

Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial

Kristina B Svendsen, Troels S Jensen, Flemming W Bach

Abstract

Objective To evaluate the effect of the oral synthetic δ -9-tetrahydrocannabinol dronabinol on central neuropathic pain in patients with multiple sclerosis.

Design Randomised double blind placebo controlled crossover trial.

Setting Outpatient clinic, University Hospital of Aarhus, Denmark.

Participants 24 patients aged between 23 and 55 years with multiple sclerosis and central pain.

Intervention Orally administered dronabinol at a maximum dose of 10 mg daily or corresponding placebo for three weeks (15-21 days), separated by a three week washout period.

Main outcome measure Median spontaneous pain intensity (numerical rating scale) in the last week of treatment.

Results Median spontaneous pain intensity was significantly lower during dronabinol treatment than during placebo treatment (4.0 (25th to 75th centiles 2.3 to 6.0) *v* 5.0 (4.0 to 6.4), $P = 0.02$), and median pain relief score (numerical rating scale) was significantly higher (3.0 (0 to 6.7) *v* 0 (0 to 2.3), $P = 0.035$). The number needed to treat for 50% pain relief was 3.5 (95% confidence interval 1.9 to 24.8). 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 number of patients with adverse events was higher during active treatment, especially in the first week of treatment. The functional ability of the multiple sclerosis patients did not change.

Conclusions Dronabinol has a modest but clinically relevant analgesic effect on central pain in patients with multiple sclerosis. Adverse events, including dizziness, were more frequent with dronabinol than with placebo during the first week of treatment.

Introduction

Pain is an important symptom accompanying multiple sclerosis; acute or chronic pain syndromes occur in 30-80% of patients.¹⁻⁶ The reported prevalence of central pain from sclerotic plaque lesions affecting pain pathways is around 33%.⁷

Recent animal studies suggest that cannabinoids can reduce allodynia or hyperalgesia in neuropathic, inflammatory, and cancer pain,⁸⁻¹⁵ but few clinical studies have evaluated the analgesic action of cannabinoids in humans.¹⁶⁻²¹ Two recent randomised trials of cannabinoids included patients with multiple sclerosis, and both reported a beneficial effect on patients' pain.²²⁻²³ A third trial, in patients with other pain syndromes, also reported that a synthetic cannabinoid alleviated neuropathic pain.²⁴

None of the previous studies has specifically explored the effect of cannabinoids on pain caused by central lesions in multiple sclerosis. We aimed to evaluate the efficacy of the synthetic δ -9-tetrahydrocannabinol dronabinol on central pain in patients with multiple sclerosis in a randomised placebo controlled study. The objective was to provide better treatment options for central pain in multiple sclerosis, and we hypothesised that dronabinol would reduce central pain in multiple sclerosis.

Methods

Protocol

We recruited participants from the population of patients with definite multiple sclerosis in Aarhus County, Denmark.²⁵ We recruited patients partly from the outpatient multiple sclerosis clinic at the University of Aarhus and partly from responders ($n = 627$) to a postal survey undertaken among all patients with multiple sclerosis in Aarhus County in 2001.⁶ All patients with suspected central pain had a clinical examination in the pain clinic.

Inclusion criteria were a diagnosis of multiple sclerosis (clinical definite multiple sclerosis and laboratory supported definite multiple sclerosis²⁵), age between 18 and 55 years, and central pain at the maximal pain site with a pain intensity score ≥ 3 on a 0-10 numerical rating scale. The definition of central pain was pain in a body territory with abnormal sensation to pinprick, touch, warmth, or cold, evaluated by the bedside or with quantitative sensory testing, corresponding to at

Danish Pain Research Center and Department of Neurology, Aarhus University Hospital, Noerrebrogade 44, DK-8000 Aarhus C, Denmark

Kristina B Svendsen
research fellow

Troels S Jensen
professor

Flemming W Bach
associate clinical professor

Correspondence to:
F W Bach
fbach@akh.aaa.dk

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least one lesion in the central nervous system.^{7 26} We allowed concurrent spasm related pain or other pain if the patient was able to distinguish it from central pain. We excluded patients who had used marijuana within the last three months, and those who were unwilling to stop using marijuana during the study period.

We designed the study as a randomised double blind placebo controlled crossover trial. We allocated patients to treatment after a one week baseline period. We planned for the patients to receive three weeks' (18-21 days') treatment with dronabinol and three weeks' (18-21 days') treatment with placebo, with a washout period of at least 21 days between the treatment periods. Any analgesic drug (except paracetamol) was discontinued at least one week before the first visit.

During active treatment, the initial dose of dronabinol was 2.5 mg daily (one capsule), and the dose was increased by 2.5 mg every other day to a maximum dose of 5 mg (two capsules) twice daily. The placebo capsules were identical to the dronabinol capsules in appearance, taste, and smell.

Assignment and masking

We assigned patients to treatment using a computer generated randomisation code. Both investigators and patients were blinded to treatment allocation, and we maintained blinding until the data analysis was completed. At the end of the study we asked the patients to identify the treatment period in which they received the active treatment and which of the two treatments they preferred.

Assessments

The predefined primary outcome measure was median spontaneous pain intensity in the last week of treatment. Secondary outcome measures were median radiating pain intensity in the last week of treatment, pain relief, use of escape medication, patient preference, health related quality of life (SF-36), expanded disability status scale score, and quantitative sensory testing.

We asked the patients to assess pain intensity and pain relief at the maximal pain site throughout the study and record their assessments in a diary. They assessed pain intensity twice daily by using a numerical rating scale from 0 to 10 (0=no pain, 10=worst imaginable pain). They recorded pain relief on a numerical scale from 0 to 10 (0=no pain relief, 10=best pain relief) at the end of each treatment period. The patients also recorded the number of paracetamol taken daily.

At the end of the baseline period and at the end of each treatment period we administered a health related quality of life questionnaire (SF-36), the expanded disability status scale,²⁷ and quantitative sensory tests. We did the sensory tests at the maximal pain site and at the same site at all three visits. These tests measured patients' sensitivity to touch, pressure, heat, cold, and vibration (see bmj.com for details). We also tested temporal summation of pain to pinprick and mechanical and cold allodynia (pain evoked by stimuli not ordinarily painful). Patients used their own words to record adverse events in their dairies during each treatment period.

Data analyses and statistics

We analysed data according to the principle of intention to treat. For the daily pain scale ratings we determined a median value for the third week of treatment. We coded and summed the item scores in SF-36 and transformed them to a scale of 0 (poor health) to 100 (optimal health). We compared the effects of dronabinol and placebo on pain intensity, pain relief, escape medication, SF-36, expanded disability status scale, and quantitative sensory testing. We also compared the incidence of adverse events, analysed patients' preference of treatment period, tested for a carryover effect between treatment periods, and tested the efficiency of blinding by using patients' guesses of their active treatment period.

We considered a 25-30% pain reduction from baseline to be clinically relevant.²⁸ We calculated that we would need 23 patients for our study to have 90% power to detect this magnitude of effect.

Results

Participants

Patients were recruited between 27 February and 21 May 2002. The last telephone follow up took place on 26 July 2002. We screened 25 patients for the study and enrolled 24. All enrolled participants completed the study protocol. We excluded SF-36 and sensory testing data from one patient. Table 1 gives the characteristics of the participants and their pain.

Primary outcome measure

We observed no significant carryover effect for the primary outcome measure ($P=0.24$). The median spontaneous pain intensity during the last week of treatment was significantly lower during dronabinol treatment than during placebo treatment (4.0 (25th to 75th centiles 2.3 to 6.0) *v* 5.0 (4.0 to 6.4), $P=0.02$). The estimated difference in pain scores between dronabinol and placebo treatments was -0.6 (95% confidence interval -1.8 to 0).

In the group of patients randomised to active medication in the first period the change in spontane-

Table 1 Characteristics of participants

Characteristic	No or median (range) (n=24)
Age (years)	50 (23-55)
Sex (male/female)	10/14
Duration of disease (years since diagnosis)	7.0 (0.3-25.0)
Disease course:	
Relapsing-remitting	9
Secondary progressive	9
Primary progressive	6
Expanded disability status scale score at inclusion	6.0 (2.5-6.5)
Duration of pain (years)	4.5 (0.3-12.0)
Intensity of pain at inclusion (numerical rating scale)	5.5 (3.0-8.0)
Site of pain:	
Lower extremities	16
Upper extremities	4
Back	2
Chest	2
Description of pain:	
Pricking	17
Hot or burning	13
Tingling	3
Tight	3
Dull	3
Other	7

Table 2 Primary and secondary outcome measures. Values are medians (25th to 75th centiles) unless stated otherwise

Measure	Active-placebo group		Placebo-active group		Difference (95% CI)*	P value (active v placebo)†
	Period 1(A)	Period 2(P)	Period 1(P)	Period 2(A)		
Reduction in median spontaneous pain from baseline (numerical rating scale)	-1.0 (-1.9 to -0.1)	0 (-2.0 to 0)	0 (0 to 0.9)	-1.5 (-2.8 to -0.3)	-0.6 (-1.8 to 0)	0.02
Pain relief (numerical rating scale)	3.0 (0.0 to 7.5)	0.5 (0 to 5.3)	0 (0 to 0)	4.0 (1.3 to 6.8)	2.5 (0.5 to 4.5)	0.035
50% pain relief (No (%))	5 (42)	3 (25)	1 (8)	6 (50)	—	0.08
Radiating pain, diary (numerical rating scale)	1.8 (0.0 to 6.0)	4.8 (0.0 to 5.8)	1.5 (0.0 to 4.0)	0.8 (0.0 to 2.0)	-0.6 (-1.3 to 0)	0.039
Treatment preference (No (%))	5 (42)	5 (42)	1 (8)	9 (75)	—	0.14
Escape medication (daily No of paracetamol)	0 (0 to 3.5)	0 (0 to 3.5)	0 (0 to 0)	0 (0 to 0)	0	0.66
Expanded disability status scale	6.0 (4.5 to 6.4)	6.0 (4.6 to 6.4)	5.8 (3.6 to 6.0)	5.5 (4.3 to 6.0)	0	1.00
Quantitative sensory testing‡						
Cold detection threshold	23.7 (16.4 to 26.9)	24.2 (20.8 to 26.1)	24.3 (22.2 to 27.0)	26.5 (24.0 to 28.3)	0.5 (-0.6 to 1.8)	0.44
Warm detection threshold	41.5 (35.1 to 45.9)	38.8 (34.6 to 44.2)	40.1 (34.4 to 47.0)	43.5 (33.5 to 46.4)	0.1 (-0.1 to 1.8)	0.83
Cold pain threshold	9.6 (0.2 to 22.2)	12.8 (1.3 to 22.5)	12.9 (5.4 to 22.8)	20.4 (0.0 to 23.2)	0.0 (-1.1 to 2.1)	1.00
Heat pain threshold	45.3 (42.6 to 46.5)	43.2 (40.7 to 47.9)	46.6 (43.3 to 48.5)	46.4 (43.1 to 49.4)	0.3 (-0.4 to 1.3)	0.46
Cold sensibility index	0.49 (0.36 to 0.61)	0.51 (0.26 to 0.70)	0.61 (0.04 to 0.76)	0.75 (0.14 to 0.80)	0.1 (-0.0 to 0.2)	0.34
Warm sensibility index	0.22 (0.08 to 0.63)	0.20 (0.10 to 0.59)	0.31 (0.07 to 0.70)	0.29 (0.16 to 0.57)	0.0 (-0.1 to 0.1)	0.52
Tactile detection threshold (g)	1.8 (0.6 to 3.6)	1.5 (0.6 to 3.6)	1.2 (1.2 to 8.5)	1.2 (0.7 to 3.6)	0.0 (-1.1 to 0.7)	0.95
Tactile pain detection threshold (g)	13.4 (6.2 to 354.0)	42.2 (4.9 to 281.8)	28.8 (11.7 to 75.9)	75.9 (5.5 to 125.9)	0.0 (-4.1 to 23.9)	0.90
Pressure pain threshold (kPa)	304 (157 to 421)	216 (170 to 437)	263 (213 to 403)	343 (245 to 462)	42.8 (1.0 to 78.5)	0.036
Vibration threshold (µm)	2.4 (1.7 to 75.2)	3.2 (1.2 to 19.3)	2.5 (1.4 to 34.3)	1.8 (1.1 to 33.3)	0.0 (-0.6 to 2.2)	0.88
Temporal summation (No (%))	5 (42)	7 (58)	5/11 (46)	4/11 (36)	—	0.43
Mechanical allodynia (No (%))§	2 (17)	1 (8)	0 (0)	0 (0)	—	—
Cold allodynia (No (%))	5 (42)	3 (25)	5/11 (46)	4/11 (36)	—	1.00
SF-36‡						
Physical functioning	40.0 (20.0 to 58.9)	35.0 (16.3 to 45.0)	30.0 (20.0 to 60.0)	40.0 (25.0 to 55.0)	5.0 (0 to 7.5)	0.06
Role physical	25.0 (0 to 50.0)	25.0 (0 to 93.8)	25.0 (25.0 to 100)	50.0 (25.0 to 100.0)	0 (-25.0 to 12.5)	0.73
Bodily pain	41.0 (22.0 to 62.0)	26.5 (21.3 to 48.5)	42.0 (31.0 to 51.0)	61.0 (42.0 to 74.0)	9.8 (0 to 21.5)	0.037
General health	43.5 (35.0 to 73.3)	46.0 (25.0 to 74.5)	35.0 (27.0 to 62.0)	32.0 (25.0 to 57.0)	0 (-6.0 to 5.0)	0.95
Vitality	42.5 (18.8 to 57.5)	27.5 (16.3 to 58.8)	40.0 (25.0 to 55.0)	35.0 (30.0 to 45.0)	2.5 (-5.0 to 10.0)	0.52
Social functioning	100.0 (62.5 to 100.0)	100.0 (53.1 to 100.0)	75.0 (50.0 to 87.5)	87.5 (75.0 to 100.0)	6.3 (0 to 12.5)	0.17
Mental health	86.0 (72.0 to 95.0)	84.0 (60.0 to 100.0)	72.0 (52.0 to 84.0)	84.0 (68.0 to 88.0)	8.0 (0 to 12.0)	0.023
Role emotional	100.0 (75.0 to 100.0)	100.0 (75.0 to 100.0)	100.0 (66.7 to 100.0)	100.0 (66.7 to 100.0)	0 (-33.0 to 0)	0.46

A=active treatment; P=placebo.

*Hodges-Lehmann estimator.

†No corrections for multiple comparisons.

‡Based on 23 patients (missing data for one patient in placebo-active group).

§Impossible to do planned test.

ous pain intensity from baseline was -1.0 (25th to 75th centiles -1.9 to -0.1) during dronabinol treatment and 0 (-2.0 to 0) during placebo treatment. In the group of patients randomised to placebo in first period the change in pain from baseline was -1.5 (-2.8 to -0.3) during dronabinol treatment and 0 (0 to 0.9) during placebo treatment. The estimated relative difference in pain reduction from baseline between dronabinol and placebo treatments was -20.5% (95% confidence interval -37.5 to -4.5).

Secondary outcome measures

Table 2 shows the secondary outcome measures. Median radiating pain intensity during the last week of treatment was lower during dronabinol treatment than during placebo treatment, and a higher pain relief score was obtained during dronabinol treatment than during placebo treatment. On the basis of pain relief scores, the number of patients that needed to be treated for one additional case of 50% pain relief was 3.45 (95%

confidence interval 1.9 to 24.8). No differences between treatments occurred in period preference, escape medication, or expanded disability status scale score.

The pressure pain threshold was higher after dronabinol treatment than after placebo treatment, but we found no other differences between the groups in results of quantitative sensory tests. On the SF-36, the patients scored slightly higher (better) in the bodily pain and mental health domains during dronabinol treatment than during placebo treatment.

Adverse events

Adverse events were more common during dronabinol treatment than during placebo treatment. During dronabinol treatment 23 (96%) patients had adverse events compared with 11 (46%) patients during placebo treatment (P=0.001) (table 3). During active treatment four (17%) patients had their doses reduced (three patients to 7.5 mg daily and one patient to 5 mg daily) because of intolerable adverse events. All the

Table 3 Adverse events during treatment with dronabinol and placebo. Values are numbers (percentages) of patients with adverse event, number of adverse events

Adverse events	Dronabinol (n=24)	Placebo (n=24)
Central nervous system	19 (79), 61	8 (33), 20
Dizziness or lightheadedness	14 (58)*, 26	4 (17), 5
Tiredness or drowsiness	10 (42), 12	6 (25), 10
Fatigue	1 (4), 2	0 (0), 0
Balance difficulty	2 (8), 2	0 (0), 0
Headache	6 (25), 10	1 (4), 1
Migraine	1 (4), 1	0 (0), 0
Speech disorders	1 (4), 1	0 (0), 0
Feeling of drunkenness	2 (8), 5	0 (0), 0
Sleep difficulty	1 (4), 1	2 (8), 2
Multiple sclerosis aggravated	1 (4), 1	2 (8), 2
Musculoskeletal system	9 (38), 13	2 (8), 2
Myalgia	6 (25), 7	1 (4), 1
Muscle weakness	3 (13), 3	1 (4), 1
Limb heaviness	1 (4), 2	0 (0), 0
Distortion of wrist	1 (4), 1	0 (0), 0
Gastrointestinal disorders	5 (21), 7	4 (17), 8
Mouth dryness	3 (13), 3	0 (0), 0
Nausea	3 (13), 4	4 (17), 5
Abdominal pain	0 (0), 0	1 (4), 3
Cardiovascular disorders	4 (17), 8	2 (8), 4
Palpitations	4 (17), 8	2 (8), 4
Psychiatric disorders	3 (13), 4	1 (4), 1
Euphoria	3 (13), 3	0 (0), 0
Hyperactivity	1 (4), 1	0 (0), 0
Nervousness	0 (0), 0	1 (4), 1
Endocrine disorders	1 (4), 2	0 (0), 0
Hot flushes	1 (4), 2	0 (0), 0
Vision disorders	0 (0), 0	1 (4), 1
Diplopia	0 (0), 0	1 (4), 1
Whole body	4 (17), 5	2 (8), 2
Anorexia	1 (4), 1	0 (0), 0
Weight decrease	1 (4), 1	0 (0), 0
Fever	0 (0), 0	1 (4), 1
Chills	1 (4), 1	0 (0), 0
Upper airway infection	1 (4), 1	1 (4), 1
Tenderness in nose	1 (4), 1	0 (0), 0
Total	23 (96)**, 100	11 (46), 38
Adverse event in first treatment week	21 (88)**†, 50	8 (33), 23
Adverse event in last treatment week	10 (42), 15	5 (21), 7
Severe adverse event	3 (13), 3	1 (4), 1

*P<0.05 versus placebo.

**P<0.01 versus placebo (Mainland-Gart test).

†P<0.01 versus last week of treatment (McNemar test).

others took 10mg daily. No withdrawals occurred. The most common adverse events during dronabinol treatment were related to the central nervous system (dizziness, headache, tiredness) and the musculoskeletal system (myalgia, muscle weakness) (table 3).

Assessment of blinding

Sixteen (67%) of the patients correctly identified the period in which they received active medication. Six (25%) patients identified the wrong period, and two (8%) patients were unable to choose one of the treatments (P = 0.19).

Discussion

Oral dronabinol, at a maximum dose of 10 mg daily, reduced central pain in patients with multiple sclerosis. The primary outcome measure—median spontaneous pain intensity during the last week of treatment—was significantly reduced during dronabinol treatment

What is already known on this topic

Cannabinoids reduce hyperalgesia in animal models of neuropathic, inflammatory, and cancer pain

Evidence from randomised controlled trials of the analgesic effect of cannabinoids in humans is sparse

A recent large study with pain as a secondary outcome measure indicated that cannabinoids may alleviate unspecified pain in multiple sclerosis

What this study adds

Dronabinol has a modest but clear and clinically relevant analgesic effect in multiple sclerosis patients with central pain

The effect size is comparable to that of other treatment options available

Dronabinol should be available for patients whose central pain is not sufficiently treated with alternative drugs such as anticonvulsants, antidepressants, or opioids

compared with placebo. The difference between treatments in pain reduction from baseline was around 21%. The results of the secondary outcome measures supported the finding that dronabinol was superior to placebo in reducing pain, although we made no statistical correction for multiple comparisons.

It could be argued that dronabinol ameliorated pain by a non-specific effect on function other than that directly linked to pain. However, dronabinol did not alter the functional multiple sclerosis disability score during the trial, and on the SF-36 general health profile the only improvements seen were in bodily pain and mental health. These observations suggest that dronabinol had a specific effect on pain.

The definition of central neuropathic pain is vague.²⁶ We included only patients with sensory abnormalities at the maximal pain site, and we did not define spasm related pain as central pain as other authors have.⁷ We instructed all patients throughout the study to assess pain only at the site that was most painful at study start and only that diagnosed as central pain. However, we cannot exclude the possibility that some of the pain reduction was related to a decrease in spasm related pain. In addition, the higher mental health subscore on the SF-36 during dronabinol treatment may indicate that some of the benefit of dronabinol on pain may be due to a central effect.

Whether the small reduction in pain intensity we found is clinically important could be debated. However, the pain reduction seen during treatment with dronabinol in this study is comparable to the effect of other drugs used in the treatment of neuropathic pain.^{29 30}

The number of patients reporting adverse events was higher during dronabinol treatment than during placebo treatment. Previous studies have reported similar adverse events associated with dronabinol,^{25 31–33} although in at least one dronabinol caused no more adverse events than placebo.³⁴ In our study, no patients

stopped their treatment because of adverse events, and only four patients had to reduce their dose.

Conclusion

In this study, oral dronabinol reduced central pain in patients with multiple sclerosis. It should be available as a treatment option to patients whose central pain does not respond adequately to other drugs.

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Competing interests: None declared.

Ethical approval: The study was approved by the regional ethics committee (Aarhus, j.no.20010143), the Danish Medicines Agency (J.no.2612-170), and the Danish Data Protection Agency.

- Archibald CJ, McGrath PJ, Ritvo PG, Fisk JD, Bhan V, Maxner CE, et al. Pain prevalence, severity and impact in a clinic sample of multiple sclerosis patients. *Pain* 1994;58:89-93.
- Clifford DB, Trotter JL. Pain in multiple sclerosis. *Arch Neurol* 1984;41:1270-2.
- Moulin DE, Foley KM, Ebers GC. Pain syndromes in multiple sclerosis. *Neurology* 1988;38:1830-4.
- Rae-Grant AD, Eckert NJ, Bartz S, Reed JF. Sensory symptoms of multiple sclerosis: a hidden reservoir of morbidity. *Mult Scler* 1999;5:179-83.
- Stenager E, Knudsen L, Jensen K. Acute and chronic pain syndromes in multiple sclerosis. *Acta Neurol Scand* 1991;84:197-200.
- Svendsen KB, Jensen TS, Overvad K, Hansen HJ, Koch-Henriksen N, Bach FW. Pain in patients with multiple sclerosis: a population-based study. *Arch Neurol* 2003;60:1089-94.
- Boivie J. Central pain. In: Wall PD, Melzack R, eds. *Textbook of pain*. New York: Churchill Livingstone, 1999:879-914.
- Jaggari SI, Hasnie FS, Sellaturay S, Rice AS. The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. *Pain* 1998;76:189-99.
- Martin WJ, Loo CM, Basbaum AI. Spinal cannabinoids are anti-allodynic in rats with persistent inflammation. *Pain* 1999;82:199-205.
- Bridges D, Ahmad K, Rice AS. The synthetic cannabinoid WIN55,212-2 attenuates hyperalgesia and allodynia in a rat model of neuropathic pain. *Br J Pharmacol* 2001;133:586-94.
- Fox A, Kesingland A, Gentry C, McNair K, Patel S, Urban L, et al. The role of central and peripheral cannabinoid1 receptors in the antihyperalgesic activity of cannabinoids in a model of neuropathic pain. *Pain* 2001;92:91-100.
- Johanek LM, Heitmilller DR, Turner M, Nader N, Hodges J, Simone DA. Cannabinoids attenuate capsaicin-evoked hyperalgesia through spinal and peripheral mechanisms. *Pain* 2001;93:303-15.
- Rukwied R, Watkinson A, McGlone F, Dvorak M. Cannabinoid agonists attenuate capsaicin-induced responses in human skin. *Pain* 2003;102:283-8.
- Richardson JD, Kilo S, Hargreaves KM. Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. *Pain* 1998;75:111-9.
- Kehl LJ, Hamamoto DT, Wacnik PW, Croft DL, Norsted BD, Wilcox GL, et al. A cannabinoid agonist differentially attenuates deep tissue hyperalgesia in animal models of cancer and inflammatory muscle pain. *Pain* 2003;103:175-86.
- Holdcroft A, Smith M, Jacklin A, Hodgson H, Smith B, Newton M, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. *Anaesthesia* 1997;52:483-6.
- Notcutt W, Price M, Chapman G. Clinical experience with nabilone for chronic pain. *Pharm Sci* 1997;3:551-5.
- Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. *Lancet* 1999;353:560.
- Noyes RJ, Brunk SF, Baram DA, Canter A. Analgesic effect of delta-9-tetrahydrocannabinol. *J Clin Pharmacol* 1975;15:139-43.
- Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. *J Clin Pharmacol* 1981;21:320-6S.
- Buggy DJ, Toogood L, Maric S, Sharpe P, Lambert DG, Rowbotham DJ. Lack of analgesic efficacy of oral delta-9-tetrahydrocannabinol in postoperative pain. *Pain* 2003;106:169-72.
- Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin Rehabil* 2003;17:21-9.
- Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial. *Lancet* 2003;362:1517-26.
- Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CF3 on chronic neuropathic pain: a randomized controlled trial. *JAMA* 2003;290:1757-62.
- Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227-31.
- Merskey H, Bogduk N, eds. *Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms prepared by the International Association for the Study of Pain, Task Force of Taxonomy*. Seattle: IASP Press, 1994.
- Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444-52.
- Vestergaard K, Andersen G, Gottrup H, Kristensen BT, Jensen TS. Lamotrigine for central poststroke pain: a randomized controlled trial. *Neurology* 2001;56:184-90.
- Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999;83:389-400.
- Gimbel JS, Richards P, Portenoy RK. Controlled-release oxycodone for pain in diabetic neuropathy: a randomized controlled trial. *Neurology* 2003;60:927-34.
- Clermont-Gnamien S, Atlani S, Attal N, Le MF, Guirimand F, Brasseur L. [The therapeutic use of D9-tetrahydrocannabinol (dronabinol) in refractory neuropathic pain.] *Presse Med* 2002;31:1840-5. (In French.)
- Noyes RJ, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clin Pharmacol Ther* 1975;18:84-9.
- Campbell FA, Tramer MR, Carroll D, Reynolds DJ, Moore RA, McQuay HJ. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. *BMJ* 2001;323:13-6.
- Killestein J, Hoogervorst EL, Reif M, Kalkers NF, Van Loenen AC, Staats PG, et al. Safety, tolerability, and efficacy of orally administered cannabinoids in MS. *Neurology* 2002;58:1404-7.

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Science commentary: High hopes for cannabinoid analgesia

Geoff Watts

Several decades of irrational prejudice may have hampered clinical research on cannabis as a medicine, but work on the pharmacology of its active ingredients has been making steady progress. Just as the body has a natural counterpart to the opiate drugs, so too it makes its own endogenous cannabinoids. These act through receptors, of which two variants—CB₁ and CB₂—have been definitely identified and at least one other is suspected. The CB₁ receptors are located only in the brain; their CB₂ counterparts are found peripherally, and

especially on the cells of the immune system. Cannabinoid receptors are present not just in vertebrates but also in molluscs, leeches, and other invertebrate groups that have been evolutionarily separate for 500 million years. The fact that natural selection has for so long conserved these receptors is an indication of their physiological importance.

Anandamide, the first natural cannabinoid to be isolated, came to light in 1992. Its precise role, and those of the other cannabinoids that have since been

28 New End Square, London NW3 1LS
Geoff Watts
science editor, *BMJ*
geoff@scileg.freeserve.co.uk