

SPECIAL ARTICLES

Position Paper for the Treatment of Nightmare Disorder in Adults: An American Academy of Sleep Medicine Position Paper

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Introduction: Nightmare disorder affects approximately 4% of adults, occurring in isolation or as part of other disorders such as posttraumatic stress disorder (PTSD), and can significantly impair quality of life. This paper provides the American Academy of Sleep Medicine (AASM) position regarding various treatments of nightmare disorder in adults.

Methods: A literature search was performed based upon the keywords and MeSH terms from the Best Practice Guide for the Treatment of Nightmare Disorder in Adults that was published in 2010 by the AASM. The search used the date range March 2009 to August of 2017, and sought to find available evidence pertaining to the use of behavioral, psychological, and pharmacologic therapies for the treatment of nightmares. A task force developed position statements based on a thorough review of these studies and their clinical expertise. The AASM Board of Directors approved the final position statements.

Determination of Position: Positions of “recommended” and “not recommended” indicate that a treatment option is determined to be clearly useful or ineffective/harmful for most patients, respectively, based on a qualitative assessment of the available evidence and clinical judgement of the task force. Positions of “may be used” indicate that the evidence or expert consensus is less clear, either in favor or against the use of a treatment option. The interventions listed below are in alphabetical order within the position statements rather than clinical preference: this is not meant to be instructive of the order in which interventions should be used.

Position Statements:

- The following therapy is recommended for the treatment of PTSD-associated nightmares and nightmare disorder: image rehearsal therapy.
- The following therapies may be used for the treatment of PTSD-associated nightmares: cognitive behavioral therapy; cognitive behavioral therapy for insomnia; eye movement desensitization and reprocessing; exposure, relaxation, and rescripting therapy; the atypical antipsychotics olanzapine, risperidone and aripiprazole; clonidine; cyproheptadine; fluvoxamine; gabapentin; nabilone; phenelzine; prazosin; topiramate; trazodone; and tricyclic antidepressants.
- The following therapies may be used for the treatment of nightmare disorder: cognitive behavioral therapy; exposure, relaxation, and rescripting therapy; hypnosis; lucid dreaming therapy; progressive deep muscle relaxation; sleep dynamic therapy; self-exposure therapy; systematic desensitization; testimony method; nitrazepam; prazosin; and triazolam.
- The following are not recommended for the treatment of nightmare disorder: clonazepam and venlafaxine.
- The ultimate judgment regarding propriety of any specific care must be made by the clinician, in light of the individual circumstances presented by the patient, accessible treatment options, and resources.

Keywords: nightmare disorder, PTSD-associated nightmares, adults

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INTRODUCTION

The treatment of nightmare disorder in adults was previously addressed in 2010 by the American Academy of Sleep Medicine (AASM) Best Practice Guide for the Treatment of Nightmare Disorder in Adults.¹ The AASM commissioned a task force of experts in sleep medicine to develop a position paper that updates and replaces the best practice guide. A position paper was developed, rather than a clinical practice guideline, due to limited direct evidence for many of the available

treatment options. This position paper provides guidance on the use of pharmacologic and nonpharmacologic treatment options to all practitioners who care for adult patients with nightmare disorder. The interventions listed within the position statements are in alphabetical order; this is not meant to suggest the order in which interventions should be used. The ultimate judgment regarding propriety of any specific care plan must be made by the clinician, in light of the individual circumstances presented by the patient, accessible treatment options, and resources.

BACKGROUND

The third edition of the International Classification of Sleep Disorders (ICSD) has classified nightmare disorder as a parasomnia usually associated with rapid eye movement (REM) sleep.² The minimal diagnostic criteria proposed by the ICSD-3 are as follows:

- A. Repeated occurrences of extended, extremely dysphoric, and well-remembered dreams that usually involve threats to survival, security, or physical integrity.
- B. On awakening from the dysphoric dreams, the person rapidly becomes oriented and alert.
- C. The dream experience, or the sleep disturbance produced by awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning as indicated by the report of at least one of the following:
 1. Mood disturbance (eg, persistence of nightmare effect, anxiety, dysphoria).
 2. Sleep resistance (eg, bedtime anxiety, fear of sleep/subsequent nightmares).
 3. Cognitive impairments (eg, intrusive nightmare imagery, impaired concentration, or memory).
 4. Negative impact on caregiver or family functioning (eg, nighttime disruption).
 5. Behavioral problems (eg, bedtime avoidance, fear of the dark).
 6. Daytime sleepiness.
 7. Fatigue or low energy.
 8. Impaired occupational or educational function.
 9. Impaired interpersonal/social function.

Nightmare disorder is common, affecting 4% of the adult population in the United States.² Nightmare disorder negatively impacts quality of life, resulting in sleep avoidance and deprivation.³⁻⁵ It can also cause or exacerbate underlying psychiatric distress and illness. Nightmare disorder has also been associated with psychopathology such as depression and anxiety.⁶ Patients who have had nightmares successfully treated report better sleep quality, improvements in insomnia symptoms, less daytime fatigue and sleepiness, and feeling more rested upon awakening.³⁻⁵

Nightmares may be idiopathic with no evidence of comorbid psychopathology or they may be associated with disorders such as posttraumatic stress disorder (PTSD), substance abuse, borderline personality, and schizophrenia-spectrum disorders. PTSD-associated nightmares are the most studied since up to 80% of patients with PTSD report having nightmares.⁷ In general, the presence of nightmares following a traumatic experience predicts subsequent onset of PTSD. The symptoms associated with PTSD are classified into three clusters: (1) intrusive/re-experiencing, (2) avoidant/numbing, and (3) hyperarousal. PTSD-associated nightmares are considered part of the intrusive/re-experiencing symptom cluster. It is unknown if nightmares that are unrelated to PTSD coexist with any of the three PTSD symptom clusters, specifically hyperarousal.⁸

PTSD-associated nightmares can persist throughout life even if PTSD resolves.²

Nightmares can be largely affected by psychosocial factors. There is a large body of evidence demonstrating the efficacy of psychotherapeutic treatment for PTSD, including trauma-focused cognitive behavioral therapy. The efficacy of trauma-focused cognitive behavioral therapy, especially image rehearsal therapy, a modified cognitive behavioral therapy technique, has been shown to be an effective treatment for sleep-related problems in PTSD as summarized in a systematic review⁹ and two meta-analyses.^{10,11} It should be noted that these studies focused on general sleep characteristics in PTSD and did not examine nightmares specifically, but it is possible that these treatments may also be effective in patients with nightmares or disturbing dreams that do not fulfill ICSD-3 criteria.

Drugs that affect the neurotransmitters norepinephrine, serotonin, and dopamine can produce nightmares.¹² The withdrawal of REM-suppressing agents and drugs which affect gamma-aminobutyric acid (GABA) and acetylcholine may also be associated with nightmares.² It is not known if there is any long-term impact on nightmares after removal of the offending drug. Finally, it is unclear if a common pathophysiology underlies the different types of nightmares.

A practical review of various treatments requires an ability to assess outcomes. The most commonly used strategies to assess nightmares are self-report retrospective questionnaires and prospective logs. An advantage to using these methods is that they can differentiate nightmare frequency from distress. However, retrospective questionnaires can lead to an underestimation of nightmare frequency due to recall bias and prospective logs may lead to an overestimation of nightmare frequency.^{13,14}

Standardized tools are best developed for those with PTSD-related nightmare disorder. The Clinician Administered PTSD Scale (CAPS), developed by the National Center for PTSD, is currently the gold standard diagnostic interview for PTSD.¹⁵ This tool is a structured interview using standard questions and behaviorally anchored rating scales to assess the frequency and intensity of 17 symptoms, including PTSD-associated nightmares (commonly referred to as the “distressing dreams item”). Historically there have been several versions of CAPS, such as the CAPS-DX (formerly CAPS-1) which is a diagnostic version used to assess PTSD symptom severity over the past month or for the worst month since the traumatic event, and the CAPS-SX (formerly CAPS-2) which is a version used for repeated symptom assessment over brief intervals. More recently these were combined into a single CAPS.¹⁶

Other psychometric tools used to assess nightmares include the Symptom Checklist-90 and Symptom Questionnaire. The Symptom Checklist-90 is a 90-question tool that evaluates a broad range of psychological problems and is also used to measure patient progress and outcomes.¹⁷ The Symptom Questionnaire is a simple yes/no questionnaire that assesses depression, anger-hostility, and somatic symptoms.¹⁸

The purpose of this position paper is to present updated recommendations on the therapy of nightmare disorder. The positions are based on a systematic review of the literature

to date, qualitative assessment of the evidence (ie, no evidence grading system was employed), and the clinical expertise and consensus of the task force. Treatment modalities for nightmare disorder include medications, most prominently prazosin, and several behavioral therapies, of which the nightmare-focused cognitive behavioral therapy variants, especially image rehearsal therapy, are effective. The ultimate judgment regarding propriety of any specific treatment must be made by the clinician, considering the individual circumstances presented by the patient, available diagnostic tools, and resources. The positions taken represent the best judgement of the task force regarding the treatment of PTSD-associated nightmares and nightmares without a clear etiology (ie, nightmare disorder).

POSITION STATEMENTS

The AASM supports the following positions on the treatment of nightmare disorder in adults. Note that the interventions are listed in alphabetical order within the position statements. The order in which they are listed is not meant to be instructive of the order in which interventions should be used.

Behavioral and Psychological Treatment Options

- Image rehearsal therapy is recommended for the treatment of PTSD-associated nightmares and nightmare disorder.
- The following may be used for the treatment of PTSD-associated nightmares: cognitive behavioral therapy, cognitive behavioral therapy for insomnia, eye movement desensitization and reprocessing, and exposure, relaxation, and rescripting therapy.
- The following may be used for the treatment of nightmare disorder: cognitive behavioral therapy, exposure, relaxation, and rescripting therapy, hypnosis, lucid dreaming therapy, progressive deep muscle relaxation, sleep dynamic therapy, self-exposure therapy, systematic desensitization, and testimony method.

Pharmacologic Treatment Options

- The following may be used for the treatment of PTSD-associated nightmares: the atypical antipsychotics olanzapine, risperidone and aripiprazole, clonidine, cyproheptadine, fluvoxamine, gabapentin, nabilone, phenelzine, prazosin, topiramate, trazodone, and tricyclic antidepressants.
- The following may be used for the treatment of nightmare disorder: nitrazepam, prazosin, and triazolam.
- The following are not recommended for the treatment of nightmare disorder: clonazepam and venlafaxine.

The ultimate judgment regarding propriety of any specific care must be made by the clinician, considering the individual circumstances presented by the patient, accessible treatment options, and resources.

For the purposes of a position paper, positions of “recommended” and “not recommended” indicate that a treatment option is clearly useful or ineffective/harmful for most patients, respectively, based on a qualitative assessment of the available evidence and clinical judgement of the task force. Positions of “may be used” indicate that the evidence or expert consensus is less clear, either in favor or against the use of a treatment option.

EVIDENCE REVIEW

Behavioral and Psychological Treatment Options for Nightmare Disorder

This section addresses the efficacy of behavioral and psychological treatments for nightmares. The sections below are listed in the order they appear in the position statements.

Image Rehearsal Therapy (IRT)

IRT is a modified cognitive behavioral therapy technique which involves altering the content of a nightmare by creating a new set of positive images and rehearsing the rewritten dream scenario for 10–20 minutes per day while awake.^{19,20} Nine randomized control trials (RCTs) report on the efficacy of IRT in the treatment of nightmare disorder in both PTSD and non-PTSD populations.^{19–27}

Two RCTs with waitlist controls evaluated the use of IRT on nightmare frequency.^{19,20} A 6-month RCT studied the effectiveness of IRT versus controls placed on a waiting list for treatment in 168 female sexual assault survivors diagnosed with PTSD.¹⁹ A nightmare frequency questionnaire was used to assess nights with nightmares per unit of time (eg, per week or per month) and the actual number of nightmares. The treatment group received three sessions of IRT (two 3-hour sessions one week apart with a 1-hour follow-up 3 weeks later). IRT significantly reduced both nights per week with nightmares (baseline: IRT 3.88 ± 2.06, control 3.68 ± 2.05; 6-month follow-up: IRT 1.33 ± 1.67, control 3.28 ± 2.31) and nightmares per week (baseline: IRT 6.37 ± 4.96, control 5.41 ± 4.31; 6-month follow-up: IRT 2.43 ± 5.21, control 5.97 ± 6.10). IRT did result in negative imagery for 4 patients who eventually withdrew from the study. An 18-month RCT assessed the effect of IRT versus waitlist control on 41 subjects with chronic nightmares.²⁰ Nightmare frequency was measured retrospectively using nights per month. The treatment group participated in a single 2.5-hour IRT session and was instructed to use IRT whenever they had nightmares. Waitlist control subjects were offered IRT at the conclusion of the 3-month control period. Interim 3-month study results are reported elsewhere.²⁸ At 18-month follow-up, 68% of the subjects decreased their nightmare frequency below the criteria for nightmare disorder (no 18-month mean or standard deviation given). One subject reported decreased visual and color intensity in non-nightmare dreams.

A third RCT with 20 participants evaluated IRT therapy based on nightmare frequency and self-rated distress at 30 months follow-up.²¹ The treatment group received one group session of IRT, while the control group recorded their nightmares in a diary for one month. Nightmare frequency was measured retrospectively in nights per month. At a 3-month

follow-up, the control group was taught IRT and the IRT group was instructed to use the technique as needed, so both groups used IRT from month 3 to 30. At the 30-month follow-up, significant decreases in nightmares were maintained for both study groups (baseline: IRT 7.11 ± 4.81 , control 9.4 ± 7.31 ; 30-month follow-up: IRT 3.24 ± 4.27 , control 5.1 ± 5.40). One participant experienced intrusive, unpleasant images while attempting IRT but was able to modify his technique and eliminate his nightmares in 3 months.

A 7-month RCT evaluated the effectiveness of IRT versus desensitization in 28 participants with chronic nightmares.²² All subjects met the criteria for the diagnosis of dream anxiety disorder (nightmare disorder) from the third edition, revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Subjects were treated with either one session of desensitization with instructions on how to practice this treatment, or one session of IRT with instructions on how to change the nightmare and rehearse the new version. The frequency of nightmares decreased significantly in both groups at follow-up (baseline: IRT 4.4 ± 0.8 , desensitization 4.2 ± 1.2 ; 7-month follow-up: IRT 2.2 ± 1.3 , desensitization 2.6 ± 1.4). Two patients, one from each group, reported an increase in the severity of nightmares despite a reduction in their frequency.

An 11-week RCT with 399 participants compared the effectiveness of IRT versus exposure (self-help) and two control groups (recording or waiting list).²⁴ Nightmare frequency for the past week was measured with the SLEEP-50 questionnaire. The IRT and exposure groups received a 6-week step-by-step program; participants in the IRT, exposure, and recording groups kept a 6-week daily diary. IRT and exposure were found to be equally effective in reducing weekly nightmare frequency (baseline: IRT 5.15 ± 3.57 , exposure 4.66 ± 3.28 ; 11-week follow-up: IRT 2.76 ± 2.74 , exposure 2.86 ± 2.67). IRT was found to be superior to recording in reducing weekly nightmare frequency (baseline: IRT 5.15 ± 3.57 , recording 5.59 ± 4.27 ; 11-week follow-up: IRT 2.76 ± 2.74 , recording 4.03 ± 3.61). A follow-up study reported the 42-week follow-up results of the IRT and exposure intervention groups and found the effects on weekly nightmare frequency to be almost completely sustained (42-week follow-up: IRT 2.52 ± 1.75 , exposure 2.82 ± 2.48).²⁹ No adverse effects of the therapy were reported in either study.

Two RCTs assessed the use of IRT in patients with existing psychiatric disorders.^{25,27} A 20-week RCT with 69 participants evaluated the effectiveness of IRT in patients suffering from nightmares in addition to a psychiatric disorder.²⁵ Study participants were assigned to one of three study groups: nightmare sufferers without comorbid depression or PTSD, major depression and nightmares, or PTSD and nightmares. The PTSD group was further subdivided into either an intervention or control group. Nightmare frequency (number of nightmares per month) was assessed with a self-report questionnaire. The nightmare sufferers, depressive, and PTSD intervention groups received IRT therapy which consisted of eight therapy sessions of 50 minutes each. Sessions 1–7 were held on a weekly basis and the final session was held 3 weeks after that. The PTSD control group was offered IRT after the first 10 weeks of the study. Nightmare frequency per month decreased for the

intervention group after treatment and was sustained at follow-up; nightmare frequency in the control group was essentially unchanged (baseline: IRT 11.3 ± 1.2 , control 17.3 ± 3.0 ; after treatment: IRT 7.4 ± 1.2 , control 16.7 ± 3.2 ; 10-week follow-up: IRT 7.1 ± 1.1). No adverse therapy effects were reported. A second 7-month RCT evaluated the effectiveness of IRT versus an active control condition in 90 patients with comorbid psychiatric disorders.²⁷ Nightmare frequency was assessed using daily nightmare logs and a nightmare frequency questionnaire. The IRT intervention consisted of 6 individual 1-hour sessions at 2-week intervals. Usual care consisted of biweekly individual psychotherapy, counseling, or psychiatric consultations; nightmares were not specifically addressed in these sessions. IRT showed a moderate effect on nightmare frequency compared to the control (baseline: IRT 6.09 ± 4.19 , control 6.37 ± 5.09 ; 7-month follow-up: IRT 2.33 ± 2.68 , control 3.15 ± 2.83). No adverse effects of the therapy were reported.

A 12-week RCT with 22 veterans diagnosed with PTSD assessed the effectiveness of a combined CBT/IRT intervention versus usual care.²⁶ Nightmare frequency was assessed with an electronic sleep diary. All participants conducted one week of sleep monitoring at home with the electronic sleep diary and completed a baseline questionnaire; they were then randomized to either the intervention or control group. The intervention consisted of 6 bi-weekly sessions for 12 weeks after which participants completed post-intervention questionnaires. The procedures for the usual care group were the same but they did not receive the intervention. The combined CBT/IRT intervention produced significantly greater improvements in nightmare frequency as compared to usual care (baseline: intervention 0.72 ± 0.43 , control 0.59 ± 0.68 ; 12-week follow-up: intervention 0.27 ± 0.76 , control 0.73 ± 2.82). No adverse effects of the therapy were reported.

A single 6-month RCT did not demonstrate any significant benefit to IRT when used in a veteran population.²³ One hundred twenty-four Vietnam War veterans diagnosed with chronic, severe PTSD assessed the effectiveness of IRT versus standard therapy for the treatment of combat-related nightmares. A nightmare frequency questionnaire was used to measure the number of nightmares per week. Ninety-minute group sessions occurred weekly for 6 weeks. By design, both treatment groups had equivalent amounts of therapist contact. Nightmare frequency did not improve significantly between the two groups (baseline: IRT 3.95 ± 2.37 , control 3.88 ± 3.95 ; 6-month follow-up: IRT 3.20 ± 2.14 , control 3.04 ± 1.89). No adverse effects of the therapy were reported.

Six small studies demonstrated the benefits of IRT in the treatment of nightmares in both civilian and veteran populations.^{30–35} Due to the small size of these studies, relative to the body of evidence supporting IRT for the reduction of nightmares, the details are not discussed in this position paper.

Cognitive Behavioral Therapy (CBT)

CBT is a short-term, goal-oriented form of psychotherapy that strives to modify a person's dysfunctional thoughts, emotions, and behaviors. CBT is a general term for a number of different therapies consisting of psychotherapeutic and behavioral techniques. Early interventions to manage

nightmares used basic CBT techniques,^{36,37} until the development of specialized CBT techniques that more effectively target the symptoms of nightmares. CBT variants that focus specifically on the treatment of nightmares include IRT (as previously described), lucid dreaming therapy, sleep dynamic therapy, and systematic desensitization. CBT also includes the IRT variant exposure, relaxation, and rescripting therapy. CBT for insomnia (CBT-I), a variant of CBT targeting the symptoms of insomnia, has also been used to treat nightmares. CBT-I and the variants of CBT that focus specifically on the treatment of nightmares are described in their own following sections. Three studies report on the efficacy of CBT in the treatment of nightmares.^{38–40}

A 15-month RCT evaluated the effectiveness of CBT in generalized anxiety disorder (GAD) in 227 older adults.³⁸ One hundred thirty-four of the subjects met the diagnostic criteria for GAD, with the remaining 93 serving as a comparison group. Subjects in the CBT group received up to 10 individual therapy sessions over 12 weeks; those receiving enhanced usual care received biweekly calls to provide support and ensure patient safety. Bad dream frequency was measured retrospectively with the Pittsburgh Sleep Quality Index (PSQI). Assessments were done at baseline, 3, 6, 9, 12, and 15 months post-baseline. The use of CBT was found to significantly reduce bad dream frequency across the assessment period (baseline: GAD 0.77 ± 1.00 , non-GAD 0.67 ± 0.94 ; 15-month follow-up: GAD 0.27 ± 0.63 , non-GAD 0.62 ± 0.88). No negative effects of the treatment were reported.

A 9-month RCT with 5- to 10-year long-term follow-up examined the effect of cognitive processing therapy (CPT) and prolonged exposure (PE) on subjective sleep measures, including nightmares, in patients with PTSD.⁴⁰ One hundred seventy-one female rape victims with PTSD were randomly assigned to CPT, PE, or minimal attention (MA). Subjects in the CPT and PE groups received twice weekly sessions for 6 weeks and those in the MA group were contacted by phone every 2 weeks. MA participants were randomized into either CPT or PE after 6 weeks. Nightmares were assessed using the CAPS. Both CPT and PE had large effects on nightmare severity compared to MA (baseline: CPT 5.24 ± 1.66 , PE 5.14 ± 1.88 , MA 4.52 ± 2.20 ; posttreatment: CPT 1.44 ± 1.76 , PE 1.85 ± 2.38 , MA 4.67 ± 1.46 ; lost to follow-up: CPT 2.44 ± 2.04 , PE 1.73 ± 2.09). No adverse effects of the therapy were reported.

A secondary analysis of a large treatment outcome trial for patients with co-occurring PTSD and substance abuse compared the effectiveness a structured CBT treatment (“Seeking Safety”) and a comparison health education intervention (“Women’s Health Education”).³⁹ Three hundred fifty-three women with coexisting PTSD and substance abuse or dependence completed a baseline assessment then were randomly assigned to 6 weeks of either Seeking Safety or Women’s Health Education. Nightmare frequency and intensity were assessed using CAPS at baseline and one week after treatment. There was a higher prevalence of nightmares in the Seeking Safety group compared to the Women’s Health Education group (44.9% versus 40.1%, respectively). There was a slightly lower prevalence of nightmares in the Seeking Safety group one week following treatment (22.2% versus 23.9% Women’s

Health Education). No adverse effects of either therapy were reported.

Cognitive Behavioral Therapy for Insomnia (CBT-I)

CBT-I is a psychological and behavioral treatment that involves sleep restriction, stimulus control, sleep hygiene, and cognitive restructuring to treat primary and comorbid insomnia. Two RCTs report on the efficacy of CBT-I in the treatment of nightmare disorder.^{41,42}

A 6-month randomized trial evaluated whether CBT-I improved nightmares in 45 veterans with a DSM-IV diagnosis of PTSD.⁴¹ Nightmare frequency and disruptions were measured by CAPS distressing dreams item scale and the Pittsburgh Sleep Quality Index-Addendum (PSQI-A) scale. Twenty-nine subjects were randomized to 8 weekly individual sessions of CBT-I while 16 were randomized to the waitlist control group. Using the CAPS distressing dreams item, both the CBT-I and the waitlist control groups improved posttreatment (baseline: CBT-I 4.38 ± 0.47 , control 4.25 ± 0.48 ; 8 weeks posttreatment: CBT-I 1.48 ± 0.43 , control 1.07 ± 0.48). The gains in the CBT-I group’s improvement were sustained at 6 months (2.23 ± 0.48 , control not reported). CBT-I participants also showed significant reductions in the PSQI-A score from the baseline assessments to the 6-month follow-up. No adverse effects were reported.

A second 8-week randomized trial evaluated whether CBT-I with adjunctive IRT improved PTSD-related nightmares in 40 combat veterans.⁴² Disruptive nocturnal behavior was assessed using the PSQI-A scale. Twenty subjects were randomized to the treatment group of 4 sessions of CBT-I with IRT and the remaining 20 subjects were placed in a waitlist group. The PSQI-A improved in the treatment group compared to the waitlist group (baseline: CBT-I 10.1 ± 3.6 , control 11.6 ± 5.8 ; 8-week follow-up: CBT-I 7.5 ± 5.6 , control 12.8 ± 5.4). Despite CBT-I and IRT, 60% of the treatment group continued to report residual nightmares at least once per week at posttreatment. No adverse effects were reported with treatment.

Eye Movement Desensitization and Reprocessing (EMDR)

EMDR is a specialized psychotherapeutic intervention integrating elements from psychodynamic, cognitive behavioral, interpersonal, experiential, and body-centered therapies.^{29,43} The principle is to induce the processing of disturbing memories and experiences by stimulating neural mechanisms that are similar to those activated during REM sleep. An 8-phase approach is employed using bilateral eye movements, tones, and taps to identify and process the disturbed memory and past experience, current triggers, and positive experiences to formulate insight and adaptive behavior in patients suffering from traumatic experience.

A single non-randomized controlled trial compared EMDR with biofeedback and group relaxation training in 83 male Vietnam veterans as part of a 90-day inpatient PTSD treatment program.⁴⁴ Nightmares were assessed at three time points (evaluation, admission to the inpatient program, and at discharge from program) with the Problem Report Form and rated on a scale from 0 (no problem) to 5 (severe problem). Thirteen subjects received EMDR, 6 received biofeedback, and 9

received relaxation therapy, with 55 control subjects. A subject was considered as having undergone EMDR if he received at least one session; the total number of sessions was not reported. Changes in self-report data at 90 days showed improvement in the EMDR group by 2 degrees of severity ($P < .01$) relative to the other groups (means and standard deviations were not reported). No adverse effects with EMDR were reported.

Exposure, Relaxation and Rescripting Therapy (ERRT)

ERRT, a modification of IRT, is a 3-week CBT for nightmares that combines sleep hygiene education, progressive muscle relaxation, and exposure to the trauma with rescripting of nightmares. The literature consists of one small case series⁴⁵ and two RCTs^{46,47} with the same lead author and institution.

The first RCT involved 32 civilians with posttraumatic nightmares.⁴⁶ Nightmares were assessed with the Trauma Related Nightmare Survey which was specifically developed for the study. The treatment group underwent ERRT with weekly 2-hour sessions for 3 consecutive weeks and follow-up assessment 1 week after the third session and at 6 months. The control group was placed on a waitlist for treatment. At 1 week posttreatment, there was a statistically significant reduction in the number of nights with nightmares and in the severity of nightmares (no means or standard deviations were reported). These effects were maintained at the 6-month follow-up. No side effects were mentioned but there was a 26% dropout rate which the authors assert is within the typical range for trauma-related therapies.

A second 6-month RCT from the same author assessed the use of ERRT in 47 civilian subjects diagnosed with nightmare disorder.⁴⁷ Nightmares were assessed with the Trauma Related Nightmare Survey. The study also evaluated additional measures of mental and physical health, quality of life, and measures of nightmare-related physiological reactivity. Subjects were randomized to either ERRT 2 hours once a week for 3 consecutive weeks or waitlist control. Study results were similar to the initial study with statistically significant reduction in nightmares per week (baseline treatment 3.19 ± 2.79 , control 3.50 ± 2.78 ; 6-month follow-up single treatment group 1.36 ± 3.56). No adverse effects were reported.

A case series of 4 civilians with a history of trauma-related nightmares (only 3 subjects met criteria for PTSD) underwent ERRT over 3 weeks with 3- to 6-month follow-up.⁴⁵ Nightmares were measured by weekly frequency and subjective severity on a 5-point scale ("not at all" to "extremely distressing"). Nightmares at baseline ranged from 1 to 3 nightmares per week of at least moderate severity. At 3-month follow-up, 3 of the 4 subjects no longer had nightmares; the fourth subject continued with 1 nightmare a week, but the intensity had decreased. The improvement was sustained at the 6-month follow-up for the 3 subjects who returned.

Hypnosis

Hypnosis creates a trance-like state of mind which allows the mind to concentrate on a specific thought or memory without distractions and makes the patient open to suggestions that can be used to change certain thoughts or behaviors. Two small case series studies report on the use of hypnosis for the treatment of nightmares.^{48,49}

The first study included 10 patients who had been previously diagnosed with nightmares. Each participant received one 50-minute hypnosis treatment.⁴⁸ Seventy-one percent had improvement after 18 months and 67% maintained improvement at the 5-year follow-up (means and standard deviations were not reported).

The second study included 3 patients who received 1 to 5 sessions of brief hypnotic treatment for repetitive nightmares.⁴⁹ The treatment was found to be beneficial in all 3 patients with no adverse effects reported.

Lucid Dreaming Therapy (LDT)

LDT is a variant of IRT, where the cognitive-restructuring technique of LDT allows one to alter the nightmare story line during the nightmare itself by realizing that one is dreaming or being "lucid" during the nightmare. Two randomized trials^{35,50} and one case series⁵¹ report on the efficacy of LDT in the treatment of nightmare disorder.

A randomized trial evaluated the use of LDT on nightmare frequency over 12 weeks in 23 participants recruited from the general population who were diagnosed with nightmares using DSM-IV criteria.⁵⁰ Nightmare frequency was measured by the self-report instrument SLEEP-50.⁵² Eight participants were randomized to a 2-hour individual session, 8 participants were randomized to a 2-hour group session, and 7 were assigned to waitlist group. Nightmare frequency was significantly decreased in both the individual and group LDT therapy groups at 12-week follow-up (baseline: individual LDT 3.5 ± 1.7 , group LDT 3.1 ± 2.0 ; 12-week follow-up: individual LDT 1.4 ± 0.7 , group LDT 2.6 ± 1.7) compared to the waitlist group (baseline: 3.7 ± 2.40 ; 12-week follow-up 3.6 ± 2.1). The individual sessions were more effective than 2 hours of group LDT although both showed a statistically significant fall in the frequency of nightmares when compared with baseline. One participant withdrew from the waitlist group. No adverse effects were reported though not all participants who had improvement in nightmare frequency used LDT.

A second randomized trial (as previously mentioned in the IRT section) evaluated the use of Gestalt therapy versus the addition of LDT to Gestalt therapy on nightmare frequency over 12 weeks in 32 civilian participants who were diagnosed with nightmares based on ICSD-2 criteria.³⁵ Gestalt therapy is a psychotherapy approach that aims to help the patient learn to focus on interpreting present circumstances with less overlay of prior experiences, often through some re-enactment of the prior experiences. Nightmare frequency was measured by sleep logs and a nightmare frequency questionnaire over a period of 6 weeks. Sixteen participants were randomly assigned to each group (no control group). The results showed significant decreases in nightmare frequency for both the Gestalt therapy group and the Gestalt therapy and LDT group (baseline: Gestalt 4.69 ± 0.95 , Gestalt + LDT 4.63 ± 1.35 ; 12-week follow-up: Gestalt 3 ± 1.47 , Gestalt + LDT 3.27 ± 1.53). There were no significant differences between the two groups. No adverse effects were reported.

A case series evaluated the use of LDT alone (3 cases) and progressive muscle relaxation, guided imagery, and LDT (2 cases) for one year to treat nightmares that were either

idiopathic or PTSD-related.⁵¹ Nightmare frequency was assessed by self-report. One-year follow-up showed that 4 of 5 subjects no longer had nightmares and that one subject saw a decrease in the frequency and intensity of her nightmares. No adverse effects were reported.

Progressive Deep Muscle Relaxation (PDMR)

PDMR involves tensing and releasing the muscles, one body part at a time, to bring about a feeling of physical relaxation and reduction in anxiety and stress. The evidence for PDMR is based on one small randomized study.⁵³

This study evaluated the effectiveness of PDMR in 32 females who self-referred with complaints of nightmares.⁵³ Subjects were randomly assigned to PDMR training, systematic desensitization, or waitlist controls. Nightmare frequency was initially assessed by self-report in a telephone interview. Subjects in both treatment groups received 6 weekly sessions followed by 9 weeks of self-monitoring with sleep and dream diaries for all three groups. Nightmare frequency and intensity were assessed at week 15 with a structured interview by an investigator who was not blinded to group assignment then again at week 25 by interviewers blinded to group assignment. Treatment of the waitlist controls with either PDMR or systematic desensitization was initiated after week 15.

At week 15 follow-up, both treatment groups showed a significant decrease in nightmare frequency relative to the controls (baseline: PDMR 11.8 ± 12.2 , systematic desensitization 6.8 ± 7.5 , control 8.5 ± 5.9 ; 15-week follow-up: PDMR 2.6 ± 3.6 , systematic desensitization 1.6 ± 1.2 , control 8.5 ± 7.0). At week 25, all groups continued to show improvement (PDMR 1.4 ± 2.6 , systematic desensitization 0.2 ± 0.4 , control 4.7 ± 9.0). Both treatments reduced nightmare frequency by 80% in 20/21 subjects and 12 of these subjects had total elimination of symptoms. After week 25 the desensitization group had a more favorable effect on intensity of the nightmares, especially favoring the earlier-treated group over the later-treated waitlist controls indicating improved benefit with longer duration of treatment. No adverse effects were recorded.

Sleep Dynamic Therapy

Sleep dynamic therapy is an integrated sleep treatment program of evidence-based, non-pharmacologic sleep medicine therapies combined with standard sleep medicine instructions administered to large audiences of trauma survivors.⁵⁴ A single small study reports on the efficacy of sleep dynamic therapy in the treatment of nightmares.

This pilot study evaluated the effectiveness of sleep dynamic therapy on 66 adults who self-reported nightmares as a result of trauma.⁵⁴ Nightmare severity was measured by the Disturbing Dream and Nightmare Severity Index at baseline, posttreatment, and at 12-week follow-up. Sleep dynamic therapy was provided to all 66 subjects in 6 weekly, 2-hour sessions. No control group was used. Nightmares decreased significantly posttreatment, and improvements were maintained at 12-week follow-up (means and standard deviations not reported). No adverse effects with sleep dynamic therapy were reported.

Self-Exposure Therapy

Self-exposure therapy is a variant of CBT that utilizes a technique of “graded exposure.” The patient is instructed to make a hierarchical list of anxiety-provoking events/dreams. The patient is then instructed to move through the situations on the list at his or her own rate, starting with lowest anxiety situation until the fear/anxiety has decreased. The exposure is done on a daily basis with documentation in a journal of his or her experiences. Two studies report on the efficacy of self-exposure therapy in the treatment of nightmare disorder.^{55,56}

A 6-month RCT involved 206 subjects randomized to self-exposure treatment at home, self-relaxation treatment at home, or a waitlist control group.⁵⁵ Nightmares were self-rated in diaries stating their frequency and intensity. At 6-month follow-up, self-exposure therapy showed a greater reduction in nightmare frequency than self-relaxation therapy (no control data was available) (baseline: exposure 19.9 ± 10.8 , relaxation 23.3 ± 16.2 , control 19.7 ± 13.6 ; 6-month follow-up: exposure 11.3 ± 7.7 , relaxation 19.0 ± 18.3). The limitations of the study included a high drop-out rate (17%) and the fact that the nightmare intensity was not greatly reduced after 12 weeks of self-exposure. In addition, subjective sleep quality improved more among group with self-exposure therapy compared to self-relaxation. No adverse effects were reported.

A second 4-year open randomized study assessed the effectiveness of self-exposure therapy on 20 adult subjects with recurrent nightmares.⁵⁶ Nightmare frequency and intensity were recorded in a daily nightmare diary. Ten subjects were randomized to a correspondence-based self-exposure therapy for four weeks and 10 to a control group. At the 4-week follow-up, the self-exposure group had significant improvements in nightmare frequency and intensity; the benefit was maintained at the 4-year follow-up (no means or standard deviations were reported). This small study had no drop-outs and the subjects served as their own controls. No adverse effects were reported.

Systematic Desensitization

Systematic desensitization is a type of behavioral therapy that uses the principle of gradually exposing the patient to what he or she fears. This technique is also called “graduated exposure therapy.” The patient is trained to cope and manage the stressors gradually before the patient is actually exposed to the feared object or situation. Three studies evaluate the use of systematic desensitization in the treatment of nightmares.^{53,57,58}

A 25-week prospective randomized control study of 32 adults (as mentioned above in the PDMR section) compared systemic desensitization with PDMR and waitlist controls.⁵³ Nightmare frequency was initially assessed by self-report in a telephone interview. Patients were required to have at least one frightening dream awakening them from sleep at least once monthly for the preceding six months. Although both intervention groups showed similar decrease in frequency of nightmares, at 25-week follow-up the desensitization group showed significantly greater reduction in nightmare intensity compared to the relaxation and control groups (baseline: desensitization 6.8 ± 7.5 , relaxation 11.8 ± 12.2 , control 8.5 ± 5.9 ; 25-week follow-up: desensitization 0.2 ± 0.4 , relaxation 1.4 ± 2.6 , control 4.7 ± 9.0). Two patients with nightmare and night terror showed

no improvement at 15 and 25 weeks with normal Minnesota Multiphasic Personality Inventory scores.

An 8-week prospective randomized control study assessed the use of systematic desensitization in 29 adult subjects with two or more weekly nightmares.⁵⁷ Subjects were randomly assigned to a systemic desensitization treatment group (10 subjects), a continuous self-recording group (9 subjects), or a nightmare-related discussion placebo treatment group (10 subjects). The short-term systemic desensitization treatment was found to produce favorable changes in frequency and rated intensity of the nightmares (means and standard deviations not reported). Follow-up nightmare information was available for only 65% of the subjects. Two subjects reported an increase in nightmare frequency after one month following the last recorded week.

A prospective randomized study examined the effects of desensitization compared with muscle relaxation for 36 adult subjects with chronic recurrent nightmares of 6 months or more.⁵⁸ Nightmare frequency for the past month was assessed using a 5-point scale (1 = not at all, 2 = 1–2 times/month, 3 = once a week, 4 = 2–3 times/week, 5 = ≥ 4 times/week). Fourteen subjects received a single treatment session that included instructions for desensitization with progressive muscle relaxation and 14 subjects received one session of rehearsal of a changed nightmare (8 subjects were excluded after intake). All subjects were contacted via telephone at 4 months and 7 months. Both the treatment groups showed a decrease in frequency of nightmares at 4 and 7 months (baseline: desensitization 4.2 ± 1.2 , rehearsal 4.4 ± 0.8 ; 4-month follow-up: desensitization 2.7 ± 1.4 , rehearsal 3.3 ± 1.5 ; 7-month follow-up: desensitization 2.6 ± 1.4 , rehearsal 2.2 ± 1.3). None of the treated patients reported an increase in nightmare frequency.

Testimony Method

The testimony method is a brief variant of a trauma exposure technique. Trauma survivors are invited to tell the story of their traumatic experiences and document them in a written format with the help of the therapist. A single case-control study showed some benefit at an 11-month follow-up, but only in the women.⁵⁹ This case-control trial of 137 Mozambican civil war survivors in a community setting randomized participants with higher posttraumatic stress scores into intervention and control groups. Prevalence of nightmares was determined with the Nocturnal Intrusions after Traumatic Experience questionnaire.⁶⁰ One 60-minute session of testimony intervention was performed with each subject, although 7 subjects required a second session. Although this study was designed as a case-control study, local circumstances interfered with the design, especially with controlling the intervention in a small rural community. There were no significant differences in nightmare impact between the intervention and control groups (baseline: intervention group 8.86 ± 4.1 , control group 9.32 ± 3.3 ; post-intervention: intervention group 6.25 ± 4.4 , control group 6.54 ± 4.6). Adverse effects were not reported.

Pharmacologic Treatment Options for Nightmare Disorder

A number of medications have been studied for use in the treatment of patients with nightmares. The focus of most studies

has been to assess their efficacy in the treatment of PTSD-associated nightmares; it is unknown if those medications that demonstrate efficacy for treating PTSD-associated nightmares would also be effective for idiopathic or drug-related nightmares, or if these medications would be useful in those patients who have bad dreams that do not fulfill the ICSD-3 criteria for nightmare disorder. It should be noted that many of the studies reviewed pre-date the ICSD-3 criteria for nightmare disorder. In addition, in many reports the active agents were administered to patients receiving other medications. Therefore, the results must be interpreted with caution, since they could be the result of combined or interactive effects. The sections below are listed in the order they appear in the position statements.

The Atypical Antipsychotic Medications Olanzapine, Risperidone, and Aripiprazole

Olanzapine is a (5-HT) 2C receptor antagonist that increases slow-wave sleep and reduces rapid-eye movements.⁶¹ Based on this mechanism of action, olanzapine has been hypothesized to be effective in the management of patients with treatment-resistant PTSD symptoms.⁶¹ A single case series compared the effectiveness of olanzapine augmentation to different psychotropic treatment regimens in 5 combat veterans with treatment-resistant PTSD.⁶¹ Subjects used a self-rating scale to report the frequency of nightmares. The dose of olanzapine ranged from 10–20 mg/day. There was a rapid improvement in nightmares after olanzapine was added to the current treatment regimen; there was no quantification of medication effect. No side effects were reported.

Risperidone is an atypical antipsychotic medication that demonstrates significant alpha-1 and alpha-2 noradrenergic antagonism.⁶² Two studies showed moderate to high efficacy of risperidone in treating patients with PTSD-related nightmares.^{63,64} A 12-week, open-label trial evaluated the effects of risperidone in veterans with chronic PTSD.⁶³ The focus of the study was the changes in sleep variables at 6 weeks; 17 of 20 male combat veterans completed 6 weeks of the trial. Nightmare frequency was assessed with CAPS, PSQI, and sleep/dream diaries. The average maximum dose of risperidone was 2.3 ± 0.6 mg (range 1–3 mg) per day. There was a statistically significant decrease in the CAPS recurrent distressing dreams item at 6 weeks (baseline: 5.4 ± 1.9 , 6 weeks: 3.8 ± 2.8). This coincided with a significant reduction in the percent of patients reporting nightmares at 6 weeks (baseline: $38.0\% \pm 36.7\%$, 6 weeks: $19.0\% \pm 21.5\%$); there was no change in the PSQI frequency of bad dreams. There was no mention of side effects in this study.

A retrospective chart review of 10 adult civilian patients at a regional burn center assessed the use of risperidone in the treatment of acute stress symptoms, including nightmares.⁶⁴ All patients were diagnosed with either Acute Stress Disorder or PTSD, based on the duration of their symptoms. Subjects were interviewed by a clinical nurse specialist to determine the frequency of trauma-related dreams. The dosage of risperidone ranged from 0.5–2.0 mg/day. Eighty percent of patients reported an improvement in their symptoms, including nightmares, after the first use. No side effects were reported.

Aripiprazole is a partial agonist of dopaminergic D2 receptors that has been found to have a better tolerability profile

compared to olanzapine and has been considered for use in the management of PTSD.⁶⁵ A single case series illustrates the potential use of aripiprazole in the treatment of nightmares in conjunction with sertraline and/or cognitive-behavioral psychotherapy in the management of PTSD.⁶⁵ Five veterans with combat-related PTSD self-reported nightmare frequency and intensity as well as agitated behaviors during sleep. The final dosage of aripiprazole at 4 weeks ranged from 15–30 mg/day. Four of the five participants reported substantial improvement but not total resolution of their nightmares. One patient discontinued treatment with aripiprazole due to paradoxical excitement; otherwise the medication was well tolerated.

Clonidine

Clonidine is an α -2 adrenergic receptor agonist that suppresses sympathetic nervous system outflow throughout the brain, and has been shown to alter REM/NREM sleep in a dose-dependent manner.⁶⁶ Two case series report on the efficacy of clonidine in the treatment of PTSD-associated nightmares.^{67,68}

A one-year prospective pilot study assessed the clinical results of combination clonidine-imipramine therapy in 9 refugees (6 women and 3 men) diagnosed with PTSD.⁶⁷ Nightmares were initially assessed with a checklist for PTSD derived from the DSM-III-R. The final dose of imipramine was 150 mg/day and the average dose of clonidine was 0.2 mg/day. The frequency of nightmares decreased in 7 patients with 1 reporting no further nightmares, and 2 saw no change. The clonidine-imipramine combination was well tolerated by all 9 participants.

A 2-week pilot study of the polysomnographic effects of clonidine on the sleep disorders of 4 female civilians with severe PTSD and frequent nightmares showed clonidine to be beneficial.⁶⁸ Self-reports of nightmare frequency ranged from nightly to three nights per week. Each participant completed two full in-home polysomnograms; polysomnogram findings showed suppression of REM sleep which is consistent with the known actions of clonidine. Each participant received 0.1 mg clonidine, twice daily, for two weeks. All 4 patients reported a decreased frequency of nightmares and overall better sleep. There was a total of 11 nightmares reported, 10 of which occurred in pre-clonidine nights. There were no significant changes in blood pressure during the study and the medication was well tolerated by all 4 participants.

Cyproheptadine

Cyproheptadine is a serotonin receptor antagonist blocking feedback inhibition and thus increasing serotonin outflow. These serotonin effects are thought to possibly occur at the 5-HT_{1A} receptors of the midbrain raphe.⁶⁹ The evidence for cyproheptadine consists of three papers with conflicting data.^{69–71}

A small case series of four veterans with combat-related PTSD, who were said to be representative of “about 80” patients treated with median effective cyproheptadine doses ranging from 16–24 mg, illustrated the use of cyproheptadine in the treatment of combat-related nightmares.⁶⁹ Nightmares both before and after cyproheptadine were assessed subjectively by the patient. Cyproheptadine eliminated nightmares in three patients on doses ranging from 2–6 mg nightly, taking effect within a few days. Significant side effects were noted in

only one case consisting of visual hallucinations manifesting as worsened flashbacks. Long-term follow-up was not reported.

A case series of 16 patients with PTSD and distressing dreams were treated with cyproheptadine at a Veterans Affairs PTSD outpatient treatment center.⁷⁰ Sleep was followed by patient diary using the Miami Veteran’s Administration Medical Center Post-Sleep Questionnaire each morning for one week preceding cyproheptadine therapy and for at least one week post-therapy. The subjects underwent four weeks of cyproheptadine therapy at a dose of 4–8 mg. There was no significant change in sleep diary questionnaire items posttreatment. All but two of the 16 patients were taking a wide variety of other psychotropic medications. Side effects included fatigue, restlessness and worsening nightmares.

A retrospective review of psychiatric records of patients who received cyproheptadine as treatment for nightmares provided incomplete information.⁷¹ Only 9 patients whose responses varied from “complete remission” to decreased intensity and frequency were described in detail, and the total number of records reviewed was not reported. Patients subjectively reported nightmares and nightmare reduction. Cyproheptadine doses ranged from 4–12 mg per day. Patients responding to cyproheptadine had either complete remission or significant reduction in nightmares within three to-four weeks. There were no side effects reported.

Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor with antidepressant and anxiolytic properties.^{72,73} It has been shown to be an effective antidepressant and its anxiolytic properties have been used to treat anxiety disorders, obsessive-compulsive, and panic disorder.⁷² There are two small studies that demonstrate the efficacy of fluvoxamine in the treatment of PTSD-associated nightmares.^{72,73}

A 12-week prospective cohort study assessed the efficacy of fluvoxamine in 24 elderly military veterans diagnosed with PTSD.⁷² Subjects self-reported nightmares using a PTSD self-rating scale at baseline, 4 weeks, and 12 weeks. Patients received weekly rising doses, up to 300 mg daily. At the end of the study 12 subjects reported a decrease in nightmares (no quantitative data provided). Nine subjects terminated the study due to gastrointestinal complaints, another subject left the study due to worsening sleep, and three subjects discontinued the study due to physical complaints not related to fluvoxamine.

A 10-week open label trial evaluated the use of fluvoxamine in 21 Vietnam combat veterans with PTSD.⁷³ Nightmares were assessed at baseline, 6 weeks, and at the end of the trial with the patient self-report tool Impact of Event Scale-Revised (IES-R) and the clinician report tool Stress Response Rating Scale (SRRS). All participants started on a dosage of 50 mg/day and were titrated to a dosage of 100–250 mg/day. The largest improvement was the reduction in “dreams about combat trauma” in the IES-R (baseline: 2.9 ± 1.8 , 6 weeks: 1.9 ± 1.6 , 10 weeks: 2.0 ± 1.5). Bad dreams as measured by the SRRS did not respond significantly to treatment (baseline: 2.7 ± 1.9 , 6 weeks: 1.3 ± 1.7 , 10 weeks: 1.6 ± 1.6). No adverse effects of the medication were reported.

Gabapentin

The exact mechanism by which gabapentin influences nightmares, as well as much of its efficacy in other clinical disorders, is unknown. It was initially designed as an analog of GABA but does not have an agonist-like effect at either the GABA_A or GABA_B receptors nor does it affect GABA levels.⁷⁴ It binds to the $\alpha_2\delta$ subunits of the voltage-gated calcium channel, with greater affinity for the $\alpha_2\delta$ -1 than the $\alpha_2\delta$ -2 and no affinity for the $\alpha_2\delta$ -3 subunit. Through this mechanism, it inhibits excitatory neurotransmitter release although the exact molecular mechanisms are still undefined.⁷⁴

There is one retrospective case series of 30 consecutive veterans with PTSD who received adjunctive treatment with gabapentin in a range of 1–30 months for insomnia and nightmares.⁷⁵ Most of the subjects were concurrently taking antidepressants and some were also on antipsychotics and anxiolytics. Efficacy was assessed with the Clinical Global Impressions scale (CGI) ranging from no improvement/worsening of symptoms to marked improvement. The CGI was used to evaluate the combined effect on insomnia and/or nightmares with follow-up ranging from 1 to 36 months. Moderate or marked improvement was noted in 23 (77%) of the patients, of whom all showed improvement in insomnia and “most” also showed a non-specified decrease in frequency and/or intensity of nightmares. The mean gabapentin dose for those patients with moderate or marked improvement was 1344 ± 701 mg ($n = 23$) and for those with mild or no improvement was 685 ± 227 mg ($n = 7$). Gabapentin was generally well-tolerated. Reported side effects included mild sedation, excessive daytime sedation, mild dizziness, and one episode of nonspecific “swelling.”

Nabilone

Nabilone is a synthetic cannabinoid receptor agonist with antiemetic and analgesic properties. The action of nabilone on sleep architecture is unknown. A randomized placebo-controlled trial of nabilone reports the effect of this medication in the treatment of PTSD-associated nightmares.⁷⁶ A 16-week randomized placebo-controlled double-blind cross-over study assessed the effects of nabilone in Canadian male military personnel, ages 18 to 65, referred to a military trauma clinic, with a current diagnosis of PTSD as per DSM-IV-TR. PTSD-associated nightmares were assessed using CAPS.⁷⁶ Subjects were to have a CAPS recurrent distressing dreams item score of 5 or more the week before entering the trial. The dosage of nabilone was started at 0.5 mg and titrated to a maximum of 3 mg based on efficacy and tolerability. The mean reduction in nightmares as measured by the CAPS distressing dream item scores were -3.6 ± 2.4 and -1.0 ± 2.1 in the nabilone and placebo groups, respectively. Five out of 10 (50%) were much improved on nabilone versus 1 out of 9 (11%) on placebo. Nabilone was reasonably well-tolerated with the most common side-effects being dry mouth and headache (6 and 4 subjects, respectively). Cannabis at present is not a prescribable, FDA-approved medication and there is no available evidence to make a recommendation.

Phenelzine

Phenelzine is a potent monoamine oxidase inhibitor. There are two studies: one is a case series and the other is an open,

prospective trial of phenelzine, in the treatment of PTSD associated nightmares.^{77,78}

The case series consisted of 5 male veteran patients who were started on phenelzine and were followed up to 18 months.⁷⁷ Nightmares were assessed based on patients’ descriptions; no tools or diaries were used. The dosage of phenelzine varied between 45 and 75 mg. Phenelzine eliminated nightmares entirely within 1 month with no recurrence on long-term follow-up (up to 18 months) and 3 out of the 5 patients remaining nightmare-free without medication. No side effects were reported in this case series.

The second study was an 18-week, open prospective study that enrolled 25 male veterans with PTSD being treated with phenelzine.⁷⁸ Nightmares were assessed using the “traumatic dream” severity scale of 0–4. The dosage of phenelzine varied between 30 and 90 mg. There was an 18% fall in an average “traumatic dream” severity scale that just missed statistical significance ($P = .05$). Six patients stopped treatment within 8 weeks because of a lack of improvement. Treatment was ultimately discontinued in the remaining subjects because the initial improvement was minor or short-lived or reached a plateau felt to be sufficiently unsatisfactory to justify a change to an alternate medication. Reported side effects included dizziness, drowsiness, and malaise. Three patients withdrew early due to side effects. As a monoamine oxidase inhibitor, phenelzine can cause a hypertensive crisis if taken with sympathomimetic medications or with high tyramine-containing foods.⁷⁹

Prazosin

Prazosin is an alpha-1 adrenergic receptor antagonist that reduces CNS sympathetic outflow throughout the brain. Several CNS phenomena implicated in the pathogenesis of PTSD are regulated by alpha-1 adrenergic receptors including a number of sleep/nightmare phenomena.^{80,81} At least ten studies demonstrate the efficacy of prazosin in the treatment of PTSD-associated nightmares.^{81–92}

Two studies by Raskind et al. evaluated the efficacy of prazosin in reducing PTSD-associated nightmares in a total of 44 military veterans.^{81,82} A 20-week double-blind crossover trial compared the efficacy of prazosin versus placebo to reduce nightmares in 10 Vietnam veterans with PTSD and severe combat-trauma-related nightmares.⁸² All participants experienced frequent nightmares as determined by CAPS recurrent distressing dreams item (score of 6 or higher). The mean dosage of prazosin was 9.5 ± 0.5 mg/day. Prazosin was found to be superior to placebo on the CAPS recurrent distressing dreams item (pretreatment: prazosin 6.9 ± 0.9 , placebo 7.1 ± 0.9 ; posttreatment: prazosin 3.6 ± 2.8 , placebo 6.7 ± 1.6). Veterans who were responsive to prazosin frequently returned to their baseline nightmare intensity when prazosin was discontinued. Prazosin was well-tolerated in this sample. Only two subjects experienced mild orthostatic systolic blood pressure reductions and dizziness which resolved during the study. An 8-week randomized controlled trial compared the use of prazosin versus placebo in 34 veterans with chronic PTSD and intractable nightmares that were either unresponsive or only partially responsive to treatment.⁸¹ All subjects had scores ≥ 5 on the CAPS distressing dreams item. The mean daily dose

of prazosin was 13 ± 3 mg/day. The distressing dreams item decreased over 50% with prazosin as compared to 15% with placebo (pretreatment: prazosin 6.5 ± 1.0 , placebo 6.1 ± 1.0 ; posttreatment: prazosin 3.2 ± 2.6 , placebo 5.2 ± 2.2). Prazosin was generally well-tolerated except for several subjects who experienced transient dizziness; there were no falls or syncopal episodes.

An 8-week 3-arm RCT of 50 United States military veterans with PTSD-associated nightmares compared the effects of prazosin versus placebo on sleep disturbances and nightmare frequency.⁸³ Eligible participants scored ≥ 3 on CAPS item 2 and > 5 on the PSQI. The efficacy of a behavioral sleep intervention was also examined; however, those data will not be discussed here. The average final nightly dose at the end of treatment was 8.9 mg; effective doses ranged from 1 to 15 mg. Posttreatment decreases in the mean weekly nightmare frequency, as measured by sleep diary, were greater for the prazosin group than for the placebo group (pretreatment: prazosin 1.0 ± 1.1 , placebo 0.4 ± 1.1 ; posttreatment: prazosin 0.3 ± 0.8 , placebo 0.5 ± 1.1). The authors concluded that these changes did not support previous reports of reduced nightmare frequency, which may be attributable to the low nightmare frequency of the participants. No significant blood pressure changes or other side effects were noted.

A 7-week cross-over RCT compared the effects of prazosin versus placebo in civilians with PTSD and frequent nightmares.⁸⁴ All participants scored at least 4 out of 8 on the CAPS distressing dreams item. The mean dose of prazosin was 3.1 mg \pm 1.3 mg. Reductions in CAPS distressing dreams item from baseline were significantly greater for prazosin than placebo (pretreatment: prazosin 4.8 ± 1.7 , placebo 3.9 ± 2.3 ; posttreatment: prazosin 3.3 ± 2.3 , placebo 3.9 ± 1.9). Another 8-week 3-arm RCT in 100 civilian trauma victims diagnosed with PTSD compared the effect of prazosin against a placebo in the treatment PTSD-related nightmares.⁸⁵ Nightmare frequency decreased more in the prazosin group versus placebo (pretreatment: prazosin 2.42 ± 0.97 , placebo 2.48 ± 0.91 ; posttreatment: prazosin 0.85 ± 1.03 , placebo 2.30 ± 0.95).

In 2013, a 15-week randomized controlled trial of prazosin for combat trauma PTSD with nightmares was conducted in active-duty soldiers returned from Iraq and Afghanistan.⁸⁶ Prazosin versus placebo was administered at bedtime and was repeated mid-morning. Both doses were titrated based on nightmare response. The mean achieved bedtime dose of prazosin was 15.6 ± 6.0 in men and 7.0 ± 3.5 for women. Primary outcome measures were the nightmare item of the CAPS, PSQI, and the change item of the CGI. Several secondary outcome measures were also reported. The mean age of the treatment group was 30.0 ± 6.6 ($n = 32$) versus 30.8 ± 6.5 for the placebo group ($n = 35$). 22% of prazosin subjects were taking maintenance selective serotonin reuptake inhibitors compared to 37% in the placebo control group. Prazosin was significantly superior to placebo for all three primary outcome measures. The decrease in CAPS nightmare item was 3.1 ± 0.3 in the prazosin group and 1.2 ± 0.3 the placebo group; PSQI 5.6 ± 0.7 versus 2.8 ± 0.6 ; and CGI proportion markedly or moderately improved 64% versus 27% ($P < .001$, $P < .003$, and $P < .001$ respectively). There was a decrease in prazosin

response in participants receiving a selective serotonin reuptake inhibitor compared to those not taking selective serotonin reuptake inhibitors. For example, the total CAPS decreased by 30.1 ± 3.8 versus 9.6 ± 6.8 . Comparable results were present with the CAPS nightmare item and the PSQI but not with the CGI change item.

The efficacy of prazosin in the treatment of PTSD-associated nightmares was also demonstrated in a retrospective chart review⁸⁷ and 4 small, uncontrolled trials.⁸⁸⁻⁹¹ Due to the small size of these studies, relative to the body of literature supporting prazosin for the reduction of nightmares, the details are not discussed in this position paper.

In contrast to the above positive results, a recent publication has resulted in downgrading the recommendation for use of prazosin in nightmare disorder.⁹² A total of 304 participants with chronic PTSD and frequent nightmares were recruited from 13 Department of Veterans Affairs medical centers and were randomized to receive prazosin or placebo for 26 weeks. Dosage was escalated to a maximum of 20 mg. The mean dose was 14.8 ± 6.1 mg. Outcome measures included the CAPS distressing dreams item score, the PSQI, and the CGI score at 10 and 26 weeks of therapy. There was no significant difference in any outcome measure at either treatment interval. Of note, 78.3% of the prazosin group and 77.0% of the placebo group were receiving a maintenance dose of an antidepressant medication.

The Task Force agreed unanimously that it was appropriate to downgrade the recommendation regarding prazosin use because of the above contradictory study. At the same time, it is clearly apparent to clinicians that many patients respond very well to prazosin and this agent remains the first choice for pharmacologic therapy. There may be an interaction with antidepressant medications across these various studies which needs to be clarified.

Topiramate

Topiramate is a sulfamate-substituted monosaccharide anti-convulsant that has been used to treat various symptoms of PTSD and migraine headaches. The mechanism of action is unclear, but it appears to work by inhibiting various sodium and calcium channels, stimulating GABA-A receptors, inhibiting glutamate, and affecting carbonic anhydrase isoenzymes. There is one randomized placebo-controlled trial⁹³ and three case series⁹⁴⁻⁹⁶ evaluating the use of topiramate in populations with PTSD that recorded effects on nightmares.

A randomized placebo-controlled, double blind trial evaluated topiramate in 40 adult civilian PTSD patients over a 12-week period.⁹³ The frequency and intensity of nightmares was assessed using CAPS. Outpatients who received topiramate monotherapy ($n = 20$), started with 25 mg/day and titrated the dose up to effect or 400 mg/day as a maximal dose, experienced a non-significant decrease in total CAPS score, but twice as many patients receiving topiramate achieved remission as in the control group. The median final dose of topiramate was 150 mg/day.

A case series assessed the efficacy of topiramate in 35 civilian patients who suffered from PTSD primarily due to physical assault or unwanted sexual experience.⁹⁴ Follow-up ranged

from 1 to 119 weeks. Nightmares were assessed by the PTSD Checklist – Civilian Version (PCL-C). Topiramate dosage began at 12.5 to 25 mg daily and was increased in 25 to 50 mg increments every 3 to 4 days until a therapeutic response was achieved or the drug was no longer tolerated. The final dosage for 91% of full responders was 100 mg/day or less, but the range was 12.5 to 500 mg/day. Topiramate reduced nightmares in 79% of patients, with full suppression in 50%. Nine patients discontinued treatment due to side effects which included urticaria, eating cessation (most likely due to nausea), acute narrow-angle glaucoma, severe headaches, overstimulation/panic, emergent suicidal ideation, and memory concerns.

A second 12-week case series of 33 civilian outpatient adults with PTSD used the same titration of topiramate as the above study.⁹⁵ Nightmare frequency was assessed using the PCL-C. Ninety-four percent of patients with nightmares at baseline reported full cessation at the end of week 4. Full cessation was noted at dosages \leq 200 mg/day, with partial responses at dosages \leq 50 mg/day. Although there were no serious adverse events during the study, 21% discontinued the study due to significant adverse events.

Finally, the effect of topiramate on nightmare frequency was studied in 29 male subjects with combat-related PTSD.⁹⁶ Nightmare presence and weekly frequency were assessed using an in-house sleep-quality questionnaire. Topiramate was added to other pharmacologic therapies for PTSD beginning with dosages of 50 mg/day, and the dose was adjusted as clinically indicated to a target dose of 200 mg/day over 10–14 days. The prevalence of nightmares declined from 100% at baseline to 60% at 8 weeks of therapy ($P < .001$), and the frequency of nightmares declined from 3.97 ± 2.10 nights/week to 2.07 ± 2.28 nights/week ($P = .0043$). There were two serious adverse events recorded in two patients and five patients experienced other transient side effects.

Trazodone

Trazodone is a triazolopyridine derivative that has been used in the treatment of insomnia and nightmares in patients with PTSD.⁹⁷ A retrospective cohort study assessed the use of trazodone in 74 male patients from the Veterans Affairs system who were enrolled in a specialized 8-week inpatient unit for the treatment of PTSD.⁹⁷ All patients had previously received trazodone to treat insomnia or nightmares, and were surveyed on its effectiveness in decreasing the frequency or intensity of nightmares. Sixty patients were able to maintain an effective dose of trazodone, and reported decreased nightmare frequency from an average of 3.3 ± 1.7 to 1.3 ± 1.4 nights/week. The mean reported effective dose of trazodone was 212 mg/day. 60% of those subjects who continued trazodone experienced some side effect, particularly daytime sedation or dizziness. The other 14 participants discontinued treatment due to intolerable side effects including priapism (5 subjects), daytime sedation (5 subjects), more vivid nightmares (1 subject), dry mouth/sinuses (1 subject), muscle pain (1 subject), and severe agitation (1 subject).

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) act primarily as serotonin-norepinephrine reuptake inhibitors. In addition, many TCAs

also have high affinity as antagonists at the 5-HT₂, 5-HT₆, 5-HT₇, α_1 -adrenergic, and N-methyl-D-aspartate receptors, and as agonists at the sigma receptors, some of which may contribute to their therapeutic efficacy, as well as their side effects. The TCAs also act as potent antihistamines and anticholinergics. TCAs have been shown to suppress REM sleep and increase REM latency.

One small case series with one-year follow-up evaluated the efficacy of tricyclic antidepressants in the treatment of PTSD-associated nightmares in 10 Cambodian concentration camp survivors.⁹⁸ Nightmares were assessed using the posttraumatic stress disorder section of the Diagnostic Interview Schedule. The paper did not detail the length of treatment with each medication and each participant was on a different medication regimen, including imipramine as monotherapy (75–125 mg; 3 subjects), imipramine (150 mg) with phenelzine alone or phenelzine and doxepin and amitriptyline (2 subjects), amitriptyline (100 mg) with doxepin (1 subject), and doxepin alone (50–100 mg, 4 subjects). The two subjects who did not have any improvement in nightmares were either on doxepin (100 mg) or imipramine (150 mg) with doxepin (150 mg), phenelzine (30 mg bid), and amitriptyline (100 mg). In addition to medication, the patients also had monthly clinic visits to discuss ways to handle stress. Nightmares ceased in 4/10 patients and improved in another 4/10 patients with no worsening of nightmares. There were no reported medication side effects.

Nitrazepam and Triazolam

Nitrazepam and triazolam are benzodiazepine hypnotics with the former having a half-life of 16–38 hours and the latter having a half-life of less than 5 hours.

A single 3-day, double-blind, cross-over trial compared triazolam with nitrazepam in 40 patients with disturbed sleep.⁹⁹ It was not clear if the study population had history of nightmare disorder or PTSD. Each patient completed a questionnaire about sleep habits, including dreaming activity, prior to starting the study. On the day following the first and third nights patients completed additional sleep questionnaires. On the first night patients took either 0.5 mg triazolam or 5 mg nitrazepam, the second night was drug-free, and on the third night the patients took the alternative medication. Both drugs were equally effective at reducing the number of subjects who noted “unpleasant dreams,” from 23 prior to medication administration to 1 subject for nitrazepam and 2 subjects for triazolam. There was no difference in side effects, which were considered minor and consisted of morning sedation and difficulty concentrating in the morning.

Clonazepam

Clonazepam is a benzodiazepine that enhances the activity of GABA which is the major inhibitory neurotransmitter in the central nervous system. One randomized single-blind, placebo-controlled, crossover clinical trial reported on the ineffective role of clonazepam in the treatment of sleep disturbances associated with combat-related posttraumatic stress disorder.¹⁰⁰

A 5-week randomized, single-blind, placebo-controlled, crossover trial compared placebo with 1 mg of clonazepam at bedtime for one week followed by 2 mg at bedtime for another

week followed by a 1-week washout period before the placebo treatment, in 6 male veteran patients with combat-related PTSD.¹⁰⁰ Nightmares were recorded on sleep diaries upon awakening each morning throughout the trial. The occurrence, the number, and intensity of nightmares on a 0–4 scale were recorded. All 6 patients received the final dose of 2mg at bedtime. There were no improvements on either frequency (1.42 ± 0.52 versus 1.33 ± 0.45) or intensity of nightmares (2.15 ± 0.7 versus 2.06 ± 0.6) compared to placebo. Reported side effects did not differ from placebo.

Venlafaxine

Venlafaxine is a serotonin norepinephrine reuptake inhibitor that is indicated for treatment of mood disorders. The position statement that venlafaxine is not recommended for nightmares associated with PTSD is based on a single study that was a pooled analysis of 12 weeks of data from two multicenter, flexible-dose, randomized, parallel-group, double-blind studies of venlafaxine ER in 687 participants with PTSD.¹⁰¹ Distressing dreams were assessed with CAPS-17 at baseline and at week 12. Participants were randomized to receive venlafaxine ER (doses ranging between 32.5 to 300 mg/day) or placebo. The study showed no significant difference between the effects of placebo and venlafaxine ER in the CAPS-SX17 in the distressing dreams item (baseline: venlafaxine ER 4.08 ± 2.58 , placebo 3.82 ± 2.79 ; 12-week follow-up: venlafaxine ER 1.83 ± 2.40 , placebo 2.06 ± 2.61). No side effects were noted and there was no long-term follow-up.

AREAS FOR FUTURE RESEARCH

As discussed in the preceding sections, there are many studies of varying design regarding a wide variety of behavioral and pharmacological interventions for treatment of nightmare disorder. Currently, access to pharmacologic therapy is likely better than for behavioral or psychological therapies, but the evidence is not particularly stronger for pharmacologic treatments. Furthermore, confidence in the recommendation of prazosin has been downgraded based on the most recent literature. There is now a need for investigations to identify subsets of patients with prazosin responsiveness and to clarify interactions with other medications, particularly antidepressants.

The time is right for some well-designed comparative efficacy trials and for enhancing training and reimbursement for non-pharmacologic treatments. Another drawback of most studies is the inherent lack of a consistent or single objective measure to assess nightmares which prevents comparing studies head to head. Furthermore, existing literature largely focuses on nightmares associated with PTSD and it is unclear if the same treatment strategies apply to nightmares of different etiologies. In addition, the delivery of non-pharmacologic treatments, such as IRT, CBT, or other forms, should be standardized to ensure that equivalent therapies are provided to patients as described in studies. Future studies should emphasize well-designed RCTs with larger sample sizes for various pharmacological therapies, trials that directly compare pharmacotherapy and behavioral techniques, or combination treatments with medication and psychotherapy

for nightmares of different etiologies. The duplication and verification of results on a broader scale involving multi-center or registry approaches would also be beneficial. Data from such studies will assist clinicians in extrapolating data to determine optimal treatment approaches for individual patients.

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