Original Article

Cannabis Use in HIV for Pain and Other Medical Symptoms

Emily Woolridge, MB BS, BSc, Simon Barton, MB BS (Distinction), BSc, FRCP (Ed), FRCP (London), Jonathon Samuel, BSc, Jess Osorio, BSc, Andrew Dougherty, BSc, and Anita Holdcroft, MB ChB, MD, FRCA
Magill Department of Anesthesia, Imperial College London (E.W., A.H.), and HIV/GUM Services (S.B., J.S., J.O., A.D.), Chelsea and Westminster Hospital, London, United Kingdom

Abstract
Despite the major benefits of antiretroviral therapy on survival during HIV infection, there is an increasing need to manage symptoms and side effects during long-term drug therapy. Cannabis has been reported anecdotally as being beneficial for a number of common symptoms and complications in HIV infections, for example, poor appetite and neuropathy. This study aimed to investigate symptom management with cannabis. Following Ethics Committee approval, HIV-positive individuals attending a large clinic were recruited into an anonymous cross-sectional questionnaire study. Up to one-third (27%, 143/523) reported using cannabis for treating symptoms. Patients reported improved appetite (97%), muscle pain (94%), nausea (93%), anxiety (93%), nerve pain (90%), depression (86%), and paresthesia (85%). Many cannabis users (47%) reported associated memory deterioration. Symptom control using cannabis is widespread in HIV outpatients. A large number of patients reported that cannabis improved symptom control. J Pain Symptom Manage 2005;29:358–367. *© 2005 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words
Cannabis, HIV, pain, symptoms

Introduction

HIV or AIDS affects over 40 million people in the world[1] and more than 49,500 in the UK.[2] Although there is still no cure available for this disease, remarkable improvements in the survival of HIV-infected individuals have been achieved.[3] This survival has lead to an increasing prevalence of individuals with HIV infection, many on long-term treatment with combinations of antiretroviral therapies. This has increased the clinical focus on the management of chronic symptoms associated with both HIV and the side effects of antiretroviral medication. Recently, in small sample studies of HIV patients, the medicinal use of cannabis has been documented as a treatment for varied symptoms.[4–7]

Symptoms associated with HIV occur as both direct and indirect consequences of the disease process and as a side effect of the antiretroviral drugs used in the treatment of the disease. These symptoms include nausea and vomiting, pain (e.g., in a nerve distribution), reduced appetite, weight loss, headaches, diarrhea, constipation, anxiety, and depression. Flu-like symptoms and severe myalgia can result directly

Address reprint requests to: Anita Holdcroft, MB ChB, Magill Department of Anesthesia, Chelsea and Westminster Hospital, 369 Fulham Road, London SW10 9NH, United Kingdom.

Accepted for publication: July 28, 2004.

© 2005 U.S. Cancer Pain Relief Committee
Published by Elsevier Inc. All rights reserved.

0885-3924/05/$–see front matter
doi:10.1016/j.jpainsymman.2004.07.011

from seroconversion early in the disease. Central pain and peripheral neuropathy can occur as a result of viral-mediated neurotoxicity, secondary to either mitochondrial damage, demyelination, or low B_{12} levels, all of which have been observed in patients with HIV. The inflammation that occurs as a result of the mitochondrial damage can result in HIV-related encephalopathy or HIV-related colitis. Symptoms may also occur secondary to infections or tumors, which have resulted from HIV-related immunosuppression. Examples of this include nausea and dysphagia from esophageal candida, or pain from a gastrointestinal lymphoma. Symptoms commonly occurring as a side effect of HIV treatment include renal colic from nephrolithiasis associated with the protease inhibitor, indinavir; painful peripheral neuropathy from use of stavudine, a nucleoside analogue; or sleep disturbances from the non-nucleoside inhibitor, efavirenz. Thus, a wide range of symptoms can significantly affect the quality of life of individuals living with HIV as a long-term chronic infection.[8,9]

It has been recognized that cannabinoids such as delta-9-tetrahydrocannabinol (THC), which is now available as a licensed pharmaceutical preparation, can improve appetite and relieve nausea and vomiting.[10] Cannabis plant material not only contains THC but also other cannabinoids, such as cannabidiol (CBD), that may mitigate psychotic mood effects of THC.[11]

The aim of this study was to measure the patterns and prevalence of cannabis use in patients presenting at a large HIV clinic and to evaluate its beneficial or detrimental effect on symptom control.

Methods

Subjects

Following Ethics Committee approval, HIV-positive patients were recruited into an anonymous cross-sectional questionnaire survey using a single center. The outpatient clinic provided a walk-in service as well as pre-arranged appointments, including pharmacy and phlebotomy sections. All patients entering the clinic were asked to verbally consent to participate in the study. Written consent was not obtained in order to protect patient anonymity. The number of patients who refused to take part was recorded. Many patients were regular clinic users, had discussed their symptoms with HIV and pain specialists, and were able to distinguish between the various types of pain described on the questionnaire. A researcher was available to answer questions (e.g., on the interpretation of words). Patients completed the questionnaire while waiting and confidentiality was maintained by enumerating the papers without patient identification.

Questionnaire

The questionnaire was piloted to refine its content, word use, and format and then issued to patients attending the clinic. The questionnaire (see Appendix) was designed to contain close-ended questions with defined yes/no or categorical responses. It was divided into sections. The first included demographics (age, sex, number of years with HIV) and a validated scale to measure degree of disability described by Sharrack and Hughes.[12] The second had specific questions concerning the patient's use of cannabis medically to treat symptoms of HIV. These symptoms included those directly related to HIV plus those resulting from their medication. Those who did not use cannabis for medicinal purposes, including those who used it solely for recreation, were not required to continue completing the questionnaire, although their demographic details were recorded. The next section included questions relating to frequency, patterns, and reasons for cannabis use. Then in tabular form, a range of symptoms were listed (Table 1), and against

Table 1
Order of Symptom List in Questionnaire as Scored by Patients for Benefit or Detriment

Lack of appetite
Feeling sick (i.e., nausea)
Tremor
Depression
Anxiety
Weight loss
Weakness
Tiredness
Vision dimness
Slurred speech
Memory loss
Constipation
Headaches
Diarrhea
Pain in muscles
Nerve pain
Tingling
Numbness

each one, the patient was invited to score benefit or detriment as 'much better,' 'little better,' 'unchanged,' 'a little worse,' and 'much worse'. For the symptoms of pain and sensory changes, the questionnaire also contained 'body diagrams', that is, pain maps, so that the patients could mark where they identified their nerve or muscle pain, tingling and numbness.

Analysis

Data from the questionnaires were entered into an Access database (Windows 98 version) and analyzed using the Statistical Package for Social Sciences (SPSS 11.5, SPSS Inc., Chicago). Categorical data comparing the sex differences between the two groups and symptom severity were analyzed using the Fisher's exact test. Because the distribution of age and the number of years with HIV were not normal and had some outliers, the differences in these variables between the two groups were analyzed using the Mann-Whitney U test. Both simple frequency analysis and the sign test were used in assessing the percentage improvement or deterioration in symptoms.

Results

A total of 523 questionnaires were completed from 565 patients approached. This was a 93% response rate. Of those who completed the study, 143 (27%) used cannabis to treat symptoms associated with HIV.

Physical Data

The sex, age, years with HIV, disability, and cannabis user status are shown in Tables 2 and 3. About 1 in 10 patients were female and few were severely disabled in this outpatient setting. Compared with females, males were statistically significantly likely to be cannabis users ($P < 0.01$) and those who had the disease for longer and were more disabled were also more likely to be users ($P < 0.01$).

When nerve pain was reported on the pain map, it was experienced mainly in the legs, and less in the feet and hands (27, 19, and 15 patients, respectively). Muscle pain was predominantly localized to the legs, but also to the lower back, shoulders and neck (46, 19, and 19 patients, respectively). Tingling and numbness was experienced in the periphery, with the hands and feet being affected (34 and 26 patients, respectively).

Patient Choice of Route and Timing for Symptom Control

Of the 143 patients who had used cannabis to treat HIV symptoms, 107 (75%) were current users. Within the whole group, smoking was the single route of administration in 101 (71%), and was combined with eating and drinking the plant in 39 (27%); ingestion was the only route in 3 (2%). On a day that cannabis was used, 50 patients (36%) would take it once, 33 (23%) twice, 23 (16%) three times, and 35 (24%) four or more times. Most patients (79/143 [55%]) were daily users and 15 (11%) used it weekly. Others reported intermittent administration during the week. Thus, all patients reported using cannabis at least once a week to relieve symptoms.

Throughout the day, the majority of patients (91/143 [64%]) took cannabis after 6 p.m. and

Table 2
Demographic Data, Disability Scores, and the Number of Patients Using Cannabis to Treat Symptoms

	Females $n = 43$ (8%)	Males $n = 480$ (92%)	All Subjects $n = 523$
Age (years)[a]	38 [32–43] (20–65)	39 [35–44] (20–69)	39 [35–44] (20–69)
Years with HIV[a]	6 [2–9] (0–18)	9 [4–13] (0–25)	8 [4–13] (0–25)
Disability[b]			
0	12 (28%)	164 (34%)	176 (34%)
1	14 (33%)	136 (28%)	150 (29%)
2	10 (23%)	100 (21%)	110 (21%)
3	4 (9%)	74 (15%)	78 (15%)
4	3 (7%)	5 (1%)	8 (2%)
5	0	1 (0.2%)	1 (0.2%)
Number that used cannabis to treat symptoms	4/43 (9%)	139/480 (29%)	143/523 (27%)

[a]Median [IQR] (range).
[b]0 = none; 1 = mild; 2 = moderate not requiring help from others; 3 = moderate requiring help from others; 4 = severe with almost total loss of function; and 5 = total loss of function.

Table 3
Demographic Differences Between Users and Non-Users of Cannabis for Symptom Control

	Users $n = 143$	Non-Users $n = 380$	Statistical Significance
Males:Females	139:4	341:39	$P < 0.01$
Age[a]	40 [36–44] (26–61)	38 [34–44] (20–69)	$P = 0.046$
Years with HIV[a]	10 [6–15] (0–25)	7 [3–12] (0–20)	$P < 0.01$
No disability:Disability	17:126	159:221	$P < 0.01$

[a]Median [IQR] (range).

before midnight. However, an overlapping group (66/143 [46%]) also reported use at any time if necessary. The reasons for taking the cannabis at these times were reported in a structured format, as detailed in Table 4. A number of reasons related to the time of administration, not least of which was recreational use together with medicinal use. Relief of symptoms of anxiety and depression was common, as was general symptom relief. The reported use for relaxation may reflect the time at which it was taken, namely, during the evening.

Effect on Symptoms

A lack of appetite was the most frequent symptom reported (Table 5) and 97% experienced improvement with cannabis use. Pain was the next most frequent, being present in 45% of patients and improved in 94% of them. The collective results demonstrated statistically significant improvement in half or more patients in symptoms of nausea, anxiety, nerve pain, depression, tingling, numbness, weight loss, headaches, tremor, constipation, and tiredness. Symptoms that were not improved included weakness and slurred speech, and statistically significant memory deterioration was recorded in 47% of users.

Discussion

The demographic characteristics of our cohort of patients (male:female, 11.2:1) is comparable with the UK population of HIV-positive patients, which has a male:female ratio of 11.5:1. In addition, their ages and duration of HIV disease were comparable with the general UK data for such patients.[13] Our sample of 523 patients has the highest response rate and is the largest study of its kind. It compares with previous studies, which have had samples ranging from 72 subjects[7] to 442.[6] This detailed report of cannabis use for symptom control in a clinically significantly large group of patients can form the basis for more extensive investigations using purified and standardized cannabis extracts.

Despite the fact that cannabis is still illegal, its use for medical purposes appears to be quite widespread. A report from the British Medical Association[14] stated "many normally law abiding citizens—probably many thousands in the developed world" use cannabis illegally for therapy. Wesner[15] reported from an anonymous mail survey of 123 HIV-positive patients in Honolulu that 36.9% of them used cannabis for therapeutic reasons. Approximately one-quarter of 228 HIV-positive men in the Sydney Men and Sexual Health study reported therapeutic use of cannabis.[16] Thirty-two percent (32%) of 72 patients at a clinic in Alabama reported the medical use of marijuana.[7] These results are comparable to a more recent study carried out in Northern California, in which 33.3% of HIV-positive patients who responded to an anonymous mailed questionnaire used cannabis to treat symptoms associated with their disease.[6] Our study expanded these findings in a large city clinic population by focusing on the patient's perceived improvement or worsening of symptoms for which cannabis was considered the origin.

The large number of patients using cannabis as medicinal therapy for symptoms related to HIV raises a number of issues. First, patients are being left with no alternative but to use a non-medical source of supply, which has the

Table 4
Reasons for Using Cannabis

Purpose	*n*	%
Treat symptoms	77	54
Aid relaxation	121	85
Reduce anxiety	94	66
Relieve depression	75	52
Reduce symptom frequency	29	20
Increase energy levels	15	11
For a 'high'	62	43

Table 5
Effect of Cannabis on Complaint of Symptoms in 143 HIV Patients

Symptom	Number of Complaints	% Responding					
		Much Better	Little Better	No Change	Little Worse	Much Worse	P-value
Lack of appetite	111	79	18	2	0	1	0.000
Pain in muscles	65	63	31	6	0	0	0.000
Nausea	62	56	37	3	2	*2*	0.000
Anxiety	98	64	29	3	2	2	0.000
Nerve pain	53	51	40	9	0	0	0.000
Depression	94	56	30	9	4	1	0.000
Tingling	46	37	48	9	7	0	0.000
Numbness	42	36	36	24	5	0	0.000
Weight loss	62	45	24	31	0	0	0.000
Headaches	46	35	30	33	2	0	0.000
Tremor	24	37	29	21	13	0	0.004
Constipation	24	21	29	46	4	0	0.003
Tiredness	60	17	33	33	15	2	0.002
Diarrhea	48	13	23	56	6	2	0.007
Vision dimness	22	9	27	55	9	0	0.109
Weakness	48	10	21	54	15	0	0.134
Memory loss	38	13	5	34	34	13	0.043
Slurred speech	9	11	0	78	11	0	1.00

Note: In ranked order of those demonstrating improvement (recorded as % much better, little better) in comparison to those recorded with no change, little worse, or much worse. The *P*-value in the last column is the exact 2-sided *P*-value for the sign test of no change.

potential for heterogeneity of active cannabinoids, toxic contaminants, inappropriate dose, and drug misuse. Second, if part of the plant material has therapeutic efficacy, the source of this material should be standardized and subjected to clinical trials so that safe and effective use is advocated. Third, the patient is unlikely to divulge cannabis use to their medical team, so that potential drug interactions with prescribed antiretroviral medications may be occurring. In addition, in this study, the number of purely recreational users was not determined so that the overall incidence of drug interactions may be far greater. The type of drug interactions to be considered include loss of cognitive function because it is well-recognized that this is an effect of both cannabis[17] and antiretroviral drugs such as efavirenz.[18] Certainly, the loss of memory reported by these patients is of clinical significance, particularly in the methodological design of clinical trials, and if it is the result of combining preparations, this may be investigated using known standardized cannabinoid therapies. This approach may be one way to reduce additive effects and prevent patients being subject to the effects of unpredictable concentrations of illicit drugs.

The positive responses to symptom control recorded in this study, as exemplified in Table 5, suggest that it is highly probable that cannabinoid medications have a medicinal role in this condition for a number of reasons. First, they are reported by patients to improve appetite, reduce weight loss, and alleviate nausea.[19–23] These effects have been recognized and synthetic THC (dronabinol) is licensed for use in the U.S. for this indication. However, no direct comparison has been attempted with a cannabis plant extract that will contain not only THC but also other cannabinoids, of which CBD is reputed to reduce the adverse effects of THC.[24] Secondly, pain relief appears to be significant in cannabis users, thereby suggesting a potential target for investigation in the use of cannabinoids as analgesics in HIV patients.

Patients have reported various forms of pain with HIV, such as muscular and neuropathic pain, and these were characterized in the pain maps drawn by the patients. Currently available analgesic drugs have limited efficacy, particularly for neuropathic pain.[25] Clearly, there is a need to develop alternative analgesic agents, such as cannabinoids, to improve the choice of therapies. There is animal evidence that cannabinoids have analgesic effects that operate in models of hyperalgesia and allodynia, both indicators of neuropathic pain states,[26,27] and the discovery of the endogenous cannabinoid system has led scientists to explore the role of endocannabinoids in chronic pain models.[28,29] However, in clinical practice the choice of natural or synthetic phyto- or endo-cannabinoids for clinical trials is very limited. There have been several anecdotal and clinical trial reports that

cannabis plant extract and synthetic THC and related analogues produce pain relief in humans.[30–33] For this present select group of HIV patients, given the reported symptoms experienced using cannabis plant material, there is a strong concern from the medical community managing these patients to limit adverse side effects from self-administered drugs and to provide cannabinoids in a formulation and dosing schedule that avoids harm to the patient. For example, there is strong evidence that the smoking route of administration of cannabis is not safe long-term because of the carcinogenic properties of a cannabis cigarette.[34]

A pattern of cannabis use emerges from this study that is regular, ongoing, and treats the symptoms of HIV patients to their satisfaction. Given the sedative properties of cannabis, it is important to assess whether evening dosing for cannabinoid therapies is more useful or appropriate. Its sedative effects may be helpful at this time but none were reported as predominant. Presumably there is tolerance to these types of effects.[29] More importantly, reduction of pain, anxiety, and gastrointestinal upset appears to be the constellation of symptom control sought by these HIV patients, as shown in Tables 4 and 5.

In relation to HIV, there have been anecdotal reports[35] of patients who were already recreational users of cannabis reporting that it improved certain symptoms, such as loss of appetite and nausea, as well as pain and general well being. A small, uncontrolled study of 10 symptomatic AIDS patients reported that dronabinol might be effective in reducing nausea and increasing appetite.[10] Where patients are also medicating with antiretroviral agents, the combination of cannabis and protease inhibitors may be detrimental by altering viral loads. Thus, the effect of smoking on the viral load of HIV-infected patients was investigated by a short-term randomized placebo controlled trial.[36] No adverse effects of either therapy were measured with respect to RNA levels, $CD4^+$ and $CD8^+$ cell counts, or protease inhibitor levels. This brief trial suggests that there are no obvious harmful effects, but these need to be determined using an appropriate route of drug administration and a longer-term study.

There is accumulating evidence that suggests that cannabinoids have therapeutic applications in a variety of neurodegenerative diseases, such as multiple sclerosis,[37,38] Huntington's disease,[39] and brain injury.[40] So far, in terms of HIV, the evidence for therapeutic efficacy of cannabinoids is still mainly anecdotal. We have sought to establish if an improvement from cannabis use, albeit self-administered and not standardized, is seen in symptoms such as pain, appetite, and nausea in a large sample of HIV patients. To do this, we expanded on previous research by determining specifically the variety and groups of symptoms that patients select to modify by their use of cannabis. We also secured a therapeutic timetable in order to predict the frequency of drug administration for the patient's selected symptoms. These results will be important in the design of a randomized, placebo-controlled clinical trial comparing conventional treatments to cannabis for symptoms of HIV.

Acknowledgments

The authors thank Dr. Elena Kulinskaya for statistical advice and Dr. Sarah Cox, Dr. Andrew Rice, and the staff at the Kobler Clinic, St. Stephen's Center.

References

1. UNAIDS. Joint United Nations Programme on HIV and AIDS 2003. Available at www.unaids.org/en/resources/epidemiology.asp.

2. ONS, Office of National Statistics. HIV infections: By year of diagnosis and route of transmission 2002. Available at www.statistics.gov.uk/cci/nugget.asp?id=654.

3. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. Lancet 1998;352:1725–1730.

4. Ware MA, Doyle CR, Woods R, Lynch ME, Clark AJ. Cannabis use for chronic non-cancer pain: Results of a prospective survey. Pain 2003;102:211–216.

5. Ware MA, Rueda S, Kilby D, Singer J. Cannabis use among patients with HIV/AIDS: Patterns and prevalence of use. J Cannabis Ther 2003;3:3–15.

6. Sidney S. Marijuana Use in HIV positive and AIDS patients: Results of an anonymous mail survey. In: Russo E, ed. Cannabis therapeutics in HIV/AIDS. The Haworth Press: New York, 2001:35–41.

7. Dansak DA. Medical use of recreational drugs by AIDS patients. J Addict Dis 1997;16:25–30.

8. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. Lancet 2000;356:423–430.

9. Keswani SC, Pardo CA, Cherry CL, et al. HIV-associated sensory neuropathies. AIDS 2002;16: 2105–2117.

10. Plasse TF, Gorter RW, Krasnow SH, et al. Recent clinical experience with dronabinol. Pharmacol Biochem Behav 1991;40:695–700.

11. Leweke FM, Schneider U, Radwan M, et al. Different effects of nabilone and cannabidiol on binocular depth inversion in man. Pharmacol Biochem Behav 2000;66:175–181.

12. Sharrack B, Hughes RA. The Guy's Neurological Disability Scale (GNDS): A new disability measure for multiple sclerosis. Multiple Sclerosis 1999;5:223–233.

13. Public Health Laboratory Report Feb 2003. Available at www.hpa.org.uk/infections/topics_az/hiv_and_sti/hiv/hiv.htm

14. Ashton CH, Holdcroft A, Mars S, et al. Therapeutic uses of cannabis, British Medical Association. The Netherlands: Harwood Academic Publishers, 1997, p. 77.

15. Wesner B. The medical marijuana issue among PWAs: Reports of therapeutic use and attitudes towards legal reform. Working Paper No. 3, Working Paper series. Drug Research Unit, Social Science Research Institute, University of Hawaii. Available at http://www.drugpolicy.org/library/mmwesne.cfm. Accessed June 1996.

16. Prestage GS, Kippax S, Grulich A. Use of treatments and health enhancement behaviours among HIV positive men in a cohort of homosexually active men. XI International Conference on AIDS, Vancouver, BC, Canada, July 1996. Abstract thD 5181.

17. Ameri A. The effects of cannabinoids on the brain. Prog Neurobiol 1999;58:15–48.

18. Bell C, Matthews GV, Nelson MR. Non-nucleoside reverse transcriptase inhibitors—an overview. Int J STD AIDS 2003;14:71–77.

19. Sallan SE, Zinberg NE. Frei E 3rd. Anti-emetic effects of delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. N Engl J Med 1975; 293:795–797.

20. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an anti-emetic in cancer patients receiving high dose methotrexate. Ann Intern Med 1979;91:819–824.

21. Poster DS, Penta JS, Bruno S, Macdonald JS. Delta-9-tetrahydrocannabinol in clinical oncology. JAMA 1981;245:2047–2051.

22. Carey MP, Burish TG, Brenner DE. Delta-9-tetrahydrocannabinol in cancer chemotherapy: Research problems and issues. Ann Intern Med 1983;99: 106–114.

23. Levitt M. Cannabinoids as anti-emetics in cancer chemotherapy. In: Mechoulam R, ed. Cannabinoids as therapeutic agents. Boca Raton, Florida: CRC Press, 1986.

24. Mechoulam R, Parker LA, Gallily R. Cannabidiol: An overview of some pharmacological aspects. J Clin Pharmacol 2002;42:11S–19S.

25. Meyer-Rosberg K, Kvarnstrom A, Kinnman E, et al. Peripheral neuropathic pain—a multidimensional burden for patients. Eur J Pain 2001;5: 379–389.

26. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesia circuit activated by cannabinoids. Nature 1998;395:381–383.

27. Iversen L, Chapman V. Cannabinoids: A real prospect for pain relief? Curr Opin Pharmacol 2002;2:50–55.

28. Rice AS, Farquhar-Smith WP, Nagy I. Endocannabinoids and pain: Spinal and peripheral analgesia in inflammation and neuropathy. Prostaglandins Leukot Essent Fatty Acids 2002;66:243–256.

29. Iversen L. Cannabis and the brain. Brain 2003;126:1252–1270.

30. Noyes R Jr, Brunk SF, Avery DA, Canter AC. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther 1975;18:84–89.

31. Staquet M, Gantt C, Machin D. Effect of a nitrogen analogue of tetrahydrocannabinol on cancer pain. Clin Pharm Ther 1978;23:397–401.

32. Jain AK, Ryan JR, McMahon FG, Smith G. Evaluation of intramuscular levonantradol and placebo in acute postoperative pain. J Clin Pharm 1981;21: 320S–326S.

33. Holdcroft A, Smith M, Jacklin A, et al. Pain relief with oral cannabinoids in familial Mediterranean fever. Anaesthesia 1997;52:483–486.

34. Taylor DR, Hall W. Thoracic Society of Australia and New Zealand. Respiratory health effects of cannabis: Position statement of the Thoracic Society of Australia and New Zealand. Intern Med J 2003; 33:310–313.

35. Randall R. Marijuana, medicine and the law, Vol. II. Washington, DC: Galen Press, 1999.

36. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection. Ann Intern Med 2003;139:258–266.

37. Pryce G, Ahmed Z, Hankey DJ, et al. Cannabinoids inhibit neurodegeneration in models of multiple sclerosis. Brain 2003;126:2191–2202.

38. Wade DT, Robson P, House H, et al. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. Clin Rehabil 2003;17:21–29.

39. Lastres-Becker I, De Miguel R, Fernandez-Ruiz JJ. The endocannabinoid system and Huntington's disease. Curr Drug Target CNS Neurol Disord 2003; 2:335–347.

40. Mechoulam R, Panikashvili D, Shohami E. Cannabinoids and brain injury: Therapeutic implications. Trends Mol Med 2002;8:58–61.