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More evidence of cannabis efficacy in restless legs syndrome

Imad Ghorayeb [1,2,3]

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Abstract

Restless legs syndrome (RLS) is one of the most disabling and sometimes painful sensorimotor ailment of the nervous system that has only in recent years become more widely accepted as a clinical disorder with its own distinct features. Usually, symptoms respond well to dopamine agonists, anticonvulsants, or opiates, but still a subset of patients remains refractory to medical therapy and/or reports serious side effects. Recently, patients' statement of a remarkable and total remission of RLS symptoms following cannabis use has been reported. Here, we confirm and extend these findings to more patients with RLS. The antinociceptive effect of marijuana has been documented in many painful neurological conditions, and the potential benefit of cannabis use in patients with refractory RLS should therefore be questioned by robust clinical trials.

Keywords Restless legs syndrome · Cannabis · Treatment · To the Editor

Restless legs syndrome (RLS) is a chronic sensorimotor disorder characterized by an urge to move the legs. This urge is often accompanied by pain or other uncomfortable and unpleasant sensations. Restless legs syndrome either occurs or worsens during rest, particularly in the evening and/or at night, and temporarily improves with activity. Affecting nearly 3% of the North American and European populations in its moderate-to-severe form, RLS has a considerable negative impact on the quality of life and sleep and is associated with significant morbidity. Although new developments have deepened our understanding of the disorder, the corresponding pathophysiologic features that underlie the sensorimotor presentation are still not fully understood. Usually, symptoms respond well to dopamine agonists (DA), anticonvulsants, or opiates, used either alone or in any combination, but a subset of patients remains refractory to medical therapy and serious side effects such as augmentation, and impulse control disorder may occur in patients with RLS treated with DA. Convincing treatment alternatives are lacking, but recently, patients' spontaneous reports of a remarkable and total remission of RLS symptoms following cannabis smoking has been reported in six patients [1]. Since that first report, we have identified 12 additional patients who spontaneously admitted recreational marijuana smoking. Similar to patients in the first report, the additional patients complained of severe to very severe RLS symptoms and were treated with one or more available drugs for RLS with poor or limited efficacy, except for patient 12 who declined long-term drug intake (Table 1). All but one patient (patient 2) admitted total relief of symptoms following cannabis smoking but none discontinued current RLS treatment mainly because of the illicit aspect of marijuana smoking and the concern about a potential risk for abuse and psychoactive effects. With this in mind, patient 4 restricted marijuana smoking to episodes of extremely severe symptoms, while patients 3, 10, and 11 shifted to over-the-counter sublingual cannabidiol with estimated 70, 0, and 90 percent of relief, respectively. All three of these patients admitted the superiority of cannabis smoking over the use of cannabidiol for symptom relief. Side effects were panic attacks in one patient (patient 6), but otherwise, bedtime cannabis smoking was well-tolerated.

This is the second report on the efficacy of smoking cannabis for RLS. Combined with updated data obtained from patients of the first report, marijuana smoking appears to be more efficient in abating RLS severity than sublingual

✉ Imad Ghorayeb
imad.ghorayeb@u-bordeaux.fr

[1] Département de Neurophysiologie Clinique, Pôle Neurosciences Cliniques, CHU de Bordeaux, F-33076 Bordeaux, France

[2] Université de Bordeaux, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR 5287, F-33076 Bordeaux, France

[3] Centre National de la Recherche Scientifique, Institut de Neurosciences Cognitives et Intégratives d'Aquitaine, UMR 5287, F-33076 Bordeaux, France

Table 1 Demographics of patients with restless legs syndrome

Patient no.	Age (years)	Gender	Medical history	RLS family history	Disease duration (years)	IRLSRS	Ferritin (ng/ml)	Estimated % of relief following marijuana smoking	Previous RLS treatment	Current RLS treatment
1	39	M	HIV	Yes	14	32	193	100%	Pramipexole	Pramipexole
2	40	M	None	No	25	26	138	0%	Clonazepam, codeine, ropinirole	Pregabalin
3	69	M	None	?	39	28	256	100% (70% with CBD)	Ropinirole, rotigotine, clonazepam, codeine	Pramipexole
4	67	F	Breast cancer	Yes	14	35	279	80%	Ropinirole, pregabalin	Pramipexole + codeine
5	43	M	Lumbar hernia surgery	No	16	40	129	100%	Pregabalin, tramadol, pramipexole, clonazepam	Codeine
6	31	M	None	No	22	35	NA	100%	None	Codeine
7	52	M	None	No	11	40	129	60%	Tramadol, ropinirole, pregabalin	Oxycodone/naloxone
8	50	M	Cervical hernia	?	5	32	108	100%	None	Codeine
9	35	M	None	Yes	14	36	122	100%	Clonazepam, pregabalin, gabapentin, ropinirole, pramipexole, tramadol	Rotigotine
10	54	M	Addiction to alcohol, BZD, depression	Yes	35	40	240	100% (0% with CBD)	Clonazepam, pramipexole, ropinirole, codeine, tramadol, pregabalin, gabapentin	Pramipexole + diazepam
11	67	M	Cardiac arrhythmia	No	34	30	126	100% (90% with CBD)	Levodopa, ropinirole, pramipexole, rotigotine, clonazepam, pregabalin, codeine	Pramipexole
12	34	M	None	Yes	10	23	NA	90%	None	None

HIV, human virus immunodeficiency; *BZD*, benzodiazepines; *RLS*, restless legs syndrome; *IRLSRS*, international RLS rating scale; *NA*, not available; *CBD*, cannabidiol

cannabidiol. Whether the latter is related to the potential anxiolytic and sedative-hypnotic effects of cannabinoids warrants further research. The limitations of this report include the absence of polysomnographic data on objective sleep parameters. Patients' subjective estimation of the cannabis efficacy may also be skewed by the psychoactive and anxiolytic properties of the drug. Well-controlled clinical trials are therefore required to test the short-term and long-term effectiveness and safety of medical cannabis for RLS.

As a natural component of human physiology, the endocannabinoid system, consisting of the cannabinoid type 1 receptor (CB_1R), cannabinoid type 2 receptor (CB_2R), and endogenous cannabinoid ligands (endocannabinoids), is present throughout the pain pathways. In particular, CB_1R is widely distributed at peripheral, spinal, or supraspinal sites where cannabinoids likely exert their analgesic effects through inhibition of presynaptic neurotransmitter and neuropeptide release and modulation of postsynaptic neuronal excitability. Relevant to hypothetical RLS pathophysiology, complex interactions between endocannabinoids and other neurotransmitter systems, mainly monoaminergic, have been reported [2]. Cannabinoids regulate the release of noradrenaline and serotonin by direct and indirect mechanisms, and this may underlie several behavioral effects induced by cannabis, including anxiolytic, antidepressant, and antinociceptive effects [3]. Evidence also indicates that chronic cannabis use is associated with reduced dopamine synthesis capacity which, in line with the hyperdopaminergic state that may underlie RLS symptoms, may account for the reported efficacy of cannabis in RLS [1, 4]. Finally, facilitatory and inhibitory functional interactions between striatal adenosine A_{2A} receptor and cannabinoid CB_1 receptor through heteromeric complexes have also been reported [5]. Altogether, these findings may open a new conceptual framework to understand the role of coordinated endocannabinoid signaling in the central nervous system, which may be relevant for the understanding of cannabis efficacy in RLS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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