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Nightmare Disorders: Pharmacotherapy or Psychotherapy as The First Line Treatment?

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ABSTRACT

Nightmares are almost an ubiquitous phenomenon but only nightmare disorders would need to be treated. Nightmare disorders result from a variety of causes including posttraumatic stress disorder (PTSD), psychiatric disorders, substance abuse, or idiosyncrasy. Nightmare disorders can be treated by either pharmacotherapy or psychotherapy. We performed literature search to explore eighteen possible pharmacotherapies and eleven possible psychotherapies for nightmare disorders to identify the best pharmacotherapy and psychotherapy through an evidence based approach. For PTSD-related nightmare disorders, topiramate as the first line and nabilone as the second line pharmacotherapy whereas cognitive behavior therapy, imagery rehearsal therapy (IRT), and exposure, relaxation, and rescripting therapy as the appropriate psychotherapies are recommended. For non-PTSD related nightmare disorders, triazolam or nitrazepam as the first line pharmacotherapy and IRT as the psychotherapy of choice are recommended. We then compared between all pharmacotherapies and psychotherapies to identify the best treatment for nightmare disorders in patients with and without post-traumatic stress disorder. For PTSD related nightmare disorders, pharmacotherapy is prioritized over psychotherapy. For non-PTSD related nightmare disorders, either pharmacotherapy or psychotherapy can be offered as the first line treatment.

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Introduction

Almost every person has experienced nightmares, but to be qualified for nightmare disorder, one has to have repeated nightmares that cause functional impairment in daily life [1]. A variety of etiologies can lead to nightmare disorder, including post-traumatic stress disorder (PTSD), psychiatric diagnoses such as anxiety, depression, and schizophrenia, causes for sleep deprivation such as sleep apnea, periodic limb movements of sleep, and insufficient sleep syndrome, substance misuse, drug withdrawal, alcohol abuse, and idiosyncrasy. The true prevalence of nightmare and nightmare disorder is unknown for no universal diagnostic criteria exists [2]. Nightmares occur more frequently in children and most do not require treatment, whereas nightmare disorder in adults often deserves attention as one's work and social life can be severely affected. The treatment options are pharmacological or psychological, namely, pharmacotherapies or psychotherapies. In this article, we analyzed whether pharmacotherapy or psychotherapy should be prioritized to treat nightmare disorder in adults through an evidence-based approach. We performed literature searches for "nightmare disorder" and "nightmare" in Pubmed (https://pubmed.ncbi.nlm.nih.gov/) to investigate all the germane studies on nightmare treatment for adults.

Pharmacotherapy

Numerous pharmacotherapies were derived through our literature search. These medications can be further categorized according to the main indication:

1. Anxiolytic: Prazosin, Clonidine, and Benzodiazepines.
2. Anti-Depressant: Selective Serotonin Reuptake Inhibitor (SSRI), Serotonin and Norepinephrine Reuptake Inhibitor (SNRI), Tricyclic Antidepressants (TCA), Monoamine Oxidase Inhibitors (MAOI), and Trazodone.
3. Atypical Antipsychotic.
4. Neuropathic Analgesic: Gabapentin, Nabilone, Topiramate.
5. Others such as cyproheptadine and tamsulosin.

Anxiolytic

Prazosin

Numerous smaller studies revealed effectiveness of prazosin, an alpha-1 adrenergic receptor antagonist, in reducing PTSD-related nightmares in the past that mounted up to a meta-analysis by Hudson et al. that also revealed consistent results via combining 11 studies with 4 open-label, 3 placebo-controlled, and 4 retrospective cohorts [3]. Nevertheless, a large-scale, double-blind randomized controlled trial (RCT) of 304 participants showed that prazosin did not significantly alleviate distressing dreams or improve sleep quality, and it had no substantial impact on nightmare frequency and intensity [4].

Clonidine
Two small prospective studies disclosed positive results that clonidine decreased nightmares in 7 out of 9 patients with PTSD when used alone and dreams in 4 out of 5 insomniac patients as adjunctive to atenolol, yet there is no RCT to support the benefit [5,6].

Benzodiazepine
Both triazolam at 0.5 mg and nitrazepam at 5 mg demonstrated effectiveness in reducing nightmare activities and alteration of the dream characteristics in a double-blind, cross-over RCT with similar side effect profiles among the patients diagnosed as nightmare disorder, whereas clonazepam failed to improve nightmares from combat-related PTSD in a single-blind, cross-over RCT containing six patients [7,8].

Anti-Depressants

Fluvoxamine (SSRI)
One open-label trial monitored 21 combat veterans with PTSD and it was discovered that the trauma-associated nightmares were decreased remarkably while the reduction in generic unpleasant dreams was only modest after receiving a 10-week fluvoxamine course [9].

Venlafaxine (SNRI)
Venlafaxine has been used to treat PTSD with marginal effectiveness [10]. Nonetheless, its side effect actually includes an increase in realistic nightmares [11]. A pooled analysis of 2 RCTs concluded that venlafaxine extended release form failed to reduce the distressing dreams in PTSD [12].

TCAs
No relevant RCT is available, whereas TCA was found to decrease the frequency of dream recall and reshape toward positive dreams in a case series composed of 46 reports, yet TCA discontinuation predisposes to nightmares [13]. Meanwhile, emotional positivity was associated with symptomatic relief when depressive patients took trimipramine for nightmares [14].

Phenalzine (MAOI)
Evidence supports that phenelzine withdrawal may lead to nightmares, but there has been no RCT to explore phenelzine for nightmare control [13]. One open-label prospective study on combat veterans with PTSD showed nightmare reduction who received phenelzine [15].

Trazodone
Trazodone lowered nightmares from 3.3 to 1.3 nights weekly ($p<0.005$) as well as improved the sleep quality ($p<0.005$) in a survey of 74 patients with PTSD [16]. Another prospective study on veterans with PTSD revealed 44/46 reporting fewer nightmares when taking trazodone but 9/74 developed priapism [17]. Nightmare reduction was also seen in major depressive disorder and advanced cancer [18,19]. Yet again, no RCT is available.

Atypical Antipsychotic

Aripiprazole
Four out of 5 veterans with PTSD reported improvement on nightmares in a case series study while the other trials using aripiprazole to treat patients with PTSD did not monitor for nightmare quantities [20].

Olanzapine
All 5 patients with refractory combat-related PTSD experienced nightmare improvement in a case series study at 10-20 mg daily without adverse events [21]. Another double-blind RCT showed adding olanzapine to SSRIs led to subjective nightmare relief in refractory combat-related PTSD, albeit the sample size was only nineteen [22]. Similar outcomes were seen in another case series study of 7 patients taking olanzapine as adjunctive for PTSD-related nightmares [23].

Risperidone
Nocturnal risperidone at 0.5 to 3 mg could decrease frequency and severity of nightmares for combat-related PTSD in a case series study of four patients [24]. Similar result was observed in another case series study of seven PTSD patients receiving low dose (0.5-2 mg) at night, but nightmares rebounded between 4-12 weeks for unclear reasons [25]. Tachyphylaxis may be the explanation.

Neuropathic Analgesic

Gabapentin
One retrospective, case series study reported that more than 77% of the 30 patients with PTSD had lesser frequency of nightmares after taking gabapentin at 300-3600 mg/day, though no RCT is available [26].

Nabilone
A double-blind RCT on 10 military staff with PTSD and refractory nightmares showed nabilone, a synthetic cannabinoid, could significantly decrease the frequency and intensity of nightmares ($p=0.03$) via a titratable dose from 0.5 to 3 mg over 7 weeks [27].

Topiramate
One double-blinded RCT specifically addressed the efficacy of topiramate at 150 mg daily on nightmares whereas the other studies assessed if topiramate improved non-nightmare PTSD symptoms. Significant nightmare reduction ($p = 0.04$) was observed among the civilians with PTSD receiving topiramate and no severe side effect was reported [28]. An open-label prospective study also on civilians with PTSD reported nightmares were lessened in 79% and completely stopped in 50% when patients took either topiramate alone or as add-on, with glaucoma reported in 1 out of 35 patients [29].

Others

Cyproheptadine
Contrary to two previous case reports demonstrating positive results, an open-label prospective trial including 36 veterans with PTSD showed cyproheptadine not only ineffectively reduced nightmares but 7 of them discontinued it for unbearable side effects [30-32].

Tamsulosin
Like prazosin, tamsulosin is also an alpha-1 adrenergic blocker. A pilot double-blind, cross-over RCT recently exhibited improvement in nightmare frequency and intensity toward statistical significance ($p = 0.065$) at 0.4 mg daily [33].

Discussion
Several features were appreciated from these studies:

1. Many medications did not have RCTs. The internal validity of these non-RCT studies was uncertain.
2. Their sample sizes were mostly small, so both the external validity and reliability could be affected. The low statistical

power from small sample size might also fail to detect the efficacy nuance if it was present.

3. There are many causes for nightmare disorder, but most studies were conducted on patients with PTSD, making it difficult to apply the results to the non-PTSD populations.
4. Patients with nightmare disorder often take concurrent medications for other indications that exert effects on nightmares, thus the true efficacy of the investigated medication can be challenging to recognize.
5. Studies chose various criteria to recruit patients with nightmare disorder. Diagnostic and Statistical Manual of Mental Disorders (DSM) and International Classification of Sleep Disorders (ICSD) were adopted by different researchers. Even for the same DSM or ICSD, there were multiple updated versions throughout the years. Yet, some studies used participants' subjective nightmare complaints for study inclusion criteria. The results from different studies hence are not easily comparative or additive.

For these 18 medications, unless none of the other substitutable medications has RCT data available for a positive efficacy, the ones without RCTs are not recommended due to the lack of solid validity, which includes clonidine, fluvoxamine, TCAs, phenelzine, trazodone, aripiprazole, risperidone, gabapentin, and cyproheptadine. In addition, clonazepam and venlafaxine both failed to exhibit significant efficacy in decreasing nightmare severity or frequency compared to controls, so both will not be recommended either.

Prazosin had long been recommended as the drug of choice for PTSD-related nightmare disorder, as at least 10 smaller RCTs beforehand and the meta-analysis revealed the efficacy on nightmare amelioration, until the RCT by Raskind et al. presented the opposite data [3,4]. As this RCT had the largest sample size among all the prazosin studies, we suggest that prazosin should not be recommended to treat nightmare disorder until further rigorous study provides alternative guidance. Of note, most participants in this RCT also took concurrent antidepressants, which might affect the potency of prazosin, hence the relationship in between warrants further research for clarification as this might affect the efficacy size.

Triazolam and nitrazepam are of value for their efficacy toward nightmares as both were validated via RCT, and the study participants were civilians with disturbed sleep rather than merely the patients with PTSD. Therefore, they are both considered as the first line pharmacotherapy for non-PTSD related nightmare disorders. Also, these two are the only medications studied on the patients without PTSD in RCTs so far [34]. Triazolam nevertheless appeared more effective in improving sleep quality for patients who also complained of disturbed sleep [7]. Olanzapine successfully reduced refractory PTSD-related nightmares in an RCT as an adjunctive to SSRI, yet no RCT investigated olanzapine alone for nightmare disorder, so we propose olanzapine as an adjunct for PTSD-related refractory nightmares. Albeit the sample sizes were small, nabilone and topiramate both displayed efficacy in RCTs for PTSD-related nightmares, although the benefited population was different. Given the participants in the study were not the refractory cases, topiramate is the candidate for the first line medication for PTSD-related nightmares. Nabilone, on the other hand, showed efficacy for refractory nightmares, so it should be used as second-line instead. Tamsulosin showed promising results in preliminary RCT as well, but a larger trial is required to verify if the efficacy can truly achieve statistical significance. It is also worth reporting that none of these five medications we recommend demonstrated substantial side effects in RCTs.

Regarding the aforementioned medications that did not go through RCTs, we propose that they may be considered if a patient has PTSD-related nightmares and other concomitant medical conditions that both can be treated by the same medicine. For example, fluvoxamine or trazodone can be prescribed to PTSD-related nightmares with concurrent depression, while veterans with neuropathic pain and nightmares from combat-related PTSD may benefit from gabapentin.

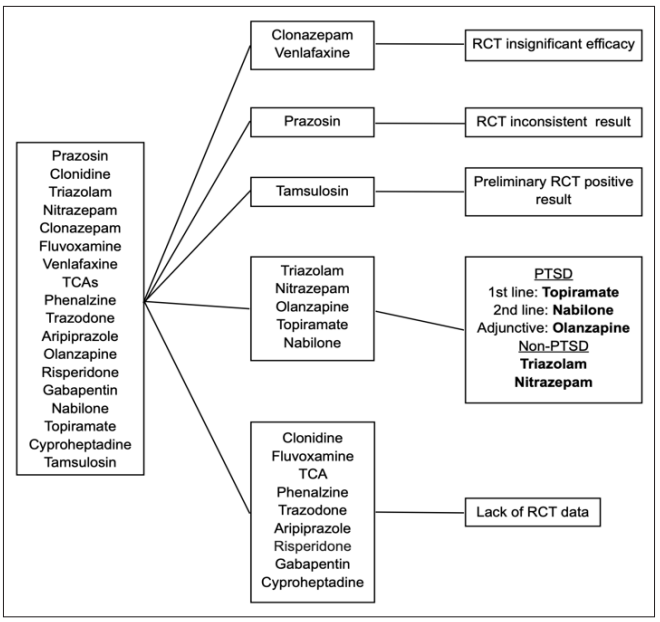

Figure 1: The workflow to sort out the valid Pharmacotherapies

Psychotherapy

The available psychotherapies for nightmare disorders via our Pubmed search were cognitive behavior therapy (CBT), cognitive behavior therapy for insomnia (CBT-I), lucid dreaming therapy (LDT), imagery rehearsal therapy (IRT), self exposure therapy (SET), exposure, relaxation, and rescripting therapy (ERRT), systematic desensitization (SD), eye movement desensitization and reprocessing (EMDR), progressive deep muscle relaxation (PDMR), sleep dynamic therapy (SDT), and hypnosis. As we have noticed a lot more studies on psychotherapies than pharmacotherapies, considering the compelling evidence of validity, only RCTs were included here. The RCTs for combined psychotherapies were also excluded due to word limits.

Cognitive Behavior Therapy

CBT includes various techniques to adjust one's distorted thoughts, behaviors, or emotions. An RCT involving 355 women with concomitant PTSD and substance use revealed no decrease in nightmares with CBT [35]. The other RCT of 227 elderly revealed the frequency of bad dreams decreased significantly by CBT among the patients with generalized anxiety disorder [36]. Another RCT of 171 subjects in which cognitive processing therapy (CPT), a CBT method, substantially improved nightmare severity among the women with PTSD from sexual assault on a 5-10 year follow up [37].

Cognitive Behavior Therapy for Insomnia

CBT-I is a modified CBT that specifically targets patients with sleep disturbance. Two RCTs with different participants sized at 31 and 108 showed significant improvement in nightmares by CBT-I in PTSD [38,39]. Another RCT of 45 patients with PTSD exhibited nightmare mitigation via CBT-I, though not statistically significant, yet the effect lasted for 6 months [40]. However, a

larger RCT with 238 subjects revealed digital CBT-I did not affect the frequency of nightmares in adult insomnia [41]. Meanwhile, contradictory results when adding IRT to CBT-I were observed on different RCTs in PTSD, while combining CPT with CBT-I displayed nightmare reduction [38,39,42-44].

Lucid Dreaming Therapy

A pilot RCT of 8 participants diagnosed with nightmare disorder by DSM-IV criteria demonstrated substantial efficacy of LDT in reducing the nightmare frequency and individual LDT was more effective than group LDT [45]. Another RCT revealed that LDT as an adjunct to Gestalt therapy, a form of psychotherapy, did not further reduce nightmare frequency for nightmare disorders diagnosed by ICSD-2 [46].

Imagery Rehearsal Therapy

More RCTs were identified for IRT than other psychotherapies and the results were mostly consistent among these trials. A same group conducted four consecutive smaller RCTs from 1992 to 1996 on volunteers with chronic nightmares who were followed between 3 to 30 months and all four showed significant reduction in nightmare frequency and number after receiving IRT compared to cohorts [47-50]. Two RCTs for IRT on PTSD-related nightmares first came in 2001 with different subject backgrounds: One from survivors of sexual assault, conducted by the same aforementioned Karkow group, and the other from combat veterans [51,52]. Both again revealed significant decreases in nightmares through IRT. The same group that worked with combat veterans published another RCT in 2003 reporting that IRT continued to retain efficacy on reduction of nightmare frequency and intensity at 12-month follow-up [53]. Moreover, Germain reported that IRT improved both retrospective and prospective nightmare frequency through polysomnogram-assisted RCT, which aimed to reduce subjectivity in participant reportage [54]. In 2010, two contrary trial results were presented that IRT showed significant reduction in nightmare frequency compared to recordings on the participants recruited from nightmare website, while IRT had no effect in decreasing nightmare frequency for the veterans with PTSD [55,56]. For the nightmares associated with psychiatric disorders, two RCTs were performed. One showed nightmare reduction by IRT among the patients with major depressive disorder or PTSD, as well as the primary nightmare sufferers [57]. The other enrolled 90 subjects based on DSM-IV criteria as psychiatric disorders and the results revealed significant decrease in nightmare frequency and distress [58].

Self-Exposure Therapy

The frequency rather than the intensity of nightmares decreased significantly after 6 months by SET compared to self-relaxation in an RCT consisting of 206 participants with recurrent nightmares [59]. In another trial of 20 subjects, SET instead remarkably reduced the frequency and intensity of nightmares in patients with recurrent nightmares after a 4-year follow-up [60].

Exposure, Relaxation and Rescripting Therapy

ERRT is derived from IRT, also a modified CBT. Significant decrease in the frequency and severity of nightmares among patients with PTSD was observed in at least four RCTs of various sample sizes from 19 to 70 participants, and one of them concluded no difference in the effect size with or without nightmare exposure and rescripting [61-64].

Systematic Desensitization

A prospective RCT of 28 subjects with chronic nightmares showed SD lowered nightmare frequency at 7-month follow-up, while the other RCT with similar scale (32 participants) and subject demographics revealed SD also significantly decreased nightmare intensity at 25-week follow-up [47,65]. Another RCT of 29 volunteers with recurrent nightmares nonetheless showed favorable but insignificant reduction in nightmare frequency and intensity by SD at 4-week follow-up [66].

Eye Movement Desensitization and Reprocessing

There is no RCT available for EMDR. One prospective study nevertheless disclosed improvement on nightmare severity ($p<0.01$) in PTSD [67].

Progressive Deep Muscle Relaxation

One old RCT was identified in which the intensity of nightmare rather than the frequency was reduced more at the 25th week among the participants with nightmare complaints receiving PDMR, yet the favorability did not reach statistical significance [65].

Sleep Dynamic Therapy

An uncontrolled prospective study enrolling 69 fire evacuees showed weekly SDT significantly improved nightmare severity at 12-week follow-up ($p<0.0001$). No RCT is referrable in this realm [66].

Hypnosis

No RCT emerged through literature search for hypnosis. Two case series studies both showed nightmare improvement, and one continued to display improvement in 40% of participants after 5 years [68,69].

Discussion

Several concerns could weaken the credibility and application of these psychotherapies:

1. Even for the same psychotherapy, trials might follow different protocols that the frequency, duration, or implementation of the therapy could all vary. The difference in efficacy could be resulted from the protocol specifics than the therapy itself.
2. The outcome of psychotherapy is highly therapist-dependent, so the result of an RCT may not apply when another therapist practices the same therapy, for bias and confounders are introduced to alter the external validity.
3. Each study measured different outcome variables such as nightmare frequency, intensity, severity, or distress, and the subjects were followed for various lengths of time, hence the studies can hardly be compared either within the same psychotherapy or between different psychotherapies for efficacy.
4. Therapists must know the therapy they offered in the studies, so double-blindness is impossible, and these RCTs as a result could not achieve the highest validity.
5. The inclusion criteria also varied among the studies like the studies for pharmacotherapies, either via SDM, ICSD, or self-reported nightmares, or the investigator's arbitrary decision. The comparison between the studies again becomes challenging.

As EMDR, SDT, and hypnosis do not have RCTs available, they are not recommended. PDMR is not recommended either, for the only RCT revealed positive yet statistically insignificant efficacy. CBT-I showed conflicting results across three RCTs, whereas the largest trial, almost twice the size of the other positive trials combined, reported a negative result, therefore it is not

recommended as well [41]. In addition, since there has been only one fairly small RCT assessing the efficacy of LDT with less than 10 participants, it is not recommended unless there is no other valid psychotherapy available in the vicinity of the patient.

For the remaining, according to the individual RCT results, our recommendation is given for each therapy's efficacy on the specific populations. For PTSD-related nightmares, CBT, IRT, or ERRT are the viable options. CBT demonstrated valid results from 3 large RCTs and ERRT from 4 RCTs of various sizes, so both deserve recommendations. All the RCTs for IRT showed positive efficacy except one trial, while the meta-analysis combining 13 RCTs disclosed large reduction in nightmare frequency for PTSD for more than 6 months, which let us believe IRT shall also be recommended for PTSD-related nightmare disorder [56,70]. We do not rank among CBT, ERRT, and IRT, given there is no comparative study between the three on this patient population. Patients can choose either according to the service convenience and availability.

For coexistent substance use and PTSD, CBT is the psychotherapy of choice, as there has been no other RCT performed on this population. Among patients with non-PTSD psychiatric comorbidities, IRT should be attempted first, for the two relevant RCTs reported positive results [57,58]. For patients with recurrent or chronic nightmares who do not have PTSD or psychiatric disorders, IRT, SET, or SD is recommended. Nonetheless, IRT should be prioritized since it was specifically tested on patients with idiopathic nightmares, followed by SET as 2 RCTs supported nightmare improvement with one study having more than 200 participants, and then SD can be offered if IRT or SET is unavailable, for 3 smaller RCTs confirmed its efficacy but one did not reach statistical significance [59].

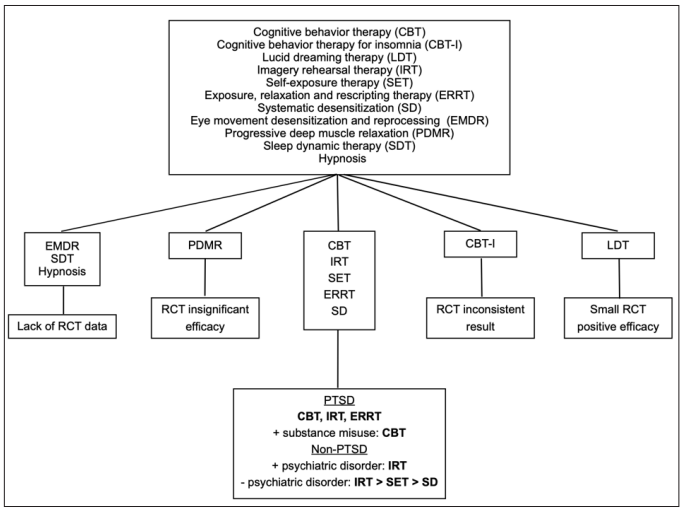

Figure 2: The workflow to sort out the valid Psychotherapies

Pharmacotherapy versus Psychotherapy

We searched through Pubmed using the aforementioned 18 pharmacological therapies and compared each with the 11 respective psychotherapies in a head-to-head manner for the efficacy of nightmare reduction. Disappointedly, very few studies emerged from our search. As prazosin used to be the drug of choice for nightmare disorder, the research mostly centered on the comparison between prazosin and the commonly prescribed psychotherapies like CBT or IRT. A meta-analysis of 26 studies showed prazosin had a larger effect size in nightmare reduction than CBT, but the difference did not reach statistical significance [71]. The other meta-analysis of 15 RCTs revealed prazosin had a slightly larger effect in decreasing nightmare frequency compared to IRT, yet statistical significance was again not achieved [72]. In another meta-analysis, even CBT combined with IRT still did not lead to significant nightmare diminution in comparison with prazosin alone ($p = 0.73$) [73]. Although prazosin was downgraded from the recommended pharmacotherapy for nightmares since the 2018 trial, we use it as a reference point to indirectly compare the efficacy between pharmacological and psychological therapies [4].

In PTSD-related nightmares, we prioritize topiramate (1st line) and nabilone (2nd line) over prazosin for they revealed consistently positive RCT results as we described in the earlier section. Meanwhile, prazosin was demonstrated superior in nightmare reduction than CBT or IRT, albeit not statistically significant. Therefore, topiramate and nabilone are recommended over CBT and IRT, except for concomitant substance abuse that CBT should be the first line therapy given no pharmacotherapy data is available for this specific population. Whether ERRT, our other recommended psychotherapy for this population, has better efficacy than topiramate or nabilone remains uncertain because there is no sortable study to compare ERRT with these three medications.

For non-PTSD related nightmare disorders, IRT is the psychotherapy of choice for patients with and without psychiatric disorders. We also recommend triazolam or nitrazepam as the pharmacotherapy over prazosin for both populations as described in the earlier section. For all 3 meta-analyses were focused on patients with PTSD-related nightmares, we cannot use prazosin as the reference point to compare the efficacy between triazolam/nitrazepam and IRT in non-PTSD nightmare disorder. Thus, either pharmacotherapy or psychotherapy can be the first line treatment for this population, depending on other considerations such as cost and availability for the patients. Although it is unclear if any of the specific pharmacotherapies has more adverse effects than the comparable psychotherapy, we do not take them into account when making recommendations for the available research including these meta-analyses that did not address the difference (s).

Table 1	Pharmacotherapy	Psychotherapy	First line
PTSD	1st line: Topiramate 2nd line: Nabilone Adjuvant: Olanzapine	CBT, IRT, ERRT Concomitant substance abuse: CBT	**Pharmacotherapy** except CBT for substance abuse & ERRT status unclear
Non-PTSD	Triazolam Nitrazepam	Psychiatric disease: IRT Non-psychiatric: IRT > SET > SD	**Inconclusive**

Conclusion

We firstly conducted literature search to explore the relevant studies of the 18 pharmacological and 11 psychological therapies for their efficacies in nightmare disorders on adults, followed by ranking the pertinent studies for each therapy according to the level of evidence, and then we selected the pharmacological and psychological therapy of choice for patients of PTSD, PTSD with concurrent substance abuse, non-PTSD with psychiatric disorder, and chronic nightmare disorder without PTSD or psychiatric disorders (Table 1). After that, we looked for any comparative study between each of the 18 pharmacotherapies and 11 psychotherapies. However, only 3 meta-analyses on prazosin versus CBT or IRT emerged. We then had to utilize prazosin as the reference point to indirectly conclude that pharmacotherapy is generally more efficacious than psychotherapy for PTSD-related nightmare disorders (Table 1) except CBT is prioritized for patients of PTSD combined with substance abuse, and ERRT

status is unclear for there is no relevant study for comparison with pharmacotherapy. As for non-PTSD related nightmare disorder, we do not recommend either pharmacological or psychological therapy as the first line treatment because there is no comparative study available for this specific population (Table 1) either. The patient can pursue either treatment according to the accessibility. We also did not consider adverse effects for either therapy when making the recommendations due to the lack of relevant comparative data.

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