



Case Report

Cannabidiol can improve complex sleep-related behaviours associated with rapid eye movement sleep behaviour disorder in Parkinson's disease patients: a case series

M. H. N. Chagas*† MD PhD, A. L. Eckeli* MD PhD, A. W. Zuardi*† MD PhD, M. A. Penna-Pereira* MD, M. A. Sobreira-Neto* MD, E. T. Sobreira* PhD, M. R. Camilo* MD, M. M. Bergamaschi*† PhD, C. H. Schenck‡ MD PhD, J. E. C. Hallak*† MD PhD, V. Tumas* MD PhD and J. A. S. Crippa*† MD PhD

*Department of Neuroscience and Behavior, Faculty of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, Brazil, †INCT Translational Medicine (CNPq), São Paulo, and ‡Minnesota Regional Sleep Disorders Center and Department of Psychiatry, Hennepin County Medical Center and the University of Minnesota Medical School, Minneapolis, MN, USA

Received 25 February 2014, Accepted 23 April 2014

Keywords: cannabidiol, Parkinson's disease, rapid eye movement sleep behaviour disorder

SUMMARY

What is known and objective: Cannabidiol (CBD) is the main non-psychotropic component of the *Cannabis sativa* plant. REM sleep behaviour disorder (RBD) is a parasomnia characterized by the loss of muscle atonia during REM sleep associated with nightmares and active behaviour during dreaming. We have described the effects of CBD in RBD symptoms in patients with Parkinson's disease.

Cases summary: Four patients treated with CBD had prompt and substantial reduction in the frequency of RBD-related events without side effects.

What is new and conclusion: This case series indicates that CBD is able to control the symptoms of RBD.

WHAT IS KNOWN AND OBJECTIVE

Cannabidiol (CBD) is the main non-psychotropic component of the *Cannabis sativa* plant. Several studies have shown that CBD has a broad spectrum of action that includes hypnotic, antipsychotic, anxiolytic and neuroprotective properties.¹

There are few investigations about the effects of CBD on the sleep-wake cycle; however, CBD 160 mg/day was shown to significantly increase the quality of sleep, with subjective reports of increased total sleep time and lesser sleep fragmentation. Three doses of CBD (40, 80 and 160 mg/day) were shown to decrease dream recall and were not related to adverse effects on the following day.²

REM sleep behaviour disorder (RBD) is an increasingly recognized parasomnia characterized by the loss of muscle atonia during REM sleep associated with nightmares and active behaviour during dreaming. The study by Schenck *et al.*³ was the first to report that patients with idiopathic RBD had high rates of conversion to pathologies related to the deposition of alpha-synuclein, especially Parkinson's disease (PD).

Nowadays, the pharmacological management of RBD is limited, as the main drug used to treat the condition is clonazepam, a

benzodiazepine with a long half-life. The use of benzodiazepines in elderly individuals is potentially problematic because of their adverse effects, which restrict the use of these drugs in patients with PD and RBD. Another drug used to treat RBD is melatonin,⁴ despite the need for more prospective clinical trials. Some side effects were described in an open-label study,⁵ such as morning headaches, somnolence and psychosis (hallucinations and delusions).

Our group has recently assessed the effects of CBD in the treatment of patients with PD and psychosis and found a significant improvement in psychotic symptoms. Also, there was a significant improvement as measured with a global scale to assess PD (Unified Parkinson's Disease Rating Scale, UPDRS) and reports of clinical improvement in sleep.⁶ Next, we started a parallel double-blind, placebo-controlled exploratory trial to assess the effects of CBD (at doses of 75 and 300 mg) on PD symptoms. This case series aimed to describe the clinical outcome relative to the patients with PD who had a previous diagnosis of RBD after breaking the blind. No patients had current or previous psychiatric disorder or were taking antidepressants.

We included in this case series all patients ($n = 4$) who fulfilled the following inclusion criteria: (i) complete clinical assessment for RBD by a neurologist specialized in sleep disorders and (ii) at least two episodes of complex sleep-related behaviours per week.

From these, two had symptoms and polysomnography (PSG) results compatible with RBD and were classified as patients with definite RBD, and two had RBD-compatible symptoms not confirmed by PSG and were classified as patients with probable RBD. None of the patients had been previously treated for RBD. Three patients received CBD 75 mg/day, and one received CBD 300 mg/day for 6 weeks. Unfortunately, no patients who took placebo had the same characteristics of our cases.

The study was approved by the local ethics committee, and all patients provided their signed consent to participate (HCRP no. 8990/2011).

DETAILS OF THE CASES

Case 1

A 61-year-old man diagnosed with PD for 18 years and with episodes of agitation and behavioural alterations during sleep

Correspondence: M. H. N. Chagas, Hospital das Clínicas da FMRP-USP- Terceiro Andar, Av. Bandeirantes, 3900, 14048-900-Ribeirão Preto, SP, Brasil. Tel./fax: +55 16 3602 2703; e-mail: mchagas@fmrp.usp.br

characterized by talking, swearing, yelling, pushing, kicking and punching, and gesturing. These features preceded the onset of PD by 2 years and had already resulted in injury to the patient's wife. Although the patient recognized the occurrence of these episodes at a frequency of one per month, the wife reported that they took place between two and four times every week, lasting for around 2 min and occurring mainly in the middle third of sleep. Dream content with these problematic behaviours consisted mostly of being at work, being attacked by animals and being in a fight. RBD was confirmed by PSG showing REM sleep without atonia. Clinical assessments were made at baseline and in the last week of treatment with CBD 75 mg/day. During the 6 weeks of treatment, the patient had no episodes of agitation, aggressive behaviour or nightmare during sleep according to his own and his wife's account.

Case 2

A 59-year-old man was diagnosed with PD at age 53 years and RBD with onset of episodes 1 year before. According to wife, the episodes were brief, lasting for seconds, and consisted of talking, yelling, laughing, gesturing, pushing and mainly kicking the bedside table. Episodes occurred between two and four times a week, mainly in the final third of sleep. The patient reported that he seldom remembered his dreams, but that when he did, contents were usually related to arguments with relatives and animal attacks. Unfortunately, the patient did not enter REM sleep during PSG, which hampered diagnostic confirmation. CBD was introduced at 75 mg/day, and no episodes of agitation, kicking or nightmare were reported during the 6 weeks of treatment.

Case 3

A 63-year-old man was diagnosed with PD 4 years earlier and also had daily episodes of talking, yelling, singing, pushing, punching and kicking during sleep. The patient reported dreams in which he was playing soccer and associated dream contents with the kicking behaviour. Also according to the patient, the symptoms began before the onset of PD and frequently led to his awakening, in addition to having caused injury to his wife. The patient's diagnosis was probable RBD as he did not wish to undergo PSG. CBD 75 mg/day was introduced, and no episodes or complaints of aggressive behaviour or nightmare were reported during the 6-week treatment period.

Case 4

A 71-year-old man was diagnosed with PD 3 years before and had between two and four episodes of complex movements during the night per week. The most common behaviours in these episodes included laughing, kicking, pushing and punching. The patient reported that he seldom remembered his dreams, but described dreams with fun content and others in which he was assaulted by people. Also according to the patient, the symptoms started long before the onset of PD, when he was 40 years old. PSG confirmed the clinical suspicion of RBD by the presence of atonia loss during REM sleep. For 6 weeks, the patient used CBD 300 mg/day with behaviour and dream improvement, describing a reduction in the frequency of episodes to one episode per week during the treatment (Table 1).

WHAT IS NEW AND CONCLUSION

We have described the beneficial effects of treatment with CBD in the reduction of symptoms highly suggestive of RBD in PD. In this case series, the four patients treated with CBD had prompt, substantial and persistent reduction in the frequency of RBD-related events. Regarding symptoms after drug discontinuation, RBD complex movements returned with the same frequency and intensity of baseline after the treatment was interrupted. All patients were referred to the local specialized sleep outpatient clinic. The mechanism of therapeutic action at present can only be speculated upon.

Concerning the effects of CBD on sleep, animal studies have found different results according to the dose and route of administration used.⁷⁻⁹ The intracerebroventricular administration of CBD led to an increase in wakefulness and consequent reduction in REM sleep in rats.⁹ A complementary study found reductions in slow-wave and REM sleep, accompanied by increased wakefulness after CBD infusion into the lateral hypothalamus and dorsal raphe nucleus.¹⁰

CB₁ receptors are found in many brain areas, including those directly related to the regulation of the sleep-wake cycle.¹¹ In animal models, the activation of CB₁ receptors by anandamide, an endogenous cannabinoid, increased the duration of slow-wave and REM sleep and reduced wakefulness.¹² Conversely, the inverse agonist of the CB₁ receptor SR141716A increased wakefulness in association with reductions in slow-wave and REM sleep.¹³

Few studies have explored the effects of CBD on sleep in humans and none investigated the effects of CBD on sleep in PD. In patients with RBD, the depletion of mesencephalic cholinergic

Table 1. Description of patients with PD and symptoms compatible with RBD

Patient	Symptoms	Polysomnography	Cannabidiol dose	Frequency of symptoms before treatment	Frequency of symptoms after treatment
1	Swearing, talking, yelling, pushing, kicking, punching and gesturing	Compatible PLMI = 0	75 mg	2-4× week	0
2	Yelling, talking, laughing, gesturing, pushing and kicking	Patient did not enter REM sleep during examination PLMI = 0	75 mg	2-4× week	0
3	Talking, yelling, singing, pushing, punching and kicking	Patient refused to undergo examination	75 mg	7× week	0
4	Laughing, kicking, pushing and punching	Compatible PLMI = 84.9	300 mg	2-4× week	1× week

PLMI (events/h), Periodic Leg Movement Index; RBD, REM sleep behaviour disorder; PD, Parkinson's disease.

neurons could be at least partially accountable for the genesis of the disorder.¹⁴ This hypothesis could explain, in part at least, the therapeutic action of cholinesterase inhibitors¹⁵ and could justify CBD's property of improving RBD-compatible symptoms. CB₁ receptors are distributed in areas related to sleep, including the basal prosencephalon and the pedunculo-pontine and laterodorsal nuclei¹⁶, and are expressed in cholinergic neurons. The activation of these receptors by CBD could favour the release of acetylcholine¹⁷ and hence cause symptom improvement through a mechanism similar to the one proposed for anticholinesterase agents.

It is interesting to note that RBD is regarded as a prodromal symptom of PD that may precede the onset of motor symptoms by many decades.¹⁸ CBD has been investigated as a possible neuroprotective agent in animal models of PD^{19–21}, and this case series suggests that CBD can have therapeutic effects in the treatment of RBD in PD. Then, this hypothesis underscores the need for studies with larger therapeutic windows exploring the endocannabinoid system in regard to its neuroprotective potential, especially when we know that CBD is a safe, well-tolerated drug.²²

Before concluding, it is important to mention that this study is based on a small case series of patients with RBD and examines secondary outcomes, which hampers a more detailed clinical

examination of the cases. Other limitations include the fact that only two patients had confirmation of REM sleep without atonia through PSG and no further PSG was repeated in the course of the use of CBD or afterwards for comparison. Finally, the short follow-up period can be considered a major limitation of our study because of the variation in the clinical manifestations of RBD over time.

Despite its intrinsic limitations, this case series indicates that CBD is able to control the symptoms of RBD. Further research is necessary to confirm the possibly beneficial effects of CBD in the treatment of RBD in patients with PD.²³ Furthermore, the enrolment of patients with idiopathic RBD in clinical trials with CBD is desirable as it would enable the investigation of the effects of the drug both on the symptoms of the disorder and as a neuroprotective agent.

ACKNOWLEDGEMENTS

A.W.Z., J.A.C. and J.E.H. have the US patent of cannabidiol derivatives. A.W.Z., J.E.H. and J.A.C. are recipients of a Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq, Brazil) fellowships award. M.M.B. is a postdoctoral fellow of Fundação de Amparo à Pesquisa de São Paulo.

REFERENCES

- Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. *Rev Bras Psiquiatr*, 2008;**30**:271–280.
- Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol*, 1981;**21**:417S–427S.
- Schenck CH, Bundlie SR, Mahowald MW. Delayed emergence of a parkinsonian disorder in 38% of 29 older men initially diagnosed with idiopathic rapid eye movement sleep behaviour disorder. *Neurology*, 1996;**46**:388–393.
- McCarter SJ, Boswell CL, St Louis EK *et al*. Treatment outcomes in REM sleep behavior disorder. *Sleep Med*, 2013;**14**:237–242.
- Boeve BF, Silber MH, Ferman TJ. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. *Sleep Med*, 2003;**4**:281–284.
- Zuardi AW, Crippa JA, Hallak JE *et al*. Cannabidiol for the treatment of psychosis in Parkinson's disease. *J Psychopharmacol*, 2009;**23**:979–983.
- Chagas MH, Crippa JA, Zuardi AW *et al*. Effects of acute systemic administration of cannabidiol on sleep–wake cycle in rats. *J Psychopharmacol*, 2013;**27**:312–316.
- Monti JM. Hypnotic effects of cannabidiol in the rat. *Psychopharmacology*, 1977;**55**:263–265.
- Murillo-Rodriguez E, Millan-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colin R. Cannabidiol, a constituent of *Cannabis sativa*, modulates sleep in rats. *FEBS Lett*, 2006;**580**:4337–4345.
- Murillo-Rodriguez E, Millan-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colin R. The nonpsychoactive Cannabis constituent cannabidiol is a wake-inducing agent. *Behav Neurosci*, 2008;**122**:1378–1382.
- Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC. Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. *J Neurosci*, 1991;**11**:563–583.
- Murillo-Rodriguez E, Sanchez-Alavez M, Navarro L, Martinez-Gonzalez D, Drucker-Colin R, Prospero-Garcia O. Anandamide modulates sleep and memory in rats. *Brain Res*, 1998;**812**:270–274.
- Santucci V, Storme JJ, Soubrie P, Le Fur G. Arousal-enhancing properties of the CB₁ cannabinoid receptor antagonist SR 141716A in rats as assessed by electroencephalographic spectral and sleep-waking cycle analysis. *Life Sci*, 1996;**58**:PL103–PL110.
- Benarroch EE, Schmeichel AM, Parisi JE. Depletion of mesopontine cholinergic and sparing of raphe neurons in multiple system atrophy. *Neurology*, 2002;**59**:944–946.
- Ringman JM, Simmons JH. Treatment of REM sleep behavior disorder with donepezil: a report of three cases. *Neurology*, 2000;**55**:870–871.
- Moldrich G, Wenger T. Localization of the CB₁ cannabinoid receptor in the rat brain. An immunohistochemical study. *Peptides*, 2000;**21**:1735–1742.
- Acquas E, Pisanu A, Marrocu P, Di Chiara G. Cannabinoid CB₁ receptor agonists increase rat cortical and hippocampal acetylcholine release in vivo. *Eur J Pharmacol*, 2000;**401**:179–185.
- Claassen DO, Josephs KA, Ahlskog JE, Silber MH, Tippmann-Peikert M, Boeve BF. REM sleep behavior disorder preceding other aspects of synucleinopathies by up to half a century. *Neurology*, 2010;**75**:494–499.
- Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res*, 2007;**1134**:162–170.
- Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiol Dis*, 2005;**19**:96–107.
- Price DA, Martinez AA, Seillier A *et al*. WIN55,212-2, a cannabinoid receptor agonist, protects against nigrostriatal cell loss in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease. *Eur J Neurosci*, 2009;**29**:2177–2186.
- Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a *Cannabis sativa* constituent. *Curr Drug Saf*, 2011;**6**:237–249.
- Schenck CH, Montplaisir JY, Frauscher B *et al*. Rapid eye movement sleep behavior disorder: devising controlled active treatment studies for symptomatic and neuroprotective therapy—a consensus statement from the International Rapid Eye Movement Sleep Behavior Disorder Study Group. *Sleep Med*, 2013;**14**:795–806.