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Cannabis and Multiple Sclerosis

Yara Dadalti Fragoso[1,2]*, Adriana Carra[3], Miguel Angel Macias[4]

1- Post-Graduate Program on Health and Environment, Universidade Metropolitana de Santos, SP, Brazil
2- MS & Headache Research, Santos, SP, Brazil
3- MS Section. Hospital Británico de CABA, Buenos Aires, Argentina.
4- Departamento de Neurociencias y Doctorado de Farmacologia, CUCS, Universidad de Guadalajara. Mexico

***Corresponding author:**

Yara Dadalti Fragoso, Medical School, UNIMES

Avenida Conselheiro Nebias 536, Santos, SP, Brazil CEP 11045-002

Telephone/Fax: +55 13 32283400

Email: yara@bsnet.com.br

Abstract

Introduction: Patients with multiple sclerosis (MS) may suffer from spasticity and pain during their disease course. Baclofen, dantrolene, diazepam and gabapentin have been used as first-line options to treat these conditions, with modest results. Medical use of marijuana smoking has bypassed traditional

clinical trials and has been legalized as a therapeutic option for MS-related spasticity and pain in some countries. Cannabis-derived drugs have been tested and approved for medical use.

Areas covered: With the development of nabiximols by the pharmaceutical industry, more countries have made it possible for patients with MS to have legal access to cannabis-related therapies. The evidence-based data on nabiximols and MS-related spasticity, pain and urinary symptoms is consistent. There are over 7,500 patients reported in 33 studies (12 from the United Kingdom and 11 from Italy).

Expert opinion: Nabiximols is safe and effective for patients with MS whose spasticity could not be treated with the first-line oral drugs. At present, legislation, bureaucracy and costs involved in prescribing this drug limit the experience of neurologists from many countries. There is no scientific evidence that smoking marijuana can be beneficial to patients with MS.

Keywords: multiple sclerosis, cannabis, nabiximols, spasticity, pain.

Multiple sclerosis, cannabis, spasticity, pain, legislation.

Article highlights

- Spasticity associated with MS is difficult to treat and may cause pain.
- Marijuana smoking has not been studied as a possible treatment in MS.
- Among cannabis products, nabiximols has been approved for MS.
- Nabiximols is an effective and safe treatment for MS-related spasticity.

1. Introduction

Cannabis sativa is the most cultivated recreational drug in the world. [ref WHO] Also known as “marijuana”, it is used by approximately 147 million individuals per year, i.e. nearly 2.5% of the global population [1]. The major psychoactive constituent in cannabis is delta-9 tetrahydrocannabinol (THC). Cannabidiol (CBD) is another constituent of cannabis, with psychoactive properties that are milder and differ from those of THC. There are over 70 compounds isolated from cannabis [2], but THC and CBD will be the focus of this review.

Medical and recreational use of cannabis has garnered increasing acceptance across the world, with many countries legalizing its use within rigorous legislation. While its recreational use (and abuse) is a matter of deep concern for many, the medical use of cannabis seems to have public support [3,4]. Unlike other drugs, medical cannabis has bypassed traditional evidence-based studies and has been legalized as a therapeutic option in several countries [5]. The high potential for abuse and dependence, and the implication of cannabis as a potential gateway to other substances, makes it hard to legislate and supervise this vilified substance that has therapeutic merits [6]. The public in general does not seem aware of the scientific rigor of medicinal cannabis studies and may consider legislation to be excessive. The lay media tends to emphasize the benefits of cannabis therapy, irrespective of evidence-based results, thus creating high expectations among patients and their relatives. It is not rare to see a patient or a relative demanding a prescription for cannabis in a wide diversity of clinical situations because they saw amazing results via the internet. While recreational cannabis presents subjective health-related benefits for users, it may also be associated with brain-related risks [7].

Cannabis has been recognized as a potential treatment for a variety of conditions, particularly when symptoms are refractory to other therapies [6]. Agents derived from cannabis containing the compounds THC and/or CBD have been reported to be relatively safe, with few deaths from their use [8].

The objective of the present study was to review data on use of cannabis for symptomatic treatment of multiple sclerosis (MS). The information will be summarized as follows:

- Cannabis pharmacology
- Drugs interacting with cannabis
- Adverse events of cannabis
- Medical use of cannabis
- Evidence-based data
- Legislation on cannabis for MS
- Options for treating spasticity in MS
- Expert opinion

2. Cannabis pharmacology

The investigation of cannabis effect in the human body led to discovery of the convoluted endocannabinoid (eCB) system that humans possess [9]. The eCB system is found throughout the human body and has a homeostatic role that can be characterized and summarized as “eat, sleep, relax, forget and protect” [10]. Many researchers refer to the whole eCB apparatus as “the endocannabinoidome”, such is its complexity [9].

There are two 7-transmembrane-domain and G protein-coupled receptors for delta(9)-THC. These are type-1 (CB1) and type-2 (CB2) receptors. The most

studied eCB ligands for these receptors are N-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG). The plant ligands for these receptors are THC and CBD, and both are found in *Cannabis sativa* [11]. For details on the receptors and ligands of the endocannabinoid system the authors recommend the work of Alexander [11].

The eCB system is particularly involved in the mechanisms of pain control through the transient receptor potential ion channels of vanilloid type-1 (TRPV1) [13]. The stimulatory, and subsequently desensitizing, effects of anandamide on TRPV1 after CB1 activation have been widely reported [14]. This is how medical cannabis found its way into the therapeutic arsenal of clinicians [12].

The pharmacokinetics of THC and CBD have been relatively difficult to study due to the adsorption of these compounds to multiple surfaces. The effect is immediate and, depending on the mode of administration, the high peak occurs after 15 to 30 minutes, with a steady decline over the next four to 12 hours [15,16].

3. Drugs interacting with cannabis

Quantification of the in vitro metabolism of THC and CBD has indicated that hepatic cytochrome 450 (CYP450) and isoenzymes 2C9 and 3A4 are involved in the primary metabolism of both THC and CBD [17]. Pharmacodynamic adverse effects of THC and CBD may occur when cannabis is coadministered with other agents that have similar effects. For example, alcohol, sedatives and antihistaminic drugs may increase sedation in patients using cannabis, while tricyclic antidepressants or stimulants plus cannabis may lead to tachycardia. In addition, smoking cannabis may increase theophylline metabolism [17,18].

4. Adverse events (AEs) of cannabis

Regular recreational use of marijuana before age 17 years reduces the odds of high-school completion and degree attainment [19]. Cannabis use seems to associate with higher risks of heart failure, stroke, coronary artery disease, sudden cardiac death, and hypertension [20]. However, these reported AEs may not be determined by cannabis use alone, since many individuals may also be malnourished, have psychiatric comorbidities, and use alcohol, tobacco and/or other drugs. Another potential determinant of AEs is the practice of illegal *Cannabis sativa* cultivation, which may involve pesticides and water contamination [21]. For the medical use of cannabis, tolerance can be increased by commencing the dose at modest levels and proceeding slowly with titration, often over a period of two weeks [22]. Long-term AEs and fatal outcomes through medical use of cannabis are rare and controversial [23, 24].

5. Medical use of cannabis

Despite having been used for thousands of years, there are controversial data on cannabis safety to support its legalization for recreational use [25]. The THC levels that are presented can be worrisome, since THC has psychoactive effects s [18]. However, anecdotal reports on patients with chronic conditions who experienced pain relief when smoking marijuana led to campaigns for legalization of medical use of cannabis. Permission to cultivate *Cannabis sativa* for personal use in relation to MS came through claims that patients experienced reduced disability progression, better pain and spasticity relief, improved bladder function, decreased tremor/ataxia, better quality of sleep and, altogether, improved quality of life. [26,27]. Based upon the reported success of this potential symptomatic therapy, the pharmaceutical industry developed a

standardized extract of THC and CBD (1:1) that also contained other minor cannabinoids, flavonoids and terpenes, from two cannabis plant varieties. Known as nabiximols (Sativex® or Movatyl®; GW Pharmaceuticals, UK), this extract was approved in the UK in 2003 [28]. Nabiximols neither induces tolerance, nor requires incremented doses for its benefits regarding quality of sleep [29]. At present, use of nabiximols for MS has been approved in 30 countries but has not yet received Food and Drug Administration (FDA) approval.

The commercially available cannabidiols approved by the FDA are nabilone (Cesamet®, Valeant Pharmaceuticals International) and its purified form dronabinol (Marinol®, Syndros®, AbbVie Inc., USA; Alkem, India). These are synthetic THC-like compounds that have been approved for treating the nausea and vomiting associated with chemotherapy, among patients who have failed to respond adequately to conventional antiemetic treatments [30, 31]. Dronabinol has also been approved for treating the anorexia and weight loss associated with AIDS and cancer. [32]

Epidiolex® (GW Pharmaceuticals, UK) is a purified extract of CBD. With less than 0.1% THC (the psychoactive component of cannabis), this compound has been approved for treating rare and severe forms of epilepsy in patients aged two years and over [33]. Three clinical trials have shown that Epidiolex® has beneficial effects on refractory epilepsy, and it has now been approved as adjunctive therapy for Lennox-Gastaut syndrome (USA, Europe) and Dravet syndrome (USA) [33,34].

6. Evidence-based data

There are no clinical trials supporting marijuana smoking for medical purposes [35]. At present, the marijuana-derived drugs approved by the FDA are dronabinol (Marinol®, Syndros®), nabilone (Cesamet®) and cannabidiol (Epidiolex). A comprehensive review of reviews on nabiximols (Sativex®, Mevatyl®) concluded that this compound has modest effects on pain and spasticity in MS [27]. Data on clinical trials of nabiximols in MS are presented in Table 1. Over 7,500 patients with MS were included in these studies.

7. Legislation on cannabis for MS

7.1 Marijuana smoking

Regulatory agencies worldwide have different rules, regulations and legislation regarding cannabis use. While in some countries (or USA states) marijuana can be legally consumed, in others the recreational use of marijuana is illegal [36]. Plausible effects of legalizing recreational *Cannabis sativa* smoking include a substantial price reduction of the drug, a risk of heavier use and a potential increase in the number of new users [37]. Regarding medical use of cultivated *Cannabis sativa*, many patients still face onerous bureaucratic requirements for obtaining legal permission to possess and cultivate a safe, reliable, legal source of marijuana plants [38].

Several countries have legislated on marijuana smoking for medical purposes: Argentina, Australia, Canada, Chile, Colombia, Croatia, Cyprus, Czech Republic, Denmark, Finland, Germany, Greece, Israel, Italy, Jamaica, Lesotho, Luxembourg, Macedonia, Malta, Mexico, Netherlands, Norway, Peru, Poland, Romania, San Marino, South Africa, Switzerland, Turkey, United States of America (most states), Uruguay and Zimbabwe [39]. While in some of the

above-listed countries it is possible to obtain recreational cannabis as well, in others the medical use is restricted and bureaucratic. Countries like Brazil, China, France, India, Japan, Russia, Sweden and the United Kingdom have harsh legal limitations for medical marijuana cultivation, although this may change [40].

7.2 Nabiximols

The main agencies responsible for evaluating and approving drugs are the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). [41, 42] In Latin America, the agencies are individually organized by each country, as they are in Asia and Oceania. Therefore, the legislation and experience with nabiximols as a complementary therapy in MS vary worldwide. Data on clinical trials are presented in Table 1 and, it is interesting to observe that a review of data on ability to drive showed that nabiximols do not affect this skill [43]. Furthermore, cessation of nabiximols therapy is generally safe, with no evidence of physiological or psychological dependence [44]. Unfortunately, many clinical trials and publications on nabiximols have focused on reduction of the withdrawal effects of THC rather than being studies on MS.

8. Options for treating spasticity in MS

Use of nabiximols and smoking marijuana are not considered to be the initial option for patients with MS who have spasticity, irrespectively of pain. Oral baclofen, gabapentin and tizanidine are often used for first-line treatment of MS spasticity. [45,46] Diazepam or dantrolene could be considered for patients not responding or not tolerating these previous drugs. Botulinum toxin can relieve

spasticity and may help other symptoms of MS such as focal tonic spasms, spastic dysphagia, neurogenic bladder and double vision in internuclear ophthalmoplegia [47]. The logistic problems of moving a spastic patient from home and/or the barriers against reaching specialized clinics and physicians are deterrents that hinder regular use of botulinum toxin [48]. All the above-mentioned treatments are ineffective in approximately 40% of the cases [45]. Furthermore, muscle weakness, nausea and somnolence are common limitation to the usefulness of many drugs. Intrathecal baclofen may be an option in these cases [48]. Although intrathecal baclofen is effective and well tolerated, [Samaraeie] its administration requires specialized units, pumps and hygiene, and it is an expensive option [49,50]. Likewise, chemodenervation and implantation of neuromodulators demands high expertise. [51]

9. Expert opinion

The issue of cannabis in MS is particularly complex since it involves stigma against the drug and its legalization, an often-appealing lay media and a relative lack of clinical trials. There are patients with MS who will certainly benefit from cannabis as symptomatic therapy, but their expectations and our recommendations are not the same.

Planting *Cannabis sativa* for self-use at home can be a problem. The origin of the plant is an important issue since fertilizers and insecticides are not themselves free from serious adverse events. Nonetheless, assuming the plant has a good origin (and there is no specific legislation about this), the central question remains: how often is it advisable to smoke marijuana if you have MS? There are very few clinical trials studying the effect of smoking cannabis versus placebo, let alone on the dose-related benefits and tolerance assessments.

Nabiximols has now been used for a few years with well-established safety and efficacy profile. I can be recommended for patients with MS who suffer from spasticity, particularly when this is associated with pain. We highlight that the studies on nabiximols are for pain related to spasticity and not for neuropathic pain. The relief obtained through using this drug is short-lived and nabiximols could be indicated prior to physical therapy or exercises, for example. Nabiximols is expensive (USD 120 to 450 per month) and its use is not reimbursed by the governments of all countries. Patients with severe spasticity are likely to be out of work and, therefore, might not be able to afford this treatment. Should nabiximols start to be reimbursed by the public and private health systems, more patients with MS would use it and have symptomatic improvement.

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Legend to the Table:

Table 1. Summarized information on 33 studies of cannabis in multiple sclerosis. Abbreviations: USA: United States of America; UK: United Kingdom; DBPC: double-blind placebo controlled; DBRPC: double-blind randomized placebo controlled; OL: open label; OLPC: open label placebo controlled; PCCO: placebo-controlled crossover trial; THC: tetrahydrocannabinol; CBD: cannabidiol.

Table 1

Type of study	Outcome	Number of patients	Results
DBPC	Spasticity	13	Improved
DBRPC	Balance	10	Improved
DBRPC with crossover	Spasticity	16	Not significant
DBRPC	Spaticity and pain	611	Improved pain
DBRPC	Spaticity	160	Improved
OL pilot study	Urinary symptoms	10	Improved
DBRPC with crossover	Spasticity	57	Improved
DBRPC with crossover	Tremor	14	Not significant
DBRPC	Spasticity follow-up	630	limited improve
DBRPC	Central Pain	66	Improved
DBRPC	Urinary symptoms	630	Improved
OLPC	Spasticity long term effect	137	Improved
DBRPC	Spasticity	189	Improved
DBPC	Cognition	17	No negative effects on cognition
DBRPC	Urinary symptoms	135	Not significant
DBRPC	Spasticity	337	Improved
DBRPC	Spasticity	572	Improved
DBRPC	Spasticity	279	Improved
PCCO	Spasticity	30	Improved
DBRPC	Central neuropathic pain	339	Not significant

OL	Spasticity	335	Improved	
OL	Walking	20	Improved	
DBPC crossover	Spasticity and cortical hyperexcitability	34	Only improved spasticity	
OL	Spasticity-related symptoms	433	Improved	
OL	Spasticity and pain	144	Improved	
Retrospective data	Spasticity	1615	Improved	
OL	neuropathies	20	Mild improvement	
DBPC	neurophatic Pain	240	Improved	
OL	Time-to-respond	30	Up to 6 weeks for response	
OL	Urinary symptoms	15	Improved	
OL	Pain modulation	19	Improved	
OL	Balance	22	Worsened	
DBPC	Spasticity and pain	106	Improved	
Retrospective data	Predictors of discontinuation	396	Cognitive and physical disabilities	