Do Cannabinoids Reduce Multiple Sclerosis-Related Spasticity?

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**Background:** The plant Cannabis sativa contains numerous cannabinoids, which are aromatic hydrocarbons that have central nervous system effects mediated through specific cannabinoid receptors. Some patients with multiple sclerosis (MS) report symptomatic relief from spasticity, pain, and other symptoms when using smoked marijuana, and small trials have suggested some symptomatic benefit.

**Objective:** Do cannabinoids improve spasticity in patients with MS?

**Methods:** We addressed the question through the development of a structured, critically appraised topic. Participants included consultant and resident neurologists, clinical epidemiologists, medical librarian, and clinical content experts in the field of MS. Participants started with a clinical scenario and a structured question, devised search strategies, located and compiled the best evidence, performed a critical appraisal, synthesized the results, summarized the evidence, provided commentary, and declared bottom-line conclusions.

**Results:** The largest randomized, placebo-controlled trial of oral cannabinoid therapy detected no improvement for MS-related spasticity as measured by the Ashworth scale. However, subjective participant reports indicated improvement in spasticity ($P < 0.01$), spasms ($P = 0.038$), sleep quality ($P = 0.025$), and pain ($P = 0.002$) without detriment to depression, fatigue, irritability, or walk time. A second randomized controlled trial, which used subjective participant report as the primary outcome, revealed the same discrepancy between subjective and objective spasticity outcome measures.

**Conclusion:** Randomized controlled trials have failed to confirm objective evidence for a beneficial effect of cannabinoids on MS-related spasticity. However, improvement in subjective assessments of spasticity and other related symptoms have been consistently noted, raising questions about the sensitivity and validity of current objective outcome instruments. Further research is warranted with regards to both outcome instrument development and the effects of cannabinoids on MS-related spasticity.

**Key Words:** cannabinoids, cannabis, spasticity, multiple sclerosis, evidence-based medicine, critically appraised topic

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A 32-year-old man with a 3-year history of relapsing-remitting multiple sclerosis presented for a follow-up visit. His disease remains in remission after 1 year of therapy with glatiramer acetate but he complained of residual left lower extremity spasticity and fatigue that persisted after his most recent clinical exacerbation. Oral baclofen was modestly helpful for the spasticity but it caused excessive tiredness. Neurologic examination revealed mild pyramidal weakness and moderate spasticity in the affected lower limb. At the end of the encounter, he mentioned that he experienced the most consistent relief from spasticity while smoking marijuana, and that he had communicated online with other multiple sclerosis (MS) patients who had similar experiences.

**BACKGROUND**

Cannabis is the third most commonly used recreational drug around the world, following alcohol and tobacco. The drug has psychoactive and hallucinogenic properties and is classified as an illicit drug in many countries. Its mechanism of action is via the cannabinoid (CB) receptors CB1 and CB2. CB1 receptors in particular are found throughout the central nervous system, most prominently in the basal ganglia, hippocampus, cerebellum, and dorsal afferent pathways of the spinal cord. This localization may explain effects such as psychomotor slowing and reduction of pain.1

Use of smoked cannabis is common in patients with MS, with more than one-third of patients using the drug for any purpose.2 Surveys in the United Kingdom and Canada suggest that 12% to 14% of patients used the drug repeatedly for relief from MS-related symptoms.2,3 Both surveys demonstrated that common MS symptoms such as anxiety or mental stress, sleep, pain, and muscle spasms, led individual patients to try cannabis for relief. Often such trials are associated with a perception or experience that prescription drugs and other therapies have failed. Differentiating any specific benefits of cannabis on the common subjective symptoms of MS from its generalized psychoactive effects is difficult. However, the evaluation of spasticity, which may be accomplished through both subjective patient report and objective examination (eg, using the Ashworth scale),4 is a possible exception.

**CLINICAL QUESTION**

Does the use of cannabinoids reduce MS-related spasticity?

**Search Strategy**

A search was performed using Ovid MEDLINE from 1950 to March 2009. The medical subject heading terms (“cannabinoids,” “cannabis”) were combined with “MS” and “spasticity” using the Boolean operator “AND.” Further refinement of the search using the term “randomized controlled trial” yielded a subset of 12 articles. The largest study, performed by Zajicek et al, is a randomized placebo-controlled trial that best addressed the question of objectively measured spasticity in MS patients using cannabinoids.5 A somewhat smaller randomized study by Collin et al also analyzed spasticity in response to cannabinoid versus placebo but used subjective reporting of spasticity as the primary outcome.6 Therefore, the Zajicek et al article was selected for critical analysis.

**Evidence, Results, and Critical Appraisal**

Zajicek et al conducted the “CAMS study,” a randomized controlled trial of cannabinoids versus placebo, between December 2000 and October 2002.5 Participants had clinically definite MS, were aged 18 to 64 years, and had stable disease over the preceding 6 months without changes in medication for spasticity over the 30 days before enrollment. They had symptomatic spasticity with 2 or more muscle groups in the lower limbs, rated with a score of greater than 2 (anything more than a catch, but not restricting movement) on the ordinal 5-point Ashworth spasticity scale, where 0 represents...
normal tone and 4 represents rigidity in flexion or extension. Patients with smoked cannabis use within 30 days or prior exposure to cannabinoid based medicine were excluded, as were those with congestive heart failure, pregnancy, current infection, history of psychosis, and severe cognitive impairment.

Participants were randomized in 1:1:1 fashion to placebo or one of 2 cannabinoid groups: synthetic Δ⁹-tetrahydrocannabinol (THC) (Δ⁹-THC; known as Marinol in the USA) or a cannabis extract containing Δ⁹-THC and cannabidiol. Dosage was based on body weight with an escalation phase; the maximum dose was 25 mg daily. The total Ashworth score, calculated by adding the individual scores from 10 different muscle groups, served as the primary outcome measure. Spasticity was measured using the Ashworth scale by a blinded physical therapist before, during, and after the 15 weeks of treatment. Evaluators were trained in advance, and efforts were made to use the same evaluator at serial visits for an individual participant. Secondary measures included the Rivermead mobility index, a timed 10 m walk test, and 4 self-report questionnaire scores concerning neurologic disability, general health, and symptoms such as irritability, depression, tiredness, muscle stiffness, tremor, pain, sleep, spasms, and energy level.

A total of 667 patients were enrolled and baseline characteristics for all 3 groups were similar. There was a 2:1 female to male gender ratio, 70% to 75% of participants had secondary progressive MS, and 50% were ambulatory. Ninety-four percent of participants had Expanded Disability Status Scale scores between 6.0 and 9.0, without significant differences across groups. Baseline total of Ashworth scores for spasticity were 21 to 23 at the initiation of the study. Mean reductions in total Ashworth scores compared with baseline were 1.86 points for the Δ⁹-THC group, −1.24 points for the cannabis extract group, and −0.92 points for placebo (overall P = 0.40). There was a noted association between assessment of group assignment by and actual allocation for both treating physicians and patients (P < 0.001) but not for the therapists assessing and recording spasticity (P = 0.72).

In contrast to the primary outcome measure, secondary outcome measures showed some significant differences between baseline and follow-up assessments. Significant improvement for the cannabinoid treated groups versus placebo were found for spasticity (P = 0.01), spasms (P = 0.038), sleep quality (P = 0.025), and pain (P = 0.002).

Adverse effects occurring more frequently in the cannabinoid arms of the study included lightheadedness, gastrointestinal upset, increased appetite, and dry mouth; all of these are known as potential autonomic side effects of cannabinoids. During the 15-week study, there were 7 MS relapses in the placebo group compared with only 1 each per treatment arm. The authors report an increase in 10m walking time for the cannabis extract group (P = 0.015); however, this group had a higher initial walk time that decreased during the study period to approximate that of the other 2 groups.

This pragmatic randomized controlled trial was well-designed with a high level of internal validity. The spectrum of participants was appropriate and losses to follow-up amounted to less than 5%. Treatment allocation was blinded, as was outcome assessment. Steps were taken to enhance the reproducibility and consistency of the Ashworth testing by training and using consistent examiners. Intention to treat analysis was appropriately performed. A potential problem with the study is the potential unblinding of patients and their physicians. However, there is no indication that the therapists scoring the primary outcome measure were similarly unblinded. Adverse effects related to the study were also documented clearly. For the category rating scales, there was a noteworthy placebo effect.

In a similar but smaller trial (n = 189), Collin et al compared an oral compound composed of both Δ⁹-THC and cannabidiol versus placebo in the treatment of spasticity over a period of 6 weeks. The primary outcome variable was changed in a subjective numerical rating scale for spasticity (scored from 0 to 10); the estimated treatment difference on the scale was a 0.52 point improvement in favor of the cannabinoid compound (P = 0.048). The Ashworth scale was used as a secondary outcome measure; the difference in improvement of spasticity was small and nonsignificant at 0.11 (P = 0.218) for study medication over placebo.

**Clinical Bottom Lines**

1. Oral cannabinoids do not improve MS-related spasticity as measured by the Ashworth scale.
2. Oral cannabinoids are associated with subjective improvement in symptoms such as muscle stiffness, spasms, pain, and sleep problems in patients with MS.
3. Further studies are needed to develop valid, reproducible measurement instruments for MS-related spasticity and to evaluate the symptomatic effects of cannabinoids for MS.

**DISCUSSION**

Despite the availability of interventions such as physical therapy, oral baclofen and tizanidine, intrathecal therapies, and other means of modifying spasticity, effective treatment of MS-related spasticity remains an unmet need. As with other chronic disorders, MS patients often turn to alternative therapies or psychoactive substances to cope with disabling symptoms. In the case of cannabis, there is a scientific rationale for potentially relevant central nervous system effects based on known cannabinoid pharmacology. Together with patient reports of symptomatic benefits, it would seem likely that a randomized controlled trial would be able to detect and confirm objective benefits. However, as the Zajicek and Collin studies demonstrate, even fairly large and well-designed protocols have failed to demonstrate a positive effect on outcomes other than patient self-report measures. On the other hand, there is the consistent improvement in those self-report measures that leaves residual uncertainty about whether the effects of cannabinoids are real but not detected by "objective" outcome measures or, rather, the perceived effects are owing to the more diffuse pleiotropic properties of the drug. Is the Ashworth scale assessment simply unreliable? There is evidence that Ashworth scores do not correlate well with function or other spasticity measures. Were participants unblinded because of those psychoactive effects? Could it be, as some patients suggest, that the oral route is simply not as effective a delivery system as smoked cannabis, leading to a discrepancy between the experimental trial and "real-world" experiences? Are there other cannabinoids or compounds in smoked cannabis, but not in the oral extracts, that are responsible for symptomatic effects?

Progress in the field has been modest, in part because of these problems, but also because of the political and legal issues that surround cannabis in most countries. Further research is needed on all fronts: development of more objective, validated, and quantitative measures of spasticity and other MS symptoms, better understanding of cannabinoid science, and then more well-designed randomized controlled trials aimed at definitively answering these questions.

**REFERENCES**


**APPENDIX**

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Mayo Clinic Evidence Based Clinical Practice, Research, Informatics, and Training (MERIT) Center Cofounders and Codirectors: Dean M. Wingerchuk, MD and Bart M. Demaerschalk, MD.

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