Cannabinoids for Treatment of Chronic Non-Cancer Pain; a Systematic Review of Randomized Trials

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Abstract

Effective therapeutic options for patients living with chronic pain are limited. The pain relieving effect of cannabinoids remains unclear. A systematic review of RCTs examining cannabinoids in treatment of chronic non-cancer pain was conducted according to the PRISMA statement update on the QUORUM guidelines for reporting systematic reviews that evaluate health care interventions. Cannabinoids studied included smoked cannabis, oromucosal extracts of cannabis based medicine, nabilone, dronabinol and a novel THC analog. Chronic non-cancer pain conditions included neuropathic pain, fibromyalgia, rheumatoid arthritis, and mixed chronic pain. Overall the quality of trials was excellent. Fifteen of the eighteen trials that met inclusion criteria demonstrated a significant analgesic effect of cannabinoid as compared to placebo, several reported significant improvements in sleep. There were no serious adverse effects. Adverse effects most commonly reported were generally well tolerated, mild to moderate in severity and led to withdrawal from the studies in only a few cases. Overall there is evidence that cannabinoids are safe and modestly effective in neuropathic pain with preliminary evidence of efficacy in fibromyalgia and rheumatoid arthritis. The context of the need for additional treatments for chronic pain is reviewed. Further large studies of longer duration examining specific cannabinoids in homogeneous populations are required.

1. Introduction

Chronic pain is common, debilitating with too few effective therapeutic options. Cannabinoids represent a relatively new pharmacological option as part of a multimodel treatment plan. With increasing knowledge of the endocannabinoid system [1-3] and compelling preclinical work supporting that cannabinoid agonists are analgesic [4, 5] there is increasing attention on their potential role in the management of pain [6-9]. A previous systematic review done a decade ago identified the need for further randomized controlled trials (RCTs) evaluating cannabinoids in management of chronic pain indicating that there was insufficient evidence to introduce cannabinoids into widespread use for pain at that time [10]. A subsequent review identified a moderately analgesic effect but indicated this may be offset by potentially serious harms [11]. This conclusion of serious harms mentioned in the more recent review is not consistent with our clinical experience. In addition there have been a number of additional RCTs published since this review. We therefore conducted an updated systematic review examining RCTs of cannabinoids in management of chronic pain.

2. Materials and Methods

2.0 We followed the PRISMA update on the QUORUM statement guidelines for reporting systematic reviews that evaluate health care interventions [12].

2.1 Systematic Search

A literature search was undertaken to retrieve Randomized Control Trials (RCT) on the efficacy of cannabinoids in the treatment for chronic pain. The databases searched were: PubMed, Embase, CINAHL (EBSCO), PsycInfo (EBSCO), The Cochrane Library (Wiley), ISI Web of Science, ABI Inform (Proquest), Dissertation Abstracts (Proquest), Academic Search Premier (EBSCO), Clinical Trials.gov, TrialsCentral.org, individual pharmaceutical company trials sites for Eli Lilly and GlaxoSmithKline, OAIster (OCLC), and Google Scholar. None of the searches was limited by language or date and were carried out between September 7 and October 7, 2010. The search retrieved all articles assigned the Medical Subject Headings (MeSH) *Cannabis, Cannabinoids, Cannabidiol, Marijuana Smoking* and *Tetrahydrocannibinol* as well as those assigned the Substance Name *tetrahydrocannabinol-cannabidiol combination*. To this set was added those articles containing any of the keywords *cannabis*, *cannabinoid*, marijuana, marihuana, dronabinol* or *tetrahydrocannibinol*. Members of this set containing the MeSH heading Pain or the title keyword "*pain*" were passed through the "Clinical Queries: therapy/narrow" filter to arrive at the final results set. For the pain aspect, the phrase "*Chronic pain*" along with title keyword "*pain*" was used to retrieve the relevant literature. We contacted authors of original reports to obtain additional information. Bibliographies of included articles were checked for additional references.

2.2 Inclusion and exclusion criteria

Included were RCTs comparing a cannabinoid with a placebo or active control group where the primary outcome was pain in subjects with chronic non-cancer pain. Relevant pain outcomes included any scale measuring pain for example the numeric rating scale for pain (NRS), visual analog scale for pain (VAS), the Neuropathy Pain Scale or the

McGill Pain Scale. We excluded (a) trials with fewer than 10 participants, (b) trials reporting on acute or experimental pain or pain caused by cancer, (c) preclinical studies and (d) abstracts, letters and posters where the full study was not published.

2.3 Data extraction and validity scoring

One author (ML) did the initial screen of abstracts, retrieved reports and excluded articles that clearly did not meet the inclusion criteria. Both authors independently read the included articles and completed an assessment of the methodological validity using the modified 7-point, 4-item Oxford scale [13, 14] (Figure 1). After reading the complete articles it was clear that several additional papers did not meet inclusion criteria and these were excluded. Discrepancies on the quality assessment scale were resolved by discussion. Trials that did not include randomization were not included and a score of 1 on this item of the Oxford scale was required and the maximum score was seven.

Information about the specific diagnosis of pain, agent and doses used, pain outcomes, secondary outcomes (sleep, function, quality of life), summary measures, trial duration and adverse events was collected. Information on adverse events was collected regarding serious adverse events, drug related withdrawals and most frequently reported side effects. A serious adverse event according to Health Canada and ICH[1] guidance documents is defined as any event that results in death, is life threatening, requires prolonged hospitalization, results in persistent of significant disability or incapacity or results in congenital anomaly or birth defects [15].

2.4 Data analysis

Quantitative meta-analysis with pooling of data from the eligible RCTs was proposed.

3. Results

3.1 Trial Flow

Eighty abstracts were identified of which 58 did not meet inclusion criteria on the initial review of records (Fig 2). Twenty two RCTs comparing a cannabinoid with either a placebo or active control group where pain was listed as an outcome were found and full text articles were reviewed, four further studies were excluded, two because pain was not the primary outcome (Zajicek), one because there were fewer than 10 participants in the study (Rintala). A further study was excluded because there were two studies reporting on what appeared to be the same group of participants (Salim, Karst), in this case we included the first study in which the pain outcomes were reported (Karst). References of the included trials were reviewed for additional trials meeting inclusion criteria. This revealed no further studies. Eighteen trials met the study criteria for inclusion. We did not retrieve any unpublished data. Given the different cannabinoids, regimens, clinical conditions, different follow up periods, and outcome measures used in these trials, pooling of data for meta-analysis was inappropriate. Results were therefore summarized qualitatively.

[1] International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use

3.2 Primary Outcome - Efficacy

Eighteen trials published between 2003 and 2010 involving a total of 766 completed participants met inclusion criteria (Table 1). The quality of the trials was very good with a mean score of 6.1 on the 7 point modified Oxford scale. The majority (fifteen trials) demonstrated a significant analgesic effect for the cannabinoid agent being investigated. Several trials also noted significant improvements in sleep [16-19].Treatment effects were generally modest, mean duration of treatment was 2.8 weeks (range 6 hours-6 weeks) and adverse events were mild and well tolerated.

3.2.2 Cannabis

Four trials examined smoked cannabis as compared with placebo; all examined populations with neuropathic pain, two involved neuropathic pain in HIV neuropathy [16, 20-22]. All four trials found a positive effect with no serious adverse effects. The median treatment duration was 8.5 days treatment (range 6 hours-14 days).

3.2.3 Oromucosal extracts of cannabis based medicine (CBM)

Seven placebo controlled trials examined CBM [17-19, 23-25]. Five examined participants with neuropathic pain, one rheumatoid arthritis and one a mixed group of people with chronic pain many of whom had neuropathic pain. Six of the seven trials demonstrated a positive analgesic effect. Of note in the one trial examining pain in rheumatoid arthritis, the CBM was associated with a significant decrease in disease activity as measured by the 28 joint disease activity score (DAS28) [18].

3.2.4 Nabilone

Four trials studied nabilone [26-29]. Three of these trials were placebo controlled and found a significant analgesic effect in spinal pain [29], fibromylagia [27] and spasticity related pain [28]. The fourth compared a daily dose of nabilone 2 mg with dihydrocodeine 240 mg in neuropathic pain. Mean baseline pain was 69.6 mm on the 100 mm VAS and dropped to 59.93 mm for participants taking nabilone and 58.58 mm for those taking dihydrocodeine [26].

3.2.5 Dronabinol

Two trials involved dronabinol. The earlier trial found that dronabinol 10 mg per day led to significant reduction in central pain in multiple sclerosis [30], a subsequent trial found that dronabinol at both 10 and 20 mg per day led to significantly greater analgesia and better relief than placebo as adjuvant treatment for a group of participants with mixed diagnoses of chronic pain on opioid therapy [31] .

3.2.6 THC-11-oic acid analog (CT-3 or ajulemic acid)

Two studies reported on various aspects of this trial examining ajulemic acid in a group of participants with neuropathic pain with hyperalgesia or allodynia [32, 33]. 19 of 21 completed the trial. It was found that ajulemic acid led to significant improvements in pain intensity at 3 hours but no difference at 8 hours as compared with placebo.

3.3 Secondary Outcome - Level of Function

Several trials included secondary outcome measures relating to level of function. Two trials examining cannabis based medicines included the Pain Disability Index (PDI) [19, 25]. Nurmikko found that 6 of 7 functional areas assessed by the PDI demonstrated significant improvement on CBM (-5.61) as compared with placebo (0.24) (estimated mean difference-5.85, P=0.003) in 125 participants with neuropathic pain while Berman noted no significant difference from placebo in 48 participants with central pain from brachial plexus avulsion. Two studies included the Barthel index for activities of daily living (ADL)[23, 28] and noted no significant improvement in ADLs with nabilone for spasticity related pain [28] or with CBMs for multiple sclerosis [23]. In one trial examining nabilone in treatment of fibromyalgia the FIQ [34] demonstrated significant improvement as compared to placebo. This measure includes a number of questions regarding function in several areas including shopping, meal preparation, ability to do laundry, vacuum, climb stairs and ability to work. The FIQ also includes questions relating to pain, fatigue, stiffness and mood. The total scores presented in this study were not presented separately so the reader cannot be certain; however given that the majority of questions relate to function it is likely that there were some improvements in function.

3.4Drug related adverse effects

There were no serious adverse events according to the Health Canada definition described above and in Table 1, The most common adverse events consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration. Other adverse events included poor coordination, ataxia, headache, paranoid thinking, agitation, dissociation, euphoria and dysphoria. Adverse effects were generally described as well tolerated, transient or mild to moderate and not leading to withdrawal from the study. This is a significant difference from the withdrawal rates seen in studies of other analgesics such as opioids where the rates of abandoning treatment are in the range of 33% [35]. Except where specifically noted in the Table there was no specific mention of whether adverse effects caused limitations in function. The most severe treatment related event in the entire sample was a fractured leg related to a fall that was thought to be related to dizziness [29]. Details regarding specific trials are presented in Table 1.

4. Discussion

4.1 Efficacy and harm

All of the trials included in this review were conducted since 2003; no trials prior to this date satisfied our inclusion criteria. This review has identified 18 trials that taken together have demonstrated a modest analgesic effect in chronic non-cancer pain; 15 of these were in neuropathic pain with 5 in other types of pain 1 in fibromyalgia, 1 in rheumatoid arthritis 1 as an adjunct to opioids in patients with mixed chronic pain and 2 in mixed chronic pain. Several trials reported significant improvements in sleep. There were no serious adverse events. Drug related adverse effects were generally described as well tolerated, transient or mild to moderate and most commonly consisted of sedation, dizziness, dry mouth, nausea and disturbances in concentration.

4.2 Limitations

The main limitations to our findings are short trial duration, small sample sizes and modest effect sizes. Thus there is a need for larger trials and for longer duration so that efficacy and safety, including potential for abuse, can be examined over the long term in a greater number of patients. It is also important to recognize that cannabinoids may only reduce pain intensity to a modest degree. It remains for the patients to decide whether this is clinically meaningful.

4.3 The context of chronic pain

Pain is poorly managed throughout the world. Eighty percent of the world population has no or insufficient access to treatment for moderate to severe pain [36]. Chronic pain affects approximately one in five people in the developed world [37-41] and two in five in less well resourced countries [42]. Children are not spared [43, 44] and the prevalence increases with age [38, 45]. The magnitude of the problem is increasing. Many people with diseases such as cancer, HIV and cardiovascular disease are now surviving their acute illness with resultant increase in quantity of life, but in many cases, poor quality of life due to persistent pain caused either by the ongoing illness or nerve damage caused by the disease after resolution or cure of the disease. In many cases the pain is also caused by the treatments such as surgery, chemotherapy or radiotherapy needed to treat the disease [46-48].

Chronic pain is associated with the worst quality of life as compared with other chronic diseases such as chronic heart, lung or kidney disease [45]. Chronic pain is associated with double the risk of suicide as compared to those living with no chronic pain [49],.

In this context, patients living with chronic pain require improved access to care and additional therapeutic options. Given that this systematic review has identified 18 RCTs demonstrating a modest analgesic effect of cannabinoids in chronic pain that are safe, we conclude that it is reasonable to consider cannabinoids as a treatment option in the management of chronic neuropathic pain with evidence of efficacy in other types of chronic pain such as fibromyalgia and rheumatoid arthritis as well. Of special importance is the fact that two of the trials examining smoked cannabis [20, 21] demonstrated a significant analgesic effect in HIV neuropathy, a type of pain that has been notoriously resistant to other treatments normally used for neuropathic pain [47]. In the trial examining cannabis based medicines in rheumatoid arthritis a significant reduction in disease activity was also noted, this is consistent with pre-clinical work demonstrating that cannabinoids are anti-inflammatory [50, 51].

5. Conclusion

In conclusion this systematic review of 18 recent good quality randomized trials demonstrates that cannabinoids are a modestly effective and safe treatment option for chronic non-cancer (predominantly neuropathic) pain. Given the prevalence of chronic pain, its impact on function and the paucity of effective therapeutic interventions, additional treatment options are urgently needed. More large-scale trials of longer duration reporting on pain and level of function are required.

Conflict of Interest Statement The authors have no conflict of interest.

References

1. Rice ASC, Farquhar-Smith WP, Nagy I. Endocannabinoids and pain: spinal and peripheral analgesia in inflammation and neuropathy. Prostaglandins, Leuktrienes and Essential Fatty Acids 2002; 66: 243-56.
2. Watson SJ, Benson JA, Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine Report. Arch Gen Psychiatry 2000; 57: 547-52.
3. Nicoll RA, Alger BE. The brain's own marijuana. Scientific American 2004; 291(6): 68-75.
4. Hohmann AG, Suplita RL. Endocannabinoid mechanisms of pain modulation. AAPS J 2006; 8(4) Article 79: (http://www.aapsj.org E693-708.
5. Guindon J, Hohmann AG. The endocannabinoid system and pain. CNS Neurol Disorder Drug Targets 2009; 8: 403-21.
6. Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB2 receptorsand the endocannabinoid systemfor the treatment of pain. Brain Res Rev 2008; 60: 255-66.
7. Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain:from the bench to bedside. Neurotherapeutics 2009; 6: 713-37.
8. Guindon J, Hohmann AG. Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain. Br J Pharm 2008; 153: 319-34.
9. Pertwee R. Emerging strategies for exploiting cannabinoid receptor agonists as medicines. Br J Pharm 2009; 156: 397-411.
10. Campbell FA, Tramer MR, Carroll D, Reynolds JM, Moore RA. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. B M J 2002; 323: 1-6.
11. Martin-Sanchez E, Furukawa TA, Taylor J, Martin JLR. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Medicine 2009; 10: 1353-68.
12. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ionnidis JPA, CLarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate health care interventions:explanation and elaboration. J Clin Epidemio 2009; 62: e1-e34.
13. Jadad AR, Moore RA, Carroll D. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Control Clin Trials 1996; 17: 1-12.
14. Elia N, Tramer MR. Ketamine and postoperative pain-a quantitative systematic review Pain 2005; 113: 61-70.
15. Health Canada adopted ICH Guidance :Good Clinical Practice Guidelines. In, edCanada H, 1997: 9
16. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, Gamsa A, Bennett G, Collett JP. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ 2010; 182: 1515-21.
17. Rog DJ, Nurmikko TJ, Friede T, Young AC. Randomized controlled trial of cannabis based medicine in central pain due to multiple sclerosis. Neurology 2005; 65: 812-19.

18. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology 2006; 45: 50-52.
19. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomized controlled trial. Pain 2004; 112: 299-306.
20. Abrams D, Jay CA, Shade SB, Vizoso H, Reda H, Press S, Kelly ME, Rowbotham MC, Peterson KL. Cannabis in painful HIV-associated sensory neuropathy, a randomized controlled trial. Neurology 2007; 68: 515-21.
21. Ellis R, Toperoff W, Vaida F, ven den Brande G, Gonzales J, Gouaux B, Bentley H, Atkinson JH. Smoked medicinal cannabis for neuropathic pain in HIV:a randomized, crossover, clinical trial. Neuropsychopharm 2009; 34: 672-80.
22. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, Fishman S. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. J Pain 2008; 9: 506-21.
23. Wade DT, Makela P, Robson P, House H, Bateman C. 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. Mutiple Sclerosis 2004; 10: 434-41.
24. 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 Rehabilitation 2003; 17: 21-29.
25. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterized by allodynia: a randomized, double-blind, placebo controlled clinical trial. Pain 2007; 133: 210-20.
26. Frank B, Serpell MG, Hughes J, Matthews NS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomised, crossover, double blind study. BMJ 2008; 336: 199-201.
27. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain 2008; 9: 164-73.
28. Wissell J, Haydn T, Muller JE, Schelosky LD, Brenneis C, Berger T, Poewe W. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-rleated pain. J Neurol 2006; 253: 1337-41.
29. Pinsger M, Schimetta W, volc D, Hiermann E, Riederer F, Polz W. Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain-a randomized controlled trial. Wein klin Wochenschr 2006; 118: 327-35.
30. Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ 2004; 329(7460): 253.Epub 2004 Jul 16.
31. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain 2008; 9: 254-64.
32. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain. JAMA 2003; 290: 1757-62.

33. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology 2005; 48: 1164-71.
34. Bennett R. The Fibromyalgia Impact Questionnaire (FIQ): a review of its development, current version, operating characteristics and uses. Clin Exp Rheumatol 2005; 23: S154-S62.
35. Furlan AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain:meta-analysis of effectiveness and side effects. CMAJ 2006; 174: 1589-94.
36. Lohman D, Schleifer R, Amon JJ. Access to pain treatment as a human right. BMC Medicine 2010; 8:8: http:/www.biomedcentral.com/1741-7015/8/8.
37. Blyth FM, March LM, Brnabic AJ, Jorm LR, Williamson M, Cousins MJ. Chronic pain in Australia: a prevalence study. Pain 2001; 89: 127-34.
38. Moulin D, Clark AJ, Speechly M, Morley-Forster P. Chronic pain in Canada, prevalence, treatment, impact and the role of opioid analgesia. Pain Res Manage 2002; 7: 179-84.
39. Eriksen J, Jensen MK, Sjogren P, Ekholm O, Rasmusen NK. Epidemiology of chronic non-malignant pain in Denmark. Pain 2003; 106: 221-28.
40. Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life and treatment. Eur J Pain 2006; 10: 287-333.
41. Huijer Abu-Saad H. Chronic pain: a review. J Med Liban 2010; 58: 21-27.
42. Tsang A, vonKorff M, Lee S, Alonso J, Karam E, Angermeyer MC, al. e. Common chronic pain conditions in developed and developing countries:gender and age differences and comorbidity with depression-anxiety disorders. The Journal of Pain 2008; 9: 883-91.
43. Stanford EA, Chambers CT, Biesanz JC, Chen E. The frequency, trajectories and predictors of adolescent recurrent pain: A population based approach. Pain 2008; 138: 11-21.
44. Stinson JN, McGrath PJ. Measurement and assessment of pain in pediatric patients. In: Clinical Pain Management: A Practical Guide, edsLynch ME, Craig KD, Peng PWH, Oxford, UK: Blackwell Publishing Ltd. , 2011: 64-71.
45. Schopflocher D, Jovey R, Taenzer P. The Burden of Pain in Canada, results of a Nanos Survey. Pain Res Manage 2010: In Press.
46. McGillion M, L'Allier PL, Arthur H, Watt-Watson J, Svorkdal N, Cosman T, Taenzer P, Nigam A, Malysh L. Recommendations for advancing the care of Canadians living with refractory angina pectoris: A Canadian Cardiovascular Society position statement. Can J Cardiol 2009; 25: 399-401.
47. Phillips TJC, Cherry CL, Moss PJ, Rice ASC. Painful HIV-associated sensory neuropathy. Pain Clinical Updates 2010; XVIII 1-8.
48. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment of cancer pain. Ann Oncology 2008; 19: 1985-91.
49. Tang N, Crane C. Suicidality in chronic pain: review of the prevalence, risk factors and psychological links. Psychol Med 2006; 36: 575-86.

50. Baker CL, McDougall JJ. The cannabinomimetic arachidonyl-2-chloroethylamide (ACEA) acts on capsaicin-sensitive TRPV1 receptors but not cannabinoid receptors in rat joints
. Br J Pharm 2004; 142: 1361-67.
51. McDougall JJ, Yu V, Thomson J. In vivo effect of CB2 receptor selective cannabinoids on the vasculature of normal and arthritic rat knee joints
. Br J Pharm 2008; 153: 358-66.

Figure 1

Modified Oxford Scale

Validity score (0-7)

Randomisation

0 None
1 Mentioned
2 Described and adequate

Concealment of allocation

0 None
1 Yes

Double blinding

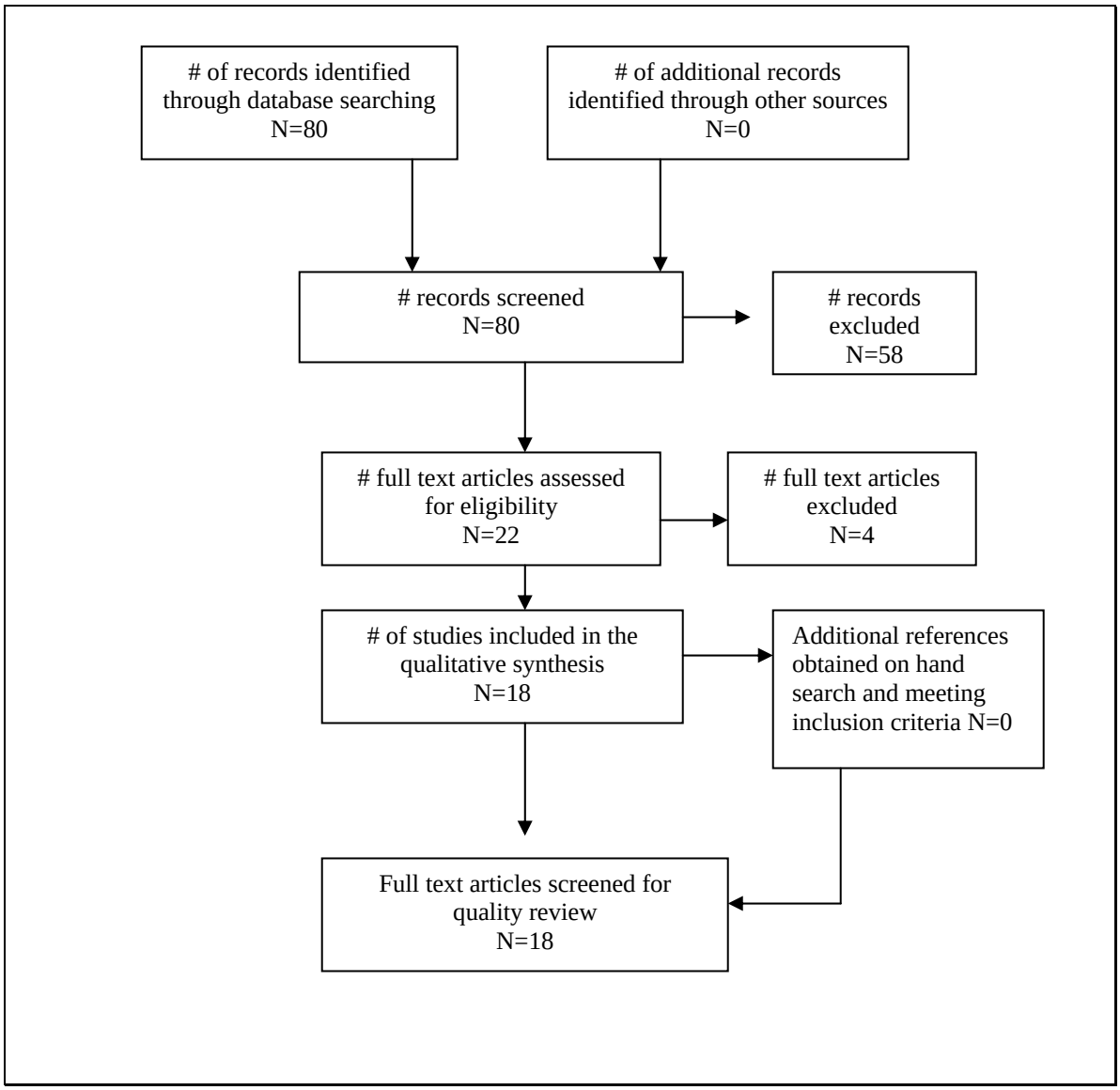
0 None
1 Mentioned
2 Described and adequate

Flow of patients

0 None
1 Described but incomplete
2 Described and adequate

Figure 2

Flow Diagram of Systematic Review



Randomized Controlled Trials Examining Cannabinoids in Treatment of Chronic Non-Cancer Pain

Author and date	Agent (control group)	Population (N) completed/randomized *design*	Core outcomes*	Summary measures used	Oxford scale score	Duration of RCT	Results (brief comments)	AEs**	Outcome summary
Ware, 2010	Cannabis smoked 0%, 2.5%, 6%, 9.4% (Placebo)	Neuropathic pain 21/23 *crossover*	NRS Pain Leeds sleep POMS	Difference in means	7	14 day treatment periods	Significantly lower average daily pain intensity on 9.4% THC (5.4) than 0% (6.1) Improved sleep No change mood	No serious AEs (Headache Dry eyes Burning sensation Dizziness Numbness Cough)	+
Ellis (2009)	Cannabis smoked 1-8% (Placebo)	HIV neuropathy 28/34 *crossover*	DDS pain McGill VAS pain POMS	Median difference pain intensity change	6	5 day treatment periods	Pain reduction significantly greater with cannabis than placebo median difference in pain reduction=3.3 DDS points, effect size =0.60 Also proportion achieving >30% reduction greater for active 0 .46 vs placebo 0.18 NNT 3.5 for 30% reduction	No serious AEs 2 participants experienced treatment limiting side effects most common AEs Decreased concentration Reduced salivation Fatigue sleepiness Sedation	+
Frank, (2008)	Nabilone 2 mg (dihydrocodeine) 240 mg	Chronic neuropathic pain 96 *crossover*	VAS pain Hamilton depression SF-36	Difference in means	7	6 weeks	Both agents resulted in approximately a 10 mm reduction in a 0-100 mm VAS pain Baseline 69.6 mm Nabilone 59.6 Dihydrocodeine 58.58 with dihydrocodeine providing marginally better pain relief	No serious AEs Tiredness, Sleepiness sickness	+/-
Narang (2008)	Dronabinol 10, 20 mg (placebo)	Chronic pain on opioids 29/30 *crossover*	NRS pain intensity and pain relief	Difference in average pain intensity and total pain relief	7	1 day each treatment RCT 4 week open extension	Dronabinol at both doses significantly less pain and greater relief than placebo SPID -6.4 placebo, 10 mg (-17.4, p<01) , 20 mg (-19.7, p<.01) TOTPAR placebo (31.1), 10 mg (39.7, p<0.5) 20 mg (41.7, p<0.01 in both the RCT and the extension	No serious AEs Drowsiness Sleepiness Dizziness Dry mouth	+

Wilsey (2008)	**Cannabis smoked 7.7%, 3.5% (placebo)**	**Neuropathic pain 38/44 *crossover***	**VAS pain intensity Pain relief PGIC**	**Difference in mean pain**	**7**	**6 hour sessions**	**Cannabis both doses significantly less pain and pain unpleasantness (combined 3.5 and 7% cannabis vs placebo differences per minute -0.0035, 95% P=.016)**	**No serious AEs or withdrawals Feeling high Stoned Impaired greater with high dose, side effects stated to be relatively inconsequential**	**+**
Skrabek (2008)	**Nabilone 0.5-1 mg bid (placebo)**	**Fibromyalgia 40 *parallel group***	**VAS pain FIQ**	**Difference in means**	**6**	**4 weeks treatment**	**Significant decrease in 10 cm VAS pain (-2.04, P< .02), total FIQ (-12.07, P<.02) and 10 point FIQ anxiety (-1.67,P<.02) with nabilone vs placebo**	**3 withdrew due to side effects Dizziness Disorientation Nausea Poor coordination Drowsiness Dry mouth Vertigo Ataxia Headache**	**+**
Abrams (2007)	**Cannabis smoked 3.56% (placebo)**	**HIV sensory neuropathy 50/55 *parallel group***	**VAS pain**	**Difference in Median daily pain ratings**	**7**	**5 day inpatient 7 day outpatient**	**Significant reduction in pain with cannabis vs placebo Median reduction in pain was 34% (17% placebo) >30% relief 52% (vs 24%) NNT=3.6**	**All side effects were mild and included Anxiety Sedation Disorientation Paranoia Confusion Dizziness Nausea**	**+**
Nurmikko (2007)	**Cannabis based medicine THC/CBD (placebo)**	**Neuropathic pain with allodynia 125 *crossover***	**NRS pain PGIC PDI HQ-12 Sleep NRS NPS**	**Mean change VAS pain**	**7**	**5 weeks plus open label extension option**	**Significantly less pain with Sativex vs placebo Mean change of -1.48 sativex vs -0.52 P a 22% reduction On sativex 26% had 30% reduction and 20% a 50% reduction vs P 15% and 8% NNT 8.5 (50%) 8.6 (30%) Secondary outcomes also improved – sleep, NPS, PGIC Open label extension showed initial pain relief maintained without dose**	**18% withdrew on sativex vs 3% on placebo No serious AEs by definition below Most described as mild Dizziness Nausea Fatigue Dry mouth But 7 in sativex group and 5 in placebo group graded them as "severe" Paranoid thinking was reported in 1 patient while on Sativex**	**+**

							escalation or toxicity for 52 weeks		
Wissel (2006)	**Nabilone 1mg/day (placebo)**	**Spasticity related pain in UMNS 11/13** ***crossover***	**11-point box test** **Ashworth scale for spasticity Motor ADLs**	**Difference in median pain**	**3**	**4 week treatment periods**	**Significant decrease in spasiticty related pain with reduction of median 2 points with Nabilone vs placebo but no significant change in spasticity according to Ashworth scale or motor or ADL**	**2 patients withdrew 1 due to a relapse felt not to be related to the nabilone the other due to leg weakness rest described as mild Drowsiness (2) Slight weakness legs (1)**	+
Pinsger (2006)	**Nabilone 0.25-1 mg/day (placebo)**	**Chronic pain (spinal) 30** ***crossover***	**VAS pain intensity Cohen QOL**	**Difference in median pain**	**3**	**4 week treatment periods**	**Significant decrease in spinal pain intensity (0.6) (0.0) P=0.006 on nabilone vs placebo**	**# leg after fall possibly related to dizziness caused by interaction of nabilone with concurrent meds during crossover Fatigue Dry mouth Dizziness**	+
Rog (2005)	**Cannabis based medicine THC/CBD (9.6 sprays/day 2-25) (placebo)**	**Central pain in MS 64/66** ***parallel group***	**NRS pain and sleep HADS PGIC NPS**	**Differences in mean intensity pain**	**7**	**4 week**	**Significant reductions in pain (NRS, NPS) and sleep disturbance (NRS) with CBM 3.85 vs placebo 4.96 NNT=3.7 NNH=5.13 No significant changes in blood pressure, weight, hematology, blood chemistry**	**No serious AEs 2 AEs led to withdrawal from trial (agitation and paranoia) Dizziness Somnolence Dissociation Dry mouth Nausea Weakness**	+
Blake (2006)	**Cannabis based medicine mean dose 5.4 sprays/day (placebo)**	**Rheumatoid arthritis 58** ***parallel group***	**NRS pain, sleep SF-MPQ DAS28**	**Differences in means**	**4**	**5 weeks**	**Significant improvements in pain on movement (difference mean/median= 0.95 ,P=0.04 at rest, 1.04,P=0.01,quality of sleep1.17,P=0.02, DAS28 , 0.76, P=0.002,and SF-MPQ, 3.00, P=0.30 with CBM vs placebo)**	**No serious AEs No treatment related withdrawals All mild to moderate Dizziness Lightheaded Dry mouth Nausea 2 noted severe constipation**	+

								Fall (2 patients)	
Berman (2004)	**Cannabis based medicine THC/CBD, THC 8 sprays/day (placebo)**	**Neuropathic pain brachial plexus avulsion 48 *crossover***	**NRS pain BS-11 for sleep quality SF-MPQ PDI**	**Difference in means**	**7**	**2 week treatment periods extension**	**Statistically significant reductions in pain (NRS) and sleep disturbance (NRS) but not to the full 2 point reduction (ie reduction of .58, P=0.005 and.64, P=0.002)**	**No serious AEs 1 drug related withdrawal feeling faint The rest mild-moderate and resolved spontaneously Dizziness Somnolence Bad taste**	**+/-**
Svendsen (2004)	**Dronabinol 10 mg (placebo)**	**Central pain in MS (24) *crossover***	**NRS pain Pain relief SF36**	**Difference in median**	**7**	**3 weeks**	**Significant reductions in pain (NRS) modest reductions 1 point on a 0-10 point scale NNT for 50% relief=3.45**	**Dizziness Headache Tiredness Myalgia Muscle weakness Dose reduction resolved the AEs in the 4 who experienced"intolerable level" of the AE 4 experienced aggravation of MS 1 during drug treatment 2 during placebo 1 during wash out**	**+**
Wade (2004)	**Cannabis based medicines HC/CBD (placebo)**	**MS 160 where 37 had pain as target symptom *parallel group***	**VAS pain spasticity, spasms, bladder problems, tremor**	**Difference in means**	**6**	**6 weeks**	**No significant difference in pain scores (VAS) between CBM and placebo all decreased *There was a significant reduction in spasticity (VAS) scores***	**Dizziness** Fatigue Headache Disturbance in attention Application site discomfort Mouth ulceration**	**_**
Karst (2003)	**CT-3 Synthetic analog of THC-11-oic acid (placebo)**	**Neuropathic pain with hyperlagesia or allodynia 19/21 *crossover***	**VAS pain Pain felief**	**Differences in means**	**7**	**1 week treatment periods**	**Significant improvement in pain intensity 3 hours after study drug (-11.54 or 9.86, p=.02) ‡ difference between CT-3 and P abated by 8 hours No significant change pain relief**	**No serious AEs 1 withdrawal from excessive drowsiness Tiredness Dizziness Dry mouth Decreased concentration Sweating**	**+**
Notcutt (2004)	**Cannabis based medicine THC CBD**	**Chronic pain 24 of 34 *"N of 1"* 2 week open/RCT 1 week Rx periods X 2**	**VAS pain for 2 worst pain symptoms**	**Difference in medians**	**4**	**2 one week treatment periods or each agent**	**Significant reduction in pain (VAS) for THC and THC;CBD Cumulative VAS (median,**	**No serious AEs 1 withdrawal due to medication AE Dry mouth**	**+**

	THC/CBD (placebo)	**for each CBME *crossover***	**BDI GHQ Sleep**				**interquartile range for worst pain Placebo 5.9 (2.8-7.3) CBD 5.45 (3.6-7.4) THC 4.63 (1.74-6.06) THC;CBD 4.4 (2.6-5.8 (p<0.001) 9/24 had a reduction of >50%with THC or THC:CBD**	**Drowsiness Euphoria/dysphoria Vasovagal episode on initial dosing**	
Wade (2003)	**Cannabis based medicine THC CBD THC/CBD (placebo)**	**Neurogenic symptoms in MS/spinal cord injury/brachial plexus injury/limb amputation 24 *"N of 1"* where 12 had target symptom of pain *crossover***	**VAS pain Intoxication Alertness Appetite Happiness etc**	**Difference in means**	**7**	**2 week study periods**	**Difference in mean VAS pain between CBM and placebo = 10.3 for CBD, 10.1 for THC , P=0.05** **Significant reductions in pain CBD and THC but not the combination**	**3 Withdrawals 1 Vasovagal 1 Intoxication 1 Psychoactive effects marked Hypotension if given too quickly Diarrhea Sleepiness Sore mouth**	+

***Examples:**

Pain: NRS, VAS other scale

- At least 50% pain reduction
- At least 30% pain reduction
- Patient global impression
- Other key measures, sleep,

****** side effects were for the whole group

****Adverse events:**

Note serious adverse events defined by :

- results in death
- is life threatening
- requires or prolongs inpatient hospitalization
- results in persistent or significant disability or incapacity
- results in congenital anomaly or birth defects

Clinical Research in Canada; Edition; January 1, 2006, Book 11; Section title; Guidance for Industry, Clinical Safety Data Management:Definitions and Standards for Expedited Reporting (ICH-E2A);;definition is on page 3 of this section, under the heading of "Serious Adverse Event or Adverse Drug Reaction"

DDS=descriptor differential scale, ratio scale 24 words describe pain 0-20
PGIC=patient global impression of change
POMS=profile of mood states
PDI=Pain Disability Index
HADS=Hospital anxiety and depression scale
SF-MPQ=McGill Pain Questionnaire, short form
DAS28=28 joint disease activity score
UMNS=Upper Motor Neuron Syndrome
TOTPAR=total pain relief
SPID=sum pain intensity difference
‡ the larger difference in the group receiving CT-3 first
BDI=Beck Depression Inventory
GHQ=General Health Questionnaire

Modified Oxford Scale

Validity score (0-7)

Randomisation

0 None
1 Mentioned
2 Described and adequate

Concealment of allocation

0 None
1 Yes

Double blinding

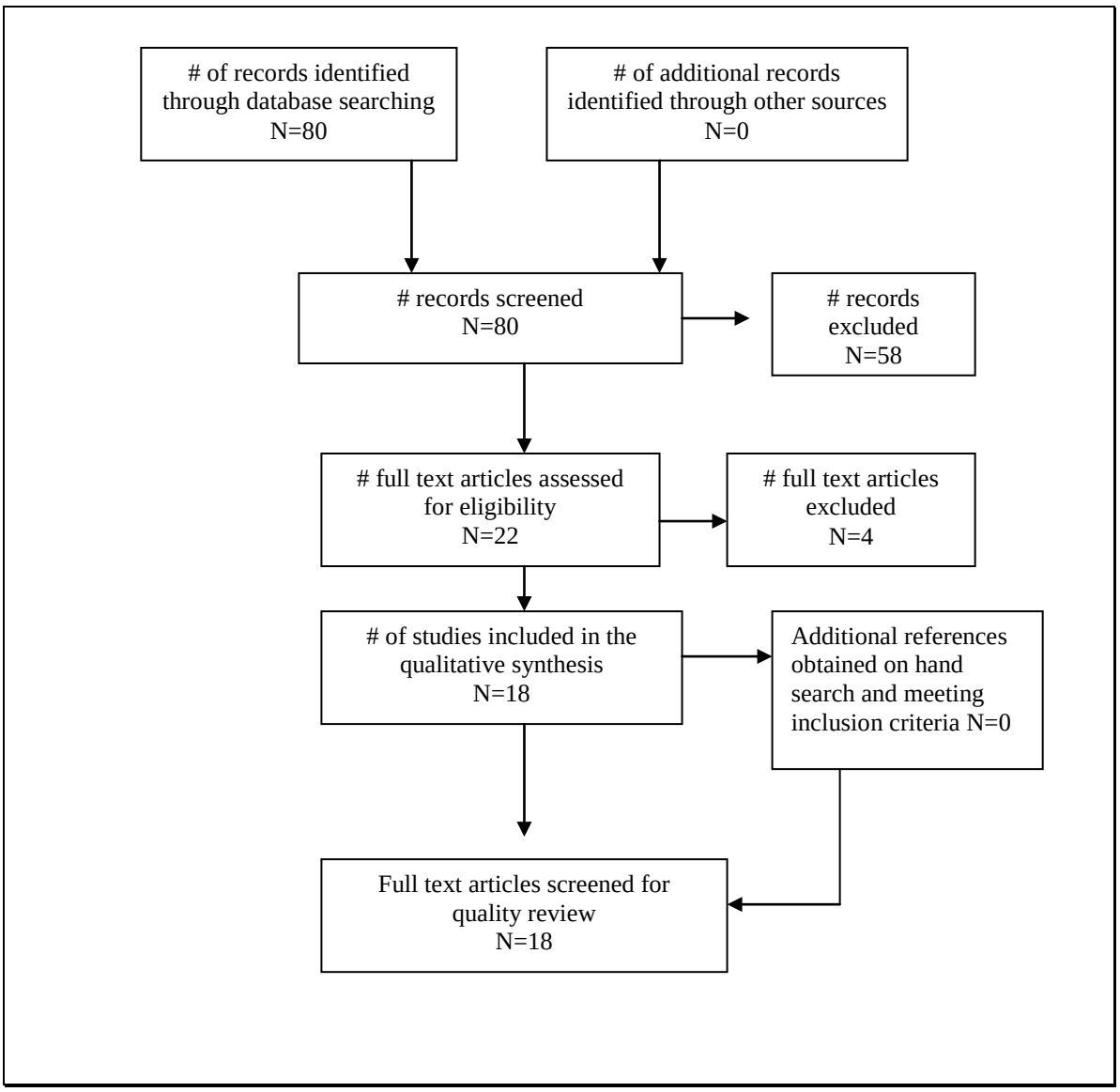
0 None
1 Mentioned
2 Described and adequate

Flow of patients

0 None
1 Described but incomplete
2 Described and adequate

f1

Flow Diagram of Systematic Review



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