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- Provide evidence-based treatment for patients with PTSD who have sleep disturbances and sleep disorders

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Diagnosis and Management of Sleep Disorders in Posttraumatic Stress Disorder: A Review of the Literature

Shahla Mohsenin, MD, and Vahid Mohsenin, MD

ABSTRACT

Objective: International and societal conflicts and natural disasters can leave physical and mental scars in people who are directly affected by these traumatic experiences. Posttraumatic stress disorder (PTSD) is the clinical manifestation of these experiences in the form of re-experiencing the trauma, avoidance of trauma-related stimuli, and persistent symptoms of hyperarousal. There is growing evidence that sleep disruption that occurs following trauma exposure may in fact contribute to the pathophysiology of PTSD and poor clinical outcomes. The purpose of this review is to highlight the importance of recognition and management of sleep disorders in patients with PTSD.

Data Sources: English-language, adult research studies published between 1985 and April 2014 were identified via the PubMed database. The search terms used were *PTSD* AND *sleep disorders*.

Study Selection: The search identified 792 original and review articles. Of these, 53 articles that discussed or researched sleep disorders in PTSD were selected. Fourteen randomized controlled trials of therapy for PTSD are included in this review.

Results: Impaired sleep is a common complaint mainly in the form of nightmares and insomnia among people with PTSD. Sleep apnea and periodic limb movement disorder are particularly prevalent in patients with PTSD and, yet, remain unrecognized. Although selective serotonin reuptake inhibitors are effective in improving PTSD global symptoms, they have a variable and modest effect on sleep disorder symptoms. Cognitive-behavioral treatment targeted to sleep and/or the use of the centrally acting selective α_1 antagonist prazosin have been more successful in treating insomnia and nightmares in PTSD than other classes of medications. In view of the high occurrence of sleep apnea and periodic leg movement disorder, a thorough sleep evaluation and treatment are warranted.

Conclusions: Patients with PTSD have a high prevalence of sleep disorders and should be queried for insomnia, nightmares, periodic limb movement disorder, and sleep-disordered breathing.

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International and societal conflicts and natural disasters can leave physical and mental scars in people who are directly affected by these traumatic experiences. Violent crimes, including rape and physical assaults, combat exposure, and natural disasters constitute examples of traumatic events.[1] Posttraumatic stress disorder (PTSD) is the clinical manifestation of these experiences due to the difficulty in justifying these events or ameliorating the mental agony resulting from these traumatic exposures. Following exposure to a traumatic event, individuals who develop PTSD experience different clusters of symptoms, which include re-experiencing the trauma, avoidance

Clinical Points

- Sleep disorders in the form of insomnia, nightmares, sleep apnea, and movement disorders during sleep are common in posttraumatic stress disorder (PTSD).
- While antidepressants are effective in the management of global symptoms of PTSD, they have variable and at best a modest effect on sleep disorder complaints.
- Cognitive-behavioral treatment targeted to PTSD and selective α_1 antagonists such as prazosin are standard therapeutic options for sleep disorders associated with PTSD.

of trauma-related stimuli, and persistent symptoms of hyperarousal.[1] Nightmares and insomnia are diagnostic symptoms of PTSD[1]; however, other sleep disturbances such as sleep avoidance, sleep terrors, nocturnal anxiety attacks, acting out dreams, sleep apnea, and periodic leg movement disorder are also frequently reported and observed in PTSD patients.[2–4]

There is growing evidence that sleep disruption that occurs following trauma exposure may in fact contribute to the pathophysiology of PTSD and poor clinical outcomes.[5,6] This review highlights the importance of sleep disorders in patients with PTSD and the challenges that physicians face in their management.

METHOD

English-language, adult research studies published between 1985 and April 2014 were identified via the PubMed database. The search terms used were *PTSD* AND *sleep disorders*. We identified 792 original and review articles. Of these, 53 articles discussed or researched sleep disorders in PTSD. Fourteen randomized controlled trials of therapy for PTSD were included in this review.[7–20]

RESULTS

Epidemiology

Epidemiologic studies indicate that the community prevalence of PTSD ranges from 1% to 10%,[21,22] with higher estimates reported in victims of interpersonal violence (20%–30%) and combat veterans (15%–30%). Reports continue to show a 20% prevalence of PTSD in veterans of foreign wars.[23] Difficulty initiating or maintaining sleep is reported by 44% of veterans with PTSD, 5.5% of veterans without PTSD, and 5% of civilians without the disorder.[24] Another common sleep-related symptom of PTSD is nightmares. Nightmares have been reported by 19% to 71% of patients with PTSD.[25] This wide variation in incidence of nightmares has been attributed to differences in the severity of PTSD,[26] exposure to combat[24] and other forms of aggression,[25] and the presence of comorbid psychiatric diagnosis.[27]

Normal Sleep

According to the US Department of Health and Human Services,[28] adults require 7 to 9 hours of sleep. Sleep comprises 2 main stages: non–rapid eye movement (NREM) and rapid eye movement (REM) sleep. Most dreams occur in REM sleep. In order to prevent acting out the dreams during REM sleep, the central nervous system inhibits voluntary muscles, with the exception of the diaphragm and extraocular muscles. Research shows the importance of sleep in memory consolidation and learning.[29]

The sleep-wake cycle is regulated by 2 processes: homeostatic and circadian drives. Homeostatic drive increases as a function of the extended wakefulness period, and its effect diminishes during sleep.[30] The biochemical basis of this drive is not entirely clear, but it has been shown that sustained neuronal activity can increase adenosine levels in the brain—adenosine levels rise in the basal forebrain during prolonged wakefulness and fall during sleep.[31] Circadian drive originates from a rhythmic internal biological clock or circadian pacemaker in the suprachiasmatic nucleus; its rhythmicity is synchronized by entraining the external light-dark cycle. Circadian drive is at its peak around 9 PM. Thus, the balance between the homeostatic and circadian systems results in the strongest sleep drive generally between 2:00 and 4:00 AM and a modest sleep drive in the afternoon between 1:00 and 3:00 PM (Figure 1). It has been shown that these drives are also shaped by emotional and cognitive inputs. Cognitive and emotional systems that may be able to override the normal homeostatic and circadian circuitry are doing so by means of inputs to the arousal system.[32] Under some conditions, such as in shift work or during an emergency situation, this ability to overcome the more basic drives can be adaptive. However, when emotional states such as stress prevent sleep, the balance between homeostatic and circadian systems is perturbed as in poor sleep hygiene and irregular sleep-wake cycles, leading to insomnia as seen in PTSD.

Sleep in PTSD

Nightmares are highly prevalent and considered hallmarks of PTSD.[4] Nightmares are reported in as many as 71% of patients with PTSD.[2] Nightmares are primarily a REM sleep phenomenon since dream recalls are more common in REM than in NREM sleep. Nightmares may cause short or prolonged awakenings from sleep. Large studies of patients who had experienced a range of traumas indicate an increase of 60% in prevalence of disturbed sleep compared to those without PTSD.[25,33] Insomnia is thought to arise primarily from NREM sleep disruption. Other NREM sleep disturbances often observed in trauma-exposed patients with PTSD include nocturnal panic attacks and sleep terrors.[34–36] Presence of both nightmares and insomnia within 1 month posttrauma predicted the development of PTSD 6 months later.[37] Further, there is evidence that disturbed sleep prior to a traumatic event poses an increased risk of PTSD.[3,38] However, despite a high prevalence of sleep disorder symptoms, objective measures of sleep efficiency and fragmentation have been inconsistent. Some polysomnographic studies in PTSD patients have reported REM sleep anomalies,[39,40] whereas others have not.[41,42] NREM sleep anomalies such

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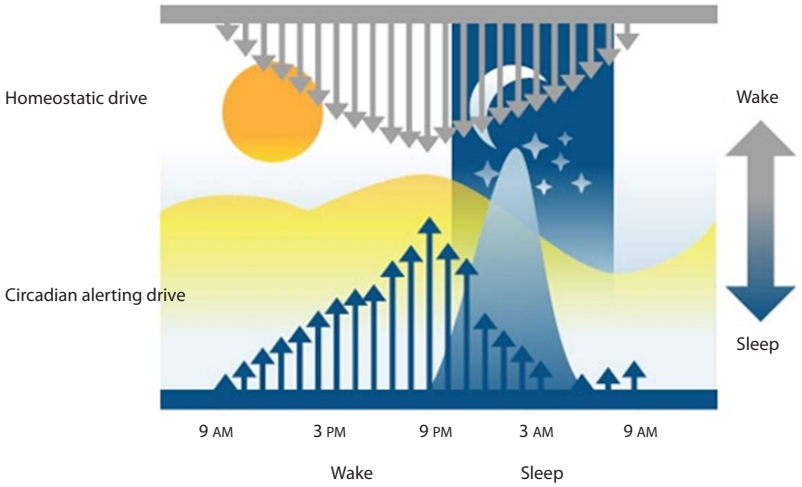
Figure 1. The Sleep-Wake Cycle[a]



[a]Based on Dijk and Edgar.[82]
[b]The sleep-wake cycle is regulated by 2 processes: homeostatic and circadian drives. The homeostatic drive increases as a function of the extended wakefulness period; its effect diminishes during sleep. The circadian drive originates from a rhythmic internal biological clock or circadian pacemaker in the suprachiasmatic nucleus; its rhythmicity is synchronized by entraining the external light-dark cycle. The circadian drive is at its peak at around 9 PM. So, the balance between the homeostatic and circadian processes results in the strongest sleep drive generally between 2 and 4 AM and a modest propensity for sleepiness in the afternoon between 1 and 3 PM.

as reduced slow-wave sleep have also been reported in some.[41] A meta-analysis of polysomnographic studies conducted on military veterans and civilian adults with PTSD[43] found a modest increase in REM density and in percentage of stage 1 sleep and reduced slow wave sleep in PTSD compared to non-PTSD groups. The detailed analysis of electroencephalogram (EEG)—for the detection of the cyclic alternating pattern (CAP) and microarousals that are closely tied to autonomic and muscle functions—is more common in patients with PTSD compared to those without PTSD.[40] The cyclic alternating pattern during sleep study is characterized by sequences of transient electrocortical events that are distinct from background EEG activity and recur at up to 1-minute intervals. This periodic activity is proposed as a measure of sleep instability and fragmentation and is a stronger predictor of subjective reports of insomnia than conventional definitions of arousals.[44,45] So, increased quantities of the cyclic alternating pattern and microarousals could result in nonrestorative sleep and serve to reinforce the perception of constant sleeplessness in these patients.

The exact neurologic mechanisms of sleep disturbances in PTSD are not established. There is accumulating evidence that PTSD is associated with altered brain responses in limbic and paralimbic brain areas—namely, the amygdala and insula—in response to emotional (and typically trauma-related) stimuli.[46,47] Recently, resting-state functional magnetic resonance imaging techniques have been applied to investigate the brain basal functional activity and connectivity between brain regions in PTSD.[47,48] Specifically, there is some emerging evidence that altered resting-state connectivity between the posterior cingulate cortex and the amygdala may be a reliable prognostic indicator of PTSD symptomatology.[49,50] Furthermore, studies have shown altered metabolic activity in frontal, parietal, temporal cortex, and limbic regions in patients with PTSD in comparison with those of controls.[51] Thus, clinical observations focusing on the nature of sleep complaints in PTSD, polysomnographic studies, and functional neuroimaging point to a dysregulation in both REM and NREM sleep.

In addition to insomnia and nightmares,[52] patients with PTSD have a higher prevalence of sleep apnea and periodic leg movement disorder of sleep.[53] Of 110 active duty military personnel with recent combat exposures with a mean age of 33.6 years and a mean body mass index of 30.0 kg/m^2, 63% met diagnostic criteria for sleep apnea and 64% for insomnia.[4] Those diagnosed with insomnia had the highest rates of PTSD, depression, and mild traumatic brain injury and were more likely to have pain syndrome.[4] Sleep disorders are increasingly recognized by medical providers; nonetheless, it is common to ascribe sleep disturbances solely to insomnia or an associated diagnosis, delaying or forgoing a definitive sleep evaluation.

A growing body of research suggests that periodic leg movements are more common in patients with PTSD than in controls. In a study of 25 Vietnam veterans with severe PTSD, 76% of patients had clinically significant periodic leg movement disorder, with a mean index (movements/h) of 38 (normal being < 15/h).[54] In another study, periodic leg movements were experienced in 33% of veterans with PTSD and not at all in controls.[55] The mechanism for the association between PTSD and periodic leg movements is not clear. It is possible that periodic leg movements

are the result of the same neural mechanisms underlying exaggerated daytime startle responses in patients with PTSD, or, alternatively, periodic leg movement disorder may be a risk factor for PTSD.[56] Periodic leg movements can be associated with restless legs syndrome and sleep disruption, resulting in complaints of insomnia or excessive daytime sleepiness.

Diagnostic Approach to Patients With PTSD

Individuals with history of physical or mental exposure to traumatic events and symptomatology consistent with PTSD based on *DSM-5* criteria should be queried for sleep disorders. The initial screening for sleep disorder may include 2 questions: "How is your sleep?" and "How do you feel when you should be awake?" If either question suggest difficulty falling asleep or staying asleep, waking up unrested, or having excessive daytime sleepiness, more detailed questionnaires containing a sleep-wake diary, Epworth Sleepiness Scale,[57] STOP-Bang Questionnaire[58] for Sleep-Disordered Breathing, and questions pertaining to restless legs syndrome and periodic leg movements[59] are available to further define the nature of the sleep problems. In view of the high prevalence of multiple sleep disorders associated with PTSD, including sleep-disordered breathing and periodic leg movement disorders, a consultation with a sleep medicine specialist might be in order for treatment planning and management. Patients with PTSD who report excessive daytime sleepiness, habitual snoring, witnessed apneas, restless legs, and hypertension on the questionnaires should be considered for sleep study. However, if symptomatology primarily suggests sleep-disordered breathing, home-based respiratory monitoring may suffice.[60] Most home-based studies use type III monitors for assessment of respiration and oxygen saturation but not sleep architecture (EEG) or movement disorders (electromyography); therefore, sleep fragmentation and leg movements cannot be assessed. Actigraphy might be a useful tool for assessment of sleep-wake rhythm in subjects with inconsistent sleep pattern and poor sleep hygiene.

Management of Sleep Disorders in PTSD

Nonpharmacologic treatment. The overall management of PTSD is beyond the scope of this review. Readers are referred to Bernardy and Friedman[61] for more information. The primary management strategies for insomnia incorporate sleep restriction (which involves curtailing the amount of time spent in bed to approximate the subjective amount of asleep) and stimulus control.[62]

Cognitive-behavioral treatment for insomnia has been shown to improve sleep disturbances and is considered the first-line therapy.[7,8,63,64] In a randomized, 3-arm placebo-controlled trial of sleep behavioral intervention versus prazosin (a centrally acting selective α_1 antagonist) and placebo in 57 US military veterans, sleep behavioral intervention and prazosin were more effective than placebo for self-reported and clinician-rated global clinical improvements, reductions in prospective self-reported and diary-based measures of sleep continuity, and nightmare frequency.[9] Sleep improvements were found in 62% of those who completed the active treatments and 25% of those randomized to placebo. The core sleep behavioral intervention components included education about nightmares and implementation of imagery rehearsal therapy, education about sleep and insomnia, and stimulus control and sleep restriction.[65]

A web-based application for smart phones was developed by the US Department of Veterans Affairs National Center for PSTD Dissemination and Training Division (http://www.ptsd.va.gov/public/pages/PTSDcoach.asp) based on fundamentals of cognitive-behavioral treatment targeted for better understanding and self-management of PTSD symptoms. The smart phone application provides educational information about PTSD (eg, symptoms, prevalence, risk factors), various treatment options, self-assessment with interpretative feedback about the severity of their symptoms, ability to track their symptoms over time, coping tools to help address acute PTSD symptoms, and links to find community-based support. In a pilot study,[66] the majority of 45 veterans who used the program reported improvement in their symptoms of PTSD. Other modalities, such as an exercise program, have shown some promising results, with a significant reduction in PTSD, anxiety, and depression symptoms that lasted during 1-month follow-up.[67,68] There is also growing evidence that mind-body practices are a viable intervention to improve the constellation of PTSD symptoms such as intrusive memories, avoidance, and increased emotional arousal.[69]

Pharmacologic Treatment

Selective serotonin-norepinephrine reuptake inhibitors. Given the high degree of comorbidity between PTSD and major depressive disorder, and the documented efficacy of selective serotonin reuptake inhibitors (SSRIs) for depressed populations (as well as for a number of other discrete anxiety disorders), SSRIs and selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are first-line medications for the treatment of PTSD.[70] In a meta-analysis of 7 randomized trials, patients treated with SSRIs were more likely to experience improvement in symptoms (on the Clinician-Administered PTSD Scale or CAPS) and functioning than the group receiving placebo (RR = 1.59, 95% CI, 1.39–1.82).[71] There is a great deal of variation in response to pharmacologic treatment, with few robust individual predictors of response available.[72] Some ancillary symptoms of PTSD, such as sleep disturbance, can be particularly difficult to treat and are among the symptoms that result in the use of polypharmacy that is so common in the treatment of PTSD. Selected pharmacologic classes of medications for PTSD that are shown to be effective in randomized controlled trials are listed in Table 1.[10–16] Specifically, sertraline and paroxetine improved PTSD symptoms on the CAPS and the clinician-administered Clinical Global Impressions–Improvement (CGI) scale compared to placebo in several randomized controlled trials (Table 1). However, sertraline

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Table 1. Pharmacotherapy Agents for Treating Posttraumatic Stress Disorder and Sleep Disturbances

Drugs	Study	Sample Size (n)	Duration (wk)	Response Rate (%)		Response Criteria	Efficacy[a]
				Drug	Control		
SSRIs							
Sertraline	RCT[10]	134	12	43	31	CAPS (primary outcome)	↑
				43	33	IES	↔
				27	18	CGI-S	↑
Sertraline	RCT[11]	208	12	45	36	CAPS-2 (primary outcome)	↑
				50	35	IES	↑
				28	22	CGI-S	↑
				26	21	PSQI	↔
Paroxetine	RCT (pooled)[12]	1,180	12	46	32	CAPS-2	↑
				57	39	CGI-I	↑
SNRIs							
Venlafaxine	RCT[13]	329	24	64	54	CAPS-Sx	↑
Non-SSRIs							
Nefazodone versus sertraline	RCT[14]	37	12	61	58	CAPS-2	↔
				44	46	CGI-I	↔
				43	43	PSQI	↔
Olanzapine	RCT[15]	19	8	17	3	CAPS	↑
				30	11	CGI-I	↔
				20	10	PSQI	↑
Prazosin	RCT[16]	40	8	49	15	CAPS (distressing dreams)	↑
				71	12	CGI-C	↑
				28	6	PSQI	↑

[a]Significant differences in PTSD symptom severity in favor of medication are indicated by ↑ and nonsignificant differences by ↔.
Abbreviations: CAPS = Clinician-Administered PTSD Scale, CGI-C = Clinical Global Impression of Change, CGI-I = Clinical Global Impressions–Improvement, CGI-S = Clinical Global Impressions–Severity, IES = Impact of Event Scale, PSQI = Pittsburgh Sleep Quality Index, RCT = randomized controlled trial, SNRI = selective serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

and paroxetine had no significant effect on sleep disturbance symptoms, including insomnia and nightmare. For a more detailed evidence-based review, the reader is referred to Ipser and Stein.[73]

Dopamine, serotonin, histamine receptor antagonists. In patients with SSRI-resistant PTSD, olanzapine augmentation was associated with a significantly greater reduction in sleep disturbance, as well as other symptoms of PTSD and depression, compared with placebo.[15] Mirtazapine, an antidepressant with serotonin and histamine receptor antagonism, has shown some benefits in PTSD as an alternative to SSRIs (sertraline) in an open-label trial, in part, due to its sedating side effect that can be therapeutically useful to some patients.[17] Trazodone, a histamine and α_1-adrenergic receptor antagonist, appears to be effective for the treatment of insomnia and nightmares associated with chronic PTSD, but it is not recommended as a first-line therapy for PTSD.[61]

Selective α_1-adrenergic antagonists. Most of the drug trials focused on global PTSD symptoms, with few reporting sleep disturbances as outcome measures. Clinical studies suggest that enhanced postsynaptic adrenergic receptor responsiveness to central nervous system norepinephrine contributes to the pathophysiology of PTSD.[74,75] Preclinical studies provide rationale for specific involvement of the postsynaptic α_1 adrenoreceptor in this pathophysiologic process. Specifically, central nervous system α_1-adrenergic receptor stimulation disrupts sleep physiology and enhances sleep-stage phenomena associated with emergence of trauma nightmares.[76] On the basis of the putative noradrenergic alterations seen in PTSD, several pharmacologic agents have been proposed as possible treatments. Prazosin has been more effective than other agents, providing the basis for the findings that α_1 receptor stimulation is linked to sleep disruption, stress-induced disruptions in prefrontal cortex cognitive processing, and increased release of corticotropin-releasing hormone,[75,77] all phenomena commonly seen in PTSD.[46,78] The principal findings of note from these trials were decreased sleep disruption and nightmares and increase in total sleep time and REM sleep.[16,18,19] In addition, the improvements in sleep with prazosin were accompanied by significant improvements in daytime symptoms of PTSD. The US Department of Veterans Affairs/Department of Defense practice guidelines recommend prazosin for sleep disturbances and nightmares in PTSD but not for global PTSD.[61]

Hypnotics. There is insufficient evidence for beneficial effect of hypnotics in PTSD.[73] In a small randomized double-blind placebo-controlled crossover trial of escopiclone for 3 weeks in 24 patients with PTSD and associated sleep disturbance, escopiclone improved PTSD symptoms as well as sleep latency and subjective sleep quality.[20] However, the current guidelines by the US Department of Veterans Affairs/Department of Defense caution health care providers against the prescription of benzodiazepines in the management of PTSD.[61] Additionally, there is evidence that benzodiazepines may interfere with psychotherapy treatments that are first-line intervention in PTSD.[79]

Treatment of Sleep Apnea

There are several treatment options available for sleep-disordered breathing. These options include positive airway pressure treatment, oral appliance therapy, and upper airway surgery. Positive airway pressure treatment using a nasal or

full face mask is the most commonly used therapy. However, it is best for the patient to be referred to a sleep medicine center for evaluation and management.[80]

Treatment of Periodic Leg Movement Disorder

Many central nervous system–acting medications, particularly SSRIs, can cause or exacerbate periodic leg movement disorders. Dose modification of SSRIs or consideration for the addition of specific therapeutic agents for periodic leg movement disorder may be necessary.[81]

SUMMARY

Among victims of violence and combat veterans, PTSD is prevalent and is associated with significant burden of anxiety and depression and poor quality of life. In addition, PTSD is associated with high risk for sleep disturbances in the form of sleep fragmentation, nightmares, sleep apnea, and periodic leg movement disorder. All of these sleep disturbances can exacerbate symptoms of PTSD. A thorough clinical evaluation including sleep quality assessment should be part of the overall management of patients with PTSD.

Drug names: mirtazapine (Remeron and others), olanzapine (Zyprexa and others), paroxetine (Paxil, Pexeva, and others), prazosin (Minipress and others), sertraline (Zoloft and others), trazodone (Oleptro and others), venlafaxine (Effexor and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, mirtazapine, olanzapine, prazosin, trazodone, venlafaxine, and nefazodone are not approved by the US Food and Drug Administration for the treatment of PTSD.

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For the CME Posttest, see next page.

Posttest

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1. **Ms A was robbed at gunpoint in a carjacking a year ago, and she reports symptoms of avoidance, hyperarousal, and re-experiencing. When you ask, "How is your sleep?" Ms A says it is inconsistent, and she always feels tired. She watches television when she can't sleep. Which of the following is the *best* next step to assess Ms A's sleep problem?**
   a. Refer her to a sleep specialist
   b. Have her undergo sleep study at a sleep center
   c. Use a questionnaire with a sleep-wake diary
   d. Set up home-based respiratory monitoring

2. **Ms A is diagnosed with posttraumatic stress disorder (PTSD), and insomnia is a treatment target. Which one of the following is a first-line treatment for her insomnia?**
   a. Cognitive-behavioral therapy for insomnia
   b. An exercise program
   c. Mind-body practices
   d. A nightly benzodiazepine for 3 weeks

3. **Mr B, who is obese, visits you for the first time because he recently moved to the area. He survived a major earthquake at his previous residence and has been taking a selective serotonin reuptake inhibitor (SSRI) for PTSD. Although the SSRI has helped, he mentions not feeling rested when he wakes up and being sleepy during the day. To help Mr B sleep better, you should take all of the following steps *except*:**
   a. Prescribe a hypnotic for bedtime and encourage daily exercise
   b. Evaluate him for periodic leg movement disorder
   c. Evaluate him for sleep apnea
   d. Ask him whether he has problems with nightmares

4. **Mr C experienced heavy combat in Vietnam and saw his best friend die. He has had a long-standing problem with nightmares, and he finally sought treatment at a sleep center. Their report found no sleep disorders and recommended an evaluation for PTSD. Your evaluation confirms that Mr C does have PTSD. He currently refuses cognitive-behavioral therapy. What is the *best* evidence-based strategy to help Mr C with PTSD, including nightmares?**
   a. Prescribe an SSRI and olanzapine
   b. Prescribe an SSRI, and, if his nightmares do not resolve, add prazosin
   c. Prescribe mirtazapine and help him find community-based support
   d. Prescribe trazodone, and, if his nightmares do not resolve, add an SSRI