THEORETICAL REVIEW

Posttraumatic stress disorder and sleep-disordered breathing: a review of comorbidity research

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SUMMARY

Posttraumatic stress disorder (PTSD) and sleep-disordered breathing (SDB) are common disorders, but limited data address their co-morbidity. Emerging research indicates PTSD and SDB may co-occur more frequently than expected and may impact clinical outcomes. This review describes historical developments that first raised suspicions for a co-morbid relationship between PTSD and SDB, including barriers to the recognition and diagnosis of this co-morbidity. Objective diagnostic data from polysomnography studies in PTSD patients reveal widely varying prevalence rates for co-morbidity (0–90%). Use of standard, recommended technology (nasal cannula pressure transducer) versus older, less reliable technology (thermistor/thermocouple) appears to have influenced objective data acquisition and therefore SDB rates in sleep studies on PTSD patients. Studies using higher quality respiratory sensors demonstrated the highest prevalence of SDB in PTSD patients. Clinical relevance, theoretical models and research recommendations are discussed. The lack of widely acknowledged, tested, or proven explanatory models and pathophysiological mechanisms to understand the relationship between these two disorders may prove formidable barriers to further investigations on prevalence and clinical relevance, albeit both conditions are associated with waking or sleeping hyperarousal activity, which may inform future studies.

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Introduction

Conceptualizations in the scientific literature about posttraumatic stress disorder (PTSD) and sleep were sparse until the past decade [1–4], at which point a clinical sleep medicine perspective on PTSD emerged [5–16]. Yet, this newer information has been slow to diffuse into the psychiatric or psychological literature where PTSD research commonly omits sleep as a primary variable of interest. While insomnia and nightmares are frequently reported sleep symptoms in PTSD [2,7,8,16,17] rare attention is given to sleep-disordered breathing (SDB) either in terms of prevalence or in developing theories addressing co-morbid sleep disorders and PTSD.

This review article examines the possible co-morbid relationship between SDB and PTSD, first by providing a brief overview of SDB pathophysiology followed by an outline of the historical developments that initially raised suspicions for a potential co-morbid relationship between SDB and PTSD. To shed more light on this historical progression, we describe key barriers that likely inhibited recognition and diagnosis of SDB in PTSD patients. With these backdrops, we describe our literature search and results for the known prevalence of SDB in PTSD patients as well as possible clinical relevance of this alleged co-morbidity. Finally, we delve into theoretical models and research recommendations to facilitate hypothesis development about this co-morbidity.

Assessment of sleep-disordered breathing

SDB is a common sleep disorder, affecting as many as 9–24% of the adult population [18]. Obstructive sleep apnea (OSA) is the most common form of sleep breathing problem, which comprises three

precisely defined obstructive breathing events known as apneas, hypopneas, and respiratory effort-related arousals (RERA), each of which collapses the airway and reduces airflow for 10 s or longer [19,20]. Apneas reflect near or total cessation of airflow; hypopneas reflect roughly 30%–70% reduction in airflow; and, RERAs, which also are termed flow limitation events (FLEs) or, more generally, upper airway resistance syndrome (UARS), comprise a less than 30% reduction in airflow but which otherwise remains ill-defined [20]. Apneas and hypopneas are often accompanied by oxygen desaturations or fluctuations; whereas RERAs show limited or no changes in oxygenation. All three sleep breathing events trigger cortical arousals or awakenings after which normal breathing resumes, and these episodes may recur throughout the sleep period, which provides a rationale for viewing SDB as a generator of nocturnal hyperarousal activity. One additional breathing event potentially relevant to patients with PTSD is the central apnea: changes in the central nervous system, usually attributed to wide fluctuations in carbon dioxide levels, cause breathing cessation while asleep despite an unobstructed airway [21]. Prior research indicates anxiety patients [22] as well as traumatic brain injury patients [23] show risks for central apneas.

Historical developments

Several papers on the potential role of SDB and posttraumatic stress symptoms or related topics appeared as early as the 1980s; Guilleminault noted a relationship between SDB and anxiety dreams [24]. In 1991, a small study of 24 war veterans demonstrated a 54% rate of SDB in combat related PTSD [25]. Later, de Groen found an association between snoring and anxiety-related dreams [26]. In 1995, another study showed nearly half of combat veterans with PTSD compared with 13% of a non-clinical sample demonstrated apneas and hypopneas, although the number of breathing events per hour was low [27].

In 1998, a study reported on 156 female sexual assault survivors with nightmares and PTSD who manifested symptoms indicating a high potential for sleep apnea [28]. The main finding showed their Pittsburgh sleep quality index [29] global scores exceeded values for patients with depression, insomnia or hypersomnia alone. These data suggested a greater degree of sleep disturbance complexity not fully explained by PTSD.

We speculated this complexity was due to intrinsic physiological sleep disorders disguised as posttraumatic insomnia [30]. For example, 52% of sexual assault survivors suffering from PTSD reported the combination of snoring and daytime sleepiness, which met screening criteria to test for sleep apnea [31]. There was also a potential for either or both sleep breathing and sleep movement disorders among these sexual assault survivors who presented with nightmares, insomnia and posttraumatic stress symptoms. When women with potential physical sleep disorders were compared to those without such symptoms, the presumptive sleep disorders' group correlated significantly with worse PTSD symptom severity [32]. This raised the question of whether or not treatment of physiological sleep disorders might decrease PTSD severity [32].

Also in 1998, Lavie and colleagues reported a controlled study on awakening thresholds in PTSD patients. Among the 12 war veterans in the PTSD group, five exhibited objective evidence for moderate sleep apnea [33], while four of 12 controls also had OSA though of lesser intensity. Lavie and colleagues speculated on whether changes in sleep depth in PTSD patients might increase susceptibility to sleep breathing events, and then expanded this theory by providing a precise pathway wherein anxiety patients might hyperventilate during sleep to produce hypocapnia—a proven risk for triggering apneas [5].

Finally in 1998, a single case report described sleep apnea in a PTSD patient [34], who eliminated PTSD symptoms when treated with positive airway pressure therapy (PAP-T), the gold standard SDB treatment [35]. Two years later, Engdahl reported improvements in psychiatric distress with regular use of PAP-T among four veterans with comorbid PTSD and SDB [36].

From 2000 to 2002, six articles were published on the specific topic of SDB and PTSD, developing hypotheses as well as presenting key objective data. Among the samples of female sexual assault survivors with nightmares and posttraumatic stress symptoms or disorders, the main findings included:

- sleep breathing symptoms were surprisingly common, often present in greater than 50% of a sample [32,37–39];
- presumptively diagnosed sleep breathing disorders presented more like psychiatric-related insomnia rather than classic sleep apnea [32,37,38];
- objectively diagnosed SDB or self-reported SDB symptoms were associated with worse psychiatric distress [37–39];
- and, treatment of sleep breathing disorders in PTSD patients was associated with decreases in nightmares, insomnia and posttraumatic stress [40].

Among this set of papers, the initial objective work used an advance respiratory sensor technology to test 44 consecutive crime victims with posttraumatic stress who sought treatment for nightmares and insomnia; 40 of 44 patients were diagnosed by polysomnography (PSG) with OSA or UARS [41]. From these results, we coined the term "complex insomnia" to describe patients with a primary complaint of insomnia who also suffer co-morbid and usually covert (to the patient and physician or therapist) SDB [41].

Barriers to diagnosis and recognition

While these earlier works were thought-provoking, three prevailing paradigms tended to dilute research on relationships between sleep breathing disorders and PTSD, and each appears to reflect a lack of recognition or application of new perspectives or technology to assess trauma survivors with sleep complaints [6]. Foremost among these barriers is the prevailing view that emphasizes the psychological or psychiatric aspects of PTSD [42–44]. Although there is considerable research on biological aspects of

PTSD, physiological studies rarely examine sleep pathophysiology. In conducting our literature searches on PTSD studies, it was rare to find an objective sleep measure as a primary variable of interest.

The second barrier involves the use of narrowly defined screening techniques to assess sleep breathing disorders. The classic approach queries patients on breathing symptoms and severity of daytime sleepiness as well as impact on daytime functioning. Yet in trauma survivors, daytime sleepiness may be difficult to assess due to counteracting forces of hyperarousal or hypervigilance [45]. Patients might never acknowledge or notice dozing off or a propensity for dozing off when surveyed with common sleep apnea screening surveys [46]. Patient reports of breathing symptoms are unreliable and often result in false negatives, because individuals may not know whether they snore, choke, gasp or cease breathing at night, or their fear, shame or embarrassment about breathing symptoms may inhibit their communications [47]. Among classic sleep apnea presentations, considerable variability is the norm even when assessing obvious factors such as obesity and sleepiness [48]. Some non-obese patients may demonstrate no objective snoring while meeting diagnostic criteria for UARS [49]. A more probing discussion of sleep quality (e.g., reports of light, fragmented, or non-restorative sleep; daytime fatigue or impairment) must be conducted with PTSD patients beyond initial presenting complaints of insomnia or nightmares to clarify suspicions about SDB [39,50], or in some cases the use of "end-organ" symptoms such as nocturia, morning headache or dry mouth upon awakening may serve as useful SDB screening questions for raising clinical suspicions [50].

The third and most problematic barrier adversely influencing objective research on sleep and PTSD is the notable lack of diagnostic polysomnography in relevant studies. Without PSG testing no evidence can be gathered to illuminate what appears to be an under-served area of research. Moreover, when PSG is performed, another barrier is the rare application of any breathing sensor. Even when breathing is assessed, few studies use current, standard technology in the field of sleep medicine—nasal cannula pressure transducers (NCPT) [20,51–53], and to our knowledge no studies used esophageal manometry, the original gold standard sensor for measuring UARS. Fortunately, NCPT technology serves as an appropriate surrogate for esophageal manometry [54]. This gap in technology produces a substandard level of assessment in contrast to the nosology of the American Academy of Sleep Medicine (AASM) [31,55]. This contrast is best exemplified in Breslau and colleagues (2004) widely cited study on objective sleep findings in patients with chronic PTSD [56]. Sleep breathing was measured solely with thermistor technology, a qualitative tool that does not effectively measure all three common types of obstructive breathing events [56]. Regrettably, five years prior to this study, the AASM ranked thermistors with a "D" grade for its capacity to measure hypopneas accurately, and it does not measure RERAs; both breathing events (hypopneas and RERAs) require pressure transducer technology [31].

Another confounding element of the Breslau et al. (2004) study was a threshold for AHI (apnea-hypopnea index) of 10 events/h or greater, which is twice the standard cut-off point in the field of sleep medicine of five events or greater [55]. The authors reported only 7–14% of PTSD patients received an OSA diagnosis [56]. Compared to other studies that used standard sensors for respiratory assessment and the standard AHI cut-off [41], the 2004 study may reflect a relative underestimation of SDB prevalence.

Last, this assessment barrier due to the absence of PSG testing or the choice of technology persists and perpetuates a lack of clarity on prevalence data. For example, sleep research studies using polysomnography in PTSD cohorts have not adopted the pressure transducer technology to measure hypopneas and RERAs as

recently as 2010 [57–59]. Indeed, these studies report conflicting values on a spectrum ranging from the absence of breathing disorders [57] to a 69% prevalence rate of sleep apnea [59].

Confusing matters further, a large percentage of labs that use NCPT will report AHI [(total apneas + total hypopneas)/total hours of sleep] but fail to report RDI [respiratory disturbance index = (total apneas + total hypopneas + total RERAs)/total hours of sleep] or erroneously report AHI as RDI [60]. Paradoxically, AASM guidelines make scoring of RERAs optional on diagnostic studies but mandate treatment of RERAs on titration studies [20]. Regardless, new AASM scoring rules allow for a broader definition of hypopneas, which will then permit some events previously scored as RERAs to now meet criteria for hypopnea. This change will lead to greater capture of breathing events and likely more accurate diagnosis of SDB in PTSD patients.

Prevalence

The search strategy identified peer reviewed articles in Medline, CINAHL, Academic Search Premier, PsycINFO, and Cochrane database of systematic reviews based on terms relevant to the literature review. Search terms included "PTSD," "Obstructive Sleep Apnea," "Upper Airway Resistance," and "Sleep Disordered Breathing" and related variants; search dates encompassed 1988–2014. All relevant database articles were reviewed for minimal inclusion criteria: 1) participants with a documented history of PTSD or posttraumatic stress (PTS) symptoms; 2) reported AHI, RDI, and/or diagnosis of SDB, either OSA or UARS; and 3) co-morbidity of PTSD and OSA/UARS as a primary variable of interest. Our initial search yielded 72 citations, but only fifteen articles remained after removing duplicates and identifying those articles meeting inclusion criteria. In Table 1, each study is described by type, sample and setting characteristics, PTSD measurements, respiratory sensor technology applied, age and BMI, and objective testing results as well as the level of evidence based on Sackett's criteria (see Table 1 footnote) [61]. Most excluded citations referenced sleep breathing problems but failed to report objective data.

There is no consensus prevalence rate for co-morbid SDB and PTSD due to wide divergence in findings (0–90%). Still, among more recent reviews, there is a growing indication that individuals with PTSD suffer a disproportionately higher rate of SDB compared to the general population [8,11,13,15]. Dagan and colleagues found 13 of 24 combat veterans diagnosed with PTSD had sleep apnea [62]. In a study of elderly war veterans ($n = 59$) with and without PTSD, the actual screening for OSA led to the exclusion of 31 patients with comorbid sleep apnea and PTSD in the recruitment phase, yet four of the remaining 30 patients were later diagnosed with OSA [36]. In our study of 44 crime victims with PTSD or clinically relevant posttraumatic stress symptoms, 50% were diagnosed with OSA and 41% with UARS [41]; however, this sample is biased as patients were seeking treatment for sleep problems. Recently, in a sample of 105 Vietnam-era veterans with PTSD, 69% had an AHI >10 [59], despite the researchers using only the thermistor technology. In another recent work with a sample of 69 combat veterans returning from war zones, rates of OSA averaged roughly 75% among three groups comprised of either PTSD patients, traumatic brain injury (TBI) patients or a group of "other diagnostic conditions." Although there was no difference in diagnostic rates, the PTSD group manifested a greater severity of breathing events than the TBI group but not the "other" group [63]. In two recent studies by Mysliwiec and colleagues, which used pressure transducer technology, the first demonstrated a 63% rate of OSA in post-deployment soldiers [64], and the second demonstrated a 51% rate of OSA in active duty soldiers [65]. Both studies, however, suffered from a strong selection bias towards those with more sleep complaints. In the most

Table 1
Prevalence data on objective sleep studies in PTSD patient samples.

Study	Study type[a]	Study quality[b]	PTSD samples recruitment[c]	Sample details or bias	Posttraumatic stress measures	Sample size[d]	Age mean (SD), y	BMI mean (SD), kg/m²	PSG airflow sensor	AHI/RDI mean (SD), events/h	OSA (O) and/or UARS (U) criteria	OSA diagnoses[e]
Breslau et al. (2004) [56]	1	3b	Health maintenance program members	Trauma exposure history	NIMH-DIS	N = 283 P = 71 C = 212	36.8 (2.2)	NA	Therm	NA	O = AHI ≥10	7-14%
Capaldi et al. (2011) [63]	2	3b	Iraq/Afghanistan war veterans	Sleep study referrals	Previously diagnosed	N = 69 P = 18	37.9 (9.7)	29.0 (4.3)	NCPT and Therm	AHI = 21.3 (22.6)	O = AHI≥10	53 of 69 (76.8%); 14 of 18 PTSD
Dagan et al. (1991) [62]	1	4	Israeli war veterans	Randomly selected	SCID	N = 24	31.9 (4.6)	NA	Therm	NA	O = AHI≥10	13 of 24 (54.2%)
Engdahl et al. (2000) [36]	1	3b	POW & combat veteran volunteers	Screened and excluded for OSA (n = 31)[f]	SCID	N = 59 P = 30 C = 29	71.3 (4.2)	NA	Not specified	NA	NA	5 of 59 (8.5%); 4 of 30 PTSD; 1 of 29 controls
Habukawa et al. (2007) [57]	1	3b	Inpatient & outpatient PTSD patients	Randomly selected	SCID, CAPS	N = 20 P = 10 C = 10	23.4 (6.1)	NA	Not specified	AHI = ~1 22.7 (10.1)	NA	Suspected link to SDB
Kinoshita et al. (2012) [70]	2	3b	Vietnam veterans	PTSD sleep apnea clinic	CAPS	N = 120	61.3 (4.0)	30.7 (5.6)	NCPT	AHI = 19 (median)	O = AHI ≥5	114 of 120 (95%)
Krakow et al. (2002) [39]	2	3b	Sexual assault survivors	Sleep treatment seeking	PSQI, CAPS, PSS	N = 21	37 (11)	25	NCPT and Therm	AHI = 13 (10.5) RDI = 39 (22.0)	O = AHI≥5 U = RDI≥15	21 of 21 (100%) w/11 of 21 UARS
Krakow et al. (2001) [41]	1	4	Crime victims with nightmares and insomnia	Sleep treatment seeking	PDS	N = 44	40.9 (12.4)	26.4 (5.9)	NCPT	AHI = 9.70 (14.00) RDI = 36.08 (20.51)	O = AHI≥5 U = RDI≥15	40 of 44 (90.9%) w/18 of 44 UARS
Lavie et al. (1998) [33]	2	3b	Israel war veterans	Randomly selected	IES	N = 24 P = 12 C = 12	31 (4.4)	NA	NCPT	NA	O = AHI≥10	9 of 24 (37.5%); 5 of 12 PTSD; 4 of 12 controls
Liempt et al. (2011) [11]	1	2b	Dutch veterans	Recruited specifically for study	CAPS, SCID	N = 61 P = 20 TC = 24 HC = 17[d]	40.75 (8.45)	27.86 (4.86)	NCPT	AHI = 6.79 (5.58)	O = AHI≥10	6 of 20 (29%) PTSD; 5 of 20 (21%) TC; 5 of 20 (29%) HC
Mellman et al. (1995) [27]	1	3b	Vietnam veterans	Screened and excluded for loud snoring	SCID	N = 29 P = 21 C = 8	42.7 (2.5)	NA	Not specified	NA	NA	11 of 29 (37.9%)[g] 10 of 21 PTSD; 1 of 8 controls
Mysliwiec et al. (2013) [64]	1	3b	Iraq/Afghanistan war veterans	Post-deployment sleep disturbances	PCL-M	N = 110	33.6 (8.0)	30 (4.3)	NCPT and Therm	AHI = 13.4 (17.3)	O = AHI>5	69 of 110 (62.7%)
Mysliwiec et al. (2013) [65]	2	3b	Iraq/Afghanistan war veterans	Records review on veterans with PSG data	Previously Diagnosed	N = 725	35.5 (8.6)	29.8 (4.1)	NCPT and Therm	AHI = 13.1 (19.6)	O = AHI≥5	390 of 725 (51.2%)
Williams et al. (2014) [66]	2	3b	Iraq/Afghanistan war veterans	Excluded patients with preexisting OSA prior to PTSD diagnosis	PCL-M	N = 130	35.1 (10.6)	28.1 (4.3)	Not specified	AHI = 24.1 (22.8)	O = AHI>5	70 of 104 (67.3%) of PSG group; 70/130 (53.8%) of entire cohort
Yesavage et al. (2012) [59]	1	3b	Vietnam veteran volunteers and referrals	Sleep study referrals	CAPS	N = 105	59.9 (3.1)	31.1 (6.1)	NCPT	NA	O = AHI≥10	72 of 105 (69%)

Note. AHI = apnea-hypopnea index (Total number of apneas and hypopneas/h); AI = apnea index; CAPS = clinician-administered PTSD scale; HC = healthy controls; IES = impact of event scale; NA = data not available; NCPT = nasal cannula pressure transducer; NIMH-DIS = National Institute of Mental Health-Diagnostic Interview Schedule; PCL-M = PTSD checklist-military version; PDS = posttraumatic diagnostic scale; POW = prisoner of war; PSG = polysomnography; PSQI = Pittsburgh sleep quality index; PSS = PTSD symptom scale; PTSD = posttraumatic stress disorder; RDI = respiratory disturbance index (Total number of apneas, hypopneas, and RERAs/h); RERA = respiratory effort-related arousal; SCID = structured clinical interview for DSM−III−R; Therm = nasal thermal sensor; TC = trauma controls; VA = veterans administration.

[a] 1 = longitudinal/prospective; 2 = retrospective chart review.

[b] Based on Sackett criteria for assessing research quality (2b = individual cohort studies and low quality RCTs using gold standard technology for diagnosis; 3b = case controlled studies; 4 = case series and poor-quality cohort and case−control studies).

[c] All study samples contain patients with diagnosed PTSD, except for Krakow et al., 2002a, which presumed PTSD based on PTS symptom severity.

[d] N = total sample size; P = PTSD Group; C = control group (if present); TC = trauma controls; HC = healthy controls.

[e] Proportion of patients diagnosed with SDB (primarily OSA).

[f] 31 patients excluded from protocol after screening positive for OSA, yet four patients still diagnosed with OSA after study PSG testing.

[g] Estimate since exact AHI/RDI not given.

recent study of veterans with combat-related PTSD ($n = 130$), 67.3% were diagnosed with OSA (80% of cohort underwent PSG). OSA was significantly more common in soldiers who did not suffer combat-related traumatic physical injuries ($n = 71$) than in injured soldiers (72.9 vs. 38.0%, $p < .001$) [66].

From a different perspective, developed within a large health-care database examining relationships between OSA and psychiatric conditions at the Veterans Administration, a cohort of 31,186 individuals (>90% male) demonstrated PTSD at nearly thrice the prevalence (11.85% vs. 4.74%) in a sleep apnea group ($N = 14,459$) compared to a non-sleep apnea group ($N = 16,727$) [67]. In a similar study, Raper and colleagues found a PTSD rate of 28% among combat veterans with sleep apnea [68].

In sum, if we look at prevalence rates distinguished by whether NCPT or thermistor was used, NCPT studies ($N = 11$) showed an average weighted SDB prevalence of 62.1%; whereas, studies using thermistors ($N = 4$) showed an average weighted SDB prevalence of 15.4%. Given NCPT is the gold standard, and juxtaposed with the data compiled for this review, we estimate the prevalence of co-morbid PTSD and SDB is much higher than initially thought and likely similar to the prevalence rate found in studies using NCPT, i.e., in the 50−90% range. However, until standard respiratory assessment tools are consistently used to test sleep-disordered breathing in PTSD patients and until recognition increases for the necessity for such testing, actual prevalence of this comorbidity cannot be determined.

Clinical relevance

The most interesting speculation on this potential co-morbidity springs from the overlapping health problems associated with or linked to both conditions (see Supplement-Table 1). Yet, few studies have focused on a potential SDB-PTSD comorbidity to inform this relationship. We found only four studies that address this possible interaction. The earliest was a group of 187 consecutive female sexual assault survivors with moderately severe posttraumatic stress symptoms who were divided into two groups based on symptom reports: those with likely sleep apnea ($n = 168$) and those unsuspected for a sleep breathing disorder ($n = 19$) [39]. Of the 168 suspected SDB cases, 21 participants completed objective tests, and all were confirmed cases of OSA ($n = 10$) or UARS ($n = 11$). Given that demographic, sleep, and psychiatric symptoms and histories in confirmed cases were no different than the remaining 147 who did not complete objective testing, the assumption was that the total group of 168 likely possessed a strong potential for sleep breathing disorders. Then, SF-36 health scales [69] for mental and physical health functioning were compared between the SDB group of 168 and the 19 women who reported no SDB symptoms. All eight physical and mental health scales showed significantly worse outcomes for the SDB group (lower scores) with medium to large effects (Cohen's d):

- Physical functioning: 67.53 (27.51) vs. 83.42 (16.92); $d = 0.59$
- Role physical: 40.06(41.09) vs. 65.79(40.15); $d = 0.62$
- Bodily pain: 47.47(26.09) vs. 63.37(19.27); $d = 0.61$
- General health perception: 47.69(25.03) vs. 69.95(18.58); $d = 0.88$
- Energy/vitality: 26.63(19.02) vs. 50.53(21.53); $d = 1.16$
- Social functioning: 48.87(24.84) vs. 67.76(26.46); $d = 0.74$
- Role emotional: 21.28(30.74) vs. 52.63(39.00); $d = 0.95$
- Mental health: 57.86(12.89) vs. 64.63(9.45); $d = 0.52$

Kinoshita et al. (2012) conducted a study through a PTSD Sleep Apnea Clinic, recruiting 120 PTSD patients to evaluate cognitive function. Patients currently treated for sleep apnea (e.g., corrective surgery, PAP-T) were excluded. Of the 120, 83% had untreated sleep apnea diagnosed on objective PSG, and 62% had hypertension. Summarizing their findings, "… deficits in auditory verbal memory and executive function were predicted by measures of OSA severity (AHI [apnea-hypopnea index] and min SpO$_2$ [minimum oxygen saturation]) and hypertension. Thus, in addition to OSA, hypertension predicted worse cognitive performance [in PTSD patients]" [70].
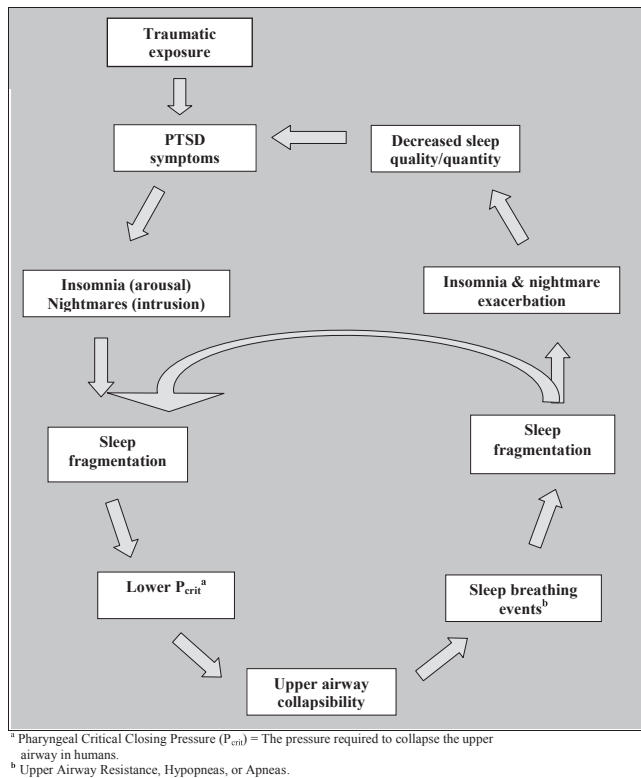
In a third article, although objective testing was not conducted, Webber et al. (2011) used the validated Berlin sleep questionnaire [71] to predict a high likelihood for the presence of sleep apnea in male firefighters and emergency medical personnel following direct environmental exposure during the few weeks in the aftermath of the World Trade Center terrorist attack on September 11, 2001. Notable findings included a high rate of presumptive OSA of 43.7%, albeit fewer than 15% of these screened cases were referred for sleep tests by primary physicians. Earlier arrival to the scene of the attack was also associated with greater risk for OSA. And, PTSD as measured on a validated scale was associated independently with an elevated risk of OSA after conducting mediational analyses that examined arrival time, obesity, or disability retirement. Additional independent predictors for high risk of OSA included gastroesophageal reflux, chronic rhinosinusitis, self-reported fair to poor health, low and high body-mass index, and weight gain of ≥ 10 lbs [72].

While these first three studies offer new speculations into a possible comorbidity between PTSD and OSA, the works reflect a lower level of evidence due to gross weaknesses in their designs. The first study reflects a skewed sample of PTSD patients seeking treatment for sleep disorders, and 87.5% of the sample did not undergo PSG including the control group of patients without suspicions for SDB [39]; the second study is markedly skewed toward recruitment of patients with both PTSD and sleep apnea, thus it offers no generalizability [59]; and, the third study, while using a large sample and validated questionnaires, did not complete PSG to diagnose sleep breathing disorders [72]. Therefore, these works may only point to a potential coincidental relationship between PTSD and OSA, given that traumatized individuals report high rates of sleep disturbances.

Notwithstanding, in a fourth and recent study conducted in Detroit, two groups of Iraqi immigrants were studied based on exposure to the Gulf War in 1991. Those exposed to the war showed an 11.7% rate of PTSD as well as 30.2% prevalence of OSA, which was markedly higher than rates in the non-exposed group (2.1%, 0.7% respectively) [73]. Unfortunately, although the reliability of the OSA diagnoses in these patients seems high, no objective data were gathered, so this study does not appear in Table 1. Using structural equation modeling, they demonstrated a "direct path between PTSD scores and OSA," even after controlling for other risk factors. They also showed a relationship between OSA and other psychosomatic and mental disorders such as migraine, fatigue and depression and concluded "[p]art of the PTSD-associated adverse health effects observed in Iraqi immigrants is mediated by obstructive sleep apnea." This research is the first to examine a group of PTSD patients outside the setting of a sleep medical center bias or related sleep treatment-seeking bias [73] and thus provides a more generalizable explanatory model for future research investigations.

Theoretical models on pathophysiological mechanisms

In 2002, we developed hypotheses about our findings of unexpectedly high rates of sleep breathing problems among trauma survivors, observed both in our research investigations and clinical practice [6]. We proposed a bidirectional pathway (Fig. 1) in which

^a Pharyngeal Critical Closing Pressure (P_{crit}) = The pressure required to collapse the upper airway in humans.
^b Upper Airway Resistance, Hypopneas, or Apneas.

Fig. 1. A bi-directional theory in which PTSD increases susceptibility to SDB, which in turn may increase PTSD symptoms.

posttraumatic stress-induced sleep fragmentation affects the human airway, increasing vulnerability to the subsequent development of upper airway collapsibility (leading to OSA or UARS) [74] and how sleep breathing problems, through sleep fragmenting effects, might worsen PTSD symptoms [6]. The former point derives from the remarkable work of Series and colleagues (1994) demonstrating how breathing worsens in normal sleepers after a single night of experimentally-induced sleep fragmentation [74]. After using auditory stimuli hundreds of times in a sleep lab to arouse (but not awaken) research participants, the very next night of testing revealed significant increases in sleep breathing abnormalities, e.g., increased hypopneas. Of clinical import, sleep fragmentation worsened upper airway collapsibility more than sleep deprivation [74]. These findings may be germane to PTSD patients who commonly suffer sleep fragmentation [11,75]; this fragmentation sometimes manifests predominantly during REM sleep [56,76] and has been demonstrated prospectively in animal models [77].

Speculatively, then, a bidirectional relationship may exist through which PTSD may worsen SDB and through which sleep breathing problems may worsen posttraumatic stress. This theory implies comorbid PTSD and SDB produce a vicious cycle where each condition may have pathophysiological effects on the other condition, which leads to or contributes to comorbidity. If this theory—that anxiety fragments sleep, which worsens breathing, which further fragments sleep, which then exacerbates anxiety and other distress symptoms—proves clinically relevant, then research and clinical paradigms will need to shift their focus on the role of sleep in PTSD. It is notable from the sequences described in Fig. 1 that both SDB and PTSD serve as generators of hyperarousal activity, which in turn could worsen either the sleep or the psychiatric condition.

Two more recent studies point to this same theory. In the work of Arnetz and colleagues above, in addition to their recognition of mediating effects of OSA on PTSD, they also proposed a bidirectional relationship stating "stress associated centrally mediated factors [may] contribute to peripheral neuromuscular change" [i.e., pharyngeal wall collapsibility] [73]. In the work of Williams and colleagues, they noted PTSD was more frequent among non-injured soldiers than injured soldiers. They speculated that non-injured soldiers may have suffered from a previously undiagnosed sleep breathing problem, which put these individuals at risk for chronic sleep fragmentation. As such, when exposed to stressors (without physical injury) during deployment, the sleep fragmentation may have reduced their resiliency and coping capacity, which in turn created a higher potential to develop posttraumatic stress symptoms [66].

Two additional models for the interplay between comorbid PTSD and SDB have previously been published. First, Lavie's theory of anxiety-induced hyperventilation as a precursor to apneas [78] suggests that during normal deep sleep, hypercapnia occurs and increases ventilatory drive and stimulates upper airway muscles. As a result, apneas are prevented and the patient remains in slow wave sleep. However, PTSD patients may have underlying hyperventilation due to anxiety, which prevents hypercapnia (or promotes hypocapnia) and thwarts protection of the airway resulting in apneas. Second, Gold's theory of neural sensitization and upper airway collapsibility [79] states that SDB, when present in patients with functional somatic syndromes (FSS) and anxiety disorders, acts as an "allostatic challenge" or a chronic physical stress, which activates the hypothalamic-pituitary-adrenal (HPA) axis thus causing symptoms found in both FSS and anxiety disorder patients. Both theories are likely to prove fruitful areas of investigation.

Last, in our 2002 review we noted a pathophysiological link between SDB and PTSD supported by studies associating PTSD, insomnia, and SDB with dysfunction of the HPA axis and alterations in the structure of the hippocampus [6]. These areas merit further investigation (see Supplemental Material and Supplement-Table 1 on Theoretical Models).

Conclusions

No conclusions can be drawn from the data currently available on the potential relationship between SDB and PTSD. Yet, emerging literature indicates these areas may have clinical relevance for an undefined proportion of PTSD patients. The pathophysiological relationship between SDB and PTSD appears to be difficult to appreciate, in particular because we do not know whether SDB is present in trauma survivors before or after they develop PTSD or whether the finding is an epiphenomenon. Regardless, in light of the emerging research indicating much stronger associations between insomnia and SDB (i.e., "complex insomnia") than previously appreciated [22,80–89], sleep breathing problems in trauma survivors with posttraumatic stress symptoms may prove more clinically relevant given that such patients report extremely high rates of insomnia complaints [90]. Moreover, as insomnia is a distinct nosologic criterion for PTSD, it is noteworthy recent findings show insomnia as an independent risk factor for the worsening of PTSD [91].

Both epidemiologic and treatment research are needed to clarify the prevalence of the problem and the best treatment practices. More prospective studies are needed to objectively monitor trauma survivors' sleep pre- and post-traumatic exposure. Although previous large-scale studies such as the Millennium Study have already looked at subjective markers for cohorts of military personnel pre- and post-deployment [92], none have used objective measurements to test for sleep breathing disorders. By adding

objective testing pre- and post-deployment we will be better able to determine whether pre-deployment sleep disturbances may be predisposing factors for post-deployment PTSD. But as stated before, studies must be designed to apply the most advanced respiratory technology so all sleep breathing events are accurately captured: sensors for measuring the RERA component of SDB are essential. Regarding treatment, one ongoing study in a small sample of PTSD patients with SDB is prospectively comparing two groups: one using only standard cognitive-behavioral therapy with prolonged exposure versus combination treatment comprising both exposure and an auto-adjusting positive airway pressure device; the preliminary data suggest more benefit in the latter group [93]. A retrospective study recently published demonstrated a marked decrease in nightmares among PTSD patients using CPAP therapy for OSA [94]. Additional investigations could test the impact of PTSD treatment on sleep breathing problems as well as SDB treatment impact on PTSD. Likewise, treatment studies including those using PAP therapy [95], oral appliance therapy [96], surgery [97,98], or other emerging modalities [99,100] must develop appropriate models to manage the anxiety problems likely to inhibit PTSD patients from engaging and following through with SDB treatment [22]. It may also prove valuable to pursue treatment research that not only explores long-term clinical outcomes, but also measures change in biomarkers of oxidative stress, pro-inflammatory states, and endothelial dysfunction.

In closing, whereas considerably more research is needed to elucidate the relationships between PTSD and SDB, in the near term an apparent substantial proportion of trauma survivors with sleep complaints may benefit from evidence-based evaluations and treatments from the field of sleep medicine.

Practice points

1. Detection of sleep-disordered breathing in PTSD patients may be hindered by a clinical presentation that more closely resembles that of a psychiatric condition or an insomnia disorder.
2. Detection of OSA and UARS in PTSD patients requires the use of NCPT technology.
3. The index of suspicion for sleep disordered breathing may need to be increased when evaluating trauma survivors with sleep complaints in a clinical setting.

Research agenda

To further understand the relationship between co-morbid PTSD and SDB, we recommend:

1. Large-scale prevalence studies in various cohorts of PTSD patients to accurately assess rates of sleep-disordered breathing.
2. Prevalence research utilizing nasal cannula pressure transducer technology to accurately measure breathing events.
3. Longitudinal investigations to explore the potential bi-directional relationship between SDB and PTSD to inform both explanatory models and pathophysiological mechanisms.
4. Randomized controlled treatment studies to assess the clinical relevance of SDB therapies on PTSD outcomes.

Conflict of interests

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.smrv.2014.11.001.

References

[1] Pagel Jr JF. Nightmares. Am Fam Physician 1989 Mar;39(3):145–8.
[2] Ross RJ, Ball WA, Sullivan KA, Caroff SN. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry 1989 Jun;146(6):697–707.
[3] Benca RM. Sleep in psychiatric disorders. Neurol Clin 1996 Nov;14(4):739–64.
[4] Mellman TA. Psychobiology of sleep disturbances in posttraumatic stress disorder. Ann N Y Acad Sci 1997 Jun 21;821:142–9.
[5] Pillar G, Malhotra A, Lavie P. Post-traumatic stress disorder and sleep-what a nightmare! Sleep Med Rev 2000 Apr;4(2):183–200.
*[6] Krakow B, Melendrez D, Warner TD, Dorin R, Harper R, Hollifield M. To breathe, perchance to sleep: sleep-disordered breathing and chronic insomnia among trauma survivors. Sleep Breath 2002 Dec;6(4):189–202.
[7] Harvey AG, Jones C, Schmidt DA. Sleep and posttraumatic stress disorder: a review. Clin Psychol Rev 2003 May;23(3):377–407.
[8] 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(7):567–90.
[9] Mellman TA, Hipolito MM. Sleep disturbances in the aftermath of trauma and posttraumatic stress disorder. CNS Spectr 2006 Aug;11(8):611–5.
*[10] Kobayashi I, Boarts JM, Delahanty DL. Polysomnographically measured sleep abnormalities in PTSD: a meta-analytic review. Psychophysiology 2007 Jul;44(4):660–9.
[11] van Liempt S, Westenberg HG, Arends J, Vermetten E. Obstructive sleep apnea in combat-related posttraumatic stress disorder: a controlled polysomnography study. Eur J Psychotraumatol 2011 Dec. 2 Epub.
[12] Germain A, Buysse DJ, Nofzinger E. Sleep-specific mechanisms underlying posttraumatic stress disorder: integrative review and neurobiological hypotheses. Sleep Med Rev 2008 Jun;12(3):185–95.
[13] Spoormaker VI, Montgomery P. Disturbed sleep in post-traumatic stress disorder: secondary symptom or core feature? Sleep Med Rev 2008 Jun;12(3):169–84.
[14] Babson KA, Feldner MT. Temporal relations between sleep problems and both traumatic event exposure and PTSD: a critical review of the empirical literature. J Anxiety Disord 2010 Jan;24(1):1–15.
[15] Lamarche LJ, De Koninck J. Sleep disturbance in adults with posttraumatic stress disorder: a review. J Clin Psychiatry 2007 Aug;68(8):1257–70.
[16] Germain A. Sleep disturbances as the hallmark of PTSD: where are we now? Am J Psychiatry 2013 Apr 1;170(4):372–82.
[17] Pigeon WR, Campbell CE, Possemato K, Ouimette P. Longitudinal relationships of insomnia, nightmares, and PTSD severity in recent combat veterans. J Psychosom Res 2013 Dec;75(6):546–50.
[18] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993 Apr 29;328(17):1230–5.

* The most important references are denoted by an asterisk.

[19] Iber C A-ISCAQS. The AASM manual for the scoring of SLeep and associated events: rules, terminology and technical specifications. Westchester, Ill: American Academy of Sleep Medicine; 2007.

[20] Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for scoring respiratory events in sleep: update of the 2007 AASM manual for the scoring of sleep and associated events. Deliberations of the sleep apnea definitions task force of the American Academy of Sleep Medicine. J Clin Sleep Med 2012 Oct 15;8(5):597–619.

[21] Sanner B, Schafer T. Central sleep apnea syndrome. Dtsch Med Wochenschr 2008 Apr;133(14):722–6.

[22] Krakow B, Romero EA, Ulibarri VA, Kikta S, Thomas RJ. ASV therapy in anxious or insomnia patients with complex sleep apnea. Sleep 2010;33: A146 [Abstract].

[23] Webster JB, Bell KR, Hussey JD, Natale TK, Lakshminarayan S. Sleep apnea in adults with traumatic brain injury: a preliminary investigation. Arch Phys Med Rehabil 2001 Mar;82(3):316–21.

[24] Guilleminault C. Sleep disorders. In: Vinken PJ, Bruyn GW, Klawans Harold L, Frederiks JAM, editors. Handbook of clinical neurology: clinical neuropsychology. Amsterdam: Elsevier; 1985. p. 129–45.

[25] Dagan Y, Lavie P. Sleep apnea syndrome in war-related PTSD victims. Sleep Res 1991;20:448 [Abstract].

[26] de Groen JH, Op d V, Hovens JE, Falger PR, Schouten EG, van Duijn H. Snoring and anxiety dreams. Sleep 1993 Jan;16(1):35–6.

[27] Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry 1995 Jan;152(1):110–5.

[28] Krakow B, Tandberg D, Sandoval D, Cutchen L, Schrader R. Severity of sleep disturbances in sexual assault survivors. Sleep 4-15-1998;21(3):150 [Abstract].

[29] Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193–213.

[30] Krakow B. Severity of sleep disturbances in sexual assault survivors. New Orleans: Associated Professional Sleep Societies; 1998 Jun 22.

[31] American Academy of Sleep Medicine. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. Sleep 1999;22:667–89.

[32] Krakow B, Germain A, Tandberg D, Koss M, Schrader R, Hollifield M, et al. Sleep breathing and sleep movement disorders masquerading as insomnia in sexual-assault survivors. Compr Psychiatry 2000 Jan;41(1): 49–56.

[33] 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 Nov 15;44(10):1060–5.

[34] Youakim JM, Doghramji K, Schutte SL. Posttraumatic stress disorder and obstructive sleep apnea syndrome. Psychosomatics 1998 Mar;39(2): 168–71.

[35] Kushida CA, Littner MR, Hirshkowitz M, Morgenthaler TI, Alessi CA, Bailey D, et al. Practice parameters for the use of continuous and bilevel positive airway pressure devices to treat adult patients with sleep-related breathing disorders. Sleep 2006 Mar 1;29(3):375–80.

[36] 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 Mar 15;47(6):520–5.

[37] Krakow B, Artar A, Warner TD, Melendrez D, Johnston L, Hollifield M, et al. Sleep disorder, depression, and suicidality in female sexual assault survivors. Crisis 2000;21(4):163–70.

[38] Krakow B, Germain A, Warner TD, Schrader R, Koss M, Hollifield M, et al. The relationship of sleep quality and posttraumatic stress to potential sleep disorders in sexual assault survivors with nightmares, insomnia, and PTSD. J Trauma Stress 2001 Oct;14(4):647–65.

[39] Krakow B, Melendrez D, Johnston L, Warner TD, Clark JO, Pacheco M, et al. Sleep-disordered breathing, psychiatric distress, and quality of life impairment in sexual assault survivors. J Nerv Ment Dis 2002 Jul;190(7): 442–52.

[40] Krakow B, Lowry C, Germain A, Gaddy L, Hollifield M, Koss M, et al. A retrospective study on improvements in nightmares and post-traumatic stress disorder following treatment for co-morbid sleep-disordered breathing. J Psychosom Res 2000 Nov;49(5):291–8.

*[41] Krakow B, Melendrez D, Pedersen B, Johnston L, Hollifield M, Germain A, et al. Complex insomnia: insomnia and sleep-disordered breathing in a consecutive series of crime victims with nightmares and PTSD. Biol Psychiatry 2001 Jun 1;49(11):948–53.

[42] Lopez-Ibor JJ. The classification of stress-related disorders in ICD-10 and DSM-IV. Psychopathology 2002 Mar;35(2–3):107–11.

[43] Pearn J. Traumatic stress disorders: a classification with implications for prevention and management. Mil Med 2000 Jun;165(6):434–40.

[44] Yufik T, Simms LJ. A meta-analytic investigation of the structure of posttraumatic stress disorder symptoms. J Abnorm Psychol 2010 Nov;119(4): 764–76.

[45] Krakow B. Sound sleep, sound mind: 7 keys to sleeping through the night. New York: John Wiley & Sons; 2007.

[46] Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991 Dec;14(6):540–5.

[47] Brostrom A, Johansson P, Stromberg A, Albers J, Martensson J, Svanborg E. Obstructive sleep apnoea syndrome–patients' perceptions of their sleep and its effects on their life situation. J Adv Nurs 2007 Feb;57(3):318–27.

[48] Stoohs RA, Knaack L, Blum HC, Janicki J, Hohenhorst W. Differences in clinical features of upper airway resistance syndrome, primary snoring, and obstructive sleep apnea/hypopnea syndrome. Sleep Med 2008 Jan;9(2):121–8.

[49] Kristo DA, Lettieri CJ, Andrada T, Taylor Y, Eliasson AH. Silent upper airway resistance syndrome: prevalence in a mixed military population. Chest 2005 May;127(5):1654–7.

[50] Krakow B, Melendrez D, Warner TD, Clark JO, Sisley BN, Dorin R, et al. Signs and symptoms of sleep-disordered breathing in trauma survivors: a matched comparison with classic sleep apnea patients. J Nerv Ment Dis 2006 Jun;194(6):433–9.

[51] Norman RG, Ahmed MM, Walsleben JA, Rapoport DM. Detection of respiratory events during NPSG: nasal cannula/pressure sensor versus thermistor. Sleep 1997 Dec;20(12):1175–84.

[52] Hosselet JJ, Norman RG, Ayappa I, Rapoport DM. Detection of flow limitation with a nasal cannula/pressure transducer system. Am J Respir Crit Care Med 1998 May;157(5 Pt 1):1461–7.

[53] Montserrat JM, Badia JR. Upper airway resistance syndrome. Sleep Med Rev 1999 Mar;3(1):5–21.

[54] Johnson PL, Edwards N, Burgess KR, Sullivan CE. Detection of increased upper airway resistance during overnight polysomnography. Sleep 2005 Jan;28(1):85–90.

[55] American Academy of Sleep Medicine. International classification of sleep disorders: diagnostic & coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.

[56] 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 May;61(5):508–16.

*[57] Habukawa M, Uchimura N, Maeda M, Kotorii N, Maeda H. Sleep findings in young adult patients with posttraumatic stress disorder. Biol Psychiatry 2007 Nov 15;62(10):1179–82.

*[58] Yetkin S, Aydin H, Ozgen F. Polysomnography in patients with posttraumatic stress disorder. Psychiatry Clin Neurosci 2010 Jun;64(3): 309–17.

*[59] Yesavage JA, Kinoshita LM, Kimball T, Zeitzer J, Friedman L, Noda A, et al. Sleep-disordered breathing in vietnam veterans with posttraumatic stress disorder. Am J Geriatr Psychiatry 2012 Mar;20(3):199–204.

[60] Krakow B, Krakow J, Ulibarri VA, McIver ND. Frequency and accuracy of "RERA" and "RDI" terms in the journal of clinical sleep medicine from 2006 through 2012. J Clin Sleep Med 2014 Feb 15;10(2):121–4.

[61] Sackett DL, Straus SE, Richardson WS, Rosenberg W, Haynes RB. Evidence-based medicine: how to practice and teach EBM. 2nd ed. Edinburgh, Scotland: Churchill Linvingstone Inc; 2000. p. 173–7.

[62] Dagan Y, Lavie P, Bleich A. Elevated awakening thresholds in sleep stage 3-4 in war-related post-traumatic stress disorder. Biol Psychiatry 1991 Sep 15;30(6):618–22.

*[63] Capaldi VF, Guerrero ML, Killgore WD. Sleep disruptions among returning combat veterans from Iraq and Afghanistan. Mil Med 2011 Aug;176(8): 879–88.

*[64] Mysliwiec V, Gill J, Lee H, Baxter T, Pierce R, Barr TL, et al. Sleep disorders in US military personnel: a high rate of comorbid insomnia and obstructive sleep apnea. Chest 2013 Aug;144(2):549–57.

*[65] Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ. Sleep disorders and associated medical comorbidities in active duty military personnel. Sleep 2013 Feb;36(2):167–74.

[66] Williams SG, Collen J, Orr N, Holley AB, Lettieri CJ. Sleep disorders in combat-related PTSD. Sleep Breath 2014 Apr 22 (Epub ahead of print).

[67] Sharafkhaneh A, Giray N, Richardson P, Young T, Hirshkowitz M. Association of psychiatric disorders and sleep apnea in a large cohort. Sleep 2005 Nov;28(11):1405–11.

[68] Raper TB, Li J, Desai NR, Hayek H, Thammasitboon S. Posttraumatic stress disorder is highly prevalent in veterans with obstructive sleep apnea. Sleep 2010;33:A235 [Abstract].

[69] Ware Jr JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992 Jun;30(6):473–83.

*[70] Kinoshita LM, Yesavage JA, Noda A, Jo B, Hernandez B, Taylor J, et al. Modeling the effects of obstructive sleep apnea and hypertension in Vietnam veterans with PTSD. Sleep Breath 2012 Dec;16(4):1201–9.

[71] Netzer NC, Stoohs RA, Netzer CM, Clark K, Strohl KP. Using the Berlin questionnaire to identify patients at risk for the sleep apnea syndrome. Ann Intern Med 1999 Oct 5;131(7):485–91.

[72] Webber MP, Lee R, Soo J, Gustave J, Hall CB, Kelly K, et al. Prevalence and incidence of high risk for obstructive sleep apnea in World Trade Center-exposed rescue/recovery workers. Sleep Breath 2011 Sep;15(3):283–94.

*[73] Arnetz BB, Templin T, Saudi W, Jamil H. Obstructive sleep apnea, post-traumatic stress disorder, and health in immigrants. Psychosom Med 2012 Oct;74(8):824–31.

*[74] Series 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 Aug;150(2):481–5.

[75] Calhoun PS, Wiley M, Dennis MF, Means MK, Edinger JD, Beckham JC. Objective evidence of sleep disturbance in women with posttraumatic stress disorder. J Trauma Stress 2007 Dec;20(6):1009—18.

*[76] Insana SP, Kolko DJ, Germain A. Early-life trauma is associated with rapid eye movement sleep fragmentation among military veterans. Biol Psychol 2012 Mar;89(3):570—9.

[77] Philbert J, Pichat P, Beeske S, Decobert M, Belzung C, Griebel G. Acute inescapable stress exposure induces long-term sleep disturbances and avoidance behavior: a mouse model of post-traumatic stress disorder (PTSD). Behav Brain Res 2011 Aug 1;221(1):149—54.

*[78] Lavie P. Sleep disturbances in the wake of traumatic events. N Engl J Med 2001 Dec 20;345(25):1825—32.

*[79] Gold AR. Functional somatic syndromes, anxiety disorders and the upper airway: a matter of paradigms. Sleep Med Rev 2011 Dec;15(6):389—401.

[80] Smith S, Sullivan K, Hopkins W, Douglas J. Frequency of insomnia report in patients with obstructive sleep apnoea hypopnea syndrome (OSAHS). Sleep Med 2004 Sep;5(5):449—56.

[81] Gooneratne NS, Gehrman PR, Nkwuo JE, Bellamy SL, Schutte-Rodin S, Dinges DF, et al. Consequences of comorbid insomnia symptoms and sleep-related breathing disorder in elderly subjects. Arch Intern Med 2006 Sep 18;166(16):1732—8.

[82] Lavie P. Insomnia and sleep-disordered breathing. Sleep Med 2007 Dec;8(Suppl. 4):S21—5.

[83] Beneto A, Gomez-Siurana E, Rubio-Sanchez P. Comorbidity between sleep apnea and insomnia. Sleep Med Rev 2009 Aug;13(4):287—93.

[84] Krakow B, Ulibarri VA, Romero E. Persistent insomnia in chronic hypnotic users presenting to a sleep medical center: a retrospective chart review of 137 consecutive patients. J Nerv Ment Dis 2010 Oct;198(10):734—41.

[85] Luyster FS, Buysse DJ, Strollo Jr PJ. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med 2010 Apr 15;6(2):196—204.

[86] Wickwire EM, Collop NA. Insomnia and sleep-related breathing disorders. Chest 2010 Jun;137(6):1449—63.

[87] Krakow B, Ulibarri VA. Prevalence of sleep breathing complaints reported by treatment-seeking chronic insomnia disorder patients on presentation to a sleep medical center: a preliminary report. Sleep Breath 2013 Mar;17(1):317—22.

[88] Krakow B, Ulibarri VA, Romero EA, Thomas RJ, McIver ND. Adaptive servo-ventilation therapy in a case series of patients with co-morbid insomnia and sleep apnea. J Sleep Disord Treat Care 2013 Mar;2(1). ePub.

[89] Krakow B, Romero E, Ulibarri VA, Kikta S. Prospective assessment of nocturnal awakenings in a case series of treatment-seeking chronic insomnia patients: a pilot study of subjective and objective causes. Sleep 2012 Dec;35(12):1685—92.

[90] McLay RN, Klam WP, Volkert SL. Insomnia is the most commonly reported symptom and predicts other symptoms of post-traumatic stress disorder in U.S. service members returning from military deployments. Mil Med 2010 Oct;175(10):759—62.

[91] Wright KM, Britt TW, Bliese PD, Adler AB, Picchioni D, Moore D. Insomnia as predictor versus outcome of PTSD and depression among Iraq combat veterans. J Clin Psychol 2011 Dec;67(12):1240—58.

[92] Boyko EJ, Seelig AD, Jacobson IG, Hooper TI, Smith B, Smith TC, et al. Sleep characteristics, mental health, and diabetes risk: a prospective study of U.S. military service members in the Millennium Cohort Study 1. Diabetes Care 2013 Oct;36(10):3154—61.

[93] Amin M, Gold M, Gold AR. The effect of nasal continuous positive airway pressure (nasal CPAP) treatment on post traumatic stress disorder (PTSD) symptoms among veterans population. Sleep 6-1-2013;36:A145 [Abstract].

[94] 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(6):631—6.

[95] McDaid C, Duree KH, Griffin SC, Weatherly HL, Stradling JR, Davies RJ, et al. A systematic review of continuous positive airway pressure for obstructive sleep apnoea-hypopnoea syndrome. Sleep Med Rev 2009 Dec;13(6):427—36.

[96] Ahrens A, McGrath C, Hagg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod 2011 Jun;33(3):318—24.

[97] Caples SM, Rowley JA, Prinsell JR, Pallanch JF, Elamin MB, Katz SG, et al. Surgical modifications of the upper airway for obstructive sleep apnea in adults: a systematic review and meta-analysis. Sleep 2010 Oct;33(10):1396—407.

[98] Waite PD. Obstructive sleep apnea: a review of the pathophysiology and surgical management. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998 Apr;85(4):352—61.

[99] Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. J Clin Psychiatry 2006 Apr;67(4):554—66.

[100] Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis. JAMA 2004 Oct 13;292(14):1724—37.