Cannabinoids did not reduce muscle spasticity in stable multiple sclerosis

Zajicek J, Fox P, Sanders H, et al. **Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.** Lancet. 2003;362:1517-26.

QUESTION

In patients with stable multiple sclerosis (MS), are cannabinoids (oral cannabis extract [OCE] or synthetic Δ^9-tetrahydrocannabinol [SΔ^9-THC]) effective for reducing MS-related muscle spasticity?

DESIGN

15-week randomized (allocation concealed*), blinded (clinicians, patients, data collectors, outcome assessors, and monitoring committee),* placebo-controlled trial.

SETTING

33 neurology and rehabilitation centers in the United Kingdom.

PATIENTS

657 patients 18 to 64 years of age who had had clinically definite or laboratory-supported MS with problematic spasticity (Ashworth score ≥ 2) for the previous 6 months. Exclusion criteria included ischemic heart disease, infection or use of medication that could exacerbate spasticity, fixed-tendon contractures, and severe cognitive impairment. 630 patients (mean age 51 y, 66% women) were included in the intention-to-treat analysis.

INTERVENTION

Patients were allocated to an OCE containing Δ^9-THC and cannabidiol as the main cannabinoids (n = 219), SΔ^9-THC (n = 216), OCE placebo (n = 108), or SΔ^9-THC placebo (n = 114), taken twice daily after food for 14 weeks. Study medication was titrated to a maximum possible dose of 25 mg daily. The 2 placebo groups were combined into 1 group for data analysis purposes.

MAIN OUTCOME MEASURES

Change from baseline in MS-related muscle spasticity (0 to 4 Ashworth score of spasticity [0 = normal, 1 = slight catch when the limb is moved, 2 = anything more than a catch but not restricting movement, 3 = considerable increase in tone limiting passive flexion, and 4 = limb rigidity in flexion or extension] assessed before treatment, and during weeks 1, 6, 10, and 13 of treatment).

MAIN RESULTS

Analysis was by intention to treat. The OCE and SΔ^9-THC groups did not differ from placebo for change from baseline to the 13th week of treatment in MS-related muscle spasticity (Table).

CONCLUSION

In patients with stable multiple sclerosis (MS), cannabinoids (oral cannabis extract or synthetic Δ^9-tetrahydrocannabinol) were not effective for reducing MS-related muscle spasticity.

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*See Glossary.

Oral cannabis extract (OCE) or synthetic Δ^9-tetrahydrocannabinol (SΔ^9-THC) vs placebo in stable multiple sclerosis at 13 weeks†

Outcome	Comparisons	Mean	Difference between groups (95% CI)
Change from baseline in muscle spasticity (0 to 4 Ashworth scale scores)	OCE vs placebo	1.24 vs 0.92	0.32 (–1.04 to 1.67)‡
	SΔ^9-THC vs placebo	1.86 vs 0.92	0.94 (–0.44 to 2.31)‡

†CI defined in Glossary.
‡Not significant.

COMMENTARY

It has been suggested that marijuana has a beneficial effect on various MS-related symptoms, including spasticity, pain, and tremor. A survey in Canada (1) reported that 43% of 420 responders to a survey (62% response rate) had tried marijuana, 16% for medicinal purposes. The study by Zajicek and colleagues is larger and, hence, more powerful than the previous studies of cannabinoids in MS.

Patients in this trial were using other antispasticity drugs and physical therapy treatments, albeit at a stable dose or regimen. The study did not attempt to address the effectiveness of cannabinoids relative to conventional antispasticity drugs. Blinding was successful for the assessor but not for the treating neurologist or patients. No effect on the primary spasticity outcome, the Ashworth score, was observed. However, a statistically significant 12% (95% CI 6 to 21) improvement on timed walking was observed in the SΔ^9-THC group compared with 4% (CI 0 to 10) and 4% (CI –2 to 7) in the OCE and placebo groups, respectively. Compared with the placebo group, the improvement in the SΔ^9-THC group seemed to be in the baseline 10-meter walk time rather than in the "on treatment" walk time. Also, a substantial reduction in self-reported pain, spasms, and spasticity was observed.

Insensitivity of the Ashworth score as a measure of spasticity may have contributed to the negative result. An analgesic effect of the cannabinoids may have contributed to the improved gait, but a strong placebo effect with a 35% improvement in pain in the placebo group was also reported. Much of the benefit may actually be related to treatment or placebo effects on the psyche of patients rather than an effect on spasticity. Pharmacodynamics of the active interventions were not assessed. Whether serum levels achieved in this study are similar to those achieved by patients who smoke marijuana has yet to be determined (such studies are in progress). This study does not give much support to the use of marijuana for its effects on spasticity resulting from MS.

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Reference

1. **Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC.** Cannabis use as described by people with multiple sclerosis. Can J Neurol Sci. 2003;30:201-5.