

## **Cannabinoids and Multiple Sclerosis**

A Literature review

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### **Introduction & Overview**

Multiple sclerosis is a disease of the brain and spinal cord caused by demyelination (loss of the insulating sheath) of nerve fibres, believed to be caused by some substance dissolving or breaking-up fatty tissue of the nerve-sheath<sup>1</sup>. The condition is progressive but varies in intensity, with remission of symptoms and relapse commonly reported. Common symptoms include fatigue, balance problems, muscle weakness, incontinence, muscle spasms, pain and tremor.<sup>2</sup>

Current treatments for MS are of little benefit, expensive, and with risks of side effects. Alpha & β-interferon, and corticosteroids have been found to have some value, but symptoms are poorly-controlled by existing medications, and no cure has been found. Many patients are unable to tolerate the side-effects of conventional medication<sup>3</sup>

This section reviews and describes the published scientific evidence relating to the use of cannabis and cannabinoids in the treatment of multiple sclerosis symptoms, and the involvement of endocannabinoids in the development of the MS disease process. Scientific developments in this field are rapidly advancing, with an average of one paper published every ten days over the past four years since my last review of this field. Over that period the results of many clinical trials have been published, and the state of basic research into the disease process has advanced dramatically.

### **Anecdotal Evidence & Surveys**

The potential effect of cannabis on the symptoms of multiple sclerosis were first reported by sufferers of the disease introduced to cannabis by recreational or social users. Such anecdotal evidence – i.e. not backed up at the time by clinical assessment, animal or theoretical basis, nor by clinical trials – includes case studies and self-completion surveys.

Grinspoon<sup>4</sup> reports a number of anecdotal reports of dramatic improvement in MS symptoms attributed to marijuana (cannabis) use. Initially, these were unexpected findings following social use of the drug. In one account, Greg Paufler described a progressive degeneration, following onset of MS in 1973, to bedridden status, and severe side effects (dramatic weight gain, addiction to benzodiazepines) from prescribed medicines. Following several social ‘joints’ one evening, he astonished family and friends by standing spontaneously for the first time in months. He subsequently found that his symptoms deteriorated without the drug, but improved dramatically during periods when he was smoking cannabis. Grinspoon reviewed further cases showing improvements in muscle spasms, tremor, continence, ataxia (loss of muscle control) and insomnia. Clare Hodges,

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1 Macpherson G. (ed) [1995] Black’s Medical Dictionary 38th Edition. London: A&C Black pp332-333

2 House of Lords [1998] op cit para 5.19

3 Grinspoon L & Bakalar JB (1997) Marijuana - Forbidden Medicine (2nd Ed). Yale University Press

4 ibid pp80-94

an MS patient giving oral evidence to the House of Lords enquiry, reported cannabis ‘greatly relieved’ physical symptoms including discomfort of bladder and spine, nausea and tremors, and stated ‘*Cannabis helps my body relax, I function and move much easier. The physical effects are very clear, it is not just a vague feeling of well-being.*’

In a study of 112 MS patients self-medicating with cannabis in the US and UK, Consroe et al<sup>5</sup> reported that 70% of more respondents reported improvement in the following symptoms:

<i>Spasticity at sleep onset</i>	<i>Pain in muscles</i>
<i>Spasticity when awaking at night</i>	<i>Pain in legs at night</i>
<i>Tremor (arms/head)</i>	<i>Depression</i>
<i>Anxiety</i>	<i>Spasticity when waking in morning</i>
<i>Spasticity when walking</i>	<i>Tingling in face/arms/head/trunk</i>
<i>Numbness of chest/stomach</i>	<i>Pain in face</i>
<i>Weight loss</i>	<i>Weakness in legs</i>

The authors considered these reports ‘*strongly suggested cannabinoids may significantly relieve symptoms of MS, particularly spasticity and pain*’, and provided sufficient grounds for a properly controlled clinical trial to test such claims objectively and conclusively.

A German study<sup>6</sup> of 170 self-medicating cannabis users found 11% of respondents reported using the drug successfully in managing MS symptoms, the second most common use behind depression, and concluded “*this study demonstrates a successful use of cannabis products for the treatment of a multitude of various illnesses and symptoms. This use was usually accompanied only by slight and in general acceptable side effects.*” Mechoulam<sup>7</sup> reviews illegal use of cannabis by MS patients. In a UK survey of 318 MS patients<sup>8</sup>, 8% reported using cannabis to relieve symptoms.

In a survey of 780 MS patients in Canada, Page et al<sup>9</sup> found “*Forty-three percent had tried cannabis at some point in their lives, 16% for medicinal purposes. Symptoms reported to be ameliorated included anxiety/depression, spasticity and chronic pain*” and concluded “*Subjective improvements in symptom experience were reported by the majority of people with MS who currently use cannabis.*” A survey of 131 patients with amyotrophic lateral sclerosis<sup>10</sup>, of which only 13 used cannabis, found “*cannabis may be moderately effective at reducing symptoms of appetite loss, depression, pain, spasticity, and drooling*”. Simmons et al<sup>11</sup> studied responses to an internet survey by 2529 respondents, finding cannabis commonly reported as beneficial. Clarke et al<sup>12</sup> surveyed 220 MS patients in Canada, finding “*Medical cannabis use was associated with male gender, tobacco use, and recreational cannabis use. The symptoms reported by medical cannabis users to*

5 Consroe P, Musty R, Rein J, Tillery W, Pertwee R (1997) The perceived effects of smoked cannabis on patients with multiple sclerosis. *Eur Neurol* 38(1):44-8

6 Schnelle M, Grotenhermen F, Reif M, Gorter RW (1999) [Results of a standardized survey on the medical use of cannabis products in the German-speaking area]. [Article in German] *Forsch Komplementarmed* 6 Suppl 3:28-36

7 Mechoulam R (1999) Recent advantages in cannabinoid research. *Forsch Komplementarmed* 6 Suppl 3:16-20

8 Somerset M, Campbell R, Sharp DJ, Peters TJ [2000] What do people with MS want and expect from health-care services? *Health Expect* 4(1):29-37

9 Page SA, Verhoef MJ, Stebbins RA, Metz LM, Levy JC. [2003] Cannabis use as described by people with multiple sclerosis. *Can J Neurol Sci.* 30(3):201-5.

10 Amtmann D, Weydt P, Johnson KL, Jensen MP, Carter GT. [2004] Survey of cannabis use in patients with amyotrophic lateral sclerosis. *Am J Hosp Palliat Care.* 21(2):95-104.

11 Simmons RD, Ponsonby AL, van der Mei IA, Sheridan P. [2004] What affects your MS? Responses to an anonymous, Internet-based epidemiological survey. *Mult Scler.* 2004 Apr;10(2):202-11.

12 Clark AJ, Ware MA, Yazer E, Murray TJ, Lynch ME. [2004] Patterns of cannabis use among patients with multiple sclerosis. *Neurology.* 62(11):2098-100.

*be most effectively relieved were stress, sleep, mood, stiffness/spasm, and pain.” Ware et al<sup>13</sup> reported results of a survey of medicinal cannabis use in the UK, noting “Medicinal cannabis use was reported by patients with chronic pain (25%), multiple sclerosis and depression (22% each), arthritis (21%) and neuropathy (19%). Medicinal cannabis use was associated with younger age, male gender and previous recreational use ( $p < 0.001$ ).”*

In the Netherlands, cannabis has been available on prescription from pharmacies since September 2003, Erkens et al<sup>14</sup> followed up 200 patients prescribed the drug with a questionnaire survey, finding “Cannabis was mainly used for chronic pain and muscle cramp/stiffness. The indication of medicinal cannabis use was in accordance with the labeled indications. However, more than 80% of the patients still obtained cannabis for medicinal purpose from the illegal circuit. Because of the higher prices in pharmacies, ongoing debate on the unproven effectiveness of the drug and the hesitation by physicians to prescribe cannabis.”

## Animal studies

Scientists have developed animal models for MS in rats, mice and guinea-pigs in the form of an experimental autoimmune encephalomyelitis (EAE). In guinea-pigs, Lyman et al<sup>15</sup> found 98% of animals treated with placebo died, whereas 95% of THC-treated animals survived the disease process, with much reduced inflammation of brain tissue. In rats, Wirguin et al<sup>16</sup> found  $\Delta^8$ THC significantly reduced neurological deficits in two strains of EAE inoculated rats.

Baker et al<sup>17</sup>, studying tremor and spasticity in mice, concluded: “The exacerbation of these signs after antagonism of the CB1 and CB2 receptors, notably the CB1 receptor... indicate that the endogenous cannabinoid system may be tonically active in the control of tremor and spasticity. This provides a rationale for patients' indications of the therapeutic potential of cannabis in the control of the symptoms of multiple sclerosis, and provides a means of evaluating more selective cannabinoids in the future.” Achiron et al<sup>18</sup> studying rats, found reduction in the inflammatory response in the brain and spinal cord in animals treated with dexanabinol, a synthetic cannabinoid, and concluded “dexanabinol may provide an alternative mode of treatment for acute exacerbations of multiple sclerosis (MS)”. Pop<sup>19</sup> reviews the development of dexanabinol, a non-psychoactive cannabinoid and NMDA antagonist developed by “Pharmos Corp for the potential treatment of cerebral ischemia... and multiple sclerosis (MS)” commenting “A Notice of Allowance was received in March 1999 on a patent covering the use of the drug in the treatment of MS [324163]. The use of dexanabinol and its derivatives to treat MS is described in US-05932610 [358503].”

Fernandez-Ruiz<sup>20</sup> noted “Data, initially anecdotal, but recently supported on more solid experimental evidence, suggest that cannabinoids might be beneficial in the treatment of some of the symptoms of multiple sclerosis (MS). Despite this evidence, there are no data on the possible changes in cannabinoid CB(1) or CB(2) receptors, the main molecular targets for the action of cannabinoids,

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- 13 Ware MA, Adams H, Guy GW. [2005] The medicinal use of cannabis in the UK: results of a nationwide survey. *Int J Clin Pract.* 59(3):291-5.
- 14 Erkens JA, Janse AF, Herings RM. [2005] Limited use of medicinal cannabis but for labeled indications after legalization. *Pharmacoepidemiol Drug Saf.* 14(11):821-2
- 15 LymanWD, Sonett JR, Brosnan CF, Elkin R & Bornstein MB (1989) Delta-9-tetrahydrocannabinol: an novel treatment for Experimental Autoimmune Encephalomyelitis. *Journal of Neuroimmunology* 23 pp73-81
- 16 Wirguin I, Mechoulam R, Breuer A, Schezen E, Weidenfeld J & Brenner T (1994) Suppression of Experimental Autoimmune Encephalomyelitis by cannabinoids. *Immunopharmacology* 28(3) pp209-214
- 17 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Huffman JW, Layward L (2000) Cannabinoids control spasticity and tremor in a multiple sclerosis model. *Nature* 404(6773):84-7
- 18 Achiron A, Miron S, Lavie V, Margalit R, Biegon A (2000) Dexanabinol (HU-211) effect on experimental autoimmune encephalomyelitis: implications for the treatment of acute relapses of multiple sclerosis. *J Neuroimmunol* 102(1):26-31
- 19 Pop E. [2000] Dexanabinol Pharmos. *Curr Opin Investig Drugs* 1(4):494-503
- 20 Berrendero F, Sanchez A, Cabranes A, Puerta C, Ramos JA, Garcia-Merino A, Fernandez-Ruiz J. [2001] Changes in cannabinoid CB(1) receptors in striatal and cortical regions of rats with experimental allergic encephalomyelitis, an animal model of multiple sclerosis. *Synapse* 41(3):195-202

*either in the postmortem brain of patients with MS or in animal models of this disease (EAE)”, concluding “generation of EAE in Lewis rats would be associated with changes in CB(1) receptors in striatal and cortical neurons, which might be related to the alleviation of some motor signs observed after the treatment with cannabinoid receptor agonists in similar models of MS” Baker et al<sup>21</sup> found “In areas associated with nerve damage, increased levels of the endocannabinoids... were detected” and concluded “These studies provide definitive evidence for the tonic control of spasticity by the endocannabinoid system and open new horizons to therapy of multiple sclerosis, and other neuromuscular diseases, based on agents modulating endocannabinoid levels and action, which exhibit little psychotropic activity.”*

Recent studies of the biological basis of MS largely confirm the efficacy of cannabinoids in relief of muscle spasticity, including the endogenous cannabinoids anandamide and 2-arachidonoyl glycerol<sup>22</sup>, and by dexanabinol via non-receptor mediated reduction of inflammation<sup>23</sup>. Baker et al<sup>24</sup> considered research to have demonstrated “definitive evidence for the tonic control of spasticity by the endocannabinoid system”. In a series of reviews of the implications of recent fundamental cannabinoid research on therapeutic potential, Pertwee<sup>25,26</sup> stated: “...uses for CB1 receptor agonists include the suppression of muscle spasm/spasticity associated with multiple sclerosis...”. The main active constituent of cannabis - THC is one such CB1 receptor agonist.

Killistein et al<sup>27</sup> concluded “endogenous cannabinoids appear to play an important role in signal transduction, which may be starting points for therapy regarding... multiple sclerosis” Klein et al<sup>28</sup> reported “The effect of cannabimimetic agents on the function of immune cells such as T and B lymphocytes, natural killer cells and macrophages has been extensively studied over the past several decades using human and animal paradigms involving whole animal models as well as tissue culture systems. From this work, it can be concluded that these drugs have subtle yet complex effects on immune cell function and that some of the drug activity is mediated by cannabinoid receptors expressed on the various immune cell subtypes... Further studies will define the precise structure and function of the putative immunocannabinoid system, the potential therapeutic usefulness of these drugs in chronic diseases such as acquired immune deficiency syndrome and multiple sclerosis” Lambert et al<sup>29</sup>, studying N-palmitoylethanolamine (PEA), an analogue of anandamide, found “PEA is accumulated during inflammation and has been demonstrated to have a number of anti-inflammatory effects... It is now engaged in phase II clinical development, and two studies regarding the treatment of chronic lumbosciatalgia and multiple sclerosis are in progress.” Brooks et al reported “Activation of cannabinoid receptors causes inhibition of spasticity, in a mouse model of multiple sclerosis”, finding that Arvanil, a “structural “hybrid” between capsaicin and anandamide, was a potent inhibitor of spasticity at doses (e.g. 0.01 mg/kg i.v.) where capsaicin and cannabinoid CB(1) receptor agonists were ineffective”

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- 21 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, Khanolkar A, Layward L, Fezza F, Bisogno T, Di Marzo V [2001] Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J* 15(2):300-2
- 22 Di Marzo V, Bifulco M, De Petrocellis L (2000) Endocannabinoids and multiple sclerosis: a blessing from the 'inner bliss'? *Trends Pharmacol Sci* 21(6):195-7
- 23 Pop E (2000) Dexanabinol *Pharmos. Curr Opin Investig Drugs* 1(4):494-503
- 24 Baker D, Pryce G, Croxford JL, Brown P, Pertwee RG, Makriyannis A, Khanolkar A, Layward L, Fezza F, Bisogno T, Di Marzo V (2001) Endocannabinoids control spasticity in a multiple sclerosis model. *FASEB J* 15(2):300-2
- 25 Pertwee RG (1999) Cannabis and cannabinoids: pharmacology and rationale for clinical use. *Forsch Komplementarmed* 6 Suppl 3:12-5
- 26 Pertwee RG (1999) Pharmacology of cannabinoid receptor ligands. *Curr Med Chem* 6(8):635-64
- 27 Killistein J, Nelemans SA (1997) [Therapeutic applications and biomedical effects of cannabinoids; pharmacological starting points]. [Article in Dutch] *Ned Tijdschr Geneesk* 141(35):1689-93
- 28 Klein TW, Newton CA, Friedman H [2001] Cannabinoids and the immune system. *Pain Res Manag* 6(2):95-101
- 29 Lambert DM, Vandevoorde S, Jonsson KO, Fowler CJ. [2002] The palmitoylethanolamide family: a new class of anti-inflammatory agents? *Curr Med Chem* 9(6):663-74

Wilkinson et al<sup>30</sup>, studying a mouse model of MS, found “*Whilst (cannabis extract) inhibited spasticity in the mouse model of MS to a comparable level, it caused a more rapid onset of muscle relaxation, and a reduction in the time to maximum effect compared with Delta9THC alone. The Delta9THC-free extract or cannabidiol (CBD) caused no inhibition of spasticity*” concluding re antispasticity “*Delta9THC was the active constituent, which might be modified by the presence of other components*” Ni et al<sup>31</sup> noted “*Cannabinoid receptor agonists have been shown to downregulate immune responses and there is preliminary evidence that they may slow the progress of MS.*” Raman et al<sup>32</sup> found “*Administration at the onset of tremors delayed motor impairment and prolonged survival in Delta(9)-THC treated mice when compared to vehicle controls*” Mestre et al<sup>33</sup> concluded their results to suggest “*manipulation of the endocannabinoid system as a possible strategy to develop future MS therapeutic drugs*” Weydt et al<sup>34</sup> noted the effect on ALS-induced mice of non-psychoactive CBN (cannabinoid) “*significantly delays disease onset by more than two weeks while survival was not affected*”

Ortega-Gutierrez et al<sup>35</sup> found that in mice, an anandamide reuptake inhibitor UCM707 would “*reduce microglial activation, diminish major histocompatibility complex class II antigen expression, and decrease cellular infiltrates in the spinal cord. Additionally, in microglial cells, UCM707 decreases the production of the proinflammatory cytokines tumor necrosis factor (TNF)-alpha, interleukin (IL)-1beta, and IL-6; reduces nitric oxide levels and inducible nitric oxide synthase expression; and is able to potentiate the action of a subeffective dose of the endocannabinoid anandamide. Overall, these results suggest that agents able to activate the endocannabinoid system could constitute a new series of drugs for the treatment of MS.*” De Lago et al<sup>36</sup> found “*UCM707, like other endocannabinoid uptake inhibitors reported previously, significantly reduced spasticity of the hindlimbs in a chronic relapsing EAE mice, a chronic model of MS.*”

Studying mice, Arevalo-Martin et al<sup>37</sup> found “*cannabinoids reduced microglial activation, abrogated major histocompatibility complex class II antigen expression, and decreased the number of CD4+ infiltrating T cells in the spinal cord. Both recovery of motor function and diminution of inflammation paralleled extensive remyelination*” and concluded there were “*potential therapeutic implications in demyelinating pathologies such as MS; in particular, the possible involvement of cannabinoid receptor CB2 would enable nonpsychoactive therapy suitable for long-term use.*” Croxford & Miller<sup>38</sup> found “*cannabinoids are useful for symptomatic treatment of spasticity and tremor in chronic-relapsing experimental autoimmune encephalomyelitis. Cannabinoids, however, have reported immunosuppressive properties. We show that the*

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- 30 Wilkinson JD, Whalley BJ, Baker D, Pryce G, Constanti A, Gibbons S, Williamson EM. [2003] Medicinal cannabis: is delta9-tetrahydrocannabinol necessary for all its effects? *J Pharm Pharmacol.* 55(12):1687-94.
- 31 Ni X, Geller EB, Eppihimer MJ, Eisenstein TK, Adler MW, Tuma RF. [2004] Win 55212-2, a cannabinoid receptor agonist, attenuates leukocyte/endothelial interactions in an experimental autoimmune encephalomyelitis model. *Mult Scler.* 10(2):158-64
- 32 Raman C, McAllister SD, Rizvi G, Patel SG, Moore DH, Abood ME. [2004] Amyotrophic lateral sclerosis: delayed disease progression in mice by treatment with a cannabinoid. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 5(1):33-9.
- 33 Mestre L, Correa F, Arevalo-Martin A, Molina-Holgado E, Valenti M, Ortar G, Di Marzo V, Guaza C. [2005] Pharmacological modulation of the endocannabinoid system in a viral model of multiple sclerosis. *J Neurochem.* 92(6):1327-39.
- 34 Weydt P, Hong S, Witting A, Moller T, Stella N, Kliot M. [2005] Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival. *Amyotroph Lateral Scler Other Motor Neuron Disord.* 6(3):182-4.
- 35 Ortega-Gutierrez S, Molina-Holgado E, Arevalo-Martin A, Correa F, Viso A, Lopez-Rodriguez ML, Di Marzo V, Guaza C. [2005] Activation of the endocannabinoid system as therapeutic approach in a murine model of multiple sclerosis. *FASEB J* 19(10):1338-40
- 36 de Lago E, Fernandez-Ruiz J, Ortega-Gutierrez S, Cabranes A, Pryce G, Baker D, Lopez-Rodriguez M, Ramos JA. [2006] UCM707, an inhibitor of the anandamide uptake, behaves as a symptom control agent in models of Huntington's disease and multiple sclerosis, but fails to delay/arrest the progression of different motor-related disorders. *Eur Neuropsychopharmacol.* 16(1):7-18.
- 37 Arevalo-Martin A, Vela JM, Molina-Holgado E, Borrell J, Guaza C. [2003] Therapeutic action of cannabinoids in a murine model of multiple sclerosis. *J Neurosci.* 23(7):2511-6.
- 38 Croxford JL, Miller SD. [2003] Immunoregulation of a viral model of multiple sclerosis using the synthetic cannabinoid R+WIN55,212. *J Clin Invest.* 111(8):1231-40.

*cannabinoid receptor agonist, R+WIN55,212, ameliorates progression of clinical disease symptoms in mice with preexisting TMEV-IDD”*

In rat model of MS (CREAE), Cabranes et al<sup>39</sup> reported “*CB(1) receptors were affected by the development of CREAE in mice exhibiting always down-regulatory responses that were circumscribed to motor-related regions and that were generally more marked during the acute and chronic phases. These observations may explain the efficacy of cannabinoid agonists to improve motor symptoms (spasticity, tremor, ataxia) typical of MS in both humans and animal models.*”

## Human studies

Several researchers<sup>40,41,42</sup> have commented upon the difficulties involved in conducting proper research on the effects of cannabinoids on medical conditions, including MS, in the light of the legal status of cannabis. Robson<sup>43</sup> comments “*the methodological challenges to human research involving a pariah drug are formidable*”

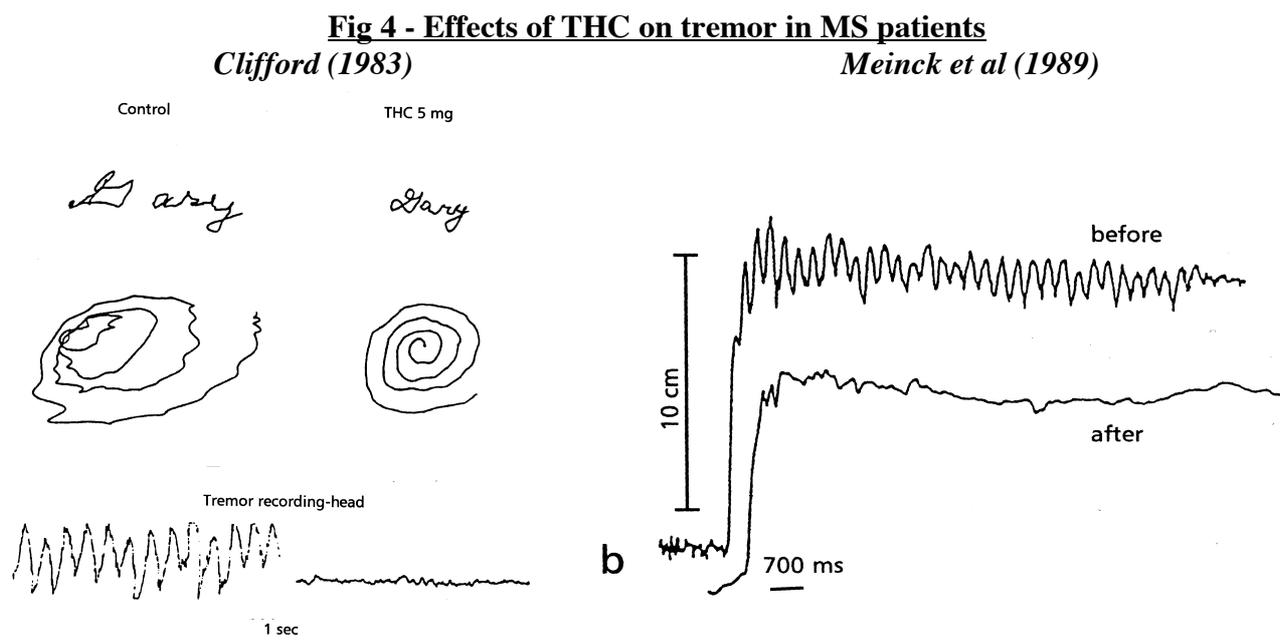
Petro & Ellenberger<sup>44</sup>, in a small double-blind clinical trial found 10mg THC significantly ( $p < .01$ ) reduced spasticity in patients with MS or similar conditions, compared to placebo. In an earlier double-blind crossover trial, Ungerleider et al<sup>45</sup> reported ‘*At doses greater than 7.5 mg there was significant improvement in patient ratings of spasticity compared to placebo. These positive findings in a treatment failure population suggest a role for THC in the treatment of spasticity in multiple sclerosis.*’ Clifford<sup>46</sup>, in a trial involving 8 patients severely disabled with tremor and ataxia, reported significant improvement in two patients. Case study reports<sup>47,48</sup> suggest that cannabis can suppress pendular nystagmus (jerky eye movements) in patients with multiple sclerosis.

In a pilot study involving two patients, Brenneisen et al<sup>49</sup> reported “*Oral and rectal THC reduced at a progressive stage of illness the spasticity, rigidity, and pain, resulting in improved active and passive mobility.*” In a single case double-blind trial, Maurer et al<sup>50</sup> found THC “*showed a significant beneficial effect on spasticity. In the dosage of THC used no altered consciousness occurred.*” Consroe et al<sup>51</sup> reported cannabidiol (CBD) to produce dose-related improvements in dystonic movement disorders. Malec et al<sup>52</sup> found spinal cord injured persons reported decreased spasticity with marijuana use. Other papers have also reported potential benefits of cannabinoids, including

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- 39 Cabranes A, Pryce G, Baker D, Fernandez-Ruiz J. [2006] Changes in CB(1) receptors in motor-related brain structures of chronic relapsing experimental allergic encephalomyelitis mice. *Brain Res.* 1107(1):199-205
- 40 Clark PA (2000) The ethics of medical marijuana: government restrictions vs. medical necessity. *J Public Health Policy* 21(1):40-60
- 41 Rosenthal MS, Kleber HD (1999) Making sense of medical marijuana. *Proc Assoc Am Physicians* 111(2):159-65
- 42 Masood E (1998) Cannabis laws 'threaten validity of trials'. *Nature* 396(6708):206
- 43 Robson P. [2005] Human studies of cannabinoids and medicinal cannabis. *Handb Exp Pharmacol.* (168):719-56.
- 44 Petro DJ, Ellenberger C Jr (1981) Treatment of human spasticity with delta 9-tetrahydrocannabinol. *J Clin Pharmacol* 21(8-9 Suppl):413S-416S
- 45 Ungerleider JT, Andyrsiak T, Fairbanks L, Ellison GW, Myers LW (1987) Delta-9-THC in the treatment of spasticity associated with multiple sclerosis. *Adv Alcohol Subst Abuse* 7(1):39-50
- 46 Clifford DB (1983) Tetrahydrocannabinol for tremor in multiple sclerosis. *Ann Neurol* 13(6):669-71
- 47 Schon F, Hart PE, Hodgson TL, Pambakian AL, Ruprah M, Williamson EM, Kennard C (1999) Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology* 53(9):2209-10
- 48 Dell'Osso LF (2000) Suppression of pendular nystagmus by smoking cannabis in a patient with multiple sclerosis. *Neurology* 54(11):2190-3
- 49 Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y (1996) The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. *Int J Clin Pharmacol Ther* 34(10):446-52
- 50 Maurer M, Henn V, Dittrich A, Hofmann A (1990) Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry Neurol Sci* 1990;240(1):1-4
- 51 Consroe P, Sandyk R, Snider SR (1986) Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci* 30(4):277-82
- 52 Malec J, Harvey RF, Cayner JJ (1982) Cannabis effect on spasticity in spinal cord injury. *Arch Phys Med Rehabil* 63(3):116-8

crude marijuana<sup>53,54</sup>, and the synthetic Nabilone<sup>55</sup>, where Martyn et al found clear improvement in well-being, reduced pain from muscle spasm, and reduced frequency of nocturia during the treatment condition (1mg Nabilone every other day) compared to worsening of symptoms during no treatment or placebo conditions.

Meinck et al<sup>56</sup> reported “The chronic motor handicaps of a 30-year-old multiple sclerosis patient acutely improved while he smoked a marijuana cigarette. This effect was quantitatively assessed by means of clinical rating, electromyographic investigation of the leg flexor reflexes and electromagnetic recording of the hand action tremor. It is concluded that cannabinoids may have powerful beneficial effects on both spasticity and ataxia that warrant further evaluation.” The improvements in tremor reported by Meinck & Clifford are dramatically demonstrated in fig 4 below.



In a small-scale Dutch trial on MS patients with severe spasticity, Killestein et al<sup>57</sup> noted “Both drugs were safe, but adverse events were more common with plant-extract treatment. Compared with placebo, neither THC nor plant-extract treatment reduced spasticity. Both THC and plant-extract treatment worsened the participant's global impression.”, prompting Thompson & Baker<sup>58</sup> to conclude that the drug was potentially useful but not yet ready for widespread clinical use. Smith<sup>59</sup>, whilst accepting the cannabinoids effectively reduce pain and spasticity in multiple sclerosis, highlighted the limited evidence from available trials, and questioned whether they are superior to conventional medications. “Whether or not cannabinoids do have therapeutic potential in the treatment of MS, a further issue will be whether synthetic cannabinoids should be used in preference to cannabis itself. Smoking cannabis is associated with significant risks of lung cancer and other respiratory dysfunction. Furthermore, delta9-THC, as a broad-spectrum cannabinoid receptor agonist, will activate both CB1 and CB2 receptors. Synthetic cannabinoids, which target specific cannabinoid receptor subtypes in specific parts of the CNS, are likely to be of more

- 53 Petro DJ (1980) Marijuana as a therapeutic agent for muscle spasm or spasticity. *Psychosomatics* 21(1):81, 85
- 54 Check WA (1979) Marijuana may lessen spasticity of MS. *JAMA* 241(23):2476
- 55 Martyn CN, Illis LS, Thom J (1995) Nabilone in the treatment of multiple sclerosis. *Lancet* 345(8949):579
- 56 Meinck HM, Schonle PW, Conrad B (1989) Effect of cannabinoids on spasticity and ataxia in multiple sclerosis. *J Neurol* 236(2):120-2
- 57 Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, Gorter RW, Uitdehaag BM, Polman CH. [2002] Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 58(9):1404-7
- 58 Thompson AJ, Baker D. [2002] Cannabinoids in MS: potentially useful but not just yet! *Neurology* 58(9):1323-4
- 59 Smith PF. [2002] Cannabinoids in the treatment of pain and spasticity in multiple sclerosis. *Curr Opin Investig Drugs* 3(6):859-64

*therapeutic use than delta9-THC itself. If rapid absorption is necessary, such synthetic drugs could be delivered via aerosol formulations.”*

Fernandez<sup>60</sup> recognised the scientific basis and called for more extensive and long-term clinical trials. Clark<sup>61</sup> called for reclassification of cannabis in the USA to allow physicians to prescribe marijuana for MS. Williamson & Evans<sup>62</sup> conducted a wide ranging review into the therapeutic uses of cannabinoids, commenting “*Cannabis is frequently used by patients with multiple sclerosis (MS) for muscle spasm and pain, and in an experimental model of MS low doses of cannabinoids alleviated tremor. Most of the controlled studies have been carried out with THC rather than cannabis herb and so do not mimic the usual clinical situation.*” Mechoulam<sup>63</sup> noted “*Clinical work in multiple sclerosis, which may lead to the approval of tetrahydrocannabinol as a drug for this condition*” Schlicker et al<sup>64</sup> noted “*Cannabis (marijuana)... has the potential for the development of useful agents for the treatment of ... multiple sclerosis.*” Carter & Rosen<sup>65</sup> reported “*Marijuana is a substance with many properties that may be applicable to the management of amyotrophic lateral sclerosis (ALS). These include analgesia, muscle relaxation, bronchodilation, saliva reduction, appetite stimulation, and sleep induction.*” Guzman et al<sup>66</sup> concluded “*The neuroprotective effect of cannabinoids may have potential clinical relevance for the treatment of neurodegenerative disorders such as multiple sclerosis*”

## Cannabinoids and Muscle Spasticity

In 1981 Petro & Ellenberger<sup>67</sup> noted “*Spasticity is a common neurologic condition in patients with multiple sclerosis, stroke, cerebral palsy or an injured spinal cord. Animal studies suggest that THC has an inhibitory effect on polysynaptic reflexes. Some spastic patients claim improvement after inhaling cannabis*” and, in a mixed patient group, found “*10 mg THC significantly reduced spasticity by clinical measurement (P < 0.01).*” In spinal injury patients, Malec et al<sup>68</sup> found “*spinal cord injured persons reported decreased spasticity with marijuana use*”. The BMA report recommended ‘*carefully controlled trials of cannabinoids in patients with chronic spastic disorders which have not responded to other drugs*’

Pertwee<sup>69</sup> reported in 2002 “*There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain.*”, noting “*Clinical ... trials have shown that cannabis, Delta(9)-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials) or spinal cord injury (1 trial).*” Pertwee & Ross<sup>70</sup> noted “*released endocannabinoids mediate reductions both in inflammatory pain and in the spasticity and tremor of multiple*

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- 60 Lorenzo Fernandez P (2000) [No title available].[Article in Spanish] An R Acad Nac Med (Madr) 117(3):595-605; discussion 616-24
- 61 Clark PA (2000) The ethics of medical marijuana: government restrictions vs. medical necessity. J Public Health Policy 2000;21(1):40-60
- 62 Williamson EM, Evans FJ (2000) Cannabinoids in clinical practice. Drugs 60(6):1303-14
- 63 Mechoulam R, Hanu L. [2001] The cannabinoids: An overview. Therapeutic implications in vomiting and nausea after cancer chemotherapy, in appetite promotion, in multiple sclerosis and in neuroprotection. Pain Res Manag 6(2):67-73
- 64 Schlicker E, Kathmann M. [2001] Modulation of transmitter release via presynaptic cannabinoid receptors. Trends Pharmacol Sci 22(11):565-72
- 65 Carter GT, Rosen BS [2001] Marijuana in the management of amyotrophic lateral sclerosis. Am J Hosp Palliat Care 18(4):264-70
- 66 Guzman M, Sanchez C, Galve-Roperh I. [2001] Control of the cell survival/death decision by cannabinoids. J Mol Med 78(11):613-25
- 67 Petro DJ, Ellenberger C Jr [1981] Treatment of human spasticity with delta 9-tetrahydrocannabinol. J Clin Pharmacol 21(8-9 Suppl):413S-416S
- 68 Malec J, Harvey RF, Cayner JJ. [1982] Cannabis effect on spasticity in spinal cord injury. Arch Phys Med Rehabil 63(3):116-8
- 69 Pertwee R. [2002] Cannabinoids and multiple sclerosis. Pharmacol Ther 2002 Aug;95(2):165
- 70 Pertwee RG, Ross RA. [2002] Cannabinoid receptors and their ligands. Prostaglandins Leukot Essent Fatty Acids 66(2-3):101-21

sclerosis”. Brooks et al<sup>71</sup> reported “Activation of cannabinoid receptors causes inhibition of spasticity”

Similarly, Smith<sup>72</sup> noted “There is a large amount of evidence to support the view that the psychoactive ingredient in cannabis, delta9-tetrahydrocannabinol (delta9-THC), and cannabinoids in general, can reduce muscle spasticity and pain under some circumstances. Cannabinoid (CB1) receptors in the CNS appear to mediate both of these effects and endogenous cannabinoids may fulfil these functions to some extent under normal circumstances” while cautioning “it is still questionable whether cannabinoids are superior to existing, conventional medications for the treatment of spasticity and pain. In the case of spasticity, there are too few controlled clinical trials to draw any reliable conclusion at this stage.” In a 2001 review, Kalant<sup>73</sup> noted “Recent evidence clearly demonstrates analgesic and anti-spasticity effects that will probably prove to be clinically useful.”

A small Dutch clinical trial<sup>74</sup> found “Compared with placebo, neither THC nor (cannabis) plant-extract treatment reduced spasticity”, prompting Thomas & Baker<sup>75</sup> to question whether western medicine was ready for cannabinoid therapy. However, a larger scale trial of MS patients by GW Pharmaceuticals<sup>76</sup> reported “THC:CBD medicine provided a highly statistically significant improvement in the symptom of spasticity”.

There is a large amount of research recently undertaken or underway into the antispastic effects of cannabinoids, particularly in patients with multiple sclerosis or spinal injury. Less research effort has been conducted to date into patients with spasticity arising from other neurological conditions, although animal studies suggest the anti-spastic effects of CB1 receptor agonists are not confined to these conditions.

## GW Pharmaceuticals & Clinical Trials

In November 2002, GW Pharmaceuticals reported the results of Phase III clinical trials of cannabis-extract based medicines on MS patients<sup>77</sup>, finding:

- (a) “In a double-blind parallel group study comparing the efficacy of GW’s THC:CBD product with placebo in the treatment of neuropathic pain in 66 patients with MS, the THC:CBD medicine provided highly statistically significant relief of pain in comparison with placebo and highly statistically significant reduction in sleep disturbance.”
- (b) “In a double-blind parallel group study comparing the efficacy of GW’s THC:CBD product with placebo in the treatment of chronic refractory pain in 70 patients with MS and other neurological conditions, the THC:CBD medicine provided statistically significant pain relief (as evidenced by the diminished use of analgesic rescue medication) and statistically significant reduction in sleep disturbance.”
- (c) “In a double-blind parallel group study comparing the efficacy of GW’s THC:CBD product with placebo in the treatment of a number of symptoms in 160 patients with MS, the THC:CBD medicine provided a highly statistically significant improvement in the symptom of spasticity. Positive trends were also observed in a number of other MS symptoms (providing useful additional support to significant results obtained in Phase II trials).”

71 Brooks JW, Pryce G, Bisogno T, Jaggar SI, Hankey DJ, Brown P, Bridges D, Ledent C, Bifulco M, Rice AS, Di Marzo V, Baker D. [2002] Arvanil-induced inhibition of spasticity and persistent pain: evidence for therapeutic sites of action different from the vanilloid VR1 receptor and cannabinoid CB(1)/CB(2) receptors. *Eur J Pharmacol* 439(1-3):83-92

72 Smith PF. [2002] Cannabinoids in the treatment of pain and spasticity in multiple sclerosis. *Curr Opin Investig Drugs* 3(6):859-64

73 Kalant H. [2001] Medicinal use of cannabis: history and current status. *Pain Res Manag* 6(2):80-91

74 Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, Gorter RW, Uitdehaag BM, Polman CH. [2002] Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 58(9):1404-7

75 Thompson AJ, Baker D. [2002] Cannabinoids in MS: potentially useful but not just yet! *Neurology* 58(9):1323-4

76 [http://www.gwpharm.com/news\\_pres\\_05\\_nov\\_02.html](http://www.gwpharm.com/news_pres_05_nov_02.html)

77 [http://www.gwpharm.com/news\\_pres\\_05\\_nov\\_02.html](http://www.gwpharm.com/news_pres_05_nov_02.html)

Dr Philip Robson, GW Medical Director, commented: “*These rigorous randomised placebo-controlled trials indicate that GW’s cannabis-based medicine can provide additional benefits over and above that of standard treatments in these serious and refractory neurological conditions. The results show statistically significant reductions in neuropathic pain, which is recognised as being difficult to treat and is often particularly distressing. There were also significant improvements in other symptoms in patients with MS, notably spasticity and sleep disturbance. In my opinion, it is this broad spectrum of activity, coupled with an excellent safety profile, which gives GW’s cannabis-based medicine the potential to make a unique contribution towards improving the quality of life of patients with these chronic disabling diseases.*”

Svendsen et al<sup>78</sup> conducted a clinical trial in Denmark using Dronabinol (synthetic THC) finding “*Median spontaneous pain intensity was significantly lower during dronabinol treatment than during placebo treatment... On the SF-36 quality of life scale, the two items bodily pain and mental health indicated benefits from active treatment compared with placebo*”, the same team<sup>79</sup> later reported “*Dronabinol reduced the spontaneous pain intensity significantly compared with placebo*” In a clinical trial of cannabis extracts in Switzerland, Vaney et al<sup>80</sup> noted “*trends in favour of active treatment were seen for spasm frequency, mobility and getting to sleep. In the 37 patients (per-protocol set) who received at least 90% of their prescribed dose, improvements in spasm frequency (P = 0.013) and mobility after excluding a patient who fell and stopped walking were seen (P = 0.01)*” and concluded “*A standardized Cannabis sativa plant extract might lower spasm frequency and increase mobility with tolerable side effects in MS patients with persistent spasticity not responding to other drugs.*”

A clinical trial of cannabis extracts on bladder function in MS patients by Brady et al<sup>81</sup> found “*Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment (P <0.05, Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly (P <0.05, Wilcoxon's signed rank test) with pain improvement continuing up to median of 35 weeks. There were few troublesome side effects*” In a large-scale (n=630) clinical trial of cannabis extract, THC and placebo on bladder function Freeman et al<sup>82</sup> found “*All three groups showed a significant reduction, p<0.01, in adjusted episode rate (i.e. correcting for baseline imbalance) from baseline to the end of treatment: cannabis extract, 38%; THC, 33%; and placebo, 18%. Both active treatments showed significant effects over placebo (cannabis extract, p=0.005; THC, p=0.039). Conclusion: The findings are suggestive of a clinical effect of cannabis on incontinence episodes in patients with MS.*”

A clinical trial of Sativex on MS symptoms including spasticity, spasms, bladder problems, tremor or pain by Wade et al<sup>83</sup> reported “*Following CBME the primary symptom score reduced from mean (SE) 74.36 (11.1) to 48.89 (22.0) following CBME and from 74.31 (12.5) to 54.79 (26.3) following placebo [ns]. Spasticity VAS scores were significantly reduced by CBME (Sativex) in comparison with placebo (P =0.001).*” A clinical trial of 1:1 THC/CBD Sativex on 66x MS patients suffering central pain by Rog et al<sup>84</sup> found

78 Svendsen KB, Jensen TS, Bach FW. [2004] Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*. 329(7460):253

79 Svendsen KB, Jensen TS, Bach FW. [2005] [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis--secondary publication] [Article in Danish] *Ugeskr Laeger*. 167(25-31):2772-4.

80 Vaney C, Heinzl-Gutenbrunner M, Jobin P, Tschopp F, Gattlen B, Hagen U, Schnelle M, Reif M. [2004] Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler*. 10(4):417-24.

81 Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ. [2004] An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis. *Mult Scler*. 10(4):425-33.

82 Freeman RM, Adekanmi O, Waterfield MR, Waterfield AE, Wright D, Zajicek J. [2006] The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). *Int Urogynecol J Pelvic Floor Dysfunct*. 2006 Mar 22; [Epub ahead of print]

83 Wade DT, Makela P, Robson P, House H, Bateman C. [2004] Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. *Mult Scler*. 10(4):434-41.

84 Rog DJ, Nurmikko TJ, Friede T, Young CA. [2005] Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology*. 65(6):812-9.

*“(Sativex) was superior to placebo in reducing the mean intensity of pain (CBM 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 (CBM mean change -2.5, 95% CI: -3.4 to -1.7, placebo -0.8, 95% CI: -1.5 to -0.1, comparison between groups,  $p = 0.003$ ). CBM was generally well tolerated, although more patients on CBM than placebo reported dizziness, dry mouth, and somnolence”*

Reviewing clinical trial evidence in 2005, Teare & Zajicek<sup>85</sup> noted *“Recent clinical studies to treat symptoms of multiple sclerosis have shown varying results, which may reflect issues relating to the way in which such studies were conducted. There is now increasing interest in the potential role of cannabinoids not only in symptom relief, but also for their possible neuroprotective actions.”* Zajicek et al<sup>86</sup> followed up clinical trial patients invited to continue treatment with THC, plant extract or placebo for 12 months, finding a *“small treatment effect on muscle spasticity as measured by change in Ashworth score from baseline to 12 months”* for THC (1.82) and extract (0.1) compared to placebo (-0.23), and concluded *“These data provide limited evidence for a longer term treatment effect of cannabinoids. A long term placebo controlled study is now needed to establish whether cannabinoids may have a role beyond symptom amelioration in MS.”* In a clinical review, Azad & Rammes<sup>87</sup> concluded *“In multiple sclerosis, cannabinoids have been shown to have beneficial effects on spasticity, pain, tremor and bladder dysfunction.”*

Solaro<sup>88</sup> conducted two clinical trials of Dronabinol and Sativex on pain in MS patients, finding *“Active drugs were superior to placebo in reducing the mean intensity of pain, although patients reported side effects such as dizziness and somnolence more frequently”* In a clinical trial of sublingual extracts, Wade et al<sup>89</sup> found *“Pain relief associated with both THC and CBD was significantly superior to placebo. Impaired bladder control, muscle spasms and spasticity were improved by CME in some patients with these symptoms.”* In a clinical trial studying effects of cannabinoids on tremor in MS patients, Fox et al<sup>90</sup> found *“no significant improvement in any of the objective measures of upper limb tremor with cannabis extract compared to placebo. Finger tapping was faster on placebo compared to cannabis extract ( $p < 0.02$ ). However, there was a nonsignificant trend for patients to experience more subjective relief from their tremors while on cannabis extract compared to placebo”* In a further clinical trial, Notcutt et al<sup>91</sup> studied the effect of extracts on relief of chronic pain, finding *“Extracts which contained THC proved most effective in symptom control.”*

GW Pharmaceuticals<sup>92</sup> reported interim results of clinical trials in 2003, including *“THC:CBD (narrow ratio) caused statistically significant reductions in neuropathic pain in patients with MS and other conditions. In addition, improvements in other MS symptoms were observed as well”* and concluding *“The phase II trials provided positive results and confirmed an excellent safety profile for cannabis-based medicines”*

Reviewing results of clinical trials, Corey<sup>93</sup> noted *“Two large trials found that cannabinoids were significantly better than placebo in managing spasticity in multiple sclerosis. Patients self-reported greater sense of motor improvement in multiple sclerosis than could be confirmed objectively. In smaller qualifying trials, cannabinoids produced significant objective improvement of tics in*

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- 85 Teare L, Zajicek J. [2005] The use of cannabinoids in multiple sclerosis. *Expert Opin Investig Drugs*. 14(7):859-69.
- 86 Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, Nunn AJ, Teare LJ, Fox PJ, Thompson AJ. [2005] Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry*. 76(12):1664-9.
- 87 Azad SC, Rammes G. [2005] Cannabinoids in anaesthesia and pain therapy. *Curr Opin Anaesthesiol*. 18(4):424-7.
- 88 Solaro C. [2006] Epidemiology and treatment of pain in multiple sclerosis subjects. *Neurol Sci*. 27 Suppl 4:s291-3.
- 89 Wade DT, Robson P, House H, Makela P, Aram J.[2003] A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil*. 17(1):21-9.
- 90 Fox P, Bain PG, Glickman S, Carroll C, Zajicek J. [2004] The effect of cannabis on tremor in patients with multiple sclerosis. *Neurology*. 62(7):1105-9.
- 91 Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. [2004] Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. *Anaesthesia*. 59(5):440-52
- 92 [No authors listed] [2003] Cannabis-based medicines--GW pharmaceuticals: high CBD, high THC, medicinal cannabis--GW pharmaceuticals, THC:CBD. *Drugs R D*. 4(5):306-9.
- 93 Corey S. [2005] Recent developments in the therapeutic potential of cannabinoids. *P R Health Sci J*. 24(1):19-26.

*Tourette's disease, and neuropathic pain. A new, non-psychotropic cannabinoid also has analgesic activity in neuropathic pain.”* Reviewing results of early clinical trials in 2004, Smith<sup>94</sup> conceded “*results of preclinical trials also lend support to the hypothesis that the endogenous cannabinoid system may be involved in the regulation of spasticity and pain*” Fernandez-Ruiz et al<sup>95</sup> concluded “*the control of movement is one of the more relevant physiological roles of the endocannabinoid transmission in the brain*”

Shakespeare et al<sup>96</sup> criticised studies of spasticity which failed to use the standardised ‘Ashworth’ scale to score results. In a controlled clinical trial Zajicek et al<sup>97</sup> found “*Treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.*” Killestein et al<sup>98</sup> conducted a clinical trial of oral THC and cannabis plant extract in 16 MS patients, finding both drugs to be safe but neither to be effective at reducing spasticity, and both ‘*worsened the participant’s global perception*’. However, another paper from the same study<sup>99</sup> noted “*The results suggest pro-inflammatory disease-modifying potential of cannabinoids in MS*” Killestein et al<sup>100</sup> concluded in 2004 that “*convincing evidence that cannabinoids are effective in MS is still lacking*” and that “*it is also not possible to conclude definitely that cannabinoids are ineffective*”<sup>101</sup>

Russo & Guy<sup>102</sup>, of GW Pharmaceuticals, reported in 2006 “*CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, (and) peripheral neuropathic pain... The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.*” Perez<sup>103</sup> reviewed the results of clinical trials of Sativex, concluding “*Clinical assessment of this combined cannabinoid medicine has demonstrated efficacy in patients with intractable pain (chronic neuropathic pain, pain due to brachial plexus nerve injury, allodynic peripheral neuropathic pain and advanced cancer pain), rheumatoid arthritis and multiple sclerosis (bladder problems, spasticity and central pain), with no significant intoxication-like symptoms, tolerance or withdrawal syndrome*”

## Treating the disease process?

Increasing evidence is emerging from receptor and animal studies that cannabinoids may be involved in the degenerative disease process involved in the development of

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- 94 Smith PF. [2004] Medicinal cannabis extracts for the treatment of multiple sclerosis. *Curr Opin Investig Drugs*. 5(7):727-30.
- 95 Fernandez-Ruiz J, Lastres-Becker I, Cabranes A, Gonzalez S, Ramos JA. [2002] Endocannabinoids and basal ganglia functionality. *Prostaglandins Leukot Essent Fatty Acids*. 66(2-3):257-67.
- 96 Shakespeare DT, Boggild M, Young C. [2003] Anti-spasticity agents for multiple sclerosis. *Cochrane Database Syst Rev*. (4):CD001332
- 97 Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A; UK MS Research Group. [2003] Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet*. 362(9395):1517-26.
- 98 Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, Gorter RW, Uitdehaag BM, Polman CH. [2002] Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology*. 58(9):1404-7.
- 99 Killestein J, Hoogervorst EL, Reif M, Blauw B, Smits M, Uitdehaag BM, Nagelkerken L, Polman CH. [2003] Immunomodulatory effects of orally administered cannabinoids in multiple sclerosis. *J Neuroimmunol*. 137(1-2):140-3.
- 100 Killestein J, Uitdehaag BM, Polman CH. [2004] Cannabinoids in multiple sclerosis: do they have a therapeutic role? *Drugs*. 64(1):1-11.
- 101 Killestein J, Bet PM, van Loenen AC, Polman CH. [2004] [Medicinal cannabis for diseases of the nervous system: no convincing evidence of effectiveness] [Article in Dutch] *Ned Tijdschr Geneesk*. 148(48):2374-8.
- 102 Russo E, Guy GW. [2006] A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses*. 66(2):234-46.
- 103 Perez J. [2006] Combined cannabinoid therapy via an oromucosal spray. *Drugs Today (Barc)*. 42(8):495-503.

MS, and that cannabinoid therapy may offer hope of halting or even reversing the disease process.

Molina-Holgado et al<sup>104</sup> found anandamide (endogenous CB1 cannabinoid receptor agonist) reduced the effects of encephalomyelitis in mice, suggesting a receptor-mediated mode of action in arresting or reducing the autoimmune response considered to be involved in the MS disease process.

Van Oosten et al<sup>105</sup> reported a case study of a 46 year old woman treated for obesity with a cannabinoid-receptor antagonist who developed MS some months later.

Jackson et al<sup>106</sup> studied genetically-modified mice where the CB1 receptors had been disabled, noting an increase in demyelination responses, and concluding that the results “*strengthen the hypothesis of neuroprotection elicited via cannabinoid receptor 1 signaling.*” Pryce et al<sup>107</sup>, in a study on neurodegeneration in mice, concluded “*in addition to symptom management, cannabis may also slow the neurodegenerative processes that ultimately lead to chronic disability in multiple sclerosis*”

In rats, Carrier et al<sup>108</sup> noted “*2-AG activation of CB(2) receptors may contribute to the proliferative response of microglial cells, as occurs in neurodegenerative disorders*” Kim et al<sup>109</sup> reported “*AM1241 is a cannabinoid CB2 receptor selective agonist that has been shown to be effective in models of inflammation and hyperalgesia... treatment with AM1241 was effective at slowing signs of disease progression when administered after onset of signs in an ALS mouse model (hSOD1(G93A) transgenic mice). Administration at the onset of tremors delayed motor impairment in treated mice when compared to vehicle controls. Three conditions of ALS, the loss of motor function, paralysis scoring and weight loss, were analyzed using a mathematical model. Loss of motor function (as assessed by performance on a rotarod) was delayed by 12.5 days in male mice by AM1241. In female mice, AM1241 extended rotarod performance by 3 days, although this was not statistically significant. In male mice, AM1241 also extended by 5 days the time to reach the 50% point on a visually-assessed performance scale.*”

Stella<sup>110</sup> investigated the effect of cannabinoids on glial cells involved in the MS disease process, noting “*Recent evidence suggests that glial cells also express components of the cannabinoid signaling system and marijuana-derived compounds act at CB receptors expressed by glial cells, affecting their functions*” Following a tissue-culture study showing that JWH-015 – a CB2 agonist, reduced neurodegenerative activity in microglial cells, Ehrhart et al<sup>111</sup> postulated “*beneficial effects provided by cannabinoid receptor CB2 modulation in neurodegenerative diseases*” Eljaschewitsch et al<sup>112</sup> found “*the*

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- 104 Molina-Holgado F, Molina-Holgado E, Guaza C (1998) The endogenous cannabinoid anandamide potentiates interleukin-6 production by astrocytes infected with Theiler's murine encephalomyelitis virus by a receptor-mediated pathway. *FEBS Lett* 14;433(1-2):139-42
- 105 van Oosten BW, Killestein J, Mathus-Vliegen EM, Polman CH. [2004] Multiple sclerosis following treatment with a cannabinoid receptor-1 antagonist. *Mult Scler.* 10(3):330-1.
- 106 Jackson SJ, Pryce G, Diemel LT, Cuzner ML, Baker D. [2005] Cannabinoid-receptor 1 null mice are susceptible to neurofilament damage and caspase 3 activation. *Neuroscience.* 134(1):261-8.
- 107 Pryce G, Ahmed Z, Hankey DJ, Jackson SJ, Croxford JL, Pocock JM, Ledent C, Petzold A, Thompson AJ, Giovannoni G, Cuzner ML, Baker D. [2003] Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. *Brain.* 126(Pt 10):2191-202.
- 108 Carrier EJ, Kearn CS, Barkmeier AJ, Breese NM, Yang W, Nithipatikom K, Pfister SL, Campbell WB, Hillard CJ. [2004] Cultured rat microglial cells synthesize the endocannabinoid 2-arachidonylglycerol, which increases proliferation via a CB2 receptor-dependent mechanism. *Mol Pharmacol.* 65(4):999-1007.
- 109 Kim K, Moore DH, Makriyannis A, Abood ME. [2006] AM1241, a cannabinoid CB2 receptor selective compound, delays disease progression in a mouse model of amyotrophic lateral sclerosis. *Eur J Pharmacol.* 542(1-3):100-5.
- 110 Stella N. [2004] Cannabinoid signaling in glial cells. *Glia.* 48(4):267-77.
- 111 Ehrhart J, Obregon D, Mori T, Hou H, Sun N, Bai Y, Klein T, Fernandez F, Tan J, Shytle RD. [2005] Stimulation of cannabinoid receptor 2 (CB2) suppresses microglial activation. *J Neuroinflammation.* 12;2:29.
- 112 Eljaschewitsch E, Witting A, Mawrin C, Lee T, Schmidt PM, Wolf S, Hoertnagl H, Raine CS, Schneider-Stock R, Nitsch R, Ullrich O. [2006] The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells. *Neuron.* 49(1):67-79.

*endocannabinoid anandamide (AEA) protects neurons from inflammatory damage by CB(1/2) receptor-mediated rapid induction of mitogen-activated protein kinase phosphatase-1 (MKP-1) in microglial cells*” Tagliaferro et al<sup>113</sup> reported “long-term neuroprotective effects observed after cannabinoid treatments”

Fujiwara et al<sup>114</sup> reported “*Delta9-THC markedly inhibited the neurodegeneration in experimental allergic encephalomyelitis (EAE), an animal model of multiple sclerosis and reduced the elevated glutamate level of cerebrospinal fluid induced by EAE. These therapeutic effects on EAE were reversed by SRI141716A*” Yang et al<sup>115</sup> reported “*ameliorating effects of cannabinoids on axonal injury associated with multiple sclerosis are achieved by its direct action*” Reviewing neurodegenerative studies, Yiangou et al<sup>116</sup> concluded “*CB2 specific agonists deserve evaluation in the progression of MS and ALS*” Witting et al<sup>117</sup> reported “*activation of cannabinoid receptors reduces the production and diffusion of harmful mediators*” Bilsland et al<sup>118</sup> concluded “*cannabinoids have significant neuroprotective effects*”

Jackson et al<sup>119</sup> concluded “*neuroprotection could be elicited through the cannabinoid receptor 1, and point towards a potential therapeutic role for cannabinoid compounds in demyelinating conditions such as multiple sclerosis*”, further concluding<sup>120</sup> “*There is increasing evidence for cannabinoid-mediated control of symptoms, which is being more supported by the underlying biology. However there is accumulating evidence in vitro and in vivo to support the hypothesis that the cannabinoid system can limit the neurodegenerative processes that drive progressive disease, and may provide a new avenue for disease control.*”

## Learned Reviews

Taylor<sup>121</sup>, reviewing potential medical uses in 1998, concluded: “*Marijuana shows clinical promise for... spasticity, multiple sclerosis... As a medical drug, marijuana should be available for patients who do not adequately respond to currently available therapies.*”

In 2002 reviews, Grundy<sup>122</sup> reports “*Cannabinoids ... provide symptomatic relief in experimental models of chronic neurodegenerative diseases, such as multiple sclerosis and Huntington's disease*”, but cautioned “*Our understanding of cannabinoid neurobiology, however, must improve if we are to effectively exploit this system and take advantage of the numerous characteristics that make this group of compounds potential neuroprotective agents.*” Pertwee<sup>123</sup> notes “*Clinical evidence comes from trials, albeit with rather small numbers of patients. These*

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*trials have shown that cannabis, Delta(9)-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials)”, noting “...experiments, ... with mice ... have provided strong evidence that cannabinoid-induced reductions in tremor and spasticity are mediated by cannabinoid receptors.” Pertwee & Ross<sup>124</sup> concluded “Potential therapeutic uses of cannabinoid receptor agonists include the management of multiple sclerosis/spinal cord injury, pain, inflammatory disorders, glaucoma, bronchial asthma, vasodilation that accompanies advanced cirrhosis, and cancer.”*

In a 2002 review Smith<sup>125</sup> concluded “There is a large amount of evidence to support the view that the psychoactive ingredient in cannabis, delta9-tetrahydrocannabinol (delta9-THC), and cannabinoids in general, can reduce muscle spasticity and pain under some circumstances. Cannabinoid (CB1) receptors in the CNS appear to mediate both of these effects and endogenous cannabinoids may fulfil these functions to some extent under normal circumstances. However, in the context of multiple sclerosis (MS), it is still questionable whether cannabinoids are superior to existing, conventional medications for the treatment of spasticity and pain. ... Synthetic cannabinoids, which target specific cannabinoid receptor subtypes in specific parts of the CNS, are likely to be of more therapeutic use than delta9-THC itself” Contemporaneously, Pertwee<sup>126</sup> concluded “There is a growing amount of evidence to suggest that cannabis and individual cannabinoids may be effective in suppressing certain symptoms of multiple sclerosis and spinal cord injury, including spasticity and pain.”, noting that “trials have shown that cannabis, Delta(9)-tetrahydrocannabinol, and nabilone can produce objective and/or subjective relief from spasticity, pain, tremor, and nocturia in patients with multiple sclerosis (8 trials) or spinal cord injury (1 trial). The clinical evidence is supported by results from experiments with animal models of multiple sclerosis. Some of these experiments, performed with mice with chronic relapsing experimental allergic encephalomyelitis (CREAE), have provided strong evidence that cannabinoid-induced reductions in tremor and spasticity are mediated by cannabinoid receptors, both CB(1) and CB(2).” In 2005 Smith<sup>127</sup> qualified his skepticism, noting “The evidence for the therapeutic efficacy of cannabinoids in the treatment of multiple sclerosis (MS) is increasing but is not as yet convincing. Although several trials have reported no significant effect, the majority of the evidence which supports a beneficial effect on spasticity and pain is based on subjective measurements in trials where unblinding was likely to be a problem. The available clinical trial data suggest that the adverse side effects associated with using cannabis-based medicinal extracts (CBMEs) are generally mild, such as dry mouth, dizziness, somnolence, nausea and intoxication, and in no case did toxicity develop.”

Baker & Pryce<sup>128</sup> noted “those with multiple sclerosis, claim that it may offer benefit in symptom control. Cannabis exerts many of its effects because it taps into an endogenous cannabinoid system... Cannabinoids provide a novel therapeutic target, not only for controlling symptoms, but also slowing disease progression through inhibition of neurodegeneration, which is the cause of accumulating irreversible disability.” Pryce & Baker<sup>129</sup> concluded “abundant experimental data have reinforced the anecdotal claims of people who perceive medicinal benefit from the currently illegal consumption of cannabis. This, combined with data from recent clinical trials, points to the prospect of cannabis as a medication in the treatment of multiple sclerosis and numerous other medical conditions.”

Croxford & Miller<sup>130</sup>, reviewing early clinical trials, noted “recent research in animal models of multiple sclerosis has demonstrated the efficacy of cannabinoids in controlling disease-induced

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*symptoms such as spasticity and tremor, as well as in ameliorating the severity of clinical disease. However, these initially promising results have not yet been fully translated into the clinic. Although cannabinoid treatment of multiple sclerosis symptoms has been shown to be both well tolerated and effective in a number of subjective tests in several small-scale clinical trials, objective measures demonstrating the efficacy of cannabinoids are still lacking.”* Reviewing clinical trial and animal evidence, Schwarz et al<sup>131</sup> concluded “*Many patients use cannabis to alleviate spasticity and pain. Small series indicated positive effects, but randomized trials were negative for spasticity. However, many patients report subjective improvement under cannabis even if their objective parameters remain unchanged*” Trebst & Sangel concluded “*there is reasonable evidence for the therapeutical employment of cannabinoids in the treatment of MS related symptoms. Furthermore, data are arising that cannabinoids have immunomodulatory and neuroprotective properties. However, results from clinical trials do not allow the recommendation for the general use of cannabinoids in MS*”

In December 2005, Malfitano et al<sup>132</sup> summarised the state of knowledge of the pharmacological, neuroanatomical and biochemical mechanisms behind the role of cannabinoids in MS thus “*An increasing body of evidence suggests that cannabinoids have beneficial effects on the symptoms of multiple sclerosis, including spasticity and pain. Endogenous molecules with cannabinoid-like activity, such as the "endocannabinoids", have been shown to mimic the anti-inflammatory properties of cannabinoids through the cannabinoid receptors. Several studies suggest that cannabinoids and endocannabinoids may have a key role in the pathogenesis and therapy of multiple sclerosis. Indeed, they can down regulate the production of pathogenic T helper 1-associated cytokines enhancing the production of T helper 2-associated protective cytokines. A shift towards T helper 2 has been associated with therapeutic benefit in multiple sclerosis. In addition, cannabinoids exert a neuromodulatory effect on neurotransmitters and hormones involved in the neurodegenerative phase of the disease. In vivo studies using mice with experimental allergic encephalomyelitis, an animal model of multiple sclerosis, suggest that the increase of the circulating levels of endocannabinoids might have a therapeutic effect, and that agonists of endocannabinoids with low psychoactive effects could open new strategies for the treatment of multiple sclerosis.*”

Pertwee<sup>133</sup> summarised “*CB1 and/or CB2 receptor activation appears to ameliorate inflammatory and neuropathic pain and certain multiple sclerosis symptoms. This might be exploited clinically by using CB1, CB2 or CB1/CB2 agonists, or inhibitors of the membrane transport or catabolism of endocannabinoids that are released in increased amounts, at least in animal models of pain and multiple sclerosis.*” McFarland et al<sup>134,135</sup> concluded “*augmentation of cannabinergic tone might be therapeutically beneficial in the treatment of multiple disease states such as chronic pain, anxiety, multiple sclerosis, and neuropsychiatric disorders*”

## Summary - Cannabinoids and M.S.

Multiple Sclerosis is a disease for which conventional medication provides little benefit.

There is a wealth of anecdotal evidence from MS patients reporting dramatic improvement in symptoms following illicit use of cannabis, from case histories and from surveys.

The results of early small-scale clinical trials were mixed, although more recent large scale clinical trials have shown THC and cannabis extracts can improve, in some cases dramatically, symptoms of MS such as pain, ataxia, muscle spasm,

131 Schwarz S, Leweling H, Meinck HM. [2005] [Alternative and complementary therapies in multiple sclerosis] [Article in German] Fortschr Neurol Psychiatr. 73(8):451-62

132 Malfitano AM, Matarese G, Bifulco M. [2005] From cannabis to endocannabinoids in multiple sclerosis: a paradigm of central nervous system autoimmune diseases. Curr Drug Targets CNS Neurol Disord. 4(6):667-75.

133 Pertwee RG. [2006] The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes (Lond). 30 Suppl 1:S13-8.

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135 McFarland MJ, Terebova EA, Barker EL. [2006] Detergent-resistant membrane microdomains in the disposition of the lipid signaling molecule anandamide. AAPS J. 8(1):E95-100.

spasticity, bladder dysfunction and tremor in many (but not all) patients. Studies failing to find, or finding non-significant effects, have tended to use subtherapeutic doses.

Recent animal research has indicated a direct receptor mediated immunosuppressive effect on microglial cells in the brain tissues which may delay or in some cases reverse the neurodegenerative process in MS-like animal models. This provides growing evidence that cannabinoids may not only benefit the symptoms of MS, but may potentially provide a treatment for the disease process itself, offering unprecedented hope to sufferers of the disease.

The House of Lords Science & Technology Committee recommended in 1998 that clinical trials of cannabinoids in the treatment of MS be undertaken as a matter of urgency, and that pending the award of product licences, doctors should be allowed to prescribe cannabis or cannabis resin as an unlicensed medicine on a named-patient basis for patients, including MS sufferers. In 2001, they went further and recommended that cannabis preparations be legalised for medical use. Since 1998 scientific investigation of the effects and causes of cannabinoid action on MS and symptoms has exploded, with the vast majority of studies and reviewers showing a potential therapeutic benefit. However the Medicines Control Agency (MCA) and National Institute for Clinical Excellence (NICE) have yet to licence cannabis, THC or Sativex for routine medical prescription.

Clinical trials of the extract *Sativex* containing roughly equal quantities of THC and CBD have found the combination more effective than THC alone, largely due to the increased amount of THC which can be administered before patients develop a 'high', but also due to the anti-inflammatory effects of CBD.