

Peripheral Neuropathy

ISSUE BRIEF ON PERIPHERAL NEUROPATHY

Introduction

Briefings such as this one are prepared in response to petitions to add new conditions to the list of qualifying conditions for the Minnesota medical cannabis program. The intention of these briefings is to present to the Commissioner of Health, to members of the Medical Cannabis Review Panel, and to interested members of the public scientific studies of cannabis products as therapy for the petitioned condition. Brief information on the condition and its current treatment is provided to help give context to the studies. The primary focus is on clinical trials and observational studies, but for many conditions there are few of these. A selection of articles on pre-clinical studies (typically laboratory and animal model studies) will be included, especially if there are few clinical trials or observational studies. Though interpretation of surveys is usually difficult because it is unclear whether responders represent the population of interest and because of unknown validity of responses, when published in peer-reviewed journals surveys will be included for completeness. When found, published recommendations or opinions of national organizations medical organizations will be included.

Searches for published clinical trials and observational studies are performed using the National Library of Medicine's MEDLINE database using key words appropriate for the petitioned condition. Articles that appeared to be results of clinical trials, observational studies, or review articles of such studies, were accessed for examination. References in the articles were studied to identify additional articles that were not found on the initial search. This continued in an iterative fashion until no additional relevant articles were found. Finally, the federal government-maintained web site of clinical trials, clinicaltrials.gov, was searched to learn about trials currently under way or under development and to check whether additional articles on completed trials could be found.

Definition

Peripheral neuropathies are common neurological disorders resulting from damage to the peripheral nervous system – the nerves that communicate information to and from the central nervous system (brain and spinal cord). There are three types of motor nerves: motor, sensory, and autonomic. Symptoms depend on whether motor, sensory, or autonomic nerves are damaged. Motor nerves control voluntary movement of muscles such as those used for walking, grasping things, or talking. Sensory nerves transmit information such as the feeling of a light touch or the pain from a cut. Autonomic nerves control organ activities that are regulated automatically such as breathing, digesting food, and heart and gland functions. Some neuropathies may affect all three types of nerves; others primarily affect one or two types (NIH Peripheral Neuropathy Fact Sheet 2017).

Symptoms vary depending on whether motor, sensory, or autonomic nerves are damaged (NIH Peripheral Neuropathy Fact Sheet 2017 for next four paragraphs)

Motor nerve damage is most commonly associated with muscle weakness. Other symptoms may include painful muscle cramps and fasciculations (uncontrolled muscle twitching visible under the skin), muscle atrophy (severe shrinkage of muscle size), and decreased reflexes.

Sensory nerve damage causes a variety of symptoms because sensory nerves have a broad range of functions. Larger sensory nerves enclosed in myelin register vibration, light touch, and position sense. Damage to large sensory fibers impairs touch, resulting in a general decrease in sensation. Since this is felt most in the hands and feet, people may feel as if they are wearing gloves and stockings even when they are not. This damage to larger sensory fibers may contribute to the loss of reflexes. Loss of position sense often makes people unable to coordinate complex movements like walking or fastening buttons, or to maintain their balance when their eyes are shut. Smaller sensory fibers without myelin sheaths transmit pain and temperature sensations. Damage to these fibers can interfere with the ability to feel pain or changes in temperature. People may fail to sense they have been injured from a cut or that a wound is becoming infected. Others may not detect pain that warns of impending heart attack or other acute conditions. Loss of pain sensation is a particularly serious problem for people with diabetes, contributing to the high rate of lower limb amputations among this population.

Neuropathic pain is a common, often difficult to control symptom of sensory nerve damage and can seriously affect emotional well-being and overall quality of life. Often worse at night, neuropathic pain seriously disrupts sleep and adds to the emotional burden of sensory nerve damage. Neuropathic pain can often be associated with an over-sensitization of pain receptors in the skin, so that people feel severe pain (allodynia) from stimuli that are normally painless. For example, some may experience pain from bed sheets draped lightly over the body. Over many years, sensory neuropathy may lead to changes in the skin and hair as well as to joint and bone damage.

Autonomic nerve damage symptoms are diverse since the parasympathetic and sympathetic nerves of the peripheral nervous system control nearly every organ in the body. Common symptoms of autonomic nerve damage include an inability to sweat normally, which may lead to heat intolerance; a loss of bladder control; and an inability to control muscles that expand or contract blood vessels to regulate blood pressure. A drop in blood pressure when a person moves suddenly from a seated to a standing position (postural hypotension) may result in dizziness, lightheadedness, or fainting. Irregular heartbeats may also occur.

Peripheral neuropathies can be classified according to categories of affected nerves into mononeuropathies, multifocal neuropathies, acute polyneuropathy, and chronic polyneuropathy. A brief example of some of the most common peripheral neuropathies within each category are presented here (Hanewinkel 2016).

*Mononeuropathies (involving only one peripheral nerve)

Carpal tunnel syndrome is the most common mononeuropathy. It results from compression of the median nerve at the wrist. Typically, patients complain of numbness, prickling or tingling sensations, and pain in the hand (sometimes extending up the arm) and sometimes weakness of the hand. Bell's palsy is paralysis of face muscles on one side due to damage to the seventh cranial nerve. The cause is unknown though it has been linked to some infections.

*Multifocal neuropathies (involves multiple nerves, but not in a symmetric fashion)

Disorders in this category are uncommon. Multifocal motor neuropathy is an immune-mediated disorder that damages the protective sheath (myelin) of motor nerves. It leads to slowly progressive, asymmetric, predominantly distal (towards hands and feet) muscle weakness and atrophy that commonly starts in the hands.

*Acute polyneuropathy

Guillain-Barre syndrome is a rapidly progressive, fairly symmetrical weakness leading to paralysis that starts in the lower legs and works its way up the legs and often involves, also, the arms and upper body. Abnormal sensations can accompany the weakness and paralysis.

*Chronic polyneuropathy

This is the category that includes some of the most common, most troublesome peripheral neuropathies. Diabetes can cause multiple types of neuropathies and it is the most common cause of chronic polyneuropathy. It is typically painful and also causes numbness, especially of the lower extremities and feet. Some types of chemotherapy characteristically cause polyneuropathy. It is predominantly a sensory polyneuropathy, but it can be accompanied by pain, autonomic dysfunction, and motor deficit. Certain nutritional deficiencies (example, thiamine) and chronic alcohol abuse (often accompanied by nutritional deficiencies) are also causes and some cases of polyneuropathy have no known cause (“idiopathic”).

Prevalence

The prevalence of peripheral neuropathy in the general population is 2.4% and increases with age to an estimated 8% in those older than 55 years (Watson 2015). Pain is a very frequent symptom in peripheral neuropathy, but in some there is little pain and other symptoms predominate. Little information could be found on the proportion of peripheral neuropathy patients, overall, whose symptoms were predominantly numbness, weakness, or autonomic symptoms rather than pain. The types of peripheral neuropathy where this is clear make up a small fraction of the total number of peripheral neuropathy cases.

Current Therapies

Treatment serves primarily to prevent further progression of the neuropathic symptoms. Symptoms present at the start of treatment or when a toxic agent is removed may improve and occasionally resolve. However, more commonly patients are left with lingering symptoms from the pretreatment neurogenic injury. In these cases and in those in which the neuropathy is idiopathic or untreatable, management is symptomatic (Watson 2015).

Most of what was found about managing symptoms of peripheral neuropathy related to pain. First line agents for management of neuropathic pain include certain anticonvulsants (gabapentin and pregabalin), tricyclic antidepressants, or selective serotonin-norepinephrine reuptake inhibitors (duloxetine). Failed medication trials are commonly caused by inadequate dosing. If a patient has a partial response to a first-line agent, a second first-line agent with a

distinct mechanism of action can be added to the first agent. Combination therapy utilizing neuropathic pain medications with different mechanisms of action has been repeatedly found to be more efficacious than single-agent treatment. If a first-line agent fails, a different first-line agent can be tried. Second- and third-line agents include opioid analgesics (Watson 2015). Transcutaneous electrical nerve stimulation (TENS) and other complementary therapies, as well as orthotic devices such as orthopedic shoes, can also be helpful (NIH Peripheral Neuropathy Fact Sheet 2017).

Pre-Clinical Research

Pre-clinical research appears to have focused on the role of the endocannabinoid system and effects of exogenous cannabinoids on the pain that often accompanies peripheral neuropathy. A detailed review of animal studies is presented in Rahn 2009 and King 2017 presents a recent example of this type of research. Numerous research articles have investigated the concept that endocannabinoids can act to protect nerves in the brain and in the eye from injury. Little appears to have been published on this topic for peripheral nerves. The review by Zogopoulos et al (Zogopoulos 2013) is a relatively current overview of research related to a potential neuroprotective role for endocannabinoids.

Rahn EJ and Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. *Neurotherapeutics* 2009;6:713-737.

A portion of this review article covers studies demonstrating involvement of the endocannabinoid system in animal models of peripheral neuropathy and the effect, in these animal models, of chemicals that manipulate the animal's endocannabinoid system. These chemicals include endocannabinoid receptor agonist and antagonists. The animal models of peripheral neuropathy include different forms of nerve trauma and models of diabetic, HIV, and chemotherapy peripheral neuropathy.

King KM, Myers AM, Soroka-Monzo AJ, Tuma RF et al. Single and combined effects of Δ^9 -tetrahydrocannabinol and cannabidiol in a mouse model of chemotherapy-induced neuropathic pain. *Br J Pharmacol* 2017;174:2832-2841.

This study investigated a potential role for cannabidiol (CBD) in treating an animal model of a peripheral neuropathy symptom: allodynia (heightened sensitivity to normal mechanical stimulation). Mice treated with three different chemotherapy agents were given either THC or CBD or both THC and CBD. Mechanical allodynia was tested over subsequent days for two weeks. The individual cannabinoids and joint administration of THC and CBD had different results for the different chemotherapeutic agents, For two of them, CBD and THC had a synergistic effect when given together. Results led the authors to conclude, "CBD may be potent and effective at preventing the development of chemotherapy-induced peripheral neuropathy, and its clinical use may be enhanced by co-administration of low doses of THC."

Zogopoulos P, Vasileiou I, Patsouris E, Theocharis S. The neuroprotective role of endocannabinoids against chemical-induced injury and other adverse effects. *J Appl Toxicol* 2013;33:246-264.

This article presents a review of in vitro (tissue culture, for example) and in vivo (effects in live animals) experimental data regarding the endocannabinoid system and its role in neuroprotection, as well as possible therapeutic perspectives. The focus is on the brain and central nervous system, but some of the findings could be relevant to the peripheral nerves.

Clinical Trials

Several clinical trials of cannabis or cannabinoids for management of symptoms in patients with peripheral neuropathy have been published. Some specifically recruited patients with peripheral neuropathy and some recruited patients with neuropathic pain more generally – so the participants included patients with peripheral neuropathy but also patients with central pain. They all focus on management of neuropathic pain. Though they typically also have, as secondary outcomes, measures of some combination of quality of life, anxiety, and sleep quality, they shed little light on the potential benefit of cannabis and cannabinoids for treating the numbness, weakness, and autonomic dysfunction that can accompany peripheral neuropathy.

Nurmikko T, Serpell MG, Hoggart B, Toomey PJ, Morton BJ, Haines D. Sativex successfully treats neuropathic pain characterized by allodynia: A randomized, double-blind, placebo-controlled clinical trial. *Pain* 2007; 133(1-3): 210-220.

This study took place over five weeks and was randomized, double-blind, and placebo-controlled involving patients with a history of nerve pain for at least six months. A total of 125 patients (74 women/51 men; average age 53 years) with unilateral peripheral neuropathy and allodynia were randomized to receive either Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100 µl actuation) (n=63) or placebo (n=62) and baseline pain and sleep disturbance were recorded daily for 7-10 days prior to start of trial. All current medications, including those for pain, were continued throughout – although any current use of cannabis products were cause for exclusion.

An initial dosing test was performed: after administration of eight sprays over two hours, any patient scoring over 25 on a 0-100 Visual Analog Scale for intoxication, or presenting with any clinical concerns, was allowed no further doses. Patients who completed the initial dosing test were subsequently allowed self-titration, up to 48 sprays/24 hours (129.6 THC/120 CBD). Throughout the trial, patients recorded daily pain and sleep patterns in a journal. The primary endpoint was pain relief based on a 0-10 scale; secondary endpoints included the Neuropathic Pain Scale (NPS), mechanical allodynia testing, verbal sleep disturbance scale, Pain Disability Index (PDI), Patient Global Impression of Change (PGIC) for pain and allodynia, the General Health Questionnaire (GHQ-12) and possible cognitive decline was assessed using the Brief Repeatable Battery of Neuropsychological tests (BRB-N). Lab values and ECG was taken prior to the study, and again at completion.

Thirteen patients from the drug arm and seven from placebo withdrew from the study prior to completion due to side effects (n=11 in treatment group; n=2 in placebo group), lack of effectiveness, and failure to comply with study requirements. The results of the primary outcome were statistically significant in favor of the drug arm and the NNT was 8.5 (50%

reduction) and 8.6 (30% reduction). All areas besides the GHQ-12 and cognitive decline showed a significant difference in favor of the Sativex arm. Fifty-seven (91%) of patients in the Sativex group experienced at least one adverse event compared with 48 (77%) in the placebo group. Most common adverse events in the Sativex group were dizziness, nausea, fatigue, vomiting, dry mouth, feeling drunk, diarrhea, somnolence, disturbance in attention, and memory deficit.

Selvarajah D, Gandhi R, Emery C, Tesfaye S. Randomized Placebo-Controlled Double-Blind Clinical Trial of Cannabis-Based Medicinal Product (Sativex) in Painful Diabetic Neuropathy. *Diabetes Care* 2010; 33(1): 128-130.

Thirty patients (11 female/19 male; average age 56 years) with painful diabetic peripheral neuropathy (DPN), despite standard treatment with a tricyclic antidepressant, were enlisted in this randomized, double-blind, placebo-controlled study testing the effectiveness of Sativex sublingual spray (27 mg/ml THC: 25 mg/ml CBD). A two-week dose titration period was followed by a 10-week maintenance phase. All current medications were continued. Pain levels for superficial, deep, and muscular pain were documented using 100-mm Visual Analogue Scale (VAS), the Neuropathic Pain Scale (NPS), and the total pain score (TPS) at baseline and study end, as were the possible level of depression using the Hospital Anxiety and Depression Scale (HADS-D), as well as the patients' quality of life (QOL) using the McGill Pain and QOL, SE-36 Health Survey, and Euro QOL. Results showed no significant difference between the Sativex and placebo groups for change in any of the measured parameters. Of the 30 patients randomized, 6 withdrew because of adverse events.

Serpell M, Ratcliffe S, Hovorka J, Schofield M, Taylor L, Lauder H, Ehler, E. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. *Eur J Pain* 2014;18:999-1012.

Patients with peripheral neuropathic pain (PNP) associated with allodynia were screened and met inclusion and exclusion criteria at 39 centers in the UK, Czech Republic, Romania, Belgium and Canada. Of 303 screened patients, 128 were randomized to THC/CBD spray (nabiximols: 2.7 mg THC and 2.5 mg CBD per 100 µl spray), and 118 to placebo. Eligible patients were ≥18, had PNP ≥ 6 months, had allodynia confirmed, were receiving the appropriate treatment for their PNP, had specified causes of their PNP (PNP due to cancer or diabetes excluded), and took no analgesics on a PRN basis. At baseline they were required to have pain not entirely relieved by their analgesic regimen with a pain rating intensity ≥ 4 on a 0-10 scale. Participants had a one-week baseline period and a 14-week treatment period with visits at the end of weeks 2, 6, 10; at the end of the study (treatment week 14 or earlier if they withdrew); and 28 days after study completion or withdrawal. Participants remained on stable dosages of their concomitant analgesic medications with the exception of acetaminophen. The rescue analgesia provided contained acetaminophen, with maximum single dose of 1000 mg and maximum total daily dose of 4 grams. Participants began nabiximols at a maximum of one spray per four hour period and self-titrated to a maximum of 24 sprays per day (limit of 8 sprays per 3 hours), increasing dosage by no more than 50% from preceding day. Patients rated their pain on a 0 – 10 numeric rating scale at the end of each day. Co-primary outcome measures were, 1) proportion of patients showing ≥ 30% reduction in pain from baseline to end of study period as measured by NRS and 2) mean change in NRS score from baseline to end of study. A total of 173 of the 246 completed the study, 21 ceased treatment by remained in the study, 52

withdrew, and six were excluded as they had no on-treatment efficacy data. A total of 34 patients (28%) receiving nabiximols were classified as responders at the 30% level compared with 19 patients (16%) on placebo, achieving a statistically significant odds ratio in favor of nabiximols treatment (OR = 1.97, 95% CI = 1.05-3.70; $p=0.034$) in the full intention to treat (ITT) cohort and in the subset of participants who completed the study with no protocol violations likely to affect outcome measures (per protocol (PP) group: OR = 2.7 CI = 1.12-4.57 $p=0.021$). The adjusted mean reduction in NRS score showed a treatment difference in favor of nabiximols, but the difference didn't meet statistical significance in either the ITT or the PP groups. A variety of secondary outcome measures were used, but only two showed statistically significant change, both in favor of nabiximols: sleep quality and Global Impression of Change (general assessment of health). Side effects were common in both nabiximols (85%) and placebo (70%) groups. Most common side effects in nabiximols group were dizziness, nausea, and fatigue. Ten nabiximols patients (8%) and six placebo patients (5%) experienced serious adverse events; none were deemed related to treatment. A total of 33 patients stopped receiving study medication due to adverse effects, 25 in the nabiximols group and 8 in the placebo group.

Abrams DI, 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 placebo-controlled trial. *Neurology* 2007;68:515-521.

This randomized, placebo-controlled trial included 55 patients with HIV infection and symptomatic HIV-associated sensory neuropathy with an average daily pain Visual Analog Score (VAS; 0-100) of 30 and were in stable health, with prior experience smoking cannabis (six or more lifetime exposures). Patients were given pre-rolled 3.56% cannabis and placebo cigarettes. The study included a pre-intervention phase to determine eligibility (7 days), a lead-in phase for acclimatization (2 days), an inpatient treatment phase (5 days) and outpatient post-intervention phase (7 days). Primary outcomes were daily pain VAS scores; secondary outcomes were ratings of chronic neuropathic pain VAS on days 1 and 5 of the intervention, long thermal stimulation (LTS) procedure to assess acute analgesia, and heat/capsaicin sensitization model to assess anti-hyperalgesic effects. A total of 50 patients (25 each in cannabis and placebo groups) completed the study; in the cannabis group, median daily pain reduction was 34% versus 17% in placebo ($p=0.03$); similarly, 52% of cannabis group patients reported a 30% or greater reduction in pain, compared to 24% of the placebo group ($p=0.04$). Cannabis smoking resulted in significant pain reduction after the first smoked cigarette ($p<0.001$); additionally, cannabis reduced experimentally-induced hyperalgesia but not pain related to heat stimulation. Reported side effects included anxiety, sedation, disorientation, paranoia, confusion, dizziness and nausea which were generally more common in the cannabis group. A non-significant reduction in mood disturbance was observed in the cannabis group when compared to placebo.

Ellis RJ, Toperoff W, Vaida F, van den Brande G, Gonzales J, Gouaux B, Bentley H, Hampton Atkinson J. Smoked Medicinal Cannabis for Neuropathic Pain in HIV: A Randomized, Crossover Clinical Trial. *Neuropsychopharmacology* 2009 Feb;34(3):672-680.

This randomized crossover trial enrolled 34 subjects with HIV infection, neuropathic pain with at least two failed trials of analgesics and an average score of 5 or higher on the pain intensity scale of the Descriptor Differential Scale (DDS). The study included five phases over 7 weeks: a

wash-in phase for baseline measurements, five days of smoked active or placebo cannabis, two weeks of wash-out, five days of smoked active or placebo cannabis, and finally two weeks of wash-out. Baseline measurements included laboratory evaluations, Total Neuropathy Score (TNS), and behavioral and mental health evaluation. Participants were given placebo and cannabis (1% to 8% THC by weight) cigarettes. During treatment phases, patients smoked cannabis or placebo cigarettes under observation by a study nurse; over four sessions, patients started with 4% THC or placebo and adjusted downwards or upwards, depending on side effects or completeness of pain relief. The primary outcome measure was pain magnitude (assessed by DDS); secondary outcomes were Sickness Impact Profile (SIP) score, Profile of Mood States (POMS) score, Brief Symptom Inventory (BSI) score, UKU Side Effect Rating Scale score for physical and psychological symptoms and Highness/Sedation Scale as well as laboratory measures for safety assessment. A total of 28 enrolled patients completed the study. Cannabis treatment significantly reduced pain compared to placebo (median difference in pain reduction was 3.3 points on DDS, $p=0.016$). Intent-to-treat analysis found similar results. Number needed to treat for 30% pain reduction was 3.5. No differences were observed between treatment and placebo groups in secondary outcomes. Two of the enrolled patients withdrew due to side effects (cannabis-induced psychosis in the first, intractable smoking-related cough in the second). Side effects included concentration difficulty, fatigue, sleepiness or sedation, increased duration of sleep, dry mouth and thirst; these were more common during cannabis treatment.

Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain. *J Pain*. 2013; 14(2):136-148.

This randomized, placebo-controlled, double-blind, crossover trial included 39 patients (28 male/11 female; average age 50 years) with various diagnoses resulting in neuropathic pain (majority had peripheral neuropathy). The cannabis used was standardized to result in two products: 3.53% and 1.29% THC, as well as a placebo. The process was similar to the above article by the same researchers; however, in this trial the patients were directed to inhale four puffs at 60 minutes, followed by 4-8 puffs after the third hour of testing and used vaporized rather than smoked cannabis. They used the Foltin Puff Procedure to standardize the dosing of the vaporized cannabis. Each patient was monitored for changes in vital signs during testing.

Like their previous trial, outcomes measured were spontaneous pain relief (on a 0-100 scale, average baseline was 58), degree of pain relief (Patient Global Impression of Change), pain unpleasantness, as well as neuropathic pain (Neuropathic Pain Scale), test of allodynia, and heat pain sensitivity. Neurocognitive effects on attention, concentration, learning and memory, as well as fine motor speed (WAIS-III, HVLT, Grooved Pegboard Test and word recall tests).

Results of the pain measurements were statistically significant when both doses of THC were compared to placebo, although there was no difference between the active doses. Allodynia generally decreased, however heat sensitivity did not. Cognitive impairment was seen in both test groups. No patients withdrew due to drug and no serious adverse effects were reported; the most common side effects were mild sedation, confusion, hunger and nausea.

Frank B, Serpell MG, Hughes J, Matthews JNS, Kapur D. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain:

randomised, crossover, double blind study. *British Medical Journal* 2008 Jan 26;336(7637):199-201.

This randomized, double-blind crossover trial enrolled 96 patients aged 24-84 years with chronic neuropathic pain who met diagnostic criteria of sensory abnormality, allodynia, burning pain, lancinating pain and sympathetic dysfunction and had a mean pain score of at least 40 on a 0-100 VAS. Stable medication regimes, other than dihydrocodeine, were continued during the study. The study included a 6-week escalating treatment period starting with 30 mg hydrocodeine or 250 µg nabilone, with a maximum of 240 mg dihydrocodeine or 2 mg nabilone. There was a two-week washout period between treatment phases. Patients were evaluated at two-week intervals during the study and asked to fill out daily pain scores, as well as amount of sleep, sleep interruptions and amount of study drug taken. The primary outcome was mean pain VAS score during the last two weeks of treatment; secondary outcomes were mood changes, quality of life, sleep and psychometric function. A total of 73 patients had data for the available case analysis and 64 supplied adequate data and complied with the protocol and could be included in the per protocol analysis. The mean baseline pain VAS score was 69.6 mm; the mean score for the last two weeks of treatment was 6.0 mm longer for nabilone treatment compared to dihydrocodeine in the available case analysis; for the per protocol analysis, mean score for nabilone was 5.6 mm longer than dihydrocodeine. Comparison of quality life scores showed that nabilone treatment resulted in better physical domain scores but also higher bodily pain scores. Nabilone generally produced more side effects than dihydrocodeine, though no adverse events were observed.

Wilsey, 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(6): 506-521.

A randomized, placebo-controlled, double-blind, crossover trial using cannabis (7% and 3.5% THC) and placebo cigarettes provided by the University of Mississippi and the National Institute on Drug Abuse. Thirty-eight patients (20 male/18 female; average age 46 years) with varying diagnoses were brought to clinic for administration for three six-hour sessions and dosed using a standard cued-puff procedure under supervision with a total of nine puffs each session. The approximate level of THC consumed at each session was 19 mg (3.5% THC) and 34 mg (7% THC). During the session, hourly evaluations and assessments were carried out and continued for two hours post session. All medications including those for pain were continued.

Outcomes measured were spontaneous pain relief (on a 0-100 scale, average baseline was 55), degree of pain relief (Patient Global Impression of Change), pain unpleasantness, as well as neuropathic pain (Neuropathic Pain Scale), test of allodynia, and heat pain sensitivity. Neurocognitive effects on attention, concentration, learning and memory, as well as fine motor speed (WAIS-III, HVLIT, Grooved Pegboard Test and word recall tests). A significant difference was seen in all pain variables (except allodynia and heat sensitivity) when both 3.5% and 7% THC was compared to placebo. Differences were also seen in the cognitive tests where the THC products resulted in greater cognitive decline than did placebo – 7% THC showed impairment in attention, memory and learning; the 3.5% group only declined in learning and memory and to a lesser extent when compared to the 7% test groups.

Attal N, Brasseur L, Guirimand D, Clermond-Gnamien S, Atlami S, Bouhassira D. Are oral cannabinoids safe and effective in refractory neuropathic pain? *European Journal of Pain* 2004;173-177.

This clinical study included seven patients with peripheral (n=3) or central neuropathic pain with a mean Visual Analog Score (1-100) of over 40 at baseline that is refractory to at least three pharmacological classes. Current analgesic medications were continued through the study. Eight cannabis-naïve patients (4 male, 4 female) were given Dronabinol (2.5 mg THC) and started at two daily doses, with upward titration in steps of 5 mg every week if tolerated, up to 25 mg/day. If side effects occurred, the dosage was adjusted downward in steps of 2.5 mg. Patients reported daily pain VAS scores starting from one week prior to treatment, until four months after treatment initiation. The McGill Pain Questionnaire (MPQ) was used to assess sensory and affective pain dimensions. Other measurements were number of painful attacks over the previous 24 hour period, mechanical allodynia intensity as measured on a VAS, the Brief Pain Inventory (BPI), the Hospital Anxiety and Depression (HAD) scale and the Nottingham Health Profile.

Seven patients reported side effects, including somnolence, fatigue, hypotonia, blurred vision and attention/memory disorders; five patients dropped out of the study between weeks 6 and 8 due to side effects. Mean achieved dosage was 16.6 mg THC/day. No significant improvement in weekly pain VAS scores, ongoing pain and paresthesias, induced allodynia, BPI, HAD, Nottingham health profile or the sensory or affective subscores of the MPQ. A non-significant decrease in number of painful attacks after one month of treatment was observed, but this effect disappeared after two months. One patient experienced a significant decrease in the intensity of spontaneous pain and paresthesias but dropped out of the study due to side effects.

Observational Studies

No observational studies were found that focused on symptoms of peripheral neuropathy (numbness, weakness) other than pain.

National Medical Organization Recommendations

In the National Academy of Sciences 2017 report, *The Health Effects of Cannabis and Cannabinoids*, there is no discussion or conclusion statement regarding evidence of therapeutic benefit of cannabis or cannabinoids for peripheral neuropathy. In its discussion of chronic pain, the report acknowledges neuropathy was the most frequent cause of chronic pain among the trials included in Whiting's *New JAMA* review (Whiting 2015) and it includes this conclusion: "There is substantial evidence that cannabis is an effective treatment for chronic pain in adults." (Conclusion 4-1).

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