The Treatment of Sleep Disturbances in the PTSD Patient

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ABSTRACT

Introduction: Post-traumatic stress disorder (PTSD) is a debilitating anxiety disorder that develops in 25-30% of individuals exposed to a traumatic event. Sleep disturbances (i.e. nightmares and restless sleep) are common symptoms of PTSD, affecting approximately 70-87% of patients. Studies have shown that improving sleep disturbances improves disease severity and therapeutic outcomes. Although selective serotonin reuptake inhibitors (SSRIs) are considered first-line therapies for PTSD, sleep disturbances often remain refractory and require additional therapies for their resolution. **Discussion**: Pharmacological and non-pharmacological modalities are available for the treatment of PTSD sleep disturbances. Although cognitive behavioural therapy (CBT) is well supported to alleviate sleep disturbances, studies have shown patient drop-out by the time of long-term follow-up, suggesting CBT may be viewed as challenging to complete. Under these circumstances, the use of pharmacological therapies can be considered independently or in adjunct. Conflicting evidence surrounds the benefit of SSRIs in the treatment of sleep disturbances. Moreover, there is limited research surrounding the use of trazodone in this patient population. Benzodiazepines are poorly supported and the side effect profile of atypical antipsychotics limits their routine use. Prazosin holds the most promise and is the most well supported pharmacological agent in the literature. Nabilone, although a controversial agent, also holds promise of benefit. **Conclusions**: Several pharmacological and behavioural therapies are available to treat PTSD sleep disturbances. However, the evidence supporting any of these modalities as being superior is limited. Larger, randomized controlled trials are needed to gain a greater understanding of efficacious therapies available to address this clinical problem.

RÉSUMÉ

Introduction: Le trouble de stress post-traumatique (TSPT) s'avère un trouble d'anxiété qui se développe chez 25 à 30% des individus qui sont exposés à des évènements traumatiques. Les troubles du sommeil tels que les cauchemars et l'insomnie sont des symptômes typiques du TSPT qui affectent entre 70 et 87% des patients. Plusieurs études démontrent qu'une amélioration des troubles du sommeil peut diminuer la sévérité du TSPT et augmenter l'effet thérapeutique. Malgré le fait que les inhibiteurs sélectifs de la recapture de sérotonine (ISRS) demeurent la première ligne de traitement pour le TSPT, les troubles du sommeil demeurent un symptôme important et des thérapies additionnelles sont nécessaires pour leur résolution. **Discussion:** Les modalités pharmacologiques et non pharmacologiques sont disponibles pour le traitement des problèmes du sommeil associés au TSPT. Malgré le fait que la thérapie cognitivo comportementale (TCC) a démontré des effets positifs pour minimiser les symptômes de troubles du sommeil, les études démontrent que les patients ont de la difficulté à respecter les critères de l'étude lorsqu'ils sont évalués au suivi, suggérant que la thérapie TCC est difficile à compléter. L'utilisation de la pharmacothérapie peut se faire de façon indépendante ou combinée à la TCC. Il y a des preuves contradictoires au sujet des bénéfices associés aux ISRS dans le traitement des troubles du sommeil. De plus, il y a des preuves limitées au sujet de l'utilisation de trazodone dans cette population cible de patients. Les benzodiazépines ne sont pas très bien tolérées par les patients à cause de leurs effets secondaires, ce qui limite leur utilisation. La prazosine donne de bons résultats et demeure l'agent pharmacologique le plus recommandé dans la littérature scientifique. Le nabilone, toutefois, est un agent controversé qui semble démontrer beaucoup de bienfaits potentiels. **Conclusion:** Plusieurs thérapies pharmacologiques et comportementales sont accessibles pour aider aux problèmes du sommeil reliés au TSPT. Toutefois, les preuves des bienfaits de ces modalités de traitement sont limitées. Des résultats d'essais aléatoires contrôlés à plus grande échelle sont nécessaires afin de mieux comprendre l'efficacité des thérapies qui sont disponibles dans le but d'optimiser le soin des patients atteints de troubles du sommeil.

CASE EXAMPLE

Mr. X is a 51-year-old male with a history of post-traumatic stress disorder (PTSD) who is currently admitted to hospital following an overdose on Seroquel (atypical antipsychotic medication). Mr. X was previously hit by an OC Transpo bus, which required amputation of his left leg. Since the accident, Mr. X reports vivid and distressing night terrors ranging anywhere from three to seven times per week where he re-experiences the traumatic event. He also reports difficulty falling asleep and staying asleep as a result of this distress. Mr. X has taken a leave of absence from work and his wife has become increasingly concerned regarding his de-

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pressive mood. She finds him to be increasingly withdrawn, not engaging in interests he previously enjoyed as well as very anxious and 'on-edge'. This is not the first time Mr. X has overdosed on Seroquel. He previously developed neuroleptic malignant syndrome (a rare and life-threatening side effect of neuroleptic medications, such as Seroquel, characterized by fever, muscular rigidity, altered mental status and autonomic dysfunction) following another overdose leading to an ICU admission a few months prior. Given his history of Seroquel misuse and his history of distressing PTSD symptoms (sleep disturbances, cognitive and mood disturbances), it was obvious to the team that Mr. X needed to switch to a new medication to help better manage his symptoms and improve his quality of sleep. This raised the clinical question, "What other options are available to treat PTSD sleep disturbances, particularly nightmares"?

INTRODUCTION

Post-traumatic stress disorder (PTSD) is a chronic and debilitating anxiety disorder that affects up to 6.8% of the United States population [3]. As defined by the *DSM-V* (Fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*), PTSD is an anxiety disorder that may develop after an individual is exposed to a traumatic event. Reports show that anywhere between 25-30% of individuals who have experienced a traumatic event go on to develop PTSD [8]. Although the exact etiology of PTSD is not fully understood, it is thought that patients with a personal or family history of major depressive disorder or anxiety disorders may be at risk for symptom development [8]. The *DSM-V* groups PTSD symptoms into four categories: intrusive/re-experiencing, avoidance, negative alterations in cognition and mood, and hyper-arousal [3]. Within these categories sleep disturbances can be grouped as hyper-arousal and/or intrusive symptoms.

Sleep disturbances are a fairly common and rather disturbing symptom of PTSD, affecting approximately 70-87% of the patient population [1]. Improving sleep quality and reducing the occurrence of nightmares has been shown to improve both disease severity and therapeutic outcomes of PTSD [2]. Sleep deprivation that occurs secondary to sleep disturbances (i.e. chronic nightmares) has been shown to negatively impact many areas of functioning including, but not limited to, memory, learning, mood, and attention [3]. Most importantly, sleep deprivation is associated with poor psychiatric outcomes such as worsening of depressive symptoms and thoughts of suicide [3]. Sleep disturbances in patients with PTSD can have variable manifestations including: nightmares, anxiety-provoking dreams, frequent awakenings, difficulty falling asleep (sleep latency), difficulty staying asleep (sleep fragmentation), decreased total sleep time, and restless sleep. Selective serotonin reuptake inhibitors (SSRIs) are well supported in the literature to improve many of the symptoms of PTSD and are considered first-line therapy for PTSD, regardless of the symptom that is most prominent [1,2,3]. However, although treatment for PTSD can lead to improved sleep in some patients, often these sleep disturbances are refractory and require additional treatment for their resolution [1,2,3].

NON-PHARMACOLOGICAL THERAPIES

COGNITIVE BEHAVIOURAL THERAPY (CBT)

The most effective form of non-pharmacological therapy shown in the literature to improve sleep disturbances in the PTSD patient is cognitive behavioural therapy (CBT). CBT is an evidence-based psychotherapy whereby a therapist helps the patient identify cognitive distortions and maladaptive beliefs. The therapist then uses behavioural therapy to facilitate symptom reduction via thought exercises and improved overall functioning. CBT incorporates education, coping skills training, stress management and relaxation exercises into its therapy. Its success hinges on applying the cognitive and behavioural skills acquired in therapy in the outside setting. More specifically, the subtype of CBT known as Image Rehearsal Therapy (IRT) is well supported as an effective non-pharmacological option for sleep disorders associated with PTSD. IRT involves having the patient recall the nightmare, write it down, and then change an aspect of the nightmare into something more positive. The patient then rehearses the positive change while awake so that they can displace the original nightmare when it reoccurs. IRT has been proven to reduce the number of nightmares per week, improve sleep quality and decrease mean PTSD severity scores (Clinical Administered PTSD Scale [CAPS]) [3].

Although the Veterans Association and Department of Defense consider CBT-based treatments as first-line therapies [3], these strategies are often difficult to implement. This is especially true in a hospitalized patient who is admitted for a short period of time, because the long-term use of CBT is a key contributor to its success. Moreover, several studies examining CBT use in PTSD patients have shown increasing drop out rates and loss to long-term follow-up (i.e. one study showed only 114 of 168 participants followed up at the three and six month mark). This data suggests that perhaps CBT may be viewed as challenging or difficult to complete by patients [3]. Pharmacological modalities are often beneficial under these circumstances and have been shown to be effective choices when used both independently and in combination with CBT [3].

PHARMACOLOGICAL THERAPIES

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)

SSRIs are typically the mainstay treatment for PTSD and are considered first-line therapies, with sertraline, paroxetine, and fluox-

etine carrying FDA indication for treatment of PTSD. However, the evidence regarding efficacy of SSRIs in treating sleep disturbances is inconsistent. Some studies have shown that SSRIs can lead to significant improvements in nightmares [1], sleep onset latency, total sleep time, and wake after sleep onset. In contrast, other studies report that SSRIs decrease total sleep time and increase daytime sleepiness [3]. Placebo-controlled trials have shown paroxetine to be effective in managing sleep disturbances [7]. However, fluvoxamine was ineffective in one study but effective in another in alleviating sleep disturbances [7]. Moreover, in a large randomized control trial, sertraline did not improve sleep quality and insomnia was a frequent side effect noted in 35% of the treatment group [7]. Given the conflicting evidence, SSRIs may have no impact or only minimally improve sleep disturbances and thus this class of medications needs to be further explored in this context [1].

TRAZODONE

Although the evidence supporting the use of trazodone for PTSD-related sleep disturbances is also limited within literature, the results have been positive. One study found that more than 70% of PTSD patients who completed an author-designed questionnaire reported improvement in sleep onset, maintenance, and nightmares with the use of trazodone [1,9, 15]. Additionally, two open-label studies with trazodone noted that sleep complaints globally improved, particularly nightmares and insomnia [7, 15, 16]. Further insight and studies examining trazodone use for PTSD-related sleep disturbances would be beneficial when considering this medication as a treatment option as it is mainly prescribed off-label for PTSD patients experiencing sleep disturbances. As well, potential side effects need to be appropriately advised to patients as one study noted a higher than expected occurrence of priapism with trazodone use [16].

BENZODIAZEPINES

Benzodiazepines are typically avoided in the PTSD patient despite being the mainstay treatment for insomnia in the general population. Substance abuse is a common co-morbidity affecting this patient population [1]. As a result, benzodiazepines should be used with caution to reduce the risk of dependence. Additionally, benzodiazepines may worsen sleep apnea or impair cognition [1,10]. Studies have shown that benzodiazepines have limited effect on improving PTSD-related sleep disturbances. For example, a single-blind, placebo controlled, crossover trial showed that with 1-2 mg of clonazepam there were improvements in sleep initiation and maintenance, but no reduction in nightmare intensity in PTSD patients [3, 13,14]. As a result, the study concluded that clonazepam was an ineffective agent for the treatment of PTSD-related sleep disturbances. Other studies have shown similar inefficacy with use of benzodiazepines in the PTSD patient population [3, 13, 14], further supporting their limited role in the treatment of PTSD-related sleep disturbances.

ATYPICAL ANTIPSYCHOTICS

Atypical antipsychotics including Seroquel, olanzapine, and risperidone, like many of the aforementioned medications are not well-supported in the literature, but are prescribed off-label to treat sleep disturbances in the PTSD patient [1, 3]. Small studies and case series have shown improvements in sleep disturbances with low doses of these medications such as, decreased sleep disturbances, reduced occurrence of nightmares and flashbacks, and decreased hyper-arousal [1, 11, 12]. One case-based series showed olanzapine to be effective for treatment-resistant nightmares [12]. Although there may be potential benefits to the use of atypical antipsychotic medications for treatment of PTSD-related sleep disturbances, their side effect profile (i.e. tardive dyskinesia, weight gain) limits their routine use [1]. As a result, they should typically be reserved for patients who have co-morbid psychosis, agitation, and aggressive behavior.

PRAZOSIN

Prazosin is the pharmacological agent with the most evidence and support in the literature for the treatment of sleep disturbances, such as reducing nightmares and improving overall sleep quality in the PTSD patient. Prazosin indicated as an anti-hypertensive agent, is an alpha-1-adrenergic receptor antagonist that is highly lipophilic and readily crosses the blood-brain-barrier. Within the central nervous system, stimulation of alpha-1-adrenergic receptors is believed to contribute to the generation of PTSD-related nightmares [1]. Moreover, PTSD nightmares appear to arise from light sleep and/or disrupted REM sleep. Studies have shown that prazosin reduces light sleep and normalizes REM sleep [4], thereby reducing nightmares. Miller, LJ showed that patients in the prazosin group reported more than a 50% reduction in recurring distressing dreams in comparison to the placebo group who reported only a 15% reduction [1]. In addition to its efficacy, prazosin is also well tolerated and side effects such as orthostatic hypotension and dizziness have been reported as minimal [4]. Several studies have shown that with prazosin use significant improvements were achieved in a short duration (within weeks) such as, improvement in trauma nightmares and fewer distressed awakenings [1,5]. Moreover, one study compared prazosin to Seroquel, and it was found that participants were more likely to continue using prazosin over Seroquel due to fewer side effects and better long-term effectiveness [5]. Prazosin is generally started at an initial dose of 1 mg, so that hypotension can be monitored after the first dose. Sudden discontinuation of prazosin could lead to rebound hypertension and patients should be cautioned accordingly. The dose is then gradually titrated up and increased to maintenance levels of 2-10 mg [5]. It is unclear if higher doses

of prazosin would serve to be beneficial in treatment-resistant patients. The current literature positively supports this agent as a treatment modality for problematic, recurrent nightmares in patients with PTSD, with the additional benefit of rapid effectiveness and minimal adverse effects.

NABILONE

One final drug to review is nabilone. It is currently controversial if the use of this endocannabinoid receptor agonist would serve as an effective agent for the treatment of PTSD-related sleep disturbances. The endocannabinoid system appears to play a role in alleviating anxiety and symptoms related to PTSD, as attributed by anecdotal reports of symptom relief through self-medication with cannabis. One study showed that a group of patients with treatment-resistant nightmares (not alleviated with SSRIs or hypnotics), benefited from adjunct nabilone therapy [6]. These patients experienced either a cessation of nightmares or a significant reduction in nightmare intensity. More specifically, this study reported that 72% of participants experienced either a total cessation or a lessening of the severity of nightmares when taking an average dose of 0.5 mg of nabilone one hour before bedtime. It is suggested that a starting dose of 0.25 mg should be initiated and then titrated up as tolerated. Nabilione certainly holds promise of benefiting patients who are refractory to other pharmacotherapies, and although it is a controversial treatment option, further studies and randomized controlled trials will provide further insight into nabilone's efficacy for the treatment of PTSD-related sleep disturbances, particularly nightmares [6].

CONCLUSIONS

In conclusion, several pharmacological options and behavioral modalities are available for the treatment of sleep disturbances and nightmares in the PTSD patient. However, the evidence supporting any of these therapies as being superior to one another is limited and there is no unified agreement amongst the medical community as to which agent is the most efficacious and which agent(s) should be considered as first-line therapy. Larger, randomized controlled trials are needed to further examine this topic in order to gain a greater understanding of efficacious treatment options. Although prazosin currently holds promise of filling the void, other medications such as nabilone, trazodone, benzodiazepines, antitypical antipsychotics, and SSRIs need to be further studied and compared to one another.

Sleep disturbances and nightmares are significant and relevant problems affecting the vast majority of PTSD patients. As exemplified by the case of Mr. X, treatment of nightmares and sleep disturbances holds the potential to improve therapeutic outcomes, such as improving underlying depressive symptoms and reducing the risk of suicide. Further insight and research holds the promise of gaining a greater understanding of efficacious modalities that can be used to treat a clinical problem that does not currently have a clear-cut answer.

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