Published in final edited form as:
Sleep Med. 2011 June ; 12(6): 591–597. doi:10.1016/j.sleep.2010.12.013.

The impact of atypical antipsychotic use on obstructive sleep apnea: A pilot study and literature review

Afshin Shirani[a,*], **Sergio Paradiso**[b], and **Mark Eric Dyken**[c]

[a]Department of Psychiatry, Dartmouth Medical School, Hanover, NH, United States

[b]Department of Psychiatry, University of Iowa Hospitals and Clinics, Roy Carver College of Medicine, University of Iowa, Iowa City, IA, United States

[c]Department of Neurology, University of Iowa Hospitals and Clinics, Roy Carver College of Medicine, University of Iowa, Iowa City, IA, United States

Abstract

Background—Limited evidence links atypical antipsychotics (AAs) use to sleep related respiratory dysfunction and greater severity of obstructive sleep apnea (OSA). The present paper reviews the published evidence and examines the impact of AA use on the presence and severity of OSA among subjects with clinically suspected OSA after adjusting for several confounds.

Methods—Archives of the University of Iowa Sleep Laboratory from 2005 to 2009 were searched for patients using AAs at the time of diagnostic polysomnogram (PSG). PSG data of the 84 AA users with heterogeneous psychiatric disorders (of these 20 diagnosed only with depression) were subsequently compared to PSG data of two randomly selected, non-AA user groups from the same patient pool: (i) 200 subjects with a depressive disorder as the only psychiatric diagnosis, and (ii) 331 mentally healthy controls. PSG data were analyzed adjusting for known demographic, medical, and psychiatric risk factors for OSA.

Results—Prevalence and severity of OSA did not differ significantly across three groups. Sex, age, body mass index (BMI), and neck circumference (NC) independently predicted OSA. Odds ratio for OSA in the subset of AA users carrying the diagnosis of depression ($n = 20$) compared with subjects without mental illness was 4.53 ($p < .05$). By contrast, AA users without depression or those with multiple psychiatric diagnoses including depression did not show a statistically significantly elevated OSA risk.

Conclusions—AA use in subjects with depression appears to increase the risk of OSA after controlling for known predisposing factors.

*Corresponding author. Address: Sleep Disorders Center, Dartmouth Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, United States. Tel.: +1 603 650 7534; fax: +1 603 650 7820. afshinshirani@hotmail.com (A. Shirani).

Disclosure Statement

This was not an industry supported study. Drs. Shirani and Paradiso indicated no financial conflict of interest. Dr. Dyken has received research support from Cephalon, Merck, and has served as a member of the speaker's bureau for Boehringer Ingelheim and Cephalon, but has indicated no conflict of interest with respect to this publication.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi:10.1016/j.sleep.2010.12.013.

Keywords

Atypical antipsychotics; Depression; Obstructive sleep apnea; Psychosis; Schizophrenia; Sleep related breathing disorder

1. Introduction

Obstructive sleep apnea (OSA) is a highly prevalent disorder that afflicts 2–4% of the adult population [1]. Major risk factors are male sex, advanced age, postmenopausal state, and excess body weight [1]. Modifiable risk factors include smoking [1,2], obesity [1], and impaired glucose tolerance (possibly independent from body weight) [1,3]. Compared to the general population, mentally ill individuals exhibit greater rates of obesity, [4,5] smoking [6] and impaired glucose tolerance [7], and carry a higher risk of OSA [8]. Moreover, mental illness itself has been independently associated with a higher risk of OSA; however, a causal relationship has not been established [8-10].

In addition to the above OSA risk factors inherently associated with mental illness, individuals with mental illness are frequently exposed to weight gain-inducing medications such as atypical antipsychotics (AAs) [11-13], and new onset OSA following AA-induced weight gain has been reported [14]. Irrespective of their impact on body mass index (BMI), however, various psychotropic agents exert a direct influence upon sleep-related respiratory function [15-18]. For instance, anxiolytic and hypnotic agents of the benzodiazepine class may exacerbate OSA due to central respiratory depression [15] or oropharyngeal muscle relaxation, [16] while antidepressants may lead to a mild reduction in OSA severity via facilitation of serotonin transmission [17,18]. Antagonism of serotonin transmission and sedative properties suggest AAs [19] could elevate the risk of OSA independent of weight gain, yet the non-obesity related effects of AAs in relation to OSA have not been systematically studied.

This article presents potential mechanisms of non-obesity related actions of AAs on respiration, reviews the published clinical evidence connecting AA use and OSA and examines the impact of AA use on OSA prevalence and severity in a large clinical sample.

1.1. Non-obesity related relationships of atypical antipsychotics and OSA

1.1.1. Atypical antipsychotics, serotonin signaling and OSA—AAs interact with a variety of central and peripheral neurotransmitter systems, particularly the serotonin (5-HT) system [19]. Serotonin transmission plays a pivotal role in the regulation of central respiratory drive, airway diameter and resistance [20-23]. The recognition of the importance of the central and peripheral serotonergic systems in the pathophysiology of OSA [24,25] has inspired a number of OSA treatment studies using serotonergic agents [17,18,26-29]. In light of inconsistent and/or unsatisfactory results the American Academy of Sleep Medicine has released recommendations against the use of serotonergic agents for pharmacologic treatment of OSA [30].

While the inadequacy of currently available serotonin agonists in the treatment of sleep related breathing disorders (SRBDs) has, thus, been established, the impact of the 5-HT receptors *antagonism* on sleep related breathing has received little attention. 5-HT receptor antagonism is a major mechanism of action of AA [19,31] and a potential contributing factor to increased upper airway resistance [23], but respiratory side effects of AAs are rarely reported [11]. The sporadic and acute nature of AA induced respiratory dysfunction discussed below suggests adverse effects of AAs on sleep related breathing require individual susceptibility. For instance, the 5-HT_{2A} single nucleotide polymorphism 1438-A/

G has been associated with a variety of psychiatric diagnoses [32], favorable response to certain AAs [33] and higher likelihood of OSA [34]. Alternatively, simultaneous administration of AAs, benzodiazepines, serotonergic and other centrally active agents with complex pharmacodynamic properties may explain certain cases of acute SRBDs or respiratory dysfunction [35].

1.1.2. Atypical antipsychotics, glucose metabolism and OSA—Another possible pathophysiological link between AAs and OSA is abnormal glucose metabolism. AA-induced weight gain has been associated with type II diabetes mellitus (DM II) in clinical and epidemiological studies [36-38]. Mounting evidence suggests a possible role for impaired glucose tolerance as a risk factor for OSA independent of weight gain [3,39,40]. If indeed the latter connection proves clinically significant, AA-induced impaired glucose tolerance may eventually be regarded as an additional risk factor for SRBDs irrespective of concomitant BMI changes.

1.1.3. Atypical antipsychotics, sleep architecture and OSA—Certain AAs increase total sleep time, while prolonging slow wave sleep (SWS) at the expense of REM sleep [41]. As obstructive respiratory events are generally more pronounced in REM sleep and SWS is known to be associated with stable respiration [1], AA-induced shifts in sleep architecture may seem theoretically beneficial with respect to respiration. Similar sleep architecture changes following acute and chronic sleep deprivation, however, suggest otherwise [42-45]. Recovery sleep following sleep deprivation increased the propensity to manifest SRBDs in healthy individuals [46] and worsened existing OSA [47]. Following one night of sleep deprivation, subjects with OSA exhibited significantly higher apnea–hypopnea indices (AHI) than baseline despite complete absence of REM sleep during recovery sleep [48]. Hence, as illustrated in recovery sleep following sleep deprivation, the propensity toward OSA can persist or increase in spite of reduced or absent REM sleep and the protective effects [1] of conserved or increased SWS. In light of these observations, an unfavorable effect of AAs on SRBDs remains a viable possibility, while hypothetical benefits from the AA-induced decreased REM to SWS ratio demand clinical corroboration.

1.2. Atypical antipsychotics, respiratory dysfunction and OSA: review of the published clinical evidence

Among 68 deaths reported during a post-marketing surveillance on 1728 patients using quetiapine (a sedating AA), 26.8% ($n = 15$) were related to unspecified respiratory causes [49]. Acute respiratory failure accompanied by stupor manifested in a middle aged, obese female with schizoaffective disorder following a single dose of quetiapine; quetiapine discontinuation led to quick recovery [50]. Suspected OSA and sleep related hypoxemia were subsequently confirmed by PSG, while pulmonary function tests were essentially unremarkable [50]. Uvulopalatopharyngoplasty successfully resolved OSA in a middle aged, depressed male, but shortness of breath and confusion ensued during postsurgical period in response to quetiapine [50]. Respiratory failure and CO_2 narcosis following oral administration of olanzapine (a sedating AA) developed in an elderly female patient with schizophrenia in context of obesity, chronic obstructive pulmonary disease (COPD) and congestive heart failure [51]. Olanzapine discontinuation resulted in rapid symptom resolution, and olanzapine re-challenge in gradual symptom reemergence [51]. Aripiprazole (a non-sedating AA) induced Cheyne-Stokes breathing (CSB) and central sleep apnea in an elderly male patient with psychotic depression in absence of cardiac abnormalities [52]. Continuous positive airway pressure (CPAP) was ineffective in treating the concomitant excessive daytime sleepiness, hence, aripiprazole was stopped. A repeat PSG three months later revealed mild OSA without periodic breathing, and aripiprazole was resumed [52]. Recurrence of severe CSB three months later prompted the substitution of aripiprazole with

clozapine (a sedating AA) [52]. Following the medication switch, CSB and central sleep apnea improved significantly but did not resolve despite unremarkable cardiopulmonary evaluations [52]. Chronic antipsychotic (predominantly typical agents) as opposed to non-chronic use presented a risk factor for the diagnosis of OSA in schizophrenia independent of BMI [53]. Greater OSA severity compared with controls was noted in 68 AA users after adjusting for age, gender, BMI, NC and hypnotic utilization [54].

The aforementioned reports suggest a possible link between AAs and presence and/or severity of OSA. A conclusive proof of the association, however, must overcome several methodological challenges. First, the impact of AAs on sleep related respiration cannot be ethically studied in subjects not requiring AAs for justified clinical purposes. Therefore, any association between OSA and AA use in patients with psychiatric disorders may be alternatively attributed to the underlying mental illness in case-control studies [8-10]. Second, the effect of known OSA risk factors (e.g., hypothyroidism, abnormal craniofacial morphology, etc.) [1] and simultaneously administered medications [15-18] in patients with mental illness may confound the study results substantially. Third, increased OSA risk may be mediated by AA-induced impaired glucose tolerance (including DM) [3,37,38], rather than being intrinsic to AA use.

1.3. The present research

The present study empirically examines the impact of AA use on the prevalence and severity of OSA in routine clinical practice while carefully accounting for demographic, medical, psychiatric and pharmacologic confounds. Three groups of subjects were selected from a common referral pool for PSG comprising patients with clinically suspected OSA (high pre-test OSA likelihood based on history of snoring, insomnia, and excessive daytime sleepiness): (1) a sample of patients using AAs irrespective of underlying psychiatric indications; (2) a sample of patients with the clinical diagnosis of depression (to control for effects of mental illness on OSA), but not using antipsychotics; (3) a sample of mentally healthy comparison subjects not taking psychotropic agents (Fig. 1). The choice of depression as a control for the effects of mental illness on OSA was based on previous research showing an increased risk of OSA in depression [8-10] and the overlapping symptomatology of both disorders (i.e., fatigue, insomnia, and unrefreshing sleep) [1]. In addition, certain AAs (aripiprazole, quetiapine, and olanzapine) have been approved by the US Food and Drug Administration (FDA) for use in depression and could potentially elevate an already increased risk of OSA in depression to a clinically relevant level. To minimize the impact of pharmacologic and medical confounds, or subjects with impaired respiratory muscle function or known anatomic abnormalities of airways or those using therapeutic agents altering central respiratory drive were excluded from the study. In addition, 11 demographic, medical (including impaired glucose tolerance/DM) and pharmacologic variables potentially significant with regard to respiration/OSA (Table 1) were recorded and used in the analyses to permit the isolation of AA effects on OSA.

2. Method

2.1. Subjects

University of Iowa Sleep Laboratory archives were accessed and electronic records of consecutively conducted PSGs between 2005 and 2009 were searched. Subjects taking AAs at the time of PSG irrespective of underlying psychiatric indication (AA group, AAG) were identified. Two comparison groups not using antipsychotic medications were randomly selected from the same patient pool. One group comprised subjects with depressive disorder (DD group, DDG), as determined by their medical record. Subjects with additional psychiatric diagnoses were excluded from DDG, but users of psychoactive agents

(antidepressants, mood stabilizers and anxiolytic agents) at the time of PSG were not. Another group (mentally healthy group, MHG) comprised subjects not carrying psychiatric diagnoses and not using psychotropics (i.e., antidepressants, lithium, stimulants, or benzodiazepines) at the time of PSG.

Following inclusion and exclusion criteria were applied across all three comparison groups. Included were adults 18 years or older who had undergone a full, attended, in laboratory PSG (type I) [55] at the University of Iowa Sleep Laboratory and whose records contained the complete set of study variables (see Table 1). To minimize the impact of medical and pharmacological confounds individuals were included from the study if they had known neuromuscular conditions including amyotrophic lateral sclerosis, diaphragmatic paresis, hereditary myopathies, multiple sclerosis, peripheral polyneuropathy, cerebral palsy; [56] gross anatomical abnormalities of airways (e.g., cleft palate and macroglossia), hypo- and retrognathia; [1] history of previously diagnosed OSA or obesity-hypoventilation syndrome, surgical intervention for treatment of primary snoring or OSA (sampling bias); undergone modified PSG with elevated head of the bed or supplemental oxygen; as well as those concurrently using opioids (with exception of tramadol and diphenoxylate), [57,58] theophylline, [59] acetazolamide, [60] and steroid sex hormones including birth control agents [61].

PSGs were scored by certified sleep technicians and reviewed by sleep specialists at the University of Iowa Sleep Disorders Center. OSA was defined by an AHI (the total of apneas and hypopneas divided by the total sleep hours) greater than or equal to 5 events/hour. Age, gender, BMI, neck circumference (NC), and diagnoses relevant to breathing function or with a known association with OSA such as hypertension (HTN), [62] were recorded (see Table 1). The study was conducted with the approval of the Institutional Review Board.

2.2. Data analysis

Hypothesis testing was carried out using regression models. The likelihood of OSA diagnosis (dependent variable) was estimated using a binary logistic regression model with group membership (i.e. AAG, DDG, MHG), age, sex, BMI, NC, DM, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), HTN, hypothyroidism, antidepressant and benzodiazepine use as predictors. Because of the heterogeneity of psychiatric diagnoses within AAG (see Table 3) and because DDG in contrast to AAG was a psychiatrically homogenous group of patients with depression only, AAG was subsequently divided according to psychiatric diagnosis into 3 subsets (Fig. 2): a subset including patients with depression only (AAG/dd, $n = 20$); another comprising patients with depression and other psychiatric disorders (AAG/dd+, $n = 18$), and a third containing subjects with psychiatric diagnoses excluding depression (AAG/dd-, $n = 46$). Regression analyses were repeated for each subset of AAG using group memberships (AAG/dd, DDG, MHG), (AAG/dd+, DDG, MHG), (AAG/dd−, DDG, MHG) as the dependent variables and the same set of predictor variables as for the whole sample analysis. Odds ratios of OSA for AAG, diagnostic subsets of AAG and DDG compared with MHG were computed. Predictors of AHI (a measure of OSA severity) among individuals with OSA were identified using linear regression and age, sex, BMI, NC, DM, CAD, COPD, HTN, hypothyroidism, antidepressant, and benzodiazepine use as predictor variables. Predictors were entered simultaneously in all models. The above predictor variables were chosen based on their known impact on OSA, OSA severity or breathing function [1].

3. Results

3.1. Demographic and clinical variables

Eighty-four patients taking AA (AAG), 200 patients diagnosed with a depressive disorder (DDG) and 331 comparison subjects (MHG) fulfilled the study criteria (Table 2). Group effects for age, BMI, sex, hypothyroidism, hypertension, antidepressant, and benzodiazepine use were found to be significant (DM just failed to reach significance). No other demographic or clinical variables showed significant group effects (Table 1).

3.2. Diagnosis of OSA

A binary logistic regression model predicting OSA diagnosis showed significant effects of sex [Wald ChiSquare (1) = 12.29, $p < .001$ – odds ratio (OR) if a woman = .4]; age [Wald ChiSquare (1) = 25.84, $p < .001$ – OR 1.04 for each year older]; BMI [Wald Chi-Square (1) = 8.3, $p < .005$ – OR 1.05 for each BMI point greater], and NC [Wald ChiSquare (1) = 5.22, $p < .03$ – OR 1.07 for each centimeter greater]. Other variables did not reach statistical significance (all F values <2.7, all p-values >.1). Sex, age, and BMI cumulatively explained about 15% of the variance in OSA diagnosis across the groups (AAG, DDG, and MHG); other variables including AA use did not add further precision to the prediction.

The logistic regression predicting OSA diagnosis for the subset of AAG with patients with depression only (AAG/dd, $n = 20$) showed significant effects for AAG/dd [Wald ChiSquare (1) = 4.16, $p < .05$ – OR of AAG/dd vs. MHG = 4.53], sex [Wald ChiSquare (1) = 11.7, $p = .001$ – OR if a woman = .38], age [Wald ChiSquare (1) = 21.2, $p < .001$ – OR 1.04 for each year older]; BMI [Wald Chi-Square (1) = 5.61, $p < .02$ – OR 1.04 for each BMI point greater], and NC [Wald ChiSquare (1) = 4.3, $p < .04$ – OR 1.07 for each centimeter greater]. In contrast, logistic regression models predicting OSA for AAG/dd+ and AAG/dd– versus DDG and MHG did not show significant group effects (Table 4). Results on sex, age, BMI and NC were essentially the same. DDG membership versus MHG did not reach statistical significance [Wald ChiSquare (1) = 3.2, $p = .072$ – OR of DDG vs. MHG = 1.93].

3.3. OSA severity in OSA positive subjects

In the linear regression model with AHI as the dependent variable sex, BMI, hypothyroidism, and benzodiazepine use were found to be independent predictors of AHI. Similarly AHI predictors in linear regression models for the subsets of AAG, i.e., AAG/dd, AAG/dd+ and AAG/dd, were BMI; BMI, NC, DM; BMI, NC, and DM, respectively. In summary, adjusting for multiple confounds, a statistically significant association between AA use and OSA in subjects with clinical diagnosis of depression was found. In addition, sex, BMI, hypothyroidism, and benzodiazepine use were independent predictors of AHI severity, whereas sex, age, and BMI independently predicted the diagnosis of OSA.

4. Discussion

The present study employed rigorous exclusion criteria to examine the AA/OSA association independent of the confounding effects of common medical and pharmacologic variables. In addition to a group of mentally healthy subjects, a comparison group of individuals with clinically diagnosed depression afforded a rational control for the effect of mental illness on OSA [8-10]. Finally, 11 demographic, medical and pharmacological variables related to respiration/OSA were included as covariates in the analyses.

Consistent with the established literature, [1] sex, age, and BMI were robust predictors of OSA diagnosis, while sex, BMI, hypothyroidism, and benzodiazepine use were associated with greater OSA severity (higher AHI among individuals with OSA). While no relationship

between AA use and OSA severity could be established for the whole sample, AA users diagnosed with depression only showed a significantly elevated OR (4.5) for OSA. The OR of OSA diagnosis for subjects diagnosed with depression but not taking AAs was non-significantly elevated (1.9) (Table 4). On the other hand, ORs for OSA were not statistically significantly higher for AA users with multiple psychiatric diagnoses or without depression. These findings suggest that AA use is a significant risk factor for OSA in a population of patients with high pre-test likelihood of OSA and clinical diagnosis of depression.

In accordance with previously reported predictive value of clinical features (i.e., age sex, BMI, bed partner's history and pharyngeal exam) the unaided clinical impression for detecting OSA correctly identified OSA in our sample (57% for the entire sample, 50–60% for the groups, Table 1) [63]. The relative overrepresentation of males in MHG was consistent with greater OSA prevalence in males [1]; the relative overrepresentation of females in AAG and DDG could in part be due to the higher prevalence of depression in females [64]. The sample and its subgroups therefore appeared representative of individuals with high pre-test likelihood of OSA and psychiatric disorders.

AA use in heterogeneous psychiatric disorders (AAG) was not associated with an increased risk of OSA. The paucity of clinical reports associating respiratory dysfunction with AA use [49-52] and absence of adverse respiratory outcomes from large scale schizophrenia trials [11] are consistent findings suggesting that additional predisposing factors are needed for AA-induced respiratory impairment. Depression increased the odds ratio of OSA to 2.7 and psychosis to 1.4 after adjusting for a number of demographic and medical confounds in a large scale study [8]. The prevalence of OSA (defined as AHI ≥ 15) in a sample of depressed subjects with insomnia was 39%, considerably higher than in general population or insomnia alone [9]. Sleep related air-flow limitations in depressed individuals were significantly commoner than in non-depressed controls [65]. In contrast, prevalence of OSA in schizophrenia was similar to controls in two other studies [66,67]. Hence, clinical observations favor the choice of depression as a permissive factor for AA-induced SRBD over psychosis. On the other hand, serotonin neurotransmission has been amply implicated both in the monoamine hypothesis of depression [68] and physiology/pathophysiology of respiration, [20,25] lending theoretical support to a possible connection of depression and OSA.

Thus far, the impact of antipsychotic use on OSA has been examined in a small number of publications. Prevalence of OSA in older patients with schizophrenia was similar to age-matched healthy controls in one study [67]; however, patients with schizophrenia exhibited greater OSA severity then healthy controls [67]. Among schizophrenia patients antipsychotic use was not found to be associated with a higher risk for OSA [67]. Of note, this study did not record medical comorbidities or account for their potential effects on OSA [67]. Rishi and colleagues [54] compared the OSA severity (i.e., AHI) in 64 AA users to non-user controls. After adjusting for age, gender, BMI, NC and hypnotic utilization, higher AHIs in the AA users were attributed to their AA use [54]. Confounding medical conditions such as hypothyroidism, DM, and anatomical abnormalities of upper airways [1] were not accounted for [54]. Lack of identification of psychiatric diagnoses in both AA users and non-users represents another potential source of bias in this report [54]. Psychiatric diagnoses have been associated with higher rates and/or severity of OSA [8-10,65,67]. Hence, it is unclear to what extent the higher severity of OSA in AA users reported by Rishi et al. [54] was related to concomitant medical or psychiatric illness. Winkelmann [53] retrospectively analyzed the risk of OSA in 283 psychiatric patients using antipsychotics. The variable of interest was chronic antipsychotic use as defined by uninterrupted use for six months. Chronic antipsychotic use was hypothesized to be qualitatively different from non-chronic use and posing an additional risk to develop OSA [53]. Subjects were divided in five

groups according to their psychiatric diagnoses (e.g., schizophrenia spectrum disorders, depression, and bipolar disorders). Each of the five groups was further subdivided in chronic versus non-chronic antipsychotic users. All subjects with schizophrenia spectrum disorders ($n = 46$) were chronic antipsychotic users (predominantly older, typical antipsychotic agents). Consequently the risk of non-chronic antipsychotic use in psychotic disorders could not be directly measured. While the risk of OSA was greater among patients with psychotic than non-psychotic disorders (OR = 6.2), accounting for chronic antipsychotic use did not equate the risk of OSA between psychotic (OR = 2.9) and non-psychotic patients [53]. The implications of this study [53] are limited by the absence of a mentally healthy control group and lack of information on medical comorbidities known to be associated with OSA [1].

The present study avoided many of the above shortcomings by employing several design strategies. Screening and elimination of patients diagnosed with OSA prior to the index sleep study averted selection bias. Rigorous exclusion criteria limited false positives driven by common medical and pharmacological confounds such as craniofacial abnormalities [1] and opioid use [58]. Variables linked to OSA, but too common to be exclusionary criteria (i.e., HTN or antidepressant use) were used as covariates to reduce the potential for spurious associations between AA use and OSA. In addition, utilization of a second comparison group comprised patients with clinical diagnosis of depression permitted to account for potential effects of mental illness in general and depression in particular on OSA. The presence of a statistically significant difference across the three study groups suggests that AA use in depression increases the risk of OSA in a population with high pre-test likelihood of OSA.

5. Study Limitations

The results of the present study should be interpreted with some caveats in mind. The study was retrospective and all subjects were clinically suspected of having OSA, (i.e., not randomly selected). The results may, therefore, not generalize to other patient populations. Data on smoking status of subjects were not available. Psychiatric diagnoses were clinical. Formal psychiatric assessment tools were not used to confirm the presence/absence of the recorded/other psychiatric disorders. Thus, caution should be exercised in drawing conclusions regarding the correlation of OSA and formally diagnosed psychiatric disorders. Since the length of AA use or dosage could not be ascertained from the medical records, dose/time dependent adverse effect AA use on SRBD could not be quantified. Poor medication compliance (AA, antidepressant and/or bezodiazepines) [69-72] in a portion of subjects may have affected the study results. It may, therefore, be prudent to verify medication compliance in future studies or require a minimum period of medication use prior to the PSG. Furthermore, due to their vast pharmacodynamic differences, [19] AA agents should ideally be studied individually or at least clustered in subgroups with respect to their relationship with OSA. The sample size needed to examine individual agents and control for psychiatric diagnosis could not be reached in this study. Finally inherent limitations of OSA diagnosis due to the night to night variability of respiratory disturbance index (RDI) [73-75] remain a challenge to the validity of this and similar studies and should be borne in mind. Ancoli-Israel et al. [67] attempted to address this problem by conducting two PSGs per study subject; however, only 44% of subjects completed the second PSG. Thus, study results may have been affected by the night to night variability of RDI in this report.

Certain limitations may, however, increase the applicability of our results to routine clinical practice. For instance, psychiatric disorders are not routinely diagnosed by administering research instruments. It may, therefore, be preferable to study patients with clinical psychiatric diagnoses to gain information applicable to clinical populations. AA agents are

often cross titrated, reduced or increased within days or weeks and/or prescribed simultaneously with other psychoactive medications, and medication adherence is typically questionable. Hence, the impact of AAs on SRBDs studied under rigorously defined conditions may not correlate with their impact in the clinical settings.

6. Conclusion

In the present study AA use was associated with a significantly increased risk of OSA in patients diagnosed with depression and high pre-test likelihood of OSA after adjusting for the effect of depression and several common medical/pharmacological confounds. The naturalistic approach extends applicability of the results to routine clinical practice. The findings in the present study are consistent with other reports suggesting a possible link between AA/depression and OSA [8-10,49-54,65]. Therefore, prospective studies of respiratory effects of AAs are needed to identify potentially vulnerable patients and define possible contraindications for individual AA agents in SRBD especially in light of their recent escalating use, specifically in depression [76-80].

Acknowledgments

The authors would like to thank the University of Iowa Sleep Laboratory staff, Zong-Ying Ren RPSGT and Linda Bachmann RPSGT for their technical support and assistance with data extraction.

Dr. Paradiso has received support by the National Alliance for Research on Schizophrenia and Depression (NARSAD), the Edward J. Mallinckrodt Jr. Foundation, the Dana Foundation and by NIH (5K23AG027837).

References

1. American Academy of Sleep Medicine. The International Classification of Sleep Disorders: Diagnostic and Coding Manual. Westchester, IL: American Academy of Sleep Medicine; 2005. p. 51-55.
2. Hoffstein V. Relationship between smoking and sleep apnea in clinic population. Sleep. 2002; 25:519–22. [PubMed: 12150318]
3. Tasali E, Mokhlesi B, Van Cauter E. Obstructive sleep apnea and type 2 diabetes. Chest. 2008; 133:496–506. [PubMed: 18252916]
4. Allison DB, Newcomer JW, Dunn AL, et al. Obesity among those with mental disorders: a National Institute of Mental Health meeting report. Am J Prev Med. 2009; 36:341–50. [PubMed: 19285199]
5. Dickerson FB, Brown CH, Kreyenbuhl JA, et al. Obesity among individuals with serious mental illness. Acta Psychiatr Scand. 2006; 113:306–13. [PubMed: 16638075]
6. Lasser K, Boyd JW, Woolhandler S, et al. Smoking and mental illness. JAMA. 2000; 284:2606–10. [PubMed: 11086367]
7. Haupt DW, Newcomer JW. Abnormalities in glucose regulation associated with mental illness and treatment. J Psychosomatic Res. 2002; 53:925–33.
8. Sharafkhaneh A, Giray N, et al. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep. 2005; 28:1405–11. [PubMed: 16335330]
9. Ong JC, Gress JL, et al. Frequency and predictors of obstructive sleep apnea among individuals with major depressive disorder and insomnia. J Psychosomatic Res. 2009; 67:135–41.
10. Ohayon MM. The effects of breathing-related sleep disorders on mood disturbances in the general population. J Clin Psychiatry. 2003; 64:1195–200. [PubMed: 14658968]
11. Lieberman JA, Stroup TS, McEvoy JP, et al. For the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. NEJM. 2005; 353:1209–23. [PubMed: 16172203]
12. Gentile S. Long-term treatment with atypical antipsychotics and the risk of weight gain. Drug Safety. 2006; 29:303–19. [PubMed: 16569080]

13. Gentile S. Contributing factors to weight gain during long-term treatment with second-generation antipsychotics. A systematic appraisal and clinical implications. Obesity Rev. 2009; 10:527–42.
14. Wirshing DA, Pierre JM, Wirshing WC. Sleep apnea associated with antipsychotic-induced obesity [letter]. J Clin Psychiatry. 2002; 63:369–70. [PubMed: 12000215]
15. Guilleminault C. Benzodiazepines, breathing, and sleep. Am J Med. 1990; 88:25S–8S. [PubMed: 1968716]
16. Drummond GB. Comparison of sedation with midazolam and ketamine: effects on airway muscle activity. Br J Anaesth. 1996; 76:663–7. [PubMed: 8688266]
17. Brownell L, West P, Sweatman P, et al. Protriptyline in obstructive sleep apnea: a double-blind trial. N Engl J Med. 1982; 307:1037–42. [PubMed: 6750396]
18. Hanzel DA, Proia NG, Hudgel DW. Response of obstructive sleep apnea to fluoxetine and protriptyline. Chest. 1991; 100:416–21. [PubMed: 1864117]
19. Gardner DM, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. CMAJ. 2005; 172:1703–11. [PubMed: 15967975]
20. Hodges MR, Tattersall GJ, Harris MB, McEvoy SD, Richerson DN, et al. Defects in breathing and thermoregulation in mice with near-complete absence of central serotonin neurons. J Neurosci. 2008; 28:2495–505. [PubMed: 18322094]
21. Popa D, Léna C, Fabre V, et al. Contribution of 5-HT2 receptor subtypes to sleep-wakefulness and respiratory control, and functional adaptations in knock-out mice lacking 5-HT2A receptors. J Neurosci. 2005; 25:11231–8. [PubMed: 16339018]
22. Brandes IF, Zuperku EJ, Stucke AG, et al. Serotonergic modulation of inspiratory hypoglossal motoneurons in decerebrate dogs. J Neurophysiol. 2006; 95:3449–59. [PubMed: 16495364]
23. Kanamaru M, Homma I. Compensatory airway dilation and additive ventilatory augmentation mediated by dorsomedial medullary 5-hydroxytryptamine 2 receptor activity and hypercapnia. Am J Physiol Regul Integr Comp Physiol. 2007; 293:R854–60. [PubMed: 17537836]
24. Ryan CM, Bradley TD. Pathogenesis of obstructive sleep apnea. J Appl Physiol. 2005; 99:2440–50. [PubMed: 16288102]
25. Veasey SC. Serotonin agonists and antagonists in obstructive sleep apnea. Am J Respir Med. 2003; 2:21–9. [PubMed: 14720019]
26. Carley DW, Olopade C, et al. Efficacy of mirtazapine in obstructive sleep apnea syndrome. Sleep. 2007; 30:35–41. [PubMed: 17310863]
27. Berry R, Yamaura E, Gill K, et al. Acute effects of paroxetine on genioglossus activity in obstructive sleep apnea. Sleep. 1999; 22:1087–92. [PubMed: 10617169]
28. Kraiczi H, Hedner J, Ejnell H, et al. Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. Sleep. 1999; 22:61–7. [PubMed: 9989366]
29. Marshall NS, Yee BJ, et al. Two randomized placebo-controlled trials to evaluate the efficacy and tolerability of mirtazapine for the treatment of obstructive sleep apnea. Sleep. 2008; 31:824–31. [PubMed: 18548827]
30. Morgenthaler TI, Sheldon K, Lee-Chiong T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep. 2006; 29:1031–5. [PubMed: 16944671]
31. Kim HJ, Choo H, et al. Classification of dopamine, serotonin, and dual antagonists by decision trees. Bioorg Med Chem. 2006; 14:2763–70. [PubMed: 16387502]
32. Seretti A, Drago A, De Ronchi D. HTR2A gene variants and psychiatric disorders: a review of current literature and selection of SNPS for future studies. Curr Med Chem. 2007; 14:2053–69. [PubMed: 17691947]
33. Ellingrod VL, Perry PJ, Lund BC, et al. Serotonin 5-HT2A and 5-HT2C receptor polymorphism responsible for predicting clinical response to the antipsychotic agent olanzapine. J Clin Psychopharm. 2002; 22:622–4.
34. Bayazit YA, Yilmaz M, Ciftci T, et al. Association of the -1438G/A polymorphism of the 5-HT_{2A} receptor gene with obstructive sleep apnea syndrome. ORL. 2006; 68:123–8. [PubMed: 16449821]
35. Fleischman JK, Ananthamoorthy R, et al. An unexplained death in the psychiatric emergency room: a case of undiagnosed obstructive sleep apnea? Gen Hosp Psychiatry. 2008; 30:83–6. [PubMed: 18164947]

36. Buse JB, Cavazzoni P, et al. A retrospective cohort study of diabetes mellitus and antipsychotic treatment in the United States. J Clin Epidemiol. 2003; 56:164–70. [PubMed: 12654411]
37. Liebzeit KA, Markowitz JS, Caley CF. New onset diabetes and atypical antipsychotics. Euro Neuropsychopharmacol. 2001; 11:25–32.
38. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. Schizophrenia Res. 2004; 71:195–212.
39. Valham F, Stegmayr B, et al. Snoring and witnessed sleep apnea is related to diabetes mellitus in women. Sleep Med. 2009; 10:112–7. [PubMed: 18207451]
40. Aronsohn RS, Knutson KL, et al. Obstructive sleep apnea (OSA) in patients with type 2 diabetes (t2dm): prevalence and impact on glucose control. Sleep. 2009; 32(abstract suppl):A174.
41. Monti JM, Monti D. Sleep in schizophrenia patients and the effects of antipsychotic drugs. Sleep Med Rev. 2004; 8:133–48. [PubMed: 15033152]
42. Cajochen C, Foy R, Dijk DJ. Frontal predominance of relative increase in sleep delta and theta EEG activity after sleep loss in humans. Sleep Res Online. 1999; 2:65–9. [PubMed: 11382884]
43. Borbély AA, Achermann P. Sleep homeostasis and models of sleep regulation. J Biol Rhythms. 1999; 14:559–70.
44. Achermann P, Finelli LA, Borbély AA. Unihemispheric enhancement of delta power in human frontal sleep EEG by prolonged wakefulness. Brain Res. 2001; 913:220–3. [PubMed: 11549390]
45. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med. 2007; 3:519–28. [PubMed: 17803017]
46. Guilleminault C, Silvestri R, Mondini S, Coburn S. Aging and sleep apnea: action of benzodiazepine, acetazolamide, alcohol, and sleep deprivation in a healthy elderly group. J Gerontol. 1984; 39:655–61. [PubMed: 6491178]
47. Stoohs RA, Dement WC. Snoring and sleep-related breathing abnormality during partial sleep deprivation. NEJM. 1993; 328:1279. [PubMed: 8464450]
48. Persson H, Svanborg E. Sleep deprivation worsens obstructive sleep apnea: comparison between diurnal and nocturnal polysomnography. Chest. 1996; 109:645–50. [PubMed: 8617071]
49. Twaites BR, Wilton LV, Shakir SAW. The safety of quetiapine: results of a post-marketing surveillance study on 1728 patients in England. J Psychopharmacol. 2007; 21:392–9. [PubMed: 17656426]
50. Freudenmann RW, Süssmuth SD, Wolf RC, et al. Respiratory dysfunction in sleep apnea associated with quetiapine. Pharmacopsychiatry. 2008; 41:119–21. [PubMed: 18484556]
51. Mouallem M, Wolf I. Olanzapine-induced respiratory failure. Am J Geriatr Psychiatry. 2001; 9:304–5. [PubMed: 11481140]
52. Kohen I, Sarcevic A. Central sleep apnea in a geriatric patient treated with aripiprazole. Am J of Therapeutics. 2009; 16:197–8.
53. Winkelmann JW. Schizophrenia, obesity and obstructive sleep apnea. J Clin Psychiatry. 2001; 62:8–11.
54. Rishi MA, Shetty M, Grigoriyan A, Vasquez R, Kremer A, et al. Atypical antipsychotics and severity of obstructive sleep apnea. Sleep. 2009; 32(abstract suppl):A38.
55. Standards of Practice Committee of the American Sleep Disorders Association. Practice parameters for the use of portable recording in the assessment of obstructive sleep apnea. Sleep. 1994; 17:372–7. [PubMed: 7973322]
56. Culebras A. Sleep disorders and neuromuscular disease. Seminars in Neurology. 2005; 25:33–8. [PubMed: 15798935]
57. Walker JM, Farney RJ, Rhondeau SM, et al. Chronic opioids use is a risk factor for the development or central sleep apnea and ataxic breathing. J Clin Sleep Med. 2007; 15:455–61. [PubMed: 17803007]
58. Webster LR, Choi Y, Desai H, et al. Sleep-disordered breathing and chronic opioid therapy. Pain Med. 2008; 9:425–32. [PubMed: 18489633]
59. Javaheri S, Parker TJ, Wexler L, et al. Effect of theophylline on sleep disordered breathing in heart failure. NEJM. 1996; 335:562–7. [PubMed: 8678934]

60. Javaheri S. Acetazolamide improves central sleep apnea in heart failure. Am J Resp Crit Care. 2006; 173:234–7.
61. Wesström J, Ulfberg J, Nilsson S. Sleep apnea and hormone replacement therapy: a pilot study and a literature review. Acta Obstet Gynecol Scand. 2005; 84:54–7. [PubMed: 15603568]
62. Nieto FJ, Young TB, Lind BK, et al. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep heart health study. JAMA. 2000; 283:1829–36. [PubMed: 10770144]
63. Hoffstein V, Szalai JP. Predictive value of clinical features in diagnosing obstructive sleep apnea. Sleep. 1993; 16:118–22. [PubMed: 8446830]
64. Diagnostic and statistical manual of mental disorders. 4. Washington: American Psychiatric Association; 2000. text revision
65. Deldin PJ, Phillips LK, Thomas RJ. A preliminary study of sleep-disordered breathing in major depressive disorder. Sleep Med. 2006; 7:131–9. [PubMed: 16260180]
66. Takahashi K, Shimizu T, et al. Prevalence of sleep-related respiratory disorders in 101 schizophrenic inpatients. Psychiatry Clin Neurosci. 1998; 52:229–31. [PubMed: 9628167]
67. Ancoli-Israel S, Martin J, Jones DW, et al. Sleep-disordered breathing and periodic limb movements in sleep in older patients with schizophrenia. Biol Psychiatry. 1999; 45:1426–32. [PubMed: 10356624]
68. Kirshnan V, Nestler EJ. The molecular neurobiology of depression. Nature. 2008; 455:894–902. [PubMed: 18923511]
69. Cramer JS, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatr Serv. 1998; 49:196–201. [PubMed: 9575004]
70. Bebbington PE. The content and context of compliance. Int Clin Psychopharmacol. 1995; 9(Suppl 5):41–50. [PubMed: 7622833]
71. Weiden P, Aquila R, Standard J. Atypical antipsychotic drugs and long-term outcome in schizophrenia. J Clin Psychiatry. 1996; 57:53–60. [PubMed: 8941171]
72. Thomas P. The stable patient with schizophrenia - from antipsychotic effectiveness to adherence. Eur Neuropsychopharmacol. 2007; 17(Suppl. 2):S115–22. [PubMed: 17336766]
73. Meyer TJ, Eveloff SE, Kline LR, Millman RP. One negative polysomnogram does not exclude obstructive sleep apnea. Chest. 1993; 103:756–60. [PubMed: 8449064]
74. Chediak AD, Acevedo-Crespo JC, Seiden DJ, Kim HH, Kiel MH. Nightly variability in the indices of sleep-disordered breathing in men being evaluated for impotence with consecutive night polysomnograms. Sleep. 1996; 19:589–92. [PubMed: 8899939]
75. Ahmadi N, Shapiro GK, Chung SA, Shapiro CM. Clinical diagnosis of sleep apnea based on single night of polysomnography vs. two nights of polysomnography. Sleep Breath. 2009; 13:221–6. [PubMed: 19067010]
76. DeBattista C. Augmentation and combination strategies for depression. J Psychopharmacol. 2006; 20(Suppl. 3):11–8. [PubMed: 16644767]
77. Jarema M. Atypical antipsychotics in the treatment of mood disorders. Curr Opin Psychiatry. 2007; 20:23–9. [PubMed: 17143078]
78. Curtis LH, Masselink LE, et al. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. Arch Pediatr Adolesc Med. 2005; 159:362–6. [PubMed: 15809391]
79. Banthin JS, Miller GE. Trends in prescription drug expenditures by Medicaid enrollees. Med Care. 2006; 44(Suppl):I-27–35. [PubMed: 16625061]
80. Yang M, Barner JC, et al. Antipsychotic medication utilization trends among Texas veterans: 1997-2002. Ann Pharmacother. 2008; 42:1229–38. [PubMed: 18682544]

Abbreviations

5-HT	serotonin
AA	atypical antipsychotic

AAG	atypical antipsychotic group
AAG/dd	AAG subset with depressive disorder only
AAG/dd+	AAG subset with depressive disorder and other diagnoses
AAG/dd-	AAG subset with depressive disorder with any psychiatric diagnosis excluding depression
AHI	apnea–hypopnea index
BMI	body mass index
COPD	chronic obstructive pulmonary disease
CSB	cheyne-stokes breathing
DDG	depressive disorder group
DM	diabetes mellitus
FDA	US Food and Drug Administration
HTN	hypertension
MHG	mentally healthy group
NC	neck circumference
OR	odds ratio
OSA	obstructive sleep apnea
PSG	polysomnogram
RDI	respiratory disturbance index
REM	rapid eye movement
SRBD	sleep-related breathing disorder
SWS	slow wave sleep

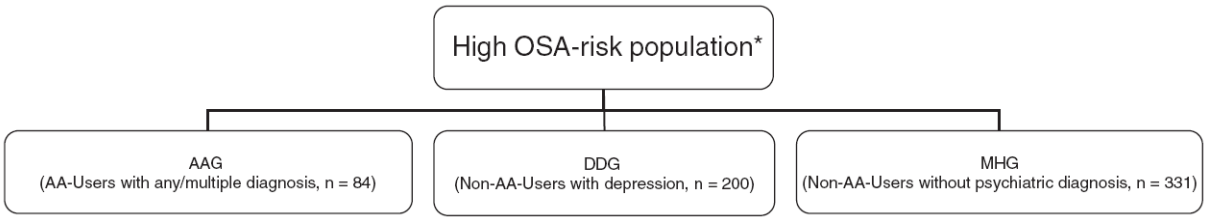

Fig. 1.
Study groups. *Indicates subject pool with clinically suspected obstructive sleep apnea (sleep laboratory referrals).

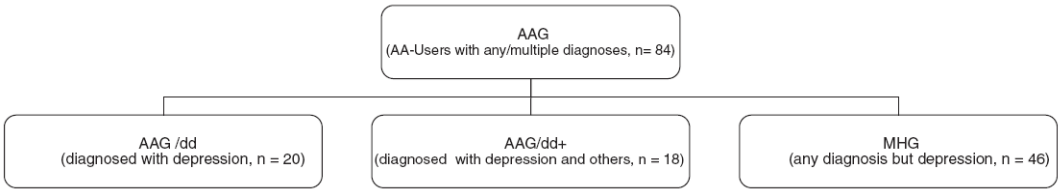

Fig. 2.
Study subgroups divided based on psychiatric diagnoses.

Table 1

Patients' characteristics by group.

	AAG	DDG	MHG
Number (*n*)	84	200	331
Gender (M/F) *	41/43	90/110	220/111
Age (mean ± SD) *	43.8 ± 12.5	47.5 ± 13.3	48.9 ± 14.8
BMI (mean ± SD) *	36.4 ± 9.9	36 ± 7.4	33.7 ± 8.4
NC in cm (mean ± SD)	42.2 ± 5.4	41.8 ± 4.7	41.7 ± 5.2
CAD (%)	8.3	11	11.5
COPD (%)	17.8	18	13.9
Impaired glucose tolerance/DM (%)	19	23.5	15.1
Hypertension (%) *	32.1	52	44.4
Hypothyroidism (%) *	23.8	15	10.3
Benzodiazepine use (%) *	34.5	9.5	0
Antidepressant use (%) *	84.5	77	0
OSA (% within group)	46 (54.8)	120 (60)	186 (55.9)

Abbreviations: AAG = atypical antipsychotic group, DDG = depressive disorder group, MHG = mentally healthy group, BMI = body mass index, NC = neck circumference, DM = diabetes mellitus, CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, OSA = obstructive sleep apnea.

* Indicates following significant group effects: for age [$F(2612) = 4.24$, $p < .02$], BMI [$F(2612) = 6.8$, $p = .001$], Sex [Chi-Square (2) = 26.1, $p < .001$], hypothyroidism [Chi-Square (2) = 10.9, $p < .005$], hypertension [Chi-Square (2) = 9.6, $p < .01$], antidepressant [Chi-Square (2) = 411, $p < .001$] and benzodiazepine use [Chi-Square (2) = 112.2, $p < .001$]. No other demographic or clinical variables showed significant group effects.

Table 2

Antipsychotic agents used in AAG*.

	Aripiprazole	Ziprasidone	Risperidone	Quetiapine	Olanzapine	Clozapine
Number (%)	26 (31)	7 (8.3)	16 (19)	34 (40.5)	7 (8.3)	3 (3.6)

AAG = atypical antipsychotic group.

*A few subjects were using multiple agents. Hence, $n > 84$.

Table 3

Psychiatric diagnoses in AAG[**].

Total	DepressiveD/O	Bipolar D/O	PsychoticD/O	Anxiety D/O	Substance use D/O	Other	Not reported
N = 84 (100%)	38 (45.2)	24 (28.6)	11 (13.1)	14 (16.7)	5 (6)	9 (10.7)	2 (2.4)

AAG = atypical antipsychotic group.

[**] Includes a subset of subjects carrying multiple diagnoses, hence, $\Sigma n > 84$.

Table 4

Odds ratios of OSA compared to MHG for AAG subsets and DDG[a].

	Odds ratio of OSA for AAG subset (*p*-values)	Odds ratio of OSA for DDG (*p*-values)
Analysis 1 (AAG/dd, *n* = 20)	4.529 (0.041)*	1.930 (0.072)
Analysis 2 (AAG/dd+, *n* = 18)	0.844 (0.8)	2.111 (0.043)*
Analysis 3 (AAG/dd−, *n* = 46)	1.303 (0.581)	1.485 (0.241)

AAG = atypical antipsychotic group, DDG = depressive disorder group, MHG = mentally healthy group, AAG/dd = AAG subset with depressive disorders only, AAG/dd− = AAG subset with psychiatric diagnoses excluding depression, AAG/dd+ = AAG subset with multiple psychiatric diagnoses including depression, OSA = obstructive sleep apnea.

[a]Significant values are marked with *.