

Cannabis Use in Multiple Sclerosis: Excited Interest

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This is an exciting time for cannabinoid research. There is a growing amount of data to suggest that cannabis (marijuana) can alleviate symptoms like muscle spasticity and pain in patients with MS.¹ Interest in the field of cannabinoids has been strengthened by the identification and cloning of cannabinoid receptors located in the central nervous system and the peripheral immune organs, and by the discovery of the endogenous cannabinoid ligands.² Cannabinoids have been shown to be efficacious in animal models of MS.³ However, there have been only ten published clinical reports on cannabis in MS, involving 78 subjects worldwide,^{4,5} and the results have been equivocal. From the studies reporting the use of cannabinoids in MS patients with spasticity, the somewhat better designed studies failed to demonstrate objective improvement, and adverse events were common; therefore, the evidence that cannabinoids are effective in MS is far from conclusive.⁴

The questionnaire study by Page, et al⁶ in this volume of the Canadian Journal of Neurological Sciences confirms subjective symptomatic relief in the majority of MS patients using cannabis. The paper clearly outlines the (medicinal) use of cannabis in MS patients in southern Alberta, Canada. Symptoms perceived to be relieved were anxiety/depression, spasticity, chronic pain and fatigue. A surprisingly large proportion of patients (43%) stated that they had used cannabis at some point in their lives – 16% for therapeutic reasons. Both the magnitude of the sample studied and description of sample size determination and study population are sound and, thereby, the report by Page, et al is timely and represents the best designed questionnaire study on cannabis use in MS so far. However, the small number of patients (n = 43) using cannabis medicinally on a regular basis is slightly limiting the possibility to draw firm conclusions.

Descriptions of the kind of benefits experienced are more or less consistent with those reported in earlier studies. Compared to another questionnaire survey,¹ the percentage of patients reporting improvement in specific symptoms is much lower. This may be due to the fact that in the Consroe, et al¹ study, 255 patients (of which 57% responded) were selected based on their therapeutic cannabis use (potentially introducing selection bias). In the Page, et al study, 420 patients (62%) responded out of 780 subjects systematically and equally drawn (stratified by impairment level) from a clinical database of 2600 MS patients. Importantly, it has previously been shown that > 65% of MS patients can report improvements in a comparable design when using ineffective treatment, suggesting that the perceived relief of symptoms in the Canadian study population might not clearly exceed a possible placebo effect.¹

Although cannabinoids are not known to cause deaths by direct toxicity, a major concern of cannabis use is its adverse effects profile. Indeed, a main reason for not using cannabinoids in the Page, et al study was concern about side effects (34%). Of

the 67 patients who had tried cannabis to manage their symptoms, only 10 seemed to have discontinued use because of side effects. Unfortunately, no information is given concerning the nature of these side effects. In general, after the initial period of excitement that accompanies taking an acute dose, cannabinoids exert a generalized central nervous system depressant effect. This effect may lead to drowsiness, sleep, impaired motor performance and general co-ordination problems. Furthermore, cannabinoids can cause specific deficits in short-term memory, and long-term heavy use may produce impairment of memory, attention, and the organization and integration of complex information.⁷ Neuropsychological investigations have demonstrated that cognitive disorders are common (45-65%) in patients with MS.⁸ Specifically, neuropsychological deficits regularly occur on measures of recent memory, attention, information-processing speed, executive functions, and visuospatial perception. Therefore, a major concern of long-term cannabinoid use in MS will be its long-term neurocognitive side effect profile. Whereas the most common psychiatric adverse effects of cannabinoids are anxiety and acute psychosis, the study by Page, et al suggests, paradoxically, that the most common symptom perceived to be relieved is anxiety/depression. This may be due to the small window between therapeutic dose and the dosing regimens causing side effects. Another concern that should not be disregarded is the fact that several recent studies suggest that cannabis use increases the risk of both the incidence of psychosis and schizophrenia in psychosis-free persons and a poor prognosis for those with an established vulnerability to psychotic disorder.⁹ Finally, as Page, et al emphasize in their discussion, it should not be ignored that cannabinoids are inhaled deeply when they are smoked and may well be associated with an increased risk of developing cancer.

Given the favorable effects observed in animal studies, the immunosuppressive and neuroprotective potential of cannabinoids, and anecdotal reports from MS patients claiming that cannabis use reduces the frequency of their MS attacks, some authors believe that cannabinoids could be used to alter the underlying course of the disease. While some of these findings are intriguing, their clinical relevance will require more study. The only human *in vivo* study so far,¹⁰ measuring immune function in MS patients treated with oral cannabinoids, showed a modest increase in pro-inflammatory cytokine production, not supporting the hypothesis of favorable disease-modifying potential in MS.

In conclusion, the Page, et al study confirms that cannabis is being used as a medicine by a large number of people with MS despite lacking a firm evidence base. Future research may provide us with safe new cannabinoids, able to modify symptoms while limiting side effects. There is little doubt about the need for more potent drugs in MS. Although well-designed

large clinical trials are now underway,² there is currently no firm evidence to suggest that cannabinoids may be more effective than other symptomatic therapies in MS. Compared to the new members of the cannabinoid family, the currently available cannabinoids may lose the battle in terms of long-term safety and tolerability.

*Joep Killestein, Chris H. Polman
Amsterdam, The Netherlands*

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