Oral cannabinoids for spasticity in multiple sclerosis: will attitude continue to limit use?

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Spasticity is a distressing and disabling symptom that many people with multiple sclerosis face daily because there is inadequate treatment. As one part of an upper motor-neuron syndrome, spasticity manifests as muscle stiffness, spasms, and pain. It also contributes to limited mobility and impaired sleep. The hypothesis that cannabis derivatives (eg, Δ-9-tetrahydrocannabinol [Δ-^{9}THC], cannabidiol) relieve spasticity and other symptoms of multiple sclerosis has received increasing attention in recent years. Identification and characterisation of cannabinoid receptors (eg, CB1, CB2), recognition of endogenous cannabinoid ligands, and evidence that activation of the CB1 receptor in the brain leads to inhibitory influences on neurotransmitter release[1] supports this hypothesis. The benefit of cannabinoids in animal models of spasticity[2] and the results of small clinical trials[3–7] have led to investigation of cannabinoids as symptomatic therapy in multiple sclerosis. The potential role of cannabinoids as neuroprotective agents is also intriguing.[1]

Although off-label use of a large variety of approved drugs is probably done every day by physicians for every condition, use of cannabinoids has remained limited. Concern about treatment risk, lack of a safe, accessible, and reliable cannabis supply, unclear dosing of smoked cannabis, and lack of social and legal acceptance of cannabinoids as legitimate treatment contribute to this limited use.[8]

The study by John Zajicek and colleagues in this issue of *The Lancet* is the first large multicentre randomised placebo-controlled trial of cannabinoid therapy in multiple sclerosis and is thus an important step forward. Although this trial failed to detect a significant treatment effect of any cannabinoid on the primary outcome, spasticity as measured by the Ashworth scale,[9] use of Δ-^{9}THC decreased timed walk (median 12%, 95% CI 6% to 21%) compared with 4% for placebo and cannabis extract (−2% to 7%, and 0% to 10%, respectively). Subjective improvement of spasticity-related symptoms (spasticity, pain, sleep, spasms) occurred more frequently with cannabinoids than with placebo, whereas there was no treatment effect on symptoms less specifically related to spasticity (irritability, depression, tiredness, tremor, energy). In previous studies[3–7] subjective reports of improvement in various symptoms of multiple sclerosis were almost universal, whereas comparison with a placebo group in Zajicek's study suggests a fairly specific effect on spasticity.

Although failing to achieve an effect on the primary outcome suggests Kajicek and colleagues' trial is negative, the Ashworth scale does not correlate with function or with other measures of spasticity.[10] Lack of benefit on the Ashworth scale might also be partly related to inclusion of non-ambulatory patients. Inclusion of patients with such a highly variable degree of spasticity could have meant that the investigators assessed patients who had greater variability than in other studies that used this scale. 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. These patients would have been non-ambulatory and hence could not have diminished the apparent effect of treatment on timed walk but might have done so for other measures assessed, including the Ashworth scale. Future studies should consider the potential confounding effect of including such patients with severe spinal-cord disease and should not rely totally on the Ashworth scale.

Another possible contribution to the limited treatment effect could have been the route of administration.[6] Oral administration of cannabinoids is unpredictable and leads to lower bioavailability than smoked cannabis. Although smoking cannabis is therapeutically unacceptable because of additional risks associated with smoking, alternative methods have met with some success and need to be further assessed.[8] In Zajicek and colleagues' study, most of the reported serious adverse events were expected in this population and minor adverse events were consistent with known side-effects of cannabis.

As noted by Zajicek and colleagues, their findings must be interpreted in light of the fact that most of participants (and physicians) correctly identified whether or not they were taking active medication, which illustrates the difficulty of blinding during trials of cannabinoids.

What does this study mean to clinicians and to people with multiple sclerosis? We now have as much evidence to support the use of these oral cannabinoids for spasticity in ambulatory people with multiple sclerosis as we do for many standard therapies for spasticity, including baclofen. However, because we do not know how these cannabinoids compare with other antispasticity treatments, they should generally only be considered when other therapy has failed. Caution should also be advised about driving while using cannabinoids. Perhaps, as in Zajicek's study, driving should not be permitted. Finally, we still have no data to compare the risks and benefits of smoked cannabis.

Hopefully Zajicek and colleagues' study will stimulate further research to develop and evaluate safe and effective formulations of cannabis, and will inform debate over the social and legal restrictions that limit its use. In the meantime, when other treatment inadequately controls spasticity, oral cannabinoids should be considered where law permits their possession and use.

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