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Are cannabinoids an effective treatment for chronic non-cancer pain?

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Abstract

The use of cannabinoids has been proposed as an analgesic for different painful conditions, especially for chronic pain refractory to usual treatment. However, its real efficacy and safety remains controversial. We sought to determine whether cannabinoids are an effective treatment for chronic non-cancer pain. To answer this question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others. We identified 37 systematic reviews including 41 studies overall, of which 32 were randomized trials relevant for the question of interest. We extracted data from the systematic reviews, reanalyzed data of primary studies, conducted a meta-analysis and generated a summary of findings table using the GRADE approach. We concluded it is not clear whether cannabinoids decrease pain in patients with chronic non-cancer pain because the certainty of available evidence is very low. On the other hand, they are associated with significant adverse effects.

Problem

Cannabis has been used for centuries for recreational and therapeutic purposes for various conditions, including pain. However, since the United Nations 1961 Single Convention on Narcotic Drugs, *Cannabis* has seen a worldwide ban and its use has been limited. Despite this, research on its therapeutic use led to the discovery of the endocannabinoid receptors CB1 and CB2, which through a mechanism associated with G protein would have an effect on pain reduction. Since many patients with different causes of chronic pain remain symptomatic despite standard therapy, it has been proposed that the use of *Cannabis sativa* plant extracts with its active ingredients delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), or its analogues, could be of use. Several studies have delved into this premise with different results and have revealed several associated adverse effects, ranging from gastrointestinal and neurological to psychiatric symptoms, with cannabinoids' clinical utility still unproven. Given this scenario, we sought to determine whether cannabinoids constitute an effective treatment for chronic non-cancer pain.

Methods

To answer the question, we used Epistemonikos, the largest database of systematic reviews in health, which is maintained by screening multiple information sources, including MEDLINE, EMBASE, Cochrane, among others, to identify systematic reviews and their included primary studies. We extracted data from the identified reviews and reanalyzed data from primary studies included in those reviews. With this information we generated a structured summary using a pre-established format, which includes

key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages

- It is not clear whether cannabinoids decrease pain in patients with chronic non-cancer pain because the certainty of the available evidence is very low.
- The use of cannabinoids is associated with a high rate of adverse events in patients with chronic non-cancer pain.
- Multiple ongoing studies or high-quality systematic reviews reanalyzing existing data could provide more certainty about these findings.

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found 37 systematic reviews reported in 38 references [1],[2],[3],[4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24],[25],[26],[27],[28],[29],[30],[31],[32],[33],[34],[35],[36],[37],[38] which include 41 primary studies reported in 85 references [39],[40],[41],[42],[43],[44],[45],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[57],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[71],[72],[73],[74],[75],[76],[77],[78],[79],[80],[81],[82],[83],[84],[85],[86],[87],[88],[89],[90],[91],[92],[93],[94],[95],[96],[97],[98],[99],[100],[101],[102],[103],[104],[105],[106],[107],[108],[109],[110],[111],[112],[113],[114],[115],[116],[117],[118],[119],[120],[121],[122],[123] of which 32 correspond to randomized controlled trials comparing cannabinoids against placebo, reported in 72 references [39],[40],[42],[43],[44],[46],[47],[48],[49],[50],[51],[52],[53],[54],[55],[56],[58],[59],[60],[61],[62],[63],[64],[65],[66],[67],[68],[69],[70],[72],[75],[76],[77],[78],[79],[80],[83],[84],[85],[86],[87],[88],[90],[91],[92],[93],[94],[96],[97],[98],[99],[100],[101],[102],[103],[104],[105],[106],[108],[109],[110],[113],[114],[115],[116],[117],[118],[119],[120],[121],[122],[123]. This table and the summary in general are based on the latter.
What types of patients were included*	Of the 32 trials comparing cannabinoids versus placebo, nine included patients with central neuropathic pain [43],[58],[76],[78],[79],[87],[108],[113],[115], nine included patients with multiple sclerosis [42],[54],[77],[93],[102],[104],[106],[119],[122], four included patients with diabetic neuropathy [61],[97],[103],[110], two included patients with HIV neuropathy [39],[56], two included patients with undifferentiated peripheral neuropathic pain [99],[114], one included patients with fibromyalgia [100], one included patients with musculoskeletal pain [90], one included patients with undifferentiated chronic non-cancer pain [85], one included patients with neurological pain of undifferentiated origin [86], one included patients with rheumatoid arthritis [46] and one included patients with pain associated with spasticity [117].
What types of interventions were included*	Cannabinoids extracted from Cannabis sativa (THC, CBD and combinations) and synthetic cannabinoids (nabilone and ajulemic acid) were used as interventions via different routes of administration. Twelve used nabiximol (Sativex®, THC and CBD) in oromucosal spray [42],[43],[46],[61],[77],[79],[86],[87],[93],[97],[99],[106], six used oral nabilone [58],[90],[100],[103],[104],[117], five used smoked THC [39],[54],[56],[113],[115], three used dronabinol (oral THC) [85],[102],[119], three used oral THC combined with CBD [108],[119],[122], two used oromucosal THC spray [43],[110], one used oral ajulemic acid [76], one used oral CBD [78] and one used vaporized THC [114].
What types of outcomes were measured	The main outcome was significant pain reduction (≥ 30%) assessed on visual-analogue scale, 11 points numerical scale or neuropathic pain scale. Other outcomes evaluated were pain reduction ≥ 50%, quality of life and presence of gastrointestinal, central nervous system and psychiatric adverse effects, among others.

* The information about primary studies is extracted from the systematic reviews identified, unless otherwise specified.

Summary of findings

Information on the effects of cannabinoids for pain reduction ≥ 30% is based on 15 randomized trials involving 1,788 patients [39],[43],[56],[76],[77],[79],[86], [87],[93],[97],[99],[101],[113], [114],[115]. The other trials did not report any outcome of interest, or did not present the information in a way it could be incorporated in a meta-analysis. Information on adverse effects is based on a systematic review [37] assessing the adverse effects of cannabinoids in different populations, and includes 3,489 patients in 29 trials reporting this outcome. The summary of findings is as follows:

- It is not clear whether cannabinoids decrease pain in patients with chronic non-cancer pain because the certainty of available evidence is very low.
- The use of cannabinoids is associated with a high rate of adverse events. The certainty of the evidence is high.

Cannabinoids for chronic non-cancer pain

Patients Adults with chronic non-cancer pain
Intervention Cannabinoids
Comparison Placebo

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of the evidence (GRADE)
	WITHOUT cannabinoids	**WITH cannabinoids**		
	Difference: patients per 1000			
Pain reduction ≥ 30%	302 per 1000	384 per 1000	RR 1.27 (1.12 a 1.44)	⨁◯◯◯[1,2] Very low
	Difference: 82 patients more per 1000 (Margin of error: from 36 to 133 more)			
Adverse effects	619 per 1000	831 per 1000	OR 3.03 (2.42 a 3.8)	⨁⨁⨁⨁ High
	Difference: 212 patients more per 1000 (Margin of error: from 178 to 242 more)			

RR= Risk ratio.
OR: Odds ratio
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article)

* The risk **WITHOUT cannabinoids** is based on the risk in the control group of the trials. The risk **WITH cannabinoids** (and its margin of error) is calculated from relative effect (and its margin of error)

[1] One level of certainty of evidence was decreased since the risk of bias reported in included studies is high.
[2] Two levels of certainty of evidence were reduced due to publication bias verified in the funnel plot and because the studies with greater weight [61], [77] delivered conclusions different from those reported by the meta-analysis.

Follow the link to access the interactive version of the Summary of Findings (iSoF) table

About the certainty of the evidence (GRADE)*

⨁⨁⨁⨁
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⨁⨁⨁◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate

⨁⨁◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⨁◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called 'quality of the evidence' or 'confidence in effect estimates'.
† Substantially different = a large enough difference that it might affect a decision.

Other considerations for decision-making

To whom this evidence does and does not apply

- This evidence applies to adults with chronic non-cancer pain.

About the outcomes included in this summary

- Critical outcomes for decision-making in this clinical scenario were included, according to the opinion of the authors of this summary. These coincide with those presented in most of the identified reviews, and the main guidelines.
- We did not include in the summary of findings table information regarding pain reduction ≥50% because the conclusions would not have changed (RR 1.69 [CI 0.97 to 2.94]) and the very low certainty of the evidence.

Balance between benefits and risks, and certainty of the evidence

- It is not possible to make an adequate risk/benefit balance because the certainty of the evidence on the effects of cannabinoids for the treatment of chronic non-cancer pain is very low. Since adverse effects are frequent, the risk/benefit balance probably does not favor their use in these patients.

Resource considerations

- Cannabinoids are generally expensive. In the case of synthetic cannabinoids, the cost is usually very high. In the case of *Cannabis*, there are high costs associated to production, regulation and distribution.

What would patients and their doctors think about this intervention

- Existing evidence should lead most patients and physicians to exercise caution in using this intervention. However, given the connotation of natural medicines and Cannabis in particular, it is likely that some clinicians and patients might favor its use despite the information provided in this summary.

Differences between this summary and other sources

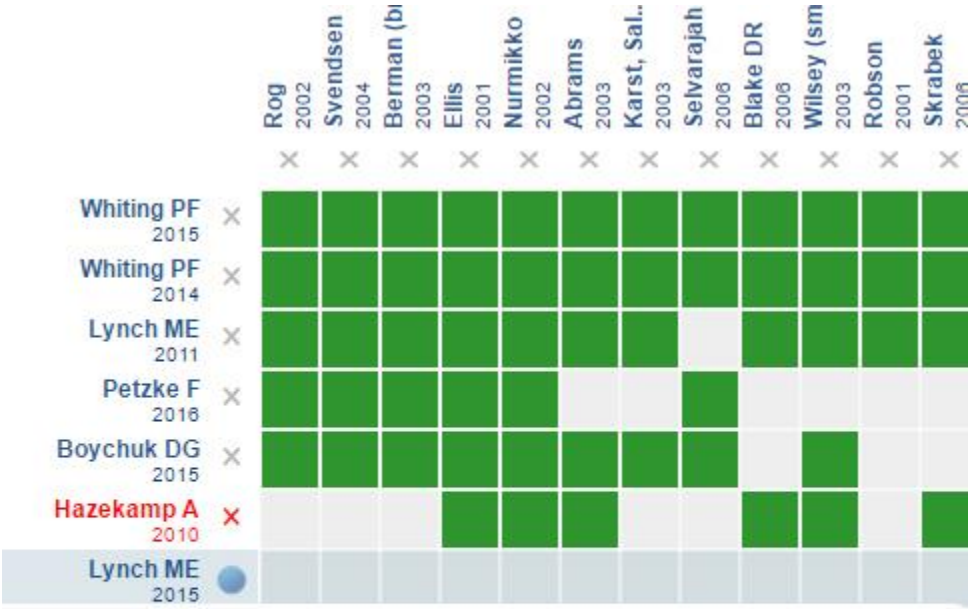
- The conclusions of this summary agree with several systematic reviews included [4],[7],[9],[10],[13],[14],[15],[17],[34]. Others were more optimistic about cannabinoids' analgesic effect [1],[5],[19],[22],[23],[24],[27],[30],[33],[36],[37], and three claim there is moderate quality evidence to support its use [24],[36],[37]. An old systematic review completely disregards the prescription of cannabinoids [35], while others discourage its use based on its adverse effects profile despite admitting its analgesic effect [2],[8],[25].
- There are at least two clinical guidelines [124],[125] that are consistent with the results of this summary stating there is low certainty evidence to provide sound conclusions. On the other hand, there are neuropathic pain clinical guidelines that consider cannabinoids as second line analgesics [126], third line analgesics [127], after failure of other options [128], as adjuvant analgesics [129] or as an alternative to consider in patients with multiple sclerosis [132]. A chronic pain guideline considers cannabinoids as an analgesic after failure of other options [130], and a fibromyalgia guideline considers them as an option in patients with sleep problems [131].

Could this evidence change in the future?

- The likelihood that the conclusions of this summary about the benefits of cannabinoids in patients with chronic non-cancer pain change with future evidence is high given the very low certainty of the evidence.
- There are at least three primary studies [133],[134],[135] not included in any systematic review so far evaluating the analgesic effect of cannabinoids in patients with chronic non-cancer pain. We were also able to identify at least eight ongoing studies [136],[137],[138], [139],[140], [141],[142],[143] that could provide relevant clinical information.
- Multiple ongoing primary studies and high quality systematic reviews reanalyzing existing data could provide more certainty to conclusions.

How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.



Starting from any systematic review, Epistemonikos builds a matrix based on existing connections in the database.
The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question.
The *rows* represent systematic reviews that share at least one primary study, and *columns* display the studies.
The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the **interactive version:** Cannabinoids for chronic non-cancer pain

Notes

The upper portion of the matrix of evidence will display a warning of "new evidence" if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrices and to receive automated notifications any time new evidence potentially relevant for the question appears.

The details about the methods used to produce these summaries are described here http://dx.doi.org/10.5867/medwave.2014.06.5997.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest
The authors do not have relevant interests to declare.

References

1. Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled Cannabis for Chronic Neuropathic Pain: A Meta-analysis of Individual Patient Data. J Pain. 2015 Dec;16(12):1221-32 | CrossRef | PubMed |
2. Bagshaw SM, Hagen NA. Medical efficacy of cannabinoids and marijuana: a comprehensive review of the literature. J Palliat Care. 2002 Summer;18(2):111-22 | PubMed |

3. Ben Amar M. Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol. 2006 Apr 21;105(1-2):1-25 | PubMed |
4. Boychuk DG, Goddard G, Mauro G, Orellana MF. The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review. J Oral Facial Pain Headache. 2015 Winter;29(1):7-14 | CrossRef | PubMed |
5. Burns TL, Ineck JR. Cannabinoid analgesia as a potential new therapeutic option in the treatment of chronic pain. Ann Pharmacother. 2006 Feb;40(2):251-60 | PubMed |
6. Cannabinoids for the management of neuropathic pain: review of clinical effectivenes. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2010 Jul 13. | Link |
7. Campbell FA, Tramèr 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 Jul 7;323(7303):13-6 | PubMed |
8. Correa D, Moreno C. Systematic review of the literature: tratment for central pain in multiple sclerosis. Acta neurol. colomb. 2009;25(1):4 - 15. | Link |
9. Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: Systematic review of randomized controlled trials. Can Fam Physician. 2015 Aug;61(8):e372-81 | PubMed |
10. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162-73 | CrossRef | PubMed |
11. Finnerup NB, Otto M, McQuay HJ, Jensen TS, Sindrup SH. Algorithm for neuropathic pain treatment: an evidence based proposal. Pain. 2005 Dec 5;118(3):289-305 | PubMed |
12. Finnerup NB, Sindrup SH, Jensen TS. The evidence for pharmacological treatment of neuropathic pain. Pain. 2010 Sep;150(3):573-81 | CrossRef | PubMed |
13. Fitzcharles MA, Baerwald C, Ablin J, Häuser W. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): A systematic review of randomized controlled trials. Schmerz. 2016 Feb;30(1):47-61 | CrossRef | PubMed |
14. Fitzcharles MA, Ste-Marie PA, Häuser W, Clauw DJ, Jamal S, Karsh J, et al. Efficacy, Tolerability, and Safety of Cannabinoid Treatments in the Rheumatic Diseases: A Systematic Review of Randomized Controlled Trials. Arthritis Care Res (Hoboken). 2016 May;68(5):681-8 | CrossRef | PubMed |
15. Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2005-2009. Cannabinoids. 2010;5(special issue):1-21.
16. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin. 2007 Jan;23(1):17-24 | PubMed |
17. Jawahar R, Oh U, Yang S, Lapane KL. A systematic review of pharmacological pain management in multiple sclerosis. Drugs. 2013 Oct;73(15):1711-22 | CrossRef | PubMed |
18. Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2014 Apr 29;82(17):1556-63 | CrossRef | PubMed |
19. Kowal MA, Hazekamp A, Grotenhermen F. Review on clinical studies with cannabis and cannabinoids 2010-2014. Cannabinoids. 2016;11(special issue):1-18. | Link |
20. Landry T, Fitzcharles MA, Ste-Marie P, Shir Y. Efficacy and safety of cannabinoid treatments in the rheumatic diseases: A systematic review of randomized controlled trials. Journal of Rheumatology. 2015;42(7):1320. | Link |
21. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. Br J Clin Pharmacol. 2011 Nov;72(5):735-44 | CrossRef | PubMed|
22. Lynch ME, Ware MA. Cannabinoids for the Treatment of Chronic Non-Cancer Pain: An Updated Systematic Review of Randomized Controlled Trials. J Neuroimmune Pharmacol. 2015 Jun;10(2):293-301 | CrossRef | PubMed |
23. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009 Nov;10(8):1353-68 | CrossRef | PubMed|
24. Meng H, Johnston B, Englesakis M, Moulin DE, Bhatia A. Selective Cannabinoids for Chronic Neuropathic Pain: A Systematic Review and Meta-analysis. Anesth Analg. 2017 May 19. | CrossRef | PubMed |
25. Merlin JS, Bulls HW, Vucovich LA, Edelman EJ, Starrels JL. Pharmacologic and non-pharmacologic treatments for chronic pain in individuals with HIV: a systematic review. AIDS Care. 2016 Dec;28(12):1506-1515 | PubMed |
26. Petzke F, Enax-Krumova EK, Häuser W. [Efficacy, tolerability and safety of cannabinoids for chronic neuropathic pain: A systematic review of randomized controlled studies]. Schmerz. 2016 Feb;30(1):62-88 | CrossRef | PubMed |
27. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: a systematic review and meta-analysis of randomised controlled trials. PLoS One. 2010 Dec 28;5(12):e14433 | CrossRef | PubMed |
28. Richards BL, Whittle SL, Buchbinder R. Neuromodulators for pain management in rheumatoid arthritis. Cochrane Database Syst Rev. 2012 Jan 18;1:CD008921 | CrossRef | PubMed |
29. Schröder S, Beckmann K, Franconi G, Meyer-Hamme G, Friedemann T, Greten HJ, et al. Can medical herbs stimulate regeneration or neuroprotection and treat neuropathic pain in chemotherapy-induced peripheral neuropathy? Evid Based Complement Alternat Med. 2013;2013:423713 | CrossRef | PubMed |

30. Seneca MJ. Meta-Analysis of Herbal Cannabis Therapy for Chronic Pain. Thesis. University of North Florida1 2014. Web. 8 Jun 2017 | Link |
31. Snedecor SJ, Sudharshan L, Cappelleri JC, Sadosky A, Mehta S, Botteman M. Systematic review and meta-analysis of pharmacological therapies for painful diabetic peripheral neuropathy. Pain Pract. 2014 Feb;14(2):167-84 | CrossRef | PubMed |
32. Torres MC, Farré M. Efficacy and tolerability of placebo and cannabinoids in multiple sclerosis. Thesis. Universitat Autònoma de Barcelona, 2015. Web. 19 May 2017 | Link |
33. Tsang CC, Giudice MG. Nabilone for the Management of Pain. Pharmacotherapy. 2016 Mar;36(3):273-86 | CrossRef | PubMed |
34. Walitt B, Klose P, Fitzcharles MA, Phillips T, Häuser W. Cannabinoids for fibromyalgia. Cochrane Database Syst Rev. 2016 Jul 18;7:CD011694 | CrossRef | PubMed |
35. WCB Evidence Based Practice Group. Efficacy of marijuana in treating chronic non cancer pain: a short review. Richmond: WorkSafe BC, 2006. Web. 19 May 2017 | Link |
36. Whiting P, Wolff R, Westwood M, Duffy S, Misso K, Keurentjes C, et al. Systematic review of cannabis for medical use. Kleijnen Systematic Reviews Ltd. 2014. | Link |
37. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. JAMA. 2015 Jun 23-30;313(24):2456-73 | CrossRef | PubMed |
38. Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals (Basel). 2012 May 21;5(5):529-52 | CrossRef | PubMed |
39. Abrams DI , Jay CA , Vizoso H, Shade SB, Reda H, Press S. Smoked cannabis therapy for HIV-related painful peripheral neuropathy: results of a randomized, placebo-controlled clinical trial. Paper presented at: IACM 3rd Conference on Cannabinoids in Medicine; September 9-10, 2005; Leiden, the Netherlands. | Link |
40. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. Neurology. 2007 Feb 13;68(7):515-21 | PubMed |
41. Berlach DM, Shir Y, Ware MA. Experience with the synthetic cannabinoid nabilone in chronic noncancer pain. Pain Med. 2006 Jan-Feb;7(1):25-9 | PubMed |
42. Berman J, Bosworth T, Guy G, Stott C. Sativex in the treatment of central neuropathic pain due to spinal cord injury: a randomised controlled study. Paper presented at: British Pain Society Annual Scientific Meeting; April 2007; Glasgow: United Kingdom. | Link |
43. Berman J, Lee J, Cooper M, et al. Efficacy of two cannabis-based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Paper presented at: Pain Society Annual Meeting; April 1-4, 2003; Glasgow, United Kingdom. Anaesthesia. 2003;58(9):938 | CrossRef |
44. 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 randomised controlled trial. Pain. 2004 Dec;112(3):299-306 | PubMed |
45. Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68 | CrossRef | PubMed |
46. 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 (Oxford). 2006 Jan;45(1):50-2 | PubMed |
47. Brigham and Women's Hospital; Solvay Pharmaceuticals. Study to evaluate the efficacy of dronabinol (Marinol) as add-on therapy for patients on opioids for chronic pain.ClinicalTrials.gov | Link |
48. Cambridge Laboratories Ltd. A randomised, crossover, double blind comparison of the analgesic effect and patient tolerability of nabilone and dihydrocodeine in chronic neuropathic pain. ISRCTN Registry | CrossRef | Link |
49. Center for Medicinal Cannabis Research. Effects of smoked marijuana on neuropathic pain. ClinicalTrials.gov | Link |
50. Center for Medicinal Cannabis Research. Efficacy of inhaled cannabis in diabetic painful peripheral neuropathy. ClinicalTrials.gov | Link |
51. Center for Medicinal Cannabis Research. Marijuana for HIV-related peripheral neuropathy. ClinicalTrials.gov | Link |
52. Center for Medicinal Cannabis Research. Medicinal cannabis for painful HIV neuropathy. ClinicalTrials.gov | Link |
53. Center for Medicinal Cannabis Research. Short-term effects of medicinal cannabis therapy on spasticity in multiple sclerosis. ClinicalTrials.gov. | Link |
54. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. CMAJ. 2012 Jul 10;184(10):1143-50 | CrossRef | PubMed |
55. Corey-Bloom J, Wolfson TJ, Anthony GC, Bentley H, Gouaux B. Short-term effects off medicinal cannabis on spasticity in multiple sclerosis. Neurology. 2008;70(11)(suppl 1):A86-A87 | Link |
56. Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. Neuropsychopharmacology. 2009 Feb;34(3):672-80 | CrossRef | PubMed |
57. Fitzcharles MA, Shir Y, Joseph L, Ware MA. The effects of nabilone on insomnia in fibromyalgia: results of a randomized controlled trial. Paper presented at: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting (ACR/ARHP 09); November 6-11, 2009; Atlanta: GA. Arthritis Rheum. 2009;60:1429 | Link |
58. Frank B, Serpell MG, Hughes J, Matthews JN, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic

pain: randomised, crossover, double blind study. BMJ. 2008 Jan 26;336(7637):199-201 | CrossRef | PubMed |
59. Gesellschaft fuer klinische Forschung e.V. Multiple Sclerosis and Extract of Cannabis (MUSEC): a randomised, double-blind, placebo-controlled phase III trial to determine the efficacy and safety of a standardised oral extract of cannabis sativa for the symptomatic relief of muscle stiffness and pain in multiple sclerosis. EU Clinical Trials Register | Link |
60. GW Pharma Ltd. A double blind, randomised, placebo controlled parallel group study of cannabis based medicine extract (CBME), in the treatment of peripheral neuropathic pain characterised by allodynia. ISRCTN Registry | CrossRef | Link |
61. GW Pharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex in the treatment of subjects with pain due to diabetic neuropathy. EU Clinical Trials Register | Link |
62. GW Pharma Ltd. A double blind, randomised, placebo controlled, parallel group study of Sativex, in the treatment of subjects with peripheral neuropathic pain associated with allodynia. EU Clinical Trials Register | Link |
63. GW Pharmaceuticals Ltd. A study of cannabis based medicine extracts and placebo in patients with pain due to spinal cord injury. ClinicalTrials.gov | Link |
64. GW Pharmaceuticals Ltd. A study of sativex in the treatment of central neuropathic pain due to multiple sclerosis. ClinicalTrials.gov | Link |
65. GW Pharmaceuticals Ltd. A study of sativex® for pain relief due to diabetic neuropathy. ClinicalTrials.gov | Link |
66. GW Pharmaceuticals Ltd. A study of Sativex® for pain relief of peripheral neuropathic pain, associated with allodynia. ClinicalTrials.gov | Link |
67. GW Pharmaceuticals Ltd. A study of sativex® for relief of peripheral neuropathic pain associated with allodynia. ClinicalTrials.gov. | Link |
68. GW Pharmaceuticals Ltd. A study to evaluate the effects of cannabis based medicine in patients with pain of neurological origin. ClinicalTrials.gov | Link |
69. GW Pharmaceuticals Ltd. An investigation of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in multiple sclerosis patients. ClinicalTrials.gov | Link |
70. GW Pharmaceuticals Ltd. Sativex versus placebo when added to existing treatment for central neuropathic pain in MS. ClinicalTrials.gov | Link |
71. Hamann W, di Vadi PP. Analgesic effect of the cannabinoid analogue nabilone is not mediated by opioid receptors. Lancet. 1999 Feb 13;353(9152):560 | PubMed |
72. Hobart JC, Zajicek JP. Cannabis as a symptomatic treatment for MS: Clinically meaningful MUSEC to the stiffness and walking problems of people with MS. Paper presented at: 28th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; October 10-13, 2012; Lyon: France. Mult Scler. 2012; 18(4 suppl 1):247. | PubMed |
73. 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 May;52(5):483-6 | PubMed |
74. Huggins JP, Smart TS, Langman S, Taylor L, Young T. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. Pain. 2012 Sep;153(9):1837-46 | CrossRef | PubMed |
75. Institut fur Klinische Forschung Germany; Weleda AG. Multiple Sclerosis and Extract of Cannabis (MUSEC) study. ClinicalTrials.gov | Link |
76. Karst M, Salim K, Burstein S, Conrad I, Hoy L, Schneider U. Analgesic effect of the synthetic cannabinoid CT-3 on chronic neuropathic pain: a randomized controlled trial. JAMA. 2003 Oct 1;290(13):1757-62 | PubMed |
77. Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcutt W, et al. A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis. J Neurol. 2013 Apr;260(4):984-97 | CrossRef | PubMed |
78. Lindstrom P, Lindblom U, Boreus L. Lack of effect of cannabidiol in sustained neuropathia. Paper presented at: International Conference on Cannabis; September 2–4, 1987; Melbourne: Australia. | Link |
79. Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. J Pain Symptom Manage. 2014 Jan;47(1):166-73 | CrossRef | PubMed |
80. Mary Lynch, Capital District Health Authority Canada. Sativex for treatment of chemotherapy induced neuropathic pain. ClinicalTrials.gov | Link |
81. Maurer M, Henn V, Dittrich A, Hofmann A. Delta-9-tetrahydrocannabinol shows antispastic and analgesic effects in a single case double-blind trial. Eur Arch Psychiatry Clin Neurosci. 1990;240(1):1-4 | PubMed |
82. McGill University Health Center. Nabilone versus amitriptyline in improving quality of sleep in patients with fibromyalgia. ClinicalTrials.gov. | Link |
83. Medical Research Council (MRC). A multiple randomised controlled trial of cannabinoids on spasticity in multiple sclerosis (MS). ISRCTN Registry. | Link |
84. Montreal General Hospital. Pilot study of smoked cannabis for chronic neuropathic pain. ISRCTN Registry | Link |
85. Narang S, Gibson D, Wasan AD, Ross EL, Michna E, Nedeljkovic SS, et al. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008 Mar;9(3):254-64 | PubMed |
86. Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, et al. Initial experiences with medicinal extracts of cannabis for chronic pain: results from 34 'N of 1' studies. Anaesthesia. 2004 May;59(5):440-52 | PubMed |
87. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats

neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. Pain. 2007 Dec 15;133(1-3):210-20 | PubMed |
88. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ. A multi-centre, double-blind, randomized, controlled trial of oro-mucosal cannabis based medicine in the treatment of neuropathic pain characterized by allodynia. Neurology. 2005;64(suppl 1):A374. | Link |
89. Pini LA, Guerzoni S, Cainazzo MM, Ferrari A, Sarchielli P, Tiraferri I, et al. Nabilone for the treatment of medication overuse headache: results of a preliminary double-blind, active-controlled, randomized trial. J Headache Pain. 2012 Nov;13(8):677-84 | CrossRef | PubMed |
90. Pinsger M, Schimetta W, Volc D, Hiermann E, Riederer F, Pölz W. [Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain--a randomized controlled trial]. Wien Klin Wochenschr. 2006 Jun;118(11-12):327-35 | PubMed |
91. Pinsger M. Benefit of an add-on-treatment with a synthetic cannabinomimeticum on patients with chronic back pain-a randomized controlled trial. Paper presented at: 8th International Conference on Early Psychosis: From Neurobiology to Public Policy; October 11-13, 2012; San Francisco: CA. Eur Spine J. 2012;21(11):2366 | CrossRef |
92. Robson P, Wade D, Makela P, House H, Bateman C. Cannabis-based medicinal extract (Sativex) produced significant improvements in a subjective measure of spasticity which were maintained on long-term treatment with no evidence of tolerance. IACM 3rd Conference on Cannabinoids in Medicine. 2005; | Link |
93. Rog DJ, Nurmikko T, Young C, Sarantis NS. Randomized controlled trial of sativex, a cannabis based medicine (CBM), in central neuropathic pain due to multiple sclerosis, followed by an open-label extension. Neurology. 2006;66(5):A31 | Link |
94. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005 Sep 27;65(6):812-9 | PubMed |
95. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther. 2007 Sep;29(9):2068-79 | PubMed |
96. Salim K, Schneider U, Burstein S, Hoy L, Karst M. Pain measurements and side effect profile of the novel cannabinoid ajulemic acid. Neuropharmacology. 2005 Jun;48(8):1164-71 | PubMed |
97. Selvarajah D, Gandhi R, Emery CJ, Tesfaye S. Randomized placebo-controlled double-blind clinical trial of cannabis-based medicinal product (Sativex) in painful diabetic neuropathy: depression is a major confounding factor. Diabetes Care. 2010 Jan;33(1):128-30 | CrossRef | PubMed |
98. Selvarajah D, Gandhi RA,Witte D, Bowler H, Emery C, Tesfaye S. Treatment of painful diabetic neuropathy with Sativex (a cannabis based medicinal product)—results of a randomised placebo controlled trial. Diabetologia. 2006;49 (suppl 1):671-672 | CrossRef |
99. Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Aug;18(7):999-1012 | CrossRef | PubMed |
100. Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. J Pain. 2008 Feb;9(2):164-73 | PubMed |
101. Svendsen KB, Jensen TS, Bach FW. [Effect of the synthetic cannabinoid dronabinol on central pain in patients with multiple sclerosis--secondary publication]. Ugeskr Laeger. 2005 Jun 20;167(25-31):2772-4 | PubMed |
102. 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 Jul 31;329(7460):253 | PubMed |
103. Toth C, Mawani S, Brady S, Chan C, Liu C, Mehina E, et al. An enriched-enrolment, randomized withdrawal, flexible-dose, double-blind, placebo-controlled, parallel assignment efficacy study of nabilone as adjuvant in the treatment of diabetic peripheral neuropathic pain. Pain. 2012 Oct;153(10):2073-82 | CrossRef | PubMed |
104. Turcotte D, Doupe M, Torabi M, Gomori A, Ethans K, Esfahani F, et al. Nabilone as an adjunctive to gabapentin for multiple sclerosis-induced neuropathic pain: a randomized controlled trial. Pain Med. 2015 Jan;16(1):149-59 | CrossRef | PubMed |
105. University of California Davis. Center for Medicinal Cannabis Research, VA NorthernCalifornia Health Care System. Effects of vaporized marijuana on neuropathic pain. ClinicalTrials.gov | Link |
106. 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. Mult Scler. 2004 Aug;10(4):434-41 | PubMed |
107. Wade DT, Makela PM, House H, Bateman C, Robson P. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. Mult Scler. 2006 Oct;12(5):639-45 | PubMed |
108. 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 Feb;17(1):21-9 | PubMed |
109. Wallace M, Atkinson J, Gouaux B, Marcotte T, Umlauf A. Effect of smoked cannabis on painful diabetic peripheral neuropathy. Paper presented at: 32nd Annual Scientific Meeting of the American Pain Society;May 9-11, 2013; New Orleans: LA. J Pain. 2013;14(4)(suppl 1):S62 | CrossRef |
110. Wallace MS, Marcotte TD, Umlauf A, Gouaux B, Atkinson JH. Efficacy of Inhaled Cannabis on Painful Diabetic Neuropathy. J Pain. 2015 Jul;16(7):616-27 | CrossRef | PubMed |
111. Ware M, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of

a randomized controlled trial. Paper presented at: Canadian Rheumatology Association Meeting; February 18-21, 2009; Kananaskis, AB: Canada. Abstract 149 J Rheumatol. 2009;36(11):2607 | Link |
112. Ware MA, Fitzcharles MA, Joseph L, Shir Y. The effects of nabilone on sleep in fibromyalgia: results of a randomized controlled trial. Anesth Analg. 2010 Feb 1;110(2):604-10 | CrossRef | PubMed |
113. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. CMAJ. 2010 Oct 5;182(14):E694-701 | CrossRef | PubMed |
114. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain. 2013 Feb;14(2):136-48 | CrossRef | PubMed |
115. 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 Jun;9(6):506-21 | CrossRef | PubMed |
116. Winnipeg Regional Health Authority; Valeant Canada Limited. A trial assessing the effect of nabilone on pain and quality of life in patients with fibromyalgia. ClinicalTrials.gov | CrossRef |
117. Wissel J, Haydn T, Müller J, Brenneis C, Berger T, Poewe W, et al. Low dose treatment with the synthetic cannabinoid Nabilone significantly reduces spasticity-related pain : a double-blind placebo-controlled cross-over trial. J Neurol. 2006 Oct;253(10):1337-41 | PubMed |
118. Young CA, Rog DJ. Randomised controlled trial of cannabis based medicinal extracts (CBME) in central neuropathic pain due to multiple sclerosis. Paper presented at: IV Congress of the European Federation of IASP Chapters (EFIC); September 2-6, 2003; Prague, Czech Republic. | Link |
119. 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 Nov 8;362(9395):1517-26 | PubMed |
120. Zajicek J, Reif M, Schnelle M. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis—Results of the MUSEC study. Paper presented at: 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis; September 9-12, 2009; Dusseldorf: Germany. Mult Scler. 2009;15(9)(suppl S):S274 | CrossRef |
121. Zajicek J, Reif M, Schnelle M; UK MUSEC Study Investigators. Cannabis extract in the treatment of muscle stiffness and other symptoms in multiple sclerosis – results of the MUSEC study. Paper presented at: IACM 5th Conference on Cannabinoids in Medicine; October 2-3, 2009; Cologne, Germany. | Link |
122. Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG; MUSEC Research Group.. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. J Neurol Neurosurg Psychiatry. 2012 Nov;83(11):1125-32 | CrossRef | PubMed |
123. Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry. 2005 Dec;76(12):1664-9 | PubMed |
124. Cannabinoid Buccal Spray for Chronic Non-Cancer or Neuropathic Pain: A Review of Clinical Effectiveness, Safety, and Guidelines [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2016 Sep 21 | PubMed |
125. Nabilone for Chronic Pain Management: A Review of Clinical Effectiveness, Safety, and Guidelines. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2011 Nov 11 | Link |
126. College of Family Physicians of Canada. Authorizing dried cannabis for chronic pain or anxiety. Preliminary guidance. Mississauga, ON: College of Family Physicians of Canada; 2014.
127. Moulin D, Boulanger A, Clark A, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag 2014;19:328–35.
128. Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010;17:1113–e88.
129. Namaka M, Leong C, Grossberndt A, Klowak M, Turcotte D, Esfahani F, et al. A treatment algorithm for neuropathic pain: an update. Consult Pharm. 2009 Dec;24(12):885-902 | PubMed |
130. Bistre S, Acevedo JC, Amaya A, De Leon CO, Chinchilla N, De GM, et al. Guidelines for the diagnosis and management of neuropathic pain: consensus of a group of Latin American experts. J Pain and Palliat Care Pharmacother. 2009;23(3):261-81.
131. Clark A, Lynch M, Ware M, et al. Guidelines for the use of cannabinoid compounds in chronic pain. Pain Res Manag 2005;10:44A–6A.
132. Fitzcharles M, Ste-Marie P, Goldenberg D, et al. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. Pain Res Manag 2013;18:119–26.
133. de Vries M, Van Rijckevorsel DC, Vissers KC, Wilder-Smith OH, Van Goor H. Single dose delta-9-tetrahydrocannabinol in chronic pancreatitis patients: analgesic efficacy, pharmacokinetics and tolerability. Br J Clin Pharmacol. 2016 Mar;81(3):525-37 | CrossRef | PubMed |
134. Degenhardt L, Lintzeris N, Campbell G, Bruno R, Cohen M, Farrell M, et al. Experience of adjunctive cannabis use for chronic non-cancer pain: findings from the Pain and Opioids IN Treatment (POINT) study. Drug Alcohol Depend. 2015 Feb 1;147:144-50 | CrossRef | PubMed |
135. Wilsey BL, Deutsch R, Samara E, Marcotte TD, Barnes AJ, Huestis MA, et al. A preliminary evaluation of the relationship of cannabinoid blood concentrations with the analgesic response to vaporized cannabis. J Pain Res. 2016 Aug 31;9:587-98 | CrossRef | PubMed |
136. Barth Wilsey MD. Effect of Cannabis and Endocannabinoids on HIV Neuropathic Pain. ClinicalTrials.gov | Link |

137. Johns Hopkins University. Maximizing Analgesia to Reduce Pain in Knee Osteoarthritis. ClinicalTrials.gov | Link |
138. New York State Psychiatric Institute. Investigation of Cannabis for Chronic Pain and Palliative Care. ClinicalTrials.gov. | Link |
139. Prairie Plant Systems Inc.. Cannabinoid Profile Investigation of Vapourized Cannabis in Patients With Osteoarthritis of the Knee (CAPRI). ClinicalTrials.gov | Link |
140. Rabin Medical Center. Analysis of Orthopedic Patients Response to New Pain Modulating Substances and Drugs. ClinicalTrials.gov. | Link |
141. Tel-Aviv Sourasky Medical Center. Cannabinoids Effects on the Pain Modulation System. ClinicalTrials.gov | Link |
142. University of California, San Diego. Trial of Dronabinol and Vaporized Cannabis in Neuropathic Low Back Pain. | Link |
143. University of Colorado, Denver. Cannabis Versus Oxycodone for Pain Relief. ClinicalTrials.gov | Link |

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