



National
Multiple Sclerosis
Society

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Expert Opinion Paper

National Clinical Advisory Board of the National Multiple Sclerosis Society

Treatment Recommendations for Physicians

Recommendations Regarding the Use of Cannabis in Multiple Sclerosis

EXECUTIVE SUMMARY

National Multiple Sclerosis Society recommendations are firmly rooted in the basic and clinical information available from studies to date and in their limitations. It is clear that cannabinoids have potential both for the management of MS symptoms such as pain and spasticity, as well as for neuroprotection. Studies to date do not demonstrate a clear benefit compared to existing symptomatic therapies and issues of side effects, systemic effects, and long-term effects are not yet clear. This situation might change, should better data become available that clearly demonstrate benefit.

Key recommendations for research priorities include:

- ◆ Better study outcome measures need to be developed.
- ◆ A consensus is needed on standards for trial design to test the efficacy of cannabinoids for symptomatic management.
- ◆ Because inhaled smoked cannabis has more favorable pharmacokinetics than administration via oral or other routes, research should focus on the development of an inhaled mode of administration that gives results as close to smoked cannabis as possible.
- ◆ Longer-term side effect data need to be obtained.
- ◆ There are sufficient data available to suggest that cannabinoids may have neuroprotective effects that studies in this area should be aggressively pursued.

INTRODUCTION

Standard therapies often provide inadequate relief for the symptoms of MS and can be limited by side effects. As a result, people with MS experiment with many alternative therapies including cannabis. There are numerous anecdotal reports of self-medication with cannabis by people with MS

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to treat symptoms, particularly pain and spasticity, and an estimated 15% of people with the disease use cannabis for symptom relief. As a result, basic and clinical research to date have been driven at least in part by patients' use of "street" marijuana, with varying levels of active cannabinoids, for self-medication.

Despite anecdotal suggestions and some evidence from clinical research that cannabis and its major components, the cannabinoids, have beneficial effects on MS symptoms, clinical trials have not provided conclusive objective evidence for such beneficial effects. This inability to conclusively demonstrate a beneficial effect of the cannabinoids on MS appears to be due to a number of factors, discussed below.

There is some clinical evidence for effectiveness in central pain, and both animal and subjective human data for effectiveness in spasticity. Many studies that failed to show a statistically significant effect have shown a trend toward efficacy. An oromucosal spray formulation of tetrahydrocannabinol (THC) 2.7 mg and cannabidiol 2.5 mg per spray, active ingredients in cannabis, has been approved in Canada for use in managing central pain associated with MS.

An unexpected result of basic research, as well as some evidence from clinical trials, led to the discovery that cannabinoids may also reduce neuronal damage through acute or chronic mechanisms and promote synaptic plasticity, thereby possibly limiting disease progression, perhaps as an add-on to other treatments. In some ways this is even more exciting than its effects on symptoms such as pain and spasticity. Of particular interest, low chronic stimulation may be sufficient for neuroprotection, in contrast to symptomatic effects that typically require doses that are often associated with psychotropic effects. Similar results have been seen in a motor neuron disease model (amyotrophic lateral sclerosis), with less axonal loss in cannabis-treated animals.

BASIC SCIENCE

The hemp plant (*Cannabis sativa*) is the source of a set of over 60 oxygen-containing aromatic hydrocarbon compounds known as *cannabinoids*. Modern research into the purported therapeutic effects of the cannabinoids began in the 1960's with the identification of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the major psychoactive and non-psychoactive cannabinoids, respectively.

Cannabis research gained legitimacy with the discovery of cannabinoid receptors in the 1990s. The cannabinoid receptor CB₁ is widely expressed throughout the CNS, and seems to modulate psychoactive effects, motor control, memory processing, and pain. The *endocannabinoids* that are the natural ligands for the CB₁ receptor are part of an endogenous physiologic system for regulating synaptic neurotransmission, analogous to that of opioids.

The distribution pattern of the CB₁ receptors suggests that the typical effects of cannabinoids on cognition, memory, and motor performance could be mediated by their effects on cortical, hippocampal, basal ganglia, and cerebellar sites. These receptors are densely concentrated on output neurons in the outflow relay stations of the basal ganglia (substantia nigra and globus pallidus), where they are well placed to affect movement control; receptors are sparser in most parts of the brain stem and spinal cord. Their presence in the nociceptive pathways of the brainstem and spinal cord suggests that they participate in a natural analgesic system.

CLINICAL STUDIES

The data from clinical studies are frustratingly unclear compared with basic science data that indicate a clear efficacy of both cannabis and its derivatives on a variety of symptoms. Nonetheless, there is a general trend toward efficacy in groups receiving cannabis through either oral or sublingual routes, but only at doses high enough to produce psychoactive side effects; there is none-to-marginal efficacy according to clinically assessed scales at lower doses. Psychoactive effects include a mildly euphoric “high” with slight changes in motor and cognitive function. Unpleasant effects include anxiety, panic, and paranoia; acute psychosis and hallucination; delusions are occasionally seen.

Two major reasons why clinical studies have consistently failed to achieve a positive result with their major endpoints appear to be that a) the clinical endpoints are not particularly responsive to drug treatments, and b) patient reports of a beneficial effect of cannabis are based on smoking as the mode of delivery, whereas clinical studies have primarily used oral administration. Inhaled cannabis has a higher bioavailability due to the high fat solubility of the cannabinoids and their rapid movement directly from the lungs to the heart; then to the general circulation, a substantial portion of which goes directly to the central nervous system. This is as compared to the longer route taken by orally ingested material, which must pass through the liver, where the active drug is subject to significant “first-pass” metabolism, before reaching the heart, lungs, and eventually the brain. The time to peak level for smoked cannabis is 7–8 minutes as opposed to 1–3 hours for orally administered drug, and its absorption phase lasts 1 hour as compared to 2–5 hours with oral administration. The effect of smoked cannabis may thus be to provide a “hit” that is at least partly responsible for the anecdotal reports of symptomatic benefit. There is also evidence that heating of the compounds has some effect as it converts THC-acid to THC, for example.

The earliest reports on the benefits of cannabis on MS symptoms were anecdotal (Clifford, 1989; Meinck et al., 1989; Consroe et al., 1997). They were followed by small studies on the effect of orally administered THC on spasticity, which used the Ashworth spasticity scale (an ordinal scale of tone, rated from 0–4) with conflicting results (Petro, 1980; Petro and Ellenberger, 1981; Ungerleider et al., 1987; Killestein et al., 2002), and largely failed to demonstrate significant improvements on outcome measures despite, in many cases, patient perceptions of a reduction in pain and spasticity.

More recent studies (Vaney et al., 2004), using synthetic or purified tetrahydrocannabinol, also failed to show a significant improvement based on the Ashworth scale, although patients reported subjective improvements in mobility and diminished spasm frequency. A similar lack of benefit compared to placebo was found for tremor (Fox et al., 2004).

The CAMS (Cannabis in MS) study (Zajicek et al., 2003), the first large-scale study of the effect of cannabinoids on MS symptoms, involved 667 people and compared the synthetic THC molecules Marinol® and Cannador® to placebo. There was no statistically significant improvement in spasticity, the primary outcome measure, and no effect on tremor. Patients self-reported improvements in pain, muscle spasms, spasticity, and sleep disturbance, and a beneficial effect on walking time was evident in both treatment groups (Zajicek et al., 2003). Furthermore, beneficial effects on urge incontinence were reported (Freeman et al., 2006). As with other studies, a basic problem may have been the use of the Ashworth scale as its primary measure. More encouraging was the 1-year followup of the CAMS study, in which two thirds of the original patients opted to continue; objective

improvements on both spasticity (Ashworth Scale) and general disability indices were reported as well as improvements on pain and tremor (Zajicek et al., 2003, 2005). Following up on CAMS, a new study, CUPID (Cannabinoid Use in Progressive Inflammatory brain Disease) has started. This trial aims to recruit 500 people with primary or secondary progressive MS from around 25 hospitals across the UK.

Sprays such as Sativex® have better pharmacokinetics than ingested agents, although not as favorable as for smoked cannabis; because it is administered oromucosally, direct delivery to the blood and much greater dose-titration are possible. Several studies (Wade et al., 2003; Wade et al., 2004; Notcutt et al., 2004; Collin et al., 2007) tested the effects of Sativex® on spasticity and pain. There was an improvement in patient-assessed scores, but again no improvement in spasticity was seen as measured by the Ashworth scale. A report by Collin and colleagues (2006) of a 15-week multi-center, double-blind, randomized, placebo-controlled, parallel group study with Sativex involving 337 patients showed a statistically significant improvement in spasticity scores with active treatment. A 2005 single-center, 5-week, randomized, double-blind, placebo-controlled, parallel group study by Rog et al. led to the approval of Sativex in Canada for the treatment of central pain associated with MS. It was concluded that Sativex “may be useful as an adjunctive treatment for symptomatic relief of neuropathic pain in MS in adults.” An open-label extension study is now ongoing.

A study on the effect of inhaled marijuana vs. oral dronabinol and placebo on MS spasticity by Agius et al. (personal communication) was designed to overcome many of the issues that affect the design and interpretation of clinical studies and is currently in progress. Instead of the Ashworth scale, spasticity is rigorously and objectively defined as increased muscle tone in which there is velocity-dependent resistance to movement of a joint as a result of increased muscle stretch reflexes; the outcome measure is a decrease in this resistance, measuring the movement of limb across the knee joint.

Secondary endpoints include:

- ◆ EMG
- ◆ Ashworth score
- ◆ EDSS (Expanded Disability Status Scale, an ordinal clinical rating scale ranging from 0 [normal neurological exam] to 10 [death due to MS])
- ◆ MSFC (MS Functional Composite: includes the PASAT [Paced Auditory Serial Addition Task] to evaluate cognitive function, 25-foot ambulation test and 9-hole peg test to evaluate arm/hand function
- ◆ MSQLI (MS Quality of Life Inventory, which includes a pain questionnaire, vital signs and physical exam).

The study has three arms, with oral (via an oromucosal spray) and smoked components (permission was obtained from California agencies for the use of smoked cannabis) plus placebo: a) oral treatment active, smoked inactive, b) smoked treatment active, oral inactive, and c) both inactive. This study was completed March 31, 2008.

NEUROPROTECTION

In addition to their effects on MS symptoms, it now appears that cannabinoids may reduce neuronal damage and thereby could limit disease progression (Pryce et al., 2003; Jackson et al., 2005). Of particular interest, chronic low-level stimulation may be sufficient for neuroprotection, in contrast to the psychotropic doses required to achieve symptomatic effects.

These neuroprotective effects appear to be related to effects on ion channels and the production of free radicals, and it is possible that the same mechanisms—possibly involving glutamate or calcium—could underlie both its neuroprotective and psychotropic effects.

RISK/BENEFIT ANALYSIS, SAFETY STUDIES, AND SYSTEMIC RISKS

A balanced assessment of the risk/benefit ratio for cannabinoids in MS is still difficult to make. Dosing/constituent issues, doubts about preferred administration routes, inconsistent or poorly chosen outcome measures, patient heterogeneity, drop-outs, and inappropriate masking all limit the interpretation of the clinical trial data reported to date. In the absence of conclusive data, the heated political and scientific debate is likely to continue. A clear priority is to determine what additional evidence is needed to properly evaluate the risk/benefit situation with cannabinoids.

For example, since low doses that do not involve major side effects may provide neuroprotection, as compared to the higher doses needed for effects on pain and spasticity but that are associated with numerous side effects, symptomatic usage may pose greater concerns relating to risk/benefit issues.

- ◆ **Cognitive Issues.** Due to the prevalence of cognitive deficits in MS, it is especially important to demonstrate whether cannabis usage might worsen this situation, especially in the longer term. It is clear that cognitive side effects occur with short-term use in dosages that provide symptom relief, including impaired memory and perception of time, and dissociation. What is not yet known is the cognitive risk of long-term use for symptom management, and what might be the possible longer-term cognitive effects of short-term use. One recent small study reported increased deficits in verbal memory and psychomotor speed in long-term cannabis users (Messinis et al., 2006). Although it is important to determine the psychological effects of cannabinoids, to keep this in perspective, it must be remembered that many existing drugs used in MS have effects on cognition. To date, the trials with cannabinoids have not found significant adverse cognitive effects, but a recent report (Moore et al., 2007) suggests the risk of psychotic illness in later life.
- ◆ **Fine Motor Skills.** A performance study on pilots in flight simulators showed a severe impairment in fine motor skills. For this reason, cannabis intoxication in drivers is treated legally like alcohol intoxication in the UK.
- ◆ **Toxicity.** All cannabinoids are fat-soluble, and toxicity increases with time because they accumulate in fatty tissues.
- ◆ **Teratogenicity.** Animal studies have indicated a risk for teratogenicity with cannabis, and patients in current studies are required to wait three months from the end of the study before becoming pregnant.

- ◆ **Cancer.** Despite the inherent risk of inhaling hydrocarbons, to date there has been no confirmed association of smoked cannabis with an increase in oral, esophageal, pulmonary, or other cancers in long-term smokers (Mehra et al., 2006). It is difficult to obtain evidence in this area given that marijuana is illegal in most countries and that patients are not likely to be forthcoming about usage. In Spain, there are currently ongoing trials on the ability of THC to control some forms of brain tumors.

NMSS RECOMMENDATIONS AND FUTURE RESEARCH

It is now clear that a number of problems are associated with clinical studies of cannabis usage in MS; these need to be addressed in a systematic fashion.

- ◆ A problem in most studies to date is the lack of sensitive, objective and well validated endpoints. The Ashworth scale, used in most studies that tested the effects of cannabinoids on spasticity, is not sufficiently sensitive to provide useful results. The same issue is encountered in studies of the benefit of cannabinoids on pain. This has led to inconclusive results, with even those studies using large numbers of patients failing to meet their objectives. This and other design issues affect obtaining “some” versus “convincing” evidence in support of cannabis usage in MS. Improvements in trial design and outcome measurements are likely to be important in clarifying the true effectiveness of cannabinoids in managing the symptoms of MS and in the area of neuroprotection (Hobart et al., 2006).
- ◆ Methodological issues and study design are an ongoing problem, and researchers encounter a number of difficulties in designing clinical studies of cannabinoids. It is especially difficult to control for their mood-enhancing effects. One way to overcome this might be to ensure that assessment of the primary outcome measure is performed by an “assessing individual” who is blinded to any medication side effects, and different from the “treating physician,” who may adjust dose and monitor adverse effects. One possible way to do this would be to develop a measuring device that is not dependent on the assessor.
- ◆ The inclusion of patients with a wide degree of variability in EDSS score in many of the spasticity studies done to date could confound the interpretation of study data. Descending inhibitory influences generated by cannabinoids could also fail to affect spasticity in people with severe spinal cord pathology, because transmission through the spinal cord is impaired.
- ◆ The route of administration and the great intra- and inter-individual variation in absorption makes it difficult to compare results from different studies. This is especially a problem when trying to compare patient reports of benefit using smoked cannabis versus studies using other modes of administration. Better methods are needed to quantify the amount of product delivered. A metered dose may be more easily obtained with sprays, mucosal administration, or the use of a vaporizer. However, this does not completely solve the problem; the device used to deliver Sativex® is metered, yet even with this there is a great variety in how different individuals tolerate cannabinoids.

- ◆ Placebo effects tend to be high in all clinical studies, but trials are particularly difficult to perform with drugs such as cannabinoids, because it is almost impossible to produce an adequate placebo—particularly when inhalation is the route of administration—as patients may be well aware of the drug’s smell, taste, and psychoactive effects.
- ◆ Its use also often leads to weight gain due to an increase in appetite, and excretion of cannabis breakdown products in sweat also produces a noticeable change in body odor. Emphasis needs to be placed on developing a product that can be used as a control that will at least partially mimic the effect of cannabis.
- ◆ The difficulty in blinding makes it extremely difficult to interpret results.
- ◆ Studies are needed to quantify the neuroprotective effects of the cannabinoids. Given a) the favorable effects observed in animal studies, b) the immunosuppressive and neuroprotective potential of cannabinoids, and c) anecdotal reports from patients with MS that cannabis reduces the frequency of their MS attacks, future studies on neuroprotection need to be designed in a fashion similar to those done for the existing disease-modifying therapies. This should include EAE animal model studies and the development of a more expeditious, streamlined approval process for performing the studies that includes more active mechanisms for oversight.
- ◆ There are distinct ligands for THC, the active compound in cannabis, yet smoked cannabis contains at least 400 compounds. It is not clear whether at least some of the benefit of smoked cannabis is due to a synergy between THC and other substances. Additionally, given the large number of cannabinoids available, the question needs to be asked as to which components should be selected for trials and, if selected, in what proportion should the components be administered.
- ◆ There is concern about the long-term effects of cannabis, especially on cognitive performance. Additionally, the possible development of tolerance is of concern, because it could limit the effects of regular doses. Repeated use induces considerable tolerance to the behavioral and pharmacologic effects within days or weeks.
- ◆ Animal models have to date had only limited usefulness in predicting clinical results. A priority should be to develop models that can better study the psychotropic effects of the cannabinoids; e.g., can we study cognitive issues in animals? In terms of cannabis and spasticity, there has only been one animal model system described. The only available comparative experimental data show that baclofen, cannabis extract and THC have the capacity to affect limb stiffness.
- ◆ New agents need to be identified, and extensive screening studies are already underway. Potentially useful agents should be studied in animals, including research designed to determine possible psychotropic effects.
- ◆ Better patient selection for clinical studies is a priority. For example, studies to date have often involved patients with different degrees of symptoms, e.g., spasticity, and different

EDSS scores (although all studies involved ambulatory patients). This makes it difficult to evaluate the data and may obscure significant effects on subpopulations. It should be possible to find subpopulations that are more likely to demonstrate benefit, and data from current and recent studies should be examined to see if a post-hoc study might identify groups that would be predicted to respond.

- ◆ Ways are needed to minimize the effects of self-selection. For example, most studies have required that participants refrain from driving for the duration of the study, making it difficult to recruit patients who are working or otherwise at an EDSS level that permits them to continue driving.

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