

Multiple sclerosis

# Cannabinoids in multiple sclerosis: urgent need for long term trials

J Killestein, B M J Uitdehaag

The CAMS study represents a substantial step forward, but not the final one

Cannabinoids have been suggested for the treatment of numerous conditions, including cancer, vascular, neurodegenerative, and inflammatory diseases.<sup>1</sup> Probably because of the nature of these substances, there is considerable interest in these drugs from the general public, lay media, and politicians. Frequently, the translation of scientific results is overly optimistic and may have contributed to extensive off label usage of cannabis among chronically ill patients. The evidence for therapeutic efficacy in humans is not as yet convincing.

The CAMS study<sup>2</sup> by Zajicek and colleagues was the first large symptomatic trial of cannabinoids in multiple sclerosis (MS). In this study, 630 patients with stable MS and muscle spasticity were treated with delta-9-tetrahydrocannabinol (THC), cannabis extract or placebo. The main part of the study (covering 15 weeks) is by far the best designed study ever undertaken in this field. There was no evidence of a treatment effect on the primary outcome, the Ashworth scale. The investigators' conclusion, however, was that improvement in mobility and patients' opinion of an improvement in pain might be clinically useful.

In light of these results, the follow up paper by Zajicek (*see p 1664 of this issue*), presenting the data of a 12-month, blinded, continuation phase, is most welcome. It is the first study to present longer term data on cannabinoids in MS. Although a small but significant change in Ashworth score was found in the THC group, the clinical

significance of this change remains uncertain.

The authors discuss several sources of bias; losses to follow up (around 20%), discontinuation of medication after the first phase (around 36%), and the potential for unmasking. The success of masking at the end of follow up is not reported. Even though they discuss that further unmasking was unlikely to occur, the marked degree of unmasking during the main study (up to 70%) warrants cautious interpretation of the results, in particular patient derived outcome measures.

The trial was not designed to detect a change in disease activity, but a reduction in relapse associated hospital admissions was suggested during the initial phase. This interesting finding indicates that the anti-inflammatory properties of cannabinoids might play a favourable role in MS disease activity.<sup>3</sup> However, if confined to relapses classified as serious adverse events, the opposite trend was found during long term follow up.

There were no major safety concerns during the CAMS follow up. Nevertheless, several studies have shown that there are deficits in the performance of complex cognitive tasks in long term cannabis users.<sup>4</sup> Controversial is the question of whether long term cannabis use can cause irreversible deficits in higher brain function that persist after drug use ceases,<sup>4</sup> especially in those suffering from diseases such as MS, who are already vulnerable for cognitive decline. In addition, there has been a long standing concern that cannabis use

might precipitate mental illness.<sup>4</sup> In this respect, final results from the CAMS substudy on psychological and cognitive functions are eagerly awaited.

The longer term data indicate that orally administered cannabinoids may hold therapeutic promise as an approach to the treatment of MS related symptoms. However, a balanced assessment of the risk-benefit ratio for cannabinoids in MS is still difficult to make. There is an urgent need for more long term cannabinoid trials in MS using carefully chosen outcome measures. These trials should also focus on different cannabinoid products, including the newer receptor agonists, and different routes of administration. The collection of scientifically sound data will eventually lead to a justified clinical use of cannabinoids, limit the extensive off label usage, and guide the excited scientific and political debate. In that respect, the CAMS study represents a substantial step forward, but not the final one.

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## Authors' affiliations

J Killestein, B M J Uitdehaag, Department of Neurology, VU Medical Centre, Amsterdam, the Netherlands

Correspondence to: Dr J Killestein, Department of Neurology, VU Medical Centre, De Boelelaan 1117, 1081 HV Amsterdam, the Netherlands; j.killestein@vumc.nl

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