often on long-term neuroleptic treatment, they may have high rates of obstructive sleep apnea, mediated via the weight gain produced by such medications. Overweight psychiatric patients and those on chronic neuroleptic treatment (e.g., patients with schizophrenia) should be evaluated for sleep apnea if signs and symptoms of this disorder are present.

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Weight gain has been recognized as a side effect of antipsychotic medications since their introduction in the mid-1950s.[1,2] Patients on chronic neuroleptic treatment may gain 15 to 75 lb (6.8–33.8 kg) over the first 2 years of treatment, and 35% to 50% of such patients may be clinically obese.[3]

Obesity is often considered to be the most important risk factor for obstructive sleep apnea (OSA).[4] In OSA, intermittent obstruction of the upper airway during sleep produces repetitive hypoxia. Termination of obstructive events by brief arousals from sleep results in daytime sleepiness. The prevalence of OSA in the general population is estimated to be 2% to 5%[4] and may be associated with severe cardiovascular morbidity and mortality.[5] An effective treatment for OSA introduced in the 1980s, nasal continuous positive airway pressure (CPAP), may prevent the long-term sequelae of this disorder and can produce dramatic improvements in patients' quality of life.

To evaluate the risk factors for OSA in psychiatric patients, we retrospectively compiled data on nearly 5 years of polysomnographic studies of patients referred from an inpatient psychiatric hospital.

METHOD

All referrals (N = 364) for sleep disturbance performed on psychiatric inpatients at McLean Hospital (Belmont, Mass.) from September 1991 to June 1996 were compiled. Patients' diagnoses were ascertained from hospital discharge summaries and based on the inpatient physician's clinical judgment. Most patients (77%) had multiple DSM-III-R psychiatric diagnoses. The mean ± SD age of patients was 38.6 ± 16.1 years, and 55% were women (Table 1). A large percentage of each diagnostic group was overweight, consistent with the many referrals to evaluate OSA. Compared with the other diagnostic groups, the schizophrenia/schizoaffective disorder group had a disproportionate percentage of men ($\chi^2 = 27.5$, df = 1, $p < .0001$) and a significantly higher body mass index (BMI; weight [kg]/height^2 [m^2]) ($t = 2.79$, df = 1, $p = .006$).

Charts were reviewed, blind to BMI and polysomnography results, to determine prior neuroleptic exposure. Patients were considered to have been on "chronic" neuroleptic treatment if they had been taking the medications continuously for 6 months prior to hospitalization. By this definition, 24% of patients were considered to have been on chronic neuroleptic treatment (see Table 1).

Table 1. Patient Characteristics by Diagnostic Group[a]

Characteristic	Schizophrenia (N = 46)	Depression (N = 176)	Bipolar Disorder (N = 92)	Posttraumatic Stress Disorder (N = 76)	Substance Use Disorder (N = 53)
Age, y, mean ± SD	35.3 ± 8.4	39.9 ± 16.6	38.0 ± 15.0	32.4 ± 9.1	38.0 ± 16.8
Gender, % male	80.4	51.1	32.4	11.8	62.3
BMI, mean ± SD	31.5 ± 8.2	27.0 ± 8.6	27.9 ± 7.6	27.5 ± 7.9	25.2 ± 5.7
Chronic neuroleptic administration, %	100.0	10.8	21.7	14.3	14.9
Overweight,[b] %	75.0	48.1	67.0	50.9	41.5
Obese,[c] %	50.0	27.1	31.2	36.4	14.6

[a]Abbreviation: BMI = body mass index.
[b]BMI > 25.
[c]BMI > 30.

Atypical neuroleptics were used by 24% of the schizophrenia group and by less than 5% of the other diagnostic groups. Neuroleptic doses were not recorded since they frequently changed over the 6 months prior to polysomnographic evaluation.

Of the 364 patients referred for sleep consultation, 284 (78%) had participated in overnight sleep studies: 72% of the schizophrenia group, 73% of the bipolar disorder group, 81% of the depressed group, 75% of the substance use disorder group, and 80% of the posttraumatic stress disorder (PTSD) group. No significant difference was found among diagnostic groups in the percentage of referred patients who had participated in sleep studies. Overnight sleep studies and scoring were performed in the Sleep Disorders Center at McLean Hospital according to previously described criteria.[6] Patients were administered all current medications on the night of their sleep study as on the psychiatric unit.

Obstructive sleep apnea was categorically defined as present if the respiratory disturbance index (RDI) exceeded 10 (or 20) apnea + hypopnea per hour of sleep. A hypopnea was defined as a discernible decrease in nasal/oral airflow lasting at least 10 seconds, associated with either an arousal from sleep[7] or a 3% decrease in oxygen saturation. An apnea was scored the same as a hypopnea except that a complete cessation of airflow for 10 seconds was required.

We performed a logistic regression with presence of sleep apnea (RDI > 10 and RDI > 20) as the dependent variables to identify significant risk factors for OSA and to control for the confounding effects of the excess of male patients, elevated BMI, and increased neuroleptic use in the schizophrenia group. All diagnoses for individual patients were entered into the logistic regression, rather than creating a hierarchical scheme of diagnoses. However, since patients had multiple diagnoses, differences in rate of OSA between diagnostic groups were analyzed using diagnosis, uncorrected by other variables, as the only predictor variable in the logistic regression model. Continuous variables (e.g., BMI) were evaluated with the Student t test. Approval for the chart review was obtained from the McLean Hospital Investigational Review Board.

RESULTS

Obstructive sleep apnea was significantly more common (odds ratio [OR] = 6.22, $p < .001$) in patients with schizophrenia/schizoaffective disorder than in patients without these disorders (Figure 1). This was true in both men (OR = 2.57, $p = .04$) and women (OR = 21.6, $p < .001$).

A logistic regression with OSA (RDI > 10) as the dependent variable (Table 2) demonstrated the substantial independent influences of gender, age, and BMI, each a known risk factor for OSA. With these variables alone, it appeared that schizophrenia contributed independently to the model (OR = 6.22, $p < .001$). However, after additionally accounting for chronic neuroleptic use, the direct impact of schizophrenia was reduced to an OR of 2.90, with a nonsignificant p value of .107. When an RDI > 20 events per hour (instead of 10 events per hour) was used as the dependent variable, the only change that occurred was that the chronic neuroleptic variable changed from a trend ($p = .07$) to statistical significance (OR = 5.02, $p = .01$) (Table 3). In a secondary analysis, a statistically significant interaction was found between BMI and chronic neuroleptic exposure (OR = 1.22, $p = .01$) when the outcome variable was RDI > 10, although this interaction did not reach significance when RDI > 20 events per hour was used. The direction of the interaction was positive, such that the additive risk of OSA associated with chronic neuroleptic use was larger as BMI increased.

Obstructive sleep apnea, when present in patients with schizophrenia, was severe, with a mean RDI of 64.8 events per hour (range, 10.5–118.5). On the basis of clinical interview and standardized sleep questionnaires, 44% (7/16) of the patients with schizophrenia who had apnea acknowledged difficulties with daytime somnolence, and only 25% (4/16) described any difficulties with sleep. However, most of the patients in the schizophrenia group were referred on the basis of concerns regarding daytime sleepiness and/or loud snoring.

DISCUSSION

Age, gender, and BMI, which are well-established predictors of obstructive sleep apnea in nonpsychiatric patients,[8] were confirmed as risk factors in this referred psychiatric population. We found that patients with schizophrenia had much higher rates of OSA than patients with other psychiatric disorders as a result of a higher propor-

Figure 1. Percentage of Patients in Each Diagnostic Group With Obstructive Sleep Apnea (respiratory disturbance index > 10 events/h)

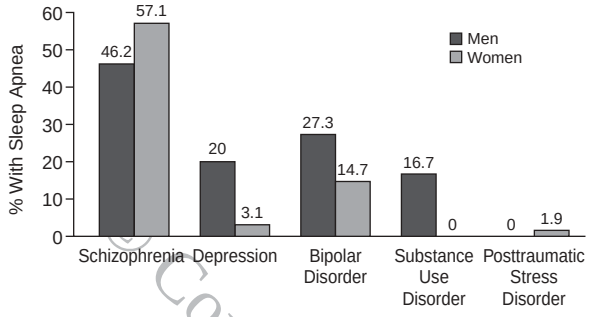

Table 2. Odds Ratios for Obstructive Sleep Apnea (respiratory disturbance index > 10) Calculated From Logistic Regression (N = 238)[a]

Variable	Odds Ratio	z	p Value	95% Confidence Interval
Male gender	5.76	3.53	.000	2.08 to 15.27
Age	1.03	2.02	.044	1.00 to 1.06
Schizophrenia	2.90	1.61	.107	0.79 to 10.57
BMI	1.14	4.76	.000	1.08 to 1.21
Chronic neuroleptic administration	2.81	1.79	.074	0.90 to 8.77

[a]Abbreviation: BMI = body mass index.

Table 3. Odds Ratios for Obstructive Sleep Apnea (respiratory disturbance index > 20) Calculated From Logistic Regression (N = 238)[a]

Variable	Odds Ratio	z	p Value	95% Confidence Interval
Male gender	5.85	3.09	.002	1.91 to 17.96
Age	1.04	2.00	.046	1.00 to 1.08
Schizophrenia	3.13	1.68	.093	0.83 to 11.81
BMI	1.14	4.56	.000	1.08 to 1.20
Chronic neuroleptic administration	5.02	2.53	.012	1.44 to 17.56

[a]Abbreviation: BMI = body mass index.

tion of male patients, high rates of obesity, and universal neuroleptic use. Although the higher proportion of men in the group with schizophrenia was an artifact of patient referral, the most powerful predictor of sleep apnea in this study, obesity, is a known concomitant of schizophrenia. One study[3] in an English depot neuroleptic clinic found that 31% of male patients and 37% of female patients with schizophrenia were obese (BMI > 30), compared with 6% and 9%, respectively, of the general U.K. population. Thus, the high rate of sleep apnea in the schizophrenia group is not surprising.

One previous study from Japan[9] demonstrated that 19% (19/101) of psychiatric inpatients with schizophrenia had sleep apnea. However, since the mean BMI of that sample was normal (24.0) (in contrast to the usual findings in schizophrenia, described above), that study may have underestimated OSA risk. In addition, the Japanese study[9] evaluated nocturnal respiration with oximetry alone (as opposed to polysomnography), which is known to underestimate risk of OSA.[10] Another recent study[11] found higher rates of OSA (48% of patients with an RDI > 10 and 20% with an RDI > 20) in elderly patients with schizophrenia (mean age = 60 years). Interestingly, they did not find any relationship between BMI and sleep apnea risk.

Much of the added risk of obesity in schizophrenia is thought to occur as a result of chronic antipsychotic administration. For instance, one study[12] of Spanish patients with schizophrenia demonstrated that neuroleptic use increased the number of those in the heaviest 15% of the population by 20% in women and 10% in men. Another study[13] of patients with schizophrenia taking clozapine found that greater than 50% of patients became overweight within 3 years of treatment. Other factors (e.g., lack of exercise, poor nutrition, lethargy) may also contribute to obesity in schizophrenia.

The presence of chronic neuroleptic administration (particularly in the RDI > 20 model) as an independent risk factor for OSA was unexpected. The influence of chronic (or for that matter, acute) neuroleptic administration on OSA, independent of its effect on weight, has not been investigated. Benzodiazepines[14] and alcohol[15] have been shown to increase the severity of sleep apnea, and neuroleptics may similarly decrease arousability from sleep (increasing the duration of respiratory obstructive events) or decrease the activity of upper airway dilator muscles. We were unable to determine whether specific classes or higher doses of neuroleptics were associated with higher rates of OSA. Future studies should investigate this important issue.

The demonstrated underdiagnosis of OSA in the general population[16] may be magnified in patients with schizophrenia, since the most common daytime symptom of OSA, excessive sleepiness, may be misattributed to patients' negative symptoms or medication side effects. Similarly, many patients with schizophrenia may not have a bed partner to report snoring or interruptions in breathing. Increased awareness by psychiatrists of these signs of OSA, as well as the anthropometric risk factors (such as obesity and neck size greater than 17 inches), will reduce underdiagnosis.

CPAP treatment of sleep apnea in the general population improves daytime alertness, cardiovascular function, and quality of life.[17] Anecdotal reports of treatment outcomes with CPAP in psychiatric patients suggest improvement in mood and psychosis (e.g., Strakowski et al.[18]); however, controlled studies have not been performed. Our study[19] of CPAP use in patients with psychiatric disorders suggests that those with schizophrenia have poor compliance, further complicating outcome studies.

The limitations of this retrospective study suggest some caution in the interpretation of our findings. Patients were not randomly selected for consultation or sleep study, but were included on the basis of the referring clinicians' or consultants' concerns regarding their sleep. High rates of sleep apnea among patients with schizophrenia found in this study thus represent, to some degree, a referral bias rather than the naturalistic rates of this disorder in the population. It is not suggested that the rates of OSA observed in these selected patients are representative of the prevalence of OSA in unselected psychiatric patients. It should also be noted that psychiatric diagnoses were established clinically, not by standardized instruments. Thus, some misdiagnoses may have occurred. However, since diagnosis was not ultimately a factor in predicting OSA, the importance of this limitation is unclear. On the other hand, although we had many patients in the study, it is possible that the finding that schizophrenia was not an independent risk factor for OSA was due to limited power.

Despite its limitations, this report has important clinical and public health implications for the management of schizophrenia. As OSA may be associated with an increased risk of hypertension and excess mortality,[5,20] sleep apnea may contribute to the 2- to 4-fold elevated risk of cardiovascular mortality observed in schizophrenia.[21] In addition, untreated sleep apnea may worsen mood and psychotic symptoms, and treatment may be associated with improvement in psychiatric status.[18] Polysomnographic evaluation of unselected patients will ultimately provide a better understanding of this potentially important clinical issue.

Drug name: clozapine (Clozaril and others).

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