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REVIEW

Emerging treatment options for spasticity in multiple sclerosis – clinical utility of cannabinoids

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Abstract: Multiple sclerosis (MS) is a widespread and common disabling autoimmune disease of the central nervous system. The main disabling symptom is muscle spasticity, which occurs in most patients. Treatment of spasticity with existing drugs is often poor, and there is a need for new and additional treatments. This article reviews the use of cannabinoids for the treatment of symptoms in MS, focusing on the pharmacology of Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol and analog drugs in various formulations, the rationale for their use, and their efficacy and safety in the treatment of MS. It is concluded that of all currently available formulations, only sublingual spray containing Δ^9-THC has a sufficient evidence base to justify its use in treatment of spasticity and patient quality of life, particularly in patients' refractory to current treatments.

Keywords: MS, Δ^9-tetrahydrocannabinol, Δ^9-THC, cannabis

Introduction: management issues for spasticity in multiple sclerosis

Multiple sclerosis (MS) is a progressive or relapsing/remitting autoimmune disease of the central nervous system. The disease is characterized by the autoimmune destruction of myelin in the central white matter, and associated inflammation. The most commonly reported symptom (90% of patients) for MS is spasticity, which not only hinders movement, but can cause pain and impact on quality of life in numerous ways, causing distress and suffering to the patient. Other symptoms include tremor, central neuropathic pain, ataxia, and urinary incontinence. MS is the most common disabling neurological condition in young adults, and the most common inflammatory disease of the central nervous system worldwide.[1]

Spasticity is characterized by sudden involuntary movements, muscle stiffness, or muscle spasms sufficient to cause pain, particularly in the lower back and legs. Although the ultimate goal of therapy for MS is modification of the underlying disease, aiming to induce remission and recovery, management of symptoms with drugs that specifically target symptoms such as spasticity are an important part of MS treatment. Standard drugs used to treat spasticity include centrally acting agents, such as benzodiazepines, baclofen, tizanidine, and gabapentin, and peripherally acting agents such as dantrolene. However, there is a very limited evidence base for these drugs,[2] and they provide only moderate relief from spasticity.[3] Because many patients are refractory to treatment with existing oral drugs, there is a clear need for new treatments for spasticity in MS.

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Pharmacology of cannabinoids used in the treatment of multiple sclerosis

Cannabinoids have been identified as promising agents to treat the symptoms of MS, particularly spasticity. The first cannabinoids to be purified were the phytocannabinoids derived from the cannabis plant, *Cannabis sativak*.[4] These include Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol, which have been extensively studied for their medicinal qualities. Dronabinol is the name given to the synthetically produced (−)-*trans*-isomer of Δ^9-THC (which is also naturally occurring).[5] Nabilone is a synthetically produced classical cannabinoid that is a more potent analog of Δ^9-THC, such that 1 mg of nabilone is approximately equivalent to 10 mg of dronabinol. Nabilone is the only synthetic cannabinoid that has been licensed for use.[6]

Phytocannabinoids are highly lipophilic and show extremely high levels of nonspecific binding in radioligand binding experiments. The development of high affinity synthetic cannabinoids was a critical step in the discovery of cannabinoid-specific bindingsites: the cannabinoid receptors.[7,8] Identification of cannabinoid CB_1 receptors and determination of their distribution in the brain revealed that CB_1 is strongly expressed in areas of the brain relevant to MS such as the motor regions of basal ganglia and striatum, and in the pain pathway.[9] Soon after the characterization of cannabinoid receptors, the first endocannabinoids were identified.[4] The prototypical endocannabinoid sanandamide and 2-arachidonylglycerol have been extensively studied for both their biochemistry and pharmacology. These act on CB_1 receptors in neurons to inhibit the release of classical neurotransmitters such as glutamate, dopamine, and γ-aminobutyric acid.[10,11] Activation of CB_1 receptors in the brain has potential therapeutic effects by inhibiting spontaneous activity in the motor and pain pathways, but also causes the characteristic intoxicating "high" of cannabis use, along with sedation, memory impairment, mood changes, and alterations in perception.[4]

The cannabinoid drugs that were first approved for clinical use were synthetic analogs or stereoisomers of Δ^9-THC. These are the (−)-*trans*-isomer of Δ^9-THC, dronabinol (Marinol®, Solvay Pharmaceuticals, Brussels, Belgium), and the more potent CB_1 agonist, nabilone (Cesamet®, Valeant Pharmaceuticals International Inc, Mississauga, ON).[12] Both of these drugs have been used in various countries to help reduce nausea and vomiting after treatment with anticancer medicines. Marinol is an oral form of dronabinol, is available in the US, Canada, and in some European countries. Marinol comes in the form of capsules, with the dronabinol dissolved in sesame seed oil; these have been available in 2.5, 5.0, and 10.0 mg.[13] Nabilone is marketed under the name Cesamet.[12] Cesamet comes in the form of crystalline powder capsules, containing 1 mg nabilone. Cesamet is available in the United Kingdom, Canada, and in some European countries.

Cannabis is available on a limited basis for medical use in some countries. Oral cannabis extracts have been used for clinical trials; Cannador® (Institute for Clinical Research, IKF, Berlin, Germany) consists of capsules containing cannabis extract standardized to contain 2.5 mg Δ^9-THC and 1.25 mg cannabidiol. However, Cannador has not been licensed anywhere in the world.[14] Cannabis leaf has been approved (as an unlicensed drug) for limited medical use in some countries including Canada. Very few clinical trial data for smoked cannabis exist, though there are some (for example, Abrams et al[15]). It is also difficult to interpret case histories and patient or doctor testimonies, mostly because of the lack of placebo controls, but also because habitual cannabis users can develop tolerance to many of the effects of the drug. Also, the amount of active cannabinoids in any given cannabis cigarette is variable. The Δ^9-THC content in cannabis cigarettes usually ranges between 1.5% and 3.7%, the size of the cigarettes can vary, and the amount of cigarette smoked at any one time can vary (*Pers comm*; New Zealand Ministry of Police, 2011).

Pharmacokinetics

Cannabinoids are highly lipophilic and are rapidly absorbed and distributed around the body. When Δ^9-THC enters the body, it is quickly distributed around the blood plasma, and then quickly moves out of the bloodstream and into surrounding tissues. Therefore, Δ^9-THC first accumulates rapidly in those tissues that have a high throughput of blood, including kidneys, liver, and the lungs, but also the brain. As concentrations build, neuronal CB_1 receptors are increasingly activated, and the psychoactive effect of Δ^9-THC also peaks. Following accumulation of Δ^9-THC in highly perfused tissue, concentrations in these tissues fall, but continue to climb in poorly perfused tissues and in lipophilic compartments.[16–18]

Absorption by inhalation of Δ^9-THC is much faster than for other routes of administration. The very high peak plasma concentrations of Δ^9-THC that are achieved very rapidly by smoking cannabis may help explain why some users claim that the medical benefits of smoked cannabis (for example pain relief) are greater than for other Δ^9-THC preparations.

However, the "peak and trough" pharmacokinetics of smoked cannabis means that users experience significantly greater psychoactivity than when using standardized formulations.[19]

To improve upon the pharmokinetics of both oral and inhaled cannabinoids, GW Pharmaceuticals (Wiltshire, UK) developed Sativex® (GW-1000), a cannabis-plant derived medicine. This combines Δ^9-THC with cannabidiol in a fixed ratio (1:1.08) and is administered using sublingual spray. Sativex was first approved for sale in Canada in 2005, to help reduce neuropathic pain, and is now licensed for use in spasticity in the UK and Spain and by special prescription in New Zealand. In contrast to inhalation, with Sativex, gradual dose titration to approximate steady-state plasma concentrations is possible. To compare Sativex with smoked cannabis, in one study inhalation of 8 mg of Δ^9-THC resulted in peak plasma concentrations 24 times higher than 10 mg of Δ^9-THC delivered by sublingual spray. Also, peak concentration was achieved 17 minutes after inhalation but 263 minutes after sublingual spray. Smoked cannabis providing 13 mg of Δ^9-THC achieved 15.7 times the peak plasma concentration of Δ^9-THC as the Sativex, taking only 9 minutes.[20–22]

Another strategy recently developed for optimal delivery of Δ^9-THC, aiming for improved pharmacokinetics and tight dosage control, has been developed. Namisol® (Echo Pharmaceuticals, Weesp, the Netherlands) contains dronabinol and has been tested in a Phase I trial as an oral and as a sublingual tablet. On the basis of this trial, oral administration appeared to be favorable,[23] with the Δ^9-THC T_{max} of Namisol faster and less variable compared with other buccal/oral administrations (competitors) (*Pers comm*; Echo Pharmaceuticals, 2011).

Rationale for the use of cannabinoids in treating multiple sclerosis

Cannabinoid receptor agonists have various effects, but the most important medical effects can be classified more simply into central nervous system effects and immune system effects. In the immune system, the effects of cannabinoids are generally immunosuppressive and anti-inflammatory, but are more properly immunomodulatory, as in some experiments cannabinoids can be immunostimulatory.[24]

The effects on the central nervous system are dose dependent and include effects on mood such as euphoria and dysphoria, hyperactivity, anxiolysis, and anxiety, and sometimes a sense of enhanced well-being. Effects on perception include a changed time sense, altered perception, hallucinations, paranoia, psychotic states, depersonalization, and dissociation. Cognition is altered so that thinking may become fragmented, and short-term memory is impaired. Body temperature is also reduced, probably through a central nervous system mechanism. Motor control is altered, potentially causing ataxia and loss of coordination, unsteady gait, and slurred speech, but also reducing muscle spasms and ameliorating tremor.[25] Cannabinoids also stimulate appetite, inhibit nausea and vomiting, and have analgesic properties. The most common neurological side effect of medical cannabinoids is drowsiness and sedation.[26]

Although two cannabinoid receptors have been well characterized, only CB_1 is thought to play a major role in the psychoactive effects of cannabinoids.[7] CB_1 is widespread in the central nervous system.[8] During normal functioning in the central nervous system, endocannabinoids activate CB_1 receptors on presynaptic terminals after they are released from depolarized postsynaptic neurons. Stimulated CB_1 receptors then activate G-proteins that in turn suppress neurotransmitter release. During retrograde transmission, CB_1 receptors are well placed to regulate discharge from hyperactive neurons during both normal neuronal functioning and during injury.[27]

CB_1 is most densely expressed in the basal ganglia, limbic system, cerebral cortex, and in the cerebellum, but in relatively low levels in both the brainstem and the spinal cord.[8,28] Importantly, there is no evidence of cannabinoid receptors in the respiratory control centers, in contrast to opioid receptors, so that even potent CB_1 agonists do not cause respiratory depression. CB_1 receptors in the basal ganglia are probably the targets for cannabinoid control of tremor, spasticity, and painful muscle spasm in MS. CB_1 is densely expressed in the output neurons of the substantia nigra pars reticulata and globus pallidus.[29] Activation of CB_1 at these neurons can suppress excessive motor output and consequent muscle spasm.

Cannabinoids reduce pain in MS not only by reducing painful muscle spasm, but by acting in both the central and peripheral pain pathway and by reducing inflammation.[30] The anti-inflammatory properties of cannabinoids are largely due to activation of a second cannabinoid receptor, CB_2. These properties have lead researchers to target the CB_2 receptor for the potential modification of disease progression in inflammation and immune disorders, including MS.[31] CB_2-expressing lymphocytes occur in the lymphoid, myeloid, and monocytic lineages. These include B-cells and T-cells, monocytes and macrophages, dendritic cells, natural killer

cells, and neutrophils;[32] cells involved in virtually all steps in leukocyte-mediated inflammation and immune processes. The endocannabinoid system appears to be active in diseased white and grey matter in patients with MS. For instance, Eljaschewitsch et al[33] found that anandamide levels were significantly increased in active lesions taken from MS patients. Autoimmunity may be moderated by cannabinoids, though this has yet to be determined.

Clinical evidence for the efficacy of cannabinoids in the management of multiple sclerosis

Survey data support the idea that many people use cannabis to self-medicate. Because cannabis is a restricted drug, for which possession and supply are both illegal in most countries, these surveys have tended to often come from Canada, where the practice of self-medication with cannabis is most tolerated.[34,35] Despite the difficulties of obtaining reliable data, epidemiological studies have found that people with conditions varying from chronic pain, MS, and spinal cord injury sometimes self-medicate with cannabis.[36] Some surveys have suggested that very large numbers of patients with MS might self-medicate with cannabis.[37,38] In one survey in the UK, 75 patients with MS were questioned. Of these patients, 83.7% had tried cannabis to help treat their condition, and 75.6% reported that it provided some relief.[39] In an earlier survey that targeted patients with MS that took cannabis for self-medication some 95% of respondents reported that cannabis improved chronic pain to their extremities, spasticity, and some other symptoms such as bladder and bowel dysfunction,[40] Bridging the gap between surveys of people that self-medicate with cannabis and large-scale and well controlled clinical trials are clinical case reports. These often suggest a therapeutic effect, but are hard to interpret as they lack placebo controls. Fortunately, the evidence base for the use of cannabinoid therapeutics is rapidly becoming dominated by larger scale clinical trials.

The main benefit that cannabinoids are hoped to confer on MS patients is reduction of spasticity and tremor, but the effects of cannabinoids on pain, particularly centrally generated paroxysmal pain, can also help MS patients. In addition, cannabinoids appear to help MS patients control their bladder function (reviewed in two papers[41,42]). For example, Svendsen et al[43] found that central pain was significantly reduced by dronabinol in patients with MS. Nabilone was tested for spasticity related pain in MS by Wissel et al,[44] who found that pain was reduced by the drug and that adverse effects were generally mild. Similar results were obtained in the Cannabinoids in Multiple Sclerosis (CAMS) trial, which studied the effects of oral administration of cannabis oil capsules (Cannador) which contained, with other constituents of cannabis, 2.5 mg of Δ^9-THC and 1.25 mg of cannabidiol.[45,46] However, some studies, such as the double-blind, placebo-controlled trial using Δ^9-THC and cannabis extract by Killestein and colleagues[47] have found that not only did the cannabinoids fail to reduce spasticity, but in fact worsened the patients global impression of their condition. Fox et al[48] also found no evidence that oral Cannador reduced upper limb tremor in MS patients. Therefore, it has been argued that there is no compelling case for the use of cannabinoids in symptom management in MS.[49] In addition, the majority of trials have used subjective assessments of spasticity. Only one study confirmed this result with objective assessments.[45,46]

However, randomized trials using Sativex, such as by Rog et al[50] and Wade et al,[51,52] have found modest but definite improvements in MS symptoms. Ben Amar[53] reviewed 12 clinical studies up to 2004 on the treatment of tremor, spasticity, and pain in MS patients with cannabinoids and found that although results were usually negative, small improvements were seen in the trials that used Sativex. These results have been confirmed in a more recent comprehensive review by Karst et al.[54] In a meta-analysis published in 2010, Wade et al[55] calculated that the odds ratio for improvement in spasticity by Sativex is 1.67 (95% confidence interval [CI]:1.05–2.65; $P = 0.030$). Due to public interest, the United Kingdom Medicines and Health care products Regulatory Agency (UK MRHA) issued a Public Information Report on Sativex.[56] The report concluded that "a positive risk-benefit has not been sufficiently demonstrated at this time". However, the report also included responder analyses, which appear to show that although average improvements in symptoms are small, some patients do seem to show marked improvement and may be designated as "cannabinoid responders". A study by Collin and colleagues studied the use of Sativex on MS-related spasticity, and concluded that it may be useful for symptom control. Specifically, 40% of patients achieved a greater than 30% benefit (21.9% of patients with placebo).

Where Sativex may be particularly useful is for advanced MS patients refractory to standard treatments. In a recent trial designed to test the efficacy of Sativex in advanced MS patients with severe spasticity,[56] 73% of patients had a 30% improvement at least once in a 4-week period.[56] In a recently reported 19-week randomized, placebo-controlled, study in patients with MS and with spasticity refractory to current antispasticity treatment,[3] when Sativex was used as an add-on

therapy for 4 weeks, 48% of patients experienced a ≥20% improvement. Of these, a further 241 were randomized, with patients continuing with Sativex showing significantly better outcomes after 19 weeks than the placebo group.

Although motor symptoms and pain have been the primary and secondary outcome measures in most studies on the treatment of MS with cannabinoids, other symptoms have also been studied. Russo and colleagues[57] reviewed clinical trials using Sativex and found that sleep quality was improved in MS patients using the drug. Also, a substudy carried out in the CAMS trials found that the active treatments significantly improved urge incontinence compared with placebo,[58] though a more recent trial by Kavia and colleagues[59] has suggested that the effect may be modest at best.

At the time of writing, the results of a Phase II trial using Namisol for the treatment of spasticity in MS are nearing completion. This is a randomized, double-blind, placebo-controlled trial that will determine efficacy of Namisol in MS patients, with the primary endpoints being spasticity and pain. The trial will consist of two phases, a dose finding and a treatment phase. Previously, a Phase I trial showed that oral Namisol up to 8 mg is safe and well-tolerated by healthy patients, has a short T_{max} and $T_{1/2}$, with quick onset of effects, peaking at approximately 1–2 hours.[23] Given the promise shown by Sativex, further results for this new cannabinoid formulation are awaited.

Safety and tolerability of clinical cannabinoids

All cannabinoids in current therapeutic use have a therapeutic index that is relatively narrow for most uses, with adverse effects limiting dose titration. Adverse effects at the acute stage are mostly psychoactive and due to activation of CB_1 receptors in the central nervous system. Acute effects on the cardiovascular system (postural changes in blood pressure and tachycardia) are also mediated by CB_1 receptors in the brain.[26] In clinical trials using cannabis, cannabis extracts, Δ^9-THC, or analogs of Δ^9-THC, adverse side effects are dose dependent and appear to vary in intensity from trial to trial and between individuals within trials. Possible side effects, adverse and otherwise, include euphoria, dysphoria, anxiety, depersonalization, sedation, and drowsiness, distorted perception, mental clouding, memory impairment, impairment on cognitively demanding tasks, fragmentation of thoughts, and even hallucinations.[60–62] Cannabinoids also stimulate appetite, and in some contexts this might possibly be considered an undesired effect; though it is an effect that is actively sought when cannabinoids are used to stimulate weight gain in patients suffering from disease-induced wasting. Large amounts of cannabis can cause psychotic episodes involving delusions and paranoia, but this has not been reported for the drugs in current clinical development.[60] With respect to motor function, cannabis can cause hypermotility (increased motor activity, movement) followed by lethargy, lack of coordination or ataxia, muscle twitches, tremors and weakness, and problems speaking (dysarthia).[61] Pregnant women should avoid cannabinoids, as this has been linked to the impairment of fetal development,[63,64] even though the evidence for this is inconsistent.[65]

Most of the clinical trials also contain data on adverse effects. These are the best source of data on side effects of Δ^9-THC because they are randomized, placebo-controlled, and use a known dose. These are mostly minor, and virtually all the trials describe the drug as "well-tolerated". The most common side effects reported in the trials are drowsiness, ataxia (loss of coordination), euphoria, and dizziness. At higher doses, dissociation and distorted perception are infrequently reported. For example, in the trials carried out by Berman et al[66] and Rog et al,[50] approximately 25 mg of Δ^9-THC was used, and adverse effects were mild to moderate, and usually spontaneously resolved. In both trials, the most common side effects were dizziness and drowsiness. In Rog et al,[50] 53% of patients experienced at least one episode of dizziness, one of 34 patients experienced drowsiness ("somnolence"), and one of 34 experienced dissociation and ataxia ("feeling drunk"). It is important to note that although this trial (which is typical) recorded at least one minor adverse event for 88.2% of patients on the drug, to put this in context, the figure is 68.8% for patients taking the placebo.

Tolerance and dependence

Cannabis dependence is a recognized syndrome under Diagnostic and Statistical Manual of Mental Disorders IV criteria and has been the subject of a number of epidemiological studies (eg, Boden et al[67] and Fergusson et al[68]). The UK MRHA 2007 report on Sativex states that 1% of cannabis users develop dependence on the drug. However, drug-seeking behavior has many determinants,[69] including self-medication, and levels of use that are typical for one type of drug user (eg, recreational) are not reliable guides to levels of use for other types of users (eg, self-medication). Therefore, the dependence on a drug used for medicinal purposes is quite different from dependence on a drug used for recreation.

One systematic source of data on amounts of Δ^9-THC that will be sought by people comes from clinical trials where

the patients are allowed to "self-titrate". This is where the patient has ad libitum access to the drug (within an upper limit), and takes the drug as required. In this way, the patient finds a balance between the desired and undesired effects to fit their individual needs. In these trials, 25 mg of Δ^9-THC is a typical amount of the drug that is taken during a day when patients in the trials are allowed to self-titrate. This is very similar to the doses that have found to be effective and tolerated when given at set amounts in clinical trials, and is therefore consistent with these patients only seeking as much cannabinoid medication as they need for an optimal treatment effect (source for these figures are the clinical trials cited in sections above).

However, people who self-medicate with Δ^9-THC may raise the dose over time as they become tolerant to the symptom-relieving effects, increasing their level of intake well above that used by occasional recreational users, although this has not been shown to be relevant for licensed medicinal cannabinoids.[70,71] At the same time, tolerance also occurs to adverse effects, such as drowsiness and sedation, and therefore the subject will function whilst receiving amounts of Δ^9-THC that may be debilitating to someone who does not regularly use cannabis. Wade et al[52] and Zajicek et al[46] have both reported on the long-term effects of Δ^9-THC medication. Wade et al[52] followed patients using higher amounts of Δ^9-THC, and minor adverse effects were well-tolerated.

Cannabinoids and the patient

For the patient with MS, Sativex is at the time of writing the only cannabinoid that is widely available for treatment of symptoms. Particularly for advanced MS patients who obtain less than satisfactory relief from standard therapy, Sativex is likely to provide a modest but meaningful improvement in spasticity in particular, and in the pain associated with muscle spasm. Sativex is indicated at present for symptom relief of spasticity, tremor, and pain in patients with MS who have not responded sufficiently well to standard medications, and who show a worthwhile degree of improvement during a 4-week trial period. Sativex is contraindicated in patients with known or suspected allergy to cannabinoids or any of the other ingredients. Like oral cannabinoid drugs, Sativex is also contraindicated for patients with significant psychiatric disorders other than illness-associated depression. Use is not advised for nursing mothers, and also not recommended for adolescents or children under 18, as these groups have not been adequately studied. Elderly patients have been poorly studied as a group, but some clinical trials have included patients up to 90 years of age. Elderly people are more prone to psychoactive adverse reactions and special care should be made for personal safety; for example, to avoid falls or burns whilst cooking or preparing hot drinks.

In addition to spasm, in the most recent trials,[3] such patients have shown additional improvements in bladder control, global impressions of their condition, sleep, quality of life, and patient satisfaction with the treatment regimen. In particular, sleep is an essential aspect of quality of life, and patients with chronic-pain MS often have difficulty sleeping. Sleep disturbance is itself disturbing and unpleasant, and lack of sleep contributes to fatigue during waking hours. Insomnia is generally treated with central nervous system depressants, which have a number of problems with long-term use, including the development of tolerance and dependence, rebound anxiety and insomnia (as well as more severe withdrawal effects), and problems with cognition. Cannabinoids have soporific effects, and the possibility that cannabinoids can help improve sleep when given to patients with chronic pain has been the subject of clinical trials, generally as a secondary outcome measure. In particular, Russo and colleagues[57] reviewed the effects of Sativex in nine clinical trials where sleep disturbance, duration and/or quality were recorded as the secondary outcome measure. Seven out of nine trials found that sleep was improved in patients receiving Sativex compared with patients receiving placebo.

Patient use of Sativex

An essential part of the therapeutic use of Sativex is patient-directed dose-optimization through self-titration. Sativex is administered by escalating doses during a self-titration period, and it may take up to 2 weeks to find the optimal dose. Adverse reactions can occur during this period, although they are generally mild and resolve in several days. If Sativex is sufficiently well-tolerated, patients should then continue the drug for 4 weeks to determine efficacy, and a decision on ongoing use then made.[56]

On the first day of the titration period, one spray in the morning and one spray in the afternoon/evening should be administered. This should be increased by one spray each day depending on efficacy and adverse effects. Following titration, patients are advised to maintain the optimal dose. The average effective dose is 8–9 sprays per day, up to a maximum of 24 sprays per day. Re-titration can be considered if there are any changes in the patient's condition, concomitant medication, or if adverse reactions occur.[56]

Each spray of Sativex delivers 100 μL of the drug and contains 2.7 mg Δ^9-THC and 2.5 mg cannabidiol. Each spray also contains up to 0.04 g alcohol (ethanol anhydrous) as well

as propylene glycol and peppermint oil. Because of concerns over irritation to the sublingual membranes, occurring in over 20% of patients in the trial,[52] each spray should be delivered to a different area of the sublingual surface. Sativex is absorbed through the sublingual membranes, after which peak concentrations of both Δ^9-THC and cannabidiol are usually reached within 2 hours.

Conclusion: the place of cannabinoids in multiple sclerosis therapy

Although there is no convincing evidence that treatment with oral cannabinoids can improve the symptoms or quality of life for patients with MS, there is evidence that a cannabinoid formulation containing Δ^9-THC delivered by sublingual spray has a role in MS management, particularly in patients who fail to gain adequate relief from standard treatments. A meta-analysis of data gathered in randomized clinical trials up to 2010[55] showed that the odds ratio for improvement in muscle spasticity in MS patients is 1.67, and in patients with advanced MS and severe spasticity refractory to standard treatment, close to half of all patients treated experience a 20% or greater improvement in symptoms.

Despite this, the randomized clinical trials used in the assessment of cannabinoids have been of inconsistent quality. A high risk of unblinding of subjects to treatment group has been an issue in several trials. For example, some trials have included an open phase prior to randomization, and others have included a high proportion of subjects with prior exposure to cannabis and its effects. In addition, there has been considerable heterogeneity of outcome measures and patient groups across different trials. There have also been concerns with respect to uncertainty about the quality of analysis in some trials.

The adverse effects of cannabinoid sublingual spray are sufficiently common that it should not be considered a front-line treatment but as a secondary or tertiary treatment, used as an add-on to existing therapy in patients who require more relief than they are able to get from other available treatments. Apart from reducing spasticity, cannabinoid sublingual spray also has moderate effects on the pain associated with muscle spasm and also with centrally generated neuropathic pain. Quality of life, particularly with respect to sleep, is improved for patients taking the drug, and urinary incontinence is moderately reduced.

Disclosure

The author has no financial or commercial interests in any of the drugs or companies discussed in this article.

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