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Prescribing Cannabinoids for Multiple Sclerosis

Current Issues

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Abstract

Anecdotal evidence and preclinical and clinical data indicate that cannabis and individual cannabinoids can suppress muscle spasticity/spasm and pain associated with multiple sclerosis (MS). Anecdotal data come from the responses to a questionnaire by 112 patients with MS who self-medicated with cannabis. The preclinical data come from animal experiments showing that cannabinoid receptor agonists are antinociceptive and can depress motor function, reduce the severity of primary generalised dystonia, and decrease inflammation and the intensity of behavioural signs of experimental autoimmune encephalomyelitis. The clinical data derive from 7 clinical trials, albeit involving small numbers of patients, which indicate that cannabis itself, the cannabinoid Δ^9-tetrahydrocannabinol (Δ^9-THC) and the synthetic analogue of Δ^9-THC nabilone can reduce the intensity of several symptoms in patients with MS or spinal cord injury, including spasticity, pain, tremor and nocturia.

These data provide sufficient evidence to warrant a large scale clinical trial to attempt to provide an objective and conclusive answer to the questions of whether cannabis and cannabinoids are effective in MS and, if they are, whether these effects are achievable at dose levels that do not provoke unacceptable adverse effects. Likely drug candidates for a clinical trial include Δ^9-THC and nabilone, both of which are already licensed medicines. When taken orally, Δ^9-THC seems to undergo variable absorption and to have a narrow 'therapeutic window'. This makes it difficult to predict an oral dose that will be both effective and tolerable, so prompting a need for better cannabinoid formulations, cannabinoid vehicles and modes of administration.

There is also a need to establish whether cannabis has any therapeutic advantages over individual cannabinoids such as Δ^9-THC and, if so, to investigate the basis for this. In addition, it will be worth seeking out a way of separating the therapeutic properties of cannabinoids from their unwanted effects, particularly their psychotropic effects, and several strategies for achieving this goal are described.

To succeed, any clinical study with cannabinoids will require sufficient funding, the use of adequate outcome measures, and the committed involvement of scientists and physicians who have appropriate cannabinoid and clinical expertise.

1. The Cannabinoid System

Cannabis sativa is the unique source of a set of more than 60 oxygen-containing aromatic hydrocarbon compounds known as cannabinoids. One of these, Δ^9-tetrahydrocannabinol (Δ^9-THC), is responsible for most of the psychopharmacological properties of cannabis.

It has been shown that Δ^9-THC and its synthetic analogues act through specific receptors. As detailed elsewhere,[1] these are cannabinoid CB_1 receptors, cloned in 1990, and CB_2 receptors, cloned in 1993. Both these receptor types are coupled to their effector systems through $G_{i/o}$ proteins. Mammalian tissues also contain agonists for cannabinoid receptors, the most important of these 'endocannabinoids' being arachidonoylethanolamide (anandamide) and 2-arachidonoyl glycerol.[1]

Cannabinoid receptors and their endogenous ligands constitute the 'endogenous cannabinoid system'. CB_1 receptors are present on certain central and peripheral nerve terminals and there is evidence that one of the physiological roles of these receptors is to modulate the release of neurotransmitters from these terminals. Little is yet known about the physiological role(s) of CB_2 receptors. However, it seems likely that this will prove to involve modulation of immune function in health and/or disease, raising the possibility that cannabinoid receptor ligands may be effective not only in treating symptoms of multiple sclerosis (MS), but also against its underlying causes.

2. Cannabinoids and Multiple Sclerosis

2.1 Current Data

The important advances in our understanding of cannabinoid pharmacology have prompted the development of selective CB_1 and CB_2 receptor agonists and antagonists.[1,2] There has also been a growing realisation that cannabis or individual cannabinoids may be effective in suppressing some of the signs and symptoms of MS, particularly muscle spasticity/spasm and any associated pain. Although the evidence for this hypothesis is partly anecdotal, it is also based on results from preclinical and clinical investigations.[3]

Among the anecdotal data are responses to a questionnaire by 112 patients with MS who claimed to self-medicate with cannabis.[4] Of the patients in this survey with specific symptoms, over 90% reported improvement in these symptoms after taking cannabis (see fig. 1).

Preclinical investigations have shown that the synthetic cannabinoid receptor agonist WIN55212-2 can decrease the severity of dystonia in mutant Syrian hamsters with primary generalised dystonia and that, in rats and guinea-pigs, Δ^8- or Δ^9-THC can delay the onset and reduce the intensity of the clinical signs of experimental autoimmune encephalomyelitis, a putative animal model of MS.[5-7] Other animal experiments have shown that cannabinoid receptor agonists suppress spinal reflexes and that they can produce hypokinesia and catalepsy, changes in motor function that are presumably mediated at least in part by the large populations of CB_1 receptors present in the basal ganglia of the brain.[1,8,9] Whether cannabinoids produce their putative anti-

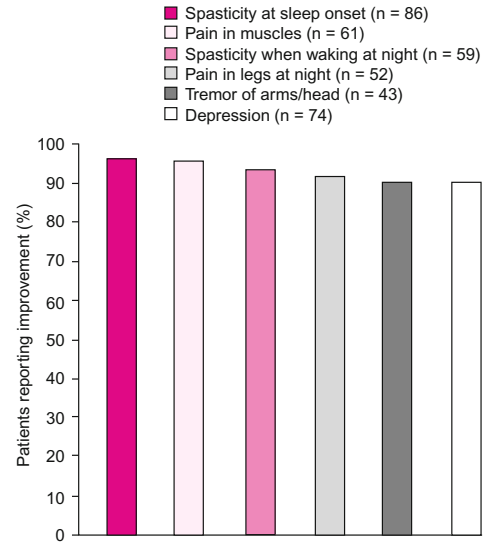

Fig. 1. Response of symptoms to self-medication with cannabis in patients with multiple sclerosis.[4]

spasticity effect by acting at these brain sites remains to be established.

Results from experiments with various animal models of pain also suggest that cannabinoid receptor agonists can act through central and/or peripheral CB_1 receptors to suppress behavioural responses to various kinds of pain including hyperalgesia and neuropathic pain.[10-18]

To date, there have been 6 clinical investigations of cannabinoids in MS (and one in patients with spinal cord injury), albeit with rather small numbers of patients (table I).[3] The resulting data suggest that cannabis, and Δ^9-THC or its synthetic analogue nabilone can reduce the intensity of at least some signs and symptoms of MS or spinal cord injury, particularly spasticity, pain, tremor and nocturia.[19-25]

There is also clinical evidence that cannabinoids can relieve other types of pain. For example, double-blind, placebo-controlled trials have shown oral Δ^9-THC to suppress continuous moderate cancer pain[26,27] and intramuscular L-nantradol, a synthetic cannabinoid receptor agonist, to be effective against acute postoperative pain.[28]

It is unlikely that all the unwanted symptoms of MS or spinal cord injury will be alleviated by cannabinoids. Indeed, Greenberg et al.[29] have reported that marijuana cigarettes (1.54% Δ^9-THC), smoked on one occasion by 10 patients with MS and associated spasticity and gait dysfunction, produced a subtle impairment of posture and balance in these patients as measured by 'dynamic posturography'. The posture and balance of 10 matched healthy controls was also impaired.

2.2 Future Clinical Studies

Although the evidence that cannabis and individual cannabinoids are effective against the muscle spasticity/spasm and pain of MS is not conclusive, it is sufficient to warrant a clinical trial with cannabinoids. The aim of such a trial should be to provide objective and decisive data about: (i) the efficacy of cannabinoids and (ii) whether significant efficacy is achievable at dose levels that do not provoke unacceptable adverse effects. The case for such a trial is reinforced by the generally acknowledged need for treatments that are more effective in suppressing these symptoms of MS and that produce less unpleasant adverse effects than currently available treatments, e.g. baclofen.

2.2.1 Trial Design

Particularly important steps in the design of a clinical trial will be the selection of the drug or drugs to be investigated, the mode of administration of these drugs and the dose levels to be used.

Drug Choice

Numerous cannabinoid receptor ligands are now available.[1,2] However, the most obvious drug candidates for a clinical trial in MS are Δ^9-THC and nabilone. Both of these agents have already been found to show promise in pilot studies in patients with MS (table I) and both are already licensed medicines, nabilone in the UK to suppress nausea and vomiting provoked by anticancer drugs and Δ^9-THC (dronabinol) in the US for the same purpose and also to boost appetite, particularly in patients with AIDS.[3] Although not licensed in the UK, Δ^9-THC is a Schedule 2 drug and can therefore be prescribed on a 'named patient' basis.

Dosage and Administration

Nabilone and dronabinol are both formulated for oral administration. However, the selection of an oral dose that will be both effective and tolerable is not straightforward. When taken orally, Δ^9-THC seems to undergo a somewhat variable absorption from the gastrointestinal tract and to have a rather narrow 'therapeutic window' (dose range in which it is effective without producing significant unwanted effects). In one clinical study, for example, Δ^9-THC was effective in one patient with MS at an oral dose of 5mg whilst in a second patient it was effective only when the dose was raised to 15mg.[20] In another clinical study in which patients with MS were given Δ^9-THC or placebo orally, both 2.5 and 5mg doses of Δ^9-THC were ineffective in producing subjective relief from spasticity, 7.5mg was effective and 10mg was intolerable to some of the patients.[21]

Table I. Summary of results of clinical trials with cannabis and cannabinoids in patients with multiple sclerosis (MS) or spinal cord injury (SC)

Disorder	Design	Drug	Dose (po)	No. of patients	Reference
MS	db, pc	Δ^9-THC	5 or 10mg sd	9	19
MS	sb, pc	Δ^9-THC	5 or 15mg sd × 2-3	2	20
MS[a]	db, co, pc	Δ^9-THC	7.5mg bid for 5 days	8	21
MS	ol	Cannabis	1 cannabis cigarette sd	1	22
MS	db, co, pc	Nabilone	1mg every other day for 1mo × 2	1	23
MS	ol	Δ^9-THC Δ^9-THC hemisuccinate	10 or 15 mg/day × 4 5 mg/day × 4 (rectal)	2	24
SC	db, pc	Δ^9-THC	5mg[b] × 18 over a 5mo period	1	25

a Standard antispasticity drugs unsuccessful or induced intolerable adverse effects.

b Δ^9-THC and placebo were taken with baclofen (40mg) and clonazepam (1mg).

bid = twice daily; **co** = cross-over; **db** = double-blind; **ol** = open label; **pc** = placebo-controlled; **po** = orally; **sb** = single-blind; **sd** = single dose; **Δ^9-THC** = Δ^9-tetrahydrocannabinol.

It would, therefore, be prudent to build a degree of flexibility into the design of any clinical trial conducted with nabilone or dronabinol with respect to dose level. Timing of administration is also important – administration in the evening should be considered, as the claimed benefits for cannabis include reduced incidence of spasticity at sleep onset and when waking at night.[4] For Δ^9-THC, a sensible treatment regimen, at least at the start of a trial, may be 2.5 or 5mg administered orally twice daily.

Route of Administration

An alternative to nabilone or dronabinol for use in clinical studies is a recently developed cannabinoid rectal suppository. This contains Δ^9-THC hemisuccinate which is converted to Δ^9-THC following its absorption.[24] Like smoked cannabis, rectally administered Δ^9-THC avoids first-pass hepatic metabolism. However, some clinicians may be reluctant to use this route of administration in clinical trials. They may anticipate, rightly or wrongly, that rectal suppositories would be unpopular with patients and so give rise to poor compliance, particularly when cannabinoids have to be taken repeatedly, as would be the case for patients with MS.

The absorption difficulties with oral Δ^9-THC may account for anecdotal claims by patients with MS that cannabis is superior to Δ^9-THC as a medicine, as the comparison is usually between oral Δ^9-THC (which has slow, unreliable absorption followed by hepatic first-pass metabolism to active and inactive metabolites) and smoked cannabis (which has faster, more reliable absorption with no first-pass metabolism).

Design

Because of their high lipophilicity (see section 2.2.4), cannabinoids are eliminated from the body very slowly.[30] Consequently, cross-over studies with cannabinoids should either be avoided or else incorporate a lengthy washout period between treatments. There is already evidence that false positive responses to placebo treatment can occur in patients recently withdrawn from a period of cannabinoid treatment.[31]

In view of the psychotropic properties of Δ^9-THC and nabilone, there is also the problem of mounting trials that are truly double-blind. In this case, one solution may be to include an active control and to work with patients who are not familiar with the effects of cannabis.

Patient Selection

Like most drugs, cannabinoids do have some adverse effects[3,32] and these dictate that certain groups of patients should be excluded from clinical trials with cannabinoids. More specifically, cannabis may aggravate existing psychoses[33] and can elevate heart rate.[32] Consequently it would be unwise to give psychotropic cannabinoids to patients with schizophrenia (overt or latent), coronary arteriosclerosis or congestive heart failure.

The clinical significance of the ability of cannabinoids to retard fetal development and to induce fetal resorption in animals remains to be established.[32] Even so, pregnant women should also be excluded from clinical studies with cannabinoids.

2.2.2 Active Constituents of Cannabis

It is possible that, in addition to Δ^9-THC, there are other constituents of cannabis that contribute to its putative beneficial effects either directly or by modulating the effect(s) of Δ^9-THC.[34-37] Clearly, it will be important to compare the effects of Δ^9-THC and cannabis in initial or subsequent clinical trials and, if cannabis does prove to be the superior agent, to investigate the basis for this.

One consideration in any study with cannabis will have to be the relative proportions of at least some of the many different cannabinoids present in the plant material used. It will be particularly important to decide on the relative proportions of Δ^9-THC, cannabinol, cannabidiol and cannabichromene: cannabinol shows weak Δ^9-THC–like activity in humans,[37] while cannabidiol has been reported to augment some effects of Δ^9-THC and to attenuate others, including Δ^9-THC–induced anxiety.[34-36,38] There is also one report that cannabichromene can potentiate Δ^9-THC–induced antinociception in mice.[39]

The oral route can be used not only for Δ^9-THC but also for cannabis. Indeed, capsules containing an extract of the plant material are already available for clinical trials and a license was recently granted to GW Pharmaceuticals to produce cloned cannabis plants in England for use in medical research.

2.2.3 Legal Issues

For studies with cannabis, as opposed to Δ^9-THC or nabilone, there is the additional problem that cannabis is classified as a Schedule 1 drug. This may limit experimental designs to those in which patients take the drug under supervision in the clinic rather than at home. If cannabis proves to be significantly better than single cannabinoids for the management of muscle spasticity/spasm/pain, its Schedule 1 classification will also create ethical difficulties since, unlike Δ^9-THC or nabilone, it will not be available to patients when the trial is over.

2.2.4 Therapeutic Drug Monitoring

Given the likelihood of variable absorption of cannabinoids from the gastrointestinal tract, the design of any clinical trial in which Δ^9-THC or cannabis is given orally should include the monitoring of plasma concentrations of Δ^9-THC. It is noteworthy that when cannabis is smoked or taken orally, the time course followed by plasma concentrations of Δ^9-THC does not correlate well with the time course of the central effects of this compound.[40] Thus, there is a time lag between the rise and subsequent fall in plasma concentrations of Δ^9-THC and the (later) rise and fall in the central effects of the drug. This lag, which is particularly prominent when Δ^9-THC is inhaled in smoke or injected intravenously, probably results from the high lipophilicity/low water solubility of Δ^9-THC, as this is expected to delay equilibration of the compound with its central sites of action.

In spite of the mismatch between the pharmacodynamic and pharmacokinetic time courses of Δ^9-THC, it is anticipated that the monitoring of plasma concentrations of the compound after its administration would provide the information needed to establish the extent to which variability of the pharmacodynamic data is attributable to variability of absorption of Δ^9-THC. Thus, the amount of Δ^9-THC absorbed into the circulation from its site of administration determines the concentration of the drug that is eventually reached at its site(s) of action and so also dictates the maximal size of any effects that it produces. Similar considerations apply to studies with nabilone.

2.2.5 Tolerance and Dependence

Withdrawal of cannabis or psychotropic cannabinoid administration can precipitate abstinence signs in humans. However, these signs are both transient and mild and their significance when cannabinoids are used clinically remains to be established.[32,41-43] The extent to which cannabinoid tolerance may present problems in the clinic has also still to be determined. Thus, although it is known that tolerance to many of the pharmacological effects of cannabin-

oids can be induced in animals and humans,[32,41-43] the extent to which tolerance develops to the sought-after effects of cannabinoids when these are administered at therapeutic doses is not known.

2.2.6 Other Issues

Other major practical difficulties, not specific to cannabinoid research, include the current dearth of outcome measures that will yield conclusive clinical data about drug-induced relief of spasticity, and the question of which ongoing treatments should be withdrawn from patients shortly before and during the trial.

Clinical studies with cannabinoids will also require adequate funding, and the committed involvement of scientists and physicians with appropriate cannabinoid and clinical expertise.

3. Future Directions

As stated previously, the aim of future clinical trials should be to establish conclusively whether cannabinoids can suppress muscle spasticity/spasm and pain of MS and whether this is achievable at dose levels that do not provoke unacceptable adverse effects. If the results obtained are sufficiently promising, one important area for future research must be the development of cannabinoid formulations, cannabinoid vehicles and modes of administration that produce more reliable cannabinoid absorption than has hitherto been possible, at least by the oral route.

Potential options include cannabinoid administration by rectal suppository (see section 2.2.1), by aerosol/vapour inhalation,[44-46] by skin patch or by use of the sublingual or intrathecal route, all modes of administration that avoid first-pass metabolism of the absorbed drug. A slow-release oral cannabinoid formulation is yet another possibility.

It will also be important to establish the extent to which tolerance develops to clinically effective cannabinoid dose regimens. Should cannabis prove to have significant advantages over individual cannabinoids, the basis for this will need to be established so that the perceived advantages can be maximised.

There will then also be a need for the World Health Organization to consider rescheduling cannabis. It is unlikely that smoked cannabis would ever be acceptable for use clinically. Because of the tars and gases produced during the combustion process, cannabis smoke is toxic to airway tissue and probably carcinogenic.[32,47] It will be necessary to subject any novel cannabinoid formulations to the usual range of tests to establish whether they satisfy statutory safety regulations. This is likely to be so for cannabis too, even though tincture of cannabis was a licensed medicine in the UK until 1971.

It would also be worth seeking out a way of separating the therapeutic properties of cannabinoids from their unwanted effects, particularly their psychotropic effects. One possibility is to administer a cannabinoid in combination with a second agent that augments only the sought-after effects of the cannabinoid. There is already evidence from animal experiments that synergistic interactions can occur between cannabinoids and opioids for antinociception[48] and between cannabinoids and benzodiazepines for depressant effects on motor function.[6,49] A second possibility is to develop drugs that activate the endogenous cannabinoid system indirectly by selectively inhibiting the tissue uptake or metabolism of endocannabinoids so as to increase their extracellular level.[50] Such drugs should be more selective than direct agonists, as they are expected to produce effects only at sites of ongoing endocannabinoid production.

As there are claims by patients with MS that cannabis can relieve their symptoms at doses that do not induce a 'high', another strategy might be to administer an agonist that has a reduced ability (efficacy) to activate CB_1 receptors (i.e. a partial agonist). This approach assumes that it should be possible to develop a partial agonist that has sufficient efficacy to relieve muscle spasticity/spasm and pain, but insufficient efficacy to produce a full range of cannabimimetic psychotropic effects even when it occupies all available CB1 receptors. One such compound may be 6′-cyanohex-2′-yne-Δ^8-THC.[51]

Since there is evidence that analgesia can be induced by the activation of CB_1 receptors on peripheral neurons,[10,13] it may also be worth designing cannabinoids that do not readily cross the blood-brain barrier and yet retain the ability to activate CB_1 receptors located outside the CNS.

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