Long-Term Care Updates

September 2022

Can cyproheptadine be used for the treatment of PTSD-associated nightmares, sleep disturbances, and flashbacks?

PharMerica®

By Judy Truong, PharmD

Introduction

Reports indicate that about 70-90% of patients with post-traumatic stress disorder (PTSD) experience sleep disturbances and trauma-related nightmares.[1] Few guidelines exist that specifically address post-traumatic nightmares, and the available evidence is small and limited in quality and quantity. A pharmacological intervention has yet to be approved for PTSD-related nightmares, but several options have been studied.[2] Cyproheptadine, a histamine and serotoninergic antagonist, has been considered for the treatment of PTSD-associated nightmares due to its ability to increase stages of slow-wave sleep without altering total sleep time.[3,4,5] This newsletter review will address the current guideline-based recommendations and clinical evidence on the use of cyproheptadine for PTSD-associated nightmares, sleep disturbances, and flashbacks.

Clinical Guidelines and Evidence

American Academy of Sleep Medicine (AASM)

The AASM published a position paper for the treatment of nightmare disorders in adults in 2018 as an update to their Best Practice Guide for the Treatment of Nightmare Disorder in Adults, published in 2010. According to AASM, cyproheptadine was classified as a "may be used" medication for the treatment of PTSD-associated nightmares. A "may be used" classification indicates that there is unclear evidence or expert consensus either in favor of or against the drug. But ultimately, AASM states that clinicians should provide care based on patient circumstances, available treatment options, and resources.[4]

According to the Best Practice Guide, cyproheptadine may be considered for the treatment of PTSD-associated nightmares, but there is spare and low-grade data available. At the time this was published (2010), AASM noted that evidence on the use of cyproheptadine for this purpose consisted of three studies with conflicting data.[1,5] Details of these are presented on the next page.

A small case series documented the use of cyproheptadine in four veterans with combat-related nightmares. The four cases were selected to represent "about 80 patients" whose nightmare symptoms appeared to respond to the addition of cyproheptadine to their antidepressant regimen. Three of the patients experienced a remission of their nightmares within several days of taking doses ranging from 2 to 4 mg of cyproheptadine nightly. One patient was prescribed cyproheptadine 28 mg nightly but quit taking it after experiencing intense dreams. The only significant safety side effect was in a patient who experienced excessive sedation, confusion, and worsening flashbacks after taking only one dose of cyproheptadine 4 mg. No follow-up period was reported.[5,6]

A retrospective chart review was conducted to determine the efficacy of cyproheptadine in relieving nightmares in nine patients with PTSD. The patient group was predominately females (79%) with sexual trauma (78%) and substance abuse. All patients were on concomitant psychotropic medications and received treatment doses of cyproheptadine ranging from 4 to 12 mg nightly. Responses to the drug varied from a reduction in the frequency and intensity of nightmares to total remission. No safety data were recorded in patient records after the addition of cyproheptadine. Overall, there was incomplete evidence and a lack of information on the methodology used.[5,7]

A clinical trial was conducted at a Veteran's Administration treatment center to study the effectiveness of cyproheptadine for PTSD-associated nightmares using a daily sleep dairy. A diagnosis of PTSD (according to DSM-IV criteria) and presence of distressing dreams were the only inclusion criteria. Patients were excluded if they had psychotic disorders or substance abuse within the past 6 months. The Miami Veteran's Administration Medical Center (VAMC) Post-Sleep Questionnaire was used by the patients as a sleep diary. Thirty-six patients completed this baseline sleep diary for one week and were prescribed cyproheptadine 4 to 8 mg nightly for 4 weeks. However, the efficacy analysis only included 16 patients who had completed at least one week of posttreatment sleep diaries. The patient population was predominately males with ages ranging from 47 to 75 years old who were taking previously prescribed psychotropic medications. The efficacy measurements included: number of awakenings, presence of dreams, and disturbance of dreams. None of the posttreatment efficacy measurements were found to be statistically different from the baseline scores. Three patients discontinued cyproheptadine due to side effects (e.g., fatigue, restlessness, worsening nightmares); and only four of the 16 patients reported the drug to be effective. This study was limited by a high dropout rate (e.g., loss due to follow-up, discontinuation due side effects), small sample size, and confounding variables such as the use of other psychotropic medications.[5,8]

Department of Veterans Affairs (VA) and Department of Defense (DOD)

A 2017 update to the VA/DOD clinical practice guidelines for the management of PTSD and related conditions reviewed evidence since the publication of the 2010 guidelines for cyproheptadine and determined that there is insufficient evidence to recommend for or against cyproheptadine as monotherapy or augmentation therapy for the treatment of PTSD.[9]

Clinical Evidence

A 2010 randomized, double-blinded, placebo-controlled trial examined the use of cyproheptadine for PTSD associated sleep problems in Vietnam veterans. The participants were primarily males with current combat related PTSD diagnosed according to the Clinician Administered PTSD Scale and had moderately severe nightmares on the Pittsburg Sleep Quality Index. Sixty-nine patients were enrolled across two study sites for a trial of 2 weeks. Posttreatment data was available for 60 subjects. The cyproheptadine group had marginally worse posttreatment scores on the Clinician Administered PTSD Scale ($p=0.81$), nightmare severity scores ($p=0.17$), and Pittsburg Sleep Quality Index scores ($p=0.06$) compared to placebo. The researchers concluded that cyproheptadine did not appear to be effective for combat-related PTSD sleep problems and may even exacerbate the issue. The investigators expressed the ongoing need for skepticism regarding anecdotal and open-label findings and further controlled clinical trials.[3]

In a letter to the Editor in the *American Journal of Psychiatry*, the effect of cyproheptadine on nightmares, electroencephalogram (EEG) sleep measures, and drug serum levels was described in a patient who was prescribed up to 12 mg of cyproheptadine for PTSD-associated nightmares. The serum level of cyproheptadine was 6 μg/L after 12 hours. The resulting effect was that the nightmares became less intense and decreased in frequency to less than once per week. However, given the small sample, single dose/strength studied, and lack of follow up, the generalizability of these findings is limited.[10]

Conclusion

Based on the evidence provided, cyproheptadine should not be recommended for the treatment of PTSD-associated nightmares due to a paucity of evidence and conflicting data. Overall, the studies conducted on cyproheptadine presented incomplete, inconsistent, and low-quality evidence. The studies contained a lot of confounding variables (i.e., differing dosages of cyproheptadine, concurrent use of other psychotropic medications, concomitant chronic conditions), lacked statistical power, and had low external validity.[1-10] If a trial of cyproheptadine for PTSD-associated nightmares is considered, clinical judgement and shared-decision making should be employed.[4,5]

References

1. Maker MJ, Rego SA, Asnis GM. Sleep disturbances in patients with post-traumatic stress disorder: epidemiology, impact and approaches to management. *CNS Drugs*. 2006;20(7):567-590. https://link.springer.com/article/10.2165/00023210-200620070-00003
2. Geldenhuys C, van den Heuvel LL, Steyn P, Seedat S. Pharmacological management of nightmares associated with posttraumatic stress disorder. *CNS Drugs*. 2022;36(7):721-737. https://link.springer.com/content/pdf/10.1007/s40263-022-00929-x.pdf
3. Jacobs-Rebhun S, Schnurr PR, Friedman MJ, Peck R, Brophy M, Fuller. Posttraumatic stress disorder and sleep difficulty. *Am J Psychiatry*. 2000;157(9):1525-1526. https://ajp.psychiatryonline.org/doi/epub/10.1176/appi.ajp.157.9.1525
4. Morgenthaler TI, Auerbach S, Casey KR, et al. Position paper for the treatment of nightmare disorder in adults: an American Academy of Sleep Medicine position paper. *J Clin Sleep Med.* 2018;14(6):1041–1055. https://jcsm.aasm.org/doi/epdf/10.5664/jcsm.7178
5. Aurora RN, Zak RS, Auerbach SH, et al. Best practice guide for the treatment of nightmare disorder in adults. *J Clin Sleep Med*. 2010;6(4):389-401. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2919672/pdf/jcsm.6.4.389.pdf
6. Brophy MH. Cyproheptadine for combat nightmares in post-traumatic stress disorder and dream anxiety disorder. *Mil Med*. 1991;156(2):100-101. https://academic.oup.com/milmed/article/156/2/100/4848683
7. Gupta S, Popli A, Bathurst E, Hennig L, Droney T, Keller P. Efficacy of cyproheptadine for nightmares associated with posttraumatic stress disorder. *Compr Psychiatry*. 1998;39(3):160-164. https://www.sciencedirect.com/science/article/pii/S0010440X98900761?via%3Dihub
8. Clark RD, Canive JM, Calais LA, Qualls C, Brugger RD, Vosburgh TB. Cyproheptadine treatment of nightmares associated with posttraumatic stress disorder. *J Clin Psychopharmacol*. 1999;19(5):486-487. https://oce.ovid.com/article/00004714-199910000-00023/HTML
9. VA/DOD Clinical Practice Guideline for the Management of Posttraumatic Stress Disorder and Acute Stress Disorder: Clinician Summary. *Am Psychiatr Publ*. 2018;16(4):430-448. https://www.healthquality.va.gov/guidelines/MH/ptsd/VADoDPTSDCPGFinal082917.pdf
10. Rijnders RJ, Laman DM, Van Diujn H. Cyproheptadine for posttraumatic nightmares. *Am J Psychiatry*. 2000;157(9):1524-1525. https://ajp.psychiatryonline.org/doi/epub/10.1176/appi.ajp.157.9.1524-a

Creighton University Center for Drug Information & Evidence-Based Practice

Drug Information Consultation Service

Monday through Friday

7:30am-3:30pm Central

1-800-561-3728

Voicemail service is available after-hours

Submit your questions HERE.