

A REVIEW OF MEDICAL CANNABIS STUDIES RELATING TO CHEMICAL
COMPOSITIONS AND DOSAGES FOR QUALIFYING MEDICAL CONDITIONS

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for Qualifying Medical Conditions**

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Executive Summary

On May 29, 2014 the Governor of Minnesota signed the medical cannabis therapeutic use law: 2014 Minnesota Laws chapter 311. This Act is designed to enable truly sick patients to engage in the therapeutic use of cannabis while preventing it from being misused or diverted from its medical purpose.

This report summarizes clinical trials and prospective observational studies in humans, published in peer reviewed journals, which focus on medical cannabis formulations consistent with Minnesota's medical cannabis program. It is produced in fulfillment of Minnesota Statutes Section 152.25, subdivision 2. The report was first produced in December, 2014, and it is

updated annually.

Medical conditions included in each update of this report are a combination of qualifying conditions named in the statute establishing the program and qualifying conditions that have been added since then. The medical conditions identified in the statute for inclusion in Minnesota's medical cannabis program are:

- 1 Cancer, if the underlying condition or treatment produces one or more of the following:
 - a. Severe or chronic pain;
 - b. Nausea or severe vomiting; or
 - c. Cachexia or severe wasting
- 2 Glaucoma
- 3 Human immunodeficiency virus or acquired immune deficiency syndrome
- 4 Tourette's syndrome
- 5 Amyotrophic lateral sclerosis
- 6 Seizures, including those characteristic of epilepsy
- 7 Severe and persistent muscle spasms, including those characteristic of multiple sclerosis
- 8 Crohn's disease (expanded to Inflammatory Bowel Disease in 2016)
- 9 Terminal illness, with a probable life expectancy of under one year, if the illness or its treatment produces one or more of the following:
 - a. Severe or chronic pain;
 - b. Nausea or severe vomiting; or
 - c. Cachexia or severe wasting

On December 2, 2015 the Commissioner announced his decision to add intractable pain to the list of the program's qualifying medical conditions, effective August 1, 2016. Similarly, post-traumatic stress disorder (PTSD) was added, effective August 1, 2017, autism spectrum disorder and obstructive sleep apnea were added, effective August 1, 2018, and Alzheimer's disease was added, effective August 1, 2019.

There are relatively few clinical trials, especially large clinical trials that can produce the most definitive results. In recent years the number of trials has increased to some degree, perhaps reflecting the commercialization of medical cannabis products around the world over the past few decades. Following are summary observations for each section.

Cancer: pain

Trial results suggest a combination of THC and CBD might be more effective than THC alone and that doses of THC higher than approximately 25 mg, even when divided over the course of a day, might be poorly tolerated by a substantial number of patients. The international trials of approximately 1:1 THC:CBD oromucosal spray (nabiximols, brand name Sativex) failed to meet their primary endpoints. However, a pre-specified pooled analysis of patients from U. S. Centers, from 2 of the 3 trials, showed better pain control with Sativex than with placebo. The maximum daily dosage allowed was 10 sprays per day, providing 27 mg THC and 25 mg CBD per day. However, patients in the Sativex arms of these trials self-titrated to an average of 6.3 or 6.4 sprays per day, providing approximately 17 mg THC and 16 mg CBD per day.

Cancer: nausea and vomiting

Several studies of plant-derived THC for chemotherapy-induced nausea and vomiting (CINV) from the late 1970s used 10 to 18 mg THC starting an hour or two before chemotherapy initiation, then repeating the dose every 2 to 4 hours for an additional 2 to 4 doses over 12 to 24 hours. Clinical trials of dronabinol, synthetic delta-9-THC, have used daily doses similar to the trials of plant-derived THC from the 1970s: 30 to 80 mg/day in divided doses. Not everyone can tolerate these doses, and the FDA

recommends a lower dronabinol dose for CINV, stating most patients respond to 5 mg three or four times daily.

Cancer: cachexia/wasting

Some small early trials showed effectiveness with doses of plant-derived THC 10 to 15 mg three to four times daily on days of chemotherapy infusion. Later trials with dronabinol, mostly in cancer patients not receiving chemotherapy, are less encouraging. Using doses of 5.0 to 7.5 mg daily in divided doses there was either modest effectiveness compared to placebo or inferior effectiveness compared to a standard appetite enhancing drug, and a substantial number of patients could not tolerate these doses. A large trial with cannabis extract treatment arms of relatively small doses of THC only (2.5 mg twice daily) or THC + CBD (2.5 mg THC/1.0 mg CBD twice daily) was stopped early for lack of effectiveness, yet dose reductions were necessary in a third of both groups.

Glaucoma

CBD does not appear to be effective at lowering intraocular pressure (IOP) and might even increase it. There is some evidence that even relatively low (5 mg) single doses of THC significantly reduces IOP for 4 to 5 hours before it returns to baseline,

but this isn't a consistent finding across studies. Larger single doses (20 and 25 mg) appear to reduce IOP longer (10 hours), but with a high occurrence of intolerable side effects.

HIV/AIDS

Each of the studies identified used dronabinol and assessed effect on appetite and weight. Most used 5.0 to 7.5 mg daily in 2 or 3 divided doses, consistent with FDA label recommendations. Though most patients tolerated this dose well, a substantial minority could only tolerate 2.5 mg daily. Results from three trials that enrolled current marijuana users suggest current marijuana users can tolerate higher doses, in the range of 20 to 40 mg daily in divided doses.

Tourette syndrome

Two small studies of oral, plant-derived THC (source not specified) in adult TS patients used single daily doses of 2.5 mg to 10 mg. About a third of the patients needed to decrease dose because of unacceptable side effects. Together, these studies provide modest evidence of effectiveness at reducing tic severity.

Three additional clinical trials are being organized. One will use nabiximols spray (approximately equal amounts of THC and CBD), one will use dronabinol (synthetic THC) and palmitoylethanolamide, and one will use vaporized cannabis flower with three different THC:CBD ratios.

A 2019 case report suggests cannabidiol (CBD) is important to clinical benefit from

medical cannabis.

Amyotrophic Lateral Sclerosis

Two small trials in ALS patients with published results used dronabinol (synthetic THC). One was reported in an abstract with few details, but started patients on 2.5 mg daily and titrated up to a maximum daily dose of 10 mg. The second used 10 mg daily in two divided doses. Both studies indicated patients tolerated the dronabinol doses well, but with little clear evidence of effectiveness. A third trial with no published results yet used nabiximols spray (approximately equal amounts of THC and CBD). A trial now recruiting patients is using capsules with 25 mg CBD and < 2mg THC.

Seizures

Recent studies mostly focusing on children have used 99% CBD extract oral solution as an adjunct to current anti-epileptic drug therapy, starting at a dose of 2 to 5 mg/kg/day, titrating up over 2 to 4 weeks to a goal of 10, 20, 25, or 50 mg/kg/day (most frequently used = 20 mg/kg/day).

Results of some of these trials and a safety study show the importance of monitoring liver enzymes when a patient is using CBD – especially when valproate is used at the same time. In addition, there is growing evidence of interaction between CBD and standard anti-epileptic drugs – especially clobazam.

Muscle spasms

Results of numerous trials focusing on spasticity and muscle spasm have been published, mostly with multiple sclerosis patients, but also some with spinal cord

injury patients. Whether in combination with CBD in various ratios or as a single agent (dronabinol), THC has been used in average dosages of 20 to 25 mg/day in divided doses. Dosages are usually started fairly low and then titrated up to achieve a balance between symptom reduction and appearance of side effects. From the trial experience, it appears that doing this titration over weeks, rather than over days, helps to reduce incidence and severity of side effects. There is some indication that THC is more effective in reducing spasticity and spasm at higher doses and that higher doses are better tolerated when given in conjunction with CBD in a THC:CBD ratio of 1:1 (versus 2:1 or 3:1). But some patients cannot tolerate even quite low doses of THC. Treatment appears to be effective in only a subset of patients, perhaps around half, and whether or not treatment will be effective can generally be determined within a few weeks.

Inflammatory bowel disease

At this point there is little guidance from clinical trials on composition or dosing, though there is an evident interest in products that are at least relatively high in CBD. The three clinical trials published to date are small. One used 99.5% pure CBD purified from cannabis extraction at a dose of 5 mg sublingually twice a day (Naftali 2017). The second used smoked cannabis with a THC=CBD ratio of approximately 50:1 (Naftali 2013). The third used a “CBD-rich cannabis extract” (Irving 2018). The trial now in the planning stage will use CBD capsules.

Terminal illness

Relevant studies can be found in other sections of this report, particularly the cancer sections. No published medical cannabis trials were found that specifically targeted patients with short life expectancy, cutting across medical conditions.

Intractable pain

For the Minnesota medical cannabis program intractable pain is defined as pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities appropriate for the patient has been used without adequate result or with intolerable side effects. Trials of cannabis for pain in the literature generally follow this definition in that their inclusion criteria specify patients with pain inadequately controlled with standard pain medications. The trials uniformly had the participants continue taking their routine pain medications, so they assess the value of cannabis treatment as an adjunct to other pain medications.

The quality of most of the studies summarized in this section is formally assessed in a report by the MN Evidence-based Practice Center called, [“Medical Cannabis for Non-Cancer Pain: A Systematic Review”](http://www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf) (<http://www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf>)

Six of the studies assessed in that report are not summarized here because they used the synthetic cannabinoid nabilone, which is similar to – but distinct from – THC.

Most of the 16 trials summarized here are relatively small (seven have >100 participants) and short (only 3 of the

controlled trials are longer than 5 weeks) and they are spread across multiple types of pain. These are important limitations to their value in giving understanding of the potential for cannabis products in pain management.

Eleven of the 16 trials studied an approximately 1:1 ratio of THC: CBD oromucosal spray (in most cases nabiximols, brand name Sativex) vs. placebo. Average dose in the clinical trials, after the titration period, of the 1:1 THC: CBD spray were around 6 to 10 sprays per day, representing a daily dose of approximately 15 to 27 mg THC and CBD per day.

Two of the articles report studies of long-term use of nabiximols. Results showed no evidence of tolerance developing with dosages a bit lower than during the underlying clinical trials lasting a month or two.

Three trials studied oral dronabinol, synthetic THC, vs. placebo. Two of them reported dosage after titration, ranging from 5 to 12.7 mg/day.

Post-traumatic stress disorder

No randomized, controlled clinical trials have reported results for cannabis product therapy in PTSD patients. One such trial was completed in January 2019 but results are not yet published. The second is now recruiting patients. In the completed trial three types of smoked cannabis (more THC than CBD; more CBD than THC; and equal amounts of THC and CBD) are compared with each other and to placebo in alleviating symptoms and in occurrence of adverse events among 76 U.S. veterans with treatment-resistant PTSD. Participants may smoke up to

1.8 grams cannabis per day. The second trial compares three types of vaporized dried cannabis (high THC/low CBD; high THC/high CBD; low THC/low CBD) with each other and with placebo in alleviating symptoms and in occurrence of adverse events among 42 patients with treatment-resistant PTSD. Participants are allowed to vaporize up to 2 grams of plant material per day as needed. Estimated completion date is June of 2020.

Two small, short-term open-label (no control group) studies of cannabinoids as adjunct therapy to routine psychiatric care (medications and psychotherapy) have been published. One used THC oil under the tongue and the other used CBD capsules or oral liquid spray. Therapies in both were well tolerated and both suggested improvement of PTSD symptoms among participants, overall.

Autism Spectrum Disorder

A randomized, controlled clinical trial was recently completed, though results have not yet been published; a second is in progress. In addition, three Israeli observational studies were recently published – one retrospective medical record review and two prospective studies. All three observational studies and the completed clinical trial used 20:1 CBD:THC oil. The trial in progress uses the cannabinoid, cannabidiol (CBDV). Results from the observational studies indicate substantial benefits for some patients.

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of complete (apnea) or partial

(hypopnea) collapse of the upper airway (mainly the oropharyngeal tract) during sleep, with a consequent cessation/reduction of airflow. The obstructive events cause a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened. These episodes cause acute physiological disruptions including fragmented sleep, intermittent hypoxia, and exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure. Over time, the acute disruptions lead to chronic conditions such as hypertension and heart disease, reduced cognitive function, depression, and impaired performance at work and while driving, as well as premature death.

One randomized, placebo-controlled clinical trial of cannabis or a cannabinoid product has been published (Carley 2018). This six week trial of dronabinol (synthetic THC) at doses of 2.5 mg and 10 mg daily, taken at bedtime, found a modest treatment benefit from dronabinol with substantial variation among patients in degree of response. The authors' responder analysis suggests only a portion – likely a rather small portion – of OSA patients receive a clinically meaningful reduction in AHI from the therapy used in this trial.

Alzheimer's Disease

Published human study evidence is limited to three small clinical trials, two small observational studies, and a fourth clinical trial now recruiting patients. Each study

uses THC as active drug, with nearly all patients receiving low dosages (≤ 5 mg daily). Two of the three published clinical trials found no beneficial treatment effect; the third found improved behavioral symptoms in the active treatment arm.

The two observational studies add some additional evidence that dronabinol use is associated with reduced behavioral symptoms in Alzheimer disease patients, but lack of a control group and small size limits the strength of these findings.

Each of the studies focuses on behavioral symptoms in persons with Alzheimer's disease (or other forms of dementia). It is important to keep in mind that the observed behavioral symptoms could be due to concurrent mental disorders (depression, schizophrenia, etc.) or physical disorders (constipation, infections), for which specific treatments are available. Careful assessment of the patient is needed so that the true cause of the observed behavioral symptoms is not missed.

Also, use of highly refined or synthetic THC in each of the published studies might be more a reflection of cannabinoids available for study at the time than evidence that cannabidiol (CBD) or other cannabinoids are not helpful. Because CBD is not intoxicating and, presumably, produces less cognitive impairment than THC, CBD could be seen as a more attractive therapeutic cannabinoid in a population already struggling with cognitive dysfunction. However, published human studies to date provide no insight on a potential therapeutic role for CBD in this population.

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Introduction

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On December 2, 2015 the Commissioner announced his decision to add intractable pain to the list of the program's qualifying medical conditions, effective August 1, 2016. Similarly, post-traumatic stress disorder (PTSD) was added, effective August 1, 2017, autism spectrum disorder and obstructive sleep apnea were added, effective August 1, 2018, and Alzheimer's disease was added, effective August 1, 2019.

To accomplish this review, the National Library of Medicine's MEDLINE database was searched using key words appropriate for each qualifying medical condition in the Minnesota medical cannabis program statute. Articles that appeared to be results of clinical trials or reviews of clinical trials were accessed through the MDH library for examination. References in such 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 government maintained web site of registered 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.

The body of this report contains a section for each of the 14 qualifying medical conditions. At the beginning of each section (or subsection, in the case of cancer) there are comments providing an overview of the scientific articles that follow. Below the citation for each article is a condensed description of the study and its results.

Trials involving non-smokeable medical cannabis usually use either extractions of cannabis, sometimes with processing that enriches specific components of the plant's constituent parts, or synthetic cannabinoids. Cannabinoids are a class of oxygen-containing aromatic hydrocarbons found distinctively in plants from the genus *Cannabis*.

The two cannabinoids typically found in greatest quantity in cannabis plants are delta-9-tetrahydrocannabinol (typically referred to as THC) and cannabidiol (CBD). THC is the cannabinoid usually present in greatest quantity and it is psychoactive, acting as a prominent cause of the euphoria - and sometimes dysphoria, - perceptions of time distortion, and so forth that are well known from recreational use of marijuana. Both THC and CBD have been studied extensively in pre-clinical research, both in basic laboratory studies and in animal models. Both have attributes and effects in animal models that suggest beneficial effects with medical use in humans. CBD is not psychoactive and might attenuate the

psychoactive effects of THC in some patients. There are relatively few clinical trials, especially large clinical trials that can produce the most definitive results. In recent years the number of such trials has increased to some degree, perhaps reflecting the commercialization of medical cannabis products around the world over the past few decades.

Cancer

If the underlying condition or treatment produces one or more of the following: severe or chronic pain, nausea or severe vomiting, or cachexia or severe wasting (three separate sections presented below)

Severe or Chronic Pain

Two early trials studied delta-9-THC sourced from the U.S. government (Noyes *J Clin Pharmacol* 1975; Noyes *Clin Pharmacol Ther* 1975) and gave single oral administrations of 5, 10, 15, and 20 mg THC to adult cancer patients. Oral administration of 20 mg was not well-tolerated. Studies where similar daily doses of THC, or larger, divided into smaller dose administrations over the course of the day, would be helpful. But such studies were not found in the published literature and do not appear to be in the planning phases on clinicaltrials.gov.

Later, larger trials have studied nabiximols, the US Adopted Name for Sativex.

Nabiximols is an oromucosal spray produced through extraction and processing of a strain of *Cannabis sativa* that results in high and stable concentrations of delta-9-THC and CBD and minor amounts of other cannabinoids

and terpenes. Each 100 micro-liter actualization (spray) contains 2.7 mg THC and 2.5 mg CBD. The high dose group in Portenoy 2012, at least 11 sprays per day (3 in the AM, 8 in the PM), was not well tolerated. 11 sprays delivers 29.7 mg THC (8.7 mg in the AM, 21.6 mg in the PM) and 25 mg CBD. Patients in Johnson 2010 self-titrated to an average of 8.75 sprays (23.6 mg THC, 21.9 mg CBD), delivered over the course of a day. Patients taking nabiximols in the Johnson 2010 study tolerated it fairly well. The Johnson 2010 study also had a group taking a cannabis extract that had only THC. Patients in this group self-titrated to 8.34 sprays over the course of a day (22.5 mg THC), tolerating it fairly well, with a side effect profile similar to the THC/CBD group. Patients in the Lynch 2014 study self-titrated to a mean of 8 sprays (21.6 mg THC and 20.0 mg CBD) spread throughout the day, with no study withdrawals due to treatment side effects. In the large study reported in Lichtman 2017 patients self-titrated to 6.4 sprays per day (17.3 mg THC and 16.0 mg CBD). Results in Fallon 2017 were very similar. These studies, as a group, suggest the wisdom of dividing a day's total dose of a balanced THC/CBD product, with total THC and CBD in the range of 15 to 25 mg (each) per day over multiple different administrations to mitigate side effects. The Johnson 2012 extension study lacked large numbers of patients followed long-term on nabiximols, but nevertheless it does provide some evidence of effectiveness over many months with no evidence of need for dose escalation over time.

Fallon MT, Lux EA, McQuade R, Rossetti S, Sanchez R, et al. Sativex oromucosal spray as adjunctive therapy in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy: two double-blind, randomized, placebo-controlled phase 3 studies. *Br J Pain* 2017;11:119-133.

This paper describes two clinical trials. Trial #1 methodology, number and location of study centers, and number of patients randomized to Sativex and placebo are very similar, but not quite the same, as the study described in Lichtman 2017. Drug exposure also very similar. Primary outcome was the biggest difference, with Sativex group showing 7.2% improvement from baseline in pain NRS score and the placebo group showing a 9.5% reduction (difference between groups not statistically significant). Trial #2 required $\geq 15\%$ reduction in NRS pain score at end of two week titration in order to move on to the three week treatment period. The average number of sprays during the two-week titration period was 6.4 (i.e. very similar to what is reported in Trial #1 [6.3 sprays/day in Sativex arm] and in Lichtman 2017 [6.4 sprays/day]). This paper also describes how, in pre-specified subanalyses of US participants in Trial #1 and in Lichtman 2017 had a primary efficacy outcome that favored Sativex – especially for participants ≥ 65 .

Johnson JR, Burnell-Nugent M, Lossignol D, Ganac-Motan ED, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC: CBD extract and THC extract in patients with intractable cancer-related pain. *J Pain Symptom Manage* 2010; 39:167-179.

The effect of two weeks of treatment with nabiximols, THC extract, or placebo was studied in this double-blind, randomized, placebo-controlled, parallel group study involving 177 adult cancer patients from 28 European centers. The patients were required to have advanced cancer with pain not adequately controlled despite optimized opioid management. Patients with chemotherapy within the preceding two weeks were excluded. Patients were randomized to nabiximols, to a cannabis extract containing only THC (2.7 mg per 100 micro-liter spray), or placebo spray.

Patients self-titrated with the instruction of increasing the number of sprays each day by a maximum of 50% until they either had satisfactory relief of their symptoms or developed unwanted side effects. Sprays were to be spread throughout the day, with at least 15 minutes between sprays.

Maximum number of sprays allowed within a 3 hour period was 8 and maximum within a 24 hour period was 48. The mean number of sprays in the nabiximols group was 8.75 (23.6 mg THC, 21.9 mg CBD) and the average number of sprays in the THC group was 8.34 (22.5 mg THC). The co- primary end-point was reduction in pain score between baseline and end of study. 43% of patients in the THC/CBD group achieved a 30% or greater reduction in their pain score, twice the

number of patients who achieved this response in the THC and placebo groups. A higher percentage of patients experienced somnolence (13%), dizziness (12%), and confusion (7%) in the nabiximols group than in placebo. Incidence of these side effects was similar in the THC/CBD and THC groups. However, 3 episodes of hypotension were seen in the nabiximols group and none was observed in the THC or placebo groups. Side effects leading to study withdrawal occurred in 17%, 12%, and 3%, respectively, for nabiximols, THC extract, and placebo.

Johnson JR, Lossignol D, Burnell-Nugent M, and Fallon MT. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal sprays and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. *J Pain Symptom Manage* 2013; 46:207-218.

This open-label extension to the parent study reported in Johnson 2010 enrolled 43 patients: 13 had received nabiximols (THC/CBD) in the parent study, 11 had received THC spray and 19 had received placebo. 39 received nabiximols in the extension study and 4 received THC spray. Though it was conceived as a long-term follow-up study, because of staggered enrollment in the parent study (creating shorter follow-up for more recently-enrolled patients before end of the extension study) and patients who dropped out of the study, median follow-up time for patients receiving nabiximols was 25 days (range 2 to 579 days) and for the four patients receiving THC spray median follow-up was 152 days (range 4 to 657 days). Patients were instructed to self-titrate dose to reach a balance between

effectiveness and side effects and to not exceed 8 sprays in a three hour period or 48 sprays per 24 hours. Actual dose experience of the patients was not reported, except that the authors noted study medication was taken for more than six months by 10% of patients and for more than one year by 5% without resulting in dose escalation. Effectiveness analyses were limited to 5 weeks of observation time, over which a trend of improvement in pain control was noted. A total of 23 patients (59%) receiving nabiximols and one of the 4 receiving THC spray withdrew because of side effects. Of these, 12 patients taking nabiximols had been in the placebo group during the parent study. Improvements over time were observed for insomnia and fatigue and worsening of nausea and vomiting was observed over time.

Lichtman AH, Lux EA, McQuade R, Rossetti S, et al. Results of a double-blind, randomized, placebo-controlled study of nabiximols oromucosal spray as adjunctive therapy in advanced cancer patients with chronic uncontrolled pain. *J Pain Symptom Manage* 2018;55:179-188.

This double-blind, randomized, placebo-controlled trial involved patients with advanced cancer and average pain score of 4 to 8 on a 0-10 scale despite optimized opioid therapy. Patients were randomized to nabiximols (n=199), a cannabis extract for oromucosal administration containing 2.7 mg THC and 2.5 mg CBD per spray, or placebo (n=198). The patients came from 114 study centers in 12 countries, including the United States. During a two-week titration period patients started with one spray per day and then gradually increased by one additional

spray per day according to a titration schedule until reaching unacceptable side effects or acceptable pain relief, up to a maximum of 10 sprays per day. Patients remained at the dose achieved at the end of the titration period for an additional three weeks for a total of five weeks on therapy. Primary outcome was change in 0-10 numerical rating scale (NRS) score between baseline and end of the five weeks on therapy. At the end of titration period, the average number of sprays in the nabiximols group was 6.4. Median improvement was 10.7% in the nabiximols group and 4.5% in the placebo group, with the difference between the groups not achieving statistical significance. Three patients experienced serious adverse events considered treatment related: two in the nabiximols group (one each, disorientation and visual hallucination) and one in the placebo group (vomiting).

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 and Symptom Manage* 2014; 47:166-173.

Randomized, placebo-controlled crossover pilot study of nabiximols vs placebo in 16 patients with chemotherapy-induced neuropathic pain. Inclusion criteria included neuropathic pain persisting for three months after completing chemotherapy with paclitaxel, vincristine, or cisplatin, average seven day intensity of pain ≥ 4 on an 11-point scale, and concurrent analgesics stable for 14 days before entry into the trial. Participants had a wide variety of cancers. Average chemotherapy cycle number when pain started was 2.8; average duration of pain was

17 months. The trial started with a one-week baseline pain assessment period, then up to two weeks of titration of medication upwards, four weeks at stable medication dose, up to two week period titrating dose down, then a two week wash- out period before a second round using the other agent. Dosing started with one spray and participants were instructed to increase the study medication by one to two sprays per day until they reached a dose that helped their pain, up to a maximum of 12 sprays per day, stopping increases if unacceptable side effects developed. The primary outcome was change in 11-point rating scale of pain over the past seven days. Secondary measures included SF-36 quality of life survey and QST sensory testing. 18 patients started the study and two dropped out for unspecified reasons. Mean dose used during active treatment was 8 sprays per day (range 3-12) and 11 sprays during placebo treatment. Mean baseline NRS score was 6.75. During active treatment, participants experienced 11.1% reduction in NRS score at week 4; during placebo treatment the reduction was 5.2% (difference not statistically significant). Five participants were reported as having a two point or greater decrease in NRS score during active treatment. Among these 5, called “responders,” the mean baseline NRS scores were 6.0. During active treatment, these participants experienced 43.3% reduction in NRS score; during placebo treatment the reduction was 10.0% (difference statistically significant). Most patients reported side effects during active treatment and only two reported side effects during placebo treatment. Most common side effects during active treatment were fatigue (n=7), dizziness (6), nausea (6), and dry mouth (5). Authors report there were no serious medication-related adverse events and that no patient

discontinued medication or withdrew from the study because of side effects.

Noyes R Jr, Brunk SF, Baram DA, and Canter A. Analgesic effect of delta-9-tetra-cannabinol. *J Clin Pharmacol* 1975; 15:139-143.

Ten adults with advanced cancer and continuous moderate pain were recruited for a double-blind trial testing the effect of single administrations of delta-9-THC at different dosages. The THC was sourced from the U.S. government and oral dosages tested were 5 mg, 10 mg, 15 mg, and 20 mg. Over 5 days patients received each of these dosages or placebo in random order. The patients remained on their usual pain medications (none on “large doses of narcotics”) until 4 AM each day and the study medication was administered at 8:30 AM and pain assessments done before administration and hourly thereafter for six hours. Measures of pain reduction and pain relief increased with larger doses. Analgesic effect increased over time, peaking at 3 hours for the lower doses and at 5 hours for the 20 mg dose. Interestingly, in all groups a secondary peak can be seen at 5 hours – perhaps the result of THC’s mobilization from the gall bladder and reabsorption following food ingestion. The most prominent side effect was dose-dependent drowsiness and slurred speech.

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

This randomized, double-blinded trial followed the preliminary trial reported in Noyes *J Clin Pharmacol* 1975. It randomized 36 advanced cancer patients with continuous

moderate pain to a morning administration of either placebo, 10 mg THC (sourced from the U.S. government), 60 mg codeine, 20 mg THC, or 120 mg codeine, in random order, on five successive days. Their usual analgesic medications (“none were receiving large doses of narcotics”) were continued until 4 AM and study medication administered at 8:30 AM. Information on pain and other symptoms was collected just before medication administration and hourly for seven hours thereafter. 10 mg THC showed improved pain control compared with placebo over 7 hours, but the difference was not statistically significant. The larger reduction in pain with 20 mg THC was a statistically significant difference from placebo but caused substantial cognitive impairments and drowsiness. Side effects were much milder and shorter lasting with 10 mg THC. The authors noted that evaluating pain relief was especially difficult in patients after receiving THC because in many instances the patients appeared exceptionally peaceful while reporting little pain relief. And, in other instances, they claimed that though the pain was unchanged, it bothered them less.

Portenoy RK, Ganae-Motan ED, Allende S, Yanagihara R, et al. Nabiximols for opioid- treated cancer patients with poorly- controlled chronic pain: a randomized, placebo-controlled, graded dose trial. *J Pain* 2012; 13:438-449.

This was a randomized, placebo-controlled graded dose study of patients with advanced cancer and pain despite optimized opioid therapy from 84 centers in North America, Europe, South America and South Africa. Patients who had received or planned to receive chemotherapy or other treatments

expected to change pain were excluded. Baseline pain had to be between 4 and 8 on an 11-point scale at baseline and stable for three consecutive days during a qualifying period when opioid management was optimized. Study treatment was nabiximols. Patients were randomized to one of three dose titration regimens and then half of each group was randomized to nabiximols and half to placebo. Patients randomized to the Low Dose group were instructed to titrate the study medication to between 1 and 4 sprays per day. Those assigned to Medium Dose group titrated the number of sprays to between 6 and 10 sprays per day, and those assigned to the High Dose group titrated to between 11 and 16 sprays per day. Daily dosage was split between morning and evening administration. All three groups were given a titration schedule that increased total dose over 7 days (3 days for the low dose group). Patients were told to increase to the maximum dose for their group unless intolerable side effects prevented further dose escalation. After the week of dose titration patients continued on stable dosing for four weeks. Daily assessments included average pain, worst pain, and sleep disruption. There were also baseline and study-end pain questionnaires and quality of life surveys. The primary endpoint was 30% or greater reduction of pain from baseline. Results showed no statistically significant difference among treatment groups, compared to placebo. However, when the full distribution of percentage of pain relief is compared among the groups, the two lower dose groups showed an improvement in pain relief, compared to placebo, which was statistically significant. Similar results were seen when “worst pain” and “disrupted sleep” scores were analyzed, where the largest improvement over placebo

– and the only statistically significant differences – were seen in the group that administered 1 to 4 sprays per day. Neither the use of regularly scheduled opioids nor the number of opioid doses taken as needed for breakthrough pain varied significantly between treatment groups. Not only did the high dose group not show effectiveness in pain relief, but the high doses were not well tolerated. Only 66% could continue at the lowest dose (11 sprays) to the end of the study.

Nausea or Severe Vomiting

Nausea and vomiting are common side effects of cancer and – especially - its treatment. There are multiple drug therapies for nausea and vomiting, but not all are effective for all patients and some patients cannot tolerate the side effects. There has been substantial study of cannabinoids for treatment of chemotherapy-induced nausea and vomiting (CINV). Most published trials have studied three synthetic versions of THC or THC analogs: dronabinol, nabilone, and levonantradol. Dronabinol, a synthetically produced delta-9-THC, and nabilone, a synthetic derivative of delta-9-THC, are both approved by the FDA for treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic therapy. Levonantradol is a synthetic analog of dronabinol that is much more potent than THC and remains an investigational drug. Of these three drugs, dronabinol is the one directly relevant to the Minnesota medical cannabis program.

A systematic review and meta-analysis of trials of dronabinol, nabilone and levonantradol for CINV, some comparing them to placebo and some comparing them

to other antiemetic drugs, covered 30 studies (Machado Rocha 2008). Limitations of sample sizes and study designs prevented firm conclusions, but the authors' general conclusion was there was evidence that dronabinol had better acute anti-emetic efficiency than the conventional anti-emetic drug comparitors. Doses of dronabinol ranged generally from 30mg/day to 80 mg/day in divided doses. The FDA label for dronabinol emphasizes the need for dosage individualization, but for use as an antiemetic, notes that most patients respond to 5 mg three or four times daily and that use of dronabinol with phenothiazines has resulted in improved efficacy as compared to either drug alone, without additional toxicity.

Two early trials of oral THC (with, in some cases, the addition of smoked marijuana) for reduction of chemotherapy-induced nausea and vomiting had mixed results. In both trials, the majority of patients were experienced marijuana smokers. The same protocol was used in both trials, administering five oral doses of approximately 18 mg delta-9-THC from one hour prior to 11 hours after time of chemotherapy infusion. Significant reduction in nausea and vomiting occurred during the trial with methotrexate therapy (Chang 1979), but no difference from placebo was observed in the trial with Adriamycin and Cytosan chemotherapy (Chang 1981). Two additional trials of THC for CINV from the same late-1970s era used similar dosing: 10 to 15 mg five times over 24 hours (Ekert 1979) and 10 to 15 mg 3 times over 12 hours (Sallan 1980).

A small randomized, double-blind trial studied nabiximols treatment as an adjunct to standard anti-emetic therapy for chemotherapy-induced nausea and vomiting

(Duran 2010). On the day of chemotherapy treatment three sprays of nabiximols were delivered and the patient was instructed to increase the number of sprays throughout the day, up to a limit of 8 sprays within any 4 hour period. The mean number of daily sprays taken during the four days after chemotherapy was 4.8 in the active treatment group (range 2.7- 5.0), representing a daily THC dose of 13.0 mg of THC per day (range 7.3 mg to 13.5 mg). One patient withdrew from active treatment because of adverse effects. A higher proportion of patients in the active treatment group (5/7) had complete response, compared to the placebo group (2/9). Complete response was defined by no vomiting and a specified score on a self-assessed nausea rating scale.

Chang AE, Shiling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Simon RM, Rosenberg SA. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. A prospective, randomized evaluation. *Ann Intern Med* 1970; 91:819-824.

Fifteen patients, age 15 to 49, with osteogenic sarcoma and receiving high dose methotrexate chemotherapy were studied. Eleven of the 15 were experienced users of marijuana. In this randomized, double-blind, placebo-controlled trial patients served as their own control. One hour prior to each instance of chemotherapy infusion the patient received a capsule containing either 10 mg/m² THC or placebo, with additional doses every three hours for a total of five doses. Based on a body surface area of 1.75 m², the oral THC dose was 17.5 mg every 3 hours for five doses. If vomiting occurred

during the treatment, patients received a marijuana cigarette instead of a capsule for the remaining doses. Results showed THC was significantly more effective than placebo in reducing the number of vomiting and retching episodes, degree of nausea, duration of nausea and volume of emesis.

Chang AE, Shling DJ, Stillman RC, Goldberg NH, Seipp CA, Barofsky I, Rosenberg S. A prospective evaluation of delta-9-tetrahydrocannabinol as an antiemetic in patients receiving Adriamycin and Cytoxan chemotherapy. *Cancer* 1981; 47:1746-1751.

Eight patients, age 17 to 58, with soft tissue sarcomas and receiving Adriamycin and Cytoxan chemotherapy were studied. Seven of the eight were experienced users of marijuana. In this randomized, double-blind, placebo-controlled trial patients served as their own control. One hour prior to each instance of chemotherapy infusion the patient received a capsule containing either 10 mg/m² THC or placebo, with additional doses every three hours for a total of five doses. Based on a body surface area of 1.75 m², the oral THC dose was 17.5 mg every 3 hours for five doses. If vomiting occurred during the treatment, patients received a marijuana cigarette instead of a capsule for the remaining doses. Results showed no effect of THC on nausea or vomiting in these chemotherapy patients.

Ekert H, Waters KD, Jurk IH, Mobilia J, et al. Amelioration of cancer chemotherapy- induced nausea and vomiting by delta-9tetrahydrocannabinol. Med J Aust 1979; 2:657-659.

This short article reports on two studies – or perhaps three. It is somewhat confusing. One study was a double-blind test of delta- 9-THC and meloclopramide on children with cancer requiring chemotherapy. Source of the THC is not described. An oral dose of 10 mg/m² (with maximum of 15 mg) was administered four hours before chemotherapy and at 4, 8, 16, and 24 hours after the first dose. Incidence of nausea, vomiting, and anorexia was less than half in the patients taking THC, compared to those taking meloclopramide, with the differences achieving statistical significance. The side effect reported, drowsiness, was not common and was similar in both groups.

Duran M, Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol 2010;70(4):656-663.

Small randomized, double-blind trial of nabiximols treatment as an adjunct to standard anti-emetic therapy for chemotherapy-induced nausea and vomiting. 16 patients suffering from CINV despite prophylaxis with standard anti- emetic treatment were randomized to placebo (n=9) or nabiximols (n=7), to be taken in conjunction with standard anti- emetic treatment. Nabiximols (Sativex) is an oromucosal cannabis extract spray developed by GW Pharmaceuticals. The whole plant extract is highly standardized, produced from

cloned cannabis chemovars grown under controlled conditions. Each 100 µliter actuation (spray) yields 2.7 mg delta-9-THC and 2.5 mg of CBD with these two cannabinoids constituting at least 90% of cannabinoid content. On the day of chemotherapy treatment three sprays of nabiximols were delivered and the patient was instructed to increase home-dose for four days, up to 8 sprays within any 4 hour period. The mean number of daily sprays taken during the four days after chemotherapy was 4.8 in the active treatment group (range 2.7-5.0), representing a daily THC dose of 13.0 mg of THC per day (range 7.3 mg to 13.5 mg).

One patient withdrew from active treatment because of adverse effects. A higher proportion of patients in the active treatment group (5/7) had complete response, compared to the placebo group (2/9). Complete response was defined by no vomiting and a specified score on a self-assessed nausea rating scale.

Machado Rocha FC, Stefano SC, DeCassia HR, Rosa Oliveira LM, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl) 2008;17:431-443.

A systematic review and meta-analysis of trials of dronabinol and nabilone for chemotherapy-induced nausea and vomiting, some comparing them to placebo and some comparing them to other antiemetic drugs.

Sallan SE, Cronin C, Zelen M, and Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980;302:135-138.

This was a study of delta-9-THC and prochlorperazine as antiemetics in cancer patients receiving chemotherapy resulting in nausea and vomiting inadequately controlled by conventional antiemetics, including phenothiazines. It was carried out in the late 1970s using delta-9-THC sourced from the National Institute on Drug Abuse. 84 patients were randomized to receive three double-blind single-day courses of drug on days of chemotherapy. The trial was structured so patients received different orderings of two kinds of one drug and one kind of the other (to address potential order effect). When the course was THC, the patient received 15 mg THC (or, in a few cases of small persons, 10 mg) an hour before start of chemotherapy and the same dose 4 and 8 hours later. “Complete response” was defined as no nausea or vomiting after chemotherapy.

Regardless of the emetic activity of the chemotherapeutic agents, there were more complete responses to THC courses (36 of 79 courses) than to prochlorperazine (16 of 78 courses). Increased food intake occurred more frequently with THC. Side effects were not recorded, other than comments on proportions of patients who “got high.” Of 36 THC courses resulting in complete response, 32 were associated with a high.

Cachexia or Severe Wasting

Results of trials on effectiveness of cannabis formulations for increasing appetite in cancer

patients are mixed and not particularly encouraging. Two early trials that used delta-9-THC derived from cannabis plants reported positive results in patients receiving chemotherapy. Maximum daily dose in the trial with plant-derived THC was up to 75 mg in five divided doses in children (Ekert 1979) and 30 to 45 mg in 3 divided doses in adults (Sallan 1980).

Three more recent trials used dronabinol, synthetic delta-9-THC. In one study with positive results cancer patients (not necessarily on chemotherapy) took 5 mg or 7.5 mg daily in divided doses with minimal side effects (Brisbois 2011). Another trial with modestly positive results used 7.5 mg/day in three divided doses, resulting in intolerable side effects for 20% of patients (Nelson 1994). A large trial that compared dronabinol and megestrol used 5 mg dronabinol daily in two divided doses. The modest improvement in weight seen with dronabinol was inferior to that seen with megestrol; patients tolerated the dronabinol well (Jatoi 2002).

A large clinical trial comparing THC:CBD extract, THC-only extract and placebo was stopped early because of lack of effectiveness (Strasser 2006). Patients in the THC:CBD arm received 5.0 mg THC and 2.0 mg CBD daily in two divided doses; patients in the THC-only arm received 5.0 mg THC daily in two divided doses. Temporary or permanent dose reductions were necessary in approximately a third of both groups.

Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, et al. Delta-9tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebocontrolled pilot trial. *Ann Oncol* 2011;2086-2093.

This was a randomized, double-blind placebo controlled pilot study of effectiveness of dronabinol (synthetic delta-9-THC) in improving taste and smell (chemosensory) perception as well as appetite, weight, and quality of life in cancer patients with chemosensory alterations. 46 adult cancer patients with poor appetite and chemosensory alterations were recruited from two Canadian centers and randomized to dronabinol or placebo for 18 days. A third of the patients were receiving chemotherapy at the time of data collection, but all patients had previously been on multiple rounds of chemotherapy. Patients were started on one capsule (2.5 mg dronabinol) daily for three days then increased to two capsules daily (5 mg dronabinol/day). Patients had the option of increasing dose to a maximum of 8 capsules (20 mg dronabinol/day). 21 patients completed the study: 11 on dronabinol and 10 on placebo. Eight of the dronabinol patients took two capsules per day (5 mg/day in 2 divided doses) and 3 patients increased dose to 3 capsules (7.5 mg/day in 3 divided doses). Most patients receiving dronabinol had increased appetite at the end of the study (7), 3 had no change and one had incomplete data. Among patients receiving placebo half had decreased appetite (5) and two showed no change (status of the remaining 3 not reported, but could be either increased appetite or incomplete data). Compared with placebo, dronabinol-treated

patients increased their protein intake as a proportion of total energy and reported better sleep. Increase in caloric intake and in quality of life scores was similar in the two groups. No differences in number of adverse events or serious adverse events between active treatment and placebo groups were reported.

Ekert H, Waters KD, Jurk IH, Mobilia J, et al. Amelioration of cancer chemotherapy- induced nausea and vomiting by delta-9tetrahydrocannabinol. *Med J Aust* 1979;2:657659.

This short article reports on two studies – or perhaps three. It is somewhat confusing. One study was a double-blind test of delta-9-THC and meloclopramide on children with cancer requiring chemotherapy. Source of the THC is not described. An oral dose of 10 mg/m² (with maximum of 15 mg) was administered four hours before chemotherapy and at 4, 8, 16, and 24 hours after the first dose. Incidence of nausea, vomiting, and anorexia was less than half in the patients taking THC, compared to those taking meloclopramide, with the differences achieving statistical significance. The side effect reported, drowsiness, was not common and was similar in both groups.

Jatoi A, Windschitl HE, Loprinzi CL, Sloan JA, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a North Central Cancer Treatment Group study. *J Clin Oncol* 2002;20:567-573.

Jatoi et al studied the effect of megestrol acetate, dronabinol (synthetic delta-9-THC)

and combination therapy on 469 patients with incurable cancer on no appetite stimulating drugs. All patients reported loss of 5 pounds or more over two months or caloric intake of less than 20 calories/kg of body weight. Patients were randomized to (1) megestrol acetate liquid suspension 800 mg orally daily plus capsule placebo; (2) dronabinol capsules 2.5 mg orally twice a day plus liquid placebo; or (3) both medications. Patients were continued on treatment for as long as the health care provider thought it beneficial or until toxic side effects prompted study withdrawal. The North Central Cancer Treatment Group questionnaires for appetite and weight were used at baseline, weekly for a month, and monthly thereafter. Duration of observation was similar among the groups (megestrol=80 days, dronabinol=57 days, combination=74 days). A greater proportion of patients taking megestrol (11%) gained more than 10% of baseline weight, by home weight measurements, than patients taking dronabinol (3%) or both drugs (8%). And a greater percentage of patients taking megestrol reported improved appetite (75%), than patients taking dronabinol (49%) or both drugs (66%). Side effects were similar across the treatment groups, except for impotence, which was reported by 18 men taking megestrol, 4 men taking dronabinol, and 14 men taking both.

Nelson K, Walsh D, Deeter P, and Sheehan F. A phase II study of delta-9-tetrahydrocannabinol for appetite stimulation in cancer-associated anorexia. *J Palliat Care* 1994;10:14-18.

Nineteen adult patients with advanced cancer were recruited into an open-label (unmasked) four week trial of dronabinol (synthetic delta-9-THC) on appetite. Some

patients were receiving chemotherapy and some were not. Patients were excluded if they were taking other drugs known to affect appetite. Each was started on 2.5 mg dronabinol three times per day (patients over the age of 65 were started on 2.5 mg twice /day for three days and then increased to three times/day). Four patients reported side effects and three dropped out because of them: one for slurred speech and two for nausea. A fourth patient experienced severe nausea but continued in the study. At four weeks 13 of 18 reported their appetite was at least slightly improved, compared with baseline (10 "slight improvement" and 3 "major improvement").

Sallan SE, Cronin C, Zelen M, and Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta-9-tetrahydrocannabinol and prochlorperazine. *N Engl J Med* 1980;302:135-138.

This was a study of delta-9-THC and prochlorperazine as antiemetics in cancer patients receiving chemotherapy resulting in nausea and vomiting inadequately controlled by conventional antiemetics, including phenothiazines. It was carried out in the late 1970s using delta-9-THC sourced from the National Institute on Drug Abuse. 84 patients were randomized to receive three double-blind single-day courses of drug on days of chemotherapy. The trial was structured so patients received different orderings of two kinds of one drug and one kind of the other (to address potential order effect). When the course was THC, the patient received 15 mg THC (or, in a few cases of small persons, 10 mg) an hour before start of chemotherapy and the same dose 4 and 8 hours later.

“Complete response” was defined as no nausea or vomiting after chemotherapy. Regardless of the emetic activity of the chemotherapeutic agents, there were more complete responses to THC courses (36 of 79 courses) than to prochlorperazine (16 of 78 courses). Increased food intake occurred more frequently with THC. Side effects were not recorded, other than comments on proportions of patients who “got high.” Of 36 THC courses resulting in complete response, 32 were associated with a high.

Strasser F, Luftner D, Possinger K, Ernst G, et al. Comparison of orally administered cannabis extract and delta-9- tetrahydrocannabinol in treating patients with cancer-related anorexiacachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo- controlled clinical trial from the Cannabis- in- Cachexia-StudyGroup. *J Clin Oncol* 2006;24:3394-3400.

A trial comparing effectiveness of cannabis extract capsules containing 2.5 mg THC and 1.0 mg CBD twice daily, cannabis extract capsules containing only 2.5 mg THC twice daily and placebo on increasing appetite and quality of life in terminal cancer patients was stopped early because of lack of effectiveness. Before the study was stopped 243 patients with at least 5% weight loss over the past 6 months, from 30 European centers, were randomly assigned to the three treatment arms for six weeks of treatment. Many patients dropped out of the study – most because they withdrew consent and 164 completed the study (CBD/THC: 66/95, THC: 65/100, placebo:33/48) Primary outcome was improvement of appetite as measured by visual analog scale. Secondary

outcome measures included a cancer-specific quality of life survey. After 6 weeks THC/CBD and placebo patients showed similar improvement in appetite; THC patients showed little improvement. Mean quality of life measures showed no significant change in any of the three groups. Side effects were common, with temporary or permanent dose reductions necessary in 78 patients (CBD/THC=34, THC=30, placebo=14). Side effects that appeared to be more common in the active treatment groups included nausea, fatigue, pain, diarrhea, and obstipation.

Glaucoma

Glaucoma is a multi-factorial disease characterized by the progressive degeneration of the optic nerve and the death of retinal ganglion cells, ultimately leading to irreversible blindness. Increased intraocular pressure (IOP) has been implicated in the pathophysiology of glaucoma; however, inadequate blood supply to the optic nerve, oxidative damage, and apoptosis (programmed death) of the retinal ganglion cells are also thought to play a role in the disease. Aside from lowering IOP, cannabinoids such as delta-9-THC and CBD may also have neuroprotective effects which could be useful in the management of glaucoma. Published trails to date have focused on reduction of IOP. The few published clinical trials of medical cannabis for glaucoma are quite small with mixed evidence of temporary reduction in IOC. An early open-label (uncontrolled) trial of single-dose administrations of dronabinol (synthetic delta-9-THC) found 20 mg and 25 mg were equally effective in reducing IOP for at least 10 hours, but side effects at these dosages

were intolerable (Merritt 1980). In a second, small, double-blinded study reported in the same article, effects of single administrations of 5 mg and 10 mg synthetic delta-9-THC were compared with placebo. No difference in IOP reduction was seen between active drug and placebo patients.

In a small prospective observational study patients were started on 2.5 mg THC four times per day and instructed to titrate dose up, balancing effectiveness of IOP reduction with appearance of side effects. During the course of the trial 2 patients received a maximum dose of 7.5 mg 4x/day, 3 pts 5.0 mg 4x/day, and 3 did not increase from 2.5 mg 4x/day. Side effects were common and severe enough in four patients to cause withdrawal from the study. This occurred at a wide range of doses. IOP reduction was inconsistent across patient weekly assessments, with only two of nine participants having reduced IOP during the majority of assessments (Flach 2002).

A well-controlled pilot study of six patients with ocular hypertension or early primary open-angle glaucoma reported that single sub-lingual doses of 5 mg delta-9-THC (applied by means of an oromucosal spray) significantly but temporarily reduced IOP 2 hours after administration. After the four hour measurement IOP had returned to normal (Tomida 2006). A single sub-lingual dose of 20 mg cannabidiol (CBD) (containing around 1 mg delta-9-THC) had no effect while a single sub-lingual dose 40 mg of CBD (containing around 2 mg of delta-9-THC) caused a significant transient increase in IOP 4 hours after administration. There were no serious or severe adverse events and all but 2 (nausea and hypertension after administration of 5 mg delta-9-THC, rated moderate) were rated mild.

Flach AJ. Delta-9-tetrahydrocannabinol (THC) in the treatment of end-stage open-angle glaucoma. *Trans Am Ophthalmol Soc* 2002;100:215-224.

Nonrandomized, uncontrolled prospective observational study of nine California adults with primary open angle glaucoma on maximally tolerated medical therapy available in the mid-1980s. Oral capsules with 2.5 mg or 5 mg THC dissolved in sesame oil were used in the study. Initial dosage for each patient was 2.5 mg or 5 mg given each 4 hours (four times daily) while awake. The dose was increased or decreased by 2.5 mg increments as needed to obtain a greater effect or less toxicity with a maximum permitted dose of 20 mg four times daily. After initiation of THC, IOP was measured weekly until satisfactory control of IOP was achieved for 2 consecutive weeks with examinations monthly thereafter. Maximum allowed dose was 15 mg THC four times daily (60 mg daily). During the course of the trial 2 patients received a maximum dose of 7.5 mg 4x/day (30 mg daily), 3 pts 5.0 mg 4x/day (20 mg daily), and 3 did not increase from 2.5 mg 4x/day (10 mg daily). All patients withdrew from the study, for a variety of reasons, between months 1 and 9. Four withdrew because of side effects (3 weeks – taking 2.5 mg 4x/day, 8 weeks – 7.5 mg 4x/day, 20 weeks – 5 mg/day, 20 weeks – 15 mg/day,) such as distortion of perception, confusion, anxiety, depression, and severe dizziness. The dizziness and lightheadedness reported by subjects in the study were never associated with systemic hypotension. All patients were observed to have at least an initial improvement in IOP. An improvement was noted during more than 50% of the office visits in two of the nine subjects. One subject was considered improved on all visits during

a 36 month treatment period (withdrew from study because of cataract surgery).

Merritt, JC, McKinnon S, Armstrong JR, Hatem G, Reid LA. Oral delta 9-Tetrahydrocannabinol in Heterogenous Glaucomas. *Ann Ophthalmol* 1980;12:947-950.

The study report contains results from two small observational trials of different designs at different US institutions. Group A was seven glaucoma patients treated with 20 mg or 25 mg synthetic delta-9-THC capsules obtained from the National Institute on Drug Abuse. The dose was given in the morning. IOP was decreased 7.8 +/- 1.7 mm Hg at 5 hours. Doses of 20 mg and 25 mg were found equally effective in lowering IOP for at least 10 hours. But adverse effects (depersonalization, acute panic reactions, and paranoia) occurred with such frequency, in the opinion of the authors (frequency not reported) as to preclude further testing at these dosages. Accordingly, Group B was administered 5 mg or 10 mg synthetic delta-9-THC or placebo in a randomized, double-masked study with 10 subjects. Gradual decreases in IOP occurred with both cannabinoid and placebo therapies for up to 5 hours. But cannabinoid therapy produced no greater IOP reduction than placebo. One subject who took 5 mg delta 9-THC experienced tachycardia, severe postural hypotension and severe anxiety and depersonalization reactions.

Tomida I, Azuara-Blanco A, House H, Flint M, Pertwee R, Robson P. Effect of sublingual application of cannabinoids on intraocular pressure: a pilot study. *J Glaucoma* 2006;15(5):349-353.

A randomized, double-masked, placebo-controlled, 4 way crossover study at a single institution. Six subjects with either ocular hypertension or primary open-angle glaucoma discontinued their topical glaucoma medication (three had none) for 4 to 6 weeks before receiving the test medication. Subjects were administered oromucosal spray preparations under the tongue. The preparations delivered 5 mg delta-9-THC, 20 mg CBD, 40 mg CBD, or placebo. The CBD preparations contained a small amount of delta-9-THC: 1 mg delta-9-THC for every 21 mg CBD. Intraocular pressure was measured at hours 0, 1, 2, 3, 4, 6, and 12. Two hours after sublingual administration of 5 mg delta 9-THC, the IOP was significantly lower than with placebo (23.5 mm Hg vs. 27.3 mm Hg, P=0.026). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9 mm Hg (P=0.028). One patient experienced a transient and mild panic-like reaction after delta 9-THC administration.

Human
Immunodeficiency
Virus or Acquired

Immune Deficiency Syndrome

Each of the relevant published trials identified used dronabinol, synthetic delta-9-THC, and most studied its effectiveness on improving appetite and increasing weight in HIV-positive patients. Dronabinol is approved by the FDA for anorexia associated with weight loss in patients with AIDS (and for nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments). The FDA label acknowledges the wide range of dosages of dronabinol used in clinical trials and that the pharmacologic effects of the drug have wide inter-individual variability. For appetite stimulation, the label recommends, for adults, to start with 2.5 mg before lunch and 2.5 mg before supper. It goes on to recommend when adverse events are absent or minimal and further therapeutic effect is desired, to increase the dose to 2.5 mg before lunch and 5 mg before supper or 5 and 5 mg. It notes that 10 mg twice daily has been tolerated in about half of the patients in appetite stimulation studies. Those recommendations are broadly consistent with the findings of the studies below (Abrams 2003, Beal 1995, Beal 1997), with the exception of trials that recruited regular marijuana users. In this patient group it appears that larger doses of dronabinol are well tolerated (Bedi 2010, Haney 2005, Haney 2007). But even at these relatively high dosages of dronabinol, its effectiveness at improving appetite and weight gain are

mixed. A study of the effect of dronabinol and smoked marijuana on viral load in HIV-infected patients taking antiretroviral protease inhibitor drugs gives some assurance that THC treatment in this patient group is not unsafe (Abrams 2003).

Two clinical trials are now being organized. The first will compare effects of three kinds of vaporized cannabis on HIV neuropathic pain (3.74% THC/0.49% CBD; 3.49% THC/4.17% CBD; 3.11% THC/15.76% CBD). An estimated 120 adults will be enrolled in California for this study and followed for six months with daily reporting of pain intensity. It is not yet open for enrollment and has a completion date of December, 2020. "Effects of Cannabis and Endocannabinoids on HIV Neuropathic Pain"

<https://clinicaltrials.gov/ct2/show/NCT03099005?term=NCT03099005&rank=1>

The second plans to enroll and follow for 18 months a cohort of 250 HIV+ and HIV- adults in New York with (a) severe or chronic pain, (b) opioid analgesic use, and (c) new certification for medical cannabis. The primary exposure measure will be number of days of medical cannabis use in each two-week period during the 18-month timeframe (type of cannabis product not specified in the trial summary). The goal of the study is to understand how medical cannabis use affects opioid analgesic use over time, with particular attention to THC/CBD content, HIV outcomes, and adverse events. Not yet recruiting; estimated study completion date: June, 2022.

<https://www.clinicaltrials.gov/ct2/show/NCT03268551?cond=NCT03268551&rank=1>

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

A total of 67 HIV-positive patients participated in this randomized, placebo-controlled trial over 25 days (4 days lead-in and 21 days inpatient treatment) whose primary objective was to determine the short-term effect of cannabis on the viral load in HIV-infected patients. Participants were at least 18 years old, experienced marijuana users, and were on stable antiretroviral protease inhibitor regimens with indinavir or nelfinavir. None of them smoked marijuana or ingested cannabinoids within 30 days of enrollment. Patients taking nelfinavir and indinavir were stratified and allocated into 3 different groups: marijuana, dronabinol, and placebo. The marijuana group (n = 22) smoked up to three 3.95% THC marijuana cigarettes 1 hour before meals daily, as tolerated. Dronabinol (n = 20) and placebo (n = 20) groups received either 2.5 mg dronabinol or placebo capsules 3 times daily before meals. HIV RNA level was monitored at baseline, days 2, 5, 8, 11, 14, 17, 19, and 21. CD4+ and CD8+ cell counts were collected at baseline and every 7 days. Five patients left the study prior to day 14 and 14 completed the trial. Results showed no significant impact from cannabinoids on HIV RNA level. Both cannabinoid groups had increased CD4+ and CD8+ cell counts, compared with placebo group, indicating benefit rather than harm. Pharmacokinetics of both protease inhibitors were also unaffected by cannabinoid exposures. Significant increases in weight gain occurred in both the dronabinol (median = 3.2 kg;

range -1.4 to 7.6 kg) and marijuana (median = 3.0 kg; range -0.75 to 8.6 kg) groups.

Beal JE, Olson R, Laubenstein L, Morales JO, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995;10:89-97.

139 patients at advanced stages of HIV with AIDS-related anorexia were included in this multi-center, randomized, double-blind, placebo-controlled, parallel-group trial over 6 weeks. All participants were marijuana free for at least 30 days before the trial. The trial had two treatment arms: dronabinol and placebo. Patients were randomized to each group and received capsules with either placebo or 2.5 mg dronabinol and received instruction to take one capsule twice a day. The dose was reduced to one capsule per day if intolerable side effects developed (n = 17 in dronabinol group). At baseline and three times weekly patients used a 100-mm visual analog scale (VAS) to rate their mood, appetite, and nausea on a scale from 0 to 100 with 0 being no appetite, no nausea, and terrible mood, and 100 representing respective opposites. Subjects were also evaluated biweekly on weight, physical exam and Karnofsky score – a performance assessment with a score of 100 representing normal activity, 50 as need for frequent assistance and medical care, and 0 representing death. Of the 139 patients, 51 were not evaluable due to protocol violation or noncompletion of study treatment. Evaluable patients' outcomes showed statistically significant improvements in appetite, mood, decreased nausea, and stabilized weight from dronabinol use compared with placebo. No significant difference was seen in the Karnofsky score

between the two groups. Overall, dronabinol was well tolerated, with central nervous system disturbances such as dizziness, euphoria, thinking abnormalities, and somnolence being the most commonly reported treatment-related side effects. Only 16 patients (8.3%) receiving dronabinol and 3 (4.5%) receiving placebo discontinued treatment due to side effects. No significant interaction occurred between dronabinol and opioid analgesics or benzodiazepines in terms of adverse events. This trial was an important part of the evidence that led the FDA to approve dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS.

Beal JE, Olson R, Lefkowitz L, Laubenstein L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage* 1997;14:7-14.

This was a follow-up study on participants from the Dronabinol as a Treatment of Anorexia Associated with Weight Loss in Patients with AIDS trial (Beal 1995) with a duration of 12 months. Ninety-four late-stage AIDS patients from the parent trial enrolled in this multi-center, open-label study. Of these, 46 received dronabinol and 48 received placebo during the parent trial. Treatment initiated at 2.5 mg dronabinol twice daily for 90% and 2.5 g daily for 10% (patients who could tolerate only 2.5 mg daily in the parent trial). Dose titration and adjustments were made according to each patient's response and side effects. Dose increases were limited to 5 mg/day every 2 weeks. Dose was decreased to 2.5 mg/day in 19% of patients and increased to 7.5 mg/day or higher (2 patients 10 mg/day, 1 patient 20

mg/day) in 19%. Only 22 patients (24%) completed the 12 month study. Side effects were the reason for discontinuation for 14 patients. The most common reason for drop-outs was intercurrent illness (n = 25). Patients treated with dronabinol in the parent trial continued to show improvements in appetite. Patients treated with placebo in the parent trial showed substantial improvement in appetite, especially during the first 4 months of dronabinol therapy. Patient weight tended to remain stable for the first 5 months and then showed modest decline. Treatment-related adverse events were reported in 44% of patients, with 2% having an adverse event considered severe (nature of events not specified). The most common side effects were anxiety, confusion, depersonalization, dizziness, euphoria, somnolence, and abnormal thinking.

Bedi G, Foltin RW, Gunderson EW, Rabkin J, Hart CL, Comer SD, Vosburg SK, Haney M. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: A controlled laboratory study. *Psychopharmacol (Berl)* 2010;212:675-686.

Seven HIV-positive adults age 21-50 on at least two antiretroviral medications and who use marijuana at least twice per week were recruited for this within-subjects, double-blind, placebo-controlled study. During one of two 16-day inpatient stays subjects received 10 mg dronabinol (synthetic delta-9-THC) 4 times per day; during the other 16 day stay they received placebo capsules. The two stays were separated by a 5 to 15 day outpatient period for study of medication clearance. Despite sustained increases in self-reported food cravings, dronabinol only

increased caloric intake in the initial eight days of dosing. During the initial eight days there was an average weight gain of 1 kg (not statistically significant) and no weight gain in the second eight days of dronabinol treatment. Similarly, sleep quality was improved only during the first 8 days of dosing. Mood was enhanced for the duration of dronabinol use. These relatively high dronabinol doses in habitual marijuana users were well tolerated with few negative subjective effects. There were minor effects of dronabinol on aspects of cognitive testing performance.

Haney M, Rabkin J, Gunderson E, and Foltin RW. Dronabinol and marijuana in HIV(+) marijuana smokers: acute effects on caloric intake and mood.

***Psychopharmacology (Berl)* 2005;181:170178**

Thirty HIV-positive marijuana-using patients were recruited; 15 with and 15 without clinically significant muscle wasting, for testing the effect of single administrations of dronabinol and marijuana. At eight 7-hour testing sessions spread out over 4 weeks, participants took capsules and then one hour afterward took three puffs of a marijuana cigarette. The capsules contained 0, 10, 20, or 30 mg of dronabinol and the cigarettes were 0.0, 1.8, 2.8, or 3.9% THC. In any one session only one dose form was active. Mood, physical symptoms, food intake, cardiovascular data, and cognitive task performance were measured before and repeatedly during each session. Caloric intake was significantly increased for the patients with muscle wasting with each of the dose forms, but not for patients without muscle wasting (who had a higher baseline caloric intake). The 10 mg and 20 mg of dronabinol

were well tolerated in this study's cohort of marijuana users. The 30 mg dronabinol administration produced at least one adverse event (headache, vomiting, and "uncomfortable level of intoxication") in 20% of participants. Drug effects on cognitive performance were minor.

Haney M, Gunderson E, Rabkin J, Hart C>, et al. Dronabinol and marijuana in HIV- positive marijuana smokers. Caloric intake, mood, and sleep. *J Acquir Immune Defic Syndr* 2007;45:545554.

Ten HIV-positive experienced marijuana smokers with an average age of 40 years were included in this research. Subjects took capsules and smoked marijuana cigarettes four times per day over sequential four day periods, with each four day period separated by a four day wash-out period. Two dosages of capsules were used, dronabinol 5 mg and 10 mg and marijuana cigarettes with two strengths of delta-9-THC were used, 2.0% and 3.6%. During any given four day treatment period, only one dose form was active. The courses of treatment were done in an inpatient setting with extensive patient assessments and testing, including a cognitive testing battery, hunger-satiety questionnaire, food intake, and subjective experience surveys. Results showed that dronabinol and smoked marijuana had similar dose-dependent improvements in total daily caloric intake and frequency of eating as compared to placebo. The higher doses of both also resulted in significant increase in weight within 4 days. Compared with placebo, neither dronabinol nor smoked marijuana significantly altered performance on any of the cognitive performance tests (e.g. measures of learning, memory, vigilance, psychomotor ability). This study

suggests that higher doses of dronabinol (40 mg per day in 4 divided doses; 8 times the standard dosing) could be used safely and effectively in HIV-positive marijuana smokers.

Timpone JG, Wright DJ, Li N, Egorin MJ, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. *AIDS Res Hum Retroviruses* 1997;13:305-315.

A total of 52 patients with HIV wasting syndrome were enrolled into this multi-center, randomized, open-label 12-week trial. The average age was 39 years.

Marijuana use in the past month was an exclusion criterion. Patients were randomized into 4 treatment arms: dronabinol 2.5 mg twice daily (D; n = 12); megestrol acetate 750 mg daily (M750; n = 12); megestrol acetate 750 mg daily + dronabinol 2.5 mg twice daily (M750 +D; n= 13); and megestrol acetate 250 mg/day; dronabinol 2.5 mg twice daily (M250+D; n = 13). The study was performed in an outpatient setting over 12 weeks. Dronabinol doses were taken 1 hour before meals at lunch and dinner. Megestrol was taken 1 hour before lunch. Subjects completed 4 different self-reported questionnaires for this study: visual analog scale for hunger (VASH) was taken 3 times daily before meals; visual analog scale for nausea (VASN), and visual analog for mood (VASM) were both taken at noon; and functional assessment for HIV (FAHI) questionnaire was completed in clinic.

VASH scale ranged from 0 (extremely hungry) to 330 (not hungry at all). No information

was provided on VASN and VASM's scoring methods. All VAS's were taken at baseline and throughout the outpatient phase on 2 weekdays and 1 weekend day. FAHI, a questionnaire with subscale and perception scores in 6 categories (physical wellbeing, social/family well-being, relationship with doctor, emotional well-being, fulfillment/contentment, and additional concerns), was also completed at baseline and every 4 weeks along with chemistry profile, physical examination, CD4+ cell count. One patient from the M750 arm was erroneously switched into M250 + D during the study. An average weight gain of 11% from baseline was seen in both M750 and M750 + D arms, and was most rapid during the first 6 weeks.

No weight gain was seen in D and M250 + D arms. Data from Karnofsky score, FAHI, and VAS questionnaire revealed no statistically significant change from the baseline or difference among treatment arms. No significant changes or differences were seen in CD4+ cell counts from baseline among all. Pharmacokinetics profiles of M750 and M750+D showed no statistically significant differences, suggesting that dronabinol has no impact on the metabolism or exposure to megestrol acetate.

Regarding adverse events, no statistically significant differences were observed among the treatment arms for nausea, vomiting, diarrhea, headache, total neurological events, and total adverse events. For central nervous system side effects, D arm reported confusion and emotional lability, hallucinations and somnolence; M750 arm had psychosis; M250 had euphoria; and M750+D had seizure, and amblyopia. Megestrol was also associated with

hypertension, deep vein thrombosis (DVT), dyspnea, and edema.

Tourette Syndrome

Tourette syndrome (TS) is a complex neurobehavioral disorder characterized by motor and vocal tics that typically has its onset during childhood. In addition to behavioral interventions, antipsychotics and other classes of drugs are used to attempt control of TS symptoms, but they are not uniformly effective and many have undesirable side effects. There are two clinical trials of medical cannabis in TS patients – both small and 8 of 12 participants from the first were recruited into the second, raising some concerns about the validity of the results. Both used single daily dosages of delta-9-THC, ranging from 2.5 mg to 10 mg. The first tested the effect of single doses of delta-9-THC (Muller-Vahl 2002). The THC dose differed based on gender, age, and prior cannabis experience, ranging from 5.0 mg to 10.0 mg. Five of the 12 subjects experienced mild side effects after THC administration and the results suggested effectiveness of THC at reducing tic severity. The second was a randomized double-blinded six week trial of delta-9-THC on 24 subjects (Muller-Vahl *J Clin Psychiatry* 2003). The daily dose started at 2.5 mg/day and was increased by 2.5 mg/day every four days to a maximum of 10 mg/day or less if intolerable side effects developed. One of the patients receiving THC dropped out because of side effects, six ended the study taking the daily maximum of 10.0 mg/day, two were taking 7.5 mg/day and one could only tolerate 2.5 mg/day. Results

suggested some reduction in tic severity. A companion paper reported on measurement of cognitive function during the trial (Muller-Vahl *Neuropsychopharm* 2003). It found no differences in cognitive testing results between the active treatment and placebo groups.

A case report (Pichler 2019) suggests cannabidiol (CBD) is important to clinical benefit from medical cannabis.

There are three additional clinical trials now under way that give insight into cannabis products and doses that are being studied. Each is now recruiting patients. The first is being conducted in Germany comparing nabiximols (a standardized cannabis extraction product delivering 2.7 mg THC and 2.5 mg CBD per spray – for oromucosal absorption) versus placebo for control of TS symptoms in adults. Patients (n=96, recruited in Germany) will start at one spray/day and increase to a maximum of 12 sprays/day. Treatment duration is 13 weeks; estimated completion is May 2019.

“CANNABINoids in the Treatment of TICS (CANNA-TICS)”

<https://clinicaltrials.gov/ct2/show/NCT03087201?term=NCT03087201&rank=1>.

The second trial is being conducted at the Yale Child Study Center in New Haven, CT. Approximately 18 persons age 18-60 will be enrolled into this investigator-initiated proof of concept study to examine the safety, tolerability and feasibility of dronabinol (synthetic THC) and the dietary supplement palmitoylethanolamide (PEA) for the treatment of adults with Tourette syndrome. The twelve week treatment periods starts with titration of dronabinol starting at 2.5 mg for 3 days, then 5 mg for 4 days, then 10 mg for the remainder of the study. All participants will receive two 400 mg tablets

of PEA daily for the same 12 weeks they receive dronabinol. The estimated completion date is January 2019 (though the entry hasn't been updated since March, 2017). "Efficacy of a Therapeutic Combination of Dronabinol and PEA for Tourette Syndrome"

<https://clinicaltrials.gov/ct2/show/NCT03066193?term=NCT03066193&rank=1>

The third study will compare with each other and against placebo effects of single vaporized administrations of three different strains of cannabis: THC 10%/CBD<0.5%, THC8.6%/CBD 8.6%, THC 0.6%/CBD 14%. Estimated completion date is May, 2019. "Safety and Efficacy of Cannabis in Tourette Syndrome"

<https://www.clinicaltrials.gov/ct2/show/NCT03247244?cond=tourette+cannabis&rank=1>

Muller-Vahl KR, Schneider U, Koblenz A, Judges M. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): a randomized crossover trial. *Pharmacopsychiatry* 2002;35(2):57-61.

A small randomized, double-blind, cross-over study of the effect of a single dose of delta-9-THC on adult patients with Tourette Syndrome. The THC dose differed based on gender, age, and prior cannabis experience. Females without prior use of marijuana and body weight ≤ 60 kg or age ≥ 50 years received 5.0 mg, otherwise 7.5 mg; men without prior use of marijuana and body weight ≤ 70 kg or age ≥ 50 years received 5.0 mg; men who used marijuana regularly, body weight > 70 kg and age < 50 years received 10 mg.; all other men received 7.5 mg. Source of the delta-9-THC was not specified. Multiple measures of TS symptoms were done just before and 3 to 4 hours after

administration. After a four week washout period subjects who received placebo at the outset received active treatment and vice-versa. Statistically significant improvements in tic severity were observed following THC treatment, as well as small benefits in some, but not all, additional measures of TS symptoms. After statistical adjustment for multiple comparisons, beneficial effects were no longer significant. No serious adverse effects occurred. Five patients experienced mild transient adverse reactions lasting between 1 and 6 hours.

Muller-Vahl KR, Schneider U, Prevedel H. Delta 9tetrahydrocannabinol (THC) is effective in the treatment of tics in Tourette syndrome: a 6-week randomized trial. *J Clin Psychiatry* 2003;64:459-465.

A small randomized, double-blind, placebo controlled six-week trial of the effectiveness of delta-9-THC at controlling TS symptoms. The 24 subjects had an average age of 33 (range=18-68 years). Fifteen patients were unmedicated for at least 6 months prior to the study and 9 were taking medications for the treatment of TS. Half the patients were randomly assigned to the THC group and half to placebo. THC was administered in gelatin capsules with a starting dose of 2.5 mg/day. Source of THC was not specified. Dose was titrated up by increasing dose 2.5 mg/day every four days. Target maximum dose was 10 mg/day. Patients were instructed to take the pills once a day with breakfast. If a subject could not tolerate the maximum dose, an adjustment could be made by decreasing study medications up to 5.0 mg until a tolerated dose was achieved. The same dosing schedule was used to reduce medication at the end of the treatment

period. Patients were examined at baseline and days 9, 20-22, 30-31, one or two days after medication stopped, and 6 weeks after medication stopped. At each visit tic severity was measured using multiple clinician-rated measurement tools. The authors report seven patients dropped out of the study or had to be excluded afterward. One patient receiving THC dropped out because of side effects (anxiety and restlessness). A companion paper for this study (Muller-Vahl *Neuropsychopharmacology* 2003) notes THC dose at end of study was 10.0 mg/day for 6 patients, 7.5 mg/day for 2 patients, and 2.5 mg/day for one. Most rating scales demonstrated marked tic reduction at visits 2, 3, and 4. However, statistical adjustment for multiple measures eliminated the statistically significant observations, except for those at visit 4. No serious adverse reactions occurred. Five of the patients in the THC group reported mild side effects (tiredness, dry mouth, dizziness), however none of these patients reduced study medication below 7.5 mg due to these side effects because none felt seriously impaired.

Muller-Vahl K. Treatment of Tourette syndrome with delta-9-tetrahydrocannabinol (delta 9THC): no influence on neuropsychological performance. *Neuropsychopharmacology* 2003;28:384-388.

This article reports on study of cognitive function during the placebo-controlled trial described above (Muller-Vahl *J Clin Psychiatry* 2003). Five tests of cognitive function were done. No significant differences in cognitive function between the two groups were seen. Though the target dose was 10.0 mg/day, only 6 of the 9 in the

placebo group titrated their dose up to that level. The reason why is not stated, but presumably it was due to unpleasant side effects. THC dose at end of study was 10.0 mg/day for 6 patients, 7.5 mg/day for two patients and 2.5 mg/day for one. One patient receiving THC dropped out of the study because of side effects (restlessness and anxiety). No serious adverse events occurred.

Pichler EM, Kawohl W, Seifritz E, Roser P. Pure delta-9-tetrahydrocannabinol and its combination with cannabidiol in treatment-resistant Tourette syndrome: A case report. *Int J Psychiatry* 2019;54:150-156.

A patient with Tourette syndrome showed no significant benefit from treatment with the antipsychotic drugs risperidone and aripiprazole and no significant benefit from treatment with pure THC. However, following administration of a daily dosage of 10 mg THC combined with 20 mg CBD, the patient showed rapid and highly significant improvement in the Yale Global Tic Severity Scale.

Amyotrophic Lateral Sclerosis

Only two published clinical trials of cannabis for the treatment of symptoms associated with ALS were found, both using dronabinol (synthetic delta-9THC). The effectiveness results of the studies are mixed, but both agree dronabinol, in the tested doses, is well tolerated with few side effects (dizziness). In one open-label crossover pilot study of 20

ALS patients, escalating doses starting at 2.5 mg/day (max 10 mg/day) of dronabinol for 3 months were associated with improvement in sleep, appetite, and spasticity, but few details are provided (Gelinas 2002). In contrast, a small crossover study using a shorter two-week treatment period reported no improvement in cramp intensity, number of cramps, fasciculation intensity, sleep, appetite, depression, or quality of life measure (Weber 2010). This study used 5 mg dronabinol (in sesame oil drops) twice daily.

A third study is reported as completed in clinicaltrials.gov, but results have not yet been published. This study, conducted in Italy, intended to recruit 60 adults with ALS. Participants were randomized to either Sativex (providing 2.7 mg THC and 2.5 mg CBD per spray) or placebo spray for six weeks of treatment. Information on starting dose, dose escalation, and maximum dose not provided. Primary outcome is clinician-assessed spasticity. (clinicaltrials.gov Identifier #NCT01776970):

<https://www.clinicaltrials.gov/ct2/show/NCT01776970?cond=als+cannabis&rank=1>).

A fourth study is now recruiting ALS patients in Australia. This trial intends to randomize 30 patients to either a daily extended-release capsule with 25 mg CBD and <2 mg THC or placebo. Duration is 6 months. Primary outcomes are change in mean ALS Functional Rating Scale-Revised total score and change in Forced Vital Capacity volume. Estimated study completion date is December 2020.

<https://www.clinicaltrials.gov/ct2/show/NCT03690791?term=cannabis&cond=ALS&rank=2>

Gelinas, D. F, Miller, R. G, and Abood, M. (2002). Pilot study of safety and tolerability of delta 9-THC (Marinol) treatment for ALS. *Amyotroph Lateral Scler Other Motor Neuron Disord* 3: 23-24 (an abstract)

In this open-label (uncontrolled) cross-over study 20 patients with ALS were recruited for a study of the effects of dronabinol (synthetic delta-9-THC) therapy. Subjects were split into two groups, with the first group receiving dronabinol for three months, followed by a month of drug wash-out and then three months of no treatment. The other group was treated with dronabinol in months 5 to 7. The dronabinol dose was started at 2.5 mg/day and then increased to a maximum of 10 mg/day. Details were not provided on achieved dose or pace of escalation. Dronabinol at these doses was reported as tolerated well with no treatment-related adverse events. Symptomatic benefits were reported to have been seen in the areas of insomnia, appetite, and spasticity (no further details provided).

Weber, M., Goldman, B., and Truniger. Tetrahydrocannabinol (THC) for cramps in amyotrophic lateral sclerosis: a randomized, double-blind crossover trial. *J Neurol Neurosurg Psychiatry* 2010;81:1135-1140.

This trial compared 10 mg dronabinol (synthetic delta-9-THC) in two divided doses to placebo as treatment for moderate to severe daily cramps in ALS patients. The 27 patients were allowed to take any medications for ALS or its symptoms but were asked not to change this medication during the study period. Cramp intensity was rated daily by the patient using a visual

analog scale. In this randomized, double-blinded, placebo-controlled crossover trial patients received dronabinol in either the first two or last two weeks of the five week study period, with week 3 serving as the run-in/wash-out period. Complete data were available from 22 patients. There were no treatment-related serious adverse effects and the only side effect was mild dizziness experienced by one patient during dronabinol treatment. There was no evidence for a treatment effect on cramp intensity, number of cramps, fasciculation intensity or any of the other secondary outcome measures.

Seizures, including those characteristic of epilepsy

Until three years ago only a few small studies of cannabinoids as therapy for seizures had been published over three decades – mostly using cannabidiol (CBD). Several larger trials have been published recently.

Devinsky 2017 presents results from a randomized, double-blind trial of 98% CBD oral solution (Epidiolex) vs. placebo as adjunctive treatment for children and young adults with Dravet syndrome. Participants were titrated up from a lower dose (details not given) over a two week period to a dose goal of 20 mg/kg/day. Reduction in seizure frequency during the 14 week study period

was greater in the CBD group (38.9%) than in the placebo group (13.3%).

Two randomized, double-blind trials used the 98% CBD oral solution (Epidiolex) vs placebo as adjunctive treatment for drop seizures in patients with Lennox-Gastaut syndrome: Thiele 2018 and Devinski 2018 *NEJM*. In the Thiele study dose was titrated up over two weeks from a starting dose of 2.5 mg/kg/day (in two divided doses) to a target dose of 20 mg/kg/day. Over 14 weeks reduction in monthly frequency of drop seizures was greater in the CBD group (median 42.9%) than in the placebo group (median 21.8%). Adverse events led to study withdrawal of 14% of CBD patients – half of them due to increase in liver enzymes – and 1% in the placebo group. In the Devinski 2018 *NEJM* study there were three arms: 20 mg/kg/day CBD, 10 mg/kg/day CBD and placebo, each delivered equally split in two daily administrations. Over the 14 week treatment period drop seizures decreased by 41.9%, 37.2% and 17.2% in the 20 mg/kg/day CBD, 10 mg/kg/day CBD and placebo groups, respectively. Six patients in the 20 mg/kg/day CBD group and one in the 10 mg/kg/day CBD group discontinued the trial because of adverse events. Fourteen patients who received CBD (9%) had elevated liver aminotransferase concentrations.

A CBD safety study builds on the results of Thiele 2018 and Devinski 2018 *NEJM*, demonstrating the importance of monitoring liver enzymes when a patient is using CBD – especially when valproate is used at the same time (Devinski 2018 *Neurology*).

Szaflarski 2018 reports on a set of open-label Expanded Access Program studies of an oral 98% CBD extract oral solution produced by GW Pharmaceuticals (brand name Epidiolex) carried out in cohorts of approximately 25

patients with treatment-resistant epilepsy carried out by multiple U.S. physician investigators. The studies started patients on 2-10 mg/kg/day divided in twice-daily dosing and then titrated up by 2-5 mg/kg once a week until intolerance or to a maximum dose of 25 mg/kg or 50 mg/kg (depending on study site).

A retrospective case review found no clinical benefit from a CBD dose higher than 8 mg/kg/day and appearance of adverse effects at doses ≥ 20 mg/kg/day (Neubauer 2018).

Geffrey 2015 describes a trial designed to assess interaction between CBD and the anti-epileptic drug clobazam, but it also describes CBD dosing and seizure outcomes. CBD was started at 5 mg/kg/day and increased weekly by 5 mg/kg/day until 25 mg/kg/day was reached. CBD was found to cause increase in an active metabolite of clobazam. Another study also demonstrated clinically relevant interaction between CBD and clobazam as well as some degree of interaction between CBD and additional anti-epileptic drugs (Gaston 2017).

The U of Colorado has completed a study that analyzed genetic differences between patients with Dravet syndrome (ages one to 50 years) who do and those who do not have a complete response (seizure free 3 months) to a proprietary CBD extract that is 98% CBD and has no THC. Results have not yet been published (clinicaltrials.com Identifier #: NCT02229032).

<https://clinicaltrials.gov/ct2/show/NCT02229032?term=NCT02229032&rank=1>.

A double-blind, randomized, placebo-controlled trial being conducted in Ontario started recruiting an anticipated 80 adults with drug-resistant epilepsy in January 2019.

Active drug will be capsules with a 16:1 ratio of CBD:THC. Dosing will start with capsules containing 100-200 mg CBD per day split into two doses. After a two week titration period treatment at a maximum dose containing 300 mg CBD/day will continue for four weeks. Study treatment is an adjunct to regular anti-epileptic drug regimen. Primary outcome is frequency of convulsive seizures. Estimated study completion date: January 2021

(<https://www.clinicaltrials.gov/ct2/show/NCT03808935?term=NCT03808935&rank=1>)

Finally, in June of 2018 the FDA approved use of a 98% CBD oral solution (brand name Epidiolex, produced through cannabis extraction by GW Pharmaceuticals) for treatment of seizure disorders in patients with Dravet Syndrome and Lennox-Gastaut syndrome. Full prescribing information can be found here:

https://www.epidiox.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf

Szaflarski JP, Bebin EM, Corni AM, Patel AD, Joshi C, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment-resistant epilepsies: Expanded access program results. *Epilepsia* 2018;59:1540-1548.

In January 2014, an expanded access program (EAP) was initiated to provide CBD to patients with treatment resistant epilepsy. This open-label EAP included 29 individual physician- or state-initiated Investigational New Drug applications, conducted at 25 US-based epilepsy centers. Patient eligibility criteria and endpoints varied by site-specific protocols, but all patients had treatment resistant epilepsy and were receiving stable

doses of anti-epileptic drugs (AEDs) for ≥ 4 weeks before enrollment.

During a 4-week baseline period, parents/caregivers kept diaries of all countable seizure types. Treatment with extraction-derived, purified CBD in oral solution (Epidiolex) was initiated at 2-10 mg/kg/day then gradually increased to a maximum dose of 25-50 mg/kg/day, depending on the site. Patients were seen every 2-4 weeks through week 16 and every 2-12 weeks thereafter.

Between January 2014 and December 2016, 607 patients were enrolled in the EAP. A total of 89 (15%) withdrew due to lack of efficacy and 32 (5%) withdrew due to adverse events. This paper describes results from patients with a wide range of duration in this ongoing study: 2-146 weeks with a median 48 weeks. Median age was 13 years (range, 0.4-62). The median number of concomitant AEDs taken at a baseline was 3 (range 0-10), and the most common medications were clobazam (51%), levetiracetam (34%), and valproic acid (29%).

Median CBD dose was 25 mg/kg/day. The adjunctive CBD reduced median monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks; reductions were similar through 96 weeks. Proportion of patients with $\geq 50\%$, $\geq 75\%$, and 100% reductions in convulsive seizures were 52%, 31%, and 11%, respectively, at 12 weeks, with similar rates through 96 weeks. CBD was generally well tolerated; most common adverse events were diarrhea (29%) and somnolence (22%). The incidences of diarrhea and somnolence tended to increase with increasing dose. Abnormal liver function tests were reported for 61 (10%) of patients; of these, 46 (75%) were on valproate.

Devinsky O, Cross JH, Laux L, Marsh E, et al for the Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;376:2011-2020.

Double-blind, placebo-controlled trial of cannabidiol (CBD) as therapy for children and young adults with the Dravet syndrome and drug resistant seizures. 120 patients aged 2-18 from 23 centers in the United States and Europe met inclusion criteria and were randomly assigned in a 1:1 ratio 100mg/ml CBD oral solution or placebo oral solution. Patients were required to have a confirmed diagnosis of the Dravet syndrome, to be taking one or more antiepileptic drugs, and to have had four or more convulsive seizures during the 28 day baseline period. A stable therapeutic regimen was required at baseline and was maintained during the trial. The trial comprised a 4-week baseline period, a 14-week treatment period (2 weeks of dose escalation and 12 weeks for dose maintenance), a 10-day taper period, and a 4-week safety follow-up period. A total of 12 patients (10%) withdrew from the trial before completion (9 in the CBD group and 3 in the placebo group). Dose goal was 20 mg/kg/day, but starting dose, escalation protocol, and achieved dose during maintenance period were not described in the article. Patients had previously tried a median of 4 antiepileptic drugs (range, 0 to 26) and were taking a median of 3 (range, 1 to 5). The most common were clobazam (65%), valproates (all forms, 59%), stiripentol (42%), levetiracetam (28%), and topiramate (26%). The most common type of convulsive seizure was generalized tonic-clonic, in 94 patients (78%), with secondarily generalized tonic-clonic seizures in 25 patients (21%).

Nonconvulsive seizures were reported in 37 patients in the CBD group (61%) and 41 patients in the placebo group (69%). In the CBD group, the primary end point of convulsive-seizure frequency decreased from a median of 12.4 seizures per month (range, 3.9 to 1717) at baseline to 5.9 (range, 0.0 to 2159) over the entire treatment period, representing a median change of -38.9%. In the placebo group, the median monthly convulsive-seizure frequency decreased from 14.9 (range, 3.7 to 718) to 14.1 (range, 0.9 to 709), representing a median change of -13.3%. The adjusted median difference in convulsive seizures between the CBD group and the placebo group was -22.8 percentage points (95% CI, -41.1 to -5.4, $P=0.01$). The difference in favor of CBD was seen in the first month of the maintenance period. There was no significant difference between the groups in non-convulsive seizures. Adverse events during the treatment period were reported by 93% of the patients in the CBD group (84% mild or moderate) and 75% of the patients in the placebo group (95% mild or moderate). Serious adverse events were reported in 10 patients in the CBD group and 3 in the placebo group (status epilepticus was reported in 3 patients in each group). None of these events led to withdrawal from the trial and none were deemed to be related to the trial agent.

Devinsky O, Patel AD, Thiele EA, Wong MH, Appleton R, et al. Randomized, dose-ranging safety trial of cannabidiol in Dravet syndrome. *Neurology* 2018 Apr 3;90(14):e1204-e1211. doi: 10.1212/WNL.0000000000005254.

For this dose-ranging safety study, children aged 4-10 years with Dravet syndrome were randomized to CBD (5 (n=10), 10 (n=8), or 20

(n=9) mg/kg/day or placebo (n=7), taken in two divided oral solution doses daily. The patients were from 8 sites in the United States and 3 in the United Kingdom. The study medication was taken in addition to the child's stable anti-epileptic drug regimen, starting at 2.5 mg/kg/day and increased by 2.5 to 5.0 mg/kg/day every other day to randomized dose. Treatment-emergent adverse events were reported by a similar proportion of patients in each group (from 63% in 5 mg/kg/day CBD group to 86% in placebo group). Two patients discontinued because of adverse events: one in the 10 mg/kg/day CBD group (pyrexia and maculopapular rash) and 1 in the 20 mg/kg/day CBD group (elevated transaminases). Six patients experienced a rash: 5 in CBD groups and 1 in the placebo group. Six patients taking CBD (22%) had elevated liver enzymes, though none met the definition of liver injury. These elevations were most common in the 20 mg/kg/day CBD group (4/6 patients). All 6 patients were taking concomitant valproate and 4 of the 6 had concomitant viral/bacterial infections.

Devinsky O, Patel AD, Cross JH, Villaneuva V, Wirrell EC, et al for the GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut Syndrome. *NEJM* 2018;378:1888-1897.

A total of 225 patients with Lennox-Gastaut syndrome (age range 2 to 55 years) were enrolled in this double-blind, placebo-controlled trial of plant-derived, purified cannabidiol (CBD): 76 assigned to 20 mg/kg/day CBD, 73 to 10 mg/kg/day CBD, and 76 to placebo. Patients were required to have stable pharmacologic and non-pharmacologic therapy regimens for four

weeks before screening and throughout the study. Study medication was delivered in two daily divided doses for the 14 week treatment period. Medication was started at 2.5 mg/kg/day and then increased by 2.5 to 5.0 mg/kg/day every other day until the target dose was reached. The median percent reduction from baseline in the frequency of drop seizures per 28 days (primary outcome) was 41.9%, 37.2% and 17.2% in the 20 mg/kg/day CBD, 10 mg/kg/day CBD, and placebo groups, respectively. Adverse events were reported in 94%, 84%, and 72% of patients in the 20 mg/kg/day CBD, 10 mg/kg/day CBD, and placebo groups, respectively. Overall, 89% of adverse events were judged mild or moderate in severity. A total of 8 patients discontinued CBD or placebo because of adverse events: 6 in the 20 mg/kg/day CBD group, one in the 10 mg/kg/day CBD group, and one in the placebo group. Seven patients receiving CBD had serious adverse events considered related to the CBD treatment: elevated aspartate aminotransferase concentration (2 patients) elevated alanine aminotransferase concentration (1 patient), elevated γ -glutamyltransferase concentration (1 patient), somnolence (1 patient), increased seizures during weaning (1 patient), non-convulsive status epilepticus (1 patient), lethargy (1 patient), constipation (1 patient), and worsening chronic cholecystitis (1 patient). Increases in serum aminotransferase concentrations greater than 3 times the upper limit of the normal range occurred in 14 of the 149 patients (9%) who received cannabidiol (11 patients in the 20 mg/kg/day group and 3 in the 10 mg/kg/day group; none in the placebo group). Of these 14 patients, 11 (79%; 9 in the 20 mg/kg/day group and 2 in the 10

mg/kg/day group) were receiving valproic acid concomitantly.

Gaston T, Bebin EM, Cutter G, Liu Y, Szaflarski J. Drug interactions between cannabidiol and commonly used anti-epileptic drugs. *Epilepsia* 2017;58:1586-1592.

Treatment-resistant epilepsy patients (39 adults and 42 children) enrolled in the State of Alabama CBD open-label safety study were studied with frequent monitoring of serum AAED levels. A flexible CBD dose adjustment schedule was used, starting at 5 mg/kg/day and increasing to tolerability and seizure control every two weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Sufficient data points were gathered to analyze potential interactions between CBD and 19 AEDs. Increase in serum levels of topiramate, rufinamide, and desmethylclobazam (active metabolite of clobazam) and decrease in levels of clobazam with increasing CBD dose was seen in combined pediatric and adult arms. In addition, a significant increase in serum levels of zonisamide and eslicarbazepine with increasing CBD dose was seen in the adult arm only. There were no significant interactions seen between CBD and the other AEDs investigated. Except for clobazam and desmethylclobazam, all noted mean level changes were within the accepted therapeutic range.

Geffrey, A.L., Pollack, S.F., Bruno, P.L., & Thiele, E.A. Drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy. *Epilepsia* 2015; 56: 1246-1251.

Study's main purpose was to look for a drug-drug interaction between clobazam (CLB) and CBD (Epidiolex), but the study also included

data on any changes in seizure frequency experienced by study participants with refractory epilepsy (ages 4-19). This was an open-label, single-center study where participants (n=13) taking CLB took CBD as an adjuvant therapy for an 8-week trial. Note that participants were also taking other anti-epilepsy drugs (AEDs) concurrently with CLB at the time of the study—study investigators note this and mention a larger analysis presumably forthcoming in a future publication. The article includes info on what these other AEDs were; most participants were on 1-2 other AEDs besides CLB. Participants started on 5 mg/kg/day of CBD and increased weekly by 5 mg/kg/day until they reached 25 mg/kg/day (reached 25 mg/kg/day at Week 5). Conclusion: roughly 70% of subjects (9 out of 13) experienced greater than 50% reduction in seizures compared to their baseline levels. Two participants showed an increase in seizure frequency over their baseline levels. Study also concluded that CBD intake was primarily affecting nCLB (norclobazam; an active metabolite of CLB) metabolism – specifically that CBD inhibited nCLB metabolism (investigators found increased concentrations of nCLB in blood levels during CBD trial).

Neubauer D, Benedik MP, Osredkar D. Cannabidiol for treatment of refractory childhood epilepsies: Experience from a single epilepsy center in Slovenia. *Epilepsy Behav* 2018 Apr;81:79-85. Doi: 10.1016/j.yebeh.2018.02.009.

Retrospective chart review of 66 children (age 0.5 to 23.0 years; median 8 years) with refractory epilepsy who were started on synthetic CBD as an adjunct to current

therapy with antiepileptic drugs (1 to 4; median=2) or vagus nerve stimulator (n=4). The starting dosage of CBD was 1-3 mg/kg/day, gradually raised each week up to a dosage that controlled the seizures or to a maximum of 16 mg/kg/day. The daily total was divided into two daily dosages (three for infants below 2 years of age). Patients provided follow-up information at least twice during the first six months of CBD therapy. Of all 66 patients, 32 (48.5%) had a 50% improvement or higher, 14 of whom (21.2%) became seizure free. The median therapeutic dosage was 8.3 mg/kg/day (range: 3.0-22.0). The authors report they did not find any benefit in increasing the dosage above 8 mg/kg/day and that with dosages \geq 20 mg/kg/day adverse effects appeared.

Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, et al. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomized, double-blind, placebo-controlled phase 3 trial. *Lancet* 2018 Mar 17;391(10125):1085-1096. doi: 10.1016/S0140-6736(18)30136-3.

Randomized, double-blind, placebo-controlled trial of cannabidiol (CBD) as add-on therapy for drop seizures in patients with Lennox-Gastaut syndrome. A total of 171 patients were randomized to CBD oral solution (n=86) or placebo (n=85) from 24 clinical sites in the USA, the Netherlands, and Poland (mean age = 15.4 years). The trial was 14 weeks including a two-week dose escalation period. Dose started at 2.5 mg/kg/day divided into two daily doses; target dose was 20 mg/kg/day. The primary outcome was percentage change from

baseline in monthly frequency of drop seizures. At baseline patients had previously tried, and stopped taking, a median of six antiepileptic drugs and took a median of three concomitant antiepileptic drugs during the trial. The most common were clobazam, valproate, and lamotrigine. In the CBD group, the monthly frequency of drop seizures decreased by a median of 42.9%; in the placebo group the median decrease was 21.8%. The estimated median difference between the two groups was -17.2 ($p=0.014$). In the CBD group, 62% of patients had treatment-related adverse events compared with 34% in the placebo group. Adverse events led to study withdrawal in 12 (14%) of patients in the CBD group and one (1%) in the placebo group. Six patients in the CBD group withdrew because of adverse events associated with increases in liver enzymes (alanine or aspartate aminotransferase concentrations). A seventh patient met criteria for withdrawal due to elevated alanine aminotransferase but was discontinued for non-compliance. All elevations of alanine or aspartate aminotransferases resolved either spontaneously during treatment (eight patients in CBD group vs one in the placebo group), after a reduction in concomitant valproate dose (three patients in the CBD group), after tapering or cessation of CBD (six patients in the CBD group) or after entry in the open-label extension trial (three patients in the CBD group). A total of 20 patients (23%) in the CBD group had elevation of liver enzymes and of those patients 16 were also taking valproate. None of the elevations suggested lasting liver damage (no concomitant increases in bilirubin concentration observed). Two patients in the CBD group had serious adverse events that were ongoing at the end of the trial: one

patient died due to acute respiratory distress syndrome and one patient had ongoing sleep apnea (considered treatment related) and status epilepticus (not considered treatment related). Concomitant antiepileptic drug doses were adjusted during the trial for 23% of patients in the CBD group and 9% of patients in the placebo group. Of the patients on clobazam during the trial, clobazam dose was reduced in 11 (27%) of 41 patients in the CBD group and four (9%) of patients in the placebo group.

Severe and persistent muscle spasms, including those characteristic of multiple sclerosis

Muscle spasm is a consequence of the underlying condition of spasticity seen often in patients with multiple sclerosis, spinal cord injury, amyotrophic lateral sclerosis (ALS), and other neurological diseases. Spasticity is an abnormal increase in muscle tone, resulting in stiffness, muscle spasm, and pain. Most studies of medical cannabis that included evaluation of muscle spasm have been in patients with multiple sclerosis. Two small trials involving spinal cord injury patients are at the end of this section. See the ALS section for additional studies.

Multiple Sclerosis

Most clinical trials involving multiple sclerosis patients have used cannabis whole plant extractions and a few have used dronabinol, synthetic delta-9-THC. The whole plant extracts in the trials have varied in THC:CBD ratio. The paragraphs below comment briefly on dosages for each of the ratios – 1:1, 2:1, and 3:1. The final paragraph addresses trials that used dronabinol.

Nabiximols (brand name Sativex, GW Pharmaceuticals) is a highly standardized oromucosal spray produced from cloned cannabis chemovars grown in controlled conditions. Each 100 µliter actuation (spray) yields 2.7 mg delta-9THC and 2.5 mg CBD. An early trial (Wade 2003) demonstrates the need to limit the number of sprays taken within a few hours of each other to avoid undesirable side effects. The typical maximum set in clinical trials is 8 sprays within any 3 hour period (Collin 2010) and 12 (Novotna 2011, Freidel 2015, Leocani 2015) or 24 (Collin 2010) within a 24 hour period. However, when the trials were carried out, patients typically came to an average daily dose of approximately 7 to 15 sprays per day (Wade 2004, Collin 2007, Collin 2010, Novotna 2011, Tomassini 2015, Leocani 2015). Most nabiximols trials in MS patients have lasted 3 months or less, but an extension to the trial reported in Wade 2004 studied participants for variable amounts of time up to more than two years (Wade 2006). Results from this trial suggest patients who continue to derive benefit from nabiximols therapy (i.e. the ones who choose to continue using it) do so at the same or somewhat lower dosing than they were using at six weeks.

Observational studies of Sativex use patterns, benefit, and safety in routine clinical practice have been organized in several European countries since regulatory authorities in these countries granted approval of the product for patients with moderate to severe multiple sclerosis spasticity resistant to other medications (depending on country, this occurred between 2010 and 2013). Fernandez 2016, Patti 2016, Vermesch 2016, and Flachenecker 2014 report on studies of this kind. Differences in methodologies and reporting make summarization across these studies a challenge, but here is an attempt at some summary observations. Though over half continued use of the product at three months, only around 20% achieved $\geq 30\%$ reduction in spasticity by 3 months. Reason for discontinuation was fairly evenly split between lack of effectiveness and side effects. Dose after several months of use varied greatly, but mean dose across the studies was 5.4 to 6.6 sprays per day – lower than the doses seen in clinical trials. Less than 20% reported side effects, with serious and severe side effects rare.

Three large trials used a commercially produced and distributed cannabis whole plant extract with 0.8 to 1.8 mg CBD for each 2.5 mg delta-9-THC (Cannador - a TBD:CBD ratio of approximately 2:1) (Cannador). Both the CAMS study (Zajicek 2003) and the MUSEC study (Zajicek 2012) started patients on 5 mg THC/day in two divided doses, then increased dose to a maximum of 25 mg THC/day in divided doses. Dose escalation was more rapid in the MUSEC trial (dose increased every 3 days vs. weekly), and patients experienced more numerous and more severe side effects than in the CAMS trial. At the end of the MUSEC trial's titration period only 47% of patients were taking 25 mg THC daily. The CAMS trial's

maximum was weight dependent with the maximum for the lightest adults 10 mg THC/day; the paper does not describe achieved dosages. Both studies found evidence of effectiveness for patient-reported improvements in muscle spasm and spasticity. The CAMS trial found no treatment effect for clinician-assessed spasticity, but the validity of the tool used for that assessment (Ashworth scale) is now suspect.

One trial used a cannabis extract with a THC:CBD ratio of approximately 3:1 (Vaney 2004). This trial started patients at a dose containing 15 mg THC and increased the dose 5 mg THC/day each day to a maximum of 30 mg THC/day. However, half of the 50 patients could tolerate a dose no larger than the starting dose of 15 mg THC/day and only about a third achieved a dose of 25 mg THC/day or more. During this cross-over study side effects were reported as being only slightly more frequent and more severe during active treatment than during placebo treatment. Results showed no effectiveness for Ashworth scale spasticity score and a trend toward effectiveness for improvement in patient-assessed spasm frequency that became statistically significant when analysis was limited to the 37 patients who took at least 90% of their prescribed doses during the 2-week treatment maintenance phase. The study suggested a correlation between tolerated dose and body weight and increased effectiveness at higher doses.

Finally, two trials used dronabinol, synthetic delta-9-THC. In one arm of the CAMS trial (Zajicek 2003) dronabinol was started at 2.5 mg twice daily (5 mg/day) and titrated up at weekly intervals by 5 mg/day to a weight-dependent maximum of 10 mg to 25 mg per day in split doses. Dizziness or lightheadedness, dry mouth, and diarrhea

were more common in the dronabinol group than in the placebo group and similar in frequency to the patients taking 2:1 THC:CBD capsules. The large 3-year CUPID trial (Zajicek 2013) used the same starting dose and titration schedule but slightly different weight-based targets of 14 mg to 28 mg daily in split doses. Results showed no effect of dronabinol on disease progression. Adverse events more common in the dronabinol group than in the placebo group were dizziness and lightheadedness (32%) and dissociative thinking or perception disorders (30%).

Spinal Cord Injury

An early trial involving only one patient gives some information on dosing and effectiveness of delta-9-THC (Maurer 1990). The investigators concluded 5 mg oral delta-9-THC and 50 mg oral codeine were equally effective, and more effective than placebo, for pain reduction. Only THC had a significant beneficial effect on spasticity. No altered consciousness occurred with the 5 mg THC.

Three small trials involving spinal cord injury patients were found. One used dronabinol, synthetic delta-9-THC (Hagenbach 2007). The second used nabilone, a synthetic derivative of THC. Since the action of nabilone is different from THC it is not directly relevant to Minnesota's medical cannabis program and is not described here. The third used nabiximols (whole plant cannabis extract with THC:CBD ratio of approximately 1:1) in a group with a variety of neurological conditions including SCI (Wade 2003). Though results for SCI patients were not broken out, the study is included here for completeness.

The dronabinol trial is a small double-blinded, placebo-controlled six week trial preceded by a dose-setting six week study in the same patients, conducted at a Swiss center (Hagenbach 2007). In the dose-setting study 25 adults with spinal cord injury (11 paraplegic, 14 tetraplegic) had their antispasticity drugs discontinued for three half-lives and were then started on dronabinol with a single 10 mg dose the first day. Titration was individualized without set protocol, with the goal of balancing maximal effectiveness with side effects. Outcomes studied at days 1, 8, and 43 included clinician-assessed Ashworth spasticity score, patient-reported numerical rating scales of spasticity, pain, attention, mood, and side effects, and more. 15 patients completed the six weeks: four dropped out because of increased pain and the other 6 because of anxiety and other side effects. Mean dose achieved was 31 mg/day in divided doses (range: 15 mg to 60 mg). Patients perceived a significant reduction in pain at day 1 compared to baseline. A second dose-setting study using rectally administered dronabinol had to be curtailed at 7 patients because of supply problems, but the daily dose achieved after dosing adjustment for those 7 patients was 43 mg (range 20-60 mg). Methodological issues make interpretation of effectiveness results problematic, but there is suggestion of early effectiveness in reduction of pain and spasticity that diminishes over weeks of treatment.

Wade and colleagues (Wade 2003) carried out a small placebo-controlled crossover trial of nabiximols (Sativex) on patients with neurological disorders and troublesome symptoms (Wade 2003) that indicates the need to set a maximum dose within specified

time periods. Twenty-four patients with a variety of neurologic disorders, including 4 with SCI, enrolled and 20 completed the study. Patients first had a two week open-label trial with nabiximols with instructions to increase frequency of sprays, balancing symptom relief with side effects up to a maximum of 8 sprays within 70 minutes. Because of side effects this was changed to four sprays over 2 hours and changed again to two sprays over two hours. After the two week open-label trial the patient entered an eight week double-blind study phase with four two-week stages using nabiximols, or CBD alone or THC alone or placebo. Across all 20 patients, spasticity severity had a statistically significant reduction on nabiximols, CBD alone, and THC alone, compared with placebo. Spasm frequency saw statistically significant reduction while on nabiximols and THC alone, but not while on CBD alone, compared with placebo.

Occurrence of side effects was similar across the four treatment conditions during the placebo-controlled phase and substantially higher during the initial open-label nabiximols treatment phase.

Collin C, Davies P, Mutiboko IK, et al. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. *Eur J Neurol* 2007;14:290-6.

This was a randomized, double-blind, placebo-controlled trial involving patients with multiple sclerosis whose symptoms were not adequately controlled on standard drugs. 189 adult patients from 8 centers in UK and 4 in Romania were randomized in a 2:1 ratio to nabiximols or placebo for a total of 6 weeks. Nabiximols (Sativex) is a highly standardized oromucosal spray developed by

GW Pharmaceuticals. It is extracted from whole cloned cannabis chemovars grown under controlled conditions. Each 100 µliter actuation yields 2.7 mg delta-9- THC and 2.5 mg of CBD. Patients were instructed to titrate their daily dose steadily as required over 2 weeks, to a maximum dose of 48 sprays per day (130 mg THC, 120 mg CBD). Total treatment time was six weeks.

Primary outcome measure was the change from baseline in the severity of spasticity based on daily diary assessments by the subject on a 0-10 numerical rating scale (NRS). Secondary outcome measures included the Ashworth scale, Motricity Index, mean daily spasm scores (five point spasm frequency score) and the patients' global impression of change in their disease (7 point scale from very much improved to very much worse). Mean and median number of sprays per day were 14.7 (40 mg THC/37 mg CBD) and 13 (35 mg THC/33 mg CBD), respectively. Results showed reduction in spasticity scores for both active treatment and placebo groups, but the larger decrease in the active treatment group was statistically significant. The difference in the proportion of active treatment patients who achieved $\geq 30\%$ improvement (40.0%), compared with controls (21.9%), was also statistically significant. There was a trend of greater reduction in spasm frequency in the active treatment group, but the difference lacked statistical significance. Serious adverse effects were equally common in the two groups. Mild and moderate CNS effects (dizziness, impaired balance, disturbance in attention and blurred vision) were more common in the active treatment group, with 32% experiencing dizziness. Eight patients withdrew because of side effects, 6 from the active treatment group and 2 from the placebo group.

Collin C, Ehler E, Waberzinek G, et al. A doubleblind, randomized, placebo-controlled, parallelgroup study of Sativex, in subjects with symptoms of spasticity due to multiple sclerosis. *Neurol Res* 2010;32:451-459.

In this multicenter, randomized, double-blinded, parallel group trial 337 MS patients with spasticity not fully relieved with current anti-spasticity medication were randomized to either nabiximols or placebo for 14 weeks. Subjects self-titrated to a maximum dose of 24 sprays daily (with a max of 8 in a 3 hour period). The mean number of daily sprays taken by the active treatment group was 8.5 (range 1-22). Nine active treatment subjects (5%) and 5 on placebo (3%) withdrew because of adverse events. The most commonly reported treatment-related adverse events which showed a higher incidence in the active treatment group compared with placebo were dizziness (32% versus 10%), fatigue (23% versus 16%), somnolence (14% versus 4%), nausea (14% versus 5%), asthenia (13% versus 6%), and vertigo (11% versus 4%). The primary outcome measured was change in 11point patient-reported spasticity scale. The estimated treatment difference in decreased mean spasticity scores, though favoring the active treatment group, did not reach statistical significance. When analysis was limited to the 79% of participants who fully followed the study protocol, the difference was statistically significant. Among the active treatment patients who achieved reduction in spasticity score of at least 30% at any time, 98, 94, and 73% reported improvements of 10, 20, and 30% respectively within the first 4 weeks.

Fernandez O. THC_CBD in daily practice: Available data from UK, Germany and Spain. *Eur Neurol* 2016;75(suppl 1):1-3.

Brief review of a retrospective registry study (UK, Germany, and Switzerland) and a prospective safety study (Spain) of Sativex in routine clinical use for patients with moderate to severe multiple sclerosis spasticity resistant to other medications. Each spray of oromucosal Sativex delivers 2.7 mg THC and 2.5 mg CBD. All prescribers of Sativex in the UK and those from about 30 selected MS centers in Germany and Switzerland were requested to voluntarily complete a 6-monthly case report form about patients' use of Sativex and adverse events. Targeted questions were asked regarding addiction potential, abuse/misuse, long-term psychiatric effects, memory impairment, driving ability and fall events requiring medical attention. Data was received for 941 patients (761 from the UK, 178 from Germany, 2 from Switzerland) up to February 2015. Reported patients in the UK represented 22% of the 3493 patients who had been prescribed Sativex in that country since June 2010. After a mean follow-up time of about a year, 68% of the patients were continuing to take Sativex with a mean dose of 5.4 (\pm 4.9) sprays/day. Among patients who had discontinued treatment, about one-third cited lack of effectiveness and about one-quarter cited lack of tolerability/adverse events. Most common adverse events were psychiatric (6%), falls (6%), dizziness (3%), fatigue (2%), and suicidality (2%). There was no evidence of addiction, abuse/misuse or memory impairment. The proportion of drivers reporting improvement in driving ability exceed that reporting impairment (7% vs 2%), perhaps reflecting the symptomatic

improvement in spasticity. The Spanish safety study involved 204 patients who were followed prospectively after being prescribed Sativex between July 2011 and December 2012. Data were collected at 6 and 12 months. After 6 months, treating physicians considered that 143 patients (70%) were deriving sufficient benefit to continue treatment. After 12 months the corresponding figure was 132 (65% of initial cohort). Mean dose of Sativex at both evaluation points was 6.6 sprays/day. Reason for discontinuation during the first six months was evenly split between lack of effectiveness and tolerability; most who quit during the second six months did so because of lack of tolerability. Altogether, 20% of patients experienced an adverse event, with most being mild to moderate in severity. Five patients experienced a psychiatric adverse event, one experienced a fall requiring medical attention, and none experienced suicidal thoughts.

Flachenecker P, Henze T, Zettl UK. Nabiximols (THC/CBD oromucosal spray, Sativex) in clinical practice – results of a multicenter, non-interventional study (MOVE 2) in patients with multiple sclerosis spasticity. *Eur Neurol* 2014;71(5-6):173-181.

Prospective observational study of effectiveness and side effects of nabiximols (Sativex) carried out at 42 centers in Germany. The purpose was to observe the impact of nabiximols in typical clinical practice, as opposed to outcomes of a clinical trial. Participating centers agreed to use consistent timeframes for follow-up appointments and assessments, which included clinician-assessed Ashworth scale of spasticity, patient self-reported 0-10

numerical rating scale of spasticity, quality of life measures, and more. Use of nabiximols was reported as being according to standard product recommendation; no dose information was included in the report. 300 adult patients with multiple sclerosis spasticity despite medical treatment initiated nabiximols therapy, with three-quarters of the group receiving concomitant anti-spasticity medication. At approximately four weeks (exact timing of follow-up visits could vary by two weeks) 76% continued therapy and at 3 months 55% were still on therapy. Reason for discontinuation: about 80% because of lack of effectiveness and 20% because of side effects. After one month 75% of patients had a reduction in spasticity according to clinical assessment and improvement of 20% or more in NRS spasticity score was achieved by 42%. Improvements achieved at one month were generally retained at 3 months. Side effects were reported by 17% of patients with most common being dizziness (4.0%), fatigue (2.5%), drowsiness (1.9%), nausea (1.9%), and dry mouth (1.2%). Serious adverse events occurred in 8 patients with four considered related to nabiximols treatment.

Freidel M, Tiel-Wilck K, Schreiber H, Prechtel A, Essner U, Lang M. Drug-resistant MS spasticity treatment with Sativex add-on and driving ability. *Acta Neurologica Scandinavica* 2015; 131: 9-16.

This prospective, multicenter (Germany) non-interventional, open-label pilot study investigated the effects of Sativex on 1) driving ability, 2) spasticity, and 3) adverse events (AEs). Thirty-three MS participants with treatment-resistant (moderate to severe) spasticity started on Sativex as an

add-on therapy. Two dropped out due to mild to moderate AEs), leading to n=31 (33-68 years old) completing this 4-6 week study. Patients started off with a two-week dose titration phase and were allowed to go up to 12 sprays per day. At baseline, the following were administered: 1) driving ability test battery (Schuhfried-Wiener Testsystem) consisting of 5 driving-related measures, and 2) MS spasticity measures (self-rated NRS of spasticity and physician rating of spasticity). While a strict 'fit to drive' criterion is when a participant scores above the 16th percentile on all 5 driving measures, they also discussed Germany's more flexible approach to driving fitness that is occasionally applied to drivers. Specifically, if a participant scores below the 16th percentile on a driving measure, they have to perform at 50% or higher to compensate for their low score on the other. At the final visit, the driving test battery and spasticity measures were performed again along with recording for AEs that were experienced by patients from Sativex administration. Conclusions: on average, spasticity had been present for 6.7 years with 39.4% of them concurrently taking other spasticity treatment drugs.

The mean dose of Sativex at the end of the study was 5.1 sprays (13.8 mg THC, 12.8 mg CBD). While a proportion of patients were considered unfit to drive at baseline, results showed that the proportion of those unfit to drive did not change at the end of the study. All of the driving ability measures in the test battery did not show a significant change from baseline to final visit except for the stress tolerance determination test (DT). There was increased performance on DT at final visit than at baseline (it measures "attention and individual reaction time in situations requiring continuous, swift and varying responses to rapidly changing visual

and acoustic stimuli”; increase on this measure was not explained nor predicted a priori). Overall, the authors interpreted the driving results as indicating that Sativex does not contribute to any significant declines in driving ability. Furthermore, average spasticity NRS self-rating scores showed a significant decrease from baseline to final visit by 2.4 points (6.0 pts at baseline to 3.6 pts at final visit). In addition, there was a reported drop in patients categorized as suffering from ‘severe spasticity’ as reported by the patients’ physicians (7 patients at baseline down to 1 at the final visit). Lastly, 13% of patients (4 out of 31 patients) experienced non-serious AEs (dizziness being the most commonly reported).

Garcia-Merino A. Endocannabinoid system modulator use in everyday clinical practice in the UK and Spain. *Expert Rev Neurother* 2013;13(3 suppl. 1):9-13.

This article is a short description and report of interim analysis of the UK and Spanish Sativex registries to monitor safety and effectiveness. Interim analyses suggest benefits are maintained over long term use and no new safety signals were seen with long term use – beyond what has been seen in published clinical trials.

Hagenbach U, Lux S, Ghafoor N, Berger JM et al. The treatment of spasticity with delta-9tetrahydrocannabinol in persons with spinal cord injury. *Spinal Cord* 2007;45:551-562.

A small double-blinded, placebo-controlled six week trial of dronabinol (synthetic delta-9-THC), preceded by a dose-setting six week study in the same patients, conducted at a Swiss center. In the dose-setting study 25

adults with spinal cord injury (11 paraplegic, 14 tetraplegic) had their anti-spasticity drugs discontinued for three half-lives and were then started on dronabinol with a single 10 mg dose the first day. Titration was individualized without set protocol, with the goal of balancing maximal effectiveness with side effects. Outcomes studied at days 1, 8, and 43 included clinician-assessed Ashworth spasticity score, patient-reported numerical rating scales of spasticity, pain, attention, mood, and side effects, and more. 15 patients completed the six weeks: four dropped out because of increased pain and the other 6 because of anxiety and other side effects. Mean dose achieved was 31 mg/day in divided doses (range: 15 mg to 60 mg). Patients perceived a significant reduction in pain at day 1 compared to baseline. A second dose-setting study using rectally administered dronabinol had to be curtailed at 7 patients because of supply problems, but the daily dose achieved after dosing adjustment for those 7 patients was 43 mg (range 20-60 mg). The planned six-week placebo controlled trial was carried out, but because of a large difference in baseline spasticity scores in the active treatment and placebo groups, planned analyses of differences in results between these groups were not conducted. Instead, results for placebo patients from this trial were compared with results for patients from the dose-setting trial. Compared with placebo patients, there were large, statistically significant reductions in clinician assessed spasticity scores in the actively-treated (dose setting) patients throughout the six week period. Patient assessments of spasticity and pain showed significantly lower pain at day one for the actively treated patients, but the difference narrowed and became non-significant as the study period progressed.

Koehler J, Feneberg W, Meier M, et al. Clinical experience with THC:CBD oromucosal spray in patients with multiple sclerosis-related spasticity. *Int J Neurosci* 2014;124(9):652-656.

Retrospective chart review of all multiple sclerosis patients at one German clinic who were started on nabiximols between September, 2011 and January, 2013.

Nabiximols is an oromucosal cannabis extract spray developed by GW Pharmaceuticals in Germany. The whole plant extract is highly standardized, produced from cloned cannabis chemovars grown under controlled conditions. Each 100 µliter actuation yields 2.7 mg delta-9-THC and 2.5 mg of CBD with these two cannabinoids constituting at least 90% of cannabinoid content. Of the 166 patients studied, 46 discontinued nabiximols therapy: 23 (13.9%) because of adverse effects (dizziness, fatigue, oral discomfort), 14 (8.4%) because of lack of efficacy, and 9 (5.4%) for other reasons. The 120 who continued therapy 95 received nabiximols in addition to other anti-spasticity medications and 25 received it as mono-therapy (prior antispasticity medications had not been tolerated or were ineffective and had been discontinued). The 120 patients achieved a 57% mean reduction in spasticity as measured on the 0-10 numerical rating scale. Response to the nabiximols usually occurred within 2 weeks, suggesting that treatment can be discontinued promptly in nonresponders. Mean dosage was 4 sprays per day with a range of 1 to 12 sprays per day, emphasizing the need to individualize therapy.

Maurer M, Henn V, Dittrich A, and Hoffmann A. Delta-9-tetrahydrocannabinol shows anti-spastic and analgesic effects in a single case double-blind trial. *Eur Arch Psychiatry* 1990;240:1-4.

Following a dosing study, one patient with spinal cord injury (paraplegia) and leg spasticity and pain despite routine medications, entered a trial to determine effect of delta-9-THC versus codeine versus placebo. At 18 times over 5 months he took by capsule, in randomized order, 5 mg THC (source not specified), 50 mg codeine, or placebo at the evening time when he regularly took codeine. Results showed THC and codeine both had an analgesic effect in comparison with placebo. Only THC showed a significant beneficial effect on spasticity. In the dosage of THC used no altered consciousness occurred.

Novotna A, Mares J, Ratcliffe S, et al. A randomized double blind placebo-controlled, parallel group, enriched design study of nabiximols (SATIVEX) as add-on therapy in subjects with refractory spasticity caused by multiple sclerosis. *Eur J Neurol* 2011;18:1122-1131.

Multi-center, double-blind randomized, placebo-controlled parallel group study in subjects with multiple sclerosis spasticity not fully relieved with current anti-spasticity therapy. Subjects were treated with nabiximols as add-on therapy in a single-blind manner for 4 weeks, after which those achieving an improvement in spasticity of 20% or more as measured by the self-reported 0-10 numerical rating scale progressed to a 12-week randomized phase.

Of the 572 subjects enrolled 272 (48%) achieved $\geq 20\%$ improvement and were randomized for 12 weeks of treatment. Most subjects were taking anti spasticity medications. The purpose of this design was to determine efficacy and safety of nabiximols in a way that more closely reflects likely clinical practice by limiting exposure to those patients who appear to attain benefit during the first few weeks of treatment. Subjects self-titrated during the first ten treatment days according to a pre- defined escalation scheme (not further defined) to their optimum dose, balancing effectiveness and side effects, to a maximum of 12 sprays per 24 hour period. During the first 4-week phase mean number of daily sprays was 6.9. In the 12-week phase mean number of sprays was 8.3 for active treatment subjects. Mean change in NRS scale for all subjects during the first 4 week phase was decrease of 3.01 units (change from 6.91 to 3.9). Half of those not randomized had an improvement of $< 5\%$.

Over the course of the 12 week second phase, mean spasticity score improved in the active treatment group by another 0.04 points from a baseline of 3.87. The placebo group worsened (increased) by 0.81 from a baseline of 3.92. The estimated treatment difference between the two groups in mean spasticity NRS was 0.84 points (CI: -1.29 to -0.40; $P = 0.0002$). A secondary outcome measure during the second phase was spasm frequency, which saw a small decrease in the active treatment group and an increase in the placebo group. The difference between the two groups was reported as being statistically significant. Across both phases, 3 subjects withdrew because of side effects. Two serious treatment-related adverse events occurred and both resolved rapidly after treatment discontinuation. Adverse events that appeared to occur at higher rates in the

active treatment group include vertigo, dry mouth, nausea, dizziness, somnolence, and urinary tract infection.

Patti F, Messina S, Solaro C, Amato, MP, et al. Efficacy and safety of cannabinoid oromucosal spray for multiple sclerosis spasticity. *J Neurol Neurosurg Psychiatry* 2016;87:944-951.

Observational study of all patients seen at 30 Italian MS clinics and started on Sativex between January 2014 and February 2015. The article states the patients were initiated on Sativex “according to the approved label and expected standards of good clinical practice” which seems to mean the inclusion and exclusion criteria established by the AIFA (Italian Medicine Agency) Sativex registry inclusion criteria of > 18 years, score ≥ 4 on 1-10 numerical rating scale for spasticity, and not responding to common and ongoing antispasticity drugs. The 1615 patients that entered into the study were evaluated at baseline, one month, three months and six months. During the six month study period 631 patients (39.5%) discontinued treatment. The main reasons for discontinuation were lack of effectiveness ($n=375$, 26.2%) and/or adverse events ($n=268$, 18.7%). The adverse events causing discontinuation were mostly cognitive/psychiatric. The five serious adverse events observed were judged to be unrelated to Sativex use. Frequency of adverse events other than those that caused discontinuation and serious adverse events were not discussed. Among those still taking Sativex at one month (1432 patients), 70.5% reached 20% improvement and 28.2% reached 30% improvement (25% of initial study population). Mean dose (SD) was 6.8 (± 2.6) sprays/day. Among those still taking Sativex at 3 months ($n=889$) 311 (35%)

reached 30% improvement (19% of initial study population) and among those still taking Sativex at 6 months (n=593) 225 (42.5%) reached 30% improvement (14% of initial study population). Mean dose (SD) for those still taking Sativex at 6 months was 6.3 (± 2.8) sprays/day.

Serpell MD, Notcutt W, Collin C. Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis. *J Neurol* 2013;260(1):285-295.

This study is an extension of the study reported in Collin 2007. Its primary objective was to assess the safety and tolerance of long-term therapy with nabiximols. Its secondary objective was to determine whether there was evidence of tolerance with long-term nabiximols use by assessing ratings of effectiveness over time. The initial trial studied effectiveness of nabiximols in multiple sclerosis patients whose spasticity was not adequately controlled with standard drugs. Nabiximols is an oromucosal cannabis extract spray developed by GW Pharmaceuticals in Germany. The whole plant extract is highly standardized, produced from cloned cannabis chemovars grown under controlled conditions. Each 100 μ liter actuation yields 2.7 mg delta-9THC and 2.5 mg of CBD with these two cannabinoids constituting at least 90% of cannabinoid content. Among the 146 patients who participated in the extension study 68% were taking additional anti-spasticity medications. Patients self-titrated nabiximols dose upward using a pre-defined scheme that limited increases to 50% of the previous day's dose with a maximum of 8 actualizations in any 3 hour period and 48 actualizations during a 24 hour period. The level of spasticity severity was rated each week with a 0-10 numerical

rating scale. Within the first 12 months of observation 20 patients (14%) withdrew because of side effects. Another 3 patients, among those followed for more than a year, withdrew because of side effects. Serious adverse events that were considered treatment-related included two cases of 'pneumonia aspiration,' and one case each of 'liver function tests abnormal,' 'convulsions,' 'dizziness,' 'paresthesia,' 'tremor,' 'nausea,' 'delusion perception,' and 'paranoia.' Minor and moderate side effects occurred among nearly all patients with dizziness and fatigue most common. Among 90% of patients some additional improvement in spasticity – beyond that observed in the original 6 week study – for approximately 8 weeks, with maintenance of the improved status for the duration of observation.

Tomassini V, Onesti E, Tinelli E, Frasca V, Antonilli L, Aragona M, et al. Assessing the Neurophysiological Effects of Cannabinoids on Spasticity in Multiple Sclerosis. *Journal of Neuroscience and Rehabilitation* 2014;1(2):1-13.

Authors cited some research evidence suggesting that cannabinoids have actions on the brain that are not specifically tied to actual stimulation of cannabinoid receptors, specifically relating to changes in cortical excitability in motor areas. Therefore, if Sativex leads to decreases in MS-related spasticity, they decided to investigate for an associated change in cortical motor regions via fMRI and TMS. Twenty cannabis-naïve MS participants initially started out in this randomized, double-blind, placebo-controlled crossover study, with eighteen (n=18) eventually completing the study (10-week study). Baseline measures were: 1) EDSS, 2) Ashworth Scale, and 3) NRS of

spasticity. Participants were randomly assigned to either a 3-week Sativex or placebo condition, during which time subjects were instructed to complete a symptom diary along with their daily usage (# of sprays) of treatment. After the 3-week treatment, the following were measured in participants 1) neurophysiological measures (fMRI and TMS), 2) clinical assessments, and 3) THC and CBD plasma measures. fMRI and TMS data were collected during drug steady state concentrations (generally within 3 hours of the last treatment intake). During the fMRI scan, participants engaged in a motor task. TMS was delivered in a region within left M1 (primary motor cortex) to optimally induce first dorsal interosseous muscle contractions. Following all these measures, there was a 2-week washout period after which time participants crossed over into the other condition for a 3-week period (same measures were collected again after this crossover treatment period, and it was followed by another 2-week washout period). Conclusions: the median number of daily sprays were 7.4 with Sativex (20 mg THC, 18.5 CBD) and 16.1 with placebo.

Mean plasma concentrations for THC was 1.84 ng/ml and for CBD was 2.13 ng/ml at the end of the Sativex treatment condition (THC/CBD was not detected at the end of placebo treatment). Compared to placebo, Sativex treatment was not any better at improving spasticity symptoms. In addition, there was no difference in cortical motor activation (based on fMRI and TMS results) between Sativex and placebo. And there was no correlation between THC/CBD plasma levels and the neurophysiological measures. They suggest that the failure to find a neurophysiological correlate be indicative of cannabinoids not heavily influencing the motor system. Rather, they suggest that

cannabinoids' actions might somehow modulate "the painful components of spasticity". Overall, while study results suggest Sativex's lack of effect on spasticity and modulation of motor regions, limitations in the study itself make their conclusions harder to interpret.

Vaney C. Heinzl-Gutenbrunner M, Jobin P, et al. Efficacy, safety and tolerability of an orally administered cannabis extract in the treatment of spasticity in patients with multiple sclerosis: a randomized, double-blind, placebo-controlled, crossover study. *Mult Scler* 2004;10:417-24.

Randomized, double-blind, placebo-controlled cross-over parallel group study of 50 Swiss multiple sclerosis patients.

Patients were randomized to early group or late group active treatment. Active treatment was a cannabis whole plant extract containing 2.5 mg THC and 0.9 mg CBD in a capsule. A five day dose titration phase increased starting dose of six active capsules daily (equivalent to 15 mg THC/day) by two capsules per day with the maximum daily dose of 12 active capsules daily (equivalent to 30 mg THC/day). After 14 days of active treatment patients were switched to placebo capsules without tapering the active dose. Patients received the same number of total capsules each day, but the ratio of active drug capsules to placebo capsules varied. Patients in the early active treatment group stayed on placebo 7 days before initiating active treatment. Outcome measures included daily self-report of spasm frequency and symptoms, clinician-assessed Ashworth Scale of muscle tone, Rivermead Mobility Index, and others. The daily self-report of spasm frequency had the patient record

spasm frequency five times per day, asking about the most recent four hours. Response categories were: 0=no spasms, 1= 1 to 3 spasms, 2 =4 to 6 spasms, 3 = >6 spasms. The maximal tolerated dose was 15 mg THC or less for half the patients and there was a weak but significant correlation between mean dose during the 2 week dose maintenance phase and body weight. Results showed no effect on Ashworth Scale measurement and a non-significant trend for spasm frequency. When analysis was limited to the 37 patients who received at least 90% of their prescribed doses (“as treated” set), the observed treatment in spasm frequency was statistically significant. Spasm frequency reduction was greater for early active treatment group patients who tolerated a significantly higher THC dose (mean 15 mg/day versus 10 mg/day). No serious adverse events were observed, but three patients dropped out of the early treatment group because of side effects. Adverse events were only slightly more common and more severe during active treatment.

Vermersch P, Trojano M. Tetrahydrocannabinol:cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice. *Eur Neurol* 2016;76:216-226.

MOVE-2 EU is a prospective, observational study of Sativex (THC:CBD oromucosal spray; each spray delivers 2.7 mg THC and 2.5 mg CBD) in routine clinical use as adjunct therapy for moderate-to-severe multiple sclerosis-related drug-resistant spasticity, according to its approved use label in Europe. This article summarizes the experience of patients in Italy, Norway, and Denmark; an article with the experience of German patients has been published previously. 433 patients were

recruited (98% from 34 centers in Italy) for the planned 3 months of data collection. At one month only the 349 patients (81%) that had achieved $\geq 20\%$ reduction in 0-10 numerical rating scale of spasticity continued on with the study. A total of 281 patients completed the 3 months of follow-up, with 86 achieving $\geq 30\%$ spasticity reduction (20% of the initial cohort). Mean dose was similar among those who made it to the end of the 3 month study, whether they achieved the $\geq 30\%$ spasticity reduction (5.8 sprays/day) or not (6.0 sprays per day). Adverse events, none of which were severe or serious, were reported by 10.4% of patients. The most common adverse events were dizziness, confusion, tremor, nausea, asthenia, and fatigue.

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

A small placebo-controlled crossover trial of nabiximols (Sativex) on patients with neurological disorders and troublesome symptoms. Twenty four patients with a variety of neurologic disorders enrolled and 20 completed the study (14 with multiple sclerosis, 4 with spinal cord injury, and one each with brachial plexus lesion with neuropathy and an amputated leg with phantom limb pain). The symptoms varied; 16 had muscle spasm as a symptom.

Patients first had a two week open-label trial with nabiximols with instructions to increase frequency of sprays, balancing symptom relief with side effects up to a maximum of 8 sprays within 70 minutes. Because of side effects this was changed to four sprays over 2

hours and changed again to two sprays over two hours. After the two week open-label trial the patient entered an eight week double-blind study phase with four two-week stages using nabiximols, or CBD alone or THC alone or placebo. Results were not reported broken out by neurologic condition. Across all 20 patients, spasticity severity had a statistically significant reduction on nabiximols, CBD alone, and THC alone, compared with placebo. Spasm frequency saw statistically significant reduction while on nabiximols and THC alone, but not while on CBD alone, compared with placebo. Occurrence of side effects was similar across the four treatment conditions during the placebo-controlled phase and substantially higher during the initial open-label nabiximols treatment phase.

Wade T. et al. 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; 10:434-441.

A randomized, double-blind, placebo-controlled, parallel group trial of nabiximols (Sativex) for patients with multiple sclerosis. 160 patients from 3 UK centers were enrolled and indicated whether their primary symptom was spasticity, spasms, bladder problems, tremor, or pain not obviously musculoskeletal. Intensity of each symptom was self-rated on a 100 mm visual analog scale throughout the study. Patients were randomized to nabiximols or placebo for the initial six week double-blind trial and told to titrate slowly during home dosing, aiming for optimal balance between symptom relief and side effects, but not to exceed 120 mg THC (44 sprays) per day or 20 mg THC (7 sprays)

within a 3 hour period. Average number of sprays per day in the active treatment group increased steadily over three weeks and then plateaued at 14 to 16 sprays per day (38 to 43 mg/day THC; 35-40 mg/day CBD). Subjects receiving nabiximols showed improvement in subjective (VAS), but not objective (Ashworth scale) measures of spasticity, compared to the placebo group. No significant difference in symptom scores between groups was found for spasms, pain, tremor, bladder control, or a composite symptom score. Side effects that occurred more often in the active treatment group included dizziness, disturbance in attention, fatigue, somnolence, disorientation, vertigo, diarrhea, and mouth ulceration.

Wade DT, Makela PM, House H, et al. Long-term use of a cannabis-based medicine in the treatment of spasticity and other symptoms in multiple sclerosis. *Mult Scler* 2006;12(5):639-645.

Patients who completed the study reported in Wade 2004 and reported receiving benefits from the 10 weeks of active treatment were offered the opportunity to participate in a long-term follow-up study. The purpose of the study was to assess whether symptom reduction achieved at 10 weeks of treatment was maintained over the long term and to further assess adverse events. 137 choose to participate. The mean duration of study participation in subjects who entered the follow-up study was 434 days (range: 21-814 days). The average number of daily doses taken by the subjects remained constant or was slightly reduced over time. The average number of daily doses of nabiximols was 11 (30 mg THC/28 mg CBD) per day. Results indicated patients with MS who derived symptom relief within 10 weeks

of nabiximols treatment generally sustained that symptom relief over an extended period without increase in dose. Side effects were generally minor, but 17 patients withdrew because of side effects.

Zajicek J, Fox P, Sanders H, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomized placebo-controlled trial. *Lancet* 2003;362:1517-26.

Randomized, placebo-controlled clinical trial involving 630 adult patients with all forms of multiple sclerosis from 33 UK medical centers. Subjects were randomized to cannabis extract (n=211), dronabinol (synthetic delta-9-THC; n=206) or placebo (n=213). The cannabis abstract was Cannador – registered trademark – manufactured to contain 2.5 mg of delta-9- THC and approximately 1.25 mg CBD and less than 5% other cannabinoids in each capsule. The dronabinol capsules contained 2.5 mg delta-9-THC. The trial included a five week titration phase, 8 weeks of maintenance treatment and weaning off treatment over several days. Subjects started with one capsule twice daily and were instructed to increase the dose by one capsule twice daily at weekly intervals. If side effects developed subjects were advised to not increase the dose and if the side effects were considered intolerable the dose was reduced. Target daily dose varied with patient weight: 4 capsules (10 mg THC) for 30-49 kg, 6 capsules (15 mg THC) for 50-69 kg, 8 capsules (20 mg THC) for 70-89 kg, and 10 capsules (25 mg THC) for >89 kg. Achieved dosages were not described. Primary outcome measure was change in spasticity as measured by the clinician-assessed Ashworth scale. Secondary measures included the

Rivermead mobility index (a timed walk) the UK neurological disability score (UKNDS), the Barthel index (an index score related to activities of daily living) and a series of nine category-rating scales – each given at the end of the study to patients with those symptoms at the beginning of the study. The patients were asked to compare their symptoms over the past week with how they were just before the study started. Symptoms surveyed included: irritability, depression, tiredness, muscle stiffness, tremor, pain, sleep, muscle spasm, and amount of energy. Results showed no treatment effect on the primary outcome. Compared to the placebo group, the active treatment groups showed significant improvement in pain, sleep quality, spasm, and spasticity, though no effect was noted with respect to irritability, depression, tiredness, tremor, or energy. Improvement in these categories was similar among patients taking cannabis extract and those taking dronabinol, with approximately half reporting improvement in each of these categories. Numbers of serious adverse events were similar across the three treatment groups, with slightly more events in the placebo group. Dizziness or lightheadedness, dry mouth and diarrhea were more common among both active treatment groups. Constipation was more common in the cannabis extract group.

Zajicek JP, Sander HP, Wright P, et al. Cannabinoids in multiple sclerosis (CAMS) study: safety and efficacy data for 12 months follow up. *J Neurol Neurosurg Psychiatry* 2005;76:1664-1669.

At the end of the 13 week CAMS study, subjects were given the option of continuing treatment, at their previously determined

dose, for a total of 52 weeks. Participation was as follows: cannabis extract group – 138, dronabinol – 125, placebo – 120. Results showed a small treatment effect on the change in Ashworth score (spasticity). Responses to category response scales, comparing symptoms at 52 weeks to those symptoms before treatment began showed significant improvement in active treatment groups, compared to placebo, in pain, shaking, spasms, spasticity, sleep, energy, and tiredness, but not in depression or irritability. All hospital admissions were classified as serious adverse events and similar numbers occurred across the three treatment groups.

Zajicek JP, Hobart JC, Slade A, Barnes D, Pattison PG, on behalf of the MUSEC Research Group. Multiple Sclerosis and Extract of Cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry* 2012;83:1125-1132.

Double-blind placebo controlled study of 279 patients age 18-64 with MS by McDonald criteria, stable disease for the last 6 months and troublesome and ongoing muscle stiffness for at least 3 months before enrollment (as shown by a current disability score of at least 4 on an 11 point category rating scale (CRS) at 22 UK centers). Treatment = 144, placebo = 135. Physiotherapy regimens or medications likely to affect spasticity were adjusted where necessary and then not altered in the 30 days before study start. Patients with active sources of infection or taking immunomodulatory drugs that might affect spasticity (e.g. Beta-interferon, but not azathioprine) were excluded. Active treatment was an extract of *Cannabis sativa L* (extraction ethanol 96%) in soft gelatin

capsules, standardized on cannabidiol (range 0.8-1.8 mg) and containing 2.5 mg delta-9 THC as the main cannabinoid (CANNADOR). The study consisted of a screening period of 1-2 weeks, 2 week dose titration phase and a 10 week maintenance phase. Total treatment duration was 12 weeks. Participants were assessed at 2, 4, 8, and 12 weeks after start of treatment.

Starting dose was 2.5 mg THC (one capsule) twice daily. Subsequent doses were individually titrated upwards by 5 mg THC/day every 3 days for up to 12 days to optimize the balance between therapeutic effect and side effects. Maximum total allowable daily dose was 25 mg THC. In the event of intolerable side effects, the daily dose was reduced by one capsule until the side effect(s) resolved. After resolution, one re-challenge with a further dose escalation was required. If the side effect(s) returned, the dose was reduced again, with no further re-challenge allowed. The primary outcome measure was perceived change in muscle stiffness after 12 weeks of treatment compared with the premedication phase. At the final visit, participants answered the following question on a symptom questionnaire: "Compared with before the study started, my muscle stiffness over the last week has been ..." providing a rating on an 11 point numerical scale where 0=very much better, 5= no difference and 10=very much worse. Categories 0-3 of the rating scale were classified as 'relief of muscle stiffness' – that is, as a clinically relevant response.

Secondary measures included relief from body pain, muscle spasms and sleep disturbance using 11 point scales. Also, the validated disease specific multi-item rating scales measuring aspects of spasticity in MS

(MS Spasticity Scale (MSSS-88), and other scales including Expanded Disability Status Scale (EDSS). Main result: proportion with self-reported relief from stiffness was higher by a statistically significant amount compared to the placebo group (29.4% vs. 15.7%; OR=2.6 95%, CI = 1.24-4.13).

Proportion of patients with relief of body pain (0-3 on 11 point scale) was higher by a statistically significant amount at each time of measurement (44% vs. 18% at week 12). At the end of the titration period approximately 87% of participants in the placebo group were taking the maximum daily dose of 25.0 mg. In contrast, only 47% of participants in the active treatment group had titrated up to a maximum daily dose of 25.0 mg. Of the active treatment patients who did not achieve the maximum daily dose, most were taking daily doses of 10.0 to 15.0 mg. Sixteen participants in the active treatment group discontinued study medication during titration, compared with four in the placebo group. At the end of the study, only 24.5% of the active treatment group was taking the 25.0 mg dose. By the end of the study, 84% of all patients experienced at least one treatment emergent adverse event: 98% in active treatment group and 74.6% in the placebo group. 23.8% in the active treatment group and 14.9% in placebo group were withdrawn from the study or discontinued study medication due to adverse events. In the active treatment group adverse events were highest during titration and decreased continuously over the course of the study. Adverse events that occurred at clearly higher rates in the active treatment group than in the placebo group were dizziness, disturbance in attention, balance disorder, somnolence, dry mouth, nausea, diarrhea, fatigue, asthenia, feeling abnormal, urinary tract infection,

disorientation, confusional state, and fall. The relatively rapid titration was done for technical study reasons – in clinical practice it is not likely to be done so rapidly. Results in this study confirm results in the CAMS study, which was larger, and are similar to two other studies that showed significant reduction in spasticity using an 11 point rating scale (Novotna 2011; Colin 2007).

Zajicek J, Ball S, Wright D, Vickery J, et al. Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomized, placebocontrolled trial. *Lancet Neurol* 2013;12(9):857-865.

Multi-center (UK), randomized, double-blind, placebo-controlled three year study of the effect of dronabinol (synthetic delta-9-THC) on MS disease progression. 493 subjects age 18-65 with primary or secondary progressive multiple sclerosis.

Dronabinol was initiated at a starting dose of one capsule (3.5 mg THC) twice daily.

Participants were instructed to increase their twice-daily dose by one capsule twice daily (i.e. first increase = 7.0 mg twice daily) at weekly intervals. If adverse effects appeared, participants were advised to not increase the dose; if unwanted side-effects were intolerable, dose was reduced.

Maximum daily dose varied by weight: < 60 kg = 14 mg/day, 60-80 kg = 21 mg/day, >90 kg = 28 mg/day. Primary outcomes were time to disease progression as measured by the expanded disability status scale (EDSS) and change from baseline to end of study in the physical impact subscale of the patient-reported 29-item MS impact scale (MSIS). Secondary measures outcomes included adverse events, MS functional composite (MSFC) Z score change from baseline to final

visit, MS walking scale (MSWS-12) and Rivermead Motility Index. Subjects were reviewed after 2 weeks and 4 weeks from when they began taking the study drug for adverse event screening and drug monitoring and dose adjustment. Assessment visits were held at 3 months, 6 months, and then every 6 months to 36 months. Results showed no overall treatment effect on clinical disease course. And results showed little evidence of an effect of treatment on MSFC, MSWS-12 or RMI. Serious adverse events (life threatening event, hospitalization, death) were common, with no significant difference between treatment (35%) and placebo (28%) groups. Moderate adverse effects were common in both groups. Those that occurred in the treatment group at a significantly higher frequency than in the control group were dizziness and lightheadedness (32%) and dissociative and thinking or perception disorders (30%).

Inflammatory Bowel Disease

Three small clinical trials of cannabis or cannabinoids for treatment of inflammatory bowel disease have been published. One was a double-blind trial of 99.5% CBD dissolved in olive oil for oromucosal absorption. It enrolled 20 patients for an eight week trial, using a very low dose of CBD. Results showed no beneficial effect (Naftali 2017). A small placebo-controlled two week trial using smoked cannabis had results suggesting better outcomes with the active drug, but the primary outcome did not achieve statistical significance (Naftali 2013). A small placebo-controlled 10-week trial of CBD-rich cannabis

extract showed no difference between groups for remission, but secondary endpoints suggested benefit for the CBD extract (Irving 2018).

A placebo-controlled trial is being organized at the University of Illinois, Chicago using CBD as adjunct therapy for Crohn's Disease. Participants will take a 25 mg capsule of CBD (or placebo) once per day for 12 weeks. Recruitment of the anticipated 36 adult participants was initially planned to start in July, 2018 with an estimated completion is July, 2019. The trial's entry in [clinicaltrials.gov](https://www.clinicaltrials.gov) has not been updated since May, 2018. <https://www.clinicaltrials.gov/ct2/show/NCT03467620?cond=inflammatory+bowel+diseases+cannabis&rank=3>

Irving PM, Iqbal T, Nwokolo C, Subramanian S, Bloom S, et al. A randomized, double-blind, placebo-controlled, parallel-group, pilot study of cannabidiol-rich botanical extract in the symptomatic treatment of ulcerative colitis. *Inflamm Bowel Dis* 2018 Mar 19;24(4):714-724. doi: 10.1093/ibd/izy002.

This trial enrolled 60 adults with mild to moderate ulcerative colitis from 9 centers in the UK; 29 were randomized to CBD-rich cannabis extract in capsules and 31 were randomized to placebo. Percentage of CBD was not specified, but the extract contained up to 4.7% THC. The CBD-rich extract (and placebo) were in 50 mg capsules and participants were started on two capsules per day (one before breakfast and one before dinner). During a two-week escalation period participants increased their daily dose to a goal of 10 capsules per day (500 mg, of which up to 23.5 mg was THC). Treatment continued for eight weeks after the dose

escalation period. Primary outcome was remission. 15 patients withdrew due to adverse events: 10 in the CBD-rich extract group and 5 in the placebo group. Most common were dizziness, nausea, and somnolence. The proportion of patients experiencing remission was similar in the two groups: 28% CBD-rich and 26% placebo. Secondary endpoints suggested benefit from the CBD-rich extract. These included quality of life measures, measures of disease severity, and fewer patients experiencing worsening of symptoms.

Naftali T, Bar-Lev Schleider L, Dolan I, Lansky EP, Skierovsky B, Konikoff F. Cannabis induces a clinical response in patients with Crohn's Disease: a prospective placebo-controlled study. Clin Gastroenterol Hepatol, 2013;11(10):1276-1280.

This randomized, placebo-controlled eight-week trial of smoked marijuana to relieve symptoms of Crohn's disease was carried out in 2010-2011 on patients with established Crohn's disease referred to a tertiary medical center in Israel. All patients had failed at least one form of therapy for the disease, had a Crohn's Disease Activity Index (CDAI) score between 200 and 450 points, and had never before used marijuana. 21 patients were recruited; 11 were randomized to active treatment and 10 to placebo. The patients were on a variety of concomitant anti-inflammatory medications. The active treatment cannabis was made from dried flowers of genetically identical plants of *Cannabis sativa* Variety Indica Erez, grown under controlled conditions, and known to contain 23% THC and less than 0.5% CBD. Plants were tested to verify an equal content of active ingredients. The placebo was made

of cannabis flowers from which THC had been extracted. Post-extraction testing was done to ensure less than 0.4% THC and undetectable amounts of all other cannabinoids including CBD. Each active treatment cigarette contained 0.5 g of dried cannabis flowers, corresponding to 115 mg THC. Detail is not provided on instructions or actual behavior regarding number of study cigarettes smoked per day. Patients were followed for two weeks plus a two-week washout period. Patient evaluations were done at weeks 1, 2, 8, and 10. The primary outcome was induction of remission, as defined by a score of 150 less on the CDAI after 8 weeks of therapy. Secondary outcomes included a 100 point reduction in CDAI, a reduction of at least 05 mg in C-reactive protein (CRP), or improvement in quality of life of at least 50 points as measured by the Short-Form 36 (SF-36) survey. Results showed five patients in the active treatment group (45%) and one patient in the placebo group (10%) achieved full remission. Though these results favored active treatment, they did not reach statistical significance. Mean reduction in CDAI score was twice as large in the cannabis group as in the placebo group. A significant increase in SF-36 score was seen in the active treatment group, compared to the placebo group, whose score was unchanged. There were no significant differences in change of CRP between the groups. There were no differences between the active treatment and placebo groups in side effects, including sleepiness, nausea, and confusion. However, the active treatment group reported significantly less pain, improved appetite, and a higher satisfaction from the treatment. CDAI scores increased (indicating relapse), between weeks 8 and 10, the period after active treatment was stopped. CDAI scores

for the placebo group changed little between weeks 8 and 10.

Naftali T, Mechulam R, Marii A, Gabay G, A Stein, Bronshtain M, Laish I, Benjaminov F, Konikoff F. Low-dose cannabidiol is safe but not effective in the treatment for Crohn’s Disease, a randomized controlled trial. *Dig Dis Sci* 2017. DOI 10.1007/s10620-017-4540-z

Double-blind clinical trial of cannabidiol (CBD – 99.5% pure) purified from a cannabis extraction. Twenty adult Crohn’s Disease patients with a Crohn’s disease activity index (CDAI) between 200 and 450 points were recruited for the study from one Israeli medical center between 2011 and 2012. Each had received at least one form of medical treatment for Crohn’s Disease with no effect. Patients were randomized in a 1:1 to ratio to receive either 5 mg CBD dissolved in olive oil sublingually twice daily or an equivalent amount of pure olive oil. Treatment duration was eight weeks with patients evaluated at weeks 0, 2, 8, and 10 for disease activity using the CDAI, medical interview, and physical examination. Blood tests were drawn for complete blood count, liver and kidney function and CRP and a quality of life questionnaire was completed on weeks 0 and 8. Patients also answered a questionnaire monitoring possible side effects. Primary outcome was reduction of 70 points in CDAI from week 0 to week 8. The active treatment group showed more reduction in CDAI than the control group, but the difference was not large and was not statistically significant. Blood tests remained unchanged and no side effects were observed. The authors conclude the observed lack of beneficial effect “could be due to lack of effect of CBD on Crohn’s disease but could also be due to the small

dose of CBD, the small number of patients in the study, or the lack of the necessary synergism with other cannabinoids. Further investigation is warranted.” They chose the very low dose of CBD because of concerns about potential drug interactions.

Terminal illness

With a probable life expectancy of under one year, if the illness or its treatment produces one or more of the following: severe or chronic pain; nausea or severe vomiting; or cachexia or severe wasting.

Relevant studies can be found in other sections of this report, particularly the cancer sections. No published medical cannabis trials were found that specifically targeted patients with short life expectancy, cutting across medical conditions.

The Connecticut Hospice has organized an open-label trial of cannabis products for reduction of pain and reduction in opioid utilization. It is currently enrolling patients by invitation at its inpatient facility; study completion is anticipated in November 2019. For details, see:

<https://www.clinicaltrials.gov/ct2/show/NCT03233633?term=connecticut+hospice&rank=1>

Intractable Pain

For the Minnesota medical cannabis program intractable pain is defined as pain whose cause cannot be removed and, according to generally accepted medical practice, the full range of pain management modalities

appropriate for the patient has been used without adequate result or with intolerable side effects. Trials of cannabis for pain in the literature generally follow this definition in that their inclusion criteria specify patients with pain inadequately controlled with standard pain medications. The trials uniformly had the participants continue taking their routine pain medications, so they assess the value of cannabis treatment as an adjunct to other pain medications.

Most of the 16 trials summarized here are relatively small (seven have >100 participants) and short (only 3 of the controlled trials are longer than 5 weeks) and they are spread across multiple types of pain. These are important limitations to their value in giving understanding of the potential for cannabis products in pain management. The quality of most of the studies summarized in this section is formally assessed in a report by the MN Evidence-based Practice Center called, "[Medical Cannabis for Non-Cancer Pain: A Systematic Review](http://www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf)" (<http://www.health.state.mn.us/topics/cannabis/intractable/medicalcannabisreport.pdf>). Six of the studies assessed in that report are not summarized here because they used the synthetic cannabinoid nabilone, which is similar to – but distinct from – THC.

Eleven of the 16 trials studied an approximately 1:1 ratio of THC:CBD oromucosal spray (in most cases nabiximols, brand name Sativex) vs. placebo (Blake 2006, Langford 2013, Nurmikko 2007, Rog 2005, Selvarajah 2010, Serpell 2014, Wade 2004) or 1:1 THC:CBD plus additional active treatment arms of mostly THC extraction product (Berman 2004, Notcutt 2004, Wade 2003) and mostly CBD extraction product (Notcutt 2004, Wade 2003) vs. placebo. There are also two open-label long-term studies of Sativex

(Hoggart 2015, Rog 2007). Average dose in the clinical trials, after the titration period, of the 1:1 THC:CBD spray, the mostly THC spray, and the mostly CBD spray were all around 6 to 10 sprays per day, representing a daily dose of approximately 15 to 27 mg THC and/or CBD per day. In the trial studying approximately 2:1 THC:CBD capsules (Zajicek 2012) the average daily dose of THC was similar. In the two long-term open-label studies of Sativex, average daily dose was somewhat less, at around 6 to 8 sprays per day (Hoggart 2015) and 6.5 to 7.5 sprays per day (Rog 2007) representing 16-22 mg THC and 15-20 mg CBD per day. These long-term studies showed no evidence of tolerance developing. Side effects were very common but mostly mild or moderate in severity. Though a few studies using nabiximols reported few or no participants withdrawing due to side effects, several reported withdrawal rates in the nabiximols treatment group in the range of 5 to 25%.

Three of the trials studied oral dronabinol, synthetic THC, vs. placebo (Narang 2008, Svendsen 2004, Schimrigk 2017). Two of them reported an average dose after titration (Svendsen 2004): 21 patients @ the study maximum of 10 mg/day, 3 patients @ 7.5 mg/day, and one patient @ 5 mg per day; (Schimrigk 2017): average dose of 12.7 mg/day (maximum allowed was 15 mg/day).

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 (3): 299-306.

This was a randomized, double-blind, placebo-controlled, crossover study involving 48 patients (46 male) with intractable pain

scoring >4 on an eleven- point scale. Patients were a minimum of 18 years of age (average 39 years) with pain due to brachial plexus avulsion occurring at least 18 months prior to the start of trial. Symptoms were assessed at baseline and were documented in a daily diary. Each patient was given a treatment or placebo for 14-20 days before switching arms.

Patients were provided either placebo or whole-plant extracts oral spray with either 1:1 THC:CBD (Sativex) or THC alone during three 2-week treatment phases. Initially, the dosing was monitored in clinic while subsequent doses were self-administered on a titration schedule with the maximum daily doses being 129.6 mg THC or 129.6mg THC/120 mg CBD in 24 hours. Starting dose was 8 to 10 sprays per day (22-27 mg THC). Forty of the 48 patients were currently taking pain medication and were instructed to remain on their current regimen.

The primary outcome measure was based on the eleven point Box Scale (BS-11) where “0” represented the ‘Best Imaginable’ and 10 the worst. The average score during the last 7 days of treatment was compared to the average during the 7 day baseline, prior to treatment initiation. Secondary outcomes included a patient-reported rating of pain over a week-long period as well as sleep quality using the BS-11 and sleep disturbance based on number of nighttime awakenings. Other measures included questionnaires such as the short form McGill questionnaire (SF-MPQ), Pain Disability Index (PDI) and General Health Questionnaire-12 (GHQ-12), administered at baseline and again at subsequent visits.

Also at each visit, a visual analogue scale (VAS) of intoxication was recorded and at two visits, a complete physical was performed.

Forty-five of the 48 enrolled patients completed the study with the main reasons for dropout being GI upset, lightheadedness, and anxiety. Pain reduction was greater for each of the two treatment arms than for placebo. The number needed to treat was 9.0 (1:1 THC:CBD) and 7.7 (THC only) based on a 30% decrease in pain. Average dose of active treatment was approximately 8 sprays per day (22 mg THC). The most commonly reported side effects were dizziness, somnolence, mild intoxication, GI upset, and unpleasant taste.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology* 2006;45(1):50-52.

This was a double-blind, randomized, placebo-controlled study carried out for five weeks in patients diagnosed with rheumatoid arthritis (RA) that were stabilized on traditional therapy but who did not gain adequate pain relief from standard treatments. A total of 58 participants (12 male/46 female; average age 62.8 years) met the inclusion criteria and 31 were randomized to treatment, while 27 received placebo. The patients were instructed to limit use to evening dosing to prevent daytime intoxication from the Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100 µl actuation) that was used throughout the trial. The

titration schedule was one actuation before bed and increase by one actuation every two days, based on patient response, up to a maximum of six actuations per night. The primary endpoint tested was based on a 0-10 pain scale assessing pain upon movement each morning and comparing the baseline rating to the average of the last 14 days of the trial. Secondary outcomes were pain at rest, sleep quality, morning stiffness and used the Short Form McGill Pain Questionnaire (SF-MPQ) as well as the 28-Joint Disease Activity score (DAS28). All outcomes except morning stiffness and SF-MPQ intensity showed a statistically significant improvement when compared to placebo, including the SF-MPQ pain at present rating. Side effects were approximately twice as common in the active treatment group than in the placebo group. All but two of the side effects in the active treatment group were mild or moderate; two patients rated side effects as severe (constipation, malaise). The side effects more common in the active treatment group than in the placebo group were mild dizziness, dry mouth, light-headedness and fall. Three patients withdrew from the study because of side effects – all 3 from the placebo group. There were no serious adverse events in the active treatment group and two in the placebo group.

Hoggart B, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejcko J, Taylor L, Lauder, Serpell M. A multicenter, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain. *J Neurol* 2015;262:27-40.

This nine month open-label study was a continuation of two parent studies: the clinical trial reported in Serpell 2014 (neuropathic pain associated with allodynia) and an unpublished clinical trial involving patients with diabetic neuropathy carried out by GW Pharma. 439 participants completed these two studies and were eligible for the continuation study; 57 (13%) chose not to continue for unspecified reasons. Of the 380 who entered the extension study, 234 (62%) completed it. Average nabiximols dose during the two parent studies was 8.9 sprays per day (Serpell 2014) and 9.5 sprays per day (GW Pharma study). Details on the starting dose of nabiximols spray (2.7 mg THC and 2.5 mg CBD per spray) are not provided, but patients self-titrated during a baseline period, increasing dose by 50% from previous day to a maximum of 8 sprays per 3 hour period and 24 sprays per 24 hours. Mean dose during months 1-9 was reported as 6 to 8 sprays per day. 84% of participants were on concomitant pain medications and 63% were on two or more. Primary outcome was pain numeric rating scale assessing pain over the past week, completed at parent study baseline and completion and at baseline and weeks 2, 14, 26, and 38 of the extension study. At the beginning of the extension study just over half of participants had reduction in pain score of 30% or greater (i.e. during parent study) and during the nine month extension trial this proportion

gradually increased to approximately 60%. 78% of participants had at least one adverse event and 59% were judged to have had a treatment-related adverse event. Four serious adverse events were reported, two patients experiencing amnesia, one event of paranoia, and one suicide attempt. Dosages of nabiximols being used when these occurred were not reported. 23% of participants permanently ceased nabiximols because of adverse events. The authors comment in the Discussion section note that no increase in dose over the parent studies was seen, suggesting no evidence of tolerance developing.

Langford RM, Mares J, Novotna A, Vachova M, Novakova I, Notcuff W, Ratcliffe S. 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; 260(4):984-997.

This was a two-part study involving patients with a diagnosis of multiple sclerosis (MS) made at least three months prior (mean of 11 years with pain an average of 5 years) and stable on prior drug therapies for at least two weeks. The study drug was an oromucosal spray containing 2.7 mg THC/2.5 mg CBD per actuation (spray). Patients were allowed up to 12 sprays/24 hours.

Phase A: double-blind, randomized, placebo-controlled, parallel-group study over 14 weeks with a week of baseline titration and observation. A total of 339 patients (109 male/ 230 female; average age 49 years; treatment arm = 167/placebo

= 172) were enrolled and response to THC/CBD, in addition to standard treatments was evaluated using pain levels on a 0-10 scale. The average number of sprays was 11.1 for placebo compared to

8.8 for THC/CBD. The primary endpoint was reduction of pain by 30% using a 0-10 scale, and secondary endpoints were sleep quality, Brief Pain Inventory-Short Form, and Subject Global Impression of Change.

At the end of Phase A the small benefits in pain reduction favoring the treatment group did not meet statistical significance, nor did any of the secondary endpoints.

Seventy-five percent of treatment patients and 62% of placebo patients reported at least one adverse event during phase A. Adverse events at least twice as common in the treatment patients than in control patients were: vertigo, vision blurred, nausea, fatigue, feeling abnormal, dizziness, somnolence, disturbance in attention, dysgeusia, and memory impairment. Thirty-five patients (10%) in phase an experienced a severe treatment-emergent adverse event, 21 (13%) in the THC/CBD spray group and 14 (8%) in the placebo group. Five patients (3%) in the THC/CBD spray group and three (1%) in the placebo group permanently stopped study medication due to severe adverse events. Dosages at which severe adverse events were experienced were not described.

Phase B: 14-week, open study with two weeks re-titration to maximum of 12 sprays/24 hours. Participants then proceeded to 12 weeks of stable dosing, followed by a 4-week, randomized withdrawal period. To enter this phase, patients were required to use at least three sprays per day for the previous seven days and had proven tolerability and stability with other

medications. The average number of sprays used during phase B was 6.7. Primary endpoint was treatment failure during withdrawal and secondary endpoints were sleep quality, Brief Pain Inventory- Short Form, and Subject Global Impression of Change.

Fifty-eight patients (21 male/37 female; average age 48 years) entered phase B and five withdrew (3 due to adverse events).

Forty-two patients (17 male/25 female; average age 48 years) entered the withdrawal phase of the trial and only one withdrew from the placebo withdrawal group due to adverse events. Time to treatment failure was significantly increased in the THC/CBD group versus placebo and the probability of treatment failure was statistically increased in the placebo group. The decrease in average pain using 0-10 scale was statistically significant in favor of the treatment when compared to placebo at the end of the phase B treatment period; the same was true for sleep quality. All other secondary endpoints favored THC/CBD, but not significantly. The most common AEs noted were dizziness/vertigo, fatigue/somnolence, and GI complaints.

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. *The Journal of Pain* 2008;3:254-264.

This study was done in two phases: a double-blinded, randomized, 3-treatment, 3-period, single-dose crossover trial (phase 1) followed by a 4 week open-label, multi-dose extension study (phase 2). Subjects in the study had been taking stable doses of opioids

for pain for at least 6 months and had pain of at least 4 on a 10-point scale. Subjects were excluded for unstable psychiatric disorders or significant depression and/or anxiety. In phase 1 subjects each received identically appearing placebo, 10 mg or 20 mg dronabinol capsules in 1 of 6 randomly allocated sequences. The 3 treatment options were separated by a minimum of 3 days between visits. Thirty patients with a variety of types of pain were enrolled in phase 1; one dropped out because of inability to concentrate (10 mg dronabinol). Total pain relief at 8 hours in Phase 1 was found to be significantly greater in subjects receiving both the 20 mg and the 10 mg dronabinol treatments compared with placebo. Side effects were more frequent with 20 mg than with 10 mg dronabinol. For both, most common side effects were drowsiness, sleepiness, dizziness, dry mouth. All were clearly more common with dronabinol than placebo except for sleepiness. All resolved within 2 hours except for sleepiness and drowsiness, which each lasted 2 to 3 hours. The authors considered side effects for two subjects "adverse events:" one subject reported anxiety, tremors, dizziness, and inability to concentrate that resolved within 3 hours.

The second occurred in a subject who reported high anxiety and dizziness that lasted for the duration of the treatment day. Both events occurred in subjects who received 20 mg of dronabinol. No one reported any psychosis or hallucinations during phase 1 or phase 2. The 28 subjects who enrolled in phase 2 started with 5 mg dronabinol twice per day and could titrate up after being on a stable dose for two days, up to a maximum of 20 mg three times per day. They could reduce their dose at any time if they experienced adverse effects. In phase 2

there was a significant decrease in average pain scores from baseline to week 4, with average pain scores dropping each week. A significant decrease was found in pain interfering with sleep. Side effects were of similar type/frequency as in phase one, and they appeared to decrease in frequency from week to week (despite increases in dose for some patients). Achieved dronabinol doses not reported. “These positive results do not address the controversy about the long-term use of cannabinoids for pain, particularly as an adjunct medication for patients with non-cancer pain on opioid therapy. “Although this study was not described to address problems that may arise from the long-term use of THC, addiction and psychosis are known risk factors that must be considered before a cannabinoid can be offered as part of a treatment regimen.”

Notcutt W, Price M, Miller R, Newport S, Phillips C, Simmons S, Sansom C. Initial experiences with medicinal extracts of cannabis for chronic pain: Results from 34 ‘N of 1’ studies. *Anaesthesia* 2004;59(5): 440-452.

The extracts used in this study were from cloned plants with standardized levels of active ingredients prepared as either an aerosol or pump-action spray where each actuation delivered either 2.5 mg THC or CBD or 2.5 mg 1:1 of both THC:CBD. All 34 patients were 18 years or older and presented with varying conditions, none of which was responsive to traditional treatments. Before beginning the trial, baseline assessments were performed for two weeks and each patient was then subjected to an observed dosing of THC:CBD (2-8 sprays per patient) before allowing the patient to self-dose at home for two weeks.

Although this study consisted of patients with several diagnoses, each experienced pain and therefore the level of pain using the Visual Analogue Scale (VAS) 0-10 and sleep patterns were the focus of the trial and each patient was responsible for documenting these values, as well as side effects in a journal daily during the two-week initial phase. To continue to the eight-week period, a patient must have shown some benefit in these areas during this time. Further evaluations used the Beck Depression Inventory (BDI) and General Health Questionnaire 28 (GHQ28). Each patient then identified their worst symptoms and were instructed to document the severity of the two worst symptoms three times each day, as well as the hours and quality (good, fair, poor) of sleep, appetite, bowel, and bladder habits and side effects. All current medications were continued.

During the two week run-in period, all 34 participants were given 1:1 spray and all had a decrease in their two main symptoms – 16 of those were a greater than 50% reduction in either symptom and 10 reported a 50% reduction in both. After the crossover, patients were entered in a randomized, double-blind, placebo-controlled testing of THC, CBD, and 1:1 for one week intervals. Each week, the test compound changed and therefore each patient was given each compound and placebo for two one-week intervals. All were allowed access to 1:1 (THC:CBD) for rescue analgesia and 24 patients completed the trial without use – these patients are included in the comparison. Patients reported using 1-8 sprays as a single dose. Average daily dose of each of the three active medications was approximately 8 sprays per day.

For symptom control, THC and THC:CBD showed a statistically significant

improvement when compared to placebo. Of the 24 patients, nine reported a decrease of at least 50% in either symptom with the use of all three cannabis-based compounds – three with CBD. When asked to compare effectiveness of current therapy with initial run-in tests, all patients reported the cannabis compounds to be equally or more effective.

Improvement in sleep quality was greater while taking the cannabis preparations, in comparison with placebo. The average duration of sleep was higher and self-reported depression levels were lower in the drug arms when compared to placebo, although not statistically. Side effects more common during active treatment, compared with placebo, were dry mouth, drowsiness, and euphoria/dysphoria. All lab values remained within normal limits.

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) were randomized to receive either drug (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.

Sativex oral spray (2.7 mg THC/2.5 mg CBD per 100 µl actuation) and all initial dosing was performed in the clinic and patients were monitored for intoxication using a 0-100 Visual Analog Scale (VAS). After administration of eight sprays over two hours, any patient scoring over 25 on the VAS, or presenting with any clinical concerns, was allowed no further doses. Once patients had completed the initial dosing test, they were 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 – the reasons were side effects, 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 showed a significant difference in favor of the Sativex arm. No difference was seen in the BRB-N test for cognitive decline. After the titration period, average dose for patients in the Sativex group was approximately 13 sprays per day. Fifty-seven (91%) of patients in the Sativex group experienced at least one

adverse event compared with 48 (77%) in the placebo group. Most were observed at onset of treatment and in the majority described as mild. Adverse events more common in the Sativex group were dizziness, nausea, fatigue, vomiting, dry mouth, feeling drunk, diarrhea, somnolence, disturbance in attention, and memory deficit. Eleven patients from the treatment group and two from placebo withdrew from the trial as a result of adverse events. Adverse events causing withdrawal in the Sativex group: dizziness, nausea, vomiting, feeling drunk, anorexia, and diarrhea.

Rog D, Nurmikko T, Friede T, Young C. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. *Neurology* 2005; 65(6): 812-819.

This randomized, double-blind, placebo-controlled, parallel-group trial lasted four weeks and included 66 patients (14 males/52 females; average age 49.2 years) diagnosed with multiple sclerosis (MS) at least six months prior and experiencing pain for at least three months. Thirty-four patients were treated with Sativex (2.7mg TCH/2.5 mg CBD) oromucosal spray and were compared to 32 patients given placebo. Patients maintained current drug therapies but were allowed a maximum of 75 mg/day of any tricyclic antidepressant. Before the trial began, each patient identified their most concerning symptom and noted most bothersome time of day as well as baseline pain levels for 7-10 days.

In addition to pain levels, sleep disturbance on an 11-point scale was completed for three days prior to start. Cognitive function (Brief Repeatable Battery of Neuropsychological Tests), mood Hospital Anxiety and

Depression Scale – HADS) and disability attributed to MS (Guy's Neurological Disability Scale) and Patient's Global Impression of Change (PGIC) were also evaluated prior to start and at completion.

Before releasing any drug for home use, each patient completed an in-clinic trial of up-to four sprays of Sativex within two hours. They were observed for intoxication levels using a 100-point visual analogue scale where any patient scoring greater than 25 would have a reduced dosing schedule. The home titration allowed for a maximum of 48 sprays (129.6 mg THC/120 mg CBD) in 24 hours with no more than eight doses in a three-hour period.

Improvement of pain in the Sativex group was larger than in the placebo group, reaching statistical significance (-2.7 [95% CI = -3.4 to -2.0] vs. 1.4 [-2.0 to -0.8]).

Improvement in sleep disturbance related to pain was also statistically significantly greater in the Sativex group. There was no significant difference between groups for PGIC, neuropsychological outcomes or HADS neurological disability.

At week 4 the mean daily number of Sativex sprays was 9.6 (range 2 to 25). Thirty patients (88%) developed at least one adverse event (AE), compared with 22 patients (69%) on placebo. Dizziness, dry mouth, somnolence, and GI upset were some of the most common side effects noted. No serious AEs were observed. However, two Sativex patients withdrew from the study due to adverse effects: one with hypertension/tachycardia and the second with paranoid ideation.

Rog DJ, Nurmikko TJ, Young CA. Oromucosal $\Delta 9$ – tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: An uncontrolled, open-label, 2- year extension trial *Clin Ther.* 2007;29(9):2068-2079.

This trial was an extension of the trial reported in Rog 2005 involving 63 patients (49 female/14 male; average age 49 years) with multiple sclerosis (MS) and related central neuropathic pain (CNP). Before beginning the extension, all patients received a complete physical, including an EKG, blood and urine labs, and etcetera.

Prior to beginning the parent trial, each patient reported their most severe symptom and recorded time of day and rating of pain (0-10) and were again instructed to document their pain rating the week prior to beginning the open-label follow-up and throughout the testing period. Patients receiving placebo in the randomized trial were now given Sativex and instructed to titrate as directed in the parent trial. Nursing staff made phone contact with patients 14-20 days after initiation to ensure tolerability. The patients were then reviewed at 4 weeks and again every 8 weeks to assess changes in pain, perceived benefit, intoxication (0-100 VAS score) as well as number of sprays taken at the time at which it was used. Participants also completed physical re-checks throughout the trial.

The primary endpoint was evaluation of adverse events (AEs) and secondary endpoints included any changes in pain score as well as hematology and lab results, vital signs, trial drug usage, and intoxication. Ninety-five percent of patients experienced at least one AE; 58 patients report treatment-

related AEs (75% of patients experienced mild AEs, 78% moderate, and 51% severe). Ten patients experienced a relapse of MS; 10 reported aggravation of MS symptoms. Of the AEs, dizziness and feeling intoxicated, GI upset, and oral/application site irritation were among the most common. Seventeen patients withdrew from the study as a result of AEs; nausea, weakness, dizziness, fatigue, and intoxication were among the reasons. Two patients experienced significant increases in white cell count, mean cell volume, and liver function tests and one participant experienced an increase in lymphocytes, neutrophils, alkaline aminotransferase, calcium, and potassium. No other changes were seen.

Thirty-four patients completed a full year of treatment and the average number of sprays per day was 7.5 throughout the year, however, during the last six days, the average was 6.1 sprays. For the 28 participants that completed two years of study, the average number of sprays was 6.5 and 10 of these patients were able to reduce or discontinue concomitant pain medication. No development of tolerance was seen from the randomized trial to the end of the first year of the extension trial. Pain levels decreased by 3.4 points (0-10 scale) when compared to the completion of the randomized trial. Intoxication levels were generally low and in patients that did experience this effect, the average level on a 0-100 VAS scale was 3-6 and stable.

Schimrigk S, Marziniak M, Neubauer C, Kugler EM, Werner G, Abramov-Sommariva D. Dronabinol is a safe long-term treatment option for neuropathic pain patients. *Eur Neurol* 2017;78:320-329.

Double-blind, placebo-controlled trial of dronabinol (synthetic THC) for treatment of central neuropathic pain in multiple sclerosis patients. A total of 240 patients were randomized to the dronabinol (n=124) or placebo (n=116) arm for four weeks of dose titration followed by a treatment period of 12 weeks and an optional open-label period of up to 144 weeks. Concomitant analgesic medications were taken by 40% of patients in the dronabinol group and 44% in the placebo group. Starting dose of dronabinol was not specified, but the dose was increased every five days by 2.5 mg to reach maximum tolerated dose of 15.0 mg or less. Primary outcome was difference in 11-point pain numeric rating scale between baseline and the average of weeks 1 through 16. Average dronabinol dose during the treatment period was 12.7 mg. Both the dronabinol group and the placebo group had clinically meaningful decreases in pain scores, with no significant difference in reduction between the two groups. Severe and serious adverse events were rare. Adverse events overall were more common in the dronabinol group (50%) than in the placebo group (26%), with most occurring during the titration period.

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. The only information on dosing was a statement that doses were administered sublingually in divided doses up to four times a day. 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; no further information was provided on whether these participants were receiving Sativex or placebo and what adverse events occurred.

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.

303 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. 57 withdrew before randomization, 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. After screening, 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 their concomitant analgesic medications with the exception of acetaminophen, provided that a stable dose was maintained throughout the study. 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 were instructed to rate 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 $\geq 30\%$ 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. The study took place from September, 2005 to October, 2006. A total of 173 of the 246 completed the study, 21 ceased treatment but remained in the study, and 52 withdrew. Six patients were not included in the analysis 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). Distribution of number of sprays per day at end of study not provided. Side effects were common in both nabiximols (85%) and placebo (70%) groups (side effect occurrence reported for both ITT

and PP groups; percentages from ITT included here). 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 (additional detail on dosage and nature of AEs in this group not provided).

Svensden KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. *BMJ*, doi:10.1136/bmj.38149.566979.AE (published 16 July 2004).

25 patients age 23-55 with MS who met criteria for central pain ≥ 3 on a 0-10 numeric rating scale were recruited and one was excluded due to EKG findings. After a one-week baseline period patients were randomized and then treated with either dronabinol or placebo for approximately 3 weeks with a three week washout period before three weeks treatment with the other medication. Primary outcome was pain intensity over the past week on a 0-10 numeric rating scale. Secondary outcomes included SF-36 quality of life survey, several sensory neurologic tests, and the expanded disability status scale score. Dronabinol 2.5 mg capsules were used, starting at one capsule per day. Participants self-titrated, increasing by one capsule every other day to a maximum of 2 capsules twice daily (10 mg dronabinol in two 5 mg doses). All participants completed the study protocol. Decrease in pain intensity rating was

significantly greater during dronabinol treatment (3.0; 25th-75th %tile = 0 to 6.7) vs. placebo (0; 0 to 2.3). The bodily pain and mental health components of the SF-36 showed modest benefits during dronabinol treatment vs. placebo. No differences between dronabinol and placebo treatment were seen for the sensory tests or functional ability. 96% of participants experienced side effects during dronabinol treatment vs. 46% during placebo treatment. Four patients reduced dosage of dronabinol because of intolerable side effects (3 reduced from 10.0 to 7.5 mg and one to 5.0 mg); the remainder continued on 10.0 mg dronabinol. Side effect severity was not described. The side effects occurring more often during dronabinol treatment included dizziness, tiredness, balance problems, headache, euphoria, feeling drunk, muscle pain, and muscle weakness.

Wade DT, Robson P, House H, Makela P, Aram J. A preliminary controlled study to determine whether whole-plant cannabis extracts can improve intractable neurogenic symptoms. *Clin. Rehabil* 2003; 17(1): 21-29.

Twenty-four patients (average age 48 years) with unresponsive neurologic symptoms, including pain, were included in this study using whole-plant extracts of cannabis. The cannabis was prepared as CBD or THC-rich extract or a 1:1 ratio of THC and CBD and delivered as a peppermint-flavored sublingual spray with 2.5 mg active ingredient per actuation. Patients were instructed to use no more than 120 mg in 24 hours. Initially, patients were subjected to a two-week, open-label THC:CBD testing under professional supervision to ensure they would tolerate the possible side effects and

intoxication. Plasma levels were collected to ensure proper absorption. Those patients that were particularly susceptible to the effects were assigned a reduced dosing regimen.

Following the open-label period, patients began a randomized controlled study lasting eight weeks, receiving each of the three treatment or placebo during one of the four 2-week stages. Patients were assigned to either a THC (mostly), CBD (mostly), 1:1 THC:CBD, or placebo arm, though all were allowed access to the 1:1 spray as a rescue medication and were instructed to use it only when needed.

Those patients that reported using the rescue spray were analyzed separately from those that reported little or no use. Throughout the trial, patients were instructed to make daily journal entries regarding their symptoms using a visual analog scale (VAS) with a 0-100 scale where 0 would be the worst possible level of severity. Patients also participated in a series of assessments every two weeks including the Short Orientation-Memory-Concentration (SOMC), Barthel Activities of Daily Living Index, the Rivermead Mobility Index and the General Health Questionnaire, as well as the Nine Hole Peg Test of manual dexterity and the Ashworth scale for spasticity when applicable.

Of the 24 initially enrolled, 20 patients (10 male, 10 female) completed the study. The reasons for withdrawal from the study were intoxication, GI upset, or local irritation.

Average dose for the three active treatments was between 8 and 10 sprays/day. Using data from all patients, 12 reported pain as a main concern, although 16 reported spasm and 8 spasticity – both of which can be linked to pain symptoms. All three of these symptoms

showed a statistically significant reduction in the treatment arms and none in the placebo arm. Pain was most relieved by CBD or THC, while spasm (frequency) strongly responded to THC and 1:1 THC:CBD and spasticity (severity) most responded to THC only. Of the additional quality-of-life tests, only the SOMC showed statistical significance in the THC group. During the open-label phase when 1:1 THC:CBD was administered 67% of patients experienced adverse events. During the 2-week treatment stages the proportion of patients with at least one adverse event were as follows: placebo – 48%, THC (mostly) – 55%, CBD (mostly) – 33%, 1:1 THC:CBD – 30%.

Wade T. et al. 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; 10:434-441.

A randomized, double-blind, placebo-controlled, parallel group trial of nabiximols (Sativex) for patients with multiple sclerosis. 160 patients from 3 UK centers were enrolled and indicated whether their primary symptom was spasticity, spasms, bladder problems, tremor, or pain not obviously musculoskeletal. Intensity of each symptom was self-rated on a 100 mm visual analog scale throughout the study.

Patients were randomized to nabiximols or placebo for the initial six week double-blind trial and told to titrate slowly during home dosing, aiming for optimal balance between symptom relief and side effects, but not to exceed 120 mg THC (44 sprays) per day or 20 mg THC (7 sprays) within a 3 hour period. Average number of sprays per day in the active treatment group increased steadily

over three weeks and then plateaued at 14 to 16 sprays per day (38 to 43 mg/day THC; 35-40 mg/day CBD). Subjects receiving nabiximols showed improvement in subjective (VAS), but not objective (Ashworth scale) measures of spasticity, compared to the placebo group. No significant difference in symptom scores between groups was found for spasms, pain, tremor, bladder control, or a composite symptom score. Side effects that occurred more often in the active treatment group included dizziness, disturbance in attention, fatigue, somnolence, disorientation, vertigo, diarrhea, and mouth ulceration.

Zajicek JP, Hobart JC, Slade A, Barnes D, Pattison PG, on behalf of the MUSEC Research Group. Multiple Sclerosis and Extract of Cannabis: results of the MUSEC trial. *J Neurol Neurosurg Psychiatry* 2012;83**:1125-1132.**

Double-blind placebo controlled study of 279 patients age 18-64 with MS by McDonald criteria, stable disease for the last 6 months and troublesome and ongoing muscle stiffness for at least 3 months before enrollment (as shown by a current disability score of at least 4 on an 11 point category rating scale (CRS) at 22 UK centers). Treatment = 144, placebo = 135. Physiotherapy regimens or medications likely to affect spasticity were adjusted where necessary and then not altered in the 30 days before study start. Patients with active sources of infection or taking immunomodulatory drugs that might affect spasticity (e.g. Beta-interferon, but not azathioprine) were excluded. Active treatment was an extract of *Cannabis sativa L* (extraction ethanol 96%) in soft gelatin capsules, standardized on cannabidiol (range

0.8-1.8 mg) and containing 2.5 mg delta-9 THC as the main cannabinoid (CANNADOR). The study consisted of a screening period of 1-2 weeks, 2 week dose titration phase and a 10 week maintenance phase. Total treatment duration was 12 weeks. Participants were assessed at 2, 4, 8, and 12 weeks after start of treatment. Starting dose was 2.5 mg THC (one capsule) twice daily. Subsequent doses were individually titrated upwards by 5 mg THC/day every 3 days for up to 12 days to optimize the balance between therapeutic effect and side effects. Maximum total allowable daily dose was 25 mg THC. In the event of intolerable side effects, the daily dose was reduced by one capsule until the side effect(s) resolved. After resolution, one re-challenge with a further dose escalation was required. If the side effect(s) returned, the dose was reduced again, with no further re-challenge allowed. The primary outcome measure was perceived change in muscle stiffness after 12 weeks of treatment compared with the premedication phase. At the final visit, participants answered the following question on a symptom questionnaire: "Compared with before the study started, my muscle stiffness over the last week has been ..." providing a rating on an 11 point numerical scale where 0=very much better, 5= no difference and 10=very much worse. Categories 0-3 of the rating scale were classified as 'relief of muscle stiffness' – that is, as a clinically relevant response. Secondary measures included relief from body pain, muscle spasms and sleep disturbance using 11 point scales. Also, the validated disease specific multi-item rating scales measuring aspects of spasticity in MS (MS Spasticity Scale (MSSS-88), and other scales including Expanded Disability Status Scale (EDSS). Main result: proportion with self-reported relief from stiffness was

higher by a statistically significant amount compared to the placebo group (29.4% vs. 15.7%; OR=2.6 95%, CI = 1.24-4.13). Proportion of patients with relief of body pain (0-3 on 11 point scale) was higher by a statistically significant amount at each time of measurement (44% vs. 18% at week 12). At the end of the titration period approximately 87% of participants in the placebo group were taking the maximum daily dose of 25.0 mg. In contrast, only 47% of participants in the active treatment group had titrated up to a maximum daily dose of 25.0 mg. Of the active treatment patients who did not achieve the maximum daily dose, most were taking daily doses of 10.0 to 15.0 mg. Sixteen participants in the active treatment group discontinued study medication during titration, compared with four in the placebo group. At the end of the study, only 24.5% of the active treatment group was taking the 25.0 mg dose. By the end of the study, 84% of all patients experienced at least one treatment emergent adverse event: 98% in active treatment group and 74.6% in the placebo group. 23.8% in the active treatment group and 14.9% in placebo group were withdrawn from the study or discontinued study medication due to adverse events. In the active treatment group adverse events were highest during titration and decreased continuously over the course of the study. Adverse events that occurred at clearly higher rates in the active treatment group than in the placebo group were dizziness, disturbance in attention, balance disorder, somnolence, dry mouth, nausea, diarrhea, fatigue, asthenia, feeling abnormal, urinary tract infection, disorientation, confusional state, and fall. The relatively rapid titration was done for technical study reasons – in clinical practice it is not likely to be done so rapidly. Results in

this study confirm results in the CAMS study, which was larger, and are similar to two other studies that showed significant reduction in spasticity using an 11 point rating scale (Novotna 2011; Colin 2007).

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a mental disorder that evokes severe distress, chronic suffering and impairment. Its core symptoms comprise re-experiencing traumatic content, persistent avoidance of traumatic content, negative alterations in cognitions, and arousal and reactivity. Certain forms of trauma-focused psychotherapy are generally recommended as first-line therapy for PTSD. There is evidence of some degree of effectiveness of some pharmaceutical agents in treating PTSD, but their role appears to be secondary to psychotherapy. Among authors of review articles and meta-analyses of therapies for PTSD patients there is widespread agreement on the need for improvement in existing PTSD treatments as well as the development and testing of novel evidence-based treatment strategies.

One randomized, controlled clinical trial was completed in January of 2019, but results are not yet published. A second trial is now recruiting patients. These trials use smoked cannabis or vaporized cannabis plant material. Because of the paucity of clinical trials using cannabis extraction products or cannabinoids, two small open-label observational studies are included in this section. One used THC administered under the tongue (Roitman 2014) and one used small amounts of CBD in a combination of capsules and oral liquid spray (Elms 2018).

In the first observational study, ten patients with PTSD received 5 mg THC dissolved in olive oil under the tongue twice daily for three weeks (Roitman 2014). Statistically significant improvement between baseline and end of study was seen for the hyperarousal component score of the Clinician-Administered PTSD scale, Clinical Global Impression-Severity scale, Clinical Global Impression – Improvement scale, sleep quality, nightmare frequency, and nightmare effects. Mild side effects were reported by four participants, with none dropping out due to side effects (Roitman 2014).

In the second observational study small doses of CBD was taken in capsule or oral spray form for at least 8 weeks. In all but one of the 11 patients for whom full study was available, PCL-5 score at 8 weeks was lower than PCL-5 score at baseline (Elms 2018).

The completed trial compared three types of smoked cannabis (more THC than CBD; more CBD than THC; and equal amounts of THC and CBD) with each other and to placebo in alleviating symptoms and in occurrence of adverse events among 76 U.S. veterans with treatment-resistant PTSD. Participants were permitted to smoke up to 1.8 grams of cannabis per day. Recruitment began January 2017 and the study was completed January, 2019. This study had funding from the state of Colorado’s pool of money to support research, derived from taxes on retail marijuana. “Study of Four Different Potencies of Smoked Marijuana in 76 Veterans With Chronic, Treatment- Resistant PTSD”
<https://www.clinicaltrials.gov/ct2/show/NCT02759185?cond=PTSD+cannabis&rank=3>

The second trial, a triple-blinded cross-over study, compares three types of vaporized dried cannabis (high THC/low CBD; high THC/high CBD; low THC/low CBD) with each other and

with placebo in alleviating symptoms and in occurrence of adverse events among 42 patients with treatment-resistant PTSD. Participants are allowed to vaporize up to 2 grams of plant material per day as needed. Study start date was September, 2016; estimated completion date is June, 2020. The sponsor for this study is Tilray, a Canadian marijuana producer. “Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder”
<https://www.clinicaltrials.gov/ct2/show/NCT02517424?cond=PTSD+cannabis&rank=4>

Elms L, Shannon S, Hughes S, Lewis N. Cannabidiol in the treatment of post-traumatic stress disorder: A case series. *J Alt Complement Med* 2018 Dec 13. doi: 10.1089/acm.2018.0437.

Retrospective medical record review of 21 patients with PTSD who initiated CBD therapy as an adjunct to their routine psychiatric care. After initiating CBD therapy, follow-up visits at 4 and 8 weeks were scheduled to assess dosing, PTSD symptoms (PCL-5 questionnaire), and side effects. At 4 weeks, 18 remained on CBD and completed the PCL-5 questionnaire. At 8 weeks this number was 14. Of the 14, 11 completed both the 4-week and the 8-week assessments. The paper focuses on these 11 patients. Average age was 40 years (range: 22-69); 8 were female.

Patients used capsules or oral liquid spray or both over the course of treatment; the CBD was from hemp extraction. The dose of CBD was smaller than what has been used in most studies of CBD for a variety of conditions. Mean total starting dose (spray or capsule or both) was 33 mg/day; at 8 weeks mean dose was 49 mg/day (range: 2-100).

At 4 weeks mean PCL-5 score dropped (improved) from 51.82 to 40.73, with an

increased score for only one patient. At 8 weeks, average score dropped further, to 37.14. Though three patients had a higher score at 8 weeks than at 4 weeks, all but one of the patients had a lower score at 8 weeks than at baseline. The CBD was generally well tolerated; none of the 21 patients who initiated CBD therapy was known to have discontinued CBD due to side effects.

Participants were all patients at a clinic with a focus on integrative medicine, potentially limiting generalizability of the results. And, as the authors acknowledge, lack of a control group makes it difficult to determine whether the changes observed were due to oral THC or to variability in the course of PTSD or expectancy (placebo) effect. The study's small size and short duration are additional important limitations.

Roitman P, Mechoulam R, Cooper-Kazaz R, Shalev A. Preliminary, open-label, pilot study of add-on oral Δ^9 -tetrahydrocannabinol in chronic post-traumatic stress disorder. *Clinical Drug Investigation* 2014, 34:587-591.

This small, short-term, open-label (no control group) study assessed the safety and benefit of THC administered under the tongue. Ten adults with PTSD diagnosed > 1 year and < 3 years since the traumatic event were recruited at one outpatient clinic in Israel. Seven were men, average age was 52, and the traumatic event was war-related in 5, road accident in 3 and assault/rape in 2. All were receiving stable psychotropic medication for at least 4 weeks, with an average of more than four different medications. They remained on their stable regimen throughout the three week study. Outcome measures included Clinician-Administered PTSD Scale total score and

three component scores, the Clinical Global Impression-Severity Scale (7 point scale from 1 "normal" to 7 "amongst the most severely ill patients"), Clinical Global Impression-Improvement Scale (7 point scale from 1 "very much improved") through 7 ("very much worse"), Pittsburgh Sleep Quality Index, Nightmare Frequency Questionnaire, and Nightmare Effects Survey. The THC was mixed with olive oil to achieve 2.5 mg/1 cc. Patients were instructed to take 1 cc under the tongue twice per day. After two days each was contacted by a study clinician to assess side effects. If well tolerated, the dose was increased to 2 cc twice per day (5 mg THC twice per day) and remained at that level. All patients went to the higher dose. Mild side effects were reported by four participants (dry mouth, headache, and dizziness); no participants stopped treatment because of side effects. Statistically significant improvement between baseline and end of study was seen for the hyperarousal component score of the Clinician-Administered PTSD scale, both CGI-S and CGI-I, sleep quality, nightmare frequency, and nightmare effects. As the authors acknowledge, lack of a control group makes it difficult to determine whether the changes observed were due to oral THC or to variability in the course of PTSD or expectancy (placebo) effect. The study's small size and short duration are additional important limitations.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized

by sustained social impairments in reciprocal social communication and interactions; and repetitive behaviors, interests, or activities. These essential markers of autism spectrum disorder present in early childhood and limit everyday functioning. The word “spectrum” is used to define ASD since the disorder manifests itself in diverse ways, depending on varying symptom severity, the individual’s developmental level, and chronological age (American Psychiatric Association 2013).

Several behavioral, educational, and pharmaceutical treatments are used to manage ASD. Pharmaceutical treatments mostly target comorbid health problems, which are common in children living with ASD.

Two randomized, controlled clinical trials for cannabis or cannabinoids as therapy for ASD have been registered on www.clinicaltrials.gov. One is completed, but results have not yet been published; the other is recruiting patients.

The completed trial is a double-blind, randomized, placebo-controlled study of two cannabis formulations to treat disruptive behaviors in children and young adults (age 5-21) with ASD. It was carried out in Israel. Approximately 150 patients were assigned to one of three olive oil-based solutions for a three-month treatment period: 1) 99% CBD and 99% THC in a ratio of 20:1 CBD:THC; 2) whole plant extract with a CBD:THC ratio of 20:1; or, 3) placebo. Primary outcome is change from baseline Home Situations Questionnaire-Autism Spectrum Disorder score, at 3 months (it is a 24-item parent-rated measure of noncompliant behavior in children with ASD). There are several other outcome measures. The study started January, 2017 and was completed December, 2018. “Cannabinoids for Behavioral Problems

in Children with ASD (CBA)”

<https://www.clinicaltrials.gov/ct2/show/NCT02956226?cond=autism+cannabis&rank=1>

The trial now recruiting patients is a double-blind, placebo-controlled clinical trial of the cannabinoid, cannabidiol (CBD), to treat children (age 5-18 years). It is being carried out in New York City. An estimated 100 patients will be assigned to either 10 mg/kg/day CBD or placebo capsule for a 12-week treatment period. Primary outcome is change in Aberrant Behavior Checklist-Irritability Subscale between baseline and 12 weeks. There are several other outcome measures. The study started April, 2019; estimated completion is September, 2021. “Cannabidiol (CBD) vs. Placebo in Children with Autism Spectrum Disorder (ASD)”

<https://www.clinicaltrials.gov/ct2/show/NCT03202303?cond=autism+cannabis&rank=2>

Two open-label prospective studies (Barchel 2019; Bar-Lev Schleider 2019) and a retrospective study (Aran 2018) – all three from Israel – have been published. All three used 20:1 CBD:THC oral preparations. Initial and maximum allowed CBD dose varied somewhat or were not reported. After titration up from starting dose, median daily CBD dose was 90 mg in Barchel 2019 and average daily CBD dose was 240 mg in Bar-Lev Schleider 2019. Maximum daily dose in Aran 2018 was 10 mg/kg/day.

Aran A, Cassuto H, Lubotzky A and Hazan E. Brief Report: Cannabidiol-rich cannabis in children *Neurology Apr 2018, 90(15 Supplement)P3.318.*

Abstract presented as a poster at the American Academy of Neurology 70th Annual Meeting, Los Angeles. The authors reviewed the records of 60 Israeli children with autism

spectrum disorder (mean age 11.8, range 5-18 years) treated with oral CBD and THC at a ratio of 20:1 CBD:THC. The dose was up-titrated to effect with maximal CBD dose 10 mg/kg/day. Following the cannabis treatment, behavior outbreaks were much improved or very much improved (Caregiver Global Impression of Change scale) in 61% of patients. Anxiety and communications problems were much or very much improved in 39% and 47% respectively. Disruptive behaviors were improved by 29% (Home Situations Questionnaire – Autism Spectrum Disorder). Parents reported 33% less stress as reflected in the Autism Parenting Stress Index. Adverse events included sleep disturbance (14%), irritability (9%) and loss of appetite (9%).

Barchel D, Stolar O, De-Haan T, Ziv-Baran T, et al. Oral cannabidiol use in children with autism spectrum disorder to treat related symptoms and co-morbidities. *Front Pharmacol* 2019 Jan 9;9:1521. Doi: 10.3389/fphar.2018.01521.

This prospective study done in Israel enrolled 53 children with ASD (mean age of 11, range 4-22) with no prior experience using cannabidiol or any other cannabinoid. Concomitant medications not described. Study drug was an oil containing a 20:1 ratio CBD:THC. Parents were instructed to start treatment at the number of drops that resulted in 16 mg/kg CBD and 0.8 mg/kg THC with maximum daily doses of 600 mg CBD and 40 mg THC. Telephone follow-up for dosing, symptom ratings, and side effects was conducted every two weeks for an average of 5 interviews per patient. Median actual dose of CBD was 90 mg/day (daily CBD dose was between 45-143 mg for half of the patients).

Self-injury and rage attacks (n=34) improved in 68% and worsened in 9%. Hyperactivity symptoms (n=36) improved in 68% and worsened in 3%. Sleep problems (n=21) improved in 71% and worsened in 5%. Anxiety (n=17) improved in 47% and worsened in 24%. The most frequent adverse effects were somnolence (n=12) and decreased appetite (n=6). The authors used published literature on effectiveness of other therapies for self-injury, hyperactivity, sleep problems, and anxiety in ASD patients to compare with the improvements observed in this study. For each, they found non-inferiority with the 20:1 CBD:THC oil treatment (i.e. the magnitude of improvements were generally equal).

Bar-Lev Schleider L, Mechoulam R, Saban N, Meiri G, Novack V. Real life experience of medical cannabis treatment in autism: Analysis of safety and efficacy. *Sci Rep* 2019 Jan 17;9(1)200.- doi: 10.1038/s-41598-018-37570-y.

This was a prospective observational study of 188 ASD patients treated with medical cannabis as adjunctive therapy between 2015-2017 in Israel. Mean age of patients was 13 years. Nearly all were treated with 20:1 CBD:THC oil applied under the tongue with an average dose of 80 mg CBD and 4 mg THC three times per day.

At six months 155 (82.4%) remained in active treatment and 93(60%) received the 6-month set of assessments. Among those 93, 28 (30%) reported significant improvement, 50 (54%) moderate improvement, 6 (6%) slight improvement and 8 (9%) no change. Twenty-three patients (25%) experienced at least one

side effect. The most common side effect was restlessness (7%).

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is a sleep disorder characterized by repetitive episodes of complete (apnea) or partial (hypopnea) collapse of the upper airway (mainly the oropharyngeal tract) during sleep, with a consequent cessation/reduction of airflow. The obstructive events cause a progressive asphyxia that increasingly stimulates breathing efforts against the collapsed airway, typically until the person is awakened. These episodes cause acute physiological disruptions including fragmented sleep, intermittent hypoxia, and exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure. Over time, the acute disruptions lead to chronic conditions such as hypertension and heart disease, reduced cognitive function, depression, and impaired performance at work and while driving, as well as premature death.

One randomized, placebo-controlled clinical trial of cannabis or a cannabinoid product has been published (Carley 2018). This six week trial of dronabinol (synthetic THC) at doses of 2.5 mg and 10 mg daily, taken at bedtime, found a modest treatment benefit from dronabinol with substantial variation among patients in degree of response. The authors' responder analysis suggests only a portion – likely a rather small portion – of OSA patients receive a clinically meaningful reduction in AHI from the therapy used in this trial.

Carley DW, Prasad B, Reid KJ, Malkani R, Attarian H, et al. Pharmacotherapy of apnea by cannabimimetic enhancement, the PACE clinical trial: Effects of dronabinol in obstructive sleep apnea. *Sleep* Jan 1;41(1). doi: 10.1093/sleep/zsx184

By random assignment 73 adults with moderate or severe obstructive sleep apnea (OSA) received either placebo (n=25) or 2.5 mg dronabinol (n=21) or 10 mg dronabinol (n=27) daily, one hour before bedtime for 6 weeks. Participants randomized to the 10 mg/day dronabinol group received 2.5 mg/day for the first seven days, then 5.0 mg/day for seven days before reaching final dosage of 10 mg/day. Inclusion criteria included apnea/hypopnea index (AHI) ≥ 15 and ≤ 50 documented by screening polysomnography (PSG). Extensive exclusion criteria included: non-invasive treatment for OSA within one month (self-report); Epworth Sleepiness Scale (ESS) score < 7 (to exclude non-sleepy subjects); body mass index (BMI) > 45 ; motor vehicle accident or “near-miss” due to sleepiness (self-report) within 2 years; arterial oxygen saturation $< 75\%$ for more than 5% of total sleep time on baseline PSG; severe OSA that in the investigator's judgment precluded delaying (re)institution of positive airway pressure treatment; use of CNS active drugs; recreational drug use or positive urine drug screen. At baseline, average AHI was 25.9 ± 11.3 , ESS score was 11.45 ± 3.8 , maintenance of wakefulness test (MWT) mean latency was 19.2 ± 11.8 min, BMI was 33.4 ± 5.4 kg/m² and age was 53.6 ± 9.0 years. The number of adverse events and treatment adherence (0.3 ± 0.6 missed doses/week) were equivalent among all treatment groups. Three participants were withdrawn from the study for adverse events

possibly related to dronabinol (dizziness and vision changes, ECG arrhythmias, headache and dizziness and vomiting) and one was withdrawn for vertigo judged probably related to dronabinol. Subjects receiving 10 mg/day of dronabinol expressed the highest overall satisfaction with treatment ($p=0.04$). In comparison to placebo, dronabinol dose-dependently reduced AHI by 10.7 ± 4.4 ($p=0.02$) and 12.9 ± 4.3 ($p=0.003$) events/hour at doses of 2.5 and 10 mg/day, respectively. Average AHI in the placebo group increased over the course of the trial, whereas average AHI for both dronabinol groups decreased from baseline – albeit modestly. Dronabinol at 10 mg/day reduced ESS score by 3.8 ± 0.8 points from baseline (<0.0001) and by 2.3 ± 1.2 points in comparison to placebo ($p=0.05$). MWT sleep latencies, gross sleep architecture and overnight oxygenation parameters were unchanged from baseline in any treatment group. An important part of this paper discusses responder analysis. Here is the beginning of that section: “No clear consensus exists regarding what is a clinically meaningful response to OSA treatment. If we arbitrarily consider a final on-treatment AHI of ≤ 15 plus a reduction from baseline AHI of $\geq 50\%$ to represent a clinically meaningful treatment response, 6 of 39 participants randomized to receive dronabinol were treatment ‘responders’ in contrast to 0 of 17 participants randomized to receive Placebo treatment.” Overall, the dronabinol treatment effect found in this trial was modest with considerable variation among patients. The proportion of patients with clinically meaningful improvement may be relatively small.

Alzheimer’s Disease

Published human study evidence is limited to three small clinical trials and two small observational studies. A fourth clinical trial is under way. Each of the studies used relatively small doses of THC as therapy. The three published clinical trials (van den Elsen 2015 Neurology, van den Elsen 2015 Am J Geriatr Psychiatry, Volicer 1997) used 1.5 to 5.0 mg THC in divided doses daily. Each found the treatment well tolerated, but only one (Volicer 1997) found a beneficial treatment effect (reduced agitated behavior and decrease in negative affect). The clinical trial, now recruiting patients, (“Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer’s Disease” <https://www.clinicaltrials.gov/ct2/show/NCT02792257?cond=nct02792257&rank=1>) starts active therapy at 5 mg THC/day in divided doses then after a week increases to 10 mg/day in divided doses during weeks 2 and 3.

The two observational studies (Shelef 2016, Walther 2006) add some additional evidence that dronabinol use is associated with reduced behavioral symptoms in Alzheimer disease patients, but lack of a control group and small size limits the strength of these findings.

Each of the studies described here focuses on behavioral symptoms in persons with Alzheimer’s disease (or other forms of dementia). It is important to keep in mind that the observed behavioral symptoms could be due to concurrent mental disorders (depression, schizophrenia, etc.) or physical disorders (constipation, infections), for which

specific treatments are available. Careful assessment of the patient is needed so that the true cause of the observed behavioral symptoms is not missed.

Also, use of dronabinol (synthetic THC) in each of the published studies might be more a reflection of cannabinoids available for study at the time than evidence that cannabidiol (CBD) or other cannabinoids are not helpful. Because CBD is not intoxicating and, presumably, produces less cognitive impairment than THC, CBD could be seen as a more attractive therapeutic cannabinoid in a population already struggling with cognitive dysfunction. However, published human studies to date provide no insight on a potential therapeutic role for CBD in this population.

van den Elsen GA, Ahmed AI, Verkes R-J, et al. Tetrahydrocannabinol for neuropsychiatric symptoms in dementia: a randomized controlled trial. *Neurology*. 2015;84:2338-2346.

This was a randomized, double-blind, placebo-controlled multi-center study with dementia patients exhibiting neuropsychiatric symptoms (n=50; Alzheimer's disease: n=34; vascular dementia: n=7; mixed dementia: n=9). Inclusion criteria included Neuropsychiatric Inventory (NPI) score ≥ 10 and symptoms of agitation, aggression, or aberrant motor behavior, existing at least one month prior to screening. Participants were assigned to either 1.5 mg THC tablet (Namisol) three times per day or placebo tablet. Patients remained on stable doses of concomitant psychotropic and non-psychotropic medications. The primary measure was NPI score, measured at baseline, 14 days, and 21 days. No difference was observed between

the two groups in change of NPI score (the score decreased in both groups) or occurrence of adverse events.

van den Elsen GA, Ahmed AI, Verkes R-J, et al. Tetrahydrocannabinol in behavioral disturbances in dementia: A crossover randomized controlled trial. *Am J Geriatr Psychiatry*. 2015;23:1214-1224.

This was a randomized, double-blind, placebo-controlled repeated crossover study with dementia patients exhibiting neuropsychiatric symptoms (n=22; Alzheimer's disease; n=18; vascular dementia: n=1; mixed dementia: n=3). Active treatment was THC in tablet form (Namisol). Within each of six treatment blocks THC (0.75 mg twice daily in blocks 1-3 and 1.5 mg twice daily in blocks 4-6) and placebo were administered in random order for 3 consecutive days, followed by a 4-day washout. Main outcome was Neuropsychiatric Inventory (NPI) score. THC treatment did not reduce NPI compared to placebo. Adverse events were similar between treatment groups.

Volicer L, Stelly M, Morris J, et al. Effects of dronabinol on anorexia and disturbed behavior in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* 1997;12:913-919.

This was a double-blind, placebo-controlled crossover study where the primary objective was to investigate the effects of dronabinol (synthetic THC) on anorexia in Alzheimer's disease patients. In this 12-week study, patients were randomly assigned to one treatment arm (dronabinol capsule or placebo) for the first six weeks and were

switched to the other treatment in the second half of the study. Dose of dronabinol was 5.0 mg/day in two divided doses. Body weight, caloric intake, and skin-fold measures were measures in this study. In addition, agitation (Cohen Mansfield Agitation Inventory, CMAI) and mood measures (Lawton Observed Affect Scale) were also collected. A total of 12 patients were included in the analysis. While the amount of calories consumed did not change over the course of the study (nor were there any differences in caloric intake between treatment groups), body weight increased over the 12-week period with greater gains found in the patients who started on dronabinol first. Tricept skin fold thickness also showed an increase over the 12-week study and was not affected by treatment order. There was a decrease in agitated behavior compared to baseline during the dronabinol treatment phase as measured by the CMAI. In addition, for patients who received dronabinol first, the decrease in agitated behavior persisted during the placebo phase that followed. Finally, there was a decrease in negative affect over the 12-week study with this decrease being more pronounced during dronabinol treatment. Those who received dronabinol first showed a greater decrease in negative affect than those receiving placebo first.

Shelef A, Barak Y, Berger U. Safety and efficacy of medical cannabis oil for behavioral and psychological symptoms of dementia: an open-label, add-on pilot study. *J Alzheimer's Dis.* 2016;51:15-19.

Eleven patients diagnosed with Alzheimer's disease were recruited for this four-week test of adjunctive dronabinol (synthetic THC) therapy. Oil containing dronabinol was

initiated at 5.0 mg/day in two divided doses. If the patient experienced no adverse effects or experienced minimal improvements dose was increased to 10 mg (5 mg twice daily) after two days. One further escalation to 15 mg (7.5 mg twice daily) was permitted in the protocol. One patient discontinued treatment. Only 3 patients tolerated a dose increase while the other 7 remained at the initial dose of 2.5 mg twice per day. Compared to baseline, total Neuropsychiatric Inventory (NPI) scores decreased in the second and fourth week, indicating improvements in neuropsychiatric symptoms. NPI domains showing a significant decrease were: delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress.

Walther S, Mahlberg R, Eichmann U, et al. Delta-9-tetrahydrocannabinol for nighttime agitation in severe dementia. *Psychopharmacology (Berl).* 2006;185:524-528.

The effects of dronabinol (synthetic THC) on nighttime agitation and neuropsychiatric behavior was investigated in six patients with dementia (5 with Alzheimer's disease and one with vascular dementia), circadian rhythm disturbance and nighttime agitation. A wrist actometer was worn by patients for the duration of the study to measure changes in nighttime motor activity compared to baseline. In addition, the Neuropsychiatric Inventory (NPI) was measured at baseline and once again at the end of treatment. Dronabinol was administered as a 2.5 mg daily evening dose for 2 weeks. Motor activity counts were aggregated daily within 3 different data collection periods for the duration of the study: evening (3 pm – 9 pm), nighttime (9 pm-6 am), and the diurnal

period (6 am -9 pm). Motor activity counts during the last 5 days compared to baseline was the primary outcome measure. Overall, results showed that activity counts had decreased by the end of the treatment period and were observed in each of the three data collection periods (evening, nighttime, diurnal). Nocturnal motor activity had, on average, decreased by 59% compared to baseline levels. Total NPI scores had also decreased by the end of the study with the following NPI sub-scores showing decreases by end of treatment: agitation, nighttime behaviors, aberrant motor behavior, irritability, and appetite disturbances. The numerical change in NPI scores was not provided in the paper to assess whether this decrease fell in a clinically meaningful range.