

Editorial

The therapeutic value of cannabinoids in MS: real or imaginary?

Interest in medical cannabis for the treatment of multiple sclerosis (MS) is still increasing: it has gained the attention not only of the scientific community but also of the general public, journalists and politicians. Although several recent studies failed to demonstrate robust improvement,^{1–4} patient self-assessment of the therapeutic effect of cannabinoids on pain and spasticity show a trend in favour of active treatment.^{2,3,5,6}

This issue of *Multiple Sclerosis* contains three interesting papers that claim beneficial effects of cannabinoids on symptoms in MS patients. The randomized, double-blind, placebo-controlled, crossover study by Vaney *et al.* aims at determining tolerability, safety and efficacy on spasm frequency of an oral cannabis extract (standardized capsules containing 2.5 mg tetrahydrocannabinol (THC) and 0.9 mg cannabidiol (CBD), dose-escalating up to a maximum of 30 mg THC per day) in MS patients with refractory spasticity.⁷ Fifty-seven patients were enrolled, 50 of whom were included in the intention-to-treat (ITT) analysis and 37 of whom (65%) completed the trial per-protocol (28 days, of which 14 days of active treatment). The ITT analysis showed no statistically significant differences between active treatment and placebo. However, improvements in patient-recorded spasm-frequency scales and the Rivermead Mobility Index (RMI) were suggested in the per-protocol data set. In general, cannabis extract was well tolerated.

The open label study by Brady *et al.* assessed safety, tolerability and efficacy of two sublingual sprays of cannabis medicinal extracts (CME: 2.5 mg THC and 2.5 mg CBD per spray, dose-escalating up to maximum dose of 120 mg THC and CBD a day; followed by THC-only treatment up to 120 mg a day) in MS patients with cystometry-proven detrusor overactivity.⁸ Twenty-one advanced MS patients with troublesome lower urinary tract symptoms (LUTS) for >5 years were enrolled. Fifteen patients (71%) completed 16 weeks of treatment. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia decreased significantly on both extracts. Also voided, catheterized and urinary pad weights diminished. Fourteen patients were entered into the long-term extension and all opted to take the THC-only extract. There were few troublesome side effects.

The paper by Wade *et al.* reports the results of a relatively large, three-centre, double blind, randomized trial with oromucosal sprays of THC and CBD (CME: 2.5–120 mg of each a day, for 6 weeks) versus placebo in 160 MS patients.⁹ The primary outcome was a Visual Analogue Scale (VAS) score for the patient's most problematic symptom. Although the combination of VAS scores from the different symptoms was not significantly reduced following CME, spasticity VAS scores showed significant improvement in comparison with placebo. Intoxication was generally mild.

These three studies provide important data, but have their limitations. Both placebo-controlled studies show positive subjective results without reporting the success of masking.^{7,9} It is well described that the side effects of cannabinoids, especially those enhancing mood, potentially introduce bias by unmasking. According to patients' reports in the CAMS study, 77% of the active treatment group correctly thought that they had been on active treatment.³ Vaney *et al.* suggested improvement in mobility as measured by the (subjective) RMI. However, this finding was not confirmed in the time needed to walk 10 m. In addition, there was no evidence of a treatment effect on the RMI in the CAMS study.³ Thirty-five per cent of the patients enrolled in the Vaney study did not complete the protocol, even though it only included a short phase of active treatment (14 days). The statement that the cannabis extract was well tolerated must be interpreted in this context. Besides the risk of inappropriate blinding, other potential limitations of the study by Wade *et al.* are its unconventional primary outcome measure and the unspecified heterogeneity of the study population.⁹ As the authors discuss themselves, combining VAS scores from multiple symptoms as primary outcome measure assumes that each symptom shows equal responsiveness to the study drug and variability, which probably is not completely accurate. A strong point of the study, however, is the fact that 154 patients out of 160 (96%) completed the six weeks of treatment.

Brady *et al.* state that self-titrated treatment with CME appears safe and efficacious.⁸ Besides the fact that efficacy is hard to establish in a small and open-label study, the authors themselves give an important limitation of their positive findings: a significant decrease in urinary output occurred during treatment as compared to baseline, suggesting that patients might have reduced their fluid intake during the study. Furthermore, their results might be interpreted as showing regression towards the mean. Additionally, six patients (29%) withdrew from the study, making it difficult to draw firm conclusions on safety as well. A remarkable finding of this study, however, was the fact that all patients entering the long-term follow-up chose the THC-only option as they found it more effective. Although the range of doses was rather wide across the group, the patients took significantly less THC-only compared to THC/CBD to achieve the same therapeutic effect. This suggests that either CBD is not contributing to the putative therapeutic effects or that another proportion of CBD might be preferable. Publication of the CAMS-LUTS substudy will address efficacy of cannabis capsules on LUTS in a larger cohort of patients.³

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, inconsistently or poorly chosen outcome measures, patient heterogeneity, drop-outs and inappropriate

masking all limit the interpretation of the clinical trial data reported so far. In the absence of conclusive data, the heated political and scientific debate is likely to continue.^{5,6}

It is time now for the MS community to work on a consensus on standards for trial design to test the efficacy of cannabinoids and other symptomatic interventions in MS, because only results from such trials will be widely accepted.

References

- 1 Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG *et al.* Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002; **58**: 1404–407.
- 2 Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* 2003; **17**: 21–29.
- 3 Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A *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.
- 4 Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology* 2004; **62**: 1105–109.
- 5 Goodin D. Marijuana and multiple sclerosis. *Lancet Neurol* 2004; **3**: 79–80.
- 6 Metz L, Page S. Oral cannabinoids for spasticity in multiple sclerosis: will attitude continue to limit use? *Lancet* 2003; **362**: 1513.
- 7 Vaney C, Heinzel-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, Schnelle M, Reif M. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Multiple Sclerosis* **10**: 417–42.
- 8 Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Multiple Sclerosis* **10**: 425–33.
- 9 Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Multiple Sclerosis* **10**: 434–41.

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