Marijuana and multiple sclerosis

Marijuana—*Cannabis sativa*—has been used for centuries, both as a recreational drug and as a herbal medicine. It contains more than 450 substances, including at least 66 aromatic hydrocarbon compounds collectively referred to as cannabinoids.1 The main active cannabinoid in marijuana is Δ⁹-tetrahydrocannabinol (Δ⁹-THC), which is available in several countries as a prescription medication. Two endogenous cannabinoid receptors (CB₁ and CB₂), and a series of arachadonic acid-derived endogenous ligands (eg, anandamide and 2-arachidonylglycerol), have been identified.1 Only CB₁ receptors are ligands (eg, anandamide and arachadonic acid-derived endogenous substances, including at least 66 aromatic hydrocarbon compounds, are expressed in the brain, where they are localised to axons and nerve terminals—mainly in the frontal cortex, basal ganglia, cerebellum, hypothalamus, anterior cingulate cortex, and hippocampus—but are absent from soma and dendrites. Δ⁹-THC and other cannabinoids are agonists of CB₁ receptors and, presumably, modify synaptic function by inhibiting the release of monoamine and amino-acid neurotransmitters.2

Despite a long history of the medicinal use of marijuana, its therapeutic role remains both controversial and politically charged. Indeed, in the USA, a recent Federal Court decision (upheld by the US Supreme Court) effectively nullified a California state law specifically allowing medicinal use.3 Nevertheless, if the medical benefits of marijuana could be conclusively established, the nature of the debate would be fundamentally transformed.

In multiple sclerosis (MS), studies of the potential clinical value of marijuana have focused on the reduction of spasticity and pain. Several anecdotal reports and small randomised trials, from the late 1970s onwards, have suggested that marijuana reduces the severity of these symptoms in patients with MS.4–9

By contrast, the results of a small, randomised, placebo-controlled crossover trial of Δ⁹-THC and *C sativa* extract in 16 patients with MS showed that treatment was not beneficial for spasticity and was, in fact, associated with worsening of the patient’s global impression score.10

Zajicek and colleagues11 recently reported the results of a large, randomised, placebo-controlled trial of marijuana for the treatment of spasticity in MS. 630 patients were randomly assigned to receive Δ⁹-THC (2.5 mg), *C sativa* extract (2.5 mg Δ⁹-THC, 1.25 mg cannabidiol, and <5% other cannabinoids), or matched placebo at 33 centres across the UK. Total daily dose was titrated (on the basis of body weight and dose tolerated) up to a maximum dose of 25 mg Δ⁹-THC per day. The primary outcome measure was a change in spasticity as measured on the Ashworth scale.11

In this trial, no significant clinical effect was seen on this primary outcome for treatment with either Δ⁹-THC or *C sativa* extract. However, the authors argue that the Ashworth scale may be too insensitive to detect a difference between the groups. Nevertheless, this study was powered (90%) to test specifically the hypothesis that marijuana was at least as effective as other spasticity treatments on the Ashworth scale. The fact that the results do not show an effect raises the question of how much additional benefit marijuana could provide relative to available treatments.

Numerous secondary outcomes—including irritability, pain, spasticity, fatigue, depression, tremor, sleep, and mobility—were also investigated. The authors report several positive findings that led them to conclude that there might be some beneficial effect of cannabinoids in MS. This benefit may, however, be wishful thinking. For example, improved mobility, assessed by the time taken to walk 10 m, was improved in the Δ⁹-THC group compared with the placebo group (p<0.05). By contrast, *C sativa* extract provided no such benefit. This suggests either that the original observation is spurious or that other cannabinoids inhibit the beneficial effect of Δ⁹-THC. The former explanation seems more plausible. Similarly, the subjective reports of reduced pain, decreased spasticity, improved sleep, and reduced spasms (all p<0.05) are suggestive but unconvincing, especially because of the unblinding of the treating physicians and the patients (p<0.001). Moreover, none of these findings would survive even a modest statistical adjustment for multiple comparisons. In addition, the fact that few patients reached their target dose because of side-effects also suggests that the therapeutic potential of either Δ⁹-THC or *C sativa* extract in the symptomatic management of MS is limited. Perhaps most intriguing, in light of the expression of CB₁ receptors on the surfaces of immune system cells, is the observation that exacerbation rates were lower in both cannabinoid groups compared with placebo (p<0.05). Nevertheless, even this result requires replication before it can be considered reliable, because it relates only to undocumented attacks and is statistically marginal.

Despite these essentially negative results, Zajicek’s study is unlikely to resolve or even substantially add to the heated political debate. Enthusiasts for the medicinal use of marijuana will be unconvinced by the negative result and will, no doubt, focus on the suggestive (but subjective) reports in favour of treatment. Conversely, opponents of the medicinal use of marijuana will readily accept the negative findings on the primary outcome measure and will dismiss the other findings as meaningless and not worthy of further study. Unfortunately, neither viewpoint represents a balanced assessment because both are tainted by preconceived biases. On the one hand, because cannabinoids activate specific receptor systems within the brain, it is possible, and indeed probable, that marijuana will ultimately prove to be medically valuable in some clinical settings; if not in MS, then in some other diseases. On the other hand, the medical community should demand solid evidence from carefully designed clinical trials in support of any particular use. The present study11 is an excellent example of such a study, which, as it turned out, did not substantiate a role for marijuana in the management of spasticity. Whether the
subjective reports of benefit found by these authors are accurate or spurious will await further, and more focused, investigation, but the therapeutic potential of marijuana should not simply be dismissed.

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Thalamic stimulation in essential tremor

Essential tremor is one of the commonest movement disorders in adults. The efficacy of current drug treatments is moderate and side-effects are common so surgery is an alternative for disabling essential tremor. Thalamotomy can improve tremor, but permanent neurological deficits—particularly after bilateral surgery—have restricted its use. In the mid-1980s, thalamic stimulation was proposed as an alternative approach.1 A randomised study2 confirmed that thalamic stimulation results in better functional outcome and less side-effects than thalamotomy, particularly in the case of bilateral surgery. The efficacy of thalamic stimulation in essential tremor has been shown in several studies, although most have had only a short follow-up period.3,4

Now, Sydow and colleagues5 have reported the 6-year-follow-up results of 19 patients with essential tremor treated with thalamic stimulation. Many of the original cohort of 37 patients6 were lost to follow-up, mostly because of death from unrelated causes or general health problems, which reflects the advanced age of the cohort at the time of surgery. Despite the fact that essential tremor is a bilateral disease, most patients received implants on one side of the brain. The small number of patients implanted bilaterally (four at baseline, seven at 6 years) is indicative of concerns about the side-effects of bilateral stimulation, particularly on speech and balance.

Improvements in tremor were stable for 6 years and the patients did not show signs of disease progression (tremor score with the stimulator off was not significantly different from baseline). In general, patients did not report a major tolerance effect; electrical parameters were only marginally increased over time. A larger increase in voltage is generally necessary in the first year because of local changes in the thalamus and changes of impedance.

In the present study,7 upper limb postural tremor and action tremor were both significantly reduced after 6 years, but action tremor scores were higher,8 which confirms that postural tremor responds better to thalamic stimulation than action tremor. Lower-limb tremor was mild and postural lower-limb tremor improved. Tremor of the contralateral limb was unchanged and showed slow disease progression and no worsening from ipsilateral surgery.

In previous studies, some patients reported worsening of the ipsilateral side, which may simply reflect a change in focus to the untreated limb after surgery.9 Hand function and activities of daily living were improved. Disability and health-related quality of life also improved 1 year after thalamic stimulation.10 Eating, drinking, and writing, which are all major problems for patients with essential tremor, were improved. A decrease in negative emotions was also observed.11

Side-effects were common, but most were transient.12 However, patients should be carefully selected on the basis of their disability and risk factors, particularly any vascular risk factors and coagulation problems. The most severe side-effects occurred in the immediate postoperative period; one intracerebral haemorrhage and one ischaemic stroke were reported. Two infections and two erosions occurred, which in some cases necessitated the explantation of the stimulator. It is therefore particularly important to check the skin regularly for signs of infection or erosion in implanted patients.

Paraesthesia and dysarthria were the most common long-term side-effects, with dysarthria more common in patients with bilateral implants, but could be reversed. In some patients, a compromise had to be made between effective tremor control and dysarthria or paraesthesia, or partial tremor control without side-effects. No patients reported any adverse effects on balance, although this side-effect has been reported in previous studies, typically in the case of thalamic stimulation contralateral to thalamotomy.3

Sydow and colleagues5 have confirmed that thalamic stimulation is useful in the long-term management of severe forms of essential tremor. Long-term assessments of the effect of stimulation on quality of life and cost efficacy are still awaited.

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References