DEPARTMENT OF HEALTH

Dosing and Chemical Composition Report: A Review of Medical Cannabis Studies Relating to Chemical Compositions and Dosages for Qualifying Medical Conditions

May 11, 2022

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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 also summarizes existing dosing guidelines and identifies documents and resources that may be useful to health care providers, pharmacists, patients, and their caregivers. 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 regularly.

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 by the Commissioner of Health since then. The medical conditions identified in the statute for inclusion in Minnesota's medical cannabis program are:

- Cancer, if the underlying condition or treatment produces one or more of the following:

    1. Severe or chronic pain;

    2. Nausea or severe vomiting; or

    3. Cachexia or severe wasting

- Glaucoma

- HIV/AIDS

- Tourette syndrome

- Amyotrophic lateral sclerosis (ALS)

- Seizures, including those characteristic of epilepsy

- Severe and persistent muscle spasms, including those characteristic of multiple sclerosis (MS)

- Inflammatory bowel disease (IBD), including Crohn's disease

- Terminal illness, with a probable life expectancy of under one year, if the illness or its treatment produces one or more of the following:

    1. Severe or chronic pain;

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The Commissioner of Health approved the addition of these medical conditions after they were submitted to MDH through a petitions process:

- Intractable pain, effective Aug. 1, 2016.

- Post-traumatic stress disorder, effective Aug. 1, 2017.

- Autism spectrum disorder and obstructive sleep apnea, effective Aug. 1, 2018.

- Alzheimer's disease, effective Aug. 1, 2019.

- Chronic pain, effective Aug. 1, 2020.

- Sickle cell disease and chronic motor or vocal tic disorder, effective Aug. 1, 2021.

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. This increase in interest may also be due, in part, to the movement away from opiates as an analgesic, especially for chronic non-cancer-related pain. Following are summary observations for each section.

General dosing guidelines and consensus statements

While there are no federal guidelines for dosing medical cannabis in the United States, there is a growing body of resources that provide general guidance around dosing cannabis products for different conditions.

In nearly all dosing guidelines, the general approach to cannabis initiation is "start low, go slow, and stay low" (College of Family Physicians of Canada 2014, MacCallum and Russo 2018, Sawtelle and Holle 2021). Emphasis on slow titration is a common recommendation, up to the point where the desired treatment effect is realized (MacCallum and Russo 2018, Canadian Pharmacists Association 2019, Inglet, Winter et al. 2020). Most guidelines also point to an upper threshold of efficacy for symptom relief beyond which additional benefit is not gained, somewhere between 20-40 mg/day for THC. The upper threshold for CBD has been reported as high as 800 mg/day, but is typically much closer to 50-100 mg/day (College of Family Physicians of Canada 2014, MacCallum and Russo 2018, Inglet, Winter et al. 2020, Uliel-Sibony, Hausman-Kedem et al. 2021). Starting dose and upper threshold vary based on mode of administration, as well as the THC:CBD ratio.

There are also several consensus statements that were arrived at using a modified Delphi process. While there have been concerns raised about relying solely on consensus processes for dosing guidelines in the absence of large-scale clinical trials (Hill and Abrams 2021), Delphi processes were designed to develop consensus best practice where guidelines are not available.

Recently published consensus statements using a modified Delphi process include:

- Consensus-based recommendations for **titrating cannabinoids and tapering opioids for chronic pain control** (Sihota, Smith et al. 2021). For patients with chronic pain taking opioids not reaching treatment goals, cannabinoids may be considered. Initiation with a CBD predominant oral extract during the day was recommended, with the addition of THC if needed. Dosing of THC was recommended to start at 0.5 to 3 mg, and increase by 1-2 mg once or twice weekly up to 30-40 mg/day. Opioid tapering should begin as soon as tolerated, when the patient reports an improvement in function, seeks less as-needed medication to control pain, and/or the optimal cannabis dose has been reached. Opioid tapering may be 5-10% of the morphine equivalent dose every one to four weeks.

▪ Consensus recommendation on **dosing and administration of medical cannabis to treat chronic pain** (Bhaskar, Bell et al. 2021). There was consensus that medical cannabis may be considered for patients experiencing neuropathic, inflammatory, nociplastic, and mixed pain. Three treatment protocols were developed:

   1. A routine protocol where the clinician initiates the patient on a CBD-predominant variety at a dose of 5 mg CBD twice daily and titrates the CBD-predominant dose by 10 mg every two to three days until the patient reaches their goals, or up to 40 mg/day.

   2. A conservative protocol where the clinician initiates the patient on a CBD-predominant variety at a dose of 5 mg once daily and titrates the CBD-predominant dose by 10 mg every two to three days until the patient reaches their goals, or up to 40 mg/day. At a CBD-predominant dose of 40 mg/day, clinicians may consider adding THC at 1 mg/day and titrate by 1 mg every seven days until a maximum daily dose of 40 mg/day of THC.

   3. A rapid protocol where the clinician initiates the patient on a balanced THC:CBD variety at 2.5–5 mg of each cannabinoid once or twice daily and titrates by 2.5–5 mg of each cannabinoid every two to three days until the patient reaches his/her goals or to a maximum THC dose of 40 mg/day.

▪ Consensus recommendations for **perioperative management of cannabis and cannabinoid-based medicine users** (Ladha, McLaren-Blades et al. 2021). Recommendations include obtaining a clear history of pre-surgery cannabis use, considerations for anesthesia during surgery, and postoperative needs for pain relief and possible withdrawal syndrome concerns.

Limitations/Research gaps

Due to its classification as a Schedule I drug, very limited research on medical cannabis has been conducted in the U.S. Most existing studies are small, many are dated, most are rated low quality with unclear or moderate to high risk of bias, and few examine currently available alternative treatments in addition to placebo (Smith, Azariah et al. 2015, Abrams 2016, Ko, Bober et al. 2016, Dosenovic, Jelicic Kadic et al. 2017, Inglet, Winter et al. 2020, Levy, Galenbeck et al. 2020, Sturgeon, Khan et al. 2020, Abu-Amna, Salti et al. 2021, Fisher, Moore et al. 2021, McKee, Hmidan et al. 2021). In addition, many lack quality safety assessment and reporting (Mohiuddin, Mizubuti et al. 2020). These limitations make it difficult to assess effectiveness, determine drug interactions, or conduct sub-group analysis to assess varying impacts of cannabis products on younger or older persons, racial or ethnic groups, or people with varying histories of cannabis use.

Additional research has been called for in the following specific areas:

▪ Health harms or benefits of cannabis (National Academies of Sciences 2017)

▪ Safety and dosing information (Bhaskar, Bell et al. 2021, Dos Santos, Hallak et al. 2021, Meng, Page et al. 2021)

▪ Best practices for THC:CBD ratios for different indications (Levy, Galenbeck et al. 2020, Sawtelle and Holle 2021)

▪ Cannabis use among older adults (Minerbi, Hauser et al. 2019, Levy, Galenbeck et al. 2020)

The following sections provide summaries of the published literature around dosing of medical cannabis for each of the 17 conditions included in the Minnesota program. Additional details can be found in the full report.

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 two of the three 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. More recent studies have investigated the impact THC:CBD ratios have on different conditions.

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 two to four hours for an additional two to four 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.

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, de Kock et al. 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, Walsh et al. 1994). A large trial that compared dronabinol and megestrol used 5 mg

dronabinol daily in two divided doses; patients tolerated the dronabinol well (Jatoi, Windschitl et al. 2002).

A more recent pilot study found a positive impact on weight gain in three of 17 study participants using 5mg THC once or twice daily without significant side effects (Bar-Sela, Zalman et al. 2019).

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 four to five 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 early clinical trials of medical cannabis in Tourette syndrome patients used single daily dosages of delta-9-THC, ranging from 2.5 mg to 10 mg. About a third of the patients needed to decrease dose because of unacceptable side effects.

More recently, one investigator-initiated proof of concept study was designed 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 (Bloch, Landeros-Weisenberger et al. 2021). The 12-week treatment periods started with titration of dronabinol starting at 2.5 mg for three days, then 5 mg for four days, then 10 mg for the remainder of the study. Tic symptoms improved by more than 20% (as assessed by the YGTSS).

Amyotrophic lateral sclerosis (ALS)

Two small trials in ALS patients with published results used dronabinol (synthetic THC). One 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 study (Riva, Mora et al. 2019), conducted in Italy, recruited 60 adults with motor neuron disease who 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.

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 two to four 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.

Based on initial results from the GWPCARE studies, 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.

While there is general consensus that there is sufficient evidence to support the use of CBD for children and adolescents with treatment-resistant epilepsy, more recent studies and reviews suggest there may be some safety concerns, drug interactions, age-dose interactions, and/or tolerance possibilities that should be considered by clinicians and patients.

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

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 of starting any treatment protocol.

Inflammatory bowel disease

To date, five clinical studies of cannabis or cannabinoids for treatment of inflammatory bowel disease have been published. Early studies showed tolerance for treatment, but no significant effects.

While more recent results have shown CBD to be more effective than placebo for reducing symptoms (Naftali, Bar-Lev Schleider et al. 2021, Naftali, Bar-Lev Schleider et al. 2021), no

studies have yet shown reduction in inflammatory markers. One randomized, double-blind study assessed the effect of cannabidiol [CBD]-rich cannabis oil for induction of remission in Crohn's disease (CD) Patients received up to 80 mg CBD and 20 mg THC. A similar randomized trial assessed the effect of THC-rich cannabis in improving clinical and inflammatory outcomes in ulcerative colitis patients. Patients started smoking 0.25 gr and increased until a final dose of 0.5 gr twice daily was reached (160 mg THC).

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 assess the value of cannabis treatment as an adjunct to other pain medications.

Most of the 16 trials summarized in this section were relatively small (seven had >100 participants) and short (only three of the controlled trials were longer than five weeks) and they are spread across multiple types of pain. The quality of most of the studies summarized in this section is formally assessed in the report Medical Cannabis for Non-Cancer Pain: A Systematic Review (PDF) (https://www.health.state.mn.us/people/cannabis/docs/intractable/medicalcannabisreport.pdf).

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 or 1:1 THC:CBD plus additional active treatment arms vs. placebo. 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 six to 10 sprays per day, representing a daily dose of approximately 15 to 27 mg THC and/or CBD per day. In the two long-term open-label studies of Sativex, average daily dose was somewhat less, at around six to eight sprays per day 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.

Three of the trials studied oral dronabinol, synthetic THC, vs. placebo. The average dose after titration was reported 10-12 mg/day (Svendsen, Jensen et al. 2004, Narang, Gibson et al. 2008, Schimrigk, Marziniak et al. 2017).

Post-traumatic stress disorder (PTSD)

One randomized, controlled clinical trial was completed in January 2019. It 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 PTSD symptoms. Participants were permitted to smoke up to

1.8 grams of cannabis per day, with average amounts per day ranging from 0.4 grams – 0.8 grams, depending on the condition. Overall, investigators did not find a significant difference in reported PTSD symptoms between the three treatment arms and placebo.

Autism spectrum disorder (ASD)

One double-blind, randomized, placebo-controlled study of two cannabis formulations to treat disruptive behaviors in children and young adults (age 5-21) with ASD. One hundred-fifty patients were assigned to one of three olive oil-based solutions for a three-month treatment period:

1. pure CBD and pure THC in a ratio of 20:1 CBD:THC;

2. whole plant extract with a CBD:THC ratio of 20:1; or,

3. placebo.

The whole-plant extract group showed superior outcomes in disruptive behavior compared to placebo.

Two open-label prospective studies (Bar-Lev Schleider, Mechoulam et al. 2018, Barchel, Stolar et al. 2018) and a retrospective study (Aran, Cassuto et al. 2019) – 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 2018 and average daily CBD dose was 240 mg in Bar Lev Schleider 2018. Maximum daily dose in Aran 2019 was 10 mg/kg/day.

Obstructive sleep apnea

One randomized, placebo-controlled clinical trial of cannabis or a cannabinoid product has been published on obstructive sleep apnea (Carley, Prasad et al. 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 obstructive sleep apnea patients receive a clinically meaningful reduction in their apnea-hypopnea index (AHI) from the therapy used in this trial.

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 used 1.5 to 5.0 mg THC in divided doses daily. Each found the treatment well tolerated, but only one found a beneficial treatment effect (reduced agitated behavior and decrease in negative affect).

One recent meta-analysis examined six studies (N=251) (Ruthirakuhan, Lanctot et al. 2019). While there was no effect of cannabinoids on agitation, there was a trend for greater difference in agitation with synthetic cannabinoids compared to THC. Sedation was much greater with cannabinoids compared to placebo. The authors note that existing evidence for efficacy of cannabinoids on agitation and aggression is inconclusive, although there is a potential benefit of synthetic cannabinoids that should be investigated further.

Chronic pain

Much of the literature on dosing of medical cannabis for chronic pain is summarized in the section Cancer: Severe or Chronic Pain. Additional studies focusing on chronic pain in patients who do not have cancer are included here. There has been a recent increase in interest in the use of cannabinoids in the treatment of chronic non-cancer-related pain due to the movement away from opiates as an analgesic.

One prospective observational cohort study followed 1,000 patients with a chronic disease authorized for medical cannabis in Canada. 75-80% of participants reported using <1 to 2g of cannabis daily throughout the study period, with <1% of study participants using more than 5g of cannabis in any form at any time point. While participants in the study reported improvements with pain intensity, pain-related interference, quality of life, and general health symptoms over time, this finding is counter to trends reported elsewhere that the effects of cannabis use wane over time. The authors point to the high rate of attrition over time (both response and use of cannabis) and suggest that cannabis may only be effective at relieving chronic pain for a subset of patients.

In a study of 367 fibromyalgia patients, participants selected the strain of cannabis and mode of administration (oil vs. inflorescence/whole flower). Dosing began at sub-therapeutic levels (e.g., 1 drop of 15% THC oil, 1 breath of a 0.75g cannabis cigarette every three to four hours) and patients were instructed to increase doses gradually (e.g., by one drop per day) until therapeutic effect was reached. Adverse events included dizziness, dry mouth, nausea/vomiting, and hyperactivity. None were reported by more than 8% of patients.

Sickle cell disease

Only one randomized trial has been completed in the area of sickle cell disease (SCD) and medical cannabis. It should be noted that as of 2020, only four states included SCD in their medical cannabis programs, which may be a contributing factor to why there is little data in this area.

In this small crossover randomized trial, 23 people with chronic pain associated with SCD were enrolled. Participants were enrolled in two five-day (four-night) hospital stays, separated by at least three days. Participants were given either 1:1 THC/CBD vapor or placebo vapor three times daily (8 a.m., 2 p.m., and 8 p.m.). The difference between pain ratings for cannabis vs. placebo was greater for cannabis on all five days, but the finding was not statistically significant. No differences in treatment-related adverse effects were observed. Concurrent use of opioids was similar during both treatment periods.

Chronic motor or vocal tic disorder

Chronic motor or vocal tics are a characterizing feature of Tourette syndrome. Most research on medical cannabis for motor or vocal tics are summarized in the section Tourette Syndrome. Research in this section focuses on motor or vocal tics not necessarily encompassed under Tourette syndrome.

There is one pilot study that looked at the effectiveness and safety of medical cannabis in pediatric patients (n=25) with complex motor disorder (Libzon et al. 2018). CBD enriched 5% oil

was administered in two formulations: one with 0.25% THC (20:1 group), and one with 0.83% THC (6:1 group). Medications were given for five months. Improvements were seen in spasticity and dystonia, sleep issues, pain severity, and quality of life without significant difference between the two groups. Adverse effects included worsening of seizures in two patients, behavioral changes in two patients, and somnolence in one patient.

Introduction

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- Sickle cell disease and chronic motor or vocal tic disorder, effective Aug. 1, 2021.

To accomplish this review, the National Library of Medicine's PubMed 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 website 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 17 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-smokable 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-tetrahydrocannibinol (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. This increase in interest may also be due, in part, to the movement away from opiates as an analgesic, especially for chronic noncancer-related pain.

General Dosing Guidelines

Because cannabis is still classified as a Schedule I drug under the federal Controlled Substances Act of 1970, there are no federal guidelines for its use, or federally reviewed dosing protocols for its use. Its classification also makes it very difficult to conduct research on cannabis to determine whether it is an effective treatment for various conditions, and what the optimal dosing protocols

are for various products and conditions. Most of the larger studies have occurred in countries outside the U.S.

There is also a growing body of resources that provide general guidance around dosing cannabis products for different conditions. This section summarizes this small, but growing, collection of documents.

General recommendations

In nearly all dosing guidelines, the general approach to cannabis initiation is "start low, go slow, and stay low" (College of Family Physicians of Canada 2014, MacCallum and Russo 2018, Sawtelle and Holle 2021). Emphasis on slow titration is a common recommendation, up to the point where the desired treatment effect is realized. (MacCallum and Russo 2018, Canadian Pharmacists Association 2019, Inglet, Winter et al. 2020). Most guidelines also point to an upper threshold of efficacy for symptom relief beyond which additional benefit is not gained, somewhere between 20-40 mg/day for THC. The upper threshold for CBD has been reported as high as 800 mg/day, but is typically much closer to 50-100 mg/day (College of Family Physicians of Canada 2014, MacCallum and Russo 2018, Inglet, Winter et al. 2020, Uliel-Sibony, Hausman-Kedem et al. 2021). Starting dose and upper threshold vary based on mode of administration, as well as the THC:CBD ratio

MacCallum CA and Russo EB. Practical considerations in medical cannabis administration and dosing. *Eur J Intern Med* 2018 Vol. 49 Pages 12-19.

MacCallum and Russo (2018) provide a review of the literature and recommendations for "Good Clinical Practice" based on the authors' clinical experience. They recommend starting at a low dose and titrating to the desired response, in part because many of the adverse events present early in treatment, and tolerance develops over time.

Guidance for dosing ranges for various modes of administration from this source are as follows:

- Inhaled cannabis: start with 1 inhalation and wait 15 minutes. Increase by one inhalation every 15–30 minutes until desired symptom control has been achieved.

- Herbal cannabis: Most patients use 1-3 g per day. Fewer than 5% of patients use more than 5 g per day. Escalating the dose beyond 5g per day requires assessment.

- Nabiximols (spray form): most patients require six to eight sprays per day with a limit of 12. Above this dose, "adverse events are increased without improved efficacy."

- Oral cannabis: independent of indication, start at 2.5 mg THC (1.25 if patient is young, elderly, or if there are other concerns), and titrate by 1.25 to 2.5 mg THC every other day. Increase the dose until the desired effect is obtained. Doses of THC greater than 20 or 30 mg/day may increase the risk of adverse events without increasing drug efficacy (MacCallum and Russo 2018).

Canadian Pharmacists Association. Medical Cannabis: How to help patients find a safe and effective dose. 2019.

The Canadian Pharmacists Association (2019) has published a dosing guide to help providers determine the appropriate dose for an individual patient "How to help patients find a safe and effective dose." As part of the guideline, they caution:

"Cannabis is available to patients in many strains and formulations, with varying THC and CBD concentrations. Due to limited evidence on dosage and interval, there are no validated dosage recommendations. Many variables can influence the efficacy and safety. Slow titration with careful assessment in collaboration with the patient and prescriber is recommended."

They also note that "Patient response to cannabis can vary by:

- Patient's other medications, conditions, prior exposure, age, genetics, food

- Route of administration: inhalation, ingestion, product formulation

- THC and CBD concentrations" (Canadian Pharmacists Association 2019)

National Institute for Health and Care Excellence (NICE) guideline for Cannabis-based medicinal products (NG144) https://www.nice.org.uk/guidance/ng144

NG144 covers prescribing of cannabis-based medicinal products for people with intractable nausea and vomiting, chronic pain, spasticity, and severe treatment-resistant epilepsy.

College of Family Physicians of Canada (CFPC): Authorizing Dried Cannabis for Chronic Pain or Anxiety. (Sept 2014)

This guidance document was prepared on behalf of the College of Family Physicians of Canada (CFPC) by members of the Addiction Medicine and Chronic Pain Program Committees, in collaboration with members of the Child and Adolescent Health, Maternity and Newborn Care, Mental Health, Palliative Care, and Respiratory Medicine Program Committees, of CFPC's Section of Family Physicians with Special Interests or Focused Practices.

The authors point to the known risks of using cannabis, as well as the lack of strong evidence, and conclude "the only sensible advice for physicians involved with authorizing dried cannabis is the maxim "Start low, and go slow" (College of Family Physicians of Canada 2014).

Regarding dosing for chronic pain, the authors summarize existing evidence and make dosing recommendations as follows:

- Studies of smoked cannabis for neuropathic pain conditions suggest effective doses ranging from one single inhalation from 25 mg of herbal cannabis containing 9.4% THC three times daily using a pipe, (Ware, Wang et al. 2010) to 9 inhalations from a 900 mg "joint" of herbal cannabis containing 7% THC (Abrams, Jay et al. 2007, Wilsey, Marcotte et al. 2008). Based on a standard inhalation procedure where the patient is directed to inhale slowly over 5 seconds, hold breath for 10 seconds, then gently exhale, this translates into current evidence for a daily inhaled dose of 100–700 mg of up to 9% THC content dried cannabis.

- Based on the evidence reviewed, the authors anticipate the upper range for safe use of dried cannabis is around 3.0 g/day, and only after careful and slow titration to that level. (This is consistent with recommended range in MacCallum and Russo 2018.)

- It is worth noting that in all studies reviewed, the incidence of adverse events increases with increasing THC levels.

Consensus statements

There are also several consensus statements that were arrived at using a modified Delphi process. It should be noted that there have been concerns raised about relying solely on consensus processes for dosing guidelines in the absence of large-scale clinical trials (Hill and Abrams 2021). Hill and Abrams rightly commented that "Delphi processes are not a substitute for rigorous RCTs with large sample sizes, adequate duration, and standardized outcome measures." That said, Delphi processes were designed to develop consensus best practice where guidelines are not available.

Recently published consensus statements using a modified Delphi process include the following:

Sihota A, Smith BK, Ahmed S-A, et al. 2021. Consensus-based recommendations for titrating cannabinoids and tapering opioids for chronic pain control. *Int J. Clin Practice* **2021;75:e13871.**

This five-stage modified Delphi process led to the development of consensus-based recommendations surrounding the safe introduction and titration of cannabinoids in concert with tapering opioids. Twenty-one cannabinoid subject matter experts from the U.S. and Canada participated.

Participants reached consensus that for patients with chronic pain taking opioids not reaching treatment goals, cannabinoids may be considered. Initiation with a CBD predominant oral extract during the day was recommended, with the addition of THC if needed.

Dosing of THC was recommended to start at 0.5 to 3 mg, and increase by 1-2 mg once or twice weekly up to 30-40 mg/day. Opioid tapering can begin when the patient reports an improvement in function, seeks less as-needed medication to control pain, and/or the optimal cannabis dose has been reached. Opioid tapering may be 5-10% of the morphine equivalent dose every one to four weeks.

Success could be measured by an improvement in function or quality of life, a 30% or greater reduction in pain intensity, a reduction in opioid dose of 25% or more, a reduction in opioid dose to less than 90 mg morphine equivalent dose, and/or reduction in opioid-related adverse events.

Bhaskar et al. Consensus recommendations on dosing and administration of medical cannabis to treat chronic pain: results of a modified Delphi process. *Journal of Cannabis Research* **2021;3:22.**

Using a multistage modified Delphi process, 20 global experts across nine countries developed consensus-based recommendations on how to dose and administer medical cannabis in patients with chronic pain.

There was consensus that medical cannabis may be considered for patients experiencing neuropathic, inflammatory, nociplastic, and mixed pain. Three treatment protocols were developed.

1. A routine protocol where the clinician initiates the patient on a CBD-predominant variety at a dose of 5 mg CBD twice daily and titrates the CBD-predominant dose by 10 mg every

two to three days until the patient reaches their goals, or up to 40 mg/day. At a CBD-predominant dose of 40 mg/day, clinicians may consider adding THC at 2.5 mg and titrate by 2.5 mg every two to seven days until a maximum daily dose of 40 mg/day of THC.

2. A conservative protocol where the clinician initiates the patient on a CBD-predominant variety at a dose of 5 mg once daily and titrates the CBD-predominant dose by 10 mg every two to three days until the patient reaches their goals, or up to 40 mg/day. At a CBD-predominant dose of 40 mg/day, clinicians may consider adding THC at 1 mg/day and titrate by 1 mg every seven days until a maximum daily dose of 40 mg/day of THC.

3. A rapid protocol where the clinician initiates the patient on a balanced THC:CBD variety at 2.5–5 mg of each cannabinoid once or twice daily and titrates by 2.5–5 mg of each cannabinoid every two to three days until the patient reaches his/her goals or to a maximum THC dose of 40 mg/day.

Ladha KS et al. Perioperative Pain and Addiction Interdisciplinary Network (PAIN): consensus recommendations for perioperative management of cannabis and cannabinoid-based medicine users by a modified Delphi process. *Br J Anaesth.* 2021 Jan;126(1):304-318. doi: 10.1016/j.bja.2020.09.026. Epub 2020 Oct 29.

This statement includes recommendations developed through a modified Delphi method for the perioperative care of cannabis-using patients. Seventeen experts on the care of cannabis-consuming patients participated.

The major recommendations obtained included:

- Emphasizing the importance of eliciting a history of cannabis use, quantifying it, and ensuring contact with a cannabis authorizer (if one exists);

- Consideration of perioperative cannabis weaning, additional postoperative nausea and vomiting prophylaxis, and additional attention to monitoring and maintaining anaesthetic depth; and

- Anticipating increased postoperative analgesic requirements and maintaining vigilance for cannabis withdrawal syndrome.

Limitations/Research Gaps

Due to its classification as a Schedule 1 drug, very limited research has been conducted in the U.S. Most existing studies are small, many are dated, most are rated low quality with unclear or moderate to high risk of bias, and few examine currently available alternative treatments in addition to placebo (Smith, Azariah et al. 2015, Abrams 2016, Ko, Bober et al. 2016, Dosenovic, Jelicic Kadic et al. 2017, Inglet, Winter et al. 2020, Levy, Galenbeck et al. 2020, Sturgeon, Khan et al. 2020, Abu-Amna, Salti et al. 2021, Fisher, Moore et al. 2021, McKee, Hmidan et al. 2021). In addition, many lack quality safety assessment and reporting (Mohiuddin, Mizubuti et al. 2020). These limitations make it difficult to assess effectiveness, determine drug interactions, or conduct sub-group analysis to assess varying impacts of cannabis products on younger or older persons, racial or ethnic groups, or people with varying histories of cannabis use.

Additional research has been called for in the following areas:

Health harms or benefits of cannabis

"…The federal government has not legalized cannabis and continues to enforce restrictive policies and regulations on research into the health harms or benefits of cannabis products that are available to consumers in a majority of states. As a result, research on the health effects of cannabis and cannabinoids has been limited in the United States, leaving patients, health care professionals, and policy makers without the evidence they need to make sound decisions regarding the use of cannabis and cannabinoids. This lack of evidence-based information on the health effects of cannabis and cannabinoids poses a public health risk." (National Academies of Sciences 2017)

Safety and dosing information

"…there are few randomized control trials studying medical cannabis indicating expert guidance on how to dose and administer medical cannabis safely and effectively is needed." (Bhaskar, Bell et al. 2021)

"What is needed as the cannabis industry moves forward, are several large-scale observational real-world evidence studies for which we know the inputs (i.e., what people are actually consuming from chemical composition standpoint—i.e., verified strains/ final products), which would then lead to meaningful randomized-controlled trials informed by the products being consumed in the real world" (Meng, Page et al. 2021).

"More RCTs are needed to explore the effectiveness and safety of herbal cannabis and cannabis oils on specific disorders, and these products need to be standardized for cannabinoid content" (Dos Santos, Hallak et al. 2021).

Best practices for THC:CBD ratios for different indications

"When using products that have both THC and CBD, identifying the best ratio will depend on what is the intended effect. Guidance on the best ratio of THC to CBD for various indications is lacking" (Sawtelle and Holle 2021). Similar calls for research on efficacy and safety for different THC:CBD ratios came from Levy et al. in their review of the literature on medical cannabis use for older adults (Levy, Galenbeck et al. 2020).

Cannabis use among older adults

Levy et al. (2020) reviewed literature on the use of cannabis among older adults. While they found eight randomized controlled trials to review, the studies were small, and did not provide high quality evidence on the efficacy of medical cannabis for symptoms frequently experienced by older adults, such as pain, neurologic symptoms, and mood disorders. They pointed to the need for future research due to the increased likelihood of older adults experiencing side effects from cannabis use that may differ from those experienced by younger populations (Minerbi, Hauser et al. 2019). Unless and until such research is conducted, physicians will be unable to make informed recommendations and clinical decisions regarding cannabis use for older adults.

Cancer

Cancer is a qualifying condition 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 are presented below).

Severe or chronic pain

Two early trials studied delta-9-THC sourced from the U.S. government (Noyes, Brunk et al. 1975, Noyes, Brunk et al. 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.

Later, larger trials have studied nabiximols, the U.S. 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. Eleven sprays deliver 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 eight 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 2013 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.

One study by Bar-Lev Schleider et al. (2018) is regularly cited as one of the main sources of evidence of safety and efficacy of medical cannabis for cancer and cancer-related symptoms, including pain. It is a large, prospective study of nearly 3,000 patients. Participants were not randomly selected, and there was no control arm. The process of selecting a cannabis strain and patient education was discussed, but dosing protocols were not included. Results showed impressive decreases in pain and improvements in quality of life. The authors note, however, that results may be biased due to those experiencing positive effects being more likely to respond at follow-up. Adverse events were reported by 30% of participants. Specific adverse events reported were relatively mild, including dizziness, dry mouth, increased appetite, sleepiness, and psychoactive effect.

More recent studies have investigated the impact THC:CBD ratios have on different conditions. In Casarett et al. (2019), symptom relief improved with an increase in the proportion of THC compared to CBD for neuropathic pain, insomnia, and depressive symptoms, over the range of 0-100% THC to CBD. For PTSD-related flashbacks and anorexia, the trend was positive but not significant for increased THC:CBD ratios. For depressive symptoms, the result was U-shaped, with maximum benefit at a 1:1 ratio of THC:CBD.

One ongoing study (Hardy, Haywood et al. 2020) is the first placebo-controlled trial to examine escalating doses of 1:1 THC/CBD on the management of symptom burden in patients with advanced cancer undergoing standard palliative care. Doses will range from 2.5 mg – 30 mg per day. Measures will include efficacy on reduction of total symptom score on day 14; the effect of a patient-determined effective dose on symptom scores at days 7, 21, and 28; and the change in anxiety and depression, opioid use, and quality of life at days 7, 21, and 28. Enrollment will continue through April 2022, and data collection will end by May 31, 2022.

Casarett DJ, Beliveau JN, Arbus MS. Journal of Palliative Medicine. Volume 22, Number 10, 2019 Benefit of Tetrahydrocannabinol versus Cannabidiol for Common Palliative Care Symptoms

This study examined the medical records of 2,431 Canadian patients to determine the relative contributions of tetrahydrocannabinol (THC) and cannabidiol (CBD) to patients' self-ratings of efficacy for common palliative care symptoms. Model development used logistic regression with bootstrapped confidence intervals (CIs), with standard errors clustered to account for multiple observations by each patient.

Main outcome measures included self-ratings of efficacy of cannabis, defined as a three-point reduction in neuropathic pain, anorexia, anxiety symptoms, depressive symptoms, insomnia, and post-traumatic flashbacks.

Of the six symptoms, response was associated with increased THC:CBD ratio for neuropathic pain (odds ratio [OR]: 3.58; 95% CI: 1.32–9.68; $p = 0.012$), insomnia (OR: 2.93; 95% CI: 1.75–4.91; $p < 0.001$), and depressive symptoms (OR: 1.63; 95% CI: 1.07–2.49; $p = 0.022$). Increased THC:CBD ratio was not associated with a greater response of post-traumatic stress disorder (PTSD)-related flashbacks (OR: 1.43; 95% CI: 0.60–3.41; $p = 0.415$) or anorexia (OR: 1.61; 95% CI: 0.70-3.73; $p = 0.265$). The response for anxiety symptoms was not significant (OR: 1.13; 95% CI: 0.77–1.64; $p = 0.53$), but showed an inverted U-shaped curve, with maximal benefit at a 1:1 ratio (50% THC).

While the total dose of either CBD or THC was not reported, the study underscores the importance of the THC/CBD ratio in effectiveness of symptom relief for various conditions, and the range of effectiveness for increasing THC:CBD ratios.

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 was also very similar. The 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 ≥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 U.S. participants in Trial #1 and in Lichtman 2017 had a primary efficacy outcome that favored Sativex – especially for participants ≥65.

Hardy J, Haywood A, Gogna G, Martin J, Yates P, Greer R, Good P. Oral medicinal cannabinoids to relieve symptom burden in the palliative care of patients with advanced cancer: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety of 1:1 delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Trials (2020) 21:611.

This multicenter, randomized, placebo-controlled, two-arm study aims to define the role of a 1:1 delta-9-tetrahydrocannabinol/cannabidiol (THC/CBD) cannabinoid preparation in the management of symptom burden in patients with advanced cancer undergoing standard palliative care.

One hundred fifty participants will be recruited from five sites within the Queensland Palliative Care Research Group (QPCRG) and randomly assigned to an active treatment or placebo group. Escalating doses of an oral 1:1 THC/CBD cannabinoid preparation will be administered to compare efficacy and safety outcomes of a titrated dose (10 mg/10 mg/mL oral solution formulation, dose range 2.5 mg/2.5 mg–30 mg/30 mg/day) against placebo. During a two-week titration phase, patients will escalate doses of 1:1 THC/CBD or placebo until the dose achieves symptom relief with tolerable side effects.

Objectives include the following:

- Assess the effect of escalating doses of a 1:1 THC/CBD cannabinoid preparation against placebo on total symptom score at day 14 as measured by the Edmonton Symptom Assessment Scale (ESAS) (change in score from baseline).

- Establish a patient-determined effective dose of a 1:1 THC/CBD formulation and assess the effect on symptom scores at days 7, 21, and 28.

- Assess the change in total physical and emotional scores, global impression of change, anxiety and depression, opioid use and quality of life at days 7, 21, and 28.

- Document adverse effects associated with cannabinoid use.

Trial registration: ACTRN, ACTRN12619000037101. Registered on Jan. 14, 2019.

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 three-hour period was eight 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. Forty-three percent 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, three 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. Thirty-nine received nabiximols in the extension study and four 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 eight 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 five 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 four 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. Eighteen patients started the study and two dropped out for unspecified reasons.

Mean dose used during active treatment was eight 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 four; 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- tetracannabinol. *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 five 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 three hours for the lower doses and at five hours for the 20 mg dose. Interestingly, in all groups a secondary peak can be seen at five 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-9 tetrahydrocannibinol 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 a.m. and study medication administered at 8:30 a.m. Information on pain and other symptoms was collected just before medication administration and hourly for seven hours thereafter. Ten mg THC showed improved pain control compared with placebo over seven 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 one and four sprays per day. Those assigned to Medium Dose group titrated the number of sprays to between six 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 seven days (three 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 end point 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 one to four 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.

Bar-Lev Schleider L, Mechoulam LR, Lederman V, et al. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. *Eur J Intern Med* 2018; 49:37–43.

This observational study, conducted as part of Israel's government-mandated medical cannabis program, describes a cohort of patients who had improvements in quality of life and reduction in opioid use following the use of cannabis products.

Analysis of routinely collected data regarding the benefits and burdens of medical marijuana, prescribed to almost 3,000 cancer patients with symptomatic disease who were followed over 2 years. This article also describes the processes of physician prescription and nurse selection (with patient) of particular cannabis strains, dose escalation, and patient and family teaching. The proportion of participants using different strains of cannabis (and THC:CBD ratios) were reported, but strain, THC:CBD ratio, or actual dose used, were not reported relative to outcomes observed. Dosing protocols (titration schedules etc.) were not discussed.

Study participants were assessed on pain intensity and quality of life at six months (1,144 and 1,165 patients, respectively). Prior to treatment initiation 52.9% of patients reported their pain to be in the interval of eight to 10 (out of 10), while only 4.6% reported this intensity after six months of treatment ($p < 0.001$). Similarly, only 18.7% of patients reported good quality of life prior to treatment initiation while 69.5% reported good quality of life at 6 months ($p < 0.001$).

The authors conclude that cannabis appears to be well-tolerated, effective, and safe for cancer patients coping with malignancy-related symptoms. Thirty percent of patients reported at least one side effect at six months, but the side effects were relatively minor and easy to cope with: dizziness, dry mouth, increased appetite, sleepiness, and psychoactive effect.

While this is a large prospective study, it was observational with no control group, and no causality can be drawn between cannabis use and alleviation of symptoms. At six months, one-third of the study sample had died or stopped treatment, and of the remaining participants, 60% responded at six months. Therefore, results may be biased, due to patients experiencing positive results being more likely to respond to the follow-up survey.

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, Stefano et al. 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 comparators. 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, Shiling et al. 1979), but no difference from placebo was observed in the trial with Adriamycin and Cytoxan chemotherapy (Chang, Shiling et al. 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, Waters et al. 1979) and 10 to 15 mg three times over 12 hours (Sallan, Cronin et al. 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, Perez et al. 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 eight sprays within any four-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* **1979; 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/m^2 THC or placebo, with additional doses every three hours for a total of five doses. Based on a body surface area of 1.75 m^2, the oral THC dose was 17.5 mg every three 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/m^2 THC or placebo, with additional doses every three hours for a total of five doses. Based on a body surface area of 1.75 m^2, the oral THC dose was 17.5 mg every three 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.

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-emitic therapy for chemotherapy-induced nausea and vomiting. Sixteen 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 eight sprays within any four-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.

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

This article reports on 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/m^2 (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.

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. The authors noted that adverse effects were more intense and occurred more frequently in patients using cannabinoids.

Sallan SE, Cronin C, Zelen M, and Zinberg NE. Antiemetics in patients receiving chemotherapy for cancer: a randomized comparison of delta 9 tetrahydrocannibinol 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. Eighty-four 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 four and eight 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, Waters et al. 1979) and 30 to 45 mg in three divided doses in adults (Sallan, Cronin et al. 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, de Kock et al. 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, Walsh et al. 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, Windschitl et al. 2002).

A large clinical trial comparing THC:CBD extract, THC-only extract, and placebo was stopped early because of lack of effectiveness (Cannabis In Cachexia Study, Strasser et al. 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.

A more recent pilot study found a positive impact on weight gain in three of 17 study participants using 5mg THC once or twice daily without significant side effects (Bar-Sela, Zalman et al. 2019).

Bar-Sela G, Zalman D, Semenysty V, Ballan E. The effects of dosage-controlled Cannabis capsules on cancer-related cachexia and anorexia syndrome in advanced cancer patients: pilot study. *Integr Cancer Ther.* 2019;18:153473541988149.

In this small, single-arm study aimed to evaluate the effect of dosage-controlled cannabis capsules on cancer related anorexia and cachexia syndrome (CACS) in advanced cancer patients. Treatment was 2 x 10 mg per 24 hours for six months of THC (9.5 mg), CBD (0.5 mg). If patients suffered from side effects, dosage was reduced to 5 mg x 2 per day (THC 4.75 mg, CBD 0.25 mg). A weight increase of ≥ 10% in 3/17 (17.6%) patients with a dose of 5mgX1 or 5mgX2 capsules daily, without significant side effects, was reported. The authors conclude that these results justify a more extensive study with dosage-controlled cannabis capsules in CACS.

Brisbois TD, de Kock IH, Watanabe SM, Mirhosseini M, et al. Delta 9 tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled 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. Forty-six 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). Twenty-one 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 three 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 9 tetrahydrocannabinol. *Med J Aust* 1979;2:657659.

This article reports on 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/m^2 (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 uncurable 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, four men taking dronabinol, and 14 men taking both.

Nelson K, Walsh D, Deeter P, and Sheehan F. A phase II study of delta-9- tetrahydrocannibinol 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 9tetrahydrocannibinol 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. Eighty-four 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 four and eight 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-tetrahydrocannbinol in treating patients with cancer-related anorexiacachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-in Cachexia-Study Group. *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 six 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 six 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, Olsen et al. 1981). 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 two patients received a maximum dose of 7.5 mg 4x/day, 3 pts 5.0 mg 4x/day, and three 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 two hours after administration. After the four-hour measurement IOP had returned to normal (Tomida, Azuara-Blanco et al. 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 four hours after administration. There were no serious or severe adverse events and all but two (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 every four 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 two 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 two 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 three 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 one and nine. Four withdrew because of side effects (three weeks – taking 2.5 mg 4x/day, eight 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 Opthalmol* 1981;12:947- 950.

The study report contains results from two small observational trials of different designs at different U.S. 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 mg at five 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 five 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, four-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 four to six 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 four 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.

HIV/AIDS

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 (Beal, Olson et al. 1995, Beal, Olson et al. 1997, Abrams, Hilton et al. 2003), with the exception of trials that

recruited regular marijuana users. In this patient group it appears that larger doses of dronabinol
are well tolerated (Haney, Rabkin et al. 2005, Haney, Gunderson et al. 2007, Bedi, Foltin et al.
2010). 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, Hilton et al. 2003).

In 2017, two clinical trials were organized. The first seeks to 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. As of January 2022, the study was
listed as open for enrollment and with a completion date of December 2022. See Effects of
Cannabis and Endocannabinoids on HIV Neuropathic Pain
(https://clinicaltrials.gov/ct2/show/study/NCT03099005?cond=Effects+of+Cannabis+and+Endoca
nnabinoids+on+HIV+Neuropathic+Pain&draw=2&rank=1).

The second seeks 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. This study is listed as active but not recruiting and the estimated study
completion date is June 2022. See Medical Marijuana and Opioids Study
(https://www.clinicaltrials.gov/ct2/show/NCT03268551?term=Severe+chronic+pain&cond=HIV&
draw=2&rank=2).

**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 (four 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 nelinavir. None of them smoked
marijuana or ingested cannabinoids within 30 days of enrollment. Patients taking nefinavir 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 three 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 seven 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.

One hundred thirty-nine 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 six 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 l6 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 two weeks. Dose was decreased to 2.5 mg/day in 19% of patients and increased to 7.5 mg/day or higher (two patients 10 mg/day, one 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 dropouts 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 four months of dronabinol therapy. Patient weight tended to remain stable for the first five 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 ages 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) four 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 eight 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 four 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 washout 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 four 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 four divided doses; eight 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 was 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 one hour before meals at lunch and dinner. Megestrol was taken one hour before lunch. Subjects completed four different self-reported questionnaires for this study: visual analog scale for hunger (VASH) was taken three 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 two weekdays and one weekend day. FAHI, a questionnaire with subscale and perception scores in six 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 four 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 six 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 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 Tourette syndrome symptoms, but they are not uniformly effective, and many have undesirable side effects. Medical cannabis is a therapy of interest, but to date very few clinical trials have been conducted.

There were two earlier clinical trials of medical cannabis in Tourette syndrome patients published in 2002 and 2003 respectively – both studies were small, and eight 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, Schneider et al. 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, Schneider et al. 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, Prevedel et al. 2003). It found no differences in cognitive testing results between the active treatment and placebo groups.

More recently, one investigator-initiated proof of concept study was designed 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 (Bloch, Landeros-Weisenberger et al. 2021). Seventeen individuals ages 18-60 were enrolled. The 12-week treatment periods started with titration of dronabinol starting at 2.5 mg for three days, then 5 mg for four days, then 10 mg for the remainder of the study. All participants received two 400 mg tablets of PEA daily for the same 12 weeks they received dronabinol. The investigators found over the 12-week study period tic symptoms improved by more than 20% (as assessed by the YGTSS). There were no fatal or serious side effects reported. See Efficacy of a Therapeutic Combination of Dronabinol and PEA for Tourette Syndrome (https://www.clinicaltrials.gov/ct2/show/study/NCT03066193?cond=Efficacy+of+a+Therapeutic++Combination+of+Dronabinol+and+PEA+for+Tourette+Syndrome&draw=2&rank=1).

There is one additional clinical trial in Germany that began recruiting in 2017. It compares 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 Tourette syndrome symptoms in adults. Patients (n=96) started one spray/day and increased to a maximum of 12 sprays/day. Treatment duration was 13 weeks. The study was completed November 2020 and as of March 2022 no results have been published or posted. See CANNAbinoids in the Treatment of TICS (CANNA-TICS) (https://www.clinicaltrials.gov/ct2/show/NCT03087201?cond=CANNAbinoids+in+the+Treatment +of+TICS&draw=2&rank=1).

Bloch MH, Landeros-Weisenberger A, Johnson JA, Leckman JF. A Phase-2 Pilot Study of a Therapeutic Combination of Δ⁹-Tetrahydracannabinol and Palmitoylethanolamide for Adults With Tourette's Syndrome. *J Neuropsychiatry Clin Neurosci*. **2021 Fall;33(4):328-336. doi: 10.1176/appi.neuropsych.19080178. Epub 2021 Aug 3. PMID: 34340527.**

For this proof-of-concept study, investigators enrolled 17 individuals with Tourette syndrome, ages 18-60. The 12-week treatment periods started with titration of dronabinol starting at 2.5 mg for three days, then 5 mg for four days, then 10 mg for the remainder of the study. All participants received two 400 mg tablets of PEA daily for the same 12 weeks they received dronabinol. Improvement in tic symptoms was statistically significant within one week of starting treatment compared with baseline. Treatment led to an average improvement in tic symptoms of more than 20%, or a 7-point decrease in the YGTSS score. Twelve of the 16 participants elected to continue to the extension phase, and only two participants dropped out early. Side effects were common but were generally managed by decreasing delta-9-THC dosing, slowing the dosing titration, and shifting dosing to nighttime.

Muller-Vahl KR, Schneider U, Koblenz A, Jodges M. Treatment of Tourette's syndrome with Delta 9-tetrahdrocannabinol (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 Tourette syndrome symptoms were done just before and three to four 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 Tourette syndrome 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 one and six 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 Tourette syndrome symptoms. The 24 subjects had an average age of 33 (range=18-68 years). Fifteen patients were unmedicated for at least six months prior to the study and nine 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 six 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 six patients, 7.5 mg/day for two 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-tetrahudrocannabinol (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 six of the nine 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 six 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.

Amyotrophic Lateral Sclerosis (ALS)

Only two published clinical trials of cannabis for the treatment of symptoms associated with ALS were found, both using dronabinol (synthetic delta-9-THC). 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 three months were associated with

improvement in sleep, appetite, and spasticity, but few details are provided (Gelinas, Miller et al. 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, Goldman et al. 2010). This study used 5 mg dronabinal (in sesame oil drops) twice daily.

A third study (Riva, Mora et al. 2019), conducted in Italy, recruited 60 adults with motor neuron disease who 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. Participants were instructed to self-titrate for the first 14 days of treatment (maximum of 12 actuations per 24-hour time-period) and then maintained the optimal self-titrated dose for four weeks. The primary outcome measure (Modified Ashworth Scale) improved by a mean of 0.11 (SD = 0.48) for the treatment group and decreased by a mean of 0.16 (SD = .47) in the placebo group. No serious side effects were reported.

A fourth study, started in 2018, continues to recruit 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 six 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 January 2023. See Efficacy of Cannabinoids in Amyotrophic Lateral Sclerosis or Motor Neurone Disease (https://www.clinicaltrials.gov/ct2/show/NCT03690791?term=Marijuana&cond=ALS&draw=2&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 to examine 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 five to seven. 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).

Riva N, Mora G, Sorarù G, Lunetta C, Ferraro OE, Falzone Y, Leocani L, Fazio R, Comola M, Comi G; CANALS Study Group. Safety and efficacy of nabiximols on spasticity symptoms in patients with motor neuron disease (CANALS): a multicentre, double-blind, randomised, placebo-controlled, phase 2 trial. *Lancet Neurol*. **2019 Feb;18(2):155-164. doi: 10.1016/S1474-4422(18)30406-X. Epub 2018 Dec 13.**

This investigator-initiated, randomized, placebo-controlled, double-blind, phase-2 clinical trial recruited 60 individuals with motor neuron disease and diagnosed or probable ALS between 18 and 80 years old between Jan 19, 2013, and Dec 15, 2014. Participants were randomized to either a standardised oromucosal spray (nabiximols) or to placebo for six weeks. The naboximols spray

contained a defined combination of delta-9-tetrahydrocannabinol and cannabidiol (each 100 µL actuation contained 2·7 mg delta-9-THC and 2·5 mg CBD). Participants self-titrated during the first 14 days of treatment (maximum 12 actuations per 24 h), then maintained that dose for four weeks. The primary endpoint was the change in the score on the Modified Ashworth Scale, which was assessed at baseline and after six weeks. Findings showed that nabiximols had a positive effect on spasticity symptoms – Modified Ashworth Scale scores improved by a mean of 0.11 in the nabiximols group and declined by a mean of 0.16 in the placebo group. Nabiximols was well tolerated, and no participants withdrew from the double-blind phase of the study. No serious adverse effects occurred.

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 three 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 2016 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 (GWPCARE1)(Devinsky, Cross et al. 2017). 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: GWPCARE4 (Thiele, Marsh et al. 2018) and GWPCARE3 (Devinsky, Patel et al. 2018). 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, Patel, et al. 2018 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 published in *Neurology* builds on the results of Thiele 2018 and Devinski, Patel, et al. 2018, demonstrating the importance of monitoring liver enzymes when a patient is using CBD – especially when valproate is used at the same time (Devinsky, Patel et al. 2018).

Miller et al. 2020 examined the efficacy and safety of two dosing regimens of CBD (10 mg/kg/day and 20 mg/kg/day) in children with treatment-resistant Dravet syndrome (GWPCARE2)(Miller, Scheffer et al. 2020). Results showed similar reductions in seizure frequency in both 10 and 20 mg/kg/day groups, but a better safety and tolerability profile for the 10 mg/kg/day dose. The authors recommend that dosing in excess of 10 mg/kg/day be done so with individual efficacy and safety profiles in mind.

The meta-analysis of the four clinical trials (GWPCARE 1,2,3,4) examined the effect of CBD with and without a commonly used treatment, clobazam (CLB). In each trial, CBD significantly reduced seizure frequency (primary endpoint) and higher proportions of patients had ≥50% reduction (key secondary) vs. placebo. The meta-analysis favored CBD vs. placebo regardless of CLB use (Devinsky, Thiele et al. 2020).

Based on initial results from the GWPCARE studies, 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. See full prescribing information (https://www.epidiolex.com/sites/default/files/EPIDIOLEX_Full_Prescribing_Information.pdf).

Szaflarsi (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, Perkovic Benedik et al. 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, Bebin et al. 2017).

While there is general consensus that there is sufficient evidence to support the use of CBD for children and adolescents with treatment-resistant epilepsy, more recent studies and reviews suggest there may be some safety concerns, drug interactions, age-dose interactions, and/or tolerance possibilities that should be considered by clinicians and patients.

Pawliuk et al. (2021) conducted a scoping review that included many of the studies cited in this report. While they acknowledged the level of evidence supporting the use of CBD for treatment-resistant epilepsy, they noted a high rate of treatment discontinuation due to adverse events (range: 0.17% - 20%). Adverse events were lower in RCTs than in open-label, observational, or case studies, with discontinuation in RCTs ranging from 1.82-7.02% in the CBD groups and 0.47 – 5.55% in the placebo groups. Common short-term adverse events reported in the reviewed studies included pyrexia, vomiting, diarrhea, and dizziness. Longer-term adverse events were also observed in the studies, including weight gain or loss, changes in appetite, fatigue, somnolence, changes in mood, and increase in seizure frequency.

One prospective study of 92 children and adults with treatment-resistant epilepsy reported possible tolerance to CBD 25% of patients (Uliel-Sibony, Hausman-Kedem et al. 2021). Tolerance was defined as either the need to increase the dose by ≥30% due to reduced treatment efficacy or as an increase of ≥30% in mean monthly seizure frequency in patients treated for at least three months with no change in other anti-seizure medications. Per study protocol, CBD dose was increase incrementally until intolerance or maximum dose of 50 mg/kg per day However, most patients did not receive more than 30 mg/kg/day of CBD. Dose was increased to >=800 mg/day in only three patients. The possibility of tolerance has treatment implications for both children and adults.

In additional analyses of the same study published separately (Cohen, Kramer et al. 2021), study authors conducted an age-dose analysis of 44 patients ages 2-31, because drug exposure can change over childhood. The study authors found an inverse relationship between age and nominal dose. The median final dose was 1.8 times higher in younger (1–9 years old; n = 22) than in older (15+ years old; n = 11) patients (16.1 ± 8.3 mg/kg/day versus 8.8 ± 4.5 mg/kg/day, respectively, $p < 0.01$). Because clobazam can interfere with CBD metabolism, the analysis was repeated without clobazam-treated patients, and results remained significant.

In 2017, the University of Colorado 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 three months) to a proprietary CBD extract that is 98% CBD and has no THC. As of March 2022, the results have not yet been published (clinicaltrials.com Identifier #: NCT02229032). See Genetic Analysis Between Charlotte's Web Responders Versus Non-Responders in a Dravet Population (https://clinicaltrials.gov/ct2/show/NCT02229032?id=NCT02229032&draw=2&rank=1)

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. One hundred twenty 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 four-week baseline period, a 14-week treatment period (two weeks of dose escalation and 12 weeks for dose maintenance), a 10-day taper period, and a four-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 1,717) at baseline to 5.9 (range, 0.0 to 2,159) 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 three in the placebo group (status epilepticus was reported in three 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: 10.1212WNL.0000000000005254.

For this dose-ranging safety study, children ages 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 six patients were taking concomitant valproate and four of the six 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) was 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 eight patients discontinued CBD or placebo because of adverse events: six 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 (two 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 three 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 two in the 10 mg/kg/day group) were receiving valproic acid concomitantly.

Devinsky O, Thiele EA, Wright S, Checketts D, Morrison G, Dunayevich E, et al. Cannabidiol efficacy independent of clobazam: Meta-analysis of four randomized controlled trials. *Acta Neurol Scand* **2020 Vol. 142 Issue 6 Pages 531-540. Accession Number: 32592183 PMCID: PMC7689899 DOI: 10.1111/ane.13305**

The four consecutive randomized, placebo-controlled clinical trials (GWPCARE 1,2,3,4) that examined the impact of CBD (Epidiolex) on seizure frequency for Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) (Devinsky, Cross et al. 2017, Devinsky, Patel et al. 2018, Thiele, Marsh et al. 2018, Miller, Scheffer et al. 2020) were combined by Devinsky et al. in a meta-analysis (2020). All four trials had a similar design. The meta-analysis examined the effect of CBD with and without a commonly used treatment, clobazam (CLB).

The pooled population comprised 714 patients, with similar sample sizes for each trial: 396 with LGS and 318 with DS; 429 treated with add-on CBD (240 with CLB and 189 without CLB) and 285 with add-on placebo. In the LGS cohort, 73 patients received CBD 10 mg/kg/day, 162 received

CBD 20 mg/kg/day, and 161 received placebo. In the DS cohort, 66 patients received CBD 10 mg/kg/day, 128 received CBD 20 mg/kg/day, and 124 received placebo.

In each trial, CBD significantly reduced seizure frequency (primary endpoint) and higher proportions of patients had ≥50% reduction (key secondary) vs. placebo. The meta-analysis favored CBD vs. placebo regardless of CLB use. The treatment ratio (95% CI) of CBD over placebo for the average reduction in seizure frequency was 0.59 (0.52, 0.68; $P < .0001$) with CLB and 0.85 (0.73, 0.98; $P = .0226$) without CLB, and the 50% responder rate odds ratio (95% CI) was 2.51 (1.69, 3.71; $P < .0001$) with CLB and 2.40 (1.38, 4.16; $P = .0020$) without CLB.

Adverse events (AEs) related to somnolence, rash, pneumonia, or aggression were more common in patients where CLB was also used alongside CBD.

Gaston T, Bebin EM, Cutter G, Liu Y, Szaflarski J. 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 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 eight-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 information on what these other AEDs were; most participants were on one to two 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 five). 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).

Miller I, Scheffer I, Gunning B, et al. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in dravet syndrome. *JAMA Neurol.* **2020;77(5):613.**

This double-blind, placebo-controlled, randomized clinical trial (GWPCARE2) was designed to evaluate the efficacy and safety of a pharmaceutical formulation of cannabidiol, 10 and 20 mg/kg/d, vs. placebo for adjunctive treatment of convulsive seizures in patients with Dravet syndrome. Patients were recruited from April 13, 2015, to Nov. 10, 2017, with follow-up completed on April 9, 2018. Patients were ages 2 to 18 years with a confirmed diagnosis of Dravet syndrome and at least four convulsive seizures during the four-week baseline period while receiving at least 1 antiepileptic drug.

Patients received cannabidiol oral solution at a dose of 10 or 20 mg/kg per day (CBD10 and CBD20 groups, respectively) or matched placebo in 2 equally divided doses for 14 weeks. Of 198 eligible patients 66 were randomized to the CBD10 group, 67 to the CBD20 group, and 65 to the placebo group, and 190 completed treatment.

The primary outcome was change from baseline in convulsive seizure frequency during the treatment period. Secondary outcomes included change in all seizure frequency, proportion with at least a 50% reduction in convulsive seizure activity, and change in Caregiver Global Impression of Change score. The percentage reduction from baseline in convulsive seizure frequency was 48.7% for CBD10 group and 45.7% for the CBD20 group vs 26.9% for the placebo group; the percentage reduction from placebo was 29.8% (95% CI, 8.4%-46.2%; P = .01) for CBD10 group and 25.7% (95% CI, 2.9%-43.2%; P = .03) for the CBD20 group.

The most common adverse events were decreased appetite, diarrhea, somnolence, pyrexia, and fatigue. Five patients in the CBD20 group discontinued owing to adverse events. Elevated liver transaminase levels occurred more frequently in the CBD20 (n = 13) than the CBD10 (n = 3) group. Based on the improved safety and tolerability of 10 mg/kg/day over 20 mg/kg/day with similar reductions in seizure frequency, the authors recommended that children with treatment-resistant Dravet syndrome be treated with doses up to 10-mg/kg/day. Doses exceeding this limit should be tailored to individual efficacy and safety.

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 ≥ 20 mg/kg/day adverse effects appeared.

Pawliuk C, Chau B, Rassekh SR, McKellar T, Siden HH. Efficacy and safety of paediatric medicinal cannabis use: A scoping review. *Paediatr Child Health* 2021 Vol. 26 Issue 4 Pages 228-233. Accession Number: 34131459 PMCID: PMC8194766 DOI: 10.1093/pch/pxaa031

This scoping review examined available evidence on the efficacy and safety of medicinal cannabis in children and adolescents. Of 36 studies included, 32 investigated the efficacy or safety of cannabis in treatment-resistant epilepsy. While they acknowledged the level of evidence supporting the use of CBD for treatment-resistant epilepsy, the authors noted a high rate of treatment discontinuation due to adverse events (range: 0.17% - 20%). Adverse events were lower in RCTs than in open-label, observational, or case studies, with discontinuation in RCTs ranging from 1.82-7.02% in the CBD groups and 0.47 – 5.55% in the placebo groups. Common short-term adverse events reported in the reviewed studies included pyrexia, vomiting, diarrhea, and dizziness. Longer-term adverse events were also observed in the studies, including weight gain or loss, changes in appetite, fatigue, somnolence, changes in mood, and increase in seizure frequency. While decreased appetite, anorexia, diarrhea, drowsiness, fatigue, movement disorders, somnolence, and vomiting were common adverse events amongst all product types, some adverse events reported were specific to the pharmaceutical and nonpharmaceutical preparations. Pharmaceutical preparations led to increase in seizures, status epilepticus, and weight loss, while nonpharmaceutical preparations resulted in depression and mood changes, increased appetite, weight gain, and memory loss.

The authors concluded there is a lack of evidence on the efficacy and safety of medicinal cannabis for many conditions, and caution against extrapolating from drug-resistant epilepsy to other conditions. For example, the scoping review found no pediatric studies regarding pain, despite pain being a well-studied area in adults. The authors called for more studies that look at dosing, efficacy, and short- and long-term safety outcomes for other pediatric conditions.

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 U.S.-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 four-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 two to four weeks through week 16 and every two to 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 ≥50%, ≥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.

**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 was randomized
to CBD oral solution (n=86) or placebo (n=85) from 24 clinical sites in the U.S., 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.

Uliel-Sibony S, Hausman-Kedem M, Fattal-Valevski A, Kramer U. Cannabidiol-enriched oil in children and adults with treatment-resistant epilepsy-does tolerance exist? *Brain Dev.* **2021 Jan;43(1):89-96. doi: 10.1016/j.braindev.2020.06.018. Epub 2020 Jul 24. PMID: 32713661.**

In this prospective study, authors evaluated the long-term effectiveness of cannabidiol (CBD)-enriched oil for the treatment of refractory epilepsy, and assessed the development of tolerance to its anti-seizure effect. Patients were treated with cannabis oil extract (CBD/tetrahydrocannabinol [THC] ratio of 20:1. Tolerance was defined as either the need to increase the dose by ≥30% due to reduced treatment efficacy or as an increase of ≥30% in mean monthly seizure frequency in patients treated for at least three months with no change in other anti-seizure medications. Average follow-up time was 19.8 months (range 3-45). Average CBD dose was 11.3 (4-38) mg/kg/day. Tolerance was observed in 21 (25%) patients after an average duration of 7.3 months of CBD-enriched oil treatment. This study is the first to show the possible development of tolerance to CBD, and may have treatment implications for both children and adults.

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 (MS)

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-9-THC and 2.5 mg CBD. An early trial (Wade, Robson et al. 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 eight sprays within any three-hour period (Collin, Ehler et al. 2010) and 12 (Novotna, Mares et al. 2011, Freidel, Tiel-Wilck et al. 2015, Leocani, Nuara et al. 2015) or 24 (Collin, Ehler et al. 2010) within a 24-hour period. However, when the trials were carried out, patients typically came to an average daily dose of approximately seven to 15 sprays per day (Wade, Makela et al. 2004, Collin, Davies et al. 2007, Collin, Ehler et al. 2010, Novotna, Mares et al. 2011, Tomassini, Onesti et al. 2014, Leocani, Nuara et al. 2015). Most nabiximols trials in MS patients have lasted three 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, Makela et al. 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), 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 ≥30% reduction in spasticity by three 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 (brand name Cannador - a TBD:CBD ratio of approximately 2:1). Both the CAMS study (Zajicek, Fox et al. 2003) and the MUSEC study (Zajicek, Hobart et al. 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 three 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, Heinzel-Gutenbrunner et al. 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 two-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, Fox et al. 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 three-year CUPID trial (Zajicek, Ball et al. 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, Henn et al. 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, Luz et al. 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, Robson et al. 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, Luz et al. 2007). 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. Fifteen patients completed the six weeks: four dropped out because of increased pain and the other six 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 seven patients because of supply problems, but the daily dose achieved after dosing adjustment for those seven 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, Robson et al. 2003) carried out a small placebo-controlled crossover trial of nabiximols (Sativex) on patients with neurological disorders and troublesome symptoms (Wade, Robson et al. 2003) that indicates the need to set a maximum dose within specified time

periods. Twenty-four patients with a variety of neurologic disorders, including four 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 eight sprays within 70 minutes. Because of side effects this was changed to four sprays over two 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. One hundred eighty-nine adult patients from eight centers in UK and four in Romania were randomized in a 2:1 ratio to nabiximols or placebo for a total of six 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 two 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 (seven-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 ≥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, six from the active treatment group and two from the placebo group.

Collin C, Ehler E, Waberzinek G, et al. A doubleblind, randomized, placebo-controlled, parallel group 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 three-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 five 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 11-point 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 four 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 spay 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, and two from Switzerland) up to February 2015. Reported patients in the UK represented 22% of the 3,493 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 (±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 six and 12 months. After six 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. Three hundred 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 three 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 three 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 eight patients with four considered related to nabiximols treatment.

Freidel M, Tiel-Wilck K, Schreiber H, Prechtl 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 four–six-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 five 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 five 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 (seven patients at baseline down to one at the final visit). Lastly, 13% of patients (four 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. Fifteen patients completed the six weeks: four dropped out because of increased pain and the other six 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 seven patients because of supply problems, but the daily dose achieved after dosing adjustment for those seven 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 two weeks, suggesting that treatment can be discontinued promptly in nonresponders. Mean dosage was four sprays per day with a range of one 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 five 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 four 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 >=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 10 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 four-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 four-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, three 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 anti-spasticity drugs. The 1,615 patients 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 (1,432 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 three months (n=889) 311 (35%) reached 30% improvement (19% of initial study population) and among those still taking Sativex at six months (n=593) 225 (42.5%) reached 30% improvement (14% of initial study population). Mean dose (SD) for those still taking Sativex at six 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 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. 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 three-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 three 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 six-week study – for approximately eight 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 18 (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 three-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 three-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 three 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 two-week washout period after which time participants crossed over into the other condition for a three-week period (same measures were collected again after this crossover treatment period, and it was followed by another two-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. Heinzel-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 seven 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 two-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. Four hundred thirty-three patients were recruited (98% from 34 centers in Italy) for the planned three months of data collection. At one month only the 349 patients (81%) that had achieved ≥20% reduction in 0-10 numerical rating scale of spasticity continued on with the study. A total of 281 patients completed the three months of follow-up, with 86 achieving ≥30% spasticity reduction (20% of the initial cohort). Mean dose was similar among those who made it to the end of the three-month study, whether they achieved the ≥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 eight sprays within 70 minutes. Because of side effects, this was changed to four sprays over two 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. One hundred sixty patients from three 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 (seven sprays) within a three-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.
One hundred thirty-seven 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, eight
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 ages 18-64 with MS by McDonald criteria, stable disease for the last six months and troublesome and ongoing muscle stiffness for at least three 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 one to two weeks, two-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 three 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 last one treatment emergent adverse events: 98% in active treatment group and 74.6% in the placebo group. In addition, 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, confused 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, placebo-controlled 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. The study included 493 subjects ages 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 two weeks and four weeks from when they began taking the study drug for adverse event screening and drug monitoring and dose adjustment. Assessment visits were held at three months, six months, and then every six months to 36 months. Results showed no overall treatment effect on clinical disease course. 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

To date, five clinical studies of cannabis or cannabinoids for treatment of inflammatory bowel disease have been published. Early studies showed tolerance for treatment, but no significant effects. One 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, Bar-Lev Schleider et al. 2013). A second study 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, Mechulam et al. 2017). 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, Iqbal et al. 2018).

While more recent results have shown CBD to be more effective than placebo for reducing symptoms, no studies have yet shown reduction in inflammatory markers. One randomized, double-blind study assessed the effect of cannabidiol [CBD]-rich cannabis oil for induction of remission in Crohn's disease (CD) (Naftali, Bar-Lev Schleider et al. 2021). Fifty-six patients with

mild-to-moderate CD received eight weeks of treatment in oral form – either cannabis oil containing 160/40 mg/ml cannabidiol/ tetrahydrocannabinol [CBD/THC] or placebo. Patients started with a dose of 2 drops/day, equivalent to 16 mg CBD and 4 mg THC, and increased it gradually. The final volume taken per administration in the study group was 10 drops, equivalent to 0.5 ml, and in the placebo group 15 drops, equivalent to 0.75 ml, p = 0.004. This corresponds to a final median dose taken by the study group of 80 mg CBD and 20 mg THC. Results showed that Crohn's Disease Activity Index and quality of life scores favored the cannabis group over placebo. However, significant changes in inflammatory markers or endoscopic scores were not seen. As a result, the authors recommended that cannabis for CD should be reserved for clinical trials and research purposes.

A similar RCT (Naftali, Bar-Lev Schleider et al. 2021) assessed the effect of THC-rich cannabis in improving clinical and inflammatory outcomes in ulcerative colitis patients. Thirty-two patients were randomized to treatment (smoked medical cannabis cigarettes, 16% THC (80mg)) or placebo (smoked cigarettes of dried cannabis flower where the THC had been removed and contained <0.4% THC). Patients were required to start gradually, smoking half a cigarette (0.25gr) in the first day and increasing by 0.25 gr until a final dose of 0.5 gr twice daily was reached. The study did not report whether all participants reached the target final dose. Measures included the Lichtiger index, quality of life, and Mayo endoscopic score. Results showed improvements in Lichtiger index and quality of life for cannabis over placebo, but significant anti-inflammatory improvement was not seen. Minor side effects were reported by 15-45% of participants (cough, dizziness, confusion, difficulty to stop use, behavior change, restlessness, shortness of breath) but did not lead to cessation of treatment in any patients. The authors called for additional research using different modes of administration as well as different cannabinoid compounds (such as CBD).

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 nine 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. Fifteen 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. Twenty-one 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% TCH 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 eight 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 eight 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 eight. 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.

Naftali T, Bar-Lev Schleider L, Almog S, Meiri D, Konikoff FM. Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial. J Crohns Colitis. 2021 Nov 8;15(11):1799-1806. doi: 10.1093/ecco-jcc/jjab069. PMID: 33858011.

This randomized, double-blind study was conducted at one clinic site, assessed the effect of cannabidiol [CBD]-rich cannabis oil for induction of remission in Crohn's disease (CD). Fifty-six patients with mild-to-moderate CD, aged 34.5 ± 11 years, received eight weeks of treatment in oral form – either cannabis oil containing 160/40 mg/ml cannabidiol/ tetrahydrocannabinol [CBD/THC] or placebo. Thirty patients were in the cannabis group and 26 patients were in the placebo group.

Patients started with a dose of two drops/day, equivalent to 16 mg CBD and 4 mg THC, and increased it gradually. The final volume taken per administration in the study group was 10 drops, equivalent to 0.5 ml, and in the placebo group 15 drops, equivalent to 0.75 ml, p = 0.004. This corresponds to a final median dose taken by the study group of 80 mg CBD and 20 mg THC.

Disease activity was determined by the Crohn's Disease Activity Index [CDAI] ≥200 and Simple Endoscopic Score for Crohn's Disease [SES-CD] ≥ 2. CDAI and SES-CD were assessed before and after treatment.

Results showed that CDAI reduced more for the cannabis group (282 before treatment to 166 after treatment) than for the placebo group (264 to 237) (p<0.05). The median quality of life score increased from 74 (both groups) to 91 and 75 for cannabis and placebo groups, respectively (p=0.004). Endoscopic disease activity (SES-CD) improved one point for each group before and after treatment (10 to 11 for cannabis; seven to eight for placebo), but the difference between groups was not significant (p=0.75). In addition, inflammatory markers (C-reactive protein, calprotectin) remained unchanged for either group.

A sub-group of seven participants provided blood plasma samples to assess uptake of medical cannabis. Blood samples for THC and CBD levels were drawn before and 10, 20, 60, 120, 180, and 240 min after cannabis consumption. Results showed that the oral delivery of CBD and THC was characterized by a latency period of 1 h following delivery, slow absorption and low CBD and THC peak plasma concentrations occurring within about 2 h.

The only adverse symptom reported was memory loss. None of the patients reported trouble stopping the treatment at the end of the study.

The authors acknowledge that CBD-rich cannabis extract was well absorbed, well tolerated, and induced symptomatic improvement in the study population. However, they cautioned that significant changes in inflammatory markers or endoscopic scores were not seen, and recommended that cannabis for CD should be reserved for clinical trials and research purposes.

Naftali T, Bar-Lev Schleider L, Scklerovsky Benjaminov F, Konikoff FM, Matalon ST, Ringel Y. Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial. *PLoS One*. **2021 Feb 11;16(2):e0246871. doi: 10.1371/journal.pone.0246871. PMID: 33571293; PMCID: PMC7877751.**

This single-center, prospective, randomized, double-blind, placebo-controlled, parallel-arm clinical study aimed to assess the effect of cannabis in improving clinical and inflammatory outcomes in ulcerative colitis patients. The protocol included a two-week screening period to evaluate for baseline symptoms, an eight-week treatment period, and a two-week follow-up period after the intervention was discontinued. Non-responders were offered to participate in an open arm eight-week treatment period.

Male and female patients with mild to moderate ulcerative colitis (UC) diagnosed at least three months prior to enrollment were enrolled in the study (n=32). The average age was 30 years (range 20-80). Just under half were female (43%).

Treatment consisted of smoked medical cannabis cigarettes. The content of each cigarette was 16% THC (80mg). Patients were required to start gradually, smoking half a cigarette (0.25gr) in the first day and increasing by 0.25 gr until a final dose of 0.5 gr twice daily was reached. Note: this final dose is beyond the recommended amount by most guidelines, especially for cannabis-naive users (MacCallum and Russo 2018). The study did not report whether all participants reached the target final dose. The control arm smoked cigarettes of dried cannabis flower where the THC had been removed and contained <0.4% THC.

Measures included the Lichtiger index, a clinical index used to help rate the severity of UC and to determine if a treatment is effective or not. A score of >10 points defines the acute severe colitis, whereas the response to medical treatment is defined by a score less than 10 two days consecutively, or a decrease of at least 3 points when comparing with the initial score. Other measures included quality of life and Mayo endoscopic score.

Results showed that the Lichtiger index improved in the cannabis group from 10.9 to 5 (p<0.000), and in the placebo group from 11 to 8 (p = 0.15). (Between group comparison was significant, p < 0.001.) Quality of life measures improved in the cannabis group from 77±4 to 98±20 (p = 0.000) but not in the placebo group (78±3 at week 0 and 78±17 at week eight; p = 0.459 (between-group comparison was significant, p = 0.007). Mayo endoscopic score changed in the cannabis group from 2.13±1 to 1.25±2 (p = 0.015) and in the placebo group from 2.15±1to 1.69±1 (p = 0.367) (between-group comparison was not significant, p = 0.17).

Between 15-45% of participants reported minor side effects (cough, dizziness, confusion, difficulty to stop use, behavior change, restlessness, shortness of breath). These side effects did not lead to cessation of treatment in any patients.

The authors concluded short-term treatment with THC-rich medical cannabis was helpful with inducing clinical remission and improving quality of life, but cautioned that significant anti-

inflammatory improvement was not seen. They did find associated reduction in mucosal inflammation, and called for additional research using different modes of administration as well as different cannabinoid compounds (such as CBD).

Terminal Illness

Terminal illness, with a probable life expectancy of under one year, is a qualifying medical condition 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 May 2024. For details, see HOPE Consortium Trial to Reduce Pain and Opioid Use in Hemodialysis (HOPE) (https://www.clinicaltrials.gov/ct2/show/NCT04571619?cond=reduction+of+pain+and+reduction +in+opioid+utilization&cntry=US&state=US%3ACT&draw=2&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 three of the controlled trials are longer than five 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 Medical Cannabis for Non-Cancer Pain: A Systematic Review (PDF) (https://www.health.state.mn.us/people/cannabis/docs/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 (Wade, Makela et al. 2004, Rog, Nurmikko et al. 2005, Blake, Robson et al. 2006, Nurmikko, Serpell et al. 2007, Selvarajah, Gandhi et al. 2010, Langford, Mares et al. 2013, Serpell, Ratcliffe et al. 2014) or 1:1 THC:CBD plus additional active treatment arms of mostly THC extraction product (Wade, Robson et al. 2003, Berman, Symonds

et al. 2004, Notcutt, Price et al. 2004) and mostly CBD extraction product (Wade, Robson et al. 2003, Notcutt, Price et al. 2004) vs. placebo. There are also two open-label long-term studies of Sativex (Rog, Nurmikko et al. 2007, Hoggart, Ratcliffe et al. 2015). 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 six 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, Hobart et al. 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 six to eight sprays per day (Hoggart, Ratcliffe et al. 2015) and 6.5 to 7.5 sprays per day (Rog, Nurmikko et al. 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 nabiiximols treatment group in the range of 5 to 25%.

Three of the trials studied oral dronabinol, synthetic THC, vs. placebo (Svendsen, Jensen et al. 2004, Narang, Gibson et al. 2008, Schimrigk, Marziniak et al. 2017). Two of them reported an average dose after titration (Svendsen, Jensen et al. 2004): 21 patients at the study maximum of 10 mg/day, three patients at 7.5 mg/day, and one patient at 5 mg per day; (Schimrigk, Marziniak et al. 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 11-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 two-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 eight 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 11-point Box Scale (BS-11) where "0" represented the "Best Imaginable" and 10 the worst. The average score during the last seven days of treatment was compared to the average during the seven-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 eight 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 three from the placebo group. There were no serious adverse events in the active treatment group and two in the placebo group.

Hoggart B, Ratcliffe Sj, 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. Four hundred thirty-nine 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 eight sprays per three-hour period and 24 sprays per 24 hours. Mean dose during months 1-9 was reported as six to eight sprays per day. Eighty-four percent 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%. Seventy-eight percent 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. Twenty-three percent 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) was 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 four-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 (three 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, Nedeljikovic 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 four-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 six 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 three treatment options were separated by a minimum of three 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 eight 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, and dry mouth. All were clearly more common with dronabinol than placebo except for sleepiness. All resolved within two hours except for sleepiness and drowsiness, which each lasted two to three hours. The authors considered side effects for two subjects "adverse events:" one subject reported anxiety, tremors, dizziness, and inability to concentrate that resolved within three 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 four, 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 (two to eight 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 one to eight sprays as a single dose. Average daily dose of each of the three active medications was approximately eight 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. The study involved 125 patients (74 women/51 men; average age 53 years) who 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 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 included 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 four 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 Δ9 -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 four weeks and again every eight 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. The study included 240 patients who 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, six 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.**

Three hundred three 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. Fifty-seven 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 ≥ six 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 eight sprays per three 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 ≥ 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).

Svendsen 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).

Twenty-five patients ages 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 three 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 two 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 percentile = 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. Ninety-six percent of participants experienced side effects during dronabinol treatment vs. 46% during placebo treatment. Four patients reduced dosage of dronabinol because of intolerable side effects (three 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 is 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 were 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 Revermead 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 eight 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 two-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. One hundred sixty patients from three 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 (seven sprays) within a three-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 ages 18-64 with MS by McDonald criteria, stable disease for the last six months and troublesome and ongoing muscle stiffness for at least three 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 one to two weeks, two-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 three 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 last one treatment emergent adverse events: 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, confused 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 2019, with results summarized below. 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 also included in this section. One used THC administered under the tongue (Roitman, Mechoulam et al. 2014) and one used small amounts of CBD in a combination of capsules and oral liquid spray (Elms, Shannon et al. 2019).

In the first observational study, 10 patients with PTSD received 5 mg THC dissolved in olive oil under the tongue twice daily for three weeks (Roitman, Mechoulam et al. 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, Mechoulam et al. 2014).

In the second observational study, small doses of CBD was taken in capsule or oral spray form for at least eight weeks. In all but one of the 11 patients for whom full study was available, PCL-5 score at eight weeks was lower than PCL-5 score at baseline (Elms, Shannon et al. 2019).

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 (Bonn-Miller, Sisley et al. 2021). Participants were permitted to smoke up to 1.8 grams of cannabis per day, with average amounts per day ranging from 0.4 grams – 0.8 grams, depending on the condition. Recruitment began January 2017, and the study was completed January 2019 with findings published in 2021. Overall, investigators did not find a significant difference in reported PTSD symptoms between the three treatment arms and placebo. No severe treatment-related adverse effects were reported. The study was funded by the state of Colorado's pool of money to support research, derived from taxes on retail marijuana. See Pilot Study of the Safety and Efficacy of Four Different Potencies of Smoked Marijuana in 76 Veterans With PTSD (https://www.clinicaltrials.gov/ct2/show/NCT02759185?cond=PTSD+cannabis).

The second trial, a triple-blinded cross-over study, sought to compare 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. The study was able to enroll six participants total who were allowed to vaporize up to 2 grams of plant material per day as needed. The study was completed in March 2019. As of March 2022, no results have been posted. The sponsor for this study was Tilray, a Canadian marijuana producer. See Evaluating Safety and Efficacy of Cannabis in Participants With Chronic Posttraumatic Stress Disorder (https://www.clinicaltrials.gov/ct2/show/results/NCT02517424?cond=Evaluating+Safety+and+Efficacy+of+Cannabis+in+Participants+With+Chronic+Posttraumatic+Stress+Disorder&draw=2&rank=1).

Bonn-Miller MO, Sisley S, Riggs P, Yazar-Klosinski B, Wang JB, Loflin MJE, Shechet B, Hennigan C, Matthews R, Emerson A, Doblin R. The short-term impact of 3 smoked cannabis preparations versus placebo on PTSD symptoms: A randomized cross-over clinical trial. *PLoS One.* 2021 Mar 17;16(3):e0246990. doi:10.1371/journal.pone.0246990. PMID: 33730032; PMCID: PMC7968689.

The aim of this double-blind, cross-over study was to collect preliminary data on the safety and potential efficacy of three active concentrations of smoked cannabis (i.e., High THC = approximately 12% THC and < 0.05% CBD; High CBD = 11% CBD and 0.50% THC; THC+CBD = approximately 7.9% THC and 8.1% CBD) compared to placebo (< 0.03% THC and < 0.01% CBD) in the treatment of PTSD among military veterans. Participants were adults who met DSM-5 criteria

for PTSD, who reported symptoms for at least six months (note: index trauma did not need to be related to military service), and who had a PTSD of at least moderate severity (CAPS-5 score of =>25 at baseline).

Participants were randomly assigned to receive three weeks of either active treatment or placebo in Stage 1 (N = 80, 20 per group), and then were re-randomized after a two-week washout period to receive one of the other three active treatments in Stage 2 (N = 74). Re-randomized group sizes were: High THC (n = 29), High CBD (n = 27), and THC+CBD (n = 18). The study provided participants a total of 37.8 grams (1.8 grams/day) for the three-week ad libitum treatment period along with a metal pipe for treatment delivery (smoked). Participants were asked to use only study-provided cannabis, and return any remaining study cannabis that was not used each week. Total amount used (average per day) was calculated by weighing the returned product. Between stages (wash-out period) participants were asked to refrain from any cannabis use. After the two-week wash-out period, participants were re-randomized into one of three active treatment groups. All study participants were provided the option to enroll in an open label extension (Stage 3) with the cannabis of their choice in the same amount they returned unused in Stages 1 and 2 so participants had no disincentives to returning unused amounts. (Stage 3 results are reported elsewhere)

Mean (SD) grams of smoked cannabis/placebo used by each treatment group in Stage 1 (21 days total) were as follows: placebo (M = 8.4, SD = 10.1), High THC (M = 14.6, SD = 10.4), High CBD (M = 14.3, SD = 13.0), THC+CBD (M = 8.2, 6.8) (between-group differences were not significant). In stage 2, there was a significant group difference in total grams of smoked cannabis. Participants in the THC+CBD group used significantly more cannabis (M = 17.6, SD = 10.6), compared to participants randomized to High THC (M = 10.7, SD = 10.9), or High CBD (M = 9.3, SD = 10.5).

The primary outcome measure was improvement in PTSD symptom severity from baseline to end of treatment in Stage 1. No significant difference in change in PTSD symptom severity was found between the active cannabis concentrations and placebo by the end of Stage 1 as measured by CAPS-5, PCL-5, IDAS Social Anxiety, IDAS Depression, IPF, and ISI.

Number of participants who reported at least one AE did not significantly differ by treatment group in either Stage 1 (p = .38) or Stage 2 (p = .27). The most comment adverse events reported were cough (12.3%), followed by throat irritation (11.7%) and anxiety (10.4%). The proportion of participants who received an active treatment that reported at least one treatment-related adverse event was 62% (phase 1) and 61% (phase 2). One participant (THC+CBD) discontinued treatment during the introductory session in Stage 1 due to an AE, and two participants discontinued treatment during the introductory session in Stage 2 due to an AE (High CBD and High THC conditions). In total, 13 participants terminated treatment early due to an adverse event (8.4%). Across both Stages, 13 total participants terminated from the study early due to an AE (8.4%). One participant who received CBD in Stage 1 (5.0%) reported treatment-related suicidal ideation. One participant from each treatment condition (3.6% - 5.9%) reported treatment-related suicidal ideation in Stage 2.

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 four and eight weeks were scheduled to assess dosing, PTSD symptoms (PCL-5 questionnaire), and side effects. At four weeks, 18 remained on CBD and completed the PCL 5 questionnaire. At eight weeks this number was 14. Of the 14, 11 completed both the four-week and the eight-week assessments. The paper focuses on these 11 patients. Average age was 40 years (range: 22-69); eight 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 eight weeks mean dose was 49 mg/day (range: 2-100).

At four weeks mean PCL-5 score dropped (improved) from 51.82 to 40.73, with an increased score for only one patient. At eight weeks, average score dropped further, to 37.14. Though three patients had a higher score at eight weeks than at four weeks, all but one of the patients had a lower score at eight 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 Δ9-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 five, road accident in three, and assault/rape in two. All were receiving stable psychotropic medication for at least four 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 with results published in 2021 (Aran, Harel et al. 2021); 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. The study recruited 150 patients who were assigned to one of three olive oil-based solutions for a three-month treatment period: 1) pure CBD and pure 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 outcomes assessed were changes on the Home Situations Questionnaire-Autism Spectrum Disorder (HSQ-ASD) and disruptive behaviors (measured by the CGI-I) from baseline to three months. Investigators did not find any difference among groups regarding changes in the HSQ-ASD (primary-outcome) and APSI (secondary-outcome) scores. However, for the whole-plant extract group compared to placebo, disruptive behavior (measured by the CGI-I and a co-primary outcome) was improved ($p = 0.005$) and the median SRS (secondary-outcome) was improved ($p = 0.009$). No serious adverse events were reported. Common adverse events reported were somnolence and decreased appetite.

The trial now recruiting patients is a double blind, placebo-controlled clinical trial of the cannabinioid, cannabidivarin (CBDV), 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 CBDV 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 August, 2022. See Cannabidivarin (CBDV) vs. Placebo in Children with Autism Spectrum Disorder (ASD) (https://www.clinicaltrials.gov/ct2/show/NCT03202303).

Two open-label prospective studies (Bar-Lev Schleider, Mechoulam et al. 2018, Barchel, Stolar et al. 2018) and a retrospective study (Aran, Cassuto et al. 2019) – 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 (2019) was 10 mg/kg/day.

Aran A, Cassuto H, Lubotzky A, Wattad N, Hazan E. Brief Report: Cannabidiol-Rich Cannabis in Children with Autism Spectrum Disorder and Severe Behavioral Problems-A Retrospective Feasibility Study. *J Autism Dev Disord.* **2019 Mar;49(3):1284-1288. doi: 10.1007/s10803-018-3808-2. PMID: 30382443.**

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%).

Aran A, Harel M, Cassuto H, Polyansky L, Schnapp A, Wattad N, Shmueli D, Golan D, Xavier Castellanos F. Cannabinoid treatment for autism: a proof-of-concept randomized trial. Molecular Autism (2021) 12:6 https://doi.org/10.1186/s13229-021-00420-2

This "proof of concept" double-blind, randomized, placebo-controlled study assessed the effectiveness of two cannabis formulations to treat disruptive behaviors in children and young adults (ages 5-21) with Autism Spectrum Disorder (ASD). It was carried out in Israel. 150 patients were assigned to one of three olive oil-based solutions or placebo for 12 weeks, followed by a four-week washout and predetermined crossover for another 12 weeks. Treatment conditions were:

1. Whole plant CBD (ratio of CBD/THC was 20:1): n=50

2. Pure cannabinoids (ratio of CBD/THC was 20:1): n=50

3. Placebo: n=50

In each treatment period, starting dose was 1 mg/kg/day CBD (and 0.05 mg/kg/day THC). The dose was increased by 1 mg/kg/day CBD (and 0.05 mg/kg/day THC) every other day up to 10 mg/kg body weight per day CBD (and 0.5 mg/kg/day THC) for children weighing 20–40 kg or 7.5 mg/kg/day CBD (and 0.375 mg/kg/day THC) for weight>40 kg (to a maximum of 420 mg CBD and 21 mg THC per day) divided into 3 daily doses. Any ongoing stable medication was continued. At the end of each treatment period, the study treatment was gradually decreased over two weeks.

Primary outcomes assessed were changes on the Home Situations Questionnaire-Autism Spectrum Disorder (HSQ-ASD) and disruptive behaviors (measured by the CGI-I) from baseline to three months. Secondary measures included the APSI and SRS. Investigators did not show any difference between groups regarding changes in the HSQ-ASD (primary-outcome) and APSI

(secondary-outcome) scores. However, for the whole-plant extract group compared to placebo, disruptive behavior (measured by the CGI-I and a co-primary outcome) was improved. Forty-nine percent of 45 participants who received whole-plant cannabinoids responded (either much or very much improved) compared with 21% of 47 on placebo (p=0.005). Of the 45 participants who received pure cannabinoids, 38% responded, which was not significantly higher than placebo (p=0.08). Differences between whole-plant extract vs. pure cannabinoids were not significant. The median SRS-2 score (secondary-outcome) was also statistically significantly higher for whole-plant extract recipients than placebo. Median total score improved by 3.6 points after placebo (n=36) versus 14.9 on whole-plant extract (n=34; p=0.009) and 8.2 on pure cannabinoids (n=28; p=0.80).

No serious adverse events were reported. Common adverse events reported were tiredness, anxiety, somnolence and decreased appetite, and euphoria.

The investigators noted study limitations included: 1) lack of pharmacokinetic data, 2) wide range of ages and 3) wide range of functional levels among participants.

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* 2018 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 were 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 five 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 six-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, Prasad et al. 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 apnea-hypopnea index (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 six 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 two 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 ≥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 (Volicer, Stelly et al. 1997, van den Elsen, Ahmed et al. 2015, van den Elsen, Ahmed et al. 2015) used 1.5 to 5.0 mg THC in divided doses daily. Each found the treatment well tolerated, but only one (Volicer, Stelly et al. 1997) found a beneficial treatment effect (reduced agitated behavior and decrease in negative affect). The clinical trial, now recruiting patients is set to be completed in May 2023. See Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (https://www.clinicaltrials.gov/ct2/show/NCT02792257?cond=Trial+of+Dronabinol+Adjunctive+Treatment+of+Agitation+in+Alzheimer%E2%80%99s+Disease&draw=2&rank=1). It 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 (Walther, Mahlberg et al. 2006, Shelef, Barak et al. 2016) 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.

One recent meta-analysis examined six studies (N=251) (Ruthirakuhan, Lanctot et al. 2019). While there was no effect of cannabinoids on agitation, there was a trend for greater difference in agitation with synthetic cannabinoids compared to THC. Sedation was much greater with cannabinoids compared to placebo. The authors note that existing evidence for efficacy of cannabinoids on agitation and aggression is inconclusive, although there is a potential benefit of synthetic cannabinoids that should be investigated further.

Ruthirakuhan M, Lanctôt KL, Vieira D, Herrmann N. Natural and Synthetic Cannabinoids for Agitation and Aggression in Alzheimer's Disease: A Meta-Analysis. *J Clin Psychiatry.* **2019 Jan 29;80(2):18r12617. doi: 10.4088/JCP.18r12617. PMID: 30753761.**

This meta-analysis investigated the efficacy of cannabinoids on agitation and aggression in patients with Alzheimer's disease (AD). It included double-blind, placebo-controlled studies investigating the effect of cannabinoids on agitation in patients with AD. Six studies (N = 251 participants) were included. Data on demographics, study setting, trial length, intervention, outcomes, and dropouts were extracted.

There was no effect of cannabinoids as a group on agitation (standard mean difference: -0.69, P = .10), though there was significant heterogeneity (χ^2_6 = 43.53, P < .00001, I^2 = 86%). There was a trend for greater difference in agitation with synthetic cannabinoids over tetrahydrocannabinol (χ^2_1 = 3.05, P = .08). Cannabinoids had a larger effect on agitation with greater cognitive impairment compared to placebo (B = 0.27, t_6 = 2.93, P = .03). Sedation was significantly greater with cannabinoids compared to placebo (risk ratio = 1.73, P = .04). There were no differences in the occurrence of adverse events or dropouts due to an adverse event between treatment groups.

The authors point out that while there is inconclusive evidence for the efficacy of cannabinoids to reduce agitation and aggression in patients with Alzheimer's Disease, there may be a potential benefit in using synthetic cannabinoids (compared to THC). They highlight the need to monitor safety, and sedation, in particular.

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 three consecutive days, followed by a four-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 patinets 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 was 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 three patients tolerated a dose increase while the other seven 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 two weeks. Motor activity counts were aggregated daily within three different data collection periods for the duration of the study: evening (3 p.m. – 9 p.m.), period (6 a.m.-9 p.m.). Motor activity counts during the last five 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.

Chronic Pain

Much of the literature on dosing of medical cannabis for chronic pain is summarized in the section . Additional studies focusing on chronic pain in patients who do not have cancer are included here. There has been a recent increase in interest in the use of cannabinoids in the treatment of chronic non-cancer-related pain due to the movement away from opiates as an analgesic. Many of the articles reviewed for this section were observational in nature, and collected self-reported pain measures from patients enrolled in medical cannabis programs, but did not provide dosing information (Safakish, Ko et al. 2020, Sturgeon, Khan et al. 2020, Aviram, Pud et al. 2021, Coughlin, Ilgen et al. 2021, Sznitman, Vulfsons et al. 2021).

One prospective observational cohort study (Meng, Page et al. 2021) followed 1,000 patients with a chronic disease authorized for medical cannabis in Canada. Between 75-80% of participants reported using <1 to 2g of cannabis daily throughout the study period, with <1% of study participants using more than 5g of cannabis in any form at any time point. While participants in the study reported improvements with pain intensity, pain-related interference, quality of life, and general health symptoms over time, this finding is counter to trends reported elsewhere that the effects of cannabis use wane over time. The authors point to the high rate of attrition over time (both response and use of cannabis) and suggest that cannabis may only be effective at relieving chronic pain for a subset of patients.

Another prospective observational study followed 367 patients with fibromyalgia over six months (Sagy, Bar-Lev Schleider et al. 2019). Patients selected the strain of cannabis and mode of administration (oil vs. inflorescence/whole flower). Dosing began at sub-therapeutic levels (e.g.,

one drop of 15% THC oil, one breath of a 0.75g cannabis cigarette every three to four hours) and patients were instructed to increase doses gradually (e.g., by one drop per day) until therapeutic effect was reached. At six months, the majority (81.1%) reported an improvement in their fibromyalgia condition. Of those reporting sleep problems or depression symptoms at baseline, the vast majority (over 80%) reported improvements. Finally, only 2.7% of patients reported good or very good quality of life prior to treatment initiation. At six months, 61.9% reported their quality of life was good or very good. Adverse events included dizziness, dry mouth, nausea/vomiting, and hyperactivity. None were reported by more than 8% of patients.

There has been one relatively small (N=20) randomized, double-blind, placebo-controlled four-way crossover study, in which the authors tested the analgesic effects of inhaled pharmaceutical grade cannabis on several types of pain (van de Donk, Niesters et al. 2019). Study participants were female, age 18 or older diagnosed with fibromyalgia (FM) who reported a pain score >5 (on a 0-10 scale) for most of the day. The study design had participants in each arm inhaling a single vaporized dose of cannabis and then THC and CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores, and drug high were measured for three hours.

The four treatment arms were:

- Arm 1: Bedrocan cannabis with a high THC/low CBD content;

- Arm 2: Bedrolite cannabis with a high CBD/low THC content;

- Arm 3: Bediol cannabis with a combined high THC/high CBD content; and

- Arm 4: placebo "cannabis" that was similar in smell, appearance to cannabis.

Key findings included that none of the treatments had an effect greater than placebo on spontaneous pain scores. However, compared to placebo responder rates, significantly more patients responded to Bediol (containing high doses of THC and CBD) with a decrease in spontaneous pain by 30%; the two other active treatments had response profiles not different from placebo. The authors also noted the reduction in spontaneous pain scores was correlated with the magnitude of the drug high. Adverse events for the three active arms of the study included effects related to the inhalation of cannabis (coughing during inhalation in 65%-70%, sore throat and bad taste during inhalation in 25%-35% of participants). Effects not related to inhalation of cannabis included: drug high in 40% to 80%, dizziness in 15% to 20%, and nausea in 5% to 30% of participants. There were no differences in frequency of adverse effects between the three active treatment arms, and no serious adverse events occurred.

In a phase 1 clinical trial, Eisenberg et al. (2014) explored the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a novel portable thermal-metered-dose inhaler for cannabis in a cohort of eight patients suffering from chronic neuropathic pain and on a stable analgesic regimen including medicinal cannabis. Patients were included if they had ''neuropathic pain of any type for at least 3 months,'' with two of the cases due to lumbosacral radiculopathy. Dosing: patients inhaled a single 15.1 ± 0.1 mg dose of cannabis using the Syqe Inhaler device. The authors cite a 45% reduction in pain intensity at 20 minutes after inhalation (p = 0.001), returning to baseline within 90 minutes. The only reported adverse event was lightheadedness, which lasted 15–30 minutes and required no intervention. The authors pointed to the need for additional research to standardize dosing regimens for inhaled medical cannabis.

Eisenberg E, Ogintz M, Almog S. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. *J Pain Palliat Care Pharmacother*. **2014 Sep;28(3):216-25. doi: 10.3109/15360288.2014.941130. Epub 2014 Aug 13. PMID: 25118789.**

This Phase 1 clinical trial explored the pharmacokinetics, safety, tolerability, efficacy, and ease of use of a novel portable thermal-metered-dose inhaler (tMDI) for cannabis in a cohort of eight patients suffering from chronic neuropathic pain and on a stable analgesic regimen including medicinal cannabis. Participants (n=8) were patients with chronic neuropathic pain for at least three months.

Patients inhaled a single 15.1 ± 0.1 mg dose of cannabis using the Syqe Inhaler device. Blood samples for $\Delta(9)$-tetrahydrocannabinol (THC) and 11-hydroxy-$\Delta(9)$-THC were taken at baseline and up to 120 minutes. Pain intensity (0-10 VAS), adverse events, and satisfaction score were monitored following the inhalation.

A significant 45% reduction in pain intensity was noted 20 minutes post inhalation (P=.001), turning back to baseline within 90 minutes.

The study reported lightheadedness as an adverse event, lasting 15-30 minutes and requiring no intervention.

First L, Douglas W, Habibi B, Singh JR, Sein MT. Cannabis Use and Low-Back Pain: A Systematic Review. *Cannabis Cannabinoid Res.* **2020 Dec 15;5(4):283-289. doi: 10.1089/can.2019.0077.**

This review focuses on the association between cannabis and low-back pain by performing a systematic literature review via several online databases. Six studies were included in the review. The authors conclude there is a significant lack of quality evidence regarding the role of cannabinoid products in the treatment of low-back pain.

Meng H, Page MG, Ajrawat P, Deshpande A, Samman B, Dominicis M, Ladha KS, Fiorellino J, Huang A, Kotteeswaran Y, McClaren-Blades A, Kotra LP, Clarke H. Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients. *Can J Anaesth.* **2021 May;68(5):633-644. English. doi: 10.1007/s12630-020-01903-1. Epub 2021 Jan 20.**

This prospective observational cohort study assessed self-reported outcomes over 12 months among 1,000 adults diagnosed with a chronic disease and authorized for medical cannabis via Ontario Canva Rx Cannabis Clinic in Toronto. Of the 1,000 patients invited to participate:

- n=757 completed baseline
- n=394 completed three-month follow-up
- n=230 completed six-month follow-up
- n=104 completed 12-month follow-up

Between 75-80% of participants reported using <1 to 2g of cannabis daily throughout the study period, with <1% of study participants using more than 5g of cannabis in any form at any time point.

Key findings include the following:

- Over time, participants in the study reported improvements with pain intensity, pain-related interference, quality of life, and general health symptoms. However, previous studies reviewed by the authors suggested the inverse (a higher/greater benefit of pain reduction at the onset of starting medical cannabis and the effect waning over time (typically a 12-week study timeframe)). This finding should therefore be interpreted with caution. Study participants who completed follow-ups were more likely to still be using cannabis and therefore likely to still experience some level of benefit, resulting in selection bias.

- Due to the high rate of attrition (52% completed all three time-point assessments, and only one-third continued to use cannabis at the six-month assessment), the authors claim further study is warranted. Further, they suggest the pattern of attrition may be an indication that medical cannabis may only help a subset of patients effectively with chronic pain.

- The authors also noted the need for more studies that looked at sex differences. In this study, "sex was significantly associated with all outcomes of interest with females reporting worse outcomes than males did." More studies are needed to understand sex differences in pain/chronic pain and use of medical cannabis.

The observational study did not detail any adverse events. However, the high rate of attrition could hide potential adverse events experienced by participants who dropped out of the study (i.e., were lost to follow-up).

Sagy I, Bar-Lev Schleider L, Abu-Shakra M, Novack V. Safety and Efficacy of Medical Cannabis in Fibromyalgia. *J Clin Med.* 2019 Jun 5;8(6):807. doi: 10.3390/jcm8060807. PMID: 31195754; PMCID: PMC6616435.

This prospective observational study with a six-month follow-up period included 367 fibromyalgia patients in Israel who began medical cannabis treatment between January 2015 and December 2017.

Follow-up was conducted with 298 patients who received medical cannabis treatment for six months. Among those patients, 211 responded with the follow-up questionnaire (response rate = 70.8%).

Dosing protocol used a gradual titration process rather than a fixed dose. Initially, all patients selected the strain of cannabis and mode of administration (oil or inflorescence) in consultation with certified nurse. All patients received a low dose of cannabis below the therapeutic effect (e.g., a drop of 15% THC-rich cannabis TID). Patients then were instructed to increase the dosage gradually in small intervals (e.g., a single drop per day) until they reached a therapeutic effect (e.g., subjective relief of their pain, significant improvement in their quality of life). In case of inflorescence (each cigarette contained 0.75 g of cannabis), patients were instructed to use one breath every three to four hours, and to increase the amount gradually in this interval until therapeutic effect is reached. Mixing of oil and inflorescence at the same usage was not recommended. In case of adverse events, patients were instructed to use the last dosage that did not cause undesirable symptoms. The titration was similar for both THC- and CBD-rich strains.

Primary outcome measure was treatment response; i.e., moderate or significant improvement in the patient's fibromyalgia condition at six months follow-up.

Secondary outcome measures included:

- Pain intensity
- Quality of life
- Perception of the general effect of cannabis

Outcomes included the following:

- The majority of patients (194/239, or 81.1%) reported positive impact of treatment (i.e., moderate or significant improvement in the patient's fibromyalgia condition at six months follow-up).

- Sleep problems reported by 196 patients (92.9%) at intake improved in 144 patients (73.4%) and disappeared in 26 patients (13.2%, $p < 0.001$).

- Depression-related symptoms reported by 125 patients (59.2%) at the baseline improved in 101 patients (80.8%, $p < 0.001$).

- Prior to treatment initiation, 10 patients (2.7%) reported good or very good QOL, after six months of treatment 148 patients (61.9%) reported their QOL to be good or very good ($p < 0.001$).

The most common adverse events/symptoms reported included:

- dizziness (7.9% of patients)
- dry mouth (6.7% of patients)
- nausea/vomiting (5.4% of patients)
- hyperactivity (5.5% of patients)

van de Donk T, Niesters M, Kowal MA, Olofsen E, Dahan A, van Velzen M. An experimental randomized study on the analgesic effects of pharmaceutical-grade cannabis in chronic pain patients with fibromyalgia. *Pain.* 2019 Apr;160(4):860-869. doi: 10.1097/j.pain.0000000000001464.

In this relatively small (N=20) randomized, double-blind, placebo-controlled four-way crossover study, the authors tested the analgesic effects of inhaled pharmaceutical grade cannabis on several types of pain. Study participants were female, age 18 or older diagnosed with fibromyalgia (FM) who reported a pain score >5 (on a 0-10 scale) for most of the day. People who reported any medical, neurological, or psychiatric illness, use of strong opioids or other painkillers (except paracetamol and/or ibuprofen, benzodiazepine use), illicit drug or alcohol use, recent use of cannabis, pregnancy, breastfeeding, and the presence of pain syndromes other than FM were excluded from the study.

The four treatment arms were:

- Arm 1: Bedrocan cannabis with a high THC/low CBD content;
- Arm 2: Bedrolite cannabis with a high CBD/low THC content;
- Arm 3: Bediol cannabis with a combined high THC/high CBD content; and

- Arm 4: placebo "cannabis" that was similar in smell, appearance to cannabis.

Dosing:

- Bedrocan: The Bedrocan cannabis variety contains 22% THC (220 mg per gram) and less than 1% CBD. The study used 100 mg that contained 22.4-mg THC and less than 1-mg CBD.

- Bediol: The Bediol cannabis variety is characterized by the combination of 6.3% THC (63 mg per gram) and 8% CBD (80 mg per gram). The study used 200 mg that contained 13.4-mg THC and 17.8-mg CBD.

- Bedrolite: This variety is composed of 9% CBD (90 mg per gram) and less than 1% THC. The study used 200 mg that contained 18.4-mg CBD and less than 1-mg THC.

- Placebo: The placebo was derived from the Bedrocan cannabis variety after selective removal of the cannabinoids by solvent extraction by Proxy Laboratories BV under GMP conditions. After removal of the cannabinoids, the specific terpene profile (responsible for smell and taste) was restored in a subsequent manufacturing step. Consequently, the placebo had a moisture content and terpenoid profile matching the active drug (Bedrocan).

The study design had participants in each arm inhaling a single vaporized dose of cannabis and then THC and CBD plasma concentrations, pressure and electrical pain thresholds, spontaneous pain scores, and drug high were measured for three hours.

The study had six main findings:

1. None of the treatments had an effect greater than placebo on spontaneous pain scores;

2. Compared to placebo responder rates, significantly more patients responded to Bediol (containing high doses of THC and CBD) with a decrease in spontaneous pain by 30%; the two other active treatments had response profiles not different from placebo;

3. The reduction in spontaneous pain scores was correlated with the magnitude of drug high;

4. Pressure pain threshold increased significantly in patients treated with Bedrocan and Bediol, two cannabis varieties with a high THC content;

5. Bedrolite, a cannabis variety with a high CBD content was devoid of analgesic activity in any of the spontaneous or evoked pain models; and

6. CBD increased plasma concentrations of THC but had an antagonistic effect on analgesia when combined with THC.

All three active arms of the study were associated with adverse effects related to the inhalation of cannabis (coughing during inhalation in 65%-70%, sore throat and bad taste during inhalation in 25%-35% of participants). Effects not related to inhalation of cannabis included: drug high in 40% to 80%, dizziness in 15% to 20%, and nausea in 5% to 30% of participants. There were no differences in frequency of adverse effects between the three active treatment arms, and no serious adverse events occurred.

Sickle Cell Disease

Only one randomized trial has been completed in the area of sickle cell disease (SCD) and medical cannabis. It should be noted that as of 2020, only four states included SCD in their medical cannabis programs (Abrams, Couey et al. 2020), which may be a contributing factor to why there is a paucity of data in this area.

In their small crossover randomized trial, 23 people with chronic pain associated with SCD were enrolled. Participants were enrolled in two five-day (four-night) hospital stays, separated by at least three days. Participants were given either 1:1 THC/CBD vapor or placebo vapor three times daily (8 a.m., 2 p.m., and 8 p.m.). The difference between pain ratings for cannabis vs. placebo was greater for cannabis on all five days, but the finding was not statistically significant. While there was no statistically significant mean (SD) difference in pain interference ratings between cannabis and placebo between days 1 and 5 for interference in general activities, walking, sleep, or enjoyment, there was a statistically significant mean difference in decrease in interference with mood (day 1: 0.96 [0.59]; day 5: −1.4 [0.6]; P = .02). No differences in treatment-related adverse effects were observed. Concurrent use of opioids was similar during both treatment periods.

Abrams DI, Couey P, Dixit N, et al. Effect of Inhaled Cannabis for Pain in Adults with Sickle Cell Disease: A Randomized Clinical Trial. *JAMA Netw Open.* **2020;3(7):e2010874.**

This crossover randomized trial enrolled 23 people with chronic pain associated with sickle cell disease. Patients were admitted to the hospital on two separate occasions for five days each. Stays were separated by at least 30 days. Participants were given either cannabis or placebo vapor to inhale. Administrations were at 8 a.m., 2 p.m., and 8 p.m. each day.

Cannabis vapor was derived from NIDA-provided cannabis plant material containing 4.4% THC and 4.9% CBD. Placebo vapor was derived from NIDA-provided cannabis plant material from which the cannabinoids had been extracted. Participants followed a uniform Foltin puff procedure. Participants self-titrated their doses but were encouraged to inhale at least 1 full bag of vapor.

The mean (SD) difference in pain rating assessment between the cannabis and placebo groups was −5.3 (8.1) for day 1, −10.9 (7.0) for day 2, −16.5 (9.2) for day 3, −8.9 (6.7) for day 4, and −8.2 (8.1) for day 5; however, none of these differences were statistically significant. There was no statistically significant mean (SD) difference in pain interference ratings between cannabis and placebo between days 1 and 5 for interference in general activities, walking, sleep, or enjoyment, but there was a statistically significant mean difference in decrease in interference with mood (day 1: 0.96 [0.59]; day 5: −1.4 [0.6]; P = .02). No differences in treatment-related adverse effects were observed. Concurrent use of opioids was similar during both treatment periods.

The authors acknowledge several limitations of the study, including the small sample size and short duration. In addition, they suggest that ad libitum dosing might be more effective and reflective of real-world practices, rather than the strict 3x/day dosing required by the study protocol.

Chronic Motor or Vocal Tic Disorder

Chronic motor or vocal tics are a characterizing feature of Tourette syndrome. Most research on medical cannabis for motor or vocal tics are summarized in the section Tourette Syndrome. Research in this section focuses on motor or vocal tics not necessarily encompassed under Tourette syndrome.

There is one pilot study that looked at the effectiveness and safety of medical cannabis in pediatric patients (n=25) with complex motor disorder (Libzon, Schleider et al. 2018). CBD enriched 5% oil was administered in two formulations: one with 0.25% THC (20:1 group), and one with 0.83% THC (6:1 group). Medications were given for five months. Improvements were seen in spasticity and dystonia, sleep issues, pain severity, and quality of life without significant difference between the two groups. Adverse effects included worsening of seizures in two patients, behavioral changes in two patients, and somnolence in one patient.

There is one randomized, double-blind, placebo-controlled, parallel-group study recently completed in Germany that tested the safety and efficacy of nabiximols compared to placebo for patients with chronic tic disorders, including Tourette syndrome (Jakubovski, Pisarenko et al. 2020). In this study, 96 adult participants were randomized 2:1 into nabiximols or placebo arms. In the placebo arm, patients were treated with a placebo spray identical to nabiximols in visual appearance, taste, and odor. The starting dose was one spray/day (= 100 µl spray = 2.7 mg THC/2.5 mg CBD) with dose escalation over weeks one to four by one spray per day every two days until symptom relief or the maximum of 12 sprays/day was reached (= 1,200 µl spray = 32.4 mg THC/30 mg CBD). This trial is registered at clinicaltrialsregister.eu (Eudra-CT 2016-000564-42 and clinicaltrials.gov (NCT03087201). No results have been published to date.

Libzon S, Schleider LB, Saban N, Levit L, Tamari Y, Linder I, Lerman-Sagie T, Blumkin L. Medical Cannabis for Pediatric Moderate to Severe Complex Motor Disorders. *J Child Neurol.* 2018 Aug;33(9):565-571. doi: 10.1177/0883073818773028. Epub 2018 May 16. PMID: 29766748.

This small randomized two-arm study examined the efficacy, safety, and tolerability of medical cannabis in 25 children (aged 1-17) with complex motor disorder. Two products of cannabidiol (CBD) enriched 5% oil formulation of cannabis were compared: one with 0.25% delta-9-tetrahydrocannabinol (THC) 20:1 group, the other with 0.83% THC 6:1 group. The assigned medication was administered for five months. Significant improvement in spasticity and dystonia, sleep difficulties, pain severity, and QOL was observed in the total study cohort, regardless of treatment assignment. Adverse effects were rare and included worsening of seizures in two patients, behavioral changes in two, and somnolence in one.

Jakubovski E, Pisarenko A, Fremer C, Haas M, May M, Schumacher C, et al. The CANNA-TICS Study Protocol: A Randomized Multi-Center Double-Blind Placebo Controlled Trial to Demonstrate the Efficacy and Safety of Nabiximols in the Treatment of Adults With Chronic Tic Disorders. *Front Psychiatry* 2020 Vol. 11 Pages 575826. Accession Number: 33324255 PMCID: PMC7725747 DOI: 10.3389/fpsyt.2020.575826

This multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase IIIb trial tested whether treatment with nabiximols is safe and effective, as well as whether it is superior to placebo in patients with chronic tic disorders. The study completed in November 2020. Study

duration included 17 weeks of treatment per patient, including four weeks for up-titration, a nine-week maintenance phase, and four weeks of follow-up.

Study group included 96 adult patients with chronic tic disorders (Tourette syndrome or other chronic motor tic disorders) in Germany. Participants were randomized 2:1 into nabiximols or placebo arms. In the placebo arm, patients were treated with a placebo spray identical to nabiximols in visual appearance, taste, and odor.

Primary measure used was Total Tic Score of the yale Global Tic Severity Scale (YGTSS-TSS) after 13 weeks of treatment. Efficacy is defined as at least a 30% tic reduction compared to baseline. Secondary measures included changes in different psychiatric comorbidities, quality of life, driving ability, and safety assessments.

Dosing:

- Nabiximols is a sublingually administered oromucosal spray that contains 10 ml solution in one spray container. The starting dose was one spray/day (= 100 µl spray = 2.7 mg THC/2.5 mg CBD).

Dose escalation was as follows:

- Weeks 1-4, increase by one spray/day every two days, and thereafter by one spray every day up to a maximum dose of 12 sprays/day (= 1,200 µl spray = 32.4 mg THC/30 mg CBD). Slower dose increase is possible depending on individual tolerability and efficacy. For patients in the placebo arm, titration will follow the same scheme as for nabiximols.

- Weeks 5-13, continue treatment at stable dosage. Dosage adjustment is possible.

- After week 13: medication is withdrawn without down-titration.

GW Pharma Ltd. provided nabiximols and placebo as investigational medical product (IMP) for this investigator-initiated study.

No results have been published to date.

Clinical Trial Registration: This trial is registered at clinicaltrialsregister.eu (Eudra-CT 2016-000564-42) and clinicaltrials.gov (NCT03087201).

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