Cannabis-based medicines in multiple sclerosis – A review of clinical studies

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ABSTRACT

For some years a mixture of anecdotal report and data from animal models have implied a potential role for cannabis-based medicines in ameliorating a variety of symptoms of multiple sclerosis. Only recently however have large randomised controlled trials (RCTs) examined these potential effects rigorously. At present the results of RCTs have lacked a coherent message to the prescribing clinician and reasons for such heterogeneity in cannabinoid trials are discussed.

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Introduction

Other reviews in this special issue have concentrated upon the immunological effects of cannabinoids, including in animal models of Multiple Sclerosis (MS). This review, therefore, concentrates purely upon the clinical results of treating patients with MS with cannabinoids and highlights some of the conflicting evidence from recent randomised controlled trials. Before considering the results of clinical trials it is important to examine the context within which these have been conducted.

Cannabis

The cannabis plant, *cannabis sativa*, contains over 60 different polycarbon tricyclic dibenzopyran compounds, termed cannabinoids (Dewey, 1986). Cannabis has been used medicinally for thousands of years to alleviate a wide variety of conditions, including pain, dysentery, sleep disturbance and nausea and vomiting, prompting Queen Victoria's doctor Reynolds to declare it "one of the most valuable medicines we possess" (Booth, 2003). Cannabinoids affect almost every system in the human body, including the cardiovascular, respiratory, immune, reproductive and nervous systems.

Doctors in the UK were able to prescribe oral tinctures of cannabis until 1971 when both it and cannabinoids were outlawed by the Misuse of Drugs Act. They were placed in Schedule 1 along with raw opium and lysergic acid diethylamide, and this completely prohibited their use unless under exceptional circumstances such as strictly monitored scientific research.

Interactions of cannabinoids with pain pathways

Cannabinoids act upon multiple levels from peripheral sensory fibres, through spinal and supraspinal mechanisms (Walker and Huang, 2002; Hohmann and Suplita, 2006) and in animal models have demonstrated synergy (Fuentes et al., 1999) and interactions with the opioid system (Ibrahim et al., 2005) although a recent trial of 1 or 2 mg tds of nabilone and morphine in human postoperative pain lead to higher pain scores (Beaulieu, 2006).

Interactions of the endocannabinoid and opioid pathways

There are a number of lines pieces of evidence to suggest that the endocannabinoid and opioid systems interact, at least in rodents. Opioid receptor antagonists prevent the antiemetic actions of nabilone in cats (Rang and Dale, 1991). Naloxone can induce an abstinence syndrome in rats (which is ameliorated by the administration of anandamide (Vela et al., 1995a) or delta-9-tetrahydrocannabinol (Hine et al., 1975)) with either perinatal (Vela et al., 1995b) or chronic exposure to

delta-9-tetrahydrocannabinol (Kaymakcalan et al. 1977). The perinatally exposed rats had reduced sensitivity to the antinociceptive effects of morphine in their adults lives (Vela et al., 1995b). Neonatal rats exposed to delta-9-tetrahydrocannabinol have higher levels of immunoreactivity to met-enkephalin and beta-endorphin (Kumar et al., 1990).

Delta-9-tetrahydrocannabinol when delivered intrathecally into the subarachnoid space increases dynorphin A and leucine–enkephalin levels in the spinal cord, and its chronic administration also increased prodynorphin and proenkephalin gene products (Corchero et al., 1997) suggesting that its analgesic effects are mediated through the release of endogenous opioids.

However, despite this animal data, a recent trial of 1 or 2 mg three times daily of nabilone given in combination with morphine in human postoperative pain led to higher pain scores (Beaulieu, 2006).

Delta-9-tetrahydrocannabinol

The principal psychoactive component in cannabis preparations is considered to be the cannabinoid delta-9-tetrahydrocannabinol and has been the subject of most research. Tetrahydrocannabinol is a sticky resin and insoluble in water.

Cannabidiol

Cannabidiol, in addition to having inherent therapeutic properties, modulates some of the more undesirable adverse effects of Tetrahydrocannabinol such as anxiety and unpleasant psychological effects through both pharmacokinetic and pharmacodynamic mechanisms. Cannabidiol is a potent inhibitor of the liver enzyme P45003A11 which blocks the hydroxylation of tetrahydrocannabinol to its more psychoactive metabolite 11-hydroxy- tetrahydrocannabinol (Browne and Weissman, 1981; Bornheim et al., 1995). Whereas tetrahydrocannabinol leads to a reduction of acetylcholine in the hippocampus of rats which correlates with loss of short-term memory consolidation, cannabidiol does not reduce acetylcholine in the brain.

The endocannabinoid system

The resurgence of interest in cannabis-based medicines has been driven by the discovery of the endogenous cannabinoid or "endocannabinoid" system' a natural system within the human body through which cannabinoids exert their effects and which demonstrates many similarities with the endogenous opioid system such as potential perturbation by exogenous plant-derived or synthetic ligands which act upon specific receptors which have a role in modulating nociception.

Cannabinoid receptors

Cannabinoid 1 receptor

The structure of the first cannabinoid receptor, termed cannabinoid 1, was elucidated in 1990 and it was recognized that this is the most abundant receptor in the mammalian brain (Matsuda et al., 1990) with particularly high concentrations within the frontal lobes, basal ganglia, cerebellum, hippocampus, hypothalamus and anterior cingulate cortex. It is a G-protein coupled receptor which inhibits adenylyl cyclase leading to a reduction in cyclic adenosine mono-phosphate levels. Cannabi-

noid 1 receptors are thought to be coupled with various subtypes of calcium and potassium channels and activation of them leads to inhibition of the release of various neurotransmitters such as acetylcholine, dopamine, norepinephrine, glutamate and D-aspartate. In rat brain cannabinoid 1 receptors are mainly localized to axons and nerve terminals and are largely absent from the neuronal soma or dendrites (Iversen, 2003).Within the brain the highest concentrations of cannabinoid 1 receptors are within the globus pallidus and substantia nigra, with moderate concentrations in the cerebellum, hippocampus, caudate, putamen, hypothalamus and amygdala with low and very low concentrations in the cerebral cortex and white matter, respectively (Baker et al., 2003). Neurons that express high levels of cannabinoid 1 receptors include gamma amino butyric acid interneurons in the hippocampus, and amygdala. Tetrahydrocannabinol is only a partial cannabinoid 1 agonist (Pertwee, 1997; Howlett et al., 2002). The finding that cannabinoid receptors are predominantly presynaptic rather than postsynaptic is consistent with their postulated role in modulating neurotransmitter release. The regional distribution of cannabinoid 1 receptor in brain correlates only poorly with the levels of anandamide and other endocannabinoids in different brain regions (Felder et al., 1996; Bisogno et al., 1999) and a strict correlation would not be expected for ligands that are only produced on demand. There is a better correlation between the regional distribution of cannabinoid 1 and fatty acid amide hydrolase, although the latter is widely distributed in the central nervous system and other tissues, suggesting that its role is not confined to inactivating endogenous cannabinoids.

Cannabinoid 2 receptors

A second receptor with 48% homology was cloned in 1999 (Munro et al., 1993). Cannabinoid 2 receptors are mostly present in peripheral immune and haematopoietic tissues such as, bone marrow and pancreas, lung, and smooth muscle. (Munro et al., 1993) but recently were found to be present in the brain (Van Sickle et al., 2005; Gong et al., 2006). Both cannabinoid 1 and cannabinoid 2 receptors linked to inhibition of adenylate cyclase activity (Howlett et al., 1988).

Endocannabinoids

The endogenous or endocannabinoid system shares many similarities with the opioid system; exogenous plant derived and synthetic ligands are available to act upon endogenous receptor targets, mediating a variety of effects, including analgesia. The endocannabinoid system includes: (1) at least two families of lipid signalling molecules, the *N*-acyl ethanolamines (for example, anandamide (*N*-arachidonyl – ethanolamine)) and the monoacyl-glycerols (for example, 2-arachidonoyl glycerol and 2-arachidonyl glyceryl ether); (2) multiple enzymes involved in the biosynthesis and degradation of these lipids, including the integral membrane enzyme fatty acid amide hydrolase (Di Marzo et al., 1994; Piomelli et al., 1998; Giuffrida et al., 2001) and (3) two G-protein coupled receptors, cannabinoid 1 (Matsuda et al., 1990) and cannabinoid 2 (Munro et al., 1993). Selective synthetic cannabinoid 1 or cannabinoid 2 receptors antagonists are now available (D'Souza and Kosten, 2001) and cannabinoid 1 receptor antagonists have been studies in trials of human obesity (Van Gaal et al., 2005; Pi-Sunyer et al., 2006). Anandamide a lipid derived from arachidonic acid is a partial agonist of cannabinoid 1 and synthesised on demand and released from presynaptic terminals. It is recycled into the presynaptic terminal by a transporter protein and hydrolysed by the membrane associated fatty acid

amide hydrolase. It may be amenable as a therapeutic target (Piomelli et al., 1998). Mice with chronic-relapsing experimental autoimmune encephalomyelitis, a proposed animal model of MS, have increased levels of anandamide, and palmitoylethanolamide in areas associated with nerve damage (Baker et al., 2001). Endocannabinoids are involved in the rapid modulation of synaptic transmission in the central nervous system by a retrograde signalling system that can infuence synapses in a local region of some 40 mm diameter, causing inhibitory effects on both excitatory and inhibitory neurotransmitter release that persist for tens of seconds (Wilson and Nicoll, 2001).

Spasticity and tremor in mice with chronic-relapsing experimental autoimmune encephalomyelitis can be reduced by administering whole plant or synthetic cannabinoids and by selective inhibitors of endocannabinoid transport or hydrolysis and worsened by cannabinoid 1 or cannabinoid 2 antagonists (Baker et al., 2000) implying that the endocannabinoid system provides tonic control of muscle tone in this animal model (Baker et al., 2001; Ligresti et al., 2006). Cannabinoid 1-deficient mice tolerate inflammatory and excitotoxic insults poorly and developed substantial neurodegeneration after the induction of experimental autoimmune encephalomyelitis (Pryce et al., 2003) with a greater loss of myelin and axonal/neuronal proteins and increased caspase activation (Jackson et al., 2005b), the latter occurred before experimental autoimmune encephalomyelitis was induced implying the endocannabinoid system has a neuroprotective role (Jackson et al., 2005a).

Recreational use of cannabis and dosing variability

Cannabis has long been associated with recreational use, mainly by smoking dried plant material or resin from the flower heads, to obtain a rapid absorption from the lung, giving a euphoric state or 'high' although the precise effects depend upon user's mood, expectation, situation and personality (Booth, 2003). Its adverse effects compare favourably with many other drugs with similar therapeutic targets for example; tricyclic antidepressants, phenothiazines, opioid and non-opioid analgesics and anticonvulsants. It has been estimated, based on extrapolation from mouse to man, that the lethal dose to effective dose ratio is about 40,000 to 1 (Grinspoon and Bakalar, 1993) and this may reflect the low density of cannabinoid receptors within the brainstem which subserves vital functions.

Illegally sourced "street" cannabis is thought to contain approximately equal amounts of the cannabinoids delta-9-tetrahydrocannabinol and cannabidiol (Baker et al., 1983) although these substances are not standardised and are of unregulated quality. Variation in any therapeutic benefit obtained and adverse events experienced occur as a result of differing concentrations and relative quantities of specific cannabinoids available from different plants, a 1 g marijuana cigarette could contain anywhere between 3 and 150 mg of tetrahydrocannabinol (Corey, 2005).

Use of cannabis by patients with multiple sclerosis

Despite such legal and other variables many patients with MS self-medicate with cannabis. In a postal questionnaire, one hundred and ten of 254 patients (43%) with MS in the south of England acknowledged ever using cannabis, with 75 (68%) of these specifically using it medicinally to relieve symptoms of MS (Chong et al., 2006). Forty six patients had used cannabis in the month prior to the survey, 31 for symptom relief (Chong et al., 2006). Patients cited pain and spasms in over 80% of cases, as the most common symptoms accounting for their cannabis use with a

further 25 patients (53%) taking cannabis for sleep problems of which 22 (88%) reported improvement or symptom relief (Chong et al., 2006). Over 90% of 112 MS patients in the United Kingdom and the United States who self medicated with cannabis declared improvement in nocturnal pain and spasticity and muscular pain (Consroe et al., 1997). Sleep problems improved in 88%. The legal, ethical and moral implications arising from the procurement and use of an illegal substance are clearly undesirable for patients, with 71% of patients with MS who had never taken cannabis stating that they would be prepared to try a cannabis-medicine if it were legal or available on prescription (Chong et al., 2006). In a postal survey in Halifax, Nova Scotia, of 34 of 205 patients with MS (14%) who self-medicated with cannabis, 29 took cannabis at night and 22 in the late afternoon with less than 10 patients taking it earlier in the day with 10 of 12 patients (84%) reporting moderate to complete relief of pain (Clark et al., 2004).

Clinical trials of cannabinoids in multiple sclerosis

In 1997, the British Medical Association published a scientific report "Therapeutic Use of Cannabis" (British Medical Association, 1997) which highlighted the need for methodologically sound large-scale clinical trials of cannabinoids with rigorous examination of their subjective and objective effects. In 1998, The UK House of Lords Scientific Select Committee published their Ninth Report on the potential role of medical marijuana, stating that clinical trials of cannabis for the treatment of MS and chronic pain should be mounted as a "matter of urgency", requiring particular attention to the efficacy of alternative routes of administration besides smoked cannabis (House of Lords, 1998).

Practical issues relating to clinical trials of cannabinoids

Fig. 1 outlines some of the sources of variation in cannabinoid pharmacology which makes the question so often asked of us by patients with MS; "So doctor does "cannabis" work"? so difficult to address.

In order to attempt to answer this question one must consider the specific symptom or symptoms of MS one wishes to treat, the source of exogenous cannabinoid, whether plant or synthetic, the single cannabinoid under investigation or if more than one cannabinoid in what proportions, the single, fixed or variable dosing schedule and the route of administration, whether oral, oromucosal or other. All of these variables may affect the outcome of clinical trials and the interpretation of the results presented later should be considered within this context.

Exogenously administered tetrahydrocannabinol or other cannabinoids cannot mimic the physiological effects of locally released endocannabinoids as they cause long-lasting activation of cannabinoid 1 receptors in all brain regions. Clinically this could lead to unwanted adverse effects and to persistent inhibition of neurotransmitter release from nerve terminals that express cannabinoid 1 receptors. This may temporarily prevent both depolarization-induced suppression of inhibition and depolarization-induced suppression of excitation. Depolarization-induced suppression of inhibition is a form of fast retrograde signalling particularly prominent in the hippocampus and cerebellum from postsynaptic neurons back to the inhibitory cells that innervate them (Alger and Pitler, 1995). Depolarization-induced suppression of excitation is a transient inhibition of excitatory inputs to nerve cells when the cell itself is depolarised.

One of the challenges in utilising cannabis as a medicine is how to replicate the rapid absorption achieved by smoking it. Although randomised controlled trials are still being conducted
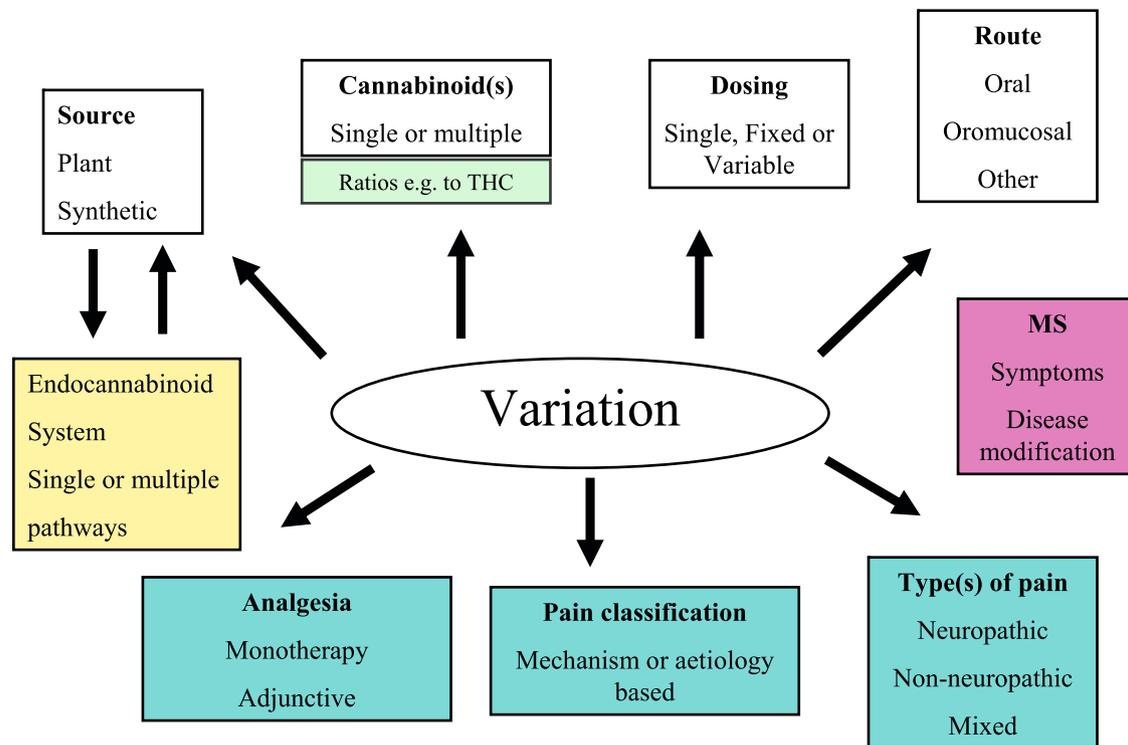
Fig. 1. Sources of variability in cannabinoid trials. Yellow – manipulation of endocannabinoid system, White – Exogenously administered cannabinoids, Pink – Purpose of study in MS, Green – Further sources of variation in symptomatic (MS Pain) trials. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

using this route of administration (Wilsey et al., 2008) the possibility of carcinogenicity rules out this method of administration as a viable long-term therapeutic option. It has been suggested that "oral administration is probably the least satisfactory route" of administration of cannabinoids (Baker et al., 2003). This is due to variable gastrointestinal absorption and first pass effect through the liver which degrades tetrahydrocannabinol and converts it to its more psychoactive metabolite 11-hydroxy-tetrahydrocannabinol and which contributes to the variability of circulating concentrations (Hawks, 1982; Agurell et al., 1986; Mattes et al., 1993; Grotenhermen, 1999; Pertwee, 1999; Kumar et al., 2001). Cannabinoids are highly lipophilic and are sequestered into body fat before being released back into the blood stream slowly and variably over several weeks (Kumar et al., 2001). Although such low levels are unlikely to exert a clinical effect crossover designs would require prolonged washout phases to avoid the potential for carryover effects (Pertwee, 1999). Others have concluded that "clinical trials of cannabis for MS will need to include early dose-finding phases and allow for considerable inter-subject variability in dose adjustments" (Clark et al., 2004).

Cannabinoid treatment of symptoms of MS

Clinical experience 1983–2002

Table 1 outlines the clinical studies using cannabinoids conducted for symptoms of MS between 1983 and 2002. It is difficult to draw firm conclusions as to any potential efficacy of cannabinoids as the trials involved were small, including case reports, used a number of different synthetic and/or plant derived cannabinoids with different routes of administration, including smoking, and, sometimes unknown, dose ranges (Petro and Ellenberger, 1981; Clifford, 1983; Ungerleider et al., 1987; Meinck et al., 1989; Davies, 1992; Doyle, 1992; Hodges, 1992;

Ferriman, 1993; Grinspoon and Bakalar, 1993; Handscombe, 1993; Hodges, 1993; James, 1993; Greenberg et al., 1994; Martyn et al., 1995; Killestein et al., 2002).

Randomised controlled trials of cannabis-based medicines in multiple sclerosis post 2002.

Since 2002 there have been a number of large randomised controlled trials of cannabis-based medicines in MS, predominantly exploring their effects on spasticity and neuropathic pain. The majority of these trials can be broadly summarised as the Cannabinoids in MS study (CAMS) and those conducted using Sativex. The trial characteristics and results are summarised in Table 2.

Cannabinoids in MS study (CAMS)

The Cannabinoids in Multiple Sclerosis (CAMS) trial remains the largest such RCT with 657 patients randomised. The trial examined the effects of Cannador, cannabis plant extract (Institute for Clinical Research, IKF, Berlin, Germany=2.5 mg THC: 1.25 mg CBD, < 5% other cannabinoids), Marinol (Solvay Pharmaceuticals, Atlanta, GA, USA=synthetic delta-9-THC in oil (2.5 mg) or Placebo on spasticty and other symptoms of MS and the dose of study medication was based on body weight, with a maximum dose of 25 mg of THC daily.

Spasticity, the primary outcome, when measured objectively using the Ashworth scale, was not significantly different between groups (mean reduction in total Ashworth score for subjects taking Cannador compared with placebo; 0.32 (95% CI −1.04–1.67), and for those taking marinol versus placebo; 0.94 (−0.44–2.31), whereas when measured subjectively using a category rating scale ("Improvement", "Same", "Deterioration") there were significant differences not only in spasticity ($P=0.010$), but also pain (421 patients of a possible 630 whose data was included in

Table 1
Cannabinoid Studies in Multiple Sclerosis (1983–2002).

Study	N	Symptom(s)	Route/Cannabinoid/Dose	Study design	Results
Killestein et al., 2002	16	Severe spasticity	Oral THC (Marinol) or plant extract THC: CBD (10–30%) up to 5 mg bd	DBPC two fold crossover 4 weeks treatment and 4 weeks washout	No significant effect
					Adverse Events higher and global impression worse with plant extract 1 episode of acute psychosis
Greenberg et al., 1994	10	Balance	Smoked single dose	Single dose	Impaired posture and balance
Martyn et al., 1995	1	Spasticity	Oral Nabilone 1mg on alternate days for 2 periods of 4 weeks	DBPC	Improved well being, spasms, frequency, nocturia
Meinck et al., 1989	1	Motor handicap	Smoked	Open label	Improved tremor, spasticity, ataxia
Various *	10	Various	Smoked or Oral dose unknown	Case reports	Improved well-being, walking, appetite, breathing, bladder control, spasms
Ungerleider et al., 1987	13	Spasticity	THC 2.5–15 mg for 5 days	DBPC crossover	Subjective improvement at > or =7.5mg No objective improvement
Clifford 1983	8	Tremor/ Ataxia	THC 5–15 mg	SBPC	5 mild subjective improvement in tremor
					2 additional objective improvement All "high" after THC, 2 dysphoric
Petro and Ellenberger, 1981	9	Spasticity	Single dose oral THC 5 mg or 10 mg	DBPC crossover	3 subjective and 2 objective improved 1 objective improvement on placebo

Key to Table 1 CBD=Cannabidiol, DBPC – Double blind placebo controlled trial, SBPC – Single Blind Placebo Controlled, QST – Quantitative Sensory Testing, VAS – Visual Analogue Scale, THC –Tetrahydrocanninol.

the primary ITT analysis=67%) (P=0.002), sleep (76%) (P=0.025) and spasms (83%) (P=0.038). In those patients who experienced them at baseline (indicated in parntheses), no effects of treatment were noted with respect to irritability (55%), depression (61%), tiredness (78%), shake/tremor (62%), or energy (86%). No evidence of a treatment effect in any of the other secondary outcome measures (Rivermead mobility index, Barthel index, General Health Questionnaire-30, and United Kingdom Neurological Disability Scale) were noted.

The median time taken to walk 10 m was reduced from baseline to follow-up by 12% with delta-9-THC (95% CI 6–21) compared with a reduction with cannabis extract of 4% (0–10) and placebo of 4% (–2–7). However the Rivermead mobility index scores did not significantly change. The authors suggested that this may related to a reduction in discomfort when walking assuming no major change in spasticity.

Subjective symptom improvements to the question "has your …improved yes or no" were noted in favour of active groups for pain and spasticity (both p=0.003) but not for tremor (p=0.052) or bladder problems (p=0.149). Only 1 MS relapse was noted in each active treatment group compared with 7 in the placebo group.

Overall, the significant subjective effects on pain and muscle spasms, together with the patients' belief that these drugs helped spasticity, suggests there might be a reduction in the manifestations of spasticity, rather than an effect on muscle stiffness per se.

The study authors specifically assessed the degree of blinding. significant association between both the treating doctor and patient were more likely to successfully guess that patients were in an active treatment than taking placebo ($p < 0.001$), however the assessor (who performed the Ashworth assessment) was not (p=0.72).

Patients were offered the opportunity to continue on their study medication (Cannador, Marinol or Placebo) in a blinded fashion for up to 1 year. At this stage there was a significant difference in the change in the Ashworth score from baseline (Marinol mean reduction 1.82 (95% CI 0.53–3.12), Cannador 0.10 (95% CI –0.99–1.19), placebo –0.23 (95% CI –1.41–0.94); p=0.04 unadjusted for ambulatory status and centre, p=0.01

adjusted). However, the trends in improvement in walking speed and Rivermead mobility index were non-significant and there were no differences in relapse rates between groups. Once again patients reported significant improvements in spasticity (P=0.004), spasms (P=0.002) and pain (P=0.002) as well as energy (P=0.004).

The results of this study draw sharply into focus the nature of the construct of spasticity, how this is best measured and by whom; the patient or an external assessor. The authors concluded that there was a need to examine whether Marinol had a role in long-term disease management in MS and have designed the ongoing Cannabinoids in Progressive Inflammatory Brain Disease (CUPID) in an attempt to answer this. The study intends to recruit 500 patients with progressive forms of MS and examine the effects on disability outcomes of delta-9-THC versus placebo over 3 years (Clinical Neurology Research Group, 2009).

A further study aimed at confirming the patient based improvements identified in the CAMS study has recently been presented (Zajicek et al., 2009). Two hundred and seventy nine patients were randomised to oral cannabis extract (2.5 mg THC: 1.25 mg CBD) or placebo. The study consisted of a 1- to 2-week screening period, followed by a 2-week dose titration phase from 5 to 25 mg THC daily based on tolerability, and a 10-week maintenance phase. Patients were required to have definite MS with stable disease for the previous 6 months, troublesome muscle stiffness, with stable antispasticity medication and physiotherapy. The primary outcome measure was the patients' assessment of change in muscle stiffness from baseline. Beneficial response ('relief') was defined as marking categories 0–3 on an 11-point category rating scale (CRS). Further measures included CRS for body pain, spasms and sleep quality. The rate of relief in muscle stiffness after 12 weeks was almost twice as large under cannabis extract compared to placebo (29.4% vs. 15.7%, p=0.004 one-sided). Similar results were found in rates of relief for body pain, spasms and sleep quality at all time points throughout in the study and in various questionnaires assessing these symptoms. The authors described a pronounced increase in the rate of drug reactions in the cannabis extract group versus placebo in the titration phase.

Table 2
Randomised Controlled Trials of cannabinoids in MS (post 2003).

Study	N	Symptom(s)	Cannabinoid/route/dose	Study design	Results
Zajicek et al., 2009	279	Muscle stiffness resistant to standard treatments	Cannabis Extract 5–25 mg depending upon tolerability	DBPC 2 week titration and 10 week maintenance phase.	Rate of relief of muscle stiffness 29.4% in Cannabis Extract group versus 15.7% in placebo group $p=0.004$ one sided). Body pain, spasms and sleep quality also improved.
Ambler and Davies, 2009	573 Phase A	Spasticity resistant to standard treatments	THC:CBD (Sativex) oromucosal spray up to 24 sprays per day	Enriched design. Phase A single blind Sativex treatment for 4 weeks. Responders (subjective NRS spasticity scores reduced by $\geq 20\%$) randomised in double blind fashion to Sativex or placebo for 12 weeks in Phase B	Significant reduction in NRS-11 spasticity rating of 0.84 on sativex versus placebo ($p=0.0002$).
	241 Phase B				74% of sativex versus 51% of placebo patients achieved $\geq 30\%$ reduction in spasticity score ($p= 0.0003$). Siginificant reductions in spasm frequency ($p=0.005$), sleep disturbance ($p < 0001$).
Ratcliffe et al., 2008	339	Central Pain	THC:CBD (Sativex) oromucosal spray up to 24 sprays per day	DBPC parallel group 14 weeks	50% in Sativex versus 45% in placebo group experienced $\geq 30\%$ reduction in pain ($p=0.234$)
Collin et al., 2007	189	Spasticity	THC:CBD (Sativex) oromucosal spray	DBPC parallel group 6 weeks	Spasticity NRS-11 reduced from 5.49 to 4.31 in the Sativex and from 5.39 to 4.76 in the placebo group a small numerical estimated treatment difference of 0.52 points, in favour of Sativex ($P=0.048$; 95% CI: -1.029, -0.004 points). Ashworth and other secondary measures non-significantly different between treatment groups.
Collin et al., 2006	337	Spasticity	THC:CBD (Sativex) oromucosal spray	DBPC parallel group 15 weeks	Only the per protocol population showed a significant treatment difference of -0.46 (95% CI:-0.88, -0.03, $p=0.035$) in NRS-11 spasticity scores favouring Sativex, an effect that was lost in the ITT group (treatment difference -0.23, 95%CI:-0.59, 0.14, $P=0.219$).
de Ridder et al., 2006	135	Urgency incontinence	THC:CBD (Sativex) oromucosal spray	DBPC parallel group 10 weeks	Primary outcome, reduction in the daily number of episodes of urgency incontinence, did not reach signifance between groups ($p=0.57$). Four of seven secondary endpoints; nocturia episodes (-0.28, $p=0.010$), reduction in number of voids per day (-0.85, $P=0.007$) and subjective improvements in patients opinion of bladder symptom severity and patients global impression of change, were statistically significant in favour of Sativex.
Freeman et al., 2006	255 of 657 in CAMS study	Urinary incontinence	THC 2.5 mg (Marinol) or THC 2.5 mg/1.25 mg CBD Plant Extract (Cannador) dosed upon weight	Substudy of CAMS.	Significant reductions in episodes of urinary incontinence of 25% (Cannador) ($p=0.005$) and 18% ($p=0.039$) (Marinol) versus placebo and pad test weight ($p=0.001$)
Wissel et al., 2006	13 (7 MS)	Spasticity-related pain	Nabilone	DBPC crossover. Two 4 week treatment blocks with 1 week washout	MS patient results not reported separately. Spasticity-related pain decreased for a median 2 points with Nabilone compared with placebo treatment ($p < 0.05$). Spasticity as assessed by Ashworth ($p=0.4$), dexterity (Rivermead Motor Assessment) and activities of daily life (Barthel-Index) showed no significant differences between treatments.
Rog et al., 2005	66	Central Pain	THC:CBD (Sativex) oromucosal spray	DBPC parallel group	Sativex was superior to placebo in reducing the mean intensity of pain (Sativex mean change -2.7, 95% CI: -3.4 to -2.0, placebo -1.4 95% CI: -2.0 to -0.8, ,$p=0.005$) and sleep disturbance (Sativex mean change -2.5, 95% CI: -3.4 to -1.7, placebo -0.8, 95% CI: -1.5 to -0.1, p $=0.003$). Long term component of the Selective Reminding Test the mean improvement in the placebo group ($n=32$) of 5.7, 95%CI: -19, 26 not matched in the Sativex group ($n=33$) of -0.9, 95%CI:-20, 23 mean treatment difference -6.95, 95%CI: -12.12, -1.77), $p=0.009$
Wade et al., 2004	160	Spasticity,Spasms Pain, Bladder	THC:CBD (Sativex) oromucosal spray	DBPC parallel group	No significant effect on composite Primary Symptom Score VAS ($p=0.124$)

Table 2 (*continued*)

Study	N	Symptom(s)	Cannabinoid/route/dose	Study design	Results
Vaney et al., 2004	57	Tremor Spasm frequency	Plant THC 2.5 mg/CBD 0.9 mg PO up to 30 mg/10.8 mg	DBPC crossover during inpatient rehabilitation	Spasticity VAS significantly lower for Sativex versus placebo ($P=0.001$) No significant differences in ITT analysis of daily self-report of spasm frequency and symptoms, Ashworth Scale, Rivermead Mobility Index, 10 m timed walk, nine-hole peg test, paced auditory serial addition test (PASAT), and the digit span test.
Svendsen et al., 2004	24	Central pain	Synthetic THC=oral up to 10mg/day	DBPC crossover. Two 3 week treatment periods separated by 3 week washout.	Significant reductions in; mean spontaneous pain intensity (0.6) Pressure pain threshold on QST Mental health and Pain Short form 36 Health Survey domains
Notcutt et al., 2004	34(16 MS)	Pain Spasms	Plant THC, CBD, THC:CBD (Sativex)	"N of 1", DBPC 4 way crossover with 2 × 1 week treatment periods of each medication	Composite of primary and secondary symptom VAS THC and THC:CBD significantly better than placebo in subgroup not requiring rescue THC:CBD
Wade et al., 2003	18	Neurogenic symptoms	Plant THC, CBD, THC:CBD (Sativex) 2.5–120 mg/24 h	Consecutive DBPC single patient crossovers with 2 week treatment periods	VAS significantly better than placebo for; Pain – CBD, THC and THC:CBD Spasm – THC and THC:CBD Spasticity THC Sleep THC:CBD NRS significantly better than placebo for; Spasm severity – CBD, THC and THC:CBD Spasm frequency THC and THC:CBD
Zajicek et al., 2003	664	Spasticity (various other symptoms assessed subjectively)	THC 2.5 mg (Marinol) or THC 2.5 mg/1.25 mg CBD Plant Extract (Cannador) dosed upon weight	DBPC 15 week parallel group with up to 1 year extension	No significant effect on Ashworth-rated spasticity – however, patients felt pain, sleep quality, spasms, and spasticity had improved while on active treatment. Significant treatment effect of Marinol on walk time ($p=0\cdot015$).

Key to Table 2. CBD – Cannabidiol, DBPC – Double blind placebo controlled trial, ITT – Intention to Treat, THC – Tetrahydrocanninol, VAS – Visual Analogue Scale.

Studies involving different proportions of oromucosal cannabis-based medicines

Notcutt conducted a series of "n of 1" crossover studies in 34 patients, 16 of whom had MS, with three different cannabinoid preparations THC, CBD and THC:CBD in approximately a 1:1 ratio (Sativex, see below), delivered via oromucocal spray (Notcutt et al., 2004). Preparations containing THC were most effective for symptom control and a wide range of dosing requirements were observed (Notcutt et al., 2004).

Wade and colleagues conducted consecutive series of double-blind, randomized, placebo-controlled single-patient cross-over trials with two-week treatment periods using the same three cannabinoid preparations in 24 patients, 18 of whom had MS (Wade et al., 2003). Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CBMs in some patients with these symptoms.

Sativex

The results of these preliminary studies prompted further development of the THC:CBD mixture. Sativex® (GW Pharmaceuticals Ltd., Salisbury, UK) is a oromucosal cannabis-based medicine, derived from strains of cannabis plant cultivars developed to produce high and reproducible yields of specified cannabinoids (Whittle et al., 2001). Sativex consists of a mixture of two principal ingredients of cannabis in approximately a 1:1 ratio (27 mg/ml tetrahydrocannabinol and 25 mg/ml cannabidiol), with small amounts < 10% of other cannabis-based compounds and terpenes and flavonoids in an alcoholic solution. These other cannabinoids and constituents may add to the therapeutic profile of sativex and help stabilise it (Whittle et al., 2001).

Oromucosal administration aims to achieve rapid absorption similar to smoking cannabis and is a convenient way to achieve accurate self-titration as minimal absorption by the oral route helps overcome the wide variability of inter-individual response known to occur with cannabis and cannabinoids, which can be accounted for in part by direct absorption into the systemic circulation bypassing both gastrointestinal absorption and first pass metabolism through the liver.

Three phase 1 studies demonstrate that sublingual administration achieves maximal plasma concentration more rapidly than via the oral route (GW Pharmaceuticals, 2001). Pooled phase 2 single case within patient crossover studies of sublingual Sativex, have indicated that this route of administration is not associated with the titration problems of the oral route (GW Pharmaceuticals, 2001). Sativex dosing patterns are similar to those used in patient controlled analgesia for control of postoperative pain. Small increments are delivered each time patients require them, up to a maximum daily limit. The phase 2 data indicate that, for many patients, the therapeutic benefits of sativex are usually delivered at doses below those which cause intoxication or the "high". However the daily dose requirement is subject to high inter-individual variability.

Sativex randomised controlled trials in multiple sclerosis

Wade and colleagues sought to assess the effects of Sativex on multiple symptoms of MS in 160 patients and, in their own words, "ambitiously attempted to amalgamate outcome measures of five MS symptoms" namely; spasticity ($n=39$), spasms ($n=38$), bladder problems ($n=32$), tremor ($n=14$) or pain that was not obviously musculoskeletal ($n=37$) into a single Primary Symptom Score (PSS) (Wade et al., 2004). Each patient nominated the most troublesome of these as their primary symptom and they then rated the severity of each of the five target symptoms on a Visual Analogue Scale (VAS) with anchors 0='no problem' to 100='very bad'. Patients were excluded if the primary symptom was rated at less than 50% of maximal severity. Patients were initially randomised to Sativex or placebo for 6 weeks then were all re-titrated onto Sativex for four weeks and all patients satisfactorily completing the 10 week trial were offered a long-term open label extension study (Wade et al., 2006).

After 6 weeks treatment the PSS following Sativex reduced by 25.29 mm and by 19.35 mm out of 100 mm on placebo which was non-sigificant ($p=0.124$), as were the scores in four of the five primary symptoms (spasms, bladder, pain and tremor), with the trend in the pain group favouring placebo and skewing the overall results. However, the difference in spasticity score between Sativex and placebo was statistically significant (-31.2 versus -8.4, $P=0.001$), even after applying a Bonferroni correction for multiple comparisons. A significant treatment difference in sleep quality was found in the Sativex group ($p=0.047$), and a difference in favour of the placebo group was seen in the GNDS scores ($p=0.048$). Although not statistically significant, the 10 m walk time improved more in the Sativex group, and greater improvements in VAS scores and in diary data were also seen for bladder control following Sativex. There were no significant differences between the groups on measures of cognition and mood.

Sativex in MS spasticity trials

The encouraging results in the spasticity sub-group have prompted three further randomised placebo controlled studies of Sativex in MS-related spasticity (Collin et al., 2006; Collin et al., 2007; Ambler and Davies, 2009). The first study randomised a total of 189 subjects with definite MS and spasticity, 124 to Sativex and 65 to placebo in a double blind study over 6 weeks (Collin et al., 2007). The primary endpoint was the change in a daily subject-recorded spasticity Numerical Rating Scale (NRS) of spasticity which reduced from 5.49 to 4.31 in the Sativex and from 5.39 to 4.76 in the placebo group a small numerical estimated treatment difference of 0.52 points, in favour of Sativex which was of borderline statistically significant ($P=0.048$; 95% CI: -1.029, -0.004 points). Secondary efficacy measures which notably included the Ashworth score (difference 0.11, 95%CI -0.29, 0.07, $P=0.218$), spasm frequency and motricity indices were all in favour of Sativex but did not achieve statistical significance. The percentage of patients achieving a 30% or more subjective reduction in spasticty (responder analysis) significantly favoured Sativex, with 48 (40.0%) of Sativex-treated subjects showing a this reduction as compared to 14 (21.9%) placebo-treated patients (difference in favour of Sativex 18.1%; 95% CI: 4.73, 31.52; $P=0.014$). This treatment effect was lost in those achieving a 50% or greater reduction in subjective NRS spasticity scores between groups ($P=0.189$).

The second study randomised 337 patients to Sativex or placebo over 15 weeks of treatment (Collin et al., 2006), with only the per protocol population showing a significant treatment difference of -0.46 (95% CI:-0.88, -0.03, $p=0.035$) in NRS-11 spasticity scores favouring Sativex, an effect that was lost in the ITT group (treatment difference -0.23, 95%CI:-0.59, 0.14, $P=0.219$). The secondary endpoints again included the modified Ashworth scale, timed 10 m walk, sleep quality and quality of life outcomes and were non-significant. The sponsor pooled the results (Collin and Duncombe, 2006) of the two studies (Collin et al., 2006; Collin et al., 2007) and achieved a combined NRS-11 spasticity treatment difference of -0.34 95%CI:-0.64, -0.04; $p=0.027$). Following these results the UK regulator requested a further enriched design spasticty study with Sativex by in order to gain approval in this indication.

Phase 3 enriched design spasticity study

The phase 3 double-blind randomised placebo-controlled study of Sativex was conducted in the UK and Europe, in patients with spasticity due to Multiple Sclerosis (MS), and targeted patients who had achieved inadequate spasticity relief with existing therapies (Ambler and Davies, 2009). The study employed an enriched design whereby 573 patients initially received Sativex for 4 weeks in a single blind manner (Phase A), following which Sativex responders ($n=241$, 42%) were randomized to continue on Sativex or switch to placebo for a further 12 weeks in a double-blinded manner (Phase B), during which they were not permitted to adjust their dose. The primary endpoint of the study was the difference between the mean change in subjective spasticity severity on a 0–10 numeric rating scale on Sativex versus Placebo in phase B and was 0.84 units which was statistically significant in favour of Sativex ($p=0.0002$).

Three quarters of Sativex patients achieved an improvement of greater than 30% in their spasticity score over the entire study versus 51% on placebo ($p=0.0003$). Statistically significant improvements were also seen in spasm frequency ($p=0.005$), sleep disturbance ($p<0.0001$), patient global impression of change ($p=0.023$), and physician global impression of change ($p=0.005$). The results of this as yet unpublished study have contributed to a UK and European submission for this indication.

Sativex in MS neuropathic pain

The rationale for performing randomised controlled trials of cannabinoids in MS related neuropathic pain is based on both animal and human studies. In experimental autoimmune encephalomyelitis (Baker et al., 2000), a proposed animal model of MS, tetrahydrocannabinol can both delay the onset and intensity of symptoms (Lyman et al., 1989; Baker et al., 2000) and cannabinoid receptor agonists can suppress behavioural responses to neuropathic pain and hyperalgesia (Maurer et al., 1990; Wirguin et al., 1994; Herzberg et al., 1997; Richardson et al., 1998; Bridges et al., 2001).

The RIII reflex is a component of the flexion withdrawal reflex and is a high-threshold nociceptive A-delta fiber mediated reflex which involves wide dynamic range neurons and neurons in the dorsal horn (You et al., 2003). It is thought to correspond to the pain threshold and the reflex size is related to the level of pain perception perception (Willer, 1977). In a randomized, double-blind, placebo-controlled, cross-over study in 18 patients with secondary progressive MS, after treatment with Sativex, RIII reflex threshold increased and RIII reflex area decreased (Conte et al., 2009). The pain VAS also decreased, though not significantly. This was the first published objective neurophysiological evidence that cannabinoids modulate the nociceptive system in patients with MS.

Phase neuropathic pain 2 study

Rog and colleagues conducted a single-centre, 5-week (1-week run-in, 4-week treatment), randomised, double-blind, placebo-controlled, parallel-group trial in 66 patients with MS and central pain states (59 dysesthetic extremity pain, seven painful spasms) of Sativex as adjunctive analgesic treatment (Rog et al., 2005). Patients could gradually self-titrate to a maximum of 48 sprays in 24 h (129.6 mg THC: 120 mg CBD). Sixty-four patients (97%) completed the trial. In week 4, the mean number of daily sprays taken of Sativex ($n=32$) was 9.6 (range 2–25, SD 6.0) and of placebo ($n=31$) was 19.1 (range 1–47, SD 12.9). Pain and sleep disturbance were recorded daily on an 11-point numerical rating scale (NRS). Sativex was superior to placebo in reducing the mean intensity of pain (Sativex mean change -2.7, 95% CI: -3.4 to -2.0, placebo -1.4 95% CI: -2.0 to -0.8, comparison between groups, $p=0.005$) and sleep disturbance (Sativex mean change -2.5, 95% CI: -3.4 to -1.7, placebo -0.8, 95% CI: -1.5 to -0.1, comparison between groups, $p=0.003$).

No statistically significant differences between mean changes on each treatment were found in the 10/36 Spatial recall test, Symbol digit modalites test, Paced serial addition test or Word generation list (Rao and Group., 1990) between treatment groupsupon neuropsychological testing. In the long term component of the selective reminding test, a significant difference was found because of a mean improvement in the placebo group ($n=32$) of 5.7, 95% confidence intervals (-19, 26) not matched in the Sativex group ($n=33$) of -0.9, 95% confidence intervals (-20, 23) mean treatment difference -6.95, 95% confidence intervals (-12.12, -1.77), $p=0.009$. No differences between mean changes on each treatment were found between treatment groups in the other secondary measures of hospital anxiety and depression scale anxiety and depression and Guy's neurological disability scale.

Thirty patients (88.2%) on Sativex developed at least one adverse event, compared with 22 patients (68.8%) on placebo (Sativex – Placebo 0.19, 95% confidence intervals (0.00,0.39), $p=0.053$). Common adverse events were dizziness, dry mouth, nausea and weakness. Fifty-three percent of the patients in the Sativex group experienced dizziness at least once, compared to 16% in the placebo group (Sativex – Placebo 0.37, 95% confidence intervals (0.16,0.58), ($p=0.002$). No serious adverse events, i.e. fatal, life-threatening or resulting in persistent or major disability/incapacity or in or prolonging hospitalisation, occurred. However two female patients in the Sativex arm experienced adverse events (one paranoid ideation, one agitation with tachycardia and hypertension) severe enough to warrant trial withdrawal. No significant changes were seen in either group in blood pressure, weight, temperature, haematology, or blood chemistry.

Phase 3 neuropathic pain study

A phase 3, 14 week randomized, placebo controlled, double-blind, parallel group study study of sativex in MS neuropathic pain was conducted in Europe and Canada and to date has not been fully published (Ratcliffe et al., 2008). Patients were still experiencing pain despite available treatment. Patients self-titrated to a maximum of 24 sprays/day (64.8 mg THC: 60 mg CBD). Daily numerical rating scale pain scores (0–10) and adverse events (AEs) were recorded throughout. 339 patients were enrolled. At baseline mean duration of pain was 5.5 years, mean EDSS score was 5.0, and mean pain score was 6.6. In the sativex group 50% (84/168) of patients reported improved pain scores of $\geq 30\%$ but 45% (77/171) of patients in the placebo group reported an equivalent improvement. Placebo group patients who

titrated to the maximum dose had disproportionate improvements in pain scores. Comparative analysis did not reach statistical significance at 14 weeks (but did reach significance at 10 weeks). Post-hoc analysis of patients with a duration of pain of less than 4 years ($n=168$) revealed a significantly better response in favour of THC:CBD ($p=0.028$). The authors are currently analysing the influence of concomitant medication.

Urinary symptoms

A substudy of the CAMS trial examined the effect of Cannador and Marinol on at lower urinary tract symptoms (Freeman et al., 2006). This involved 255 (39%) of the 657 CAMS patients who completed 3 day urinary diaries for episodes of urinary incontinence at baseline and after 13 weeks. The groups analysed were imbalanced with respect to treatment allocation but after adjusting for this all three groups showed a significant reduction, $p < 0.01$, in adjusted episode rate from baseline to the end of treatment: cannabis extract (Cannador), 38%; THC (Marinol) 33%; and 18% on placebo. Both active treatments showed significant effects over placebo (cannabis extract, $p=0.005$; THC, $p=0.039$). Although reductions in urinary pad test weight were greater in the active treatment groups than in placebo, there were less than 10 analysable patients in each group and it is therefore difficult to draw conclusions .There were no significant differences in changes in any of the urodynamic parameters or in quality of life between the groups

A 10 week RCT of Sativex in patients with MS experiencing voiding dysfunction randomised 135 patients, with a primary outcome of reduction in the daily number of episodes of urgency incontinence, which did not reach signifance between groups ($p=0.57$) (de Ridder et al., 2006). Four of seven secondary endpoints were statistically significant in favour of Sativex, namely; nocturia episodes (-0.28, $p=0.010$), reduction in number of voids per day (-0.85, $P=0.007$) and subjective improvements in patients opinion of bladder symptom severity and patients global impression of change.

Tremor

A double blind placebo controlled trial of Cannador in 14 patients found no significant improvement in any of the objective measures of upper limb tremor with cannabis extract compared to placebo (Fox et al., 2004). Finger tapping was faster on placebo compared to cannabis extract ($p < 0.02$). A further study recruited only 13 patients with MS who viewed tremor as being their worst subjective symptom on a VAS and no significant differences between those treated with Sativex or placebo was found (Wade et al., 2004).

Nabilone

Nabilone (Cesamet®) is an orally administered synthetic derivative of delta-9-tetrahydrocannabinol. It has been available for around 30 years and in the UK is licensed for chemotherapy induced nausea and vomiting and is approved by the US Food and Drugs Administration for the treatment of nausea and as an anti-emetic for patients undergoing chemotherapy.

A case report (Martyn et al., 1995) demonstrated that Nabilone 1 mg on alternate days improved well-being, spasms and nocturia in a patient with MS. Eleven of 96 patients in a UK double blind crossover study had "demyelination" related pain (Frank et al., 2008). In this trial patients received either Nabilone up to 2 mg

per day or Dihydrocodeine up to 240 mg per day. The Dihydro-codeine provided better pain relief than the synthetic cannabinoid nabilone and had slightly fewer side effects, although no major adverse events occurred for either drug. Neither the "demyelina-tion" group's diagnoses nor a sub-group analysis are explicitiy stated in the publication.

Nabilone 1 mg daily demonstrated efficacy in reducing spasticity-associated pain, defined as pain sensation correspond-ing to increased spastic muscle tone while passively moving the painful body segment or limb, in a double blind crossover study of 13 patients, 7 of whom had MS (Wissel et al., 2006). Eleven out of 13 patients completed the trial. Two drop-outs occurred in patients with MS due to acute relapse, in one two days after start of Nabilone treatment and the other exacerbation of weakness in the lower limbs 14 days after start of Nabilone. No other severe side effects were reported. Spasticity-related pain decreased for a median 2 points with Nabilone compared with placebo treatment ($p < 0.05$). Intensity of pain was the same at baseline and after one week of wash out (median 6.0, $p=0.6$), suggesting a sufficient washout period. Spasticity as assessed by Ashworth ($p=0.4$), dexterity (Rivermead motor assessment) and activities of daily life (Barthel-Index) showed no significant differences between treatments.

Other cannabinoids

A placebo-controlled crossover trial of oral dronabinol up to 10 mg per day as monotherapy in patients with MS and central neuropathic pain, found a modest benefit of -0.6 or approxi-mately 21% reduction on a NRS-11 (Svendsen et al., 2004). The pressure pain threshold was higher by 42.8 Kpa (95%CI:1.0–78.5) ($p=0.036$) after dronabinol treatment than after placebo treat-ment and the short form 36 domains of bodily pain ($p=0.037$) and mental health ($p=0.023$) were also improved.

Psychological effects associated with cannabinoid use

There appears to be some concordance in cannabis and cannabinoids reducing verbal learning memory, albeit using three different measures of this construct. Solowij and colleagues (2002) compared chronic (10.2–24 years) recreational marijuana users and general population controls using a variety of neuropsychological outcomes. On the Rey Auditory Verbal Learning Test, a significantly less steep learning curve and generally recall of fewer words were observed in long-term (mean 24 years) users of cannabis than in short-term (mean 10.2 years) users or controls. Long term users also recalled fewer words than short term users or controls. Rog et al. (Rog et al., 2005) found that patients receiving Sativex did not have the same learning effect in the selective reminding test than those receiving placebo. The preliminary results of the psychological sub-study of the CAMS trial found a significant reduction in the Californian adult verbal learning test in those receiving cannabis extracts compared with placebo (Langdon, 2003). Using the Californian adult verbal learning test and functional magnetic resonance imaging suggests that the left medial temporal lobe, right prefrontal cortex (for familiar words) and the right hippocampus (for novel words) are engaged during word processing (Johnson et al., 2001). The latter contains a particularly high density of CB1 receptors (Howlett et al., 2002) and may therefore be perturbed by the administration of exogenous cannabinoids.

A small study matched ten subjects with MS who took street cannabis, at least once in the last month, by age, gender, education, disease course, disease duration, and disability, each

with four subjects with MS who did not use cannabis (total control sample $n=40$) (Ghaffar and Feinstein, 2008). The propor-tion of patients meeting diagnostic statistical manual-IV criteria for a psychiatric diagnosis was higher in cannabis users ($p=0.04$). On the symbol digit modality test, an index of information processing speed, working memory, and sustained attention, cannabis users had a slower mean performancen time ($p=0.006$) and a different pattern of response compared to matched controls. Although a higher proportion of control subjects were on disease-modifying treatments while more cannabis users were taking antidepressants, neither of these differences achieved signifi-cance.

The effects of cannabis-based medicines require further analysis and incorporation of psychological outcomes in future trials.

Long-term follow up studies (Table 3)

It is worth noting that there is little in the literature regarding the long-term efficacy of symptomatic treatments in MS. For example, the effect of chronic (months or years) treatments used in neuropathic pain is uncertain (Breivik et al., 2000; Finnerup et al., 2005; Attal et al., 2006). The longest open label study in patients with MS and neuropathic pain or paroxysmal symptoms examined the use of anticonvulsants for up to 6 months (Solaro et al., 2005) and did not specify any changes in concomitant analgesia.

Patients from a number of Sativex RCTs (Rog et al., 2005; Wade et al., 2006; Collin et al., 2007) have been entered into an indefinite period extension, open label, non-comparative trial. The primary end point of the trial was the number, frequency, and type of adverse events reported by patients The extension trial was envisaged to last until the trial medication or a suitable alternative was available on prescription, or through a compas-sionate use programme, or until the termination of cannabinoid research by GW Pharma Ltd. (Constantinescu and Sarantis, 2006). Secondary end points included changes from baseline in NRS-11 symptom scores (the symptom being determined by primary outcome of the RCT), haematology and clinical chemistry test results, vital signs, trial drug usage, and intoxication VAS scores.

In the neuropathic pain study (Rog et al., 2005) sixty-six patients were enrolled in the randomised trial; 64 (97%) completed the randomized trial and 63 (95%) entered the open-label extension (Rog et al., 2007) of which 14 (22%) were male. The mean age was 49 (SD8.4) years [range, 27–71 years] and mean duration of open-label treatment was 463 (378) days (median, 638 days; range, 3–917 days), with 34 (54%) patients completing more than 1 year of treatment with Sativex and 28 (44%) patients completing the open-label trial with a mean duration of treatment of 839 (42) days (median, 845 days; range 701–917 days).

The mean numerical rating scale-11 at trial completion or withdrawal ($n=62$) was 4.05 (range 0, 8.57, SD 1.96) using last observation carried forward analysis for withdrawn subjects or 4.21 (range 0, 9.29, SD 2.32) assuming that subjects who withdrew had no change in their numerical rating scale-11 pain scores from the end of the randomized trial. The mean numerical rating scale-11 pain score in those completing the open-label study ($n=28$) was 2.9 (range 0, 8.0, SD 2.0), a change from the randomized study baseline of -3.4 (range -7.0, -0.14, SD 1.8).

Fifty-eight (92%) patients experienced at least 1 treatment-related adverse event. These adverse events were rated by the investigator as mild in 47 (75%) patients, moderate in 49 (78%), and severe in 32 (51%). The most commonly reported adverse events were dizziness (27%), nausea (18%), and feeling intoxicated

Table 3
Long-term open label extension trials of cannabinoids in MS.

Study	N=Originally recruited/entered extension/(%)	Duration of		Primary Symptom(s)	Cannabinoid / route/dose	Serious Adverse Events	Results
		Original Study	Extension study treatment with cannabinoid				
Collin et al., 2007	146/189=77%	6 weeks	305 days median (range 1–801),	Spasticity	Sativex	27 SAEs of which 5 judged to be treatment-related.	Spasticity NRS-11 score reduced from 5.56 to 3.83 at end of trial for those with data available.
			52 (36%) patients treated for > 1 year				
Rog et al., 2007	63/66=97%	5 weeks	638 days median (range 3–917)	Neuropathic Pain	Sativex	12 SAEs of which 2 ventricular bigemini and circulatory collapse were judged to be treatment-related.	In the 28 (44%) patients who completed the 2-year follow up, the mean (SD) NRS-11 pain score in the final week of treatment was 2.9 (2.0) (range, 0–8.0) compared with 3.8 in the Sativex group and 5.0 in the placebo group in final week of RCT.
			34 (54%) patients Treated > 1 year				
			28 (44%) patients completing trial mean (SD) duration of treatment of 839 (42) days (median, 845 days; range, 701–917 days).				
Wade et al., 2006	137/160=89%	6 weeks then 4 weeks open label	Average of 434 days (range: 21–814).	Pain, Spasticity, Spasms, Bladder symptoms, Tremor	Sativex	33 SAEs of which 5 (in 3 patients) two seizures, fatal aspiration pneumonia, loss of balance, ankle injury, diarrhoea and vomiting were judged to be treatment-related.	Of 25 patients who entered the two week treatment interruption study, five (20%) resumed Sativex before the end of 14 days because of re-emergence of marked MS symptoms. During the interruption, seven (28%) reported their MS symptoms to be much worse, 10 (40%) worse, five (20%) no change and three (12%) better.
			92 (67%) treated for ≥ 1 year				
Constantinescu and Sarantis, 2006[a]	444/930=48%	Various	Mean 455 days	Various	Sativex	SAEs in 17.1% (75) of which 3.8% (17) were judged to be treatment-related.	Mean number of sprays decreased from 9.4 in comparative study to 7.6 in extension study.
			125 subjects received > 2 years treatment				
Zajicek et al., 2005	502/630=56%	15 weeks	52 weeks	Spasticity	Cannador Marinol	51 SAEs in cannabinoid groups versus 23 in placebo group (includes those who discontinued treatment)	84% AE (see text) Small treatment effect on muscle spasticity mean reduction Ashworth score (Marinol 1.82(n=154, 95% CI: 0.53 to 3.12, Cannador 0.10 (n=172, 95% CI: −0.99 to 1.19), placebo -0.23 (n=176, 95% CI: −1.41 to 0.94);
			59% of cannabinoid patients completed 1 year of treatment	Various secondary symptoms including pain, shaking, spasms, sleep, energy, tiredness, depression			
							p=0.04

Note: patients received open-label treatment in the Wade 2006, Constantinescu 2006, Rog 2007 and Collin 2008 extension studies. Zajicek 2005 study participants remained double-blind throughout.
Sativex – 27 mg Tetrahydrocannabinol: 25 mg Cannabidiol/ml oromucosal spray. Cannador – cannabis plant extract – 2.5 mg THC: 1.25 mg CBD, < 5% other cannabinoids), Marinol – synthetic delta-9-Tetrahydrocannabinol in oil (2.5 mg per capsule).

[a] Includes results of patients separately reported in Wade 2006, Rog 2007 and Collin 2007.

(11%). Two treatment related serious adverse events (ventricular bigeminy and circulatory collapse) were judged to be treatment-related; both occurred in the same patient and resolved completely following a period of discontinuation. Eleven (17%) patients experienced oral discomfort, 4 persistently. Regular oral examinations revealed that 7 (11%) patients developed white buccal mucosal patches and 2 (3%) developed red buccal mucosal patches; all cases were deemed mild and resolved. Seventeen (25%) patients withdrew due to adverse events; nausea (5 subjects), weakness (3), dizziness (3), fatigue aggravated (3), feeling drunk (2), and vomiting, anorexia, ventricular bigeminy and circulatory collapse, oral discomfort, abnormal coordination, headache, impaired judgment, speech disorder, agitation, hallucination and facial swelling each occurred once. Twelve serious adverse events occurred in ten subjects (16%), two of which, ventricular bigeminy and circulatory collapse, were judged to be treatment related. These occurred in the same subject and resulted in a collapse which required hospital assessment. The subject made a complete recovery. She was subsequently withdrawn from the trial. The mean number of sprays and patients experiencing intoxication remained stable throughout the follow-up trial.

In the last six full days of treatment the mean number of sprays taken per day by all subjects was 6.11 (range 0.33–24.83, SD 5.17), equivalent to a mean dose of 16.5 mg of delta-9-tetrahydrocannabinol and 15.3 mg of cannabidiol. This represents approximately one fewer sprays (-0.94, range -11.7–18.74, SD 6.1) than at week 4 of the open-label trial, implying that there was no tolerance to delta-9-tetrahydrocannabinol:cannabidiol. In the 28 subjects who completed the study the mean number of sprays taken in the final 6 full days of treatment was 6.5 (range 0.5–24.8, SD 5.8), with 26 subjects taking less than 11 sprays per 24 h. Around 45% of delta-9-tetrahydrocannabinol:cannabidiol was taken from between 6 pm and 12 am.

Twenty nine subjects (46%) withdrew from the trial within the first year, this is comparable to the 50–58% of subjects in the Cannabinoids in MS Trial of oral cannabinoids, who remained on treatment at one year follow-up (Zajicek et al., 2005). Age, disability (Kurtzke, 1983), location and type of central pain and previous exposure to cannabis did not predict which patients withdrew. At the time of their withdrawal from the trial, 18 of the 35 patients (51%) still perceived benefit from Sativex.

In the long-term follow up of a Sativex RCT which examined five symptoms of MS; pain, spasticity, spasms, bladder and tremor (Wade et al., 2004), the authors state that benefits experienced in the RCT were maintained and the dose of drug taken remained stable (Wade et al., 2006). The 137 patients reported a total of 292 adverse effects, 251 of which (86%) were of mild to moderate intensity (Wade et al., 2006). The most common treatment-related adverse event was a sore mouth (20%) and eight patients also had visible changes in their oral mucosa. No psychiatric events or changes were noted and only six patients noted cognitive change. Thirty three SAEs were recorded, in 19 patients (28 events), the event was considered unrelated to Sativex. In the other three patients (five events) where the SAE was considered at least possibly related to Sativex, two patients experienced seizures with one of these patients subsequently died from aspiration pneumonia. The third patient experienced loss of balance possibly related to Sativex, sustained an ankle injury, continued taking Sativex and three months later, developed diarrhoea and vomiting requiring overnight hospital assessment. This resolved the following day and the patient continued with treatment. Two other patients died; one each due to lung and breast cancer. Four patients experienced seizures; all were taking other medications which increases the risk of epilepsy, such as anti-depressant medication.

Planned, sudden interruption of Sativex for two weeks in 25 patients (of 62 approached) led to 68% perceiving their index symptom as worse and 20% resumed their Sativex treatment early because of an escalation in their symptoms. Whilst a consistent withdrawal syndrome did not emerge, 11 patients (46%) reported at least tiredness, interrupted sleep, hot and cold flushes, mood alteration, reduced appetite, emotional lability, intoxication or vivid dreams. Twenty-two patients (88%) patients re-started CBM treatment.

Constantinescu (Constantinescu and Sarantis, 2006) analysed 444 patients with MS entering a long-term open label extension study of Sativex from a total of 930 who participated in various Sativex RCTs including Rog et al., 2005, Wade et al., 2006 and Collin et al., 2007. Patients received a mean of 455 days open-label treatment with 125 patients receiving more than 2 years of Sativex (Constantinescu and Sarantis, 2006). The mean number of sprays taken decreased from 9.4 ± 5.9 in the comparative trials to 7.6 ± 6.3 in the long-term study. In the extension study 84% of patients experienced a treatment-emergent treatment related adverse event with dizziness (27.5%), diarrhoea (13.1%), fatigue (11%) nausea (10.8%), oral pain (9.5%), headache (9%) and somnolence (7.9%) being the most common. Application site type reactions which occurred in both Sativex and Placebo patients in the acute trials occurred in half of patients receiving long-term Sativex. A total of 15.8% of patients withdrew from treatment due to AEs, the majority of which were mild to moderate and of the 17.1% of patient who experienced serious adverse events (SAEs), 3.8% were considered to be treatment related. No clinically relevant changes or notable trends were observed in long-term haematological or biochemical data.

Randomised withdrawal trial of patient stable on Sativex

Notcutt performed a randomised study with patients with multiple sclerosis and spasticity who were identified as currently receiving Sativex obtained through either supply of unlicensed Sativex of named patient supply programmes, with a mean treatment period of 3.6 years. Subjects were randomised either to continue taking Sativex at their current effective and tolerated dose ($n=18$) or the same number of sprays of placebo ($n=18$) for 28 days (Notcutt and Davies, 2009). Patients could drop out at any time and return to their own supplies of prescribed Sativex. Three patients (17%) withdrew from the study on Sativex and 16 (89%) on placebo with time to treatment failure significantly favouring Sativex, hazard ratio 0.335 (90%CI: 0.162, 0.691) $p=0.013$. The authors concluded that this demonstrated long-term efficacy of Sativex and did not identify a withdrawal syndrome.

The future of cannabis-based medicines

Endocannabinoid concentrations alter at site of pathology, for example in spastic mice with chronic relapsing experimental allergic encephalomyelitis (Baker et al., 2001) and in the future it may be considered crude to use whole plant-derived cannabinoids when more selective and targeted manipulation of the cannabinoid system using synthetic cannabinoids or targeting other components of the endocannabinoid system may result in maximising beneficial effects whilst minimising unwanted effects (Kubajewska and Constantinescu, 2009). For example, Nabilone, a synthetic delta-9-tetrahydrocannabinol has demonstrated efficacy in reducing spasticity-related pain in 13 patients (Wissel et al., 2006), modest positive effects of a synthetic cannabinoid analogue, ajulemic acid, on neuropathic pain of mixed aetiologies (Karst et al., 2003) and the first clinical trial in obesity using

Rimonabant, a selective cannabinoid 1 receptor antagonist (Van Gaal et al., 2005) has been conducted. URB597, an inhibitor of fatty acid amide hydrolase has been shown to reduce nociceptive processing in a rat model of neuropathic pain (Jhaveri et al., 2006). It is possible, however, that the mixture of cannabinoids in whole plant-derived medicines contribute to their analgesic efficacy, in particular the high proportion of cannabidiol to tetrahydrocannabinol in Sativex, the highest in any cannabis-based medicine examined so far, might be particularly important given that cannabidiol delays the conversion of tetrahydrocannabinol to 11-hydroxy-tetrahydrocannabinol, a more psychoactive metabolite and may have analgesic properties of its own (McPartland and Russo, 2001).

Cannabis-based medicines are now a reality. Examples include: Nabilone (Cesamet) has been used off-licence in pain for over a decade (Notcutt et al., 1997), Health Canada has approved Sativex as adjunctive treatment for the symptomatic relief of neuropathic pain in multiple sclerosis in adults, under the Notice of Compliance with Conditions policy (GW Pharmaceuticals, 2005) and intractable cancer pain (Health Canada, 2007), products approved under this policy have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment for the approved use. Full licensing of such products is dependent upon additional clinical trials to verify the anticipated benefit. The United Kingdom Home Office have issued a general licence permitting doctors to prescribe Sativex as an unlicensed medicine on a named patient basis (United Kingdom Home Office, 2006). GW Pharmaceuticals Ltd. have filed a regulatory submission for Sativex in the UK and Spain for the treatment of spasticity due to multiple sclerosis (GW Pharmaceuticals, 2009). However, to date the european federation of neurological societies taskforce recommend that cannabinoids be used only second or third line in central neuropathic pain only after drugs shown to be beneficial in other central pain conditions have failed, because of "potential safety concerns" (Attal et al., 2006). This and the lack of consistent results in trials of often subjective symptoms of MS have delayed the acceptance of cannabis-based medicines as an additional therapeutic class in these often intractable and debilitating conditions.

Conclusions

At present the results of large clinical trials in MS have not provided the clarity that many have hoped for. They have instead raised a substantial number of sometimes, fundamental, questions such as who is the best rater of the construct "spasticity" the doctor or the patient? Future trials will require careful patient selection and consideration of the variables outlined in Fig. 1 is required, such as which symptom or symptoms, using which constituent synthetic or plant-derived cannabinoid in isolation or if using combination of cannabinoids, in what ratios, delivered by which route and at what dose. Future trials may therefore require coordination to explore the effects of these variables and potential adverse effects of CBMs in a logical and systematic fashion. By doing this it is to be hoped that unequivocal results as to the effectiveness or otherwise of CBMs in MS will be determined soon.

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