The August 2010 issue of Journal of Clinical Sleep Medicine (Vol. 6, No. 4) included an article suggesting treatment recommendations for adult nightmare disorder. Although we appreciate the work by the authors, we were left with three basic concerns about the methodology utilized and results found. First, works providing evidence for some of the treatments were not reported in the original article. Second, search methodology in the original article was not used consistently at updated time points. Third, the original article only utilized results obtained from PubMed and did not consider other databases. The current study sought to replicate the methodology and compare findings as well as expand by equalizing search methodology across updated time points. The present study expands the original efforts further by conducting article searches again on PsycINFO. Consequent changes to evidence levels and recommendations are discussed.

Keywords: Nightmare disorder, nightmares, prazosin, levomepromazine, Nabilone, cognitive behavioral therapy, imagery rehearsal therapy, exposure relaxation, rescripting therapy, psychotherapy

Citation: Cranston CC; Davis JL; Rhudy JL; Favorite TK. Replication and expansion of “best practice guide for the treatment of nightmare disorder in adults”. J Clin Sleep Med 2011;7(5):549-553.
identified (64 fewer than stated in the original article – 1428). Because the pearling procedure was not replicated, 6 of the 57 articles identified by the authors were not identified; the remaining (51) articles were identified in our merged results. In addition, one article was identified in the search list that met inclusion criteria for review and grading. Two of these articles7,8 were also found in PI Searches.

**Method: Expansion**

We sought to expand the methods of Aurora and colleagues in several ways. First, in an effort to create consistency in methodology, we conducted the February 2010 search again (PIUPDATE), this time using key terms from Searches 1 and 2 with limits as used previously (Search 1, 2, and 3). Second, in order to expand the methodology further, we also conducted all searches in the PI database. A total of four search-erations were conducted on PI, three using the exact keywords and limits as used previously (Search 1, 2, and 3), and one using PI Search 1 and 2 again for articles published between March 2009 and February 2010 (PIUPDATE). The same selection, grading, and evidence level criteria was used.

**RESULTS: Expansion**

PMUPDATE Search 1 yielded 58 results, all of which were unique compared to the previous search conducted on “anxiety dreams.” PMUPDATE Search 2 yielded 9 results, all of which were found in PMUPDATE Search 1. Ultimately, PMUPDATE searches provided 58 new articles. Of those, 2 articles7,8 met criteria for inclusion.

PI Search 1 yielded 284 results and PI Search 2 yielded 16 (all of which were found in search one). PI Search 3 yielded 93 unique results (over and above Searches 1 and 2). After merging findings and accounting for overlap, 389 articles were identified. Of those, 31 met criteria for review and grading. After accounting for overlap between PI and PM Searches, 9 new articles6,9-16 were identified (including the article missed in PM Searches).

PIUPDATE Search 1 yielded 17 results, all of which were unique over and above those found in PI Searches 1 and 2. PIUPDATE Search 2 resulted in 2 results, both of which were included in PIUPDATE Search 1. Ultimately, PIUPDATE searches provided 17 new articles identified. Of those, 3 articles7,8,17 met criteria for review and grading. Two of these articles7,8 were also found in PMUPDATE.

**DISCUSSION**

This report set out to address basic methodological concerns with the recent article titled “Best Practice Guidelines for the Treatment of Nightmare Disorder in Adults.”1 Our first concern was brought to light by the omission of a 2007 randomized clinical trial of one of the nightmare treatments considered in the article. Because one article was known to be omitted, we were concerned that others may also have been missed. For this reason, we conducted a replication of the methodology described by Aurora and colleagues.

Overall, our replication resulted in similar findings with some exceptions. Utilizing the same search terms, limits, and database, we identified 51 of the articles used in the original article that met inclusion criteria for review and grading. We did not replicate the pearling procedure; thus 6 articles included in the original were not identified in the current study. However, in addition to the case series of ERRT18 found in both PM Searches 1 and 2, Aurora and colleagues missed the 2007 randomized controlled trial (RCT) of ERRT,6 which was found in both searches as well.

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**Table 1—Keywords used by search**

<table>
<thead>
<tr>
<th>Search</th>
<th>Keywords</th>
<th>Limits*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search 1</td>
<td>([Nightmares OR nightmare OR nightmare disorder OR nightmare disorders OR recurrent nightmares) AND (treatment OR drug therapy OR therapy)]</td>
<td>Yes</td>
</tr>
<tr>
<td>Search 2</td>
<td>[Post-traumatic stress disorder AND (nightmare disorder OR recurrent nightmares OR nightmares) AND treatment]</td>
<td>Yes</td>
</tr>
<tr>
<td>Search 3</td>
<td>“anxiety dreams”</td>
<td>No</td>
</tr>
</tbody>
</table>

*Search limits set to: English language only, human subjects, and adults (19yrs. And older).

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**Table 2—Summary of PICO questions**

1. Do patients with nightmares demonstrate clinical response to noradrenergic blocking medications compared with natural history or other medications?
2. Are there other medications to which patients with nightmare disorder demonstrate clinical response compared with natural history or other medications?
3. Do patients with nightmare disorder demonstrate clinical response to cognitive behavioral therapies and, if so, which are the most effective?

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**Table 3—AASM classification of evidence**

<table>
<thead>
<tr>
<th>Evidence Levels</th>
<th>Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>High quality randomized clinical trials with narrow confidence intervals</td>
</tr>
<tr>
<td>2</td>
<td>Low quality randomized clinical trials or high quality cohort studies</td>
</tr>
<tr>
<td>3</td>
<td>Case-control studies</td>
</tr>
<tr>
<td>4</td>
<td>Case series or poor case-control studies or poor cohort studies or case reports</td>
</tr>
</tbody>
</table>

Our second concern was that the search methodology utilized by Aurora and colleagues in their February 2010 update was inconsistent with their previous searches. Rather than using search terms from Searches 1 and 2, the authors reported searching only “anxiety dreams.” In an effort to address this issue of consistency, we conducted an additional search on the PM database using search terms and limits from Searches 1 and 2. Using the full set of search terms in the February 2010 search, we identified a pilot study of ERRT with combat veterans conducted by Swanson, Favorite, Horin, and Arnedt and another study examining IRT in veterans conducted by Lu, Wagner, Van Male, Whitehead, and Boehnlein, as we found in PMUPDATES Search 1 and 2.

Our third concern was the use of only the PubMed (PM) database to identify articles, particularly PsycINFO (PI). Although there is some overlap in journal indexing between the two databases, PI has been shown to provide unique, clinically relevant results over and above PubMed. With this in mind, we conducted all searches again using PI. After accounting for overlap in results between databases and searches, a total of 9 articles were identified as meeting criteria for review and grading. This suggests that future searches should include PI to maximize the chances of finding all relevant works.

The following represents additions and changes to recommendation levels of treatments from those listed in Aurora and colleagues based on this replication and expansion. Recommendation level was determined by considering all qualified articles for a given treatment and based on the AASM classification of evidence as used by Aurora and colleagues (see Table 4). Treatments and approaches that did not differ between Aurora and colleagues and the current review are not listed; readers are directed to the “Best Practice Guide for the Treatment of Nightmare Disorder in Adults” for further reference.

**Medication Treatments**

**Prazosin (Level A)**

Prazosin is a α1-adrenergic receptor antagonist originally released as an antihypertensive. It is thought that prazosin works in the treatment of posttraumatic nightmares due to its effect of reducing noradrenergic activity in the brain that has been found to be elevated in individuals diagnosed with PTSD. In addition to the evidence supporting this medication as a Level A treatment for nightmares, our replication and expansion identified 2 Level 4 studies. These studies evaluated the use of prazosin for treating posttraumatic nightmares in 10 Vietnam combat veterans (mean age = 53) and 22 military veterans with PTSD. These articles indicated prazosin was superior to placebo in improving nightmares, sleep, overall PTSD symptom severity, and moderate improvement in trauma-related nightmares and non-nightmare distressed awakenings. Length of treatment ranged from 3 to 20 weeks, with average dosages ranging from 9.5 mg/day to 9.6 mg/day. In both studies, prazosin was well tolerated by participants with few reports of adverse effects (e.g., mild orthostatic hypotension and/or dizziness). Taken together these articles provide further support for the use of prazosin as a Level A treatment.

**Levomepromazine (Level C)**

Levomepromazine is an antipsychotic medication used to treat schizophrenia that carries sedative and hypnogenic effects. Only one Level 4 study was found using this medication in the treatment of posttraumatic nightmares. Aukst-Margetić and colleagues reported observed reduction in sleep-related problems, including nightmares, using levomepromazine in 21 combat veterans with severe PTSD. Participants ranged in age from 30 to 68 (M = 42.66, SD = 8.58) and dose of levomepromazine ranged from 25-100 mg (M = 47.05 mg, SD = 27.78 mg). Statistically significant improvements were observed for recurrent distressing dreams, arousal, total sleep hours, sleep latency, and subjective sleepiness after waking. The authors reported no adverse effects resulting in the discontinuation of medication. This single study should be taken as pilot data and it is important to recognize that the use of levomepromazine is currently only approved for treatment of schizophrenia. This medication may be considered for use in severe cases of PTSD in combat veterans (as such is the sample examined in this study) and treatment-resistant nightmares (i.e., other, well-established Level A approaches have not worked). Because only one, small open-label trial is available for support this medication may be considered Level C, though with caution.

**Nabilone**

Nabilone is a synthetic endocannabinoid receptor (CB1 and CB2) agonist originally approved for the treatment of nausea and vomiting associated with cancer chemotherapy. In a double-blind, placebo-controlled, randomized trial, Nabilone at a dose of 5 mg/day for 3 weeks was superior to placebo in improving nightmares, sleep, overall PTSD symptom severity, and moderate improvement in trauma-related nightmares and non-nightmare distressed awakenings. Length of treatment ranged from 3 to 20 weeks, with average dosages ranging from 9.5 mg/day to 9.6 mg/day. In both studies, prazosin was well tolerated by participants with few reports of adverse effects (e.g., mild orthostatic hypotension and/or dizziness). Taken together these articles provide further support for the use of prazosin as a Level A treatment.

**Table 4—Levels of recommendation**

<table>
<thead>
<tr>
<th>Term</th>
<th>Level</th>
<th>Evidence Levels</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommended / Not recommended</td>
<td>A</td>
<td>1 or 2</td>
<td>Assessment supported by a substantial amount of high quality (Level I or II) evidence and/or based on a consensus of clinical judgment</td>
</tr>
<tr>
<td>Suggested / Not Suggested</td>
<td>B</td>
<td>1 or 2—few studies 3 or 4—many studies and expert consensus</td>
<td>Assessment supported by sparse high grade (Level I or II) data or a substantial amount of low-grade (Level III or IV) data and/or clinical consensus by the task force</td>
</tr>
<tr>
<td>May be considered / Probably should not be considered</td>
<td>C</td>
<td>3 or 4</td>
<td>Assessment supported by low grade data without the volume to recommend more highly and likely subject to revision with further studies</td>
</tr>
</tbody>
</table>

and vomiting related to chemotherapy.\textsuperscript{20} It is proposed that endocannabinoids have the effect of reducing arousal and stress response by acting on the central nervous system to regulate amygdala, hypothalamic-pituitary-adrenocortical (HPA) and hippocampal activity thereby reducing corticotrophin-release factor (CRF) through CB\textsubscript{1} and CB\textsubscript{2} receptor binding.\textsuperscript{16,21} Nabilone was not identified as a treatment in the Aurora article, as we only found 1 Level 4 article\textsuperscript{16} exclusively in the PsycINFO search. Fraser\textsuperscript{16} conducted a retrospective chart review of 47 individuals (27 women, 20 men) with chronic PTSD (2-30 year course) and treatment-resistant trauma-related nightmares. Nightmares were considered treatment-resistant if no improvement was observed after treatment with antidepressants and hypnotics. Average age of patients was 44 ($SD = 9$), average dose of nabilone was 0.5 mg per night (effective range 0.2-4.0 mg per night – 0.25 mg starting dose recommended), and average length of treatment was between 4 and 12 months. Of the 47 patients, 34 reported reduction in nightmare severity or no longer experienced nightmares. However, considerable withdrawal effects were observed in all but four patients when nabilone was discontinued. The result of withdrawal was return of nightmares within the first two nights with control regained after reinitiating nabilone. These individuals were instructed to discontinue nabilone after 6 months; however, outcome is unknown as the reinitiated treatment period was ongoing at the time of the article’s publication. Mild to moderate side effects, including memory and concentration problems, dizziness, and headaches, were observed in 28% of the sample. Due to limited empirical evidence to date, and the finding that the majority of patients receiving nabilone were unable to discontinue without nightmare recurrence, this medication cannot be recommended at this time. Further empirical investigations through larger double-blind, placebo-controlled trials is needed.

**Psychological Treatments**

**Imagery Rehearsal Therapy (IRT; Level A)**

IRT is a psychological treatment approach targeting the treatment of trauma related nightmares. The mechanism of change is thought to reside in recalling, scripting, changing (theme, story line, ending, or other part) to be more positive, and rehearsing the rewritten dream in an effort to displace the disturbing content of the actual dream. In addition to the articles identified by Aurora and colleagues,\textsuperscript{1} our replication and expansion identified 1 Level 2\textsuperscript{15} and 3 Level 4\textsuperscript{7,10,17} studies. The Level 2 study\textsuperscript{15} examined the efficacy of IRT in individuals experiencing at least one nightmare per week for at least one year. Fifty-eight individuals (45 women, 13 men) were included and randomly assigned to one of two groups, IRT treatment ($n = 39$) or waitlist ($n = 19$). Results indicated significant reduction in the number of nights with nightmares and total number of nightmares as well as improvement in overall sleep quality for individuals in the active treatment group with gains maintained at 3-month follow up.

The 3 Level 4\textsuperscript{7,10,17} studies together examined the use of IRT in a total of 37 military veterans with PTSD and nightmares. These studies did not include comparison or waitlist control groups therefore superiority could not be established nor could other influences on internal reliability be examined. However, all 3 studies lend further support to IRT as an efficacious treatment for nightmares as well as showing evidence for improvement in military populations. Taken together and in combination with the findings in Aurora and colleagues\textsuperscript{1} there is sufficient evidence for the use of IRT as a first line treatment for nightmares, thus IRT remains Level A.

**Exposure, Relaxation, and Rescripting Therapy (ERRT; Level B)**

ERRT is a psychological treatment based on IRT, exposure therapies for posttraumatic stress disorder, and insomnia treatments. The mechanism of change is currently unknown, but thought to be related to exposure to the feared content of the nightmare, mastery through rescripting the nightmare, and modifying maladaptive sleep habits. In addition to the case series identified by Aurora and colleagues, our replication and expansion identified 1 Level 2\textsuperscript{9} and 1 Level 4\textsuperscript{8} study examining the efficacy of ERRT.

The Level 2 study\textsuperscript{9} presented data from an RCT of ERRT in a community sample. Forty-nine participants (40 women, 9 men; Mean age = 40, $SD = 12$) were invited to treatment; 6 refused to participate, and the remaining 43 were randomly assigned to ERRT treatment ($n = 21$) or waitlist control group ($n = 22$). Participants were screened for inclusion over the phone and invited to participate if eligible. To be included, all participants had to be ≥ 18 years of age; have experienced a traumatic event; were experiencing at least 1 nightmare per week for the previous 3 months; and did not have a history of psychosis, active suicidality, recent parasuicidal behaviors, or current substance dependence. Treatment was provided in 3 consecutive 2-hour weekly sessions in individual or group format, and participants were evaluated at 1 week, 3 months, and 6 months post-treatment. Participants assigned to the waitlist group were not contacted during the 3-week treatment period. At 1-week follow up, the active treatment group showed significant improvement on number of nightmares in the previous week, number of nights with nightmares, nightmare severity, PTSD diagnosis, number of PTSD symptoms, PTSD symptom severity, number of sleep problems, restfulness upon awakening, and depression. These treatment gains were maintained at 6-month follow up. Small sample size and use of waitlist control rather than active comparison group relegates this study to Level 2.

The Level 4 study\textsuperscript{8} presented pilot data on 10 combat veterans with PTSD, insomnia, and nightmares. All participants were male, and the average age was 59 ($SD = 4$). Participants were evaluated pre- and post-treatment, and ERRT was provided in ten 90-minute group sessions in combination with components of CBT-Insomnia. Results indicated a strong effect for ERRT at post treatment, with significant improvement on sleep efficacy, sleep latency, mid-sleep awakening after onset, total hours of sleep time, weekly nightmare frequency and severity, overall sleep quality, and insomnia severity.

With regard to AASM classification as used by Aurora and colleagues, ERRT meets, at minimum, evidence level 2. Further, with regard to level of recommendation, at the time of their searches the limited number of studies may indicate Class B “Suggested” at minimum.

It is important to consider some limitations in the article by Aurora and colleagues, which subsequently impact the present replication and expansion. One such limitation is the use of the
term “nightmare disorder” as suggested in the original article. There appears to be a confound between trauma-related nightmares in which the sleep disturbance occurs exclusively during the course of a mood or anxiety disorder (e.g., PTSD) and non-trauma related nightmare disorder, in which the sleep disturbance does not occur as a result of another disorder (see the Diagnostic and Statistical Manual of Mental Disorders [DSM-IV-TR], p. 631). The original article appears to use the two definitions interchangeably and clustered treatment evidence across both versions. As a result of replication, the present report did not discriminate between the definitions.

Additionally, the current and original articles are intended to provide a review of treatments for nightmares and do not intend to supersede APA task force recommendations, though there is no such recommendation for nightmare treatment at this time. It is fair to say that such taskforce reports are not as frequently published or disseminated, thus the current scientific support for treatments are not always known. These articles are meant to guide practice according to the current state of the literature.

Ultimately, we believe that this report provides additional support and improved methodology to the best practice guide by Aurora and colleagues. It is our view that a best practice guide must consider multiple sources of scientific literature (e.g., PsycINFO in addition to PubMed). In this respect, the present report provides an additional source that concurs with and expands on the original best practice publication. It is hoped that these articles together will provide a literature-informed guide for treating adults suffering from nightmares.

REFERENCES


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