REVIEW ARTICLE

CNS Drugs 2011; 25 (3): 187-201
1172-7047/11/0003-0187/$49.95/0

Role of Cannabinoids in Multiple Sclerosis

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Abstract

Although extracts from the cannabis plant have been used medicinally for thousands of years, it is only within the last 2 decades that our understanding of cannabinoid physiology and the provision of evidence for therapeutic benefit of cannabinoids has begun to accumulate. This review provides a background to advances in our understanding of cannabinoid receptors and the endocannabinoid system, and then considers how cannabinoids may help in the management of multiple sclerosis (MS).

The relative paucity of treatments for MS-related symptoms has led to experimentation by patients with MS in a number of areas including the use of cannabis extracts. An increasing amount of evidence is now emerging to confirm anecdotal reports of symptomatic improvement, particularly for muscle stiffness and spasms, neuropathic pain and sleep and bladder disturbance, in patients with MS treated with cannabinoids. Trials evaluating a role in treating other symptoms such as tremor and nystagmus have not demonstrated any beneficial effects of cannabinoids. Safety profiles of cannabinoids seem acceptable, although a slow prolonged period of titration improves tolerability. No serious safety concerns have emerged.

Methodological issues in trial design and treatment delivery are now being addressed. In addition, recent experimental evidence is beginning to suggest an effect of cannabinoids on more fundamental processes important in MS, with evidence of anti-inflammation, encouragement of remyelination and neuroprotection. Trials are currently under way to test whether cannabinoids may have a longer term role in reducing disability and progression in MS, in addition to symptom amelioration, where indications are being established.

1. Cannabis and Cannabinoids

Cannabis sativa is a flowering plant thought to have originated in the mountainous regions of the northwest Himalayas. It has long been used for fibre in rope and cloth (hemp), for medicinal purposes and as a recreational drug. Cannabinoids, terpenoids, flavonoids, carotenoids and other compounds are secreted by glandular trichomes, which are most numerous in the flowers of female plants.[1] Over 60 separate cannabinoids have been identified from the original plant. These are low-molecular-weight lipophillic compounds, with a varying degree of affinity at specific cannabinoid receptors (CBRs). Wood, Spivey and Easterfield[2] isolated the first cannabinoid, cannabinol, in 1896, in the Agricultural Chemistry Laboratory in Cambridge, UK and Cahn[2] worked out its chemical structure in the 1930s. Cannabinol was later synthesized in 1940 by both Adams et al. and Ghosh et al.[3-5] The major psychoactive cannabinoid, delta-9-tetrahydrocannabinol (Δ^9-THC) or dronabinol, was isolated and characterized in 1964 by the team of Raphael Mechoulam[6] in Israel. In addition to Δ^9-THC, most cannabis extracts contain cannabidiol,[7] which is not psychoactive.

1.1 Cannabinoid Receptors and Endocannabinoids

The pharmacology of cannabinoids is becoming increasingly complex. Although most cannabinoid effects appear to be mediated through G protein-coupled CBRs, a number of effects that are not related to binding to CBRs are being described. Two types of CBR have been identified, CB_1 and CB_2. CB_1 was cloned in 1990[8] and CB_2 was cloned in 1993.[9] Cannabinoids may also show activity at other receptors including G protein-coupled receptor 55[10] (GPR-55), transient receptor potential vanniloid-1[11] (TRPV-1) and adenosine receptors.[12] CBRs are negatively coupled to adenylate cyclase and positively coupled to mitogen-activated protein (MAP) kinases. CB_1 receptors are coupled through $G_{i/o}$ proteins to potassium and calcium channels and thereby affect other neurotransmitter systems including dopamine and glutamate.[13]

The CB_1 receptor is the most common G protein-coupled receptor within the CNS, and autoradiographic studies demonstrated high CB_1 receptor densities in the cerebellum, basal ganglia, hippocampus and cerebral cortex.[14] The CB_2 receptor is most abundant on cells of the immune system.[15]

The discovery of endogenous CBRs led to the identification of endogenous cannabinoid ligands or endocannabinoids, the most common of which are anandamide[16] and 2-arachidonoylglycerol.[17,18] Rather than being stored in presynaptic vesicles as are conventional neurotransmitters, endocannabinoids are rapidly synthesized *de novo* from postsynaptic membrane-lipid precursors, act on presynaptic CBRs and are then degraded or transported. There is therefore increasing interest in compounds that alter endogenous endocannabinoid tone, by reducing degradation – particularly using inhibitors of fatty-acid amide hydrolase.[19] This may provide a more specific method of adjusting CBR activity in those receptors most active, rather than introducing exogenous cannabinoids that may have a much wider range of activities.

1.2 Neuroprotection and Inflammation

Genetic knockout animal studies have demonstrated roles for the cannabinoid system in a variety of normal responses, including memory, learning,[20,21] emotion,[22] locomotion,[22,23]

appetite,[24] cardiovascular responses[23] and nociception.[22] Neuroprotective effects have been demonstrated in animal models of cranial injury[25,26] and experimental allergic encephalomyelitis (EAE).[26,27] CB_1 receptor knockout mice demonstrate considerably more neuronal damage in EAE inflammation,[28] and CB_2 receptor knockout mice are associated with increased excitotoxicity in models of Huntington's disease.[29] Cannabinoids may be helpful by reducing glutamate release[30] and calcium flux (reducing excitotoxicity),[31,32] as well as being antioxidants,[30] thereby reducing free radical damage. In addition, of significance for the disease process in multiple sclerosis (MS), cannabinoids may reduce oligodendrocyte apoptosis,[33] ameliorate the inflammatory response and increase remyelination.[34] It is interesting to note that the market withdrawal of a CB_1 receptor antagonist (rimonabant) was largely due to its association with CNS side effects, but a case of MS has been reported following its use.[35]

1.3 Medical Cannabis Use and Approved Treatments

The prevalence of people using cannabis, mainly for recreational purposes, is around 162 million.[36] Word-of-mouth reporting of beneficial effects of smoked cannabis on MS symptoms – including pain, urinary disturbance, tremor and spasticity – led to newspaper reports and anecdotal accounts being published in the medical literature. This caused widespread unlicensed and often illegal use of cannabinoids in MS. A number of varying formulations and routes of administration, ranging from use of the smoked cannabis leaf to oral preparations including cannabis oil, extracted cannabinoids and synthetic cannabinoids (such as nabilone), have been used.

The UK MS society estimates that 1–4% of the MS population in the UK are illegally using cannabis for symptom relief (around 2750 patients).[37] This figure is thought to be higher in Canada (14–16%).[38,39]

There is no cannabinoid preparation that is licensed for treating MS across Europe or North America. Nabilone (in the US and Canada) and dronabinol (in the US) are licensed for treating nausea related to cancer chemotherapy, and availability on a named-patient basis or for off-license indications varies across Europe. Nabiximols (Sativex®) is licensed for treating MS symptoms in Canada, and is available in parts of Europe on a named-patient basis. Nabiximols was approved in UK in 2010 for treating spasticity due to MS on a prescription basis.[38,40-43]

1.4 Route of Administration and Pharmacokinetics

Cannabinoids are notoriously difficult to work with in the laboratory. They are highly lipophillic, and extracts are therefore generally dissolved either in alcohol or some form of lipid. When ingested orally, they undergo first-pass metabolism in the liver, and there is considerable interindividual dose variation. Serum levels bear little correlation with activity. Cannabinoids are then stored in fat, and since they may build up over time, cannabinoids can be detected in the urine some weeks after discontinuation. This probably explains why withdrawal responses are not a major issue.[44,45]

These factors mean that it is impossible to predict what dose may benefit any single person when administered orally. Some people will experience adverse events with as little as 2.5 mg of dronabinol at night, whereas others may not notice any effects at 15 mg twice daily. These issues have led to a search for alternative routes of administration, ranging from sublingual spray (nabiximols) to suppositories. Despite these attempts, the issue of interindividual dose variation has not been adequately investigated, and to date all preparations require a dose-titration phase. Although, in theory, sublingual preparations may be suitable for acute pain, in MS most pain tends to be more chronic, and therefore single oral doses at night may both avoid side effects and improve sleep, and work best to provide amelioration of chronic problems.

2. Multiple Sclerosis (MS) Clinical Course and Symptoms

MS is the most common cause of neurological disability in young people, with an average age of

onset around 30 years, and a prevalence of about 120/100 000 in most of Northern Europe and North America.[37] It most commonly starts as a neurological event explicable by inflammation in the CNS. At the stage of a single episode, the disease is termed a 'clinically isolated syndrome'. Evidence for further inflammation, demonstrated either by MRI or another clinical event, constitutes a diagnosis of relapsing-remitting MS (RRMS).[46] Around 85% of MS starts with these clinical episodes, occurring in more females than males with a ratio about 3 : 1. The remaining 15% of MS often starts a little later in life, occurs equally in females and males, has a progressive course from the outset and is termed primary progressive disease. In patients who are initially diagnosed with RRMS, the majority will change to a more progressive clinical course after a variable time period, and this type of MS is termed secondary progressive disease. There is an increasing array of treatments for RRMS, almost all based on the assumption that MS is a primary autoimmune disease, and these treatments are therefore immunomodulatory in some way.

Despite increasing optimism over the availability of apparent disease-modifying treatments for RRMS, the majority of people with MS tend to accumulate symptoms over time, the most common being fatigue. Other prevalent symptoms include muscle stiffness and spasticity, poor mobility, pain, memory problems, tremor and balance trouble, urinary disturbance and sexual dysfunction. A major problem in determining whether any drug has efficacy in patients in MS has been the lack of adequate means of measuring its associated symptoms beyond overly simplistic visual analogue scales. In addition, the potential for unblinding in randomized controlled trials (RCTs) in which patients are treated with cannabinoids has also been a major problem in determining the efficacy of these agents.

3. Evidence for a Therapeutic Role of Cannabinoids in Treating MS

We performed a search of the PubMed database and also of the NHS Evidence healthcare databases EMBASE and MEDLINE, with no date or language limits, for articles in order to locate studies of cannabis and cannabinoid use in MS. Keywords used in the search were: 'multiple sclerosis', 'cannabis', 'marijuana', 'cannabinoids', 'cannabinol', 'dronabinol', 'Δ9-THC', 'cannabidiol', 'Cannador®', 'Sativex®', 'trial', 'cannabinoid receptors', 'endocannabinoids', 'pharmacokinetics of cannabinoids', 'neuroprotection', 'inflammation', 'spasticity', 'spasms', 'treatment', 'pharmacotherapy', 'baclofen', 'tizanidine', 'benzodiazepines', 'dantrolene', 'bladder', 'nocturia', 'continence', 'incontinence', 'antimuscarinics', 'oxybutinin', ' tolterodine', 'desmopressin', 'tremor', 'nystagmus', 'pain', 'neuropathic pain', 'antiepileptics', 'antidepressants', 'sleep', 'cognition' and 'adverse effects'. In NHS Athens (a secure login that gives NHS professionals in England access to professional academic resources), we used the advanced search facility and Thesaurus mapping mainly on the EMBASE and MEDLINE databases. The searches have been enriched further by checking the references of the various articles uncovered during the initial work-up. We included only relevant articles published in peer-reviewed journals.

3.1 Anecdote and Postal Surveys

The relative paucity of treatments in MS, particularly for symptoms and progressive disease, has led to a wide variety of treatments being used by people with MS, often without evidence for benefit beyond anecdote. Unfortunately, when such treatments are tested they often prove far from efficacious. Whilst such desperation is understandable from the perspective of the person with MS, it often raises unfulfilled hopes and can lead to unscrupulous exploitation. Nonetheless, it is incumbent on researchers to acquire as much information as possible where RCT evidence is lacking.

There has been some evidence provided from postal surveys on the use of cannabinoids in MS. One surveyed 53 UK and 59 US MS patients who had used cannabis.[47] More than 70% of patients found cannabis to reduce spasticity, pain, sensory symptoms, tremor, anxiety and depression, and 60–70% reported cannabis to reduce weight loss, fatigue, double vision and sexual dysfunction.

Fewer than 60% reported reduction of bladder and bowel dysfunction, vision dimness, walking disability, impaired balance and memory loss. Another survey of cannabis use in Canada among 205 people with MS reported 34 using cannabis for medical reasons.[38] Cannabis use was strongly correlated with male sex ($p = 0.03$), use of tobacco ($p < 0.001$) and recreational use of cannabis ($p = 0.009$). The self-reported effects were relief of stress (moderate/complete relief vs no/mild relief: 20 patients : 1 patient), sleep disturbance (17 : 1), stiffness (16 : 1), mood disturbance (16 : 0), spasm (14 : 1), pain (10 : 2) and weight loss (4 : 1).

3.2 Clinical Trials

3.2.1 Spasticity and Spasms

The treatment of spasticity in MS is unsatisfactory. Current treatments include baclofen (a GABA agonist, given orally or intrathecally), tizanidine, benzodiazepines and gabapentin. The most common side effect of these drugs is sedation, which is dose dependent and dose limiting. Botulinum toxin injection in combination with physiotherapy can also be useful. The evidence base behind any of these drugs is not large. Baclofen was studied in very few limited-scale, blinded studies >30 years ago.[48,49] It seemed to be better tolerated than diazepam but side effects were common. Tizanidine was studied in a number of trials, with varying results. The UK Tizanidine Trial[50] showed a 21% reduction on the Ashworth score in comparison with placebo, whereas another study failed to find this.[51] The evidence for an effect from gabapentin is just as limited, coming from a single double-blind, placebo-controlled, crossover trial.[52]

Initial studies of cannabinoid use in patients with MS were small, and some seemed to show an improvement in spasticity with dronabinol compared with placebo.[53,54] Another study in 16 patients with MS found no effect on spasticity with dronabinol or a cannabis extract (Cannador®); however, the maximum dosage used was 5 mg twice daily, which is probably too low to see an effect.[55] Adverse effects were more common with the cannabis extract.

Table I summarizes the key efficacy data for cannabinoids in the treatment of MS-related spasticity. The CAMS (Cannabinoids in MS) study is the largest parallel-group RCT to date to examine whether cannabinoids are beneficial in the treatment of MS symptoms.[56] In this study, 667 patients from 33 centres in the UK were randomized to either synthetic dronabinol in sesame oil (Marinol®), a whole-plant extract of cannabis (Cannador®, containing Δ^9-THC 2.5 mg and cannabidiol 1.25 mg per capsule) or placebo capsules for a period of 15 weeks. No treatment effect on spasticity was found during the main study using the Ashworth score of spasticity, although patients felt active medication was much more helpful than placebo in alleviating some of their distressing symptoms (spasticity, spasms, pain levels, quality of sleep) [table II].

In the 12 months of follow-up there was a significant decrease in the Ashworth score in the dronabinol arm only, although both active treatment arms demonstrated a wider spectrum of symptomatic benefit than seen in the main short-term study.[57] There were also suggestions of improvements in some disability scores in the follow-up study. One of the problems with interpreting these data is knowing how much objectivity to place on patient-reported outcomes when a degree of unblinding is seen in such studies. Whether this unblinding is due to improved symptoms or unwanted side effects, or whether the unblinding matters at all, remains a matter for debate.

Another placebo-controlled trial in 57 MS patients with poorly controlled spasticity provided some further support for therapeutic benefit when Cannador® capsules were given.[58] Although they were unable to confirm benefit for spasticity, there was a positive effect with Cannador® versus placebo on spasm frequency, mobility and sleep.

A further recent study of Cannador® in people with MS and significant spasticity has been reported.[59] This placebo-controlled, parallel-group study of 279 patients across 22 UK centres demonstrated very similar efficacy to the CAMS study. The primary outcome measure of a spasticity rating scale at 12 weeks showed highly significant

Table I. Key efficacy data for cannabinoids in the treatment of multiple sclerosis-related spasticity in randomized studies

Study (year)	Study design	N	Product	Results	Level of evidence[a]
Killestein et al.[55] (2002)	db, pc, 2-fold co	16	Oral Δ^9-THC, oral cannabis extract (Cannador®)	No effect on spasticity	Class I
Zajicek et al.[56] CAMS (2003)	mc, db, pc	667	Oral Δ^9-THC, oral cannabis extract (Cannador®)	No effect on spasticity using Ashworth scale Symptomatic benefit on spasticity, spasms, pain levels and quality of sleep Tremor improvement not statistically significant	Class I
Zajicek et al.[57] (2005)	12-month follow-up	502	Oral Δ^9-THC, oral cannabis extract (Cannador®)	Significant decrease in Ashworth score for the synthetic Δ^9-THC group only Statistical improvement in 7 of 9 self-rated symptoms	Class I
Vaney et al.[58] (2004)	db, pc, co	57	Oral cannabis extract (Cannador®)	No statistical difference with placebo on spasticity Symptomatic benefit on spasm frequency, mobility and sleep	Class I
Zajicek et al.[59] (2009)	mc, pc	279	Oral cannabis extract (Cannador®)	Relief of muscle stiffness twice as large with cannabis extract on category rating scale, reduced pain	Class I
Wade et al.[60] (2004)	mc, db, pc	160	Nabiximols	No improvement in primary outcome measure of worst symptom Improvement of spasticity and quality of sleep	Class I
Collin et al.[61] (2007)	db, pc	189	Nabiximols	No statistical significance on Ashworth scale Improvement of spasticity on numerical rating scale	Class I
Ambler et al.[62] (2009)	'Enriched' study; pc study on responders from first part	241	Nabiximols	Spasticity numerical rating score clearly improved in responders	Class II (unmasked in part 1)
Wissel et al.[63] (2006)	pc, db, co	13	Nabilone	Significant decrease in pain, no change in spasticity	Class I
Freeman et al.[64] (2006)	Based on CAMS	667	Oral Δ^9-THC, oral cannabis extract (Cannador®)	Significant reduction in incontinence episodes	Class II (dropouts)
Fox et al.[65] (2004)	db, pc	14	Oral cannabis extract (Cannador®)	Not functionally significant, only subjective improvement in tremor	Class I
Svendsen et al.[66] (2004)	db, pc, co	24	Oral synthetic Δ^9-THC (Marinol®)	Pain intensity lower NNT 3.5	Class 1
Notcutt et al.[67] (2004)	db, pc, co	24	Δ^9-THC, cannabidiol, nabiximols	Pain lower	Class III or IV ('N of 1' study)
Rog et al.[68] (2005)	db, pc, pg	66	Nabiximols as adjunctive analgesic	Reduced intensity of pain and sleep disturbance NNT 3.7	Class I

a See table II.[2,69-71]

CAMS = Cannabinoids in Multiple Sclerosis study; **co** = crossover; **db** = double-blind; **mc** = multicentre; **NNT** = number needed to treat; **pc** = placebo-controlled; **pg** = parallel group; **THC** = tetrahydrocannabinol.

benefit with Cannador® compared with placebo ($p = 0.004$), with similar results at 4 and 8 weeks.

Nabiximols (Sativex®) is an oromucosal spray of cannabis extract containing similar cannabinoid proportions to Cannador®. One of the initial studies used nabiximols in a 10-week, placebo-controlled RCT in three centres involving 160 MS patients with significant problems from spasticity, spasms, bladder, tremor or pain.[60] The primary outcome measure was a visual analogue

score for each patient's most troublesome symptom. Although there was no overall improvement in the primary outcome measure of a visual analogue score of the worst symptom, in those patients whose main symptoms was spasticity, there was a significant reduction with nabiximols ($p = 0.001$). There were no significant adverse effects in recipients of nabiximols on cognition and mood, and intoxication was generally mild. A further RCT using nabiximols in 189 patients with MS[61] reported marginal benefits of this agent on the subject-recorded numerical rating scale of spasticity ($p = 0.048$), but the Ashworth scale and other secondary outcomes did not achieve statistical significance. Another recent phase III study investigated the use of nabiximols.[62] This study was not a conventional parallel-group RCT, but an 'enriched study', where all participants were initially provided active drug for 4 weeks, and responders (>20% reduction in spasticity visual analogue score) were then enrolled in a longer (12-week) placebo-controlled study. Significant benefit was reported in spasticity rating scores as well as spasms, sleep and Barthel activities of daily living (ADL) in recipients of nabiximols.

The synthetic cannabinoid nabilone (1 mg/day) has been investigated in a small placebo-controlled RCT in 13 patients with MS with disabling spasticity-related pain, and showed a significant decrease in pain using the 11-point box test but no change in spasticity, motor function and ADL.[63]

There seems to be a discrepancy between the favourable symptomatic effect of cannabinoids on spasticity and the lack of change in the Ashworth scale from most class I level of evidence studies. A potential explanation might be that the follow-up is too short.[57] Another explanation would be that the beneficial effect is more subtle than the detection range of the Ashworth scale, probably mediated through the relief of pain caused by spasms. The symptomatic benefit, with modest side effects, in recipients of cannabinoids is nonetheless clear from studies yielding class I level of evidence. On the basis of this evidence, there is a strong case for cannabinoids to be used as add-on treatment for MS-related spasticity.

Table II. American Academy of Neurology classification scheme requirements for therapeutic questions (reproduced from French and Gronseth,[72] with permission)

Class I	A randomized, controlled clinical trial of the intervention of interest with masked or objective outcome assessment, in a representative population. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences The following are also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study) and crossovers with numbers sufficiently low to have minimal potential for bias e. For noninferiority or equivalence trials claiming to prove efficacy for one or both drugs, the following are also required:[a] 1. The standard treatment used in the study is substantially similar to that used in previous studies establishing efficacy of the standard treatment (e.g. for a drug, the mode of administration, dose and dosage adjustments are similar to those previously shown to be effective) 2. The inclusion and exclusion criteria for patient selection and the outcomes of patients on the standard treatment are substantially equivalent to those of previous studies establishing efficacy of the standard treatment 3. The interpretation of the results of the study is based on an observed-cases analysis
Class II	A randomized, controlled clinical trial of the intervention of interest in a representative population with masked or objective outcome assessment that lacks one criterion a–e class I, above, or a prospective matched cohort study with masked or objective outcome assessment in a representative population that meets b–e class I, above. Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class III	All other controlled trials (including well defined, natural history controls or patients serving as their own controls) in a representative population, where outcome is independently assessed, or independently derived by objective outcome measurements
Class IV	Studies not meeting class I, II or III criteria including consensus or expert opinion

a Note that numbers 1–3 in class Ie are required for class II in equivalence trials. If any one of the three is missing, the class is automatically downgraded to a class III.

3.2.2 Bladder Symptoms

As is the case with many symptom treatments in patients with MS, evidence for the use of commonly prescribed drugs for treating bladder symptoms is sparse. The most common bladder problems in MS are detrusor hyper-reflexia, with symptoms of urinary urgency and frequency, and detrusor/sphincter dys-synergia, where relaxation of the external sphincter and bladder contraction are not coordinated. Presently, detrusor hyper-reflexia is treated non-invasively with anti-muscarinics, including oxybutinin or tolterodine. Nocturia is treated with desmopressin.[73] A class III study showed symptomatic response to oxybutinin in 67% of patients, but 21% of patients had to stop the trial because of side effects.[74] Tolterodine proved superior to placebo and comparable to oxybutinin in enhancing bladder volume and improving continence in a very small class I trial.[75]

In patients with MS, fewer studies have investigated the effect of cannabinoids on urinary symptoms than on spasticity or pain. A small open-label pilot study of 15 MS patients used nabiximols or a Δ^9-THC spray for 8 weeks followed by a long-term extension. Urinary incontinence, number and volume of incontinence episodes, frequency of urination and nocturia all decreased in recipients of both agents versus baseline ($p < 0.05$).[76] Patient self-assessment of pain, spasticity and sleep also improved significantly. Pain improvement continued up to a median of 35 weeks and side effects were mild.

A sub-study of the main CAMS study looked specifically at lower urinary tract symptoms.[64] Although CAMS randomized 667 MS patients to receive Cannador®, Marinol® or placebo, it was primarily aimed at evaluating spasticity, and there were considerable missing data from the incontinence charts used to assess episodes of urge incontinence. Nevertheless, all three groups showed a significant reduction ($p < 0.01$) in adjusted episode rate (38% cannabis extract, 33% THC, 18% placebo), with both active treatments showing significant reduction over placebo.

There is therefore limited evidence for cannabinoid action in reducing incontinence episodes in comparison with placebo in a sub-study of the largest cannabinoid study to date, the level of evidence being class II (unintentional dropouts, not due to side effects).[64]

3.2.3 Tremor

One of the most disabling symptoms in MS is a coarse tremor, which is usually very resistant to pharmacological treatment. Traditional drugs include β-adrenoceptor antagonists and primidone. Other drugs used include carbamazepine, clonazepam, isoniazid and buspirone.[77-79] Levetiracetam seemed to work in a class III level of evidence study but not according to a class I level of evidence study.[80,81]

The evidence for beneficial effects of cannabinoids on MS-related tremor is weak. There was a single case report of an MS patient with acute improvement of chronic motor handicap while smoking marijuana.[82] Another uncontrolled study used oral Δ^9-THC in eight patients with severe ataxia and tremor, two of whom demonstrated improved motor coordination.[83]

Data from the CAMS study revealed Cannador® improved tremor in 48% of patients, Marinol® in 40% and placebo in 33%, according to patient reports; the difference between active treatments and placebo was not significant.[56]

A double-blind, placebo-controlled, crossover RCT investigated the effect of 4 weeks of treatment with oral Cannador® in 14 patients with MS and upper limb tremor.[65] The primary outcome was a validated tremor rating scale. Secondary outcomes were accelerometry, ataxia scale, spiral drawing, finger tapping and the nine-hole pegboard test. Although there was no improvement in any of the objective measures of upper limb tremor, finger tapping was faster in placebo recipients ($p < 0.02$) and five patients felt a subjective improvement of tremor whilst on active treatment ($p = 0.08$).

Data from a 10-week, placebo-controlled RCT in 160 MS patients treated with nabiximols cited in section 3.2.1 failed to show any improvement in a visual analogue scale for tremor between the baseline 2 weeks and the final 2 weeks of the trial.[60]

Overall, there is no evidence for objective improvement of tremor in the class I evidence studies using cannabinoids.

3.2.4 Nystagmus

Nystagmus treatment in patients with MS is disappointing. There are isolated reports of a potential effect of gabapentin on nystagmus (class IV, class II and again class II level of evidence in three trials, respectively).[84-86]

There is a case report on an MS patient with severe pendular nystagmus who took cannabis in several preparations, some of them in a blinded fashion.[87] A dramatic suppression of the nystagmus was documented by video and infrared oculography after smoking cannabis, whilst both nabilone tablets and cannabis oil-containing capsules (up to 40 mg of THC per day) had no effect.

We cannot recommend cannabinoids for nystagmus treatment based on the present class IV level of evidence.

3.2.5 Pain

Pain is very common in MS, affecting up to 70% of patients, and treatment is often unsatisfactory.[88] Many patients with MS experience more than one pain syndrome; combinations of dysaesthesia, headaches and/or back or muscle and joint pain are frequent. The most common pains are either central chronic neuropathic pain (often described as a burning, dragging or aching in association with spasticity) or paroxysmal neuralgias (usually lancinating and sometimes difficult to distinguish from nerve root irritation when outside the cranial nerves). However, the definition of, and conditions encompassing 'neuropathic pain' remain controversial. No universally accepted and validated clinical diagnostic criteria for neuropathic pain exist and assessment of patients based on clinical examination and bedside test to decide what is, and what is not, neuropathic is difficult, even for experts.

Current options for treating central pain conditions remain limited and are based mostly on the use of CNS drugs with known problems of tolerability, particularly antiepileptic drugs (e.g. carbamazepine, oxcarbazepine, gabapentin, pregabalin, lamotrigine and levetiracetam), and tricyclic antidepressants (TCAs) such as amitriptyline, short-term non-steroidal anti-inflammatory drugs (NSAIDs) and simple analgesics.[89-91]

In two double-blind RCTs, lamotrigine failed to show any difference versus placebo as stand-alone or add-on treatment for pain in MS patients.[92,93] No other double-blind RCTs have been conducted to support the use of antiepileptic drugs for pain in MS. One follow-up study (class III evidence) reported a significant incidence of side effects in patients with MS prescribed antiepileptic drugs for pain, especially after the use of carbamazepine.[94] Gabapentin seemed to be effective in treating painful spasms in MS in an open-label unblinded trial (class III evidence).[95] Pregabalin was investigated in an open-label, pilot study in a small number of patients with MS and was found to reduce paroxysmal painful phenomena with mild side effects.[96] Levetiracetam was effective and well tolerated according to a small single-blinded, preliminary study.[97]

Nortriptyline seemed to be effective in sensory complaints and pain in a randomized trial in 59 MS patients that compared transcutaneous electrical nerve stimulation with nortriptyline (class II evidence).

Misoprostol seemed to be effective in pain due to trigeminal neuralgia in patients with MS in an open-label prospective trial (class III evidence).[98]

Pain is another area of MS-related symptoms where there is stronger evidence for an effect of cannabinoids. A crossover, double-blind RCT evaluated oral synthetic dronabinol on central neuropathic pain in 24 MS patients treated for 3 weeks with a maximum 10 mg of dronabinol or placebo, separated by a 3-week period of washout.[66] Median spontaneous pain intensity was measured with a numerical scale in the last week of treatment. The pain intensity was significantly lower ($p = 0.02$) and the pain relief score higher ($p = 0.035$) with dronabinol versus placebo.

A similar crossover RCT in 24 patients of whom 18 had MS found that pain levels were significantly lowered versus baseline when either dronabinol or nabiximols was used.[66]

A larger single-centre, double-blind RCT over 5 weeks in 66 MS patients with central pain states (59 dysaesthetic, 7 painful spasms) treated with nabiximols as adjunctive treatment was subsequently conducted.[68] Patients could self-titrate up to 48 sprays in 24 hours. Nabiximols was superior to placebo in reducing the mean intensity of pain ($p = 0.005$) and sleep disturbance ($p = 0.003$).

Most adverse effects in nabiximols recipients were minor, but were intense enough in two patients to warrant withdrawal from the study. The 2-year open-label follow-up study found that nabiximols was effective, with no evidence of tolerance in the 28 patients who completed the study.[99]

Results from the CAMS study again demonstrated significant patient-reported effects on pain with both dronabinol and Cannador® using category rating scales. These results were confirmed in the recent MUSEC (MUltiple Sclerosis and Extract of Cannabis) study using Cannador® conducted from 2006 to 2008 on 279 patients across 22 UK centres.[56,59]

A meta-analysis of nabiximols, cannabidiol and dronabinol in neuropathic and MS-related pain found a statistically significant effect of these agents on pain relief across studies. Side effects were generally mild, and the most common was dizziness.[100]

Evidence from these studies strongly suggests that cannabinoids (in the form of an oral cannabis extract,[56,59] synthetic Δ^9-THC[66] or nabiximols) are effective in pain relief.[68] The numbers needed to treat are very low at 3.5 or 3.7.[66,68] The side effects of these agents were rare, mild and well documented in the class I studies.

3.2.6 Sleep

Sleep disturbance in MS patients is improved with cannabinoid treatment. In the CAMS study, MS patients reported improved sleep with both Cannador® and dronabinol compared with placebo ($p = 0.025$).[56] Other already cited studies (see section 3.2.1 and 3.2.5) demonstrated a beneficial effect of nabiximols on pain-related sleep disturbance ($p = 0.003$)[68] and on the quality of sleep ($p = 0.047$).[60]

4. Adverse Effects of Cannabinoid Treatment

Cannabinoids appear to be well tolerated when used medicinally. Side effects appear to be generally mild, and most serious adverse events from clinical trials appear to be either unrelated, or expected from the complications of MS. Greenberg et al.[101] evaluated the effect of smoking marijuana on balance in ten patients with MS and described postural reflexes being affected more than in normal subjects. Interestingly, patients perceived an improvement despite evidence to the contrary.

A follow-up, open-label study with nabiximols reported on safety and tolerability in 137 patients with MS.[102] Patients reported 292 side effects, of which 86% were mild to moderate including oral pain, dizziness, diarrhoea, nausea and oromucosal disorder. Three patients had five serious side effects: two seizures, one fall, one aspiration and one gastroenteritis. Four patients had first-ever seizures. Planned, sudden interruption of nabiximols in 25 patients for 2 weeks failed to demonstrate any evidence for a consistent withdrawal syndrome, although 11 reported tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams.

A systematic review of the published data over the last 40 years on cannabinoids, which excluded those studies referring to recreational use, retained 31 studies, from which 23 were RCTs and eight were observational studies.[103] In the RCTs the median exposure was 2 weeks and 96.6% of the adverse effects were not serious, the most common one being dizziness if receiving active treatment (15.5%). Serious side effects listed were relapse of MS (12.8%), vomiting (9.8%) and urinary tract infection (9.1%), and non-serious side effects were more frequent if receiving active treatment (95% CI 1.57, 2.21). The rate of serious adverse effects did not differ significantly between the treated patients and the controls.

Chronic use of cannabinoids for symptom relief by people affected by MS has raised the concern of potential cognitive side effects. Several studies have quantified the neuropsychological effects of cannabinoids, with conflicting results. CAMS-PEC, a substudy on 89 patients who completed psychological tests from the original CAMS study, found a significant reduction in performance on the California Adult Verbal Learning Test (verbal learning and memory) in those patients receiving cannabis extracts compared with placebo.[104,105] Another trial reported

on a worse performance in the Selective Reminding Test (long-term memory storage capacity).[68] Other studies have not demonstrated adverse effects on cognition.[58,60,106]

Most concern with cannabinoids has been directed towards potential psychiatric side effects, particularly in light of the association between excess recreational cannabis abuse during adolescence and subsequent schizophrenia. Although there have been occasional cases of toxic psychosis associated with clinical trials of cannabinoids, to date all of these have been reversible and dose related.[54,68] Indeed, some cases of psychosis have occurred in placebo-treated patients. Nevertheless, caution must always be exercised, and slow titration is usually the best method of obtaining symptom relief and compliance.

5. Conclusion and Future Directions

Considerable effort has been expended in the last decade to conduct clinical trials using cannabinoids and to start to test which cannabinoids may be therapeutically beneficial. At present there are a number of trials providing class I evidence demonstrating a beneficial effect of cannabinoids on pain and sleep disturbance, and a class II large follow-up study that has shown a significant reduction in incontinence episodes. The side effects were carefully reported and deemed to be mild. Evidence for a beneficial effect of cannabinoids on symptomatic spasms and spasticity is persuasive from a number of trials providing class I evidence – often considerably better than the evidence on which current treatment options are based.

This evidence for the therapeutic benefit of cannabinoids has been slow to gather, although most clinicians with experience of these drugs will generally vouch for their effectiveness. The number of positive studies is now accumulating, in parallel with developments in trial methodology, including improved symptom measurement (e.g. the new patient report spasticity scale, MSSS-88)[107] and newer trial designs. Licensing authorities tend to believe 'objective' measurements more than patient report, even when older 'objective' measures such as the Ashworth scale of spasticity are inadequate for detecting meaningful symptom change from the patient perspective. There is still a considerable way to go to fully understand how symptoms interact with disability, and how we can take account of placebo effects (evidence from the CAMS study suggests that these may last at least 12 months), together with ways of accommodating potential unblinding.

Advances need to be made in reducing cannabinoid side effects, including unwanted psychoactivity. This may result from developing peripherally active compounds that may affect peripheral receptors or blood flow for symptoms such as pain and spasticity. Newer compounds altering endocannabinoid tone may also not have the same degree of psychoactivity. Drug availability may be altered by developing water-soluble compounds and newer methods of administration.

Perhaps most exciting is the possibility that cannabinoids may be neuroprotective and have a much wider role than symptom alleviation. There is considerable experimental evidence for cannabinoids being associated with reduced excitotoxicity secondary to reduced neurotransmitter release, synaptic modulation, reduced free radical damage, improved mitochondrial function and reduced inflammation together with increased repair and remyelination. One of the long-term follow-up studies has also suggested a role for cannabinoids in possibly reducing disease progression that was not seen in the short-term, 15-week, main study.[57] A further pivotal study is now under way, expected to report in 2012, where 500 people with progressive MS have been recruited to a UK 3-year, randomized, placebo-controlled, follow-up study to see whether disability progression can be slowed with cannabinoids (CUPID [Cannabinoids Use in Progressive Inflammatory brain Disease] study). We await these results with interest.

Acknowledgements

No funding has been provided to prepare this review. There has been no involvement of any funding organisation or sponsor in any of the following: collection, management, analysis and interpretation of the data; and preparation, review or approval of the manuscript. Prof. J.P. Zajicek has previously received consultancy fees from IKF and Bayer-Schering.

Dr V. Apostu has no conflicts of interest to declare. No other persons have made any substantial contributions to the work.

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