SHORT COMMUNICATION

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The Use of a Synthetic Cannabinoid in the Management of Treatment-Resistant Nightmares in Posttraumatic Stress Disorder (PTSD)

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This is the report of an open label clinical trial to evaluate the effects of nabilone, an endocannabinoid receptor agonist, on treatment-resistant nightmares in patients diagnosed with posttraumatic stress disorder (PTSD). Methods: Charts of 47 patients diagnosed with PTSD and having continuing nightmares in spite of conventional antidepressants and hypnotics were reviewed after adjunctive treatment with nabilone was initiated. These patients had been referred to a psychiatric specialist outpatient clinic between 2004 and 2006. The majority of patients (72%) receiving nabilone experienced either cessation of nightmares or a significant reduction in nightmare intensity. Subjective improvement in sleep time, the quality of sleep, and the reduction of daytime flashbacks and nightsweats were also noted by some patients. The results of this study indicate the potential benefits of nabilone, a synthetic cannabinoid, in patients with PTSD experiencing poor control of nightmares with standard pharmacotherapy. This is the first report of the use of nabilone (Cesamet; Valeant Canada, Ltd., Montreal, Canada) for the management of treatment-resistant nightmares in PTSD.

Background

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), defines posttraumatic stress disorder (PTSD) as the development of characteristic symptoms following exposure to an extreme traumatic stressor, involving direct personal experience of an event that involves actual or threatened death or serious injury or other threat to the physical integrity of another person, or learning about unexpected or violent death, serious harm or threat of death, or injury experienced by a family member or other close associate. The person's response must involve intense fear, helplessness, or horror (in children, disorganized or agitated behavior). There are many characteristic symptoms of PTSD including the persistent, intrusive recollections or re-experience of the original event (via dreams or nightmares and dissociative flashbacks), numbing and avoidance, and increased arousal [1]. The experience of these symptoms leads to functional impairment.

Although PTSD is often associated with military casualties, the majority of cases are related to traumatic events occurring in the general population. Such events may include physical or sexual abuse, traffic or natural disasters, and interpersonal violence. The lifetime prevalence of PTSD is 8.2% in the United States, and a Canadian study puts this rate at 9.2% [2,3]. PTSD's lifetime prevalence is higher than that of other anxiety disorders, including panic disorder, obsessive compulsive disorder, and generalized anxiety disorder.

Guidelines for the management of PTSD now exist [4]. However, recommended first-line and second-line agents, used alone or in combination to treat symptoms including nightmares, often show limited effectiveness in many patients. Subsequently, some patients may continue to experience symptoms, including debilitating nightmares, for years or decades. The negative impact of nightmares and the side effects of some of the current psychotherapeutic medications may potentiate other symptoms of PTSD, including those related to anxiety

and depression. Other comorbid psychiatric conditions may also worsen. Commonly, patients with PTSD are receiving more than one medication. Polypharmacy is associated with the potential for side effects and drug interactions, thus possibly creating compliance and quality-of-life issues. On the basis of these experiences, there is a definite clinical need for a medication that is effective in treating nightmares related to PTSD, with positive effects on sleep and little potential for side effects or drug interaction.

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line agents in the pharmacological treatment of PTSD in the United States (e.g., paroxetine and sertraline). Second-line agents include venlefaxine, prazosin, monoamine oxidase inhibitors, and tricyclic antidepressants. Other agents used in PTSD include atypical antipsychotics and anticonvulsants [5].

Sleep disturbances, mainly insomnia and nightmares, are present in about 70% of those with PTSD. The estimates of nightmares vary from 24.8% [6] to 60.0% [7].

Various medications have been used in attempts to control PTSD sleep disturbances, including nightmares. A review of the abovementioned classes of medications, as well as other specific agents such as clonidine and cyproheptadine, concludes, "to date an insufficient number of controlled studies are published to formulate evidence-based guidelines. Drawing on the available data it can be concluded that there is limited but promising evidence for prazosin and olanzapine for managing PTSD nightmares and insomnia" [8]. That article also points out that objective parameters for insomnia and nightmares need to be developed. The fact that so many agents have been used in attempts to manage nightmares highlights that management of these is difficult, and that there is room to explore other potentially useful classes of medications. Anecdotal reports of relief from psychiatric symptoms, with the use of marijuana or a pharmaceutical endocannabinoid receptor agonist, have created interest in investigating the role of the endocannabinoid system in PTSD and other mood disorders [5]. The endocannabinoid system has been implicated in the control of various behaviors including eating, addiction, and memory and in mediating both anxiolytic effects and pain responses [6–8]. Endocannabinoids are thought to exert an effect through a variety of interactions with the CNS related to PTSD. These include the hypothalamic–pituitary–adrenocortical (HPA) axis, function of the hippocampus and amygdala, and control of cortical regulation of memory processes [9–11].

The endocannabinoid system comprises two G-protein-coupled receptors (CB_1 and CB_2), possibly one or more atypical receptors, and several ligands (notably anandamide and 2-arachidonolglycerol [2-A]). The CB_1 receptor is distributed primarily within the CNS, particularly in the cerebellum, basal ganglia, amygdala, cerebral cortex, and hippocampus [12,13]. The CB_2 is mostly distributed peripherally [13,14]. The cannabinoid receptors show pronounced selectivity in their binding and even have distinct binding sites for different classes of ligands [14]. This selectivity may partially explain why different agonists for the same CB receptor show differing therapeutic and side effect profiles. For example, at therapeutic doses, nabilone does not appear to produce the psychological high of inhaled marijuana.

Nabilone (Cesamet; Valeant Canada, Ltd., Montreal, Canada), an endocannabinoid receptor (CB_1 and CB_2) agonist, has been in use in Europe and Canada for over 25 years and was recently granted approval in the United States for the treatment of chemotherapy-induced nausea and vomiting. The identification and cloning of cannabinoid receptors in humans have led to a better understanding of the possible mechanisms of action of nabilone and support its potential use and safety in multiple clinical settings and various patient populations [12–26].

Rational for Therapeutic Trial of Nabilone in Patients with PTSD

Patients with PTSD can be desperate to obtain relief from their symptoms and frequently turn to self-medication, including the use of alcohol and cannabis. On the basis of observations published in a single case study that mentioned nabilone's reduction of nightmares when it was employed to replace a patient's use of smoked marijuana for the relief of PTSD symptoms [22], the author of this current report decided to initiate nabilone as pharmacotherapy for several patients whose nightmares were not adequately controlled with standard therapies. When the initial three patients experienced abolition of their nightmares, it was decided to use nabilone in subsequent clinical cases with similar presentations and record the effect on nightmares.

Methods

All 47 patients who agreed to participate in this clinical study had been referred to the author's private clinic for the management of PTSD by other physicians. The clinic specialized in the management of psychological trauma. Diagnoses for the study were confirmed by DSM-IV-TR criteria using a recognized PTSD questionnaire, the Posttraumatic Stress Diagnostic Scale [9]. All patients had at least a 2-year history of PTSD-related nightmares that had not responded to conventional therapies (Tables 1 and 2). Eligibility for this study stipulated that

Table 1 Population profile

	Total	%
Total number of patients studied	47	
Mean age, years ± SD	44 ± 9	
Range	26–68	
Women/men	27/20	57/43
Time since PTSD onset (range in years)	2–30	

Table 2 Type of trauma

	Total	%
Repetitive childhood trauma (sexual/physical abuse)	18	38
Civilian adult trauma (accident, rape, injury, workplace trauma, and life-threatening illness)	18	38
Combat-associated trauma	11	23
Total	47	100

current nightmare frequency was a minimum of once weekly.

Nightmares were considered "treatment-resistant" when these persisted in spite of conventional medications employed for PTSD. Although these medications provided relief for various PTSD symptom clusters, as reported by the patients in this study, nightmares persisted unchanged and continued to cause clinical distress.

The author had to rely on subjective reports of nightmare presence and subsequent relief with the use of nabilone since, at present, there is no reliable test to objectively measure the presence or intensity of nightmares.

All patients were informed that nabilone was a synthetic cannabinoid and approved only for antiemetic use. The patients were screened for previous negative experiences with marijuana use and were advised to not use marijuana while taking nabilone. Conditions that were contraindicated with the use of nabilone were excluded from the study (e.g., sensitivity to cannabinoids and psychotic reactions). All patients were on psychotropic medications for PTSD at the start of the study, and a decision was made not to discontinue any of these in order to study the effect of the addition of nabilone. The patients were carefully monitored for any adverse reactions. Potential benefits and side effects were discussed, and the patients were advised to discontinue nabilone if they experienced any uncomfortable side effects. Verbal consent was voluntary, and continuing psychiatric treatment was not contingent on being a volunteer.

Prior to starting nabilone, the patients were given a tracking sheet that asked them to record the intensity of nightmares from 1 to 5 (5 being the most intense) and hours of sleep and provided a space for comments about that night's sleep. This nightly charting began 1 week prior to commencing the trial and weekly thereafter until satisfactory results or the trial being ended due to side effects. Previous medications, which ranged from a single SSRI to polypharmacy, were not changed during the study.

The patients were started at a dose of 0.5 mg 1 h prior to bedtime (the first patient was started at 1.0 mg based on dose availability. Soon after, the 0.5-mg capsule became available). The patients were seen within 7 days of initiating nabilone in order to determine dose response and monitor for side effects. Titration of nabilone was indicated if the medication was well tolerated and effective control of nightmare symptoms had not been achieved. The patients continued to be seen weekly until a satisfactory response was achieved or nabilone was stopped due to side effects. All doses were kept below the maximum 6 mg daily, as per the Cesamet (nabilone) product monograph [28]. Patients having a positive response to nightmare cessation or reduction were permitted to continue nabilone therapy and were individually monitored for its use in ongoing therapy. All patients gave consent for a review of their clinical charts in order that their response to nabilone therapy be documented.

Results

For 47 patients, standard PTSD medications being maintained, the usual starting dose was 0.5 mg and was titrated up or down to effect. The average effective dose of nabilone was 0.5 mg one hour before bedtime, with an effective dose range of 0.2 mg to 4.0 mg nightly. Thirty-four (72%) patients experienced total cessation or lessening of severity of nightmares (28 patients had total cessation of nightmares and 6 had satisfactory reduction). The discontinuation of medication was successful in four patients following 4–12 months of nabilone therapy (nightmares did not return or returned at a reduced level, not needing further medication control), whereas the other patients experienced a recurrence of nightmares upon nabilone withdrawal (usually within the first two nights). These patients experienced control of nightmares once nabilone treatment was reinitiated. These patients were asked to attempt withdrawal at least every 6 months, but the therapy was ongoing at the time of this chart review. Three patients, who initially responded positively, were lost to follow-up.

In some cases, the benefits including an improvement in sleep time and a reduction of daytime flashbacks were subjectively noted. Several patients also stated that they no longer experienced nightsweats while on nabilone. Once effective relief of nightmares was achieved, no

further increase in nabilone was necessary (patients' doses remained stable). Thirteen (28%) patients experienced mild-to-moderate side effects (shortly following nabilone initiation), leading to discontinuation of nabilone therapy. The side effects experienced included lightheadedness, forgetfulness, dizziness, and headache.

Conclusion

A chart review of patients diagnosed with PTSD who were referred to a private psychiatric clinic suggests that the synthetic cannabinoid, nabilone, has beneficial effects beyond its official indication in regard to abolishing or greatly reducing nightmares that persisted in spite of treatment with conventional PTSD medications.

The subjects concomitantly received nabilone in addition to the one or more psychiatric medications that they were already taking for 2 years or more. No tolerance to nabilone was observed among the patients. This may indicate its potential longer-term safety and efficacy.

The author recognizes the limits of this study (e.g., there was no placebo control, the measurements were limited to subjective reports to nightmare changes, the study was on a small number of patients, and there was a selective bias by nature of referrals to a specific clinic from which the patients were selected). Nonetheless, on the basis of these retrospective findings, nabilone appears to be a significant treatment for nightmares in the PTSD population. This initial positive clinical report on 34 of the 47 patients will hopefully inspire other physicians to consider using nabilone in those with persistent PTSD nightmares. Nabilone should be evaluated further through randomized clinical trials involving PTSD patients, including studies looking at its effects on the full spectrum of PTSD symptoms. Baseline and follow-up polysomnography recordings for patients on nabilone therapy would likely provide useful information. In addition, nabilone's effect in other anxiety disorders and primary parasomnias may be the areas to investigate.

Addendum

Since this study was done, Health Canada has approved a 0.25-mg capsule of nabilone. This would be the preferred starting dose of this author. The United States has only the 1-mg capsule available, so dilution by a pharmacist for the initial doses is recommended. Available strengths may vary in different countries where nabilone is available.

Conflict of Interest

The authors declare no conflict of interest.

References

1. *Diagnostic and statistical manual of mental disorders, DSM-IV-TR*. Washington, DC: American Psychiatric Association, 2000.
2. Kessler R, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. *Arch Gen Psychiatry* 1995;**52**:1048–1060.
3. Van Ameringen M. Posttraumatic Stress Disorder in Canada. *CNS Neurosci & Ther* 2009; in press.
4. Clinical practice guidelines. Management of anxiety disorders. *Can J Psychiatry* 2006;**51**(Suppl. 2):57S–62S.
5. Friedman, M. *Post-traumatic and acute stress disorders: The latest assessment and treatment strategies, 4th Edition*. Kansas City: Compact Clinicals, 2006; 58–64.
6. Ohayon M, Shapiro C. Sleep disturbances and psychiatric disorders associated with posttraumatic stress disorder in the general population. *Compr Psychiatry* 2000;**41**:469–478.
7. Krakow B, Schrader R, Tandberg D, Hollifield M, Koss MP, Yau CL, Cheng DT. Nightmare frequency in sexual assault survivors with PTSD. *J Anxiety Disord* 2002;**16**:175–190.
8. Van Liempt S, Vermetten E, Geuze E, Westenberg H. Pharmacotherapeutic treatment of nightmares and insomnia in post traumatic stress disorders: An overview of the literature. *Ann NY Acad Sci* 2006;**1071**:502–507.
9. Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorders. *Psychol Assess* 1997;**9**:445–451.
10. Witkin JM, Tzavara ET, Nomikos GG. A role for cannabinoid CB1 receptors in mood and anxiety disorders. *Behav Pharmacol* 2005;**16**:315–331.
11. Marsicano G, Wotjak CT, Azad SC, Bisogno T, Rammes G, Cascio MG, Hermann H, Tang J, Hofmann C, Zieglgänsberger W, et al. The endogenous cannabinoid system controls extinction of aversive memories. *Nature* 2002;**418**:530–534.
12. Kathuria S, Gaetani S, Fegley D, Valiño F, Duranti A, Tontini A, Mor M, Tarzia G, La Rana G, Calignano A, et al. Modulation of anxiety through blockade of anandamide hydrolysis. *Nat Med* 2003;**9**:76–81.
13. Lynch ME. Preclinical science regarding cannabinoids as analgesics: An overview. *Pain Res Manage* 2005;**10**(Suppl. A):7A–14A.
14. Barna I, Zelena D, Arszovski AC, Ledent C. The role of endogenous cannabinoids in the hypothalamo-pituitary-adrenal axis regulation: *In vivo* and *in vitro* studies in CB_1 receptor knockout mice. *Life Sci* 2004;**75**:2959–2970.
15. Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, Zhang X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. *J Clin Invest* 2005;**115**:3104–3116.

16. Chhatwal JP, Davis M, Maguschak KA, Ressler KJ. Enhancing cannabinoid neurotransmission augments the extinction of conditioned fear. *Neuropsychopharmacology* 2005;**30**:516–524.
17. Devane WA, Dysarz FA III, Johnson MR, Melvin LS, Howlett AC. Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* 1988;**34**:605–613.
18. Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie K, Martin BR, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev* 2002;**54**:161–202.
19. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. *Nature* 1990;**346**:561–564.
20. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev* 2006;**58**:389–462.
21. Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. *J Ethnopharmacol* 2006;**105**:1–25.
22. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid in chronic noncancer pain. *Pain Med* 2006;**7**:25–29.
23. Wissel J, Haydn T, Muller J, Brenneis C, Berger T, Poewe W, Schelosky LD. Low dose treatment with the synthetic cannabinoid nabilone significantly reduces spasticity-related pain. A double-blind placebo-controlled cross-over trial. *J Neurol* 2006;**20**:2218–2220.
24. Glass RM, Uhlenhuth EH, Hartel FW, Schuster CR, Fischman MW. Single-dose study of nabilone in anxious volunteers. *J Clin Pharmacol* 1981;**21**:383S–396S.
25. Fabre LF, McLendon D. The efficacy and safety of nabilone (a synthetic cannabinoid) in the treatment of anxiety. *J Clin Pharmacol* 1981;**21**:377S–382S.
26. Ashton CH, Moore PB, Gallagher P, Young AH. Cannabinoids in bipolar affective disorder: A review and discussion of their therapeutic potential. *J Psychopharmacol* 2005;**19**:293–300.
27. Bartolucci G. Nabilone and posttraumatic stress disorder in a user of therapeutic marijuana. *Four Zero One Pharma*, August 2004.
28. CESAMET™ (nabilone) Product Monograph. Valeant Canada, Ltd. Montreal, Quebec, Canada, 2006.