Sleep-Disordered Breathing in Patients with Post-traumatic Stress Disorder

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Abstract

Post-traumatic stress disorder (PTSD) and sleep-disordered breathing (SDB) are shared by many patients. They both affect sleep and the quality of life of affected subjects. A critical review of the literature supports an association between the two disorders in both combat-related and non–combat-related PTSD. The exact mechanism linking PTSD and SDB is not fully understood. A complex interplay between sleep fragmentation and neuroendocrine pathways is suggested. The overlap of symptoms between PTSD and SDB raises diagnostic challenges that may require a novel approach in the methods used to diagnose the coexisting disorders. Similar therapeutic challenges face patients and providers when treating concomitant PTSD and SDB. Although continuous positive airway pressure therapy imparts a mitigating effect on PTSD symptomatology, lack of both acceptance and adherence are common. Future research should focus on ways to improve adherence to continuous positive airway pressure therapy and on the use of alternative therapeutic methods for treating SDB in patients with PTSD.

Keywords: sleep-disordered breathing; obstructive sleep apnea; post-traumatic stress disorder; treatment

(Received in original form July 5, 2014; accepted in final form December 15, 2014)

Supported by Merit Review Grant CX000478 from the Department of Veterans Affairs (A.A.E.-S.).

The views expressed in this review do not communicate an official position of the Department of Veterans Affairs.

Author Contributions: P.J. and A.A.E.-S. determined the scope and structure of the review. L.N.V. and J.P. conducted the majority of the literature review. P.J. and A.A.E.-S. drafted and made critical revisions to the manuscript. All authors have given final approval of the manuscript.

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Ann Am Thorac Soc Vol 12, No 2, pp 259–268, Feb 2015

DOI: 10.1513/AnnalsATS.201407-299FR
Internet address: www.atsjournals.org

Based on the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V), post-traumatic stress disorder (PTSD) is characterized by the development of a specific cluster of symptoms after exposure to a traumatic event that elicits a response of fear, helplessness, or horror. A constellation of indicators from four symptom clusters, including intrusion, avoidance, negative alterations in cognitions and mood, and alterations in arousal and reactivity, is required (1) (Table 1). Typical examples of traumatic experiences that may predispose to PTSD include sexual assault, military combat, mass conflict and displacement, and life-threatening physical illness (2–5).

The earliest historical reference to a post-traumatic condition was deciphered from a cuneiform tablet detailing the death of King Ur-Namma on the battlefield against the Gutians (6). The inscription described significant sleep problems in the survivors. Ancient Greek and Roman accounts of war included similar references to sleep ailments in soldiers returning from battles. American writers have referred to this condition as "Soldier's heart" during the U.S. Civil War (a reference to the autonomic hyperarousal), "shell shock" during World War I (a description of the numbing and dissociation), and "combat neurosis" during World War II (7). The term "PTSD" was introduced for the first time during the Vietnam War after its description by Friedman in 1980 as the Post-Vietnam Syndrome (8). It is estimated that the lifetime prevalence of the disease varies from 15 to 30% in Vietnam combat veterans (9) and 11 to 17% of those returning from Iraq and Afghanistan (10) compared with 7.8 to 12.3% in the general adult population of the United States (3, 11).

Sleep disturbances remain a common complaint of those afflicted with the condition and may even be a predictor of PTSD progression. Despite the intensified campaign in highlighting the sequelae of PTSD on the quality of life of these patients, the literature has been scarce on providing

Table 1. Classification of mental and behavioral disorders for post-traumatic stress disorder

A. The patient must have been exposed to a stressful event or situation (either short or long lasting) of exceptionally threatening or catastrophic nature, which would be likely to cause pervasive distress in almost anyone.
B. There must be persistent remembering of "reliving" of the stressor in intrusive "flashbacks," vivid memories or recurring dreams, or in experiencing distress when exposed to circumstances resembling or associated with the stressor.
C. The patient must exhibit an actual or preferred avoidance of circumstances resembling or associated with the stressor which was not present before exposure to the stressor.
D. Either of the following must be present:
(1) inability to recall, either partially or completely, some important aspects of the period of exposure to the stressor;
(2) persistent symptoms of increased psychological sensitivity and arousal (not present before exposure to the stressor), shown by any two of the following:
(a) difficulty in falling or staying asleep
(b) irritability or outbursts of anger
(c) difficulty in concentrating
(d) hypervigilance
(e) exaggerated startle response.
E. Criteria B, C, and D must all be met within 6 months of the stressful event or of the end of a period of stress. (For some purposes, onset delayed more than 6 months may be included, but this should be clearly specified).

Adapted from Reference 68.

effective management of sleep-related complaints. Although nightmares and insomnia are common features of PTSD-related sleep disturbances, there is growing evidence that an increased prevalence of sleep-disordered breathing (SDB) is also present in patients suffering from PTSD. In addition, PTSD-related sleep disturbances can persist long after the original trauma has subsided.

In the last decade, several studies have documented a broad array of comorbid sleep disorders in subjects with PTSD, including insomnia, nightmares, SDB, and sleep arousal and dream enactment behavior (12, 13). Sleep impairment accounts for a significant portion of the variance in physical health complaints even after controlling for other PTSD symptoms and depression (14). It follows that the significant and chronic sleep loss commonly endorsed in individuals with PTSD contributes to additional worsening of health-related quality of life.

Although different aspects of PTSD sleep disturbances have been reviewed recently (15, 16), the purpose of this article is to present a critical review of the evidence and the research on SDB in patients with PTSD, the interrelation between the two disorders, existing treatment options, and future research. Although obstructive sleep apnea (OSA) and respiratory effort–related arousals are frequently reported in patients with PTSD, no studies addressing the association between PTSD and central sleep apnea have been identified.

Association between SDB and PTSD

Many studies have claimed a link between SDB and PTSD (13, 17–27) (Table 2). Youakim and coworkers (28) were the first to report on the association between OSA and PTSD in a Vietnam veteran. The case described a man with PTSD and OSA whose PTSD symptoms abated after treatment with continuous positive airway pressure (CPAP). A subsequent report from women with PTSD who experienced sexual trauma identified SDB in 52% of the sample (13). Although the diagnosis of SDB was based on self-report, a follow-up study using polysomnography (PSG) confirmed that 90% of the participants had clinically significant levels of SDB (23). The association between the two disorders was further highlighted by the fact that trauma survivors with SDB exhibited worse symptoms of PTSD compared with trauma survivors without SDB (24). Women with both sexual trauma–related PTSD and SDB had worse nightmares, major depression, and impaired quality of life (24). Interestingly, those with PTSD had atypical phenotypic expression of their SDB; there were fewer objective snoring and more upper airway resistance syndrome findings on PSG (24). The sleep profile was dominated with frequent insomnia, cognitive-affective symptoms, and higher psychotropic medication use compared with patients without PTSD (24). Accordingly, it has been suggested that underlying SDB should be ruled out when response to PTSD treatment is lacking.

The small sample size of these studies raised doubts about the relationship between SBD and PTSD. However, in one of the largest studies conducted by the Veterans Health Administration, whereby the medical records of 4 million Veterans were examined for the association between psychiatric disorders and sleep apnea (19), PTSD was present in 11.85% of the apneic group compared with 4.74% of the nonapneic group (odds ratio, 2.7 [95% confidence interval, 2.65–2.74]). Later, many authors reported similar association between PTSD and SDB. Some used questionnaires to assess the presence of SDB, such as the Cleveland Sleep Habits Questionnaire or the Pittsburgh Sleep Quality Index (20, 29). The use of these questionnaires was deemed problematic because it addressed variables that might be shared by PTSD and SDB, such as sleep-related issues, chronic fatigue, and daytime sleepiness. Others, however, confirmed SDB with objective sleep testing (21, 22). Another confounding element that undermined the association between PTSD and SDB came from the fact that many patients with PTSD are overweight or obese (21, 22). In these cases, the potential for SDB was strongly correlated with body mass index (BMI), increase in arousal symptoms, and greater PTSD severity. However, the reports of obesity in patients with SDB were not universal, and PTSD spanned across the entire BMI spectrum.

In addition to combat-related PTSD, SDB has been found to be frequent in patients with PTSD related to other types of trauma. One cohort reported 90% prevalence of SDB in crime victims (23). Similarly, 95% of fire evacuees with PTSD had SDB on portable sleep testing (25), although a selection bias and diagnostic inaccuracies may have been responsible for this excessively high prevalence. More recently, a study of 501 Israeli subjects living along the Gaza strip established presence of PTSD in 5.5% of this highly

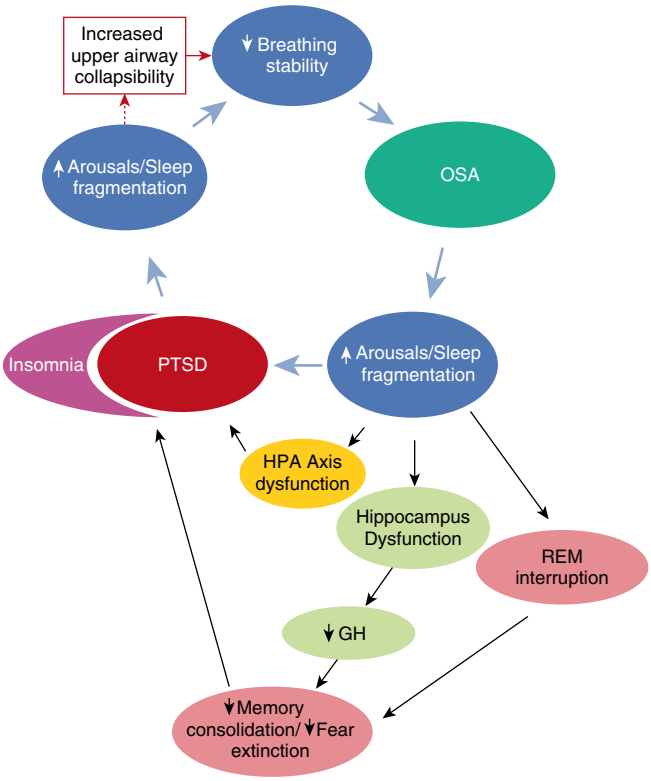

Figure 1. Proposed interactions between post-traumatic stress disorder (PTSD) and sleep-disordered breathing. GH = growth hormone; HPA = hypothalamic-pituitary-adrenal; OSA = obstructive sleep apnea.

exposed cohort and depression in an additional 3.8%. Clinical sleep disturbance, assessed using the 18-item Pittsburgh Sleep Quality Index, was present in 37.4% of the cohort but reached 82% among those identified with PTSD and 79% among those who were depressed (29). Not surprisingly, epidemiologic investigations documented increased prevalence of SDB in patients with World Trade Center–related PTSD (26) and in post–Gulf War Iraqi immigrants (27). In one of these studies, researchers linked particulate matter inhalation to a surge in inflammatory response resulting in upper airway obstruction and OSA.

Despite the multiple reports linking the two disorders, the association between PTSD and SDB has not been consistent (30–33) (Table 3). In one small study of 14 injured victims from traffic-related accidents, no difference between patients with and without PTSD were noted on any of the PSG measures (30). The two groups did not differ from each other with respect to awakening thresholds during REM sleep. Other authors could not also elicit a difference in the prevalence of SDB between patients with and without PTSD despite the increased rate of SDB (76.8%) in active duty military personnel (32). These conflicting conclusions emanate from the heterogeneity in the study populations that differ from each other in terms of stress severity and intensity of exposure. In addition, there were significant methodological differences in the preexistent research addressing the relation between PTSD and SDB. The diagnosis of sleep apnea was based on myriad of diagnostic tools, including nonstandardized sleep questionnaires, portable monitoring devices, and in-lab polysomnography (Table 3). Even with the latter technique, usage of both a nasal pressure transducer and a nasal-oral thermistor to monitor respiration could not be ascertained across these studies. Inconsistency in scoring rules and variability in the night-to-night degree of SDB, particularly in this population with high comorbid conditions, may have accounted also for these opposite findings.

Potential Mechanisms

PTSD and SDB share disturbed sleep as a common feature. It is hypothesized that the two disorders act as a catalyst for one another. SDB may exacerbate, accentuate, or perpetuate preexisting PTSD, and vice versa. Sleep fragmentation represents the common thread in this relationship (Figure 1).

OSA Effects on PTSD

Knowing that adequate sleep is important for synaptic plasticity and memory formation, interruption of the sleep continuity by obstructive airway events followed by short arousal compromises the beneficial process of fear extinction. The latter is a process of "forgetting" the association between a certain neutral trigger and an aversive stimulus. Longitudinal studies have reported an association between sleep disturbances in the early aftermath of trauma and the development of PTSD (34, 35). Additionally, studies have found that sleep disturbances before traumatic events predict PTSD (36, 37). Although results of EEG findings during sleep in patients with PTSD have been inconsistent, a metaanalysis concluded that individuals with PTSD had more stage 1 sleep, greater REM density, and decreased slow wave sleep than individuals without PTSD (38). More recently, van Liempt and colleagues (39) showed an increase in awakenings in veterans with PTSD compared with control patients who had experienced trauma and to healthy control patients. The increased frequency of awakenings was documented during REM sleep (40). Given that REM sleep enhances the process of fear extinction (41), several authors have concluded that interruption of memory consolidation contributes to the resurgence of maladaptive fear and anxiety in patients with PTSD. This process is accentuated in SDB, where sleep fragmentation, commonly more severe during REM sleep, may worsen the severity of preexisting PTSD.

Other potential mechanisms for the link between SDB and PTSD have been postulated, including a derangement within the neuroendocrine and neuroanatomical pathways expressed by a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis and by anatomical alterations in the hippocampus (42). Changes in the functioning of the HPA axis have repeatedly been associated with PTSD

Table 2. Studies supporting an association between sleep-disordered breathing and post-traumatic stress disorder

Study Reference	Study Design	PTSD/Total No. of Participants	Objective/PTSD Exposure	Methods to Diagnose OSA	Findings/Comments
Lavie *et al*. (17)	Observational cross-sectional	12/24	Compare sleep between subjects with and without PTSD/combat	In-lab PSG done on 4 nonconsecutive nights. Prevalence of SDB was not a primary objective. Air flow measured by nasal thermistor.	Patients with PTSD had more consistent SDB findings on repeated PSGs (using AHI $>$ 10).
Engdahl *et al*. (18)	Observational cross-sectional	30/59	Comparing subjects with and without PTSD in elderly war veterans/combat	In-lab PSG done on 3 consecutive nights. Subjects suspected to have SDB on screening were excluded.	Despite excluding suspected SDB from study, 4 out of 30 patients with PTSD had SDB diagnosed on PSG.
Sharafkhaneh *et al*. (19)	Retrospective cross-sectional	14,054/118,105	Study association between OSA and comorbid psychiatric disorders/veterans (combat)	Database review of all VHA outpatient clinic file or patient treatment file records between years1998 and 2001, using ICD-9-CM codes.	Large cohort. Of 118,105 patients with diagnosis of SDB, 11.9% had PTSD, compared with 4.74% of the group without apnea. OR, 2.7 (95% CI, 2.65–2.74)
Ocasio-Tascón *et al*. (20)	Observational cross-sectional	24/245	Study sleep disorders and related conditions in veterans/combat	Used the CSHQ to assess probability for OSA. Mainly Hispanic male veterans	Probability of OSA assessed by questionnaire (CSHQ) without confirmatory PSG. There was higher number of patients with high pretest probability for OSA in subjects with PTSD
Yesavage *et al*. (21)	Observational cross-sectional	105/105	Study prevalence of SDB in Vietnam veterans/combat	Unattended overnight PSG. Airflow determined by nasal and oral thermistor.	69% of the subjects had an AHI $\geq$ 10
Williams *et al*. (22)	Retrospective	130/130	Study sleep disorders in active duty soldiers with PTSD/combat	Review of records of 130 consecutive soldiers with PTSD diagnosis. OSA diagnosed based on AHI $\geq$ 5	OSA was present in 67.3% of subjects in cohort (80% had PSG). No control group. Possible selection bias
Krakow *et al*. (13)	Observational cross-sectional	148/156	Study sleep disorders in subjects with sexual assault–related PTSD	Used an algorithm (including EDS, snoring, witnessed apnea) to determine the need to refer for PSG, indicating a potential SDB	SDB assessment was based on questionnaire (not PSG). Potential SDB reported in 52% of subjects and was strongly correlated with BMI, an increase in arousal symptoms, and greater PTSD severity
Krakow *et al*. (23)	Observational cross-sectional	44/39	Study sleep disorders in crime victims	Participants underwent in-lab PSG (nasal pressure transducer to measure airflow) and home monitoring test	SDB diagnosis based on RDI $>$ 15. 90% of the participants had clinically significant SDB. No age-matched control group. Many patients were diagnosed with UARS. RERAs were more frequent than apnea and hypopnea

(Continued)

Table 2. (*Continued*)

Study Reference	Study Design	PTSD/Total No. of Participants	Objective/PTSD Exposure	Methods to Diagnose OSA	Findings/Comments
Krakow *et al.* (24)	Observational	187/187	Study SDB, distress, and related conditions in sexual assault survivors with post-traumatic stress symptoms	Different sleep testing methods: (*1*) PSG with nasal pressure transducer, (2) PSG with thermal sensor, (3) Autoset portable monitoring device with built-in nasal pressure transducer	168 with suspected SDB (21 with confirmed SDB). Women with diagnosed or suspected SDB reported worse nightmares, sleep quality, anxiety, depression, post-traumatic stress, and impaired quality of life
Krakow *et al.* (25)	Observational	46/78	Assess and treat fire evacuees with post-traumatic sleep disturbances/ natural disaster	Subjects with potential SDB diagnosis underwent sleep testing with Autoset portable monitoring device with built-in nasal pressure transducer	Out of a cohort of 78 subjects with post-traumatic sleep disturbances, 50% underwent portable sleep testing; 95% of them screened positive for SDB
Webber *et al.* (26)	Observational cohort	998/11,701	Study the relationship between WTC-related conditions and being at high risk for SDB	The risk for SDB was assessed using the FDNY sleep apnea questionnaire	Patients with PTSD had a 1.96 adjusted OR for being at high risk for OSA (95% CI, 1.65–2.34). SDB risk was based on questionnaires without confirmatory PSG
Arnetz *et al.* (27)	Observational	27/350	Study prevalence of SDB in Iraqi immigrants from pre-GW era compared with post-GW era/war	Used survey questionnaires. SDB diagnosis based on preexisting physician diagnosis or current use of CPAP therapy	There was a significant association between PTSD and the presence of SDB diagnosis. No PSG data confirming SDB diagnosis

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CI = confidence interval; CSHQ = Cleveland Sleep Habits Questionnaire; CPAP = continuous positive airway pressure; EDS = excessive daytime sleepiness; FDNY = Fire Department of the City of New York; GW = Gulf War; ICD-9-CM = International Classification of Disease, 9th revision, Clinical Modification; OR = odds ratio; OSA = obstructive sleep apnea; PSG = polysomnography; PTSD = post-traumatic stress disorder; RDI = Respiratory Distress Index; RERA = respiratory effort–related arousal; SDB = sleep-disordered breathing; UARS = upper airway resistance syndrome; VHA = Veterans Health Administration; WTC = World Trade Center.

(42, 43). Noticeably, increased responsivity to dexamethasone has been described. Such patients exhibit higher corticotropin-releasing factor in the cerebrospinal fluid (44, 45), higher glucocorticoid receptor expression in lymphocytes, and greater glucocorticoid receptor sensitivity (46). Yet, most studies report low to normal peripheral cortisol values in patients with PTSD (47, 48). Because adrenocorticotropic hormone is positively related to the number of awakenings, the response of adrenals to adrenocorticotropic hormone stimulation may be attenuated in patients with PTSD and SDB. Whether treatment of SDB mitigates the HPA axis dysfunction remains unknown. Future research investigating stress and post-traumatic symptoms should focus on the dynamic characteristics of the HPA axis, sensitivity, and up-regulation of receptors involved in the HPA axis in patients with SDB.

In parallel, growth hormone (GH) levels are decreased in patients with PTSD compared with healthy control subjects (49). This reduction in GH secretion correlates with awakenings during the night. In the absence of GH, *N*-methyl-D-aspartate receptor-mediated synaptic currents decrease in hippocampal neurons (50). *N*-methyl-D-aspartate receptor loss is accentuated, as is a decline in long-term potentiation. A recent functional magnetic resonance imaging study in healthy volunteers showed decreased hippocampus activation and impaired performance on a memory task after a night of experimentally induced sleep fragmentation (51). Using delayed recall as dependent variable, both sleep fragmentation and GH secretion were significant predictors for memory retention of a declarative memory task (52). These processes normalized when GH injections were administered during sleep deprivation (50). Interestingly, these changes are accompanied by structural transformations in hippocampal volume (53). In one of the first neuroimaging studies of PTSD, there was an 8% decrease in magnetic resonance imaging–based measurement of right hippocampal volume in patients with combat-related PTSD in comparison with matched control subjects (54). Although these findings were replicated subsequently in adults with chronic longstanding PTSD (55, 56), none of these studies entertained the possibility of coexisting SDB. Taken together, SDB-related sleep fragmentation may augment

Table 3. Studies lacking association between sleep-disordered breathing and post-traumatic stress disorder

Study Reference	Study Design	PTSD/Total No. of Participants	Objective/PTSD Exposure	Methods	Findings/Comments
Klein *et al.* (30)	Observational cross-sectional	8/14	Study sleep disturbances in traffic accident–related PTSD	3 nights PSG 1 year after accident	No significant difference noted between subjects with and without PTSD
Breslau *et al.* (31)	Observational	71/292	Study sleep in lifetime PTSD/ traumatic event	In-lab PSG done on 2 consecutive nights. Airflow determined by nasal and oral thermistor	Using an AHI cutoff of 10 events/h, no difference was present between groups with and without PTSD. Only 12 of the patients with PTSD had current PTSD (59 had past PTSD)
Capaldi *et al.* (32)	Retrospective chart review	18/69	Study sleep disorders in active duty military coming back from Iraq and Afghanistan/combat	Reviewed charts of patients who had in-lab PSG (airflow determined using thermocouple sensors and pressure transducer)	Rates of OSA were high in the whole sample but were not significantly different among those with (78.6%) or without PTSD (75.0%).
Mysliwiec *et al.* (33)	Observational cross-sectional	39/110	Study sleep disorders in military personnel referred for sleep disturbances/combat	In-lab PSG; airflow determined by oronasal-thermal sensors and nasal pressure transducers	62.7% of participants had OSA (AHI > 5). Comorbid insomnia and OSA were associated with PTSD. No association between PTSD and OSA only.

Definition of abbreviations: AHI = apnea-hypopnea index; OSA = obstructive sleep apnea; PSG = polysomnography; PTSD = post-traumatic stress disorder.

the structural and functional impairment of the hippocampus in patients with PTSD. The resulting drop in GH secretion compromises fear extinction, synaptic plasticity, and recovery, hence perpetuating PTSD symptomatology.

PTSD Effects on OSA

Although inconclusive, the background of hyperarousability in patients with PTSD may contribute to the development of obstructive and hypopneic events. Sériès and colleagues (57) demonstrated previously that SDB abnormalities were frequent after sleep fragmentation. In these patients, the critical pressure was significantly lower after sleep fragmentation than after sleep deprivation corresponding to increased airway collapsibility. The difference in critical pressure between each condition was independent of age or BMI. In cases of PTSD, concomitant insomnia appears to reinforce that concept. Although some studies have shown increased arousal and sleep fragmentation in patients with PTSD, these findings have not been consistent. Sleep fragmentation is, however, a common feature of insomnia (40). It is possible that patients with PTSD who suffer from insomnia have a particularly increased sleep fragmentation that may predispose subjects to develop OSA. Progressive development of OSA may reflect a particular phenotype of patients with PTSD.

Confounding Factors

Although a genuine association between SDB and PTSD can be explained by the described mechanisms, numerous uncertainties are raised by the overlap of symptoms between the two conditions, which may lead to a nonfactual association between the two disorders. Sleep disturbances are a hallmark of PTSD symptoms but are also tightly related to SDB. Patients with SDB may present with frequent awakenings and disturbed sleep architecture. Negative dream emotions and increased number of violent and highly anxious dreams have been described in patients with untreated sleep apnea (58). In addition, SDB can be associated with abnormal motor activity during sleep (59). Some of these symptoms are shared by PTSD and are part of the diagnostic criteria for the disorder (1), such as alterations in arousal and reactivity, depression-like symptoms, and concentration difficulties.

Conceivably, SDB-related nocturnal and diurnal symptoms may be erroneously attributed to a post-traumatic experience. For instance, a clear distinction between nightmares and SDB-related violent dreams ought to be made so as not to overestimate PTSD in this population. Hence, specific diagnostic criteria need to be established to avoid the pitfall of inaccurate diagnosis of PTSD.

Diagnostic challenges may also be encountered when interpreting polysomnography in patients with PTSD. Because increased arousals and awakenings are seen in those patients, a strict adherence to the American Academy of Sleep Medicine criteria for scoring of respiratory events should be ascertained. Even then, it may be particularly challenging to differentiate spontaneous arousals (which may be related to PTSD) from respiratory events–related arousals during REM sleep, where significant irregularities in breathing pattern and air flow are often observed. In the absence of due diligence, it is conceivable that respiratory events–related arousals are overscored, leading to an overestimation of the apnea–hypopnea index.

Treatment of OSA in Patients with PTSD

Managing patients with PTSD and SDB is challenging. Although it is suggested that treatment of SDB may lead to an improvement in PTSD symptoms, PTSD itself seems to hinder OSA therapy.

CPAP remains the mainstay of therapy for OSA. CPAP therapy exerts its beneficial effects by acting as a pneumatic splint to prevent the upper airway soft tissue from collapsing. Other effects include a change in the upper airway muscle tone and increasing functional residual capacity (60). CPAP therapy has been demonstrated to resolve SDB events and improve many aspects of OSA syndrome. To that effect, adequate treatment of SDB has been shown to improve anxiety, depression, and other cognitive symptoms (61). In a case report by Youakim and colleagues (28), CPAP therapy resulted in dramatic improvement in sleep quality and daytime sleepiness of a Vietnam veteran with PTSD. There was a reduction in nightmare frequency and severity as well as an improvement in daytime flashbacks. Similar results were reported from a retrospective review of 15 patients with PTSD and SDB (62). In that study, nine had 75% improvement in their PTSD symptoms after CPAP therapy, whereas four of the six who refused or did not tolerate positive airway pressure had worsening symptoms (62). The improvement of both sleep-related and PTSD symptoms with CPAP treatment suggests that a potential complex interplay may exist between the two disorders. Although these studies are promising, there are number of methodological problems including, but not limited to, small sample size, selection bias, retrospective design, and lack of comparative intervention. Future longitudinal studies are needed to elucidate the strength and direction of these associations.

A major determinant of the effectiveness of CPAP therapy is patient compliance. Despite the overall improvement in PTSD symptomatology with CPAP therapy (63), adherence to treatment is far worse in these patients compared with the general population with OSA (64, 65). Although not statistically significant, insomnia tended to be more common in the PTSD group. Whether insomnia alone can account for the difference in CPAP compliance is open to debate. However, the retrospective nature of these studies did not allow an assessment of the severity of insomnia and its relation with CPAP compliance in this PTSD population.

Mask discomfort, claustrophobia, and air hunger were among the reported reasons for CPAP nonadherence in the PTSD group (64). It is somewhat intuitive to consider that having a mask on the face with positive pressure may awake dormant memories or experiences in patients with combat-related PTSD. Interestingly, nightmares were more frequently reported in those who were nonadherent to CPAP, which suggest that nightmares may be one of the factors infringing on CPAP compliance in patients with PTSD. It may also indicate a bidirectional relationship, with nightmare-related anxiety leading to reduced CPAP use or, alternatively, CPAP-related increases in nightmare propensity worsening adherence to treatment. The latest evidence seems to favor the former hypothesis. A recent retrospective study suggests that CPAP therapy is associated with decrease in frequency of PTSD-related nightmares (63). However, these results would need confirmation in future prospective trials.

In view of the poor adherence, it is important to consider alternative methods for conditioning patients with PTSD to CPAP. Cognitive behavioral therapy has been promising in improving CPAP adherence (66), although its efficacy has yet to be demonstrated in subjects with PTSD. For those intolerant to CPAP, alternative measures (i.e., oral appliances, nasal expiratory positive airway pressure) may be considered. A randomized trial comparing the efficacy of CPAP to oral appliance in PTSD with SDB is underway (NCT01569022). Other trials involving alternative or combination therapy should be the subject of future research to confirm their effectiveness in the coexisting PTSD and SDB population.

Future Directions

The growing population of combat veterans returning from recent wars will be facing significant clinical challenges in managing their concomitant disorders. Although studies to date have demonstrated sleep disturbances as a fundamental issue in trauma-exposed populations, the current research into PTSD and sleep disorders is limited by the fact that: (*1*) the vast majority of the work to date has been retrospective or cross-sectional in design, with the exception of a few small prospective studies in trauma-exposed study groups and treatment studies. A minority of the latter have included objective clinical assessments of PTSD that may provide insights into the physiological or neural underpinnings of the relationships of sleep to PTSD symptoms; (*2*) the effect of comorbid psychiatric disorders that are associated with sleep disturbances in PTSD has not been explored; (*3*) despite effective treatment of OSA with CPAP, adherence to therapy is poor and no alternative treatment has been studied; (*4*) no long-term prospective studies have evaluated the impact of sleep disturbances on cardiovascular and behavioral outcomes; (*5*) and the longitudinal implications of non-SDB (i.e., insomnia) in PTSD with OSA across the lifespan have not been investigated.

Two general areas of research are needed to advance understanding of why traumatic events increase the likelihood of developing sleep problems. First, it is

important to consider the characteristics of the traumatic event exposure. The time since the traumatic event, type of traumatic event exposure, and number of traumatic event exposures may differentially affect sleep. Direct prospective tests of the relation between specific traumatic event types and the development of sleep problems are needed. Second, future investigations using full PSG are integral to our understanding how changes in REM sleep (or more generally, sleep physiology and neurobiology) contribute to increased risk of poor psychiatric outcomes in patients with PTSD and SDB. To the best of our knowledge, no study has directly tested the role of undiagnosed SDB problems prospectively on subsequent traumatic event exposure. Analog designs that aim to experimentally test the effects of OSA-related sleep fragmentation on reactivity to traumatic event cues could shed light on how sleep problems may maintain traumatic event–related affective reactivity. Research in this domain is necessary to better conceptualize the interplay between sleep problems and traumatic event exposure.

In terms of treatment, randomized clinical trials are paramount in determining alternative treatments for CPAP. Would mandibular advancement devices, although less effective, prove to be more successful in reducing PTSD symptomatology by the mere fact of being better tolerated than CPAP? Would combination of cognitive behavioral therapy with CPAP improve adherence? Finally, as pharmacological interventions focused on PTSD symptom reduction alone (e.g., monoamine oxidase inhibitors, benzodiazepines, tricyclic antidepressants) have been shown to increase sleep problems (67), the exploration of psychopharmacologic interventions that target neuroanatomical structures implicated in both PTSD and sleep problems are sorely needed.

Summary

PTSD and SDB share common features: they have common symptoms that overlap, and they both affect quality of sleep and quality of life. Although not consistent, there is mounting evidence that an association between PTSD and OSA exists and can be explained by more than one mechanistic theory. In addition, both disorders seem to mutually affect and perpetuate each other, creating a vicious cycle of symptoms. With the increasing rate of PTSD among veterans returning from the Iraq and Afghanistan wars, there is a growing urgency to identify gaps in the quality of care provided to these patients. Among these unmet needs is the approach to the management of SDB in veterans with PTSD. Both diagnostic and therapeutic challenges are faced by clinicians caring for patients who may be suffering from both disorders. A thorough sleep assessment should be done when evaluating patients for PTSD, and extreme care should be taken to avoid inaccurate diagnosis of PTSD based on SDB-related symptoms. A screening protocol for OSA ought to be implemented for all patients with PTSD exhibiting symptoms of excessive daytime sleepiness and for those who fail to respond to standard PTSD treatment. Disturbed sleep is a modifiable risk factor, and sleep restoration through effective targeted sleep treatments may accelerate recovery from trauma exposure and PTSD. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1 American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 2013.
2 Chivers-Wilson KA. Sexual assault and posttraumatic stress disorder: a review of the biological, psychological and sociological factors and treatments. *Mcgill J Med* 2006;9:111–118.
3 Resnick HS, Kilpatrick DG, Dansky BS, Saunders BE, Best CL. Prevalence of civilian trauma and posttraumatic stress disorder in a representative national sample of women. *J Consult Clin Psychol* 1993;61:984–991.
4 Grieger TA, Cozza SJ, Ursano RJ, Hoge C, Martinez PE, Engel CC, Wain HJ. Posttraumatic stress disorder and depression in battle-injured soldiers. *Am J Psychiatry* 2006;163:1777–1783; quiz 1860.
5 Steel Z, Chey T, Silove D, Marnane C, Bryant RA, van Ommeren M. Association of torture and other potentially traumatic events with mental health outcomes among populations exposed to mass conflict and displacement: a systematic review and meta-analysis. *JAMA* 2009;302:537–549.
6 Ezra MB. Earliest evidence of post-traumatic stress? *Br J Psychiatry* 2001;179:467.
7 Crocq MA, Crocq L. From shell shock and war neurosis to posttraumatic stress disorder: a history of psychotraumatology. *Dialogues Clin Neurosci* 2000;2:47–55.
8 Friedman MJ. Post-Vietnam syndrome: recognition and management. *Psychosomatics* 1981;22:931–943.
9 Jordan BK, Marmar CR, Fairbank JA, Schlenger WE, Kulka RA, Hough RL, Weiss DS. Problems in families of male Vietnam veterans with posttraumatic stress disorder. *J Consult Clin Psychol* 1992;60:916–926.
10 Hoge CW, Castro CA, Messer SC, McGurk D, Cotting DI, Koffman RL. Combat duty in Iraq and Afghanistan, mental health problems, and barriers to care. *N Engl J Med* 2004;351:13–22.
11 Edmondson D, Richardson S, Falzon L, Davidson KW, Mills MA, Neria Y. Posttraumatic stress disorder prevalence and risk of recurrence in acute coronary syndrome patients: a meta-analytic review. *PLoS ONE* 2012;7:e38915.
12 Krakow B, Hollifield M, Johnston L, Koss M, Schrader R, Warner TD, Tandberg D, Lauriello J, McBride L, Cutchen L, *et al*. Imagery rehearsal therapy for chronic nightmares in sexual assault survivors with posttraumatic stress disorder: a randomized controlled trial. *JAMA* 2001;286:537–545.
13 Krakow B, Germain A, Tandberg D, Koss M, Schrader R, Hollifield M, Cheng D, Edmond T. Sleep breathing and sleep movement disorders masquerading as insomnia in sexual-assault survivors. *Compr Psychiatry* 2000;41:49–56.
14 Clum GA, Nishith P, Resick PA. Trauma-related sleep disturbance and self-reported physical health symptoms in treatment-seeking female rape victims. *J Nerv Ment Dis* 2001;189:618–622.
15 Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? *Sleep Med Rev* 2008;12:169–184.
16 Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? *Am J Psychiatry* 2013;170:372–382.
17 Lavie P, Katz N, Pillar G, Zinger Y. Elevated awaking thresholds during sleep: characteristics of chronic war-related posttraumatic stress disorder patients. *Biol Psychiatry* 1998;44:1060–1065.
18 Engdahl BE, Eberly RE, Hurwitz TD, Mahowald MW, Blake J. Sleep in a community sample of elderly war veterans with and without posttraumatic stress disorder. *Biol Psychiatry* 2000;47:520–525.
19 Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. *Sleep* 2005;28:1405–1411.
20 Ocasio-Tascón ME, Alicea-Colón E, Torres-Palacios A, Rodríguez-Cintrón W. The veteran population: one at

high risk for sleep-disordered breathing. *Sleep Breath* 2006;10:70–75.
21 Yesavage JA, Kinoshita LM, Kimball T, Zeitzer J, Friedman L, Noda A, David R, Hernandez B, Lee T, Cheng J, O'Hara R. Sleep-disordered breathing in Vietnam veterans with posttraumatic stress disorder. *Am J Geriatr Psychiatry* 2012;20:199–204.
22 Williams SG, Collen J, Orr N, Holley AB, Lettieri CJ. Sleep disorders in combat-related PTSD. *Sleep Breath* (In press)
23 Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, Koss M, Warner TD, Schrader R. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. *Biol Psychiatry* 2001;49:948–953.
24 Krakow B, Melendrez D, Johnston L, Warner TD, Clark JO, Pacheco M, Pedersen B, Koss M, Hollifield M, Schrader R. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. *J Nerv Ment Dis* 2002;190:442–452.
25 Krakow B, Haynes PL, Warner TD, Santana E, Melendrez D, Johnston L, Hollifield M, Sisley BN, Koss M, Shafer L. Nightmares, insomnia, and sleep-disordered breathing in fire evacuees seeking treatment for posttraumatic sleep disturbance. *J Trauma Stress* 2004;17:257–268.
26 Webber MP, Lee R, Soo J, Gustave J, Hall CB, Kelly K, Prezant D. Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers. *Sleep Breath* 2011;15:283–294.
27 Arnetz BB, Templin T, Saudi W, Jamil H. Obstructive sleep apnea, posttraumatic stress disorder, and health in immigrants. *Psychosom Med* 2012;74:824–831.
28 Youakim JM, Doghramji K, Schutte SL. Posttraumatic stress disorder and obstructive sleep apnea syndrome. *Psychosomatics* 1998;39: 168–171.
29 Johnson K. Sleep Problems, PTSD, Obesity 'Related, but to What Degree?' *Clinical Psychiatry News* 2014;38:46.
30 Klein E, Koren D, Arnon I, Lavie P. No evidence of sleep disturbance in post-traumatic stress disorder: a polysomnographic study in injured victims of traffic accidents. *Isr J Psychiatry Relat Sci* 2002;39:3–10.
31 Breslau N, Roth T, Burduvali E, Kapke A, Schultz L, Roehrs T. Sleep in lifetime posttraumatic stress disorder: a community-based polysomnographic study. *Arch Gen Psychiatry* 2004;61:508–516.
32 Capaldi VF II, Guerrero ML, Killgore WD. Sleep disruptions among returning combat veterans from Iraq and Afghanistan. *Mil Med* 2011; 176:879–888.
33 Mysliwiec V, Gill J, Lee H, Baxter T, Pierce R, Barr TL, Krakow B, Roth BJ. Sleep disorders in US military personnel: a high rate of comorbid insomnia and obstructive sleep apnea. *Chest* 2013;144:549–557.
34 Kobayashi I, Sledjeski EM, Spoonster E, Fallon WF Jr, Delahanty DL. Effects of early nightmares on the development of sleep disturbances in motor vehicle accident victims. *J Trauma Stress* 2008;21:548–555.
35 Koren D, Arnon I, Lavie P, Klein E. Sleep complaints as early predictors of posttraumatic stress disorder: a 1-year prospective study of injured survivors of motor vehicle accidents. *Am J Psychiatry* 2002;159: 855–857.
36 Bryant RA, Creamer M, O'Donnell M, Silove D, McFarlane AC. Sleep disturbance immediately prior to trauma predicts subsequent psychiatric disorder. *Sleep* 2010;33:69–74.
37 Mellman TA, Bustamante V, Fins AI, Pigeon WR, Nolan B. REM sleep and the early development of posttraumatic stress disorder. *Am J Psychiatry* 2002;159:1696–1701.
38 Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. *Psychophysiology* 2007;44:660–669.
39 van Liempt S, Arends J, Cluitmans PJ, Westenberg HG, Kahn RS, Vermetten E. Sympathetic activity and hypothalamo-pituitary-adrenal axis activity during sleep in post-traumatic stress disorder: a study assessing polysomnography with simultaneous blood sampling. *Psychoneuroendocrinology* 2013;38:155–165.
40 Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995;152:110–115.
41 Spoormaker VI, Schröter MS, Andrade KC, Dresler M, Kiem SA, Goya-Maldonado R, Wetter TC, Holsboer F, Sämann PG, Czisch M. Effects of rapid eye movement sleep deprivation on fear extinction recall and prediction error signaling. *Hum Brain Mapp* 2012;33:2362–2376.
42 de Kloet CS, Vermetten E, Geuze E, Kavelaars A, Heijnen CJ, Westenberg HG. Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. *J Psychiatr Res* 2006;40:550–567.
43 Golier JA, Caramanica K, Makotkine I, Sher L, Yehuda R. Cortisol response to cosyntropin administration in military veterans with or without posttraumatic stress disorder. *Psychoneuroendocrinology* 2014;40:151–158.
44 Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr. Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. *Am J Psychiatry* 1999;156:585–588.
45 Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS. Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. *Am J Psychiatry* 1997;154:624–629.
46 de Kloet CS, Vermetten E, Geuze E, Lentjes EG, Heijnen CJ, Stalla GK, Westenberg HG. Elevated plasma corticotrophin-releasing hormone levels in veterans with posttraumatic stress disorder. *Prog Brain Res* 2008;167:287–291.
47 Klaassens ER, Giltay EJ, Cuijpers P, van Veen T, Zitman FG. Adulthood trauma and HPA-axis functioning in healthy subjects and PTSD patients: a meta-analysis. *Psychoneuroendocrinology* 2012;37:317–331.
48 Meewisse ML, Reitsma JB, de Vries GJ, Gersons BP, Olff M. Cortisol and post-traumatic stress disorder in adults: systematic review and meta-analysis. *Br J Psychiatry* 2007;191:387–392.
49 Abedelmalek S, Souissi N, Chtourou H, Denguezli M, Aouichaoui C, Ajina M, Aloui A, Dogui M, Haddouk S, Tabka Z. Effects of partial sleep deprivation on proinflammatory cytokines, growth hormone, and steroid hormone concentrations during repeated brief sprint interval exercise. *Chronobiol Int* 2013;30:502–509.
50 Kim E, Grover LM, Bertolotti D, Green TL. Growth hormone rescues hippocampal synaptic function after sleep deprivation. *Am J Physiol Regul Integr Comp Physiol* 2010;298:R1588–R1596.
51 van Zuiden M, Geuze E, Willemen HL, Vermetten E, Maas M, Heijnen CJ, Kavelaars A. Pre-existing high glucocorticoid receptor number predicting development of posttraumatic stress symptoms after military deployment. *Am J Psychiatry* 2011;168:89–96.
52 van Liempt S. Sleep disturbances and PTSD: a perpetual circle? *Eur J Psychotraumatol* 2012;3.
53 Bremner JD. Stress and brain atrophy. *CNS Neurol Disord Drug Targets* 2006;5:503–512.
54 Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. *Am J Psychiatry* 1995;152: 973–981.
55 Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. *Psychol Med* 1997;27:951–959.
56 Schuff N, Neylan TC, Lenoci MA, Du AT, Weiss DS, Marmar CR, Weiner MW. Decreased hippocampal N-acetylaspartate in the absence of atrophy in posttraumatic stress disorder. *Biol Psychiatry* 2001;50: 952–959.
57 Sériès F, Roy N, Marc I. Effects of sleep deprivation and sleep fragmentation on upper airway collapsibility in normal subjects. *Am J Respir Crit Care Med* 1994;150:481–485.
58 Carrasco E, Santamaria J, Iranzo A, Pintor L, De Pablo J, Solanas A, Kumru H, Martínez-Rodríguez JE, Boget T. Changes in dreaming induced by CPAP in severe obstructive sleep apnea syndrome patients. *J Sleep Res* 2006;15:430–436.
59 Guilleminault C. Obstructive sleep apnea syndrome. A review. *Psychiatr Clin North Am* 1987;10:607–621.
60 Rapoport DM, Garay SM, Goldring RM. Nasal CPAP in obstructive sleep apnea: mechanisms of action. *Bull Eur Physiopathol Respir* 1983;19:616–620.
61 McMahon JP, Foresman BH, Chisholm RC. The influence of CPAP on the neurobehavioral performance of patients with obstructive sleep apnea hypopnea syndrome: a systematic review. *WMJ* 2003;102:36–43.

62 Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M, Tandberg D, Johnston L, Melendrez D. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. *J Psychosom Res* 2000;49:291–298.
63 Tamanna S, Parker JD, Lyons J, Ullah MI. The effect of continuous positive air pressure (CPAP) on nightmares in patients with posttraumatic stress disorder (PTSD) and obstructive sleep apnea (OSA). *J Clin Sleep Med* 2014;10:631–636.
64 El-Solh AA, Ayyar L, Akinnusi M, Relia S, Akinnusi O. Positive airway pressure adherence in veterans with posttraumatic stress disorder. *Sleep* 2010;33:1495–1500.
65 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;8:667–672.
66 Richards D, Bartlett DJ, Wong K, Malouff J, Grunstein RR. Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. *Sleep* 2007;30:635–640.
67 Maher MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. *CNS Drugs* 2006;20:567–590.
68 World Health Organization. Pocket guide to the ICD-10 classification of mental and behavioral disorders. Washington, DC: American Psychiatric Press; 1994. pp.168–169.