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Obstructive Sleep Apnea and Psychiatric Disorders: A Systematic Review

Madhulika A. Gupta, MD, FAASM; Fiona C. Simpson, HBSc

Department of Psychiatry, Schulich School of Medicine and Dentistry, University of Western Ontario, London, Ontario, Canada

Study Objectives: Obstructive sleep apnea (OSA) has been associated with psychiatric pathology. Psychiatric comorbidity in OSA may affect patient quality of life and adherence to CPAP. A focused evaluation of OSA in highly selected groups of primarily psychiatric patients may provide further insights into the factors contributing to comorbidity of OSA and psychopathology. The goal of this study is to examine the prevalence and treatment of OSA in psychiatric populations.

Methods: A systematic review following the PRISMA guidelines was conducted to determine the prevalence of OSA in schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders, and to examine potential interventions. The PubMed, EMBASE, and PsycINFO databases were searched (last search April 26, 2014) using keywords based on the ICD-9-CM coding for OSA and the DSM-IV-TR diagnostic groups.

Results: The search retrieved 48 records concerning studies of OSA in the selected disorders. The prevalence studies indicate that there may be an increased prevalence of OSA in individuals with major depressive disorder (MDD) and posttraumatic stress disorder (PTSD), despite considerable heterogeneity and a high risk of bias. There was insufficient evidence to support increased OSA in schizophrenia and psychotic disorders, bipolar and related disorders, and anxiety disorders other than PTSD. Studies of treatment of OSA indicate an improvement in both OSA and psychiatric symptoms. CPAP adherence was reduced in veterans with PTSD.

Conclusions: OSA prevalence may be increased in MDD and PTSD. In individuals with OSA and psychiatric illness, treatment of both disorders should be considered for optimal treatment outcomes.

Keywords: obstructive sleep apnea, psychiatry, PTSD, depression, comorbidity

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Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by repeated episodes of upper airway obstruction during sleep.[1] According to a major US study of OSA diagnosed by polysomnography (PSG), the prevalence of OSA, as defined by an apnea-hypopnea index (AHI) ≥ 5 and without inclusion of a daytime sleepiness criterion, was reported as 24% for men and 9% for women under the age of 65 years; addition of a daytime sleepiness criterion reduced these estimates to 4% for men and 2% for women.[1,2] OSA is commonly associated with metabolic syndrome including comorbid obesity, hypertension, and diabetes.[1] Upper airway obstruction may present as apneas, hypopneas, or respiratory effort-related arousals (RERAs), resulting in oxygen desaturation, repeated arousals and sleep fragmentation.[1] Recently, there has been an increase in reports of comorbidity of OSA with psychological/psychiatric symptoms. Psychiatric comorbidity in OSA has been reported to adversely affect the quality of life of OSA patients and adherence to CPAP therapy.[3–5]

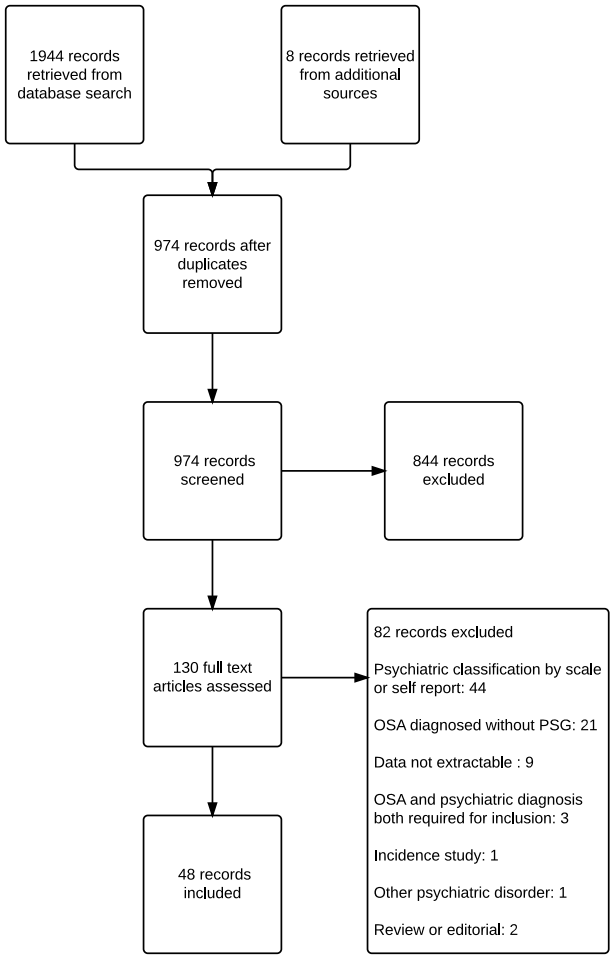
Psychological symptoms such as depression and anxiety are commonly reported in adults with OSA; however, the relationship between OSA and full psychiatric syndromes is less clear. Global prevalence studies and reviews have suggested that there are elevated rates of psychological symptoms in individuals with OSA.[6–16] These studies are limited in their ability to confirm psychiatric diagnoses, as psychiatric symptoms are commonly evaluated using self- or clinician rated psychiatric severity scales, not a diagnostic evaluation by an experienced clinician. Sleep symptoms may also artificially elevate patient scores on psychiatric scales. Popular scales, such as the Beck Depression Inventory (BDI), Profile of Mood States (POMS), and Minnesota Multiphasic Personality Inventory (MMPI), have questions relating to sleep symptoms such as insomnia and fatigue that are common to both OSA and psychiatric conditions.[17–19] Studies that have evaluated the prevalence of OSA in the highly selected groups of psychiatric populations may provide additional insight into the factors contributing to the comorbidity of OSA and psychopathology.

Our objectives were (1) to perform a comprehensive evaluation of the prevalence of OSA in the major psychiatric disorders including schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders; and (2) to perform a narrative evaluation of interventions for the treatment of OSA in individuals with schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders.

METHODS

The methodology for the systematic review was carried out according to the PRISMA guidelines.[20]

Figure 1—Flow diagram of study selection.



Eligibility Criteria

The inclusion criteria are: subjects with clinically diagnosed schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders and an OSA diagnosis conducted using PSG. A clinical diagnosis for a psychiatric disorder must have been established by a clinician using an interview or clinician-rated scale. Psychiatric disorders were classified based on the system used in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision (DSM-IV-TR), although studies using prior editions were also acceptable.[21] This diagnosis could be determined prospectively from the patient, through a chart review, or through the use of insurance coding using the International Classification of Diseases, Ninth Revision (ICD-9) or 10th Revision (ICD-10).[22,23] The criteria for OSA required a PSG (single or split-night) meeting the International Classification of Sleep Disorders, 2nd edition (ICSD-2) criteria for OSA with AHI $\geq$ 5 events/h or the respiratory disturbance index (RDI) equivalent.[1] The exclusion criteria were: non-English language articles, review articles, and animal studies.

Information and Sources

The search was conducted in PubMed (including MEDLINE), EMBASE (from 1974) via OVID, and PsycINFO (from 1806) via OVID up to April 26, 2014. The search terms were based on the ICD-9 codes for schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders. These diagnostic groups coincided with the respective DSM-IV-TR categories for these disorders.[21,22] The full search strategy for PubMed can be viewed in **Table S1** (**Appendix 1**). Additional articles were identified by hand search of the reference sections of relevant papers.

Study Selection

Full text articles were evaluated for inclusion by 2 independent reviewers (FS and KK), and disagreements were resolved by discussion to reach a consensus. Study populations discussed in multiple articles were grouped under a single study identifier by the final report (i.e., preliminary conference abstracts would be found under the identifier for the final published journal article) (**Appendix 2**).

Data Extraction

Data extraction was conducted independently by FS using a standard form for prevalence and intervention studies. The data collected for prevalence studies included the study identifier, sample size for any groups, gender, characteristics of the study population, the mean age, mean BMI, psychiatric medications used, psychiatric diagnostic criteria, and OSA diagnostic criteria. The data collected for intervention studies included the study identifier, sample size for any groups, gender, characteristics of the study population, psychiatric medications used, psychiatric diagnostic criteria, OSA diagnostic criteria, type of intervention, duration of intervention, study outcome measures, and results of the outcome measures. The authors of studies with missing or incomplete data were contacted via email to request additional data. In several large epidemiological studies of concurrent diagnoses of OSA and psychiatric disorders, the scores of the prevalence of psychiatric disorders in OSA were converted into scores for the prevalence of OSA in psychiatric disorders where the data permitted conversion.[24–26]

Risk of Bias

The quality of the included studies was evaluated by 2 independent reviewers (FS and KK) using the Hoy tool for assessing risk of bias (RoB) in prevalence studies and the Cochrane Risk of Bias tool for interventions.[27,28] Case reports were not assessed for RoB. The inter-rater reliability between the reviewers' RoB assessments was assessed using Cohen's κ in IBM SPSS Statistics 20 (Armonk, NY).[29]

RESULTS

Included Studies

Our search identified 974 individual manuscripts relating to psychiatric disorders in subjects diagnosed with OSA. Of these, 48 records containing 44 studies concerned subjects with clinically diagnosed schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders, who were evaluated by polysomnography for OSA (**Figure 1**; **Table S2**, **Appendix 1**).

Study Design

The included studies for prevalence were categorized based on whether they were population-based samples, clinical or

Table 1—Summary of findings: prevalence.

	Clinic-Based Prevalence			Population-Based Prevalence		
Psychiatric Disorder	**Range**	**Median**	**Number of Studies**	**Range**	**Median**	**Number of Studies**
Schizophrenia	0.7–47.8%	–	2[24,30]	–	–	–
Schizoaffective Disorder	3.2%	–	1[30]	–	–	–
Schizophrenia and Psychotic Disorders	48%	–	1[31]	4.52%	–	1[25]
BD-I and BD-II	2.9–69%	19.8%	4[24,30,32–34]	6.9%	–	1[25]
MDD	0–66%	48.1%	8[24,26,30,32,35–38]	7.4–44%	–	2[25,39]
Anxiety Disorders	47.5%*	–	1[26]	6.4–58.1%**	–	2[25,39]
PTSD	1.3–83%	42.7%	7[24,26,40–44]	46.4–50%	–	2[25,39]

*Includes PTSD. **Excludes PTSD. (–), not reported; BD-I, Bipolar Disorder Type I; BD-II, Bipolar Disorder Type II; MDD, major depressive disorder; PTSD, posttraumatic stress disorder.

inpatient samples. Overall, most prevalence studies were based on sleep clinic referrals or inpatient psychiatric populations. Due to the heterogeneous nature of the study populations, no pooled estimates of population prevalence were possible (**Appendix 3**, Section A). The inter-rater reliability score for RoB for prevalence studies was 0.871.

The search for intervention studies resulted in a combination of case reports and prospective and retrospective studies. These studies also presented a wide variety of interventions for OSA in subjects with psychiatric disorders, including CPAP, armodafinil, and uvulopalatopharyngoplasty (UPPP). RoB was only assessed for prospective and retrospective studies meeting the inclusion criteria, due to the obvious sample size bias of a report on a single individual (**Appendix 3**, Section B). The inter-rater reliability score for RoB for intervention studies was 0.828. Intervention data, categorized by psychiatric diagnosis, are subsequently presented.

Subjects

Excluded Studies

There were 82 excluded studies based on the full text review (**Figure 1**; **Table S3**, **Appendix 1**). The reasons for exclusion are presented in **Table S4** (**Appendix 1**). The most common reason for exclusion was the lack of a clinical psychiatric diagnosis, followed by lack of diagnostic PSG.

Prevalence

Schizophrenia and Psychotic Disorders

Schizophrenia: There have been 2 clinic-based studies conducted on the prevalence of OSA in schizophrenia (**Table 1**; **Table S5**, **Appendix 2**).[24,30] The clinic-based studies reported a prevalence range of 0.73% to 48.0%, and both studies had high risk of selection bias. The discrepancy between the reported prevalence is likely due to Levine reporting prevalence in consecutive psychiatric inpatients, while Winkelman reported prevalence in psychiatric patients with sleep clinic referrals, which is a substantial bias towards a higher prevalence of OSA.[24,30]

Schizoaffective Disorder: A single clinic-based prevalence study has been conducted on the prevalence of OSA in schizoaffective disorder (**Table 1**; **Table S5**, **Appendix 2**).[30] Levine found that the prevalence of OSA was 3.2% in 93 subjects with schizoaffective disorder.

Pooled Schizophrenia and Psychotic Disorders: There has been one clinic-based and one population-based study on pooled schizophrenia and other psychotic disorders.[25,31] The clinic-based population showed a 48% prevalence of OSA in mixed schizophrenia and schizoaffective disorder participants.[31] The population-based study conducted using the United States Veterans Health Administration (VHA) records reported an OSA prevalence in pooled schizophrenia and psychotic disorders of 4.52%.[25]

Mood Disorders

Bipolar I and II Disorder: There were 5 studies that reported the prevalence of OSA in bipolar I and II disorders (BD); 4 clinical studies and a single population-based study (**Table 1**; **Table S6**, **Appendix 2**).[24,25,30,32–34] In the clinic-based studies, the prevalence of OSA ranged from 2.9% to 69%. All 4 studies were at a high risk of selection bias. The range of prevalence may be related to the clinical population studied. Hattori reported the highest prevalence of 69% in a population of individuals with BD requiring a depression score on the HAM-D ≥ 10 and clinical signs of OSA.[32] This study has the greatest selection bias for OSA due to the requirement for active depressive symptoms and clinical signs of OSA. The lowest prevalence reported was 2.9% by Levine in a study of consecutive psychiatric patients at a state hospital where no pre-existing sleep symptoms were required for inclusion.[30] The populations of psychiatric inpatient sleep clinic referrals and consecutive BD patients showed moderate prevalence of 18.5% and 21%, respectively.[24,33] In Winkelman, there is a selection bias for psychiatric inpatients with sleep disturbance that is not specific to OSA and a reduced diagnostic threshold of an RDI > 10.[24] In Kelly, the study participants are consecutive outpatients, but the criteria for OSA are more stringent; requiring presenting EDS for diagnosis if the AHI is > 5 and < 15 events per hour or an AHI ≥ 15.[33,34] In the population-based study, the reported rate of OSA in BD was 6.94% in the VHA database.[25]

Major Depressive Disorder: Ten studies on the prevalence of OSA in individuals with major depressive disorder (MDD) were identified—8 clinic-based studies and 2 population-based

Table 2—Summary of findings: interventions.[45–74]

Disorders	Case Reports	Single-Assignment Trials or Retrospective Reviews	Randomized Controlled Trials
Schizophrenia and Psychotic Disorders	CPAP with psychopharmaceuticals improved psychosis: 9 cases[46–55] AT resolved OSA: 1 case[45]	–	–
BD: Manic Episodes	CPAP induced manic episode: 4 cases[55,56,58] ECT and BiPAP resolved mania and psychosis: 1 case[57] Topiramate 100 mg/day reduced apneas and snoring: 1 case[59]	–	–
MDD	–	UPPP decreased EDS and current depression: 1 study[60] CPAP reduced depression severity. In two studies CPAP also decreased EDS: 3 studies[61–63]	Armodafinil 200 mg/day was superior to placebo at reducing EDS: 1 study[64–67]
Panic Disorder	–	–	CPAP vs. Sham CPAP. CPAP reduced panic attacks, symptom severity and alprazolam use: 1 study[68]
PTSD	CPAP reduced symptoms of PTSD: 2 cases[73,74]	CPAP compliance was reduced in participants with PTSD. CPAP compliance reduced nightmare frequency: 4 studies[69–72]	–

(–), not reported; AT, adenotonsillectomy; BD, bipolar disorder; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; MDD, major depressive disorder; PSTD, posttraumatic stress disorder; RCT, randomized controlled trial; SAT, single-assignment trial; UPPP, uvulopalatopharyngoplasty.

studies (**Table 1**; **Table S7**, **Appendix 2**).[24–26,30,32,35–39] The clinic-based studies range in prevalence from 0% to 66%. Seven studies were at high risk of selection bias, and one study was at moderate risk of selection bias. The lowest prevalence of 0% was found by Levine in a sample of consecutive psychiatric inpatients without sleep symptoms.[30] The highest prevalence of 66% was found by Carney in subjects with comorbid coronary heart disease who have an increased risk for both depression secondary to CHD and for OSA due to pathophysiologic factors underlying CHD including obesity.[36] High selection bias for pre-existing sleep symptoms was present for sleep disturbance in Winkelman (12%) and insomnia in Ong (39%).[24,37] A specific depression severity was required for inclusion for the studies of Deldin (53%), Hattori (53%), and Summers (46.7%).[32,35,38] The final study, Mysliwiec, was conducted in a military population where routine PSG is a postcombat requirement, which may increase the reporting bias for OSA.[26] Overall, 6 of the 8 clinic-based samples reported an elevated rate of OSA in MDD. In population based studies, Sharafkhaneh reported a prevalence of 7.4% in the VHA vs. 44% for a community population sample in Hrubos-Strom.[25,39] This difference may be affected by sample size, as the final sample of MDD patients in Hrubos-Strom was 36 subjects, compared to 358,817 in Sharafkhaneh.

Dysthymia: A single study was identified that reported the prevalence of OSA in dysthymia. Hrubos-Strom 2012 reported that 3 of 5 (60%) individuals with dysthymia had a clinical diagnosis of OSA; however, the sample size and moderate RoB limit the generalizability of this data.[39]

Anxiety Disorders

Three studies reported the prevalence of pooled anxiety diagnoses (**Table 1**; **Table S8**, **Appendix 2**).[25,26,39] The clinic-based sample in Mysliwiec reported a prevalence of anxiety disorders excluding PTSD as 47.5% for their time interval.[26] This study was at a moderate RoB, as it included all diagnostic PSG performed on postcombats veterans as a routine measure. Hrubos-Strom reported a rate in current anxiety disorders including PTSD as 58.1% in a moderate RoB community survey-based sample.[39] This study is also the only study to report prevalence for individual anxiety disorders other than PTSD (**Table 1**; **Table S8**, **Appendix 2**). The prevalence of OSA was 58.8% in panic disorder (n = 17), 100% in agoraphobia without panic disorder (n = 2), 53.8% in social phobia (n = 13), 40% in obsessive compulsive disorder (n = 5), and 57.1% in generalized anxiety disorder (n = 14), respectively. However, the small sample sizes limit the generalizability of these results. The population-based study Sharafkhaneh reported an OSA prevalence of 6.4% in anxiety disorders including PTSD in the VHA.[25] The anxiety disorders represented the most heterogeneous group, as some studies pooled all anxiety disorders under one grouping while others either excluded PTSD or reported on individual diagnoses.

Posttraumatic Stress Disorder (PTSD): There were 9 studies that reported the prevalence of OSA in PTSD; 7 studies were clinic-based and 2 studies were population-based (**Table 1**; **Table S9**, **Appendix 2**).[24–26,39–44] The clinic-based studies reported a prevalence range of 0.7% to 83%.[24,26,40–44] Six studies were considered to have high risk of selection bias,

and one had a moderate risk of selection bias due to population sample, sleep symptom requirements, and/or PTSD severity. Kinoshita (83%) and Yesavage (69%) required participants to be male, aged ≥ 55 with a CAPS score ≥ 40, each of which acts as a selection bias towards increased OSA prevalence.[41,42] Two studies by Mysliwiec[26,43] examined postcombat PSG in military personnel, and the second of these[43] required a PTSD Checklist Military Version score ≥ 50, both of which act as selection biases. The van Liempt study also included male veterans with a CAPS score > 50.[44] The 2 civilian clinic samples reported the lowest prevalence of OSA in PTSD. Winkelman included consecutive psychiatric inpatients with sleep disturbances as selection bias. Krakow recruited crime victims with nightmares and insomnia with a PTSD severity requirement of Posttraumatic Stress Diagnostic Scale (PSDS) score ≥ 11.[40] The population-based studies reported a prevalence range of 46.4% to 50%.[25,39] These studies were at a low and moderate RoB, respectively. Six of the 9 studies were conducted in past and present military populations, which reported a range of 42.7% to 50% for both classes of study.[25,26,41–44] Civilian populations had the greatest discrepancy in prevalence rates from 0.7% to 50%.[24,39,40]

Interventions

Schizophrenia and Psychotic Disorders

Ten case studies were identified concerning the treatment of a spectrum of schizophrenia and psychotic disorders in individuals with undiagnosed OSA (**Table 2**; **Table S10**, **Appendix 2**).[45–54] Case reports concerned men in 83.3% of included studies. The most common intervention for OSA was CPAP in combination with existing psychiatric medications. In all but one case, CPAP resulted in improvement in excessive daytime sleepiness and negative psychotic symptoms. Chiner was the sole report of an acute psychotic episode induced by CPAP therapy.[47] Lee was the sole case report on adenotonsillectomy resolving a subject's psychosis and OSA; this patient also had temporal lobe epilepsy, which could have been the basis for the psychotic symptoms.[45] There are no available clinical trials evaluating the impact of the treatment of OSA on the presentation of symptoms of schizophrenia.

Mood Disorders

Bipolar Disorder: Four case reports on the relationship between CPAP and manic episodes have been reported for individuals with BD (**Table 2**; **Table S11**, **Appendix 2**).[55–58] In 4 cases, male subjects were admitted for depressive episodes where OSA was diagnosed after observation and PSG.[55,56,58] The subjects developed mania after 2–4 weeks of CPAP use. These patients required mood stabilizers or atypical antipsychotics to stabilize the manic episode, and it is clear that only 2 subjects continued with long-term CPAP use. The fifth case report concerns a female subject with a mixed manic and psychotic episode, who was treated with 12 sessions of ECT followed by CPAP and psychiatric drugs.[57]

An additional case study by Weber examined the effect of adding 100 mg/day of topiramate to the existing drug regimen of a 50-year-old man with BD.[59] The topiramate resulted in a reduction of snoring and a decrease in apneas from 20.0/h to 6.6/h. There was no weight change observed during the course of treatment.

The systematic review did not identify any clinical trials which evaluated the impact of treating OSA on symptoms of BD. The 4 case studies on emergent mania during treatment with CPAP may not be indicative of the overall effect of treating OSA in individuals with BD, as there is a tendency to publish case reports on exceptional circumstances, not successful routine treatment. The successful use of topiramate, which falls outside the parameters of routine treatment for OSA, further illustrates the high likelihood that publication bias is present for OSA and BD. Randomized controlled trials (RCTs) are required to determine the impact of treating OSA on symptoms of BD.

Major Depressive Disorder: Five intervention studies were included concerning the treatment of subjects with depressive disorders and OSA (**Table 2**; **Table S12**, **Appendix 2**).[60–67] A single study examined the effect UPPP on patients with a current major depressive episode (MDE).[60] At 6-month follow-up, the rate of current MDE had decreased to 10% from 34%, and hypersomnia decreased from 98% to 6%. Three studies examined the effect of CPAP in OSA in individuals with MDD. In all studies, CPAP reduced the severity of depression measured by the BDI and the Hamilton Rating Scale for Depression (HAM-D). Habukawa demonstrated that the decrease in BDI and HAM-D correlated with decreases in the Epworth Sleepiness Scale (ESS) score.[62] El-Sherbini reported resolution of MDD for 6 of 11 subjects with Structured Clinical Interview for DSM-IV Disorders diagnosed MDD.[63] The final study examined the effect of armodafinil in individuals with MDD or dysthymic disorder on stable antidepressant regimens and a stable CPAP regimen.[64–67] The study showed that armodafinil resulted in minimal Clinical Global Impression of Change improvement over placebo and a significant decrease in ESS scores.

There is significant publication and clinical trial design bias present in the studies conducted in individuals with MDD and OSA. UPPP has only been evaluated in a single-open label trial which limits the generalizability of the conclusions of this study. The 3 trials on CPAP were also single-assignment, open-label trials that each had different inclusion criteria for OSA. In addition, Habukawa was the sole study that required concurrent antidepressant treatment. For all 4 single arm trials, the lack of comparison to a sham-control group or alternate active therapy makes it difficult to determine if the depressive symptoms respond to the specific treatment or to placebo effect. The fifth trial, Krystal, fulfills the criteria for a gold standard RCT; however, armodafinil is intended to treat symptoms of EDS secondary to OSA. This therapy may be of benefit to individuals who present with EDS and OSA, but it is not indicative of the effect of treating the primary OSA on symptoms of MDD. RCTs are required to determine the impact of treating OSA on symptoms of MDD.

Anxiety Disorders

Panic Disorder: A randomized, crossover, sham-controlled study of CPAP was conducted in individuals with panic disorder (**Table 2**).[68] In Takaesu, participants were randomized to 4 weeks CPAP, 4 weeks off, and 4 weeks of sham CPAP, or the

same regimen with CPAP and sham CPAP reversed. At follow-up, individuals who underwent CPAP therapy showed reduction in panic attacks, symptom severity, and alprazolam use when compared to the sham treated subjects. The presence of a single study evaluating the impact of treating OSA on symptoms of panic disorder implies a high risk of publication bias; further RCTs are required to determine the impact of treating OSA in individuals with panic disorder.

Posttraumatic Stress Disorder: Four studies were identified concerning the treatment of OSA in subjects with PTSD (**Table 2**; **Table S13**, **Appendix 2**).[69–72] All 4 studies that had a high RoB were retrospective analyses of subjects undergoing CPAP treatment. CPAP compliance was the primary outcome for all studies, which was lower in individuals with PTSD than controls. In El-Sohl, lack of CPAP adherence was associated with increased baseline nightmare severity and less baseline EDS.[70] Krakow, Collen, and Gharaibeh found that reduction in nightmare frequency was associated with CPAP compliance.[69,71,72]

Two case reports concerning the treatment of OSA in PTSD were also identified (**Table 2**).[73,74] Youakim reported a case of a 42-year-old male veteran with PTSD and severe OSA who was treated with CPAP, resulting in control of OSA symptoms, nightmare reduction, and improvement in PSTD symptoms.[74] Yarlagadda reported a case study of a 35-year-old male with DSM-IV PTSD and chronic pain treated with fluoxetine 20 mg/day and lorazepam 0.5 mg as needed, resulting in OSA, weight gain, and hypertension. CPAP treatment was initiated in combination with lorazepam and antihypertensives.[73]

The studies of the treatment of OSA in PTSD were all retrospective reviews. The primary outcome for 3 of 4 studies was CPAP compliance. While these studies had the advantage of being able to identify factors that determine CPAP compliance, they are less effective than randomized, prospective studies at examining the treatment impact on PSTD severity. The control groups of these studies were more clearly oriented around CPAP compliance than PTSD symptom reduction. Gharaibeh used non-compliant participants as controls, whereas El-Sohl and Collen employed a control group of individuals with OSA without PTSD. The Krakow, El-Sohl, and Gharaibeh studies also employed comparison to CPAP non-compliant participants who were unaware of their compliance scores to examine baseline and follow-up symptom severity, which helped control for the placebo effect to an extent. Prospective, controlled RCTs with PTSD severity scales as outcome measures are required to determine the impact of treating OSA on PTSD symptoms.

DISCUSSION

Summary of Evidence

The first goal of this systematic review was to determine if there are elevated levels of OSA in individuals with psychiatric disorders. The prevalence of OSA in the general population is 24% for men and 9% for women, using a definition of AHI ≥ 5 without EDS.[1,2] Overall, there were insufficient reports on the prevalence of OSA in schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders to draw conclusions about the prevalence of OSA in psychiatric patients. There were two disorders, MDD and PTSD, in which the quantity of reports was higher, although the RoB for these studies was still moderate-high for all clinical populations. Despite the selection bias identified for the studied populations with MDD and PTSD, it appears that there is an elevated prevalence of OSA in these disorders. The median prevalence of OSA in MDD in eight clinical populations was 48.1% (range: 0% to 66%), which is substantially higher than the general population. In the population-based samples, the range was 7.4% to 44%; however, the 7.4% prevalence for OSA in MDD is higher than the 3.3% prevalence of OSA in the total study population. The median prevalence of OSA in PTSD was 42.7% in seven clinic-based populations (range: 1.3% to 83%). Both population-based studies also identified an elevated prevalence of OSA in PSTD (range: 46.4% to 50%). In contrast, four clinical reports on the prevalence of OSA in BD have a median prevalence of 19.8%, which is within the range of the general population, despite a similarly wide range of prevalence of 2.9% to 66%. Due to the high RoB for these studies, future prevalence studies will be required to confirm the findings in MDD and PTSD and to begin to evaluate the prevalence of OSA in other psychiatric diagnoses.

The second goal of this review was to identify and evaluate interventions for OSA in individuals with psychiatric disorders. The systematic review found reports on the use of CPAP, UPPP, adenotonsillectomy, and armodafinil alone and in conjunction with psychopharmaceuticals in psychiatric populations. These studies were predominantly case studies, single assignment trials, and retrospective chart reviews with high RoB. The only RCT included was for the use of armodafinil in subjects with MDD. CPAP therapy had positive outcomes in all populations tested, except for BD. A series of case studies suggests that CPAP may be linked to the development of manic episodes in patients with BD, so these patients should be observed carefully in the first months of treatment. In MDD, single assignment trials of CPAP were associated with improved symptom severity and decreased EDS. In subjects with PTSD, CPAP reduced nightmare frequency and PTSD symptoms; however, PTSD was also a predictive factor for CPAP non-compliance. UPPP conducted in unmedicated subjects with MDD decreased hypersomnia by 92% and reduced current depression to 10% from 34%. The use of armodafinil in participants with a current major depressive episode in conjunction with an antidepressant resulted in improvement in subjective, but not objective symptoms of EDS. However, many of these results were obtained in studies without placebo or sham controls, so these conclusions are preliminary and indicate a need for further study. Due to the scarcity of studies evaluating the treatment of OSA in individuals and the high RoB for the included studies, RCTs are required to assess the efficacy of OSA treatment in individuals with psychiatric disorders.

Limitations

Overall, the systematic review reveals that the relationship between OSA and psychiatric disorders is an area requiring substantial further study. There are few studies examining OSA in individuals with clinically diagnosed psychiatric disorders. The available data are largely concentrated in patient populations with MDD or PTSD. This may be related to (1) the clinical observation that patients with OSA show increased

depressive symptoms and (2) the interest of the military in the effective treatment of PTSD from a multisystem perspective.

The primary limitation of this systematic review is the overall quality of evidence. The RoB assessment was high for 78.9% of the included prevalence studies. In addition, there is substantial heterogeneity in study design for both prevalence and intervention studies with a lack of global agreement on the OSA and psychiatric diagnostic criteria. The retrospective studies for both prevalence and intervention are also further complicated by the use of lifetime psychiatric disorder diagnoses (as opposed to current episodes), which confounds the relationship between the severity of the psychiatric disorder and the presence and severity of OSA.

It is also apparent that many studies are conducted in samples of convenience, such as sleep clinic patient referrals with psychiatric diagnoses, psychiatric inpatients, or members of the military. While these studies present important preliminary findings, they are highly subject to publication bias. Populations selected from sleep clinic referrals for PSG due to reported symptoms of OSA are also subject to a selection bias. A sample that presents with clinical signs of OSA is significantly more predisposed to a high rate of OSA than a random sample of individuals with psychiatric disorders. Psychiatric inpatients have a selection bias due to their clinical status. Inpatients may have more severe psychiatric disorders than community dwelling individuals, which may increase the levels of obesity due to more expansive drug regimens that may contribute to metabolic syndrome. In addition, inpatients are likely to have a lower level of activity than community dwelling subjects due to the restrictions placed on their movements, which in turn could contribute to obesity and increased risk of developing OSA. The military population is primarily, if not exclusively, composed of male combat veterans and is the subject of the largest population-based study included in this review. This population may also have a different presentation of psychiatric disorders than the general population, as psychological testing a is a routine part of joining the armed forces and military personnel are exposed to different acute stressors than the general population.

The intervention studies are also subject to an overall high RoB. The scarcity of data is problematic, as the major interventions for OSA such as CPAP, adenotonsillectomy, UPPP, and wake-promoting drugs have not been studied in many psychiatric disorders. It is also problematic that many of these studies are single-assignment, open-label studies or retrospective chart reviews. In the absence of adequate sham or active controls, participant and personnel blinding, and randomization, it is difficult to determine if the improvement in psychiatric symptom severity is an effect of the treatment or the result of the placebo effect. Prospective, randomized controlled trials will be required to improve the quality of evidence to support the conclusions of these studies across all diagnoses.

CONCLUSIONS

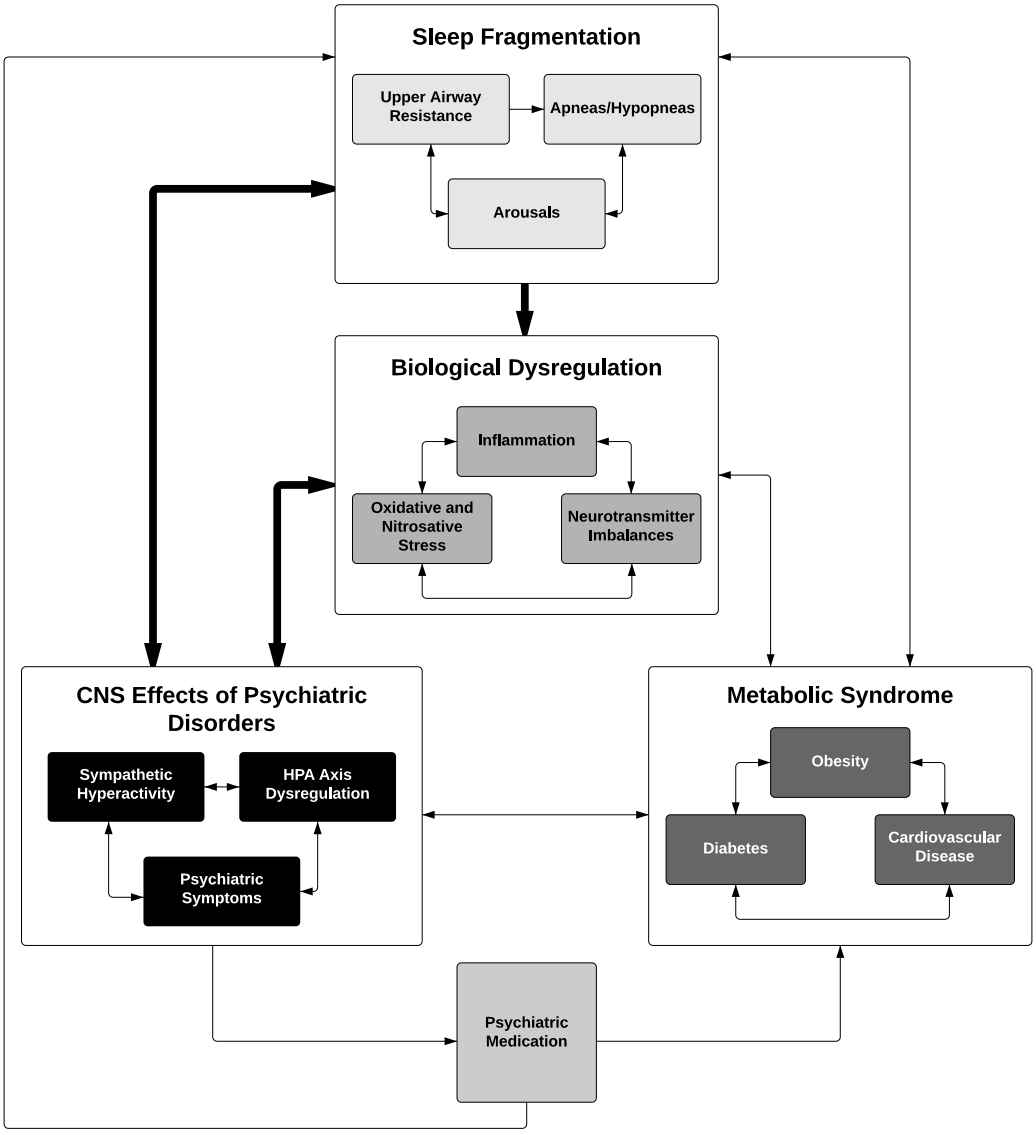
The results of this systematic review point to limited evidence that OSA may be elevated in MDD and PTSD, with insufficient evidence to draw conclusions on any other DSM-IV-TR diagnoses for schizophrenia and other psychotic disorders, mood disorders, and anxiety disorders. This does not necessarily indicate the absence of elevated levels of OSA in these populations, but points to the necessity of further study.

A number of factors may play a role in the association between psychiatric disorders such as MDD and PTSD with OSA (**Figure 2**). Oxidative and nitrosative stress, inflammation, and neurotransmitter imbalances play a role in all of the included psychiatric disorders.[75] This underlying molecular dysregulation manifests as psychiatric symptoms, but it also alters the neurobiological and endocrine function of these individuals, leading to the association of psychiatric disorders with obesity, diabetes, and cardiovascular disease. Psychiatric disorders have independent associations with obesity, metabolic syndrome, cardiovascular disease, and smoking, which are all independent predictors of OSA.[75–82] Central nervous system (CNS) alterations in psychiatric disorders may also lead to an increased risk of OSA, as sympathetic hyperactivity and hyperarousal states and resultant sleep fragmentation may lead to upper airway instability, which may contribute to subsequent OSA.[83,84] In chronic psychiatric disorders such as MDD and PTSD, it can be hypothesized that the severity of the dysfunction in each of these areas leads to slow and incremental increases in CNS activation and endocrine dysregulation. Eventually, as all of these changes affect homeostasis, the individual responds with further biological dysregulation, and the feed-forward process continues with a probable end result of metabolic syndrome, severe CNS dysregulation, and OSA.

The addition of psychiatric medication to correct the underlying molecular dysfunction and treat psychiatric symptoms may alleviate the issues in the CNS, but contributes to the further development of metabolic syndrome and possibly upper airway resistance as a result of extrapyramidal side effects, which in turn continue to stimulate the proposed feed-forward mechanisms leading to OSA.[85–87] The association between obesity and psychiatric medication is well known,[79,82,85,87,88] but the direct effects of these drugs on the upper airway and breathing during sleep are important factors. The tranquilizing effects of sleep medications and benzodiazepines may have direct effects on breathing during sleep which results in airway obstruction.[89–93] Atypical antipsychotics, a group of medications that are generally associated with fewer extrapyramidal side effects, have been associated with an increased AHI in a cross-section of psychiatric patients, even when compared to patients with similar BMI and neck circumference taking benzodiazepines, opioids, and sleeping agents.[86] This result points to an obesity independent effect of antipsychotics on OSA, possibly due to their extrapyramidal side effects.

The feed-forward mechanism proposed for the development of OSA (**Figure 2**) is a general hypothesis for the co-evolution of OSA in psychiatric disorders, and not all aspects will be present in every patient. Psychiatric disorders are associated with different types of neurobiological dysregulation that manifests as specific secondary effects. For example, HPA axis dysregulation is a prominent feature of PTSD and MDD, both of which appear to be associated with increased OSA. Anxiety disorders are associated with increased activity in the amygdala and insula, but only PTSD is correlated with additional decreased activity in the hippocampus, anterior cingulate cortex, and medial prefrontal cortex, which leads to a reduced ability to regulate the fear response.[94] This contributes to sympathetic

Figure 2—Proposed feed-forward pathway for the development of symptoms of upper airway instability and OSA from biological, psychiatric, and metabolic dysregulation.



Each symptom cluster is an independent entry point to the cycle. If left untreated, the presence of a risk factor increases the likelihood of the synergistic development of more symptoms from each cluster, resulting in OSA. The bolded arrows denote the most salient associations in the model.

hyperarousal during both sleep and wakefulness, and the hypervigilant states observed in PTSD and resultant sleep fragmentation, which may lead to instability of upper airways during sleep and upper airway resistance. In MDD, HPA axis dysregulation is a result of increased corticotrophin releasing hormone sensitivity, glucocorticoid resistance, and increased cortisol levels.[93,95] The downstream effects of this dysregulation are more likely to manifest as metabolic syndrome. These are both examples of disorder specific HPA axis dysregulation that manifest differently, but which have feed-forward effects into sleep symptoms eventually manifesting as OSA.

The most clinically significant finding of this review is the importance of recognizing and treating OSA when it occurs in an individual with a psychiatric disorder. OSA results in chronic intermittent hypoxia and arousals from sleep leading to sleep fragmentation, which has been shown to cause neurocognitive and mood deterioration in otherwise mentally robust individuals.[96,97] In psychiatric populations who already experience dysregulation of mood and possible neurocognitive deficits, it is likely that the same degree of hypoxic insult and sleep fragmentation may result in greater decompensation of the psychiatric disorder. Case study reports and clinical trials both suggest that the treatment of OSA with CPAP can help to reduce the need for psychopharmaceuticals, and to help clarify which symptoms originate from the primary psychiatric illness. Polysomnographic evaluation of treatment-resistant psychiatric patients (for example, MDD and PTSD) can be considered an excellent tool to determine if a sleep disorder is complicating a refractory psychiatric disorder. In cases where OSA is present, a combination of CPAP and pharmaceutical

treatment may result in greater therapeutic efficacy than traditional psychopharmacology alone.

Future studies on prevalence, incidence, and interventions need to be conducted to better ascertain the relationship between psychiatric disorder and OSA. There is a pressing need for additional population-based studies of OSA in community dwelling individuals with psychiatric disorders to allow for better comparison to the general population. Clinicians who wish to initiate trials of interventions for OSA in psychiatric population should consider sham or active comparator RCTs to better understand the impact of specific treatments in psychiatric populations. In light of the heterogeneity in study populations, participants in these studies should be diagnosed with OSA following the newly introduced ICSD-3 criteria, and the use of standard sleep outcomes should be encouraged to ensure that inter-study comparisons are possible in the future. Psychiatric diagnoses should continue to be made using a clinical interview following current DSM criteria, and validated psychiatric severity scales should be included as outcome measures, even where the primary trial goal is ascertaining compliance. This review reveals that there is a substantial opportunity to develop research projects to better understand the relationship between OSA and psychiatric disorders.

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SUBMISSION & CORRESPONDENCE INFORMATION

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Address correspondence to: Dr. Madhulika A. Gupta, 585 Springbank Drive, Suite 101, London, Ontario, Canada N6J 1H3; Tel: (519) 641-1001; Fax: (519) 641-1033; Email: magupta@uwo.ca

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. Off-label or Investigational Use: This article reports clinical trial and case study outcomes that may include investigational use of drugs or devices. The authors do not make any recommendations to use drugs or devices off-label.

APPENDICIES

Appendix 1: Included and Excluded Studies

Table S1—PubMed search strategy.

DSM-IV-TR Category	ICD-9-CM Code	Keywords
Schizophrenia and Other Psychotic Disorders	295	(sleep apnea OR upper airway resistance syndrome) AND (Schizophrenia OR schizophreniform disorder OR schizoaffective disorder)
	297	(sleep apnea OR upper airway resistance syndrome) AND (paranoia OR delusional disorder OR paraphrenia OR shared psychotic disorder OR paranoid state)
	298	(sleep apnea OR upper airway resistance syndrome) AND (nonorganic psychoses OR reactive confusion OR acute paranoid reaction OR psychogenic paranoid psychosis OR psychosis)
Mood Disorders	296	(sleep apnea OR upper airway resistance syndrome) AND (mood disorder OR bipolar disorder OR manic disorder OR major depressive disorder OR atypical manic disorder OR atypical depressive disorder OR episodic mood disorder)
Anxiety Disorders	300	(sleep apnea OR upper airway resistance syndrome) AND (anxiety OR panic disorder OR agoraphobia OR generalized anxiety disorder OR dissociative disorder OR conversion disorder OR factitious disorder OR hysteria OR dissociative amnesia OR dissociative fugue OR dissociative identity disorder OR phobia OR social phobia OR acrophobia OR claustrophobia OR obsessive-compulsive disorder OR dysthymic disorder OR neurasthenia OR depersonalization disorder OR hypochondriasis OR somatization OR somatoform disorder OR psychoneurosis)
	308	(sleep apnea OR upper airway resistance syndrome) AND (acute stress OR catastrophic stress OR combat fatigue OR gross stress reaction)
	309	(sleep apnea OR upper airway resistance syndrome) AND (adjustment reaction OR prolonged depressive reaction OR separation anxiety disorder OR posttraumatic stress disorder)

Table S2—Included studies.

Study Identifier	References
Aggarwal 2013	Aggarwal R, Baweja R, Saunders EF, Singareddy R. CPAP-induced mania in bipolar disorder: a case report. Bipolar Disord 2013;15:803–7.
Ancoli-Israel 1999	Ancoli-Israel S, Martin J, Jones DW, Caligiuri M et al. Sleep-disordered breathing and periodic limb movements in sleep in older patients with schizophrenia. Biol Psychiatry 1999;45:1426–32.
Bastiampillai 2011	Bastiampillai T, Khor LJ, Dhillon R. Complicated management of mania in the setting of undiagnosed obstructive sleep apnea. J ECT 2011;27:e15–6.
Berge 2008	Berge D, Salgado P, Rodriguez A, Bulbena A. Onset of mania after CPAP in a man with obstructive sleep apnea. Psychosomatics 2008;49:447–9.
Bottlender 1999	Bottlender R, Moller HJ. Negative symptoms due to sleep apnea syndrome in a patient with a delusional disorder. Eur Psychiatry 1999;14:352.
Boufidis 2003	Boufidis S, Kosmidis MH, Bozikas VP, Daskalopoulou-Vlahoyianni E, Pitsavas S, Karavatos A. Treatment outcome of obstructive sleep apnea syndrome in a patient with schizophrenia: case report. Int J Psychiatry Med 2003;33:305–10.
Carney 2006	Carney RM, Howells WB, Freedland KE, et al. Depression and obstructive sleep apnea in patients with coronary heart disease. Psychosom Med 2006;68:443–8.
Chiner 2001	Chiner E, Arriero JM, Signes-Costa J, Marco J. Acute psychosis after CPAP treatment in a schizophrenic patient with sleep apnoea-hypopnoea syndrome. Eur Respir J 2001;17:313–5.
Collen 2012	Collen JF, Lettieri CJ, Hoffman M. The impact of posttraumatic stress disorder on CPAP adherence in patients with obstructive sleep apnea. J Clin Sleep Med 2012;8:667–72.
Dahlöf 2000	Dahlöf P, Ejnell H, Hällström T, Hedner J. Surgical treatment of the sleep apnea syndrome reduces associated major depression. Int J Behav Med 2000;7:73–88.
Deldin 2006	Deldin PJ, Phillips LK, Thomas RJ. A preliminary study of sleep-disordered breathing in major depressive disorder. Sleep Med 2006;7:131–9.
Dennis 2001	Dennis JL, Crisham KP. Chronic assaultive behavior improved with sleep apnea treatment. J Clin Psychiatry 2001;62:571–2.
El-Sherbini 2011	El-Sherbini AM, Bediwy AS, El-Mitwalli A. Association between obstructive sleep apnea (OSA) and depression and the effect of continuous positive airway pressure (CPAP) treatment. Neuropsychiatr Dis Treat 2011;7:715–21.

Table S2 continues on the following page

Table S2 (*continued*)—Included studies.

Study Identifier	References
El-Sohl 2010	El-Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. Sleep 2010;33:1495–500.
Gharaibeh 2013	Gharaibeh K, Tamanna S, Ullah M, Geraci SA. Effect of continuous positive airway pressure therapy on nightmares in patients with post-traumatic stress disorder and obstructive sleep apnea. J Invest Med 2013;61:480–1.
Habukawa 2010	Habukawa M, Uchimura N, Kakuma T, et al. Effect of CPAP treatment on residual depressive symptoms in patients with major depression and coexisting sleep apnea: Contribution of daytime sleepiness to residual depressive symptoms. Sleep Med 2010;11:552–7.
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Study Identifier	References
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Study Identifier	References
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Study Identifier	References
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Uloza 2010	Uloza V, Balsevicius T, Sakalauskas R, Miliauskas S, Zemaitiene N. Changes in emotional state of bed partners of snoring and obstructive sleep apnea patients following radiofrequency tissue ablation: a pilot study. Sleep Breath 2010;14:125–30.
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Table S4—Reasons for exclusion.

Psychiatric Classification Evaluated by Scale or Self-Report (44)		OSA Reported without PSG (21)	Data not Extractable (9)	OSA and Psychiatric Diagnosis both Required for Inclusion (3)	Incidence Study (1)	Psychiatric Disorder of Interest not Included in this Review (2)	Review or Editorial (2)
Aikens 1999	Klonoff 1987	Cheng 2013	Babson 2013	Edlund 1991	Chen 2013	Berrettini 1980	Kierlin 2009
Aikens 1999b	Krakow 2007	Einvik 2011	Balan 1998	Sforza 2002		Munoz 1998	Moldofsky 1999
Asghari 2012	Lau 2010	Einvik 2013	Best 2013	Yesavage 2010			
Bakim 2012	Lehto 2012	Gupta 2014	Breslau 2004				
Balsevicius 2012	Machado 2006	Krakow 2002	Krakow 2000b				
Beutler 1981	Moroni 2011	McCall 2009	Krakow 2001				
Borak 1996	Nambu 1999	Mellman 1997	Krakow 2001b				
Calhoun 2011	Profant 2003	Motomura 2004	Krakow 2004				
Carney 2011	Ramos Platon 1992	Nasr 2010	Reynolds 1982				
Castro 2013	Rey de Castro 2013	Naismith 2004					
Chai-Coetzer 2013	Reyes-Zúñiga 2012	Naismith 2005					
DeZee 2005	Sanchez 2001	Ohayon 2003					
DeZee 2006	Schwartz 2003	Soreca 2011					
Doherty 2003	Skinner 2013	Soreca 2012					
Douglas 2013	Stepnowsky 2002	Spoormaker 2005					
Ekici 2013	Tihacek-Sojic 2012	Takahashi 1998					
Farney 2004	Uloza 2009	Turvey 2008					
George 1987	Uloza 2010	Vukin 2009					
Grunstein 1996	Valipour 2007	Waters 2013					
Hayashida 2007	Vgontzas 2011	Wheaton 2012					
Jacobsen 2013	Wallace 2013	Whooley 2012					
Jennum 1994	Yang 2011						

Appendix 2: Systematic Review Results

Table S5—Studies of the prevalence of OSA in individuals with schizophrenia and psychotic disorders.[24,25,30,31]

Study		Clinic-Based Studies				Population-Based Studies
		Ancoli-Israel 1999	Levine 2001		Winkelman 2001	Sharafkhaneh 2005
Participants with Schizophrenia and Psychotic Disorders	n	52	143	93	46	138,371
	M/F	35/17	104/39	50/43	37/9	Overall sample was 90.2% male
	OSA %	48%	0.7%	3.2%	47.8%	4.52%
Study Population		Participants from a larger study of late-life psychosis	Consecutive psychiatric patients at state hospital		Referrals for sleep disturbances on psychiatric inpatients	Inpatient records of Veteran's Health Administration from 1992–2001
Age (mean ± SD)		59.6 ± 8.9	41 ± 13	41 ± 10	35.3 ± 8.4	–
BMI (mean ± SD)		28.5 ± 7.4	–	–	31.5 ± 8.2	–
Psychiatric Drug Use		85%	–	–	100%	–
Schizophrenia Criteria		DSM-III-R schizophrenia or schizoaffective disorder	DSM-IV schizophrenia	DSM-IV schizoaffective disorder	DSM-III-R schizophrenia	ICD-9-CM: 295, 297, 298
OSA Criteria		RDI ≥ 10	Overnight PSG and oxyhemoglobin desaturation		RDI > 10	ICD-9-CM: 780.51, 780.53, 780.57
Overall Risk of Bias Assessment		High	High		High	Low

(–), not reported; BMI, body mass index; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PSG, polysomnography; RDI, respiratory disturbance index.

Table S6—Prevalence of OSA in individuals with bipolar disorders (BD).[24,25,30,32–34]

Study		Clinic-Based Studies				Population-Based Studies
		Winkelman 2001	Levine 2001	Hattori 2009	Kelly 2013	Sharafkhaneh 2005
BD	n	92	66	13	482	71,362
	M/F	30/62	39/27	Overall sample was 75% male	193/289	Overall sample was 90.2% male
	OSA %	18.5%	2.9%	69%	21%	6.94%
Study Population		Referrals for sleep disturbances on psychiatric inpatients	Consecutive psychiatric patients at state hospital	Mood disorder patients with HAM-D ≥ 10 and clinical signs of OSA	Consecutive patients at a depression and bipolar disorder clinic from October 2005 to December 2008	Inpatient records of Veteran's Health Administration from 1992–2001
Age (mean ± SD)		38.0 ± 15.0	42 ± 12	–	M: 43.53 ± 15.10 W: 45.37 ± 14.17	–
BMI (mean ± SD)		27.9 ± 7.6	–	–	26.7 ± 5.51	–
Psychiatric Drug Use		21.7%	–	–	–	–
BD Criteria		DSM-III-R BD-I and BD-II	DSM-IV bipolar disorder	DSM-IV bipolar affective disorder, HAM-D ≥10	BD-I, BD-II, BD-NOS	ICD-9-CM: 296.1, 296.4–296.8
OSA Criteria		RDI >10	Overnight PSG and oxyhemoglobin desaturation	AHI ≥5	AHI ≥15 or AHI ≥5 with EDS	ICD-9-CM: 780.51, 780.53, 780.57
Overall Risk of Bias Assessment		High	High	High	High	Low

(–), not reported; AHI, apnea hypopnea index; BMI, body mass index; BD, bipolar disorder; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EDS, excessive daytime sleepiness; HAM-D, Hamilton Rating Scale for Depression; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; RDI, respiratory disturbance index.

Table S7—Studies of the prevalence of OSA in individuals with depressive disorders (MDD).[24–26,30,32,35–39]

Study		Clinic-Based Studies								Population-Based Studies	
		Winkelman 2001	Levine 2001	Deldin 2006	Carney 2006	Hattori 2009	Ong 2009	Summers 2010	Mysliwiec 2013	Hrubos-Strom 2012	Sharafkhaneh 2005
MDD	n	176	43	19	53	19	51	60	164	36	358,817
	M/F	90/86	28/15	4/15	28/25	Overall sample was 75% male	22/29	–	Overall sample was 93.2% male	Overall sample was 55.5% male	Overall sample was 90.2% male
	OSA %	12%	0%	53%	66%	53%	39%	46.7%	49.4%	44%	7.4%
Study Population		Referrals for sleep disturbances on psychiatric inpatients	Consecutive psychiatric patients at state hospital	Participants recruited from a larger study on depression and memory.	Subjects with coronary heart disease and MDD	Mood disorder patients with HAM-D ≥10 and clinical signs of OSA	Participants from a RCT with comorbid MDD and insomnia	Subjects from a tertiary mood disorders clinic	Subjects with diagnostic PSG at a military medical facility	Participants from a population-based survey at high risk for OSA based on the BQ	Inpatient records of Veteran's Health Administration from 1992–2001
Age (mean ± SD)		39.9 ± 6.6	41 ± 13	37.37 ± 11.52	53.8 ± 9.0	–	52.42 ± 9.82	–	–	–	–
BMI (mean ± SD)		27.0 ± 8.6	–	26.13 ± 7.40	30.1 ± 6.8	–	30.26 ± 9.07	–	–	–	–
Psychiatric Drug Use		Neuroleptics: 10.8%	–	Antidepressants: 37% Sedative hypnotics: 16%	Excluded	–	Excluded	–	–	–	–
MDD Criteria		DSM-III-R MDD	DSM-IV MDD	SCID-I for DSM-IV MDD	Depression Interview and Structured Hamilton (DISH) for the DSM-IV MDD criteria and HAM-D for severity.	DSM-IV Major Depressive Disorder	DSM-IV-TR MDD and ≥14 on the HAM-D (also required to have DSM-IV insomnia)	Treatment resistant depression, HAM-D > 18	EMR problem list diagnosis of depression	SCID-I for DSM-IV MDD	ICD-9-CM: 296.2, 296.3, 296.9, 311
OSA Criteria		RDI >10	Overnight PSG and oxyhemoglobin desaturation	RDI > 5 major events per hour	AHI ≥ 5 events per hour	AHI ≥ 5	AHI ≥ 15	RDI >10	ICSD-2 OSA , AHI >5	AHI ≥ 5	ICD-9-CM 780.51, 780.53, 780.57
Overall Risk of Bias Assessment		High	High	High	High	High	High	High	Moderate	Moderate	Low

(–) not reported; AHI, apnea hypopnea index; BMI, body mass index; BQ, Berlin questionnaire; CBT, cognitive behavioral therapy; CHD, coronary heart disease; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EMR, electronic medical records; HAM-D, Hamilton Rating Scale for Depression; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICSD-2, International Classification of Sleep Disorders, 2nd edition; RDI, respiratory disturbance index; RCT, randomized controlled trial; SCID-I, Structured Clinical Interview for the DSM-IV axis I disorders.

Table S8—Prevalence of OSA in individuals with anxiety disorders.[25,26,39]

Study		Clinic-Based Studies	Population-Based Studies						
		Mysliwiec 2013	Sharafkhaneh 2005	Hrubos-Strom 2012					
Anxiety Disorder Diagnosis		Pooled Anxiety	Pooled Anxiety	Panic Disorder	Agoraphobia w/o panic disorder	Social phobia	Obsessive compulsive disorder	Generalized anxiety disorder	Current anxiety
Anxiety	n	122	316,060	17	2	13	5	14	43
	M/F	Overall sample was 93.2% male	Overall sample was 90.2% male	Overall sample was 55.5% male					
	OSA %	47.5%	6.4%	58.8%	100%	53.8%	40%	57.1%	58.1%
Study Population		Subjects with diagnostic PSG at a military medical facility	Inpatient records of Veteran's Health Administration from 1992–2001	Participants from a population-based survey at high risk for OSA based on the BQ					
Age (mean ± SD)		–	–	–	–	–	–	–	–
BMI (mean ± SD)		–	–	–	–	–	–	–	–
Diagnostic Criteria		EMR Problem List excludes PTSD	ICD-9-CM: 300, 308, 309, 306	SCID-I for DSM-IV					SCID-I for DSM-IV Includes PTSD
OSA Criteria		ICSD-2 OSA , AHI >5	ICD-9-CM: 780.51, 780.53, 780.57	AHI ≥ 5					
Overall Risk of Bias Assessment		Moderate	Low	Moderate					

(–), not reported; AHI, apnea hypopnea index; BMI, body mass index; BQ, Berlin questionnaire; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EMR, electronic medical records; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICSD-2, International Classification of Sleep Disorders, 2nd edition; RDI, respiratory disturbance index; SCID-I, Structured Clinical Interview for the DSM-IV axis I disorders.

Table S9—Prevalence of OSA in individuals with PTSD.[24–26,39–44]

Study Identifier		Clinic Based-Studies							Population-Based Studies	
		Winkelman 2001	Krakow 2006	Kinoshita 2012	Yesavage 2012	Mysliwiec 2013	Mysliwiec 2013b	van Liempt 2011	Sharafkhaneh 2005	Hrubos-Strom 2012
PTSD	n	76	89	120	105	96	39	20	31,186	16
	M/F	9/67	11/78	120/0	105/0	Overall sample was 93.2% male	Overall sample was 97.3% male	20/0	Overall sample was 90.2% male	Overall sample was 55.5% male
	OSA %	0.7%	13.5%	83%	69%	42.7%	69%	29%	46.40%	50%
Study Population		Referrals for sleep disturbances on psychiatric inpatients	Crime victims self-referred for insomnia or nightmares	Community-dwelling male veterans age 55 years or older with PSTD	Community-dwelling male veterans age 55 years or older with PSTD	Subjects with diagnostic PSG at a military medical facility	Military personnel deployed within 18 months presenting for sleep evaluation	Male veterans with PTSD from outpatient Military Mental Healthcare clinic	Inpatient records of Veteran's Health Administration from 1992–2001	Participants from a population-based survey at high risk for OSA based on the BQ
Age (mean ± SD)		32.4 ± 9.1	40.36 ± 12.3	61.3 ± 4.0	59.9 ± 3.1	–	–	40.75 ± 8.45	–	–
BMI (mean ± SD)		27.5 ± 7.9	26.97 ± 6.41	30.7 ± 5.6	31.1 ± 6.10	–	–	27.86 ± 4.86	–	–
Psychiatric Drugs		14.3%	–	–	–	–	–	–	–	–
PTSD Criteria		DSM-III-R PTSD	DSM-IV criteria for PTSD, PSDS ≥ 11	CAPS current or lifetime score ≥ 40	CAPS current or lifetime score ≥ 40	EMR problem list diagnosis of PTSD	PTSD Checklist Military Version, with a score of ≥ 50	SCID for DSM-IV, CAPS > 50, two physician consensus	ICD-9-CM: 309.81	SCID-I for DSM-IV
OSA Criteria		RDI > 10	AASM guidelines for SDB	AHI ≥ 5	AHI > 10	ICSD-2 OSA, AHI > 5	AHI > 5	AHI > 10	ICD-9-CM: 780.51, 780.53, 780.57	AHI ≥ 5
Overall Risk of Bias Assessment		High	High	High	High	Moderate	High	High	Low	Moderate

AASM, American Academy of Sleep Medicine; AHI, apnea hypopnea index; BQ, Berlin questionnaire; DSM-III-R, Diagnostics and Statistics Manual of Mental Disorders, Third Edition, Revised; BQ, Berlin questionnaire; CAPS, Clinician Administered PTSD Scale; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; SCID for DSM-IV, Structured Clinical Interview for the DSM-IV axis I disorders; PSDS, Posttraumatic Stress Diagnostic Scale; UARS, upper airway resistance syndrome.

Table S10—Case studies of interventions for individuals with schizophrenia and psychotic disorders and OSA.[45–54]

First Author	Age	Sex	Diagnosis	Psychiatric Symptoms	Presenting Medical Comorbidities	Initial Medications	OSA Symptoms	Treatment	Outcome
Lee 1989	30	M	atypical psychosis, mild grade mental retardation	EDS, talking nonsense, yelling and stripping in public, drinking insecticide, confusional behavior, loosening of association, self-muttering, inappropriate giggling, irrational behaviors, paranoid delusions	obesity, temporal lobe epilepsy (grand mal seizures), obstructed oropharyngeal space	phenytoin 300 mg/day, carbamazepine 800 mg/day, haloperidol 20 mg/day	AHI 10, SaO_2 78%, No SWS	adenotonsillectomy	cessation of EDS and apneas, no further need for neuroleptics
Bottlender 1999	60	M	delusional disorder, jealous type (DSM-IV 297.1)	blunted affect, affective rigidity, retarded, inhibited and restricted thinking, lack of drive, social withdrawal, systematized, low dynamic delusional thinking	parkinsonian syndrome	haloperidol 20 mg/day, haloperidol-decanoate 3 mL i.m. 14 day interval, chlorprothixene 80 mg/day, theralene 10 drops/day	Unspecified	risperidone 6 mg/day, monotherapy,CPAP	CPAP continued to improve negative symptoms such as lack of drive, general loss of energy and affective blunting
Chiner 2001	52	M	episodic schizophrenia with inter-episodic residual symptoms, undifferentiated type (DSM-IV 295.92)	social isolation, lack of initiative, weight gain, EDS, severe snoring	–	chlorpromazine	AHI 52, AI 36, ESS 19, SaO_2 95%, Min SaO_2 81%	CPAP at 8cm H_2O	CPAP reduced EDS but induced an acute psychotic episode requiring hospital admission
Dennis 2001	38	M	DSM-IV schizoaffective disorder	aggression, physically assaultive behavior, auditory hallucinations, delusions, impaired memory	obesity	quetiapine 800 mg/day, lithium carbonate 900 mg/day, valproic acid 1500 mg/day	MinSaO_2: 51%, AHI 168	CPAP, continued psychiatric medication	improved memory, cessation of aggressive and assaultive behavior
Wirshing 2002	45	F	DSM-IV schizophrenia	rapid weight gain, voracious appetite	obesity, hypertriglyceridemia, glucose Intolerance	clozapine 300 mg/day	AHI 36, Min SaO_2 87%	CPAP, clozapine 300 mg/day	improvement in sleep difficulty, EDS and OSA
	50	M	schizophrenia	weight gain, difficulty sleeping, frequent unrestful daytime naps, snoring and apnea	obesity, diabetes	risperidone 6 mg/day	Min SaO_2 71%	CPAP, risperidone 6 mg/day	improvement in OSA symptoms
Boufidis 2003	36	M	schizophrenia	BPRS 64, BDI-II 35, insomnia, fatigue, EDS, nightmare, choking sensation	obesity	risperidone 16 mg, lormetazepam 4 mg, zolpidem 20 mg, diazepam 3 0 mg, clorazepate dipotassium 15 mg, biperiden 2 mg	RDI 88, SaO_2 86%, ESS 14	nCPAP, weight loss diet, risperidone 6 mg, zolpidem 10 mg, clorazepate dipotassium 60 mg, biperiden 4 mg	at 8-month follow-up the patient had lost 14 kg, with significant improvement in clinical symptoms, BPRS 38, BDI 19, ESS 9
Sugishita 2003	44	M	ICD-10 schizophrenia	depressive mood, fatigue, EDS, mild brain atrophy	weight 72 kg, BMI 24.3		AHI 43.6	CPAP reducing AHI to 2.3	PNSS improved to 20 from 34, GAF improved to 38 from 31
Velasco-Rey 2012	51	M	depressive disorder with psychotic symptoms	mutism, listless, motionless, self-referential and prejudicial-type delusions, depressive symptoms, delusions of reference, auditory hallucinations, two suicide attempts, snoring, EDS		venlafaxine 150 mg/day ketazolam 30 mg/day risperidone 4 mg/day	AHI 32	CPAP at 9 cm H_2O	one month after CPAP the patient was asymptomatic, so medication was withdrawn; complete remission persisted at one year follow-up
Troy 2013	39	M	schizophrenia	snoring, EDS	obesity 137 kg, type II diabetes mellitus, blood pressure: 119/64 mmHg	oral hypoglycemics Insulin	RDI 108, Min SaO_2 59%, ESS 19	CPAP at 20 cm H_2O, clozapine 425 mg, diabetic-integrated care	ESS = 7, improvement in memory, positive symptoms of schizophrenia less distressing but constant
Seeman 2014	55	F	psychosis	fatigue, EDS	BMI 28.32, blood pressure: 140/90 mmHg	fluphenazine 4 mg/day metoprolol 25 mg BID	AHI 30	CPAP, weight loss program	CPAP resolved EDS, weight loss, decrease in blood pressure

(–), not reported; AHI, apnea hypopnea index; AI, arousal index; BDI, Beck Depression Inventory; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CPAP, continuous positive airway pressure; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; ICD-10, International Classification of Diseases, 10th Revision; Min SaO_2, minimum oxygen saturation; SaO_2, oxygen saturation; PNSS, Positive and Negative Syndrome Scale; RDI, respiratory disturbance index.

Table S11—Case reports of mania in OSA.[55–58]

First Author	Age	Sex	Symptoms Prior to OSA Diagnosis	Presenting Medical Comorbidities	Medications at Admission	OSA Symptoms	Treatment	Manifestation of Mania	Outcome and Long Term Therapies
Hilleret 2001	50	M	EDS, drowsiness, speech impairment, anhedonia, anxiety, loss of appetite, suicidal ideation	right hemiplegia, motor deficiency	clorazepate 20 mg, venlafaxine 300 mg, trazodone 50 mg	AHI 44, MinSaO_2 59%	CPAP	15 days on CPAP: quarrelsome and uninhibited	CPAP continued with concomitant valproate
Berge 2008	64	M	tired, sleepy, without energy	type 2 diabetes mellitus	metformin 850 mg every 8 hours	AHI 47, MinSaO_2 73%	CPAP, 9 h at 20 cm continuous pressure, venlafaxine	1 month CPAP: motor hyperactivity, euphoria, excessive socialization, verbal aggression, verbosity, weight gain	risperidone 9 mg/day, valproate 1200 mg/day, weight loss of 1 kg in 2 weeks following admission
Bastiampillai 2010	40	F	Bipolar affective disorder diagnosed at 16, manic and psychotic symptoms	obesity	olanzapine 5 mg	type II respiratory failure, obesity	failed numerous drug therapies, continual respiratory failure, 12 ECT treatments initiated, BiPAP between treatments	on admission: manic and psychotic symptoms	CPAP, lithium 450 mg BID, olanzapine 5 mg/morning
Aggarwal 2013	51	M	BD-I since 16, GAD, depressed mood, anhedonia, decreased concentration, isolation, fatigue, anxiety, difficulty maintaining sleep	ulcerative colitis, hypertension, borderline diabetes	lithium 900 mg, gabapentin 600 mg	AHI 94.6, MinSaO_2 85%	CPAP 7 cm H_2O	3 weeks CPAP: euphoria, physical aggression, motor hyperactivity, racing thoughts, decreased sleep, pressured speech	lithium 1200 mg, gabapentin 900 mg, risperidone 3 mg
	60	M	BD-I disorder, snoring, restless sleep	hypercholesterolemia, benign prostatic hyperplasia, postcolon resection due to colon cancer	divalproate 1500 mg, quetiapine 400 mg, lamotrigine 200 mg	AHI 64.7, MinSaO_2 88%	CPAP 11 cm H_2O	2–3 weeks CPAP: pressured speech, euphoric mood, psychomotor agitation, grandiose delusions	olanzapine 25 mg/day, lithium 600 mg/day, divalproate 1500 mg, quetiapine 400 mg, continued CPAP

(–), not reported; AHI, apnea hypopnea index; BD-I, bipolar disorder type I; BMI, body mass index; BPRS, Brief Psychiatric Rating Scale; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; Min SaO_2, minimum oxygen saturation; SaO_2, oxygen saturation.

Table S12—Interventions for depressive disorders and OSA.[60–67]

Authors	Dahlöf 2000	Mackinger 2004	Habukawa 2010	El-Sherbini 2011	Krystal 2011
Study Design	Prospective, Single-Assignment, Open-Label	Prospective, Single-Assignment, Open Label	Prospective, Single-Assignment, Open-Label	Prospective, Single-Assignment, Open-Label	Prospective, randomized, double-blind, parallel-group, placebo controlled
Number of Patients	MDD: 12 Dysthymia: 5 Depression NOS: 1 Control: 35	MDD History: 18 Control: 18	17	MDD: 11 Control: 26	Armodafinil: 125 Placebo: 124
M/F	Depression: 18/0 Control: 35/0	MDD: 7/11 Control: 10/9	15/2	24/13	Armodafinil: 57/68 Placebo: 58/66
Study Population	Consecutive patients diagnosed with OSA at a sleep clinic	Patients at a sleep disorders center	Patients with MDD referred to sleep clinic for suspected OSA on stable antidepressants or benzodiazepines	Participants with suspected OSA evaluated for MDD	Outpatients with a stable CPAP and antidepressant regimen
Age (mean ± SD)	50 ± 9	MDD: 47.3 ± 8.6 Control: 49.0 ± 7.8	47.6 ± 7.5	–	Armodafinil: 49.5 ± 10.3 Placebo: 49.5 ± 9.7
BMI (mean ± SD)	–	–	28.2 ± 4.0	–	Armodafinil: 37.3 ± 7.9 Placebo: 36.2 ± 7.8
Psychiatric drugs	Excluded	–	100%	–	100%
MDD Criteria	SCID for DSM-III-R current major depressive episode	SCID-I for DSM-IV, codes 296.xx and 300.4	DSM-IV MDD, receiving anti-depressants at a stable dose for ≥ 2 months	SCID-I for DSM-IV	DSM-IV-TR MDD or dysthymic disorder, HAM-D < 17, stable SSRI or SNRI for ≥ 8 weeks at study baseline
OSA Criteria	DI ≥ 5 or minimum 30 desaturations during 7 hour sleep study	RDI unspecified	AHI ≥ 10	AHI > 5	ICSD OSA, stable CPAP regimen for ≥ 4 weeks resulting in AHI ≤ 10 at baseline, CPAP use ≥ 4 h per night, ESS ≥ 10, CGI-C ≥ 4
Intervention	Uvulopalatopharyngoplasty	nCPAP	CPAP	CPAP	Armodafinil titrated to 200 mg or placebo daily
Treatment Duration	N/A, follow up 6 months postsurgery	6–9 weeks	2 months	2 months	12 weeks
Outcome Measures	PSG, SCID, GAF, CPRS, DST	RDI, BDI, AM	PSG, BDI, HAM-D, ESS	HAM-D, ESS, SCID-I	CGI-C, MWT, ESS, PSG, QIDS-SR-16, TEAEs
Relevant Results	Hypersomnia decreased from 98% to 6% postoperatively. The rate of current depression decreased from 34% to 10% and GAF score increased.	CPAP reduced the nightly RDI of participants in both groups. Pre and post BDI scores were significantly reduced for the MDD group. Group × time interactions did not show a difference between change in MDD and Con.	CPAP reduced depression on both the BDI and HAM-D scales. The improvement in depression correlated with improved ESS scores.	HAM-D scores decreased significantly for all subjects post-CPAP. SCID-I diagnosed MDD resolved for 6 subjects; the remaining 5 were classified with mild MDD. Total ESS score decreased from 11.6 ± 8.6 to 5.1 ± 3.1. HAM-D scores were correlated with ESS scores ($r = 0.7$, $p = 0.000$).	Minimal CGI-C improvement was greater with armodafinil (68%) than placebo (53%) ($p = 0.003$). MWT showed no significant changes. ESS score showed a greater decrease for armodafinil (−6.3) than placebo (−4.8)
Overall Risk of Bias Assessment	High	High	High	High	Moderate

AHI, apnea hypopnea index; AM, autobiographical memory; BDI, Beck Depression Inventory; CPAP, continuous positive airway pressure; CGI-C, Clinical Global Impression of Change; CPRS, Comprehensive Psychopathological Rating Scale; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd edition revised; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DST, dexamethasone suppression test; ESS, Epworth Sleepiness Scale; GAF, Global Assessment of Functioning Scale; HAM-D, Hamilton Rating Scale Depression; MWT, maintenance of wakefulness test; NOS, not otherwise specified; PSG, polysomnography; QIDS-SR-16, Quick Inventory of Depressive Symptomatology Self Report; SCID, Structured Clinical Interview for DSM-III-R; SCID-I, Structured Clinical Interview for DSM-IV axis I disorders; SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TEAE, treatment emergent adverse events.

Table S13—Interventions for PTSD and OSA.[69–72]

Study ID	Krakow 2000	El-Sohl 2010	Collen 2012	Gharaibeh 2013
Study Design	Retrospective Survey	Retrospective case-control study	Retrospective case-control study	Retrospective Review
Number of Patients	Tx: 14 (10 OSA, 4 UARS) NoTx: 9 (6 OSA, 3 UARS)	OSA+PTSD: 148 OSA-PTSD: 148	OSA+PTSD: 45 OSA-PTSD: 45	43
M/F	–	OSA+PTSD: 148/0 OSA-PTSD: 148/0	OSA+PTSD: 38/7 OSA-PTSD: 38/7	–
Study Population	Veterans with chronic nightmares	Male veterans with PTSD referred to a sleep clinic between January 2005 and June 2009	Adult patients at military sleep clinic between January and October 2009	Patients with OSA and PTSD treated at a VHA sleep clinic between May 2011 and May 2012
Age (mean ± SD)	Tx: 43.8 ± 14.1 NoTx: 50.8 ± 14.9	OSA+PTSD: 59.7 ± 7.9 OSA-PTSD: 61.5 ± 8.3	OSA+PTSD: 38.6 ± 9.2 OSA-PTSD: 37.0 ± 11.2	–
BMI (mean ± SD)	Tx: 35.8 ± 10.2 NoTx: 31.8 ± 6.0	OSA+PTSD: 35.4 ± 6.9 OSA-PTSD: 34.9 ± 6.3	OSA+PTSD: 27.8 ± 4.4 OSA-PTSD: 26.9 ± 9.2	–
Psychiatric drugs	Excluded	Tx Antidepressants: 57.1% Benzodiazepines: 35.7% Antipsychotics: 21.4% NoTx Antidepressants: 77.7% Benzodiazepines: 55.5% Antipsychotics: 0%	Sedatives: OSA+PTSD: 82.9% OSA-PTSD: 13.3%	–
PTSD Criteria	Weekly nightmares for > 6 months, psychosocial impairment from dreams	DSM-IV PTSD	Structured clinical interview for DSM-IV-TR PTSD and PCL-M > 50	Diagnostic code for PTSD
OSA Criteria	OSA: AHI > 10 UARS: airflow irregularities below hypopnea threshold, excessive EEG micro-arousals, intermittent or frequent snoring culminating in an EEG micro-arousal	AHI ≥ 5 Mild: 5 ≤ to < 15 Moderate: 15 ≤ to <30 Severe: > 30	AASM criteria	Diagnostic code for OSA
Intervention	CPAP	CPAP	CPAP	CPAP
Treatment Duration	≈ 21 months	30 days	4–6 weeks	–
Outcome Measures	Change in nightmares and PTSD symptoms quantified by survey	Compliance (> 4 h/night, > 70% of days)	Compliance (regular use > 4 h/night, > 70% of nights)	Compliance (> 4 h/night), nightmare frequency
Relevant Results	More individuals in the CPAP compliant group showed improvement in nightmare and PTSD symptoms. Participants in the NoTx group were more likely to stay the same or worsen.	Compliance was 41% in OSA+PTSD and 70% in OSA-PTSD PAP non-adherent veterans had a higher prevalence of nightmares than adherent subjects (56% vs. 28%). They were also less sleepy at baseline (ESS: 12.1 ± 5.9 vs. 14.4 ± 5.3) Psychiatric Drug Use after CPAP Tx Antidepressants: 28.6% Benzodiazepines: 28.6% Antipsychotics: 0% NoTx Antidepressants: 44.4% Benzodiazepines: 66.6% Antipsychotics: 0%	Participants with PTSD had lower overall compliance with CPAP on all measures of compliance. Regular use was 25.2% compared to 58.3% on non-PTSD controls.	Nightmare frequency was reduced in both classes of OSA, and predicted by CPAP compliance.
Overall Risk of Bias Assessment	High	High	High	High

(–), not reported; AASM, American Academy of Sleep Medicine; AHI, apnea hypopnea index; CPAP, continuous positive airway pressure; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision; ESS, Epworth Sleepiness Scale; NoTx, untreated; PTSD, posttraumatic stress disorder; Tx, treatment; UARS, upper airway resistance syndrome; VHA, Veteran's Health Administration.

Appendix 3: Risk of Bias

Section A: Prevalence Studies

ANCOLI-ISRAEL 1999

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	
	4. Was the likelihood of non-response bias minimal?	Yes	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	
	7. Was the study instrument that measured the parameter of interest (e.g,. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: Moderate			

CARNEY 2006

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	Single Location
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	
	4. Was the likelihood of non-response bias minimal?	No	134/503 agreed to participate. Black patients were more likely to participate than white, but no other significant differences between participants and non-participants.
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	PSG & DISH (DSM-IV)
	7. Was the study instrument that measured the parameter of interest (e.g,. prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

DELDIN 2006

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited by flyers
	4. Was the likelihood of non-response bias minimal?	No	Not mentioned
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	SCID DSM-IV & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

HATTORI 2009

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	
	4. Was the likelihood of non-response bias minimal?	Unclear	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

HRUBOS-STROM 2012

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	Yes	Randomly drawn from National Population Register
	2. Was the sampling frame a true or close representation of the target population?	Yes	Randomly drawn from National Population Register
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes	Randomly selected
	4. Was the likelihood of non-response bias minimal?	Yes	55.7% response to initial survey. At next randomization stage (participants from BQ high risk), a significantly higher proportion of participants were categorised as BQ somnolent when compared with BQ high-risk responders who did NOT participate. No differences with respect to age, sex, snoring, obesity, or hypertension.
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	SCID DSM-IV & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: Moderate			

KELLY 2013

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Consecutive
	4. Was the likelihood of non-response bias minimal?	N/A	Chart review
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	Diagnosed & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

KINOSHITA 2012

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	Yes	San Francisco Bay Area veterans
	2. Was the sampling frame a true or close representation of the target population?	Yes	168 veterans who responded to ads or were referred
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited by advertisements
	4. Was the likelihood of non-response bias minimal?	No	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	All assessments were conducted prospectively
	6. Was an acceptable case definition used in the study?	Yes	CAPS & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

KRAKOW 2006

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Convenience samples
	4. Was the likelihood of non-response bias minimal?	No	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	PTSD Diagnostic Scale & PSG/Autoset
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	Some participants received AutoSet home monitoring instead of PSG.
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

LEVINE 2001

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	Single hospital
	2. Was the sampling frame a true or close representation of the target population?	Unclear	Psychiatric patients from referrals for greater Pittsburgh
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Consecutive patients
	4. Was the likelihood of non-response bias minimal?	N/A	Chart review
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	Medical records
	6. Was an acceptable case definition used in the study?	Yes	DSM-IV criteria and PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	DSM-IV & PSG (from records)
	8. Was the same mode of data collection used for all subjects?	Yes	Medical records
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

MYSLIWIEC 2013

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	Only military personnel were eligible.
	2. Was the sampling frame a true or close representation of the target population?	Yes	All military personnel who underwent sleep medicine evaluations 2011–2012 were eligible.
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited by advertisements, 160/1416 volunteered
	4. Was the likelihood of non-response bias minimal?	N/A	Only 11.3% of potentially eligible military personnel were referred for screening.
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	PSG & PTSD checklist
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	No	6 completed split-night PSG
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: Moderate			

MYSLIWIEC 2013B

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	Yes	Major military medical treatment facility
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	ALL diagnostic PSGs
	4. Was the likelihood of non-response bias minimal?	No	Chart review
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	Diagnosis from electronic medical records problem list & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	No	Patients who met criteria for severe OSA underwent split-night PSG
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

ONG 2009

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited by flyers
	4. Was the likelihood of non-response bias minimal?	No	Not mentioned
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	DSM-IV-TR & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

SHARAFKHANEH 2005

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	The VA serves current and former soldiers and military families.
	2. Was the sampling frame a true or close representation of the target population?	Yes	The entire VA EMR system was used over the time period assessed.
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	Yes	The entire VA EMR system was used over the time period assessed.
	4. Was the likelihood of non-response bias minimal?	N/A	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	Data was retrieved from EMR
	6. Was an acceptable case definition used in the study?	Yes	ICD-9-CM coding
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	EMR
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: Low			

SUMMERS 2010

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	Yes	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	
	4. Was the likelihood of non-response bias minimal?	No	Not mentioned
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	Diagnosed TRD & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

VAN LIEMPT 2013

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	
	2. Was the sampling frame a true or close representation of the target population?	No	
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited through outpatient clinic, controls recruited through ads
	4. Was the likelihood of non-response bias minimal?	No	Not mentioned
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	SCID-DSM-IV & PSG
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

WINKELMAN 2001

Criteria		Retrospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	No	Single center
	2. Was the sampling frame a true or close representation of the target population?	No	Single center
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Consecutive referrals
	4. Was the likelihood of non-response bias minimal?	N/A	Chart review
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	
	6. Was an acceptable case definition used in the study?	Yes	DSM-III-R and PSG (RDI >10)
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

YESAVAGE 2012

Criteria		Prospective	
External Validity	1. Was the study's target population a close representation of the national population in relation to relevant variables, e.g., age, sex, occupation?	Yes	San Francisco Bay Area
	2. Was the sampling frame a true or close representation of the target population?	Unclear	"expected demographic make-up of Vietnam-era veterans living in this region"
	3. Was some form of random selection used to select the sample, OR, was a census undertaken?	No	Recruited through media advertisement & local veteran agencies
	4. Was the likelihood of non-response bias minimal?	No	
Internal Validity	5. Were data collected directly from the subjects (as opposed to a proxy)?	Yes	All assessments were conducted prospectively
	6. Was an acceptable case definition used in the study?	Yes	
	7. Was the study instrument that measured the parameter of interest (e.g., prevalence of low back pain) shown to have reliability and validity (if necessary)?	Yes	CAPS & PSG
	8. Was the same mode of data collection used for all subjects?	Yes	
	9. Was the length of the shortest prevalence period for the parameter of interest appropriate?	Yes	
	10. Were the numerator(s) and denominator(s) for the parameter of interest appropriate?	Yes	
Overall Risk: High			

Section B: Interventions

COLLEN 2012

Study design	Observational, case-controlled study	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	Unclear	
Blinding of outcome assessment	High	Participants were blind to compliance data
Incomplete outcome data	Low	No records were excluded from the analysis
Selective reporting	Low	
Other sources of bias	Unclear	

DAHLOF 2000

Study design	Single-assignment, open-label	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	High	None
Blinding of outcome assessment	High	None
Incomplete outcome data	Low	Seven excluded. One patient was excluded due to alcohol abuse, two patients due to current treatment with psychotropic drugs, and three patients due to known psychiatric illness.
Selective reporting	Low	
Other sources of bias	High	

El-Sherbini 2011

Study design	Single-assignment, open-label	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	High	The psychiatrist was blinded to the severity of sleep disturbance while conducting psychiatric assessment
Blinding of outcome assessment	Unclear	
Incomplete outcome data	Low	Seven excluded. Two refused to contribute in the study, two had a previous psychiatric diagnosis, two refused treatment with CPAP, and one was not compliant with CPAP.
Selective reporting	Low	
Other sources of bias	Unclear	

El-Sohl 2010

Study design	Single-assignment, case-control, open-label	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	High	None
Blinding of outcome assessment	Low	Participants were blind to the assessment of CPAP compliance
Incomplete outcome data	Low	At 1-month follow-up, 6 PTSD veterans and 1 control failed to return to clinic
Selective reporting	Low	
Other sources of bias	Unclear	

Gharaibeh 2013

Study design	Single-assignment, case-control, open-label	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	High	None
Blinding of outcome assessment	Low	Participants were blind to the assessment of CPAP compliance
Incomplete outcome data	Unclear	
Selective reporting	Low	
Other sources of bias	Unclear	

Habukawa 2010

Study design	Single-assignment, open-label	
Random sequence generation	N/A	Single allocation

Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	Unclear	
Blinding of outcome assessment	Unclear	"respiratory events were scored…by a technician blind to the aim of the study and the subject's identity"
Incomplete outcome data	Low	Three excluded for AHI <10
Selective reporting	Low	
Other sources of bias	Unclear	

KRYSTAL 2011

Study design	Randomized, double-blind, parallel-group study	
Random sequence generation	Unclear	Randomization stratified by center. Methodology not described.
Allocation concealment	Unclear	Unclear
Blinding of participants and personnel	Unclear	States double-blind
Blinding of outcome assessment	Unclear	States double-blind
Incomplete outcome data	Low	47 excluded. 14 consent withdrawn, 2 lost to follow-up, 31 other reasons.
Selective reporting	Low	
Other sources of bias	Unclear	

MACKINGER 2004

Study design	Single-assignment, parallel group study	
Random sequence generation	N/A	Single allocation
Allocation concealment	N/A	Single allocation
Blinding of participants and personnel	Unclear	
Blinding of outcome assessment	Unclear	
Incomplete outcome data	Low	3 excluded: 1 acute schizophrenic psychosis, 2 history of BP
Selective reporting	High	Missing post treatment total BDI scores
Other sources of bias	Unclear	

TAKAESU 2012

Study design	Randomized, crossover study	
Random sequence generation	Unclear	States randomization
Allocation concealment	Low	Use of sham CPAP and CPAP
Blinding of participants and personnel	Unclear	
Blinding of outcome assessment	Unclear	
Incomplete outcome data	Low	7 excluded due to CPAP discomfort
Selective reporting	Low	
Other sources of bias	Unclear	