The Medical Application of Marijuana: A Review of Published Clinical Studies
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Executive Summary

Marijuana is a Schedule I substance under the Controlled Substances Act (CSA). Schedule I indicates a high potential for abuse, no currently accepted medical use in the United States, and a lack of accepted safety for use under medical

supervision. To date, marijuana has not been subject to an approved new drug application (NDA) that demonstrates its safety and efficacy for a specific indication under the Food Drug and Cosmetic Act (FDCA).

Nevertheless, as of October 2014, twenty-three states and the District of Columbia have passed state-level medical marijuana laws that allow for marijuana use within that state; similar bills are pending in other states.

The present review was undertaken by the Food and Drug Administration (FDA) to analyze the clinical studies published in the medical literature investigating the use of marijuana in any therapeutic areas. First, we discuss the context for this scientific review. Next, we describe the methods used in this review to identify adequate and well-controlled studies evaluating the safety and efficacy of marijuana for particular therapeutic uses.

The FDA conducted a systematic search for published studies in the medical literature that meet the described criteria for study design and outcome measures prior to February 2013. While not part of our systematic review, we have continued to routinely follow the literature beyond that date for subsequent studies. Studies were considered to be relevant to this review if the investigators administered marijuana to patients with a diagnosed medical condition in a well-controlled, double-blind, placebo-controlled clinical trial. Of the eleven studies that met the criteria for review, five different therapeutic areas were investigated:

- Five studies examined chronic neuropathic pain
- Two studies examined appetite stimulation in human immunodeficiency virus (HIV) patients
- Two studies examined glaucoma
- One study examined spasticity and pain in multiple sclerosis (MS)
- One study examined asthma.

For each of these eleven clinical studies, information is provided regarding the subjects studied, the drug conditions tested (including dose and method of administration), other drugs used by subjects during the study, the physiological and subjective measures collected, the outcome of these measures comparing treatment with marijuana to placebo, and the reported and observed adverse events. The conclusions drawn by the investigators are then described, along with potential limitations of these conclusions based on the study design. A brief summary of each study's findings and limitations is provided at the end of the section.

The eleven clinical studies that met the criteria and were evaluated in this review showed positive signals that marijuana may produce a desirable therapeutic outcome, under the

specific experimental conditions tested. Notably, it is beyond the scope of this review to determine whether these data demonstrate that marijuana has a currently accepted medical use in the United States. However, this review concludes that these eleven clinical studies serve as proof-of-concept studies, based on the limitations of their study designs, as described in the study summaries. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug's effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. However, the studies reviewed produced positive results, suggesting marijuana should be further evaluated as an adjunct treatment for neuropathic pain, appetite stimulation in HIV patients, and spasticity in MS patients.

The main limitations identified in the eleven studies testing the medical applications of marijuana are listed below:

- The small numbers of subjects enrolled in the studies, which limits the statistical analyses of safety and efficacy.

- The evaluation of marijuana only after acute administration in the studies, which limits the ability to determine efficacy following chronic administration.

- The administration of marijuana typically through smoking, which exposes ill patients to combusted material and introduces problems with determining the doses delivered.

- The potential for subjects to identify whether they received marijuana or placebo, which breaks the blind of the studies.

- The small number of cannabinoid naïve subjects, which limits the ability to determine safety and tolerability in these subjects.

- The low number of female subjects, which makes it difficult to generalize the study findings to subjects of both genders.

Thus, this review discusses the following methodological changes that may be made in order to resolve these limitations and improve the design of future studies which examine the safety and efficacy of marijuana for specific therapeutic indications:

- Determine the appropriate number of subjects studied based on recommendations in various FDA *Guidances for Industry* regarding the conduct of clinical trials for specific medical indications.

- Administer consistent and reproducible doses of marijuana based on recommendations in the FDA *Guidance for Industry: Botanical Drug Products (2004)*[27].

- Evaluate the effects of marijuana under therapeutic conditions following both acute and chronic administration.

- Consider alternatives to smoked marijuana (e.g., vaporization).

- Address and improve whenever possible the difficulty in blinding of marijuana and placebo treatments in clinical studies.

- Evaluate the effect of prior experience with marijuana with regard to the safety and tolerability of marijuana.

- Strive for gender balance in the subjects used in studies.

In conclusion, the eleven clinical studies conducted to date do not meet the criteria required by the FDA to determine if marijuana is safe and effective in specific therapeutic areas. However, the studies can serve as proof-of-concept studies and support further research into the use of marijuana in these therapeutic indications. Additionally, the clinical outcome data and adverse event profiles reported in these published studies can beneficially inform how future research in this area is conducted. Finally, application of the recommendations listed above by investigators when designing future studies could greatly improve the available clinical data that can be used to determine if marijuana has validated and reliable medical applications.

[27] This Guidance is available on the internet at http://www.fda.gov/Drugs/default.htm under Guidance (Drugs).

1. Introduction

In response to citizen petitions submitted to the Drug Enforcement Administration (DEA) requesting DEA to reschedule marijuana, the DEA Administrator requested that the U.S. Department of Health and Human Services (HHS) provide a scientific and medical evaluation of the available information and a scheduling recommendation for marijuana, in accordance with 21 U.S.C. 811(b). The Secretary of HHS is required to consider in a scientific and medical evaluation eight factors determinative of control under the Controlled Substance Act (CSA). Administrative responsibilities for evaluating a substance for control under the CSA are performed by the Food and Drug Administration (FDA), with the concurrence of the National Institute on Drug Abuse (NIDA). Part of this evaluation includes an assessment of whether marijuana has a currently accepted medical use in the United States. This assessment necessitated a review of the available data from published clinical studies to determine whether there is adequate scientific evidence of marijuana's effectiveness.

Under Section 202 of the CSA, marijuana is currently controlled as a Schedule I substance (21 U.S.C § 812). Schedule I includes those substances that have a high potential for abuse, have no currently accepted medical use in treatment in the United States, and lack accepted safety for use under medical supervision (21 U.S.C. § 812(b)(1)(A)-(C)).

A drug product which has been approved by FDA for marketing in the United States is considered to have a "currently accepted medical use." Marijuana is not an FDA-approved drug product, as a New Drug Application (NDA) or Biologics License application (BLA) for marijuana has not been approved by FDA. However, FDA approval of an NDA is not the only means through which a drug can have a currently accepted medical use in the United States.

In general, a drug may have a "currently accepted medical use" in the United States if the drug meets a five-part test. Established case law (Alliance for Cannabis Therapeutics v. DEA, 15 F.3d 1131, 1135 (D.C. Cir. 1994)) upheld the Administrator of DEA's application of the five-part test to determine whether a drug has a "currently accepted medical use." The following describes the five elements that characterize "currently accepted medical use" for a drug[28]:

i. the drug's chemistry must be known and reproducible

> "The substance's chemistry must be scientifically established to permit it to be reproduced into dosages which can be standardized. The listing of the substance in a current edition of one of the official compendia, as defined by section 201(j) of

[28] 57 FR 10499, 10504-06 (March 26, 1992).

the Food, Drug and Cosmetic Act, 21 U.S.C. 321(j), is sufficient to meet this requirement."

ii. there must be adequate safety studies

"There must be adequate pharmacological and toxicological studies, done by all methods reasonably applicable, on the basis of which it could fairly and responsibly be concluded, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, that the substance is safe for treating a specific, recognized disorder."

iii. there must be adequate and well-controlled studies proving efficacy

"There must be adequate, well-controlled, well-designed, well-conducted, and well-documented studies, including clinical investigations, by experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, on the basis of which it could be fairly and responsibly concluded by such experts that the substance will have the intended effect in treating a specific, recognized disorder."

iv. the drug must be accepted by qualified experts

"The drug has a New Drug Application (NDA) approved by the Food and Drug Administration, pursuant to the Food, Drug and Cosmetic Act, 21 U.S.C. 355. Or, a consensus of the national community of experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, accepts the safety and effectiveness of the substance for use in treating a specific, recognized disorder. A material conflict of opinion among experts precludes a finding of consensus." and

v. the scientific evidence must be widely available.

"In the absence of NDA approval, information concerning the chemistry, pharmacology, toxicology, and effectiveness of the substance must be reported, published, or otherwise widely available, in sufficient detail to permit experts, qualified by scientific training and experience to evaluate the safety and effectiveness of drugs, to fairly and responsibly conclude the substance is safe and effective for use in treating a specific, recognized disorder."

One way to pass the five-part test for having "currently accepted medical use" is through submission of an NDA or BLA which is approved by FDA. However, FDA approval of an NDA or BLA is not required for a drug to pass the five-part test.

This review focuses on FDA's analysis of one element of the five-part test for determining whether a drug has "currently accepted medical use". Specifically, the present review assesses the 3rd criterion that addresses whether marijuana has "adequate and well-controlled studies proving efficacy". Thus, this review evaluates published clinical studies that have been conducted using marijuana in subjects who have a variety of medical conditions by assessing the adequacy of the summarized study designs and the study data. The methodology for selecting the studies that were evaluated is delineated below.

FDA's evaluation and conclusions regarding the remaining four criteria for whether marijuana has a "currently accepted medical use," as well as the eight factors pertaining to the scheduling of marijuana, are outside the scope of this review. A detailed discussion of these factors is contained in FDA's scientific and medical evaluation of marijuana.

2. Methods

The methods for selecting the studies to include in this review involved the following steps, which are described in detail in the subsections below:

1. Define the objective of the review.
2. Define "marijuana" in order to facilitate the medical literature search for studies that administered the substance,
3. Define "adequate and well-controlled studies" in order to facilitate the search for relevant data and literature,
4. Search medical literature databases and identify relevant adequate and well-controlled studies, and
5. Review and analyze the adequate and well-controlled clinical studies to determine if they demonstrate efficacy of marijuana for any therapeutic indication.

2.1 Define the Objective of the Review

The objective of this review is to assess the study designs and resulting data from clinical studies published in the medical literature that were conducted with marijuana (as defined below) as a treatment for any therapeutic indication, in order to determine if they meet the criteria of "adequate and well-controlled studies proving efficacy".

2.2 Define "Marijuana"

In this review, the term "marijuana" refers to the flowering tops or leaves of the *Cannabis* plant. There were no restrictions on the route of administration used for marijuana in the studies.

Studies which administered individual cannabinoids (whether experimental substances or marketed drug products) or marijuana extracts were excluded from this review. Additionally, studies of administered neutral plant material or placebo marijuana (marijuana with all cannabinoids extracted) that had subsequently been supplemented by the addition of specific amounts of THC or other cannabinoids were also excluded (Chang et al., 1979).

2.3 Define "Adequate and Well-Controlled Clinical Studies"

The criteria for an "adequate and well-controlled study" for purposes of determining the safety and efficacy of a human drug is defined under the Code of Federal Regulations (CFR) in 21 CFR 314.126. The elements of an adequate and well-controlled study as described in 21 CFR 314.126 can be summarized as follows:

1. The main objective must be to assess a therapeutically relevant outcome.
2. The study must be placebo-controlled.
3. The subjects must qualify as having the medical condition being studied.
4. The study design permits a valid comparison with an appropriate control condition.
5. The assignment of subjects to treatment and control groups must be randomized.
6. There is minimization of bias through the use of a double-blind study design.
7. The study report contains a full protocol and primary data.
8. Analysis of the study data is appropriately conducted.

As noted above, the current review examines only those data available in the public domain and thus relies on clinical studies published in the medical literature. Published studies by their nature are summaries that do not include the level of detail required by studies submitted to FDA in an NDA.

While the majority of the elements defining an adequate and well-controlled study can be satisfied through a published paper (elements #1-6), there are two elements that cannot be met by a study published in the medical literature: element #7 (availability of a study report with full protocol and primary data) and element #8 (a determination of whether the data analysis was appropriate). Thus, for purposes of this review, only elements #1-6 will be used to qualify a study as being adequate and well-controlled.

2.4 Search Medical Literature Databases and Identify Relevant Studies

We identified randomized, double-blind, placebo-controlled clinical studies conducted with marijuana to assess marijuana's efficacy in any therapeutic indication. Two primary medical literature databases were searched for all studies posted to the databases prior to February 2013[29]:

- PubMed: PubMed is a database of published medical and scientific studies that is maintained by the U.S. National Library of Medicine (NLM) at NIH as a part of the Entrez system of information retrieval. PubMed comprises more than 24 million citations for biomedical literature from MEDLINE, life science journals, and online books (http://www.ncbi.nlm.nih.gov/pubmed).

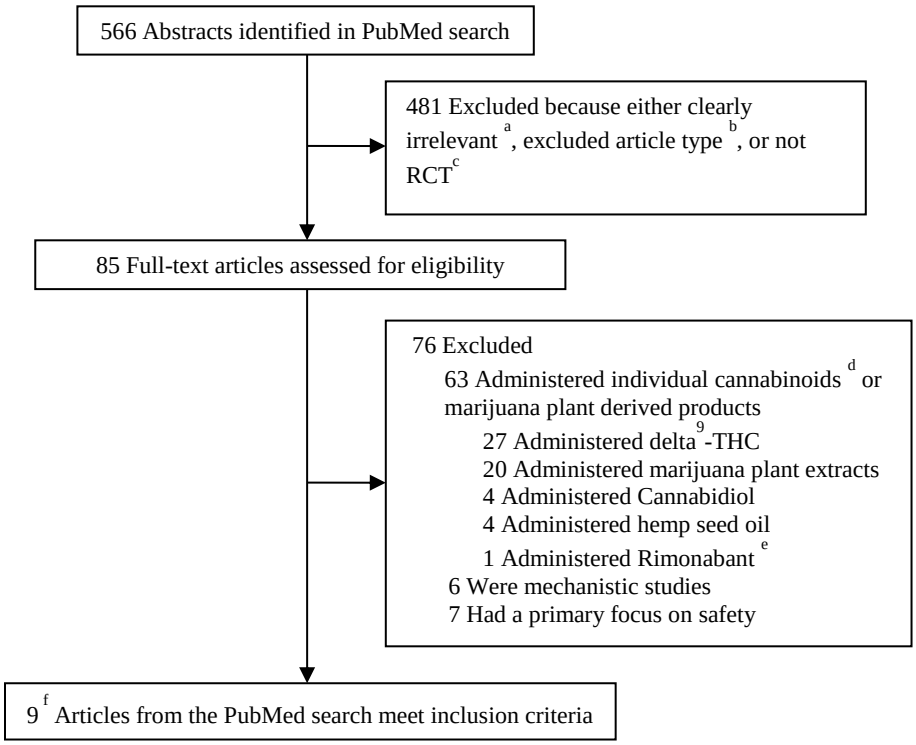
- ClinicalTrials.gov: ClinicalTrials.gov is a database of publicly and privately supported clinical studies that is maintained by the NLM. Information about the clinical studies is provided by the Sponsor or Principal Investigator of the study. Information about the studies is submitted to the website ("registered") when the studies begin, and is updated throughout the study. In some cases, results of the study or resulting publication citations are submitted to the website after the study ends (https://clinicaltrials.gov/ct2/about-site/background).

ClinicalTrials.gov was searched for all studies administering marijuana. The results of this search were used to confirm that no completed studies with published data were missed in the literature search. During the literature search, references found in relevant studies and systematic reviews were evaluated for additional relevant citations. All languages were included in the search. The PubMed search yielded a total of 566 abstracts[30]. Of these abstracts, a full-text review was conducted with 85 papers to assess eligibility. From this evaluation, only eleven of 85 studies met the 6 CFR elements for inclusion as adequate and well-controlled studies.

Figure 1 (below) provides an overview of the process used to identify studies from the PubMed search. The eleven studies reviewed were published between 1974 and 2013. Ten of these studies were conducted in the United States and one study was conducted in Canada. These eleven studies examined the effects of smoked and vaporized marijuana for the indications of chronic neuropathic pain, spasticity related to multiple sclerosis (MS), appetite stimulation in patients with human immunodeficiency virus (HIV), glaucoma, and asthma. All included studies used adult patients as subjects. All studies conducted in the United States were conducted under an IND as Phase 2 investigations.

[29] While not a systematic review, we have followed the recent published literature on marijuana use for possible therapeutic purposes and, as of January 2015, we found only one new study that would meet our criteria (Naftali et al., 2013). This study examined the effects of smoked marijuana on Crohn's disease.
[30] The following search strategy was used, "(cannabis OR marijuana) AND (therapeutic use OR therapy) AND (RCT OR randomized controlled trial OR "systematic review" OR clinical trial OR clinical trials) NOT ("marijuana abuse"[Mesh] OR addictive behavior OR substance related disorders)".

Figure 1: Identification of Studies from PubMed Search



[a]Articles were deemed irrelevant if they examined safety or adverse event related outcomes, including psychoactive effects or other adverse events. [b]Excluded article types included comments, reviews, meta-analyses, and news articles. [c]Randomized Controlled Trials. [d]Cannabinoids administered included synthetic cannabinoids. [e]Rimonabant is a cannabinoid receptor antagonist. [f]An additional 2 studies meeting the inclusion criteria were found through

Two qualifying studies, which assessed marijuana for glaucoma, were previously reviewed in the 1999 Institute of Medicine (IOM) report entitled "Marijuana and Medicine: Assessing the Science Base"[31]. We did our own analysis of these two studies and concurred with the conclusions in the IOM report. Thus, a detailed discussion of the two glaucoma studies is not included in the present review. The present review only discusses 9 of the identified 11 studies. For a summary of the study design for all eleven qualifying studies, see Tables 1-5 (located in the Appendix).

[31] In January 1997, the White House Office of National Drug Control Policy (ONDCP) requested that the IOM conduct a review of the scientific evidence to assess the potential health benefits and risks of marijuana and its constituent cannabinoids. Information for this study was gathered through scientific workshops, site visits to cannabis buyers' clubs and HIV/Acquired Immunodeficiency Syndrome (AIDS) clinics, analysis of the relevant scientific literature, and extensive consultation with biomedical and social scientists. The report was finalized and published in 1999.

Based on the selection criteria for relevant studies described in Section 2.3 (Define Adequate and Well-Controlled Clinical Studies), a number of clinical studies that investigated marijuana, as defined in this review, were excluded from this review. Studies that examined the effects of marijuana in healthy subjects were excluded because they did not test a patient population with a medical condition (Flom et al., 1975; Foltin et al., 1986; Foltin et al., 1988; Hill et al., 1974; Milstein et al., 1974; Milstein et al., 1975; Soderpalm et al., 2001; Wallace et al., 2007; Greenwald and Stitzer, 2000). A 1975 study by Tashkin et al. was excluded because it had a single-blind, rather than double-blind, study design. Two other studies were excluded because the primary outcome measure assessed safety rather than a therapeutic outcome (Greenberg et al., 1994; Abrams et al., 2003).

2.5 Review and Analyze Qualifying Clinical Studies

Qualified clinical studies that evaluated marijuana for therapeutic purposes were examined in terms of adequacy of study design including method of drug administration, study size, and subject inclusion and exclusion criteria. Additionally, the measures and methods of analysis used in the studies to assess the treatment effect were examined.

3. Results and Discussion

The eleven qualifying studies in this review assessed a variety of therapeutic indications. In order to better facilitate analysis and discussion of the studies, the following sections group the studies by therapeutic area. Within each section, each individual study is summarized in terms of its design, outcome data and important limitations. This information is also provided in the Appendix in tabular form for each study.

3.1 Neuropathic Pain

Five randomized, double-blind, placebo-controlled Phase 2 clinical studies have been conducted to examine the effects of inhaled marijuana smoke on neuropathic pain associated with HIV-sensory neuropathy (Abrams et al., 2007; Ellis et al., 2009) and chronic neuropathic pain from multiple causes (Wilsey et al., 2008; Ware et al., 2010; Wilsey et al., 2013). Table 1 of the Appendix summarizes these studies.

3.1.1 Neuropathic Pain Associated with HIV-Sensory Neuropathy

Two studies examined the effect of marijuana to reduce the pain induced by HIV-sensory neuropathy.

Abrams et al. (2007) conducted the first study entitled, "Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial". The

subjects were 50 adult patients with uncontrolled HIV-associated sensory neuropathy, who had at least 6 experiences with smoking marijuana. The subjects were split into two parallel groups of 25 subjects each. More than 68% of subjects were current marijuana users, but all individuals were required to discontinue using marijuana prior to the study. Most subjects were taking medication for pain during the study, with the most common medications being opioids and gabapentin. Upon entry into the study, subjects had an average daily pain score of at least 30 on a 0-100 visual analog scale (VAS).

Subjects were randomized to receive either smoked marijuana (3.56% THC[32]) or smoked placebo cigarettes three times per day for 5 days, using a standardized cued smoking procedure: (1) 5 second inhale, (2) 10 second holding smoke in the lungs, (3) 40 second exhale and breathing normally between puffs. The authors did not specify how many puffs the subjects smoked at each smoking session, but they stated that one cigarette was smoked per smoking session.

Primary outcome measures included daily VAS ratings of chronic pain and the percentage of subjects who reported a result of more than 30% reduction in pain intensity. The ability of smoked marijuana to induce acute analgesia was assessed using both thermal heat model and capsaicin sensitization model, while anti-hyperalgesia was assessed with brush and von Frey hair stimuli. The immediate analgesic effects of smoked marijuana was assessed using a 0-100 point VAS at 40-minute intervals three times before and three times after the first and last smoking sessions, which was done to correspond to the time of peak plasma cannabinoid levels. Notably, not all subjects completed the induced pain portion of the study (n = 11 in marijuana group, 9 in placebo group) because of their inability to tolerate the stimuli. Throughout the study, subjects also completed the Profile of Mood States (POMS) questionnaire, as well as subjective VAS measures of anxiety, sedation, disorientation, paranoia, confusion, dizziness, and nausea.

As a result, the median daily pain was reduced 34% by smoked marijuana compared to 17% by placebo ($p = 0.03$). Fifty-two percent of subjects who smoked marijuana reported a >30% reduction in pain compared to 24% in the placebo group ($p = 0.04$). Although marijuana reduced experimentally-induced hyperalgesia ($p \leq 0.05$) during the first smoking sessions, marijuana did not alter responses to acutely painful stimuli.

There were no serious AEs and no episodes of hypertension, hypotension, or tachycardia requiring medical intervention. No subjects withdrew from the study for drug related reasons. Subjects in the marijuana group reported higher ratings on the subjective measures of anxiety, sedation, disorientation, confusion, and

[32] The drug dose is reported as percentage of THC present in the marijuana rather than milligrams of THC present in each cigarette because of the difficulty in determining the amount of THC delivered by inhalation (see discussion in the section entitled "3.7.2 Marijuana Dose Standardization").

dizziness compared to the placebo group. There was one case of severe dizziness in a marijuana-treated subject. By the end of the study, subjects treated with marijuana and placebo reported a reduction in total mood disturbance as measured by POMS.

The authors conclude that smoked marijuana effectively reduced chronic neuropathic pain from HIV-associated sensory neuropathy with tolerable side effects. However, limitations of this study include: maintenance of subjects on other analgesic medication while being tested with marijuana and a lack of information about the number of puffs during each inhalation of smoke. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled HIV-associated sensory neuropathy.

Ellis et al. (2009) conducted a more recent study entitled "Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial". The subjects were 28 HIV-positive adult male patients with intractable neuropathic pain that was refractory to the effects of at least two drugs taken for analgesic purposes. Upon entry into the study, subjects had a mean score of > 5 on the Pain Intensity subscale of the Descriptor Differential Scale (DDS). Subjects were allowed to continue taking their current routine of pain medications, which included opioids, non-narcotic analgesics, antidepressants, and anticonvulsants. Previous experience with marijuana was not required for participation in the study, but 27 of 28 subjects (96%) reported previous experience with marijuana. However, of these 27 experienced subjects, 63% (n = 18) reported no marijuana use within the past year.

The study procedures compared the effects of the target dose of marijuana and placebo during two treatment periods lasting 5 days, with 2 weeks washout periods. The marijuana strengths available were 1%, 2%, 4%, 6%, or 8% THC concentration by weight. Subjects smoked marijuana or placebo cigarettes four times per day, approximately 90-120 minutes apart, using a standardized cued smoking procedure: (1) 5 second smoke inhalation, (2) 10 second hold of smoke in lungs, (3) 40 second exhale and normal breathing between puffs. The investigators did not provide a description of the number of puffs taken at any smoking session. All subjects practiced the smoking procedures using placebo marijuana prior to test sessions.

On the first day of each test period, dose titration occurred throughout the four smoking sessions scheduled for that day, with a starting strength of 4% THC concentration. Subjects were allowed to titrate to a personalized "target dose", which was defined as the dose that provided the best pain relief without intolerable adverse effects. This dose titration was accomplished by allowing subjects to either increase the dose incrementally (to 6% or 8% THC) to improve

analgesia, or to decrease the dose incrementally (to 1% or 2% THC) if AEs were intolerable. For the next 4 days of each test period, the subjects smoked their target dose during each of the four daily smoking sessions. To maintain the blind, placebo marijuana was represented as containing 1%-8% THC, even though it did not contain any cannabinoids.

The primary outcome measure was the change in pain magnitude on the DDS at the end of each test period compared to baseline, with a clinically significant level of analgesia considered to be a reduction in pain of at least 30%. Additional measures included the POMS, the Sickness Impact Profile (SIP), the Brief Symptom Inventory (BSI) and the UKU Side Effect Rating Scale and a subjective highness/sedation VAS.

During the marijuana treatment week, 19 subjects titrated to the 2%-4% THC dose while the 6%-8% dose was preferred by 8 subjects and 1 subject chose the 1% dose. In contrast, during the placebo treatment week, all 28 subjects titrated to the highest possible dose of "8% THC" that contained no actual cannabinoids, suggesting that placebo treatment provided little analgesic relief.

The degree of pain reduction was significantly greater after administration of marijuana compared to placebo (median change of 3.3 points on DDS, $p=0.016$). The median change from baseline in VAS pain scores was −17 for marijuana treatment compared to −4 for placebo treatment ($p<0.001$). A larger proportion of subjects who were treated with marijuana (0.46) reported a >30% reduction in pain, compared to placebo (0.18). Additionally, the authors report improvements in total mood disturbance, physical disability, and quality of life as measured on POMS, SIP, and BSI scales after both placebo and marijuana treatment (data not provided in paper).

In terms of safety, there were no alterations in HIV disease parameters in response to marijuana or placebo. The authors report that marijuana led to a greater degree of UKU responses as well as AEs such as difficulty in concentration, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation and thirst compared to placebo (data not provided in paper). Two subjects withdrew from the study because of marijuana-related AEs: one subject developed an intractable smoking-related cough during marijuana administration and the sole marijuana-naïve subject in the study experienced an incident of acute cannabis-induced psychosis[33].

The authors conclude that smoked marijuana effectively reduced chronic neuropathic pain from HIV-associated sensory neuropathy. The limitations of

[33]At the time of the study, the following criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000) were used to diagnose substance-induced psychotic disorders: Prominent hallucinations or delusions; Hallucinations and/or delusions that develop during, or within one month of, intoxication or withdrawal; The disturbance is not better accounted for by a psychotic disorder that is not substance induced. The disturbance does not occur exclusively during the course of a delirium.

this study include: a lack of information about the number of puffs during each inhalation of smoke; a lack of information about the specific timing of the subjective assessments and collection of AEs relative to initiation of the smoking sessions; and the inclusion of only one marijuana-naïve subject. These limitations make it difficult to conclude that the actual AEs experienced during the study in response to marijuana are tolerable. It is especially concerning that the only marijuana-naïve subject left the study because of serious psychiatric responses to marijuana exposure at analgesic doses. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled HIV-associated sensory neuropathy.

3.1.2 Central and Peripheral Neuropathic Pain

Three studies examined the effect of marijuana on chronic neuropathic pain.

Wilsey et al. (2008) examined chronic neuropathic pain from multiple causes in the study entitled, "A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain". The subjects were 32 patients with a variety of neuropathic pain conditions, including 22 with complex regional pain syndrome, 6 with spinal cord injury, 4 with multiple sclerosis, 3 with diabetic neuropathy, 2 with ilioinguinal neuralgia, and 1with lumbosacral plexopathy. All subjects reported a pain intensity of at least 30 on a 0-100 VAS and were allowed to continue taking their regular medications during the study period, which included opioids, antidepressants, anticonvulsants, and NSAIDs. All subjects were required to have experience with marijuana but could not use any cannabinoids for 30 days before study sessions.

The study consisted of three test sessions with an interval of 3-21 days between sessions. Treatment conditions were high-strength marijuana (7% delta-9-THC), low-strength marijuana (3.5% delta-9-THC), and placebo cigarettes, administered through a standardized cued-puff procedure: (1) "light the cigarette" (30 seconds), (2) "get ready" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), (5) "exhale," and (6) wait before repeating the puff cycle (40 seconds). Participants took 2 puffs after baseline measurements, 3 puffs an hour later, and 4 puffs an hour after that, for a cumulative dose of 9 puffs per test session.

Hourly assessment periods were scheduled before and after each set of puffs and for 2 additional hours during the recovery period. Plasma cannabinoids were measured at baseline, 5 minutes after the first puff and again at 3 hours after the last puff cycle.

The primary outcome measure was spontaneous pain relief, as measured by a 0-100 point VAS for current pain. Pain unpleasantness was measured on a 0-100 point VAS, and degree of pain relief was measured on a 7-point Patient Global Impression of Change (PGIC) scale. Secondary measures included the

Neuropathic Pain Scale (NPS), a 0-100 point VAS for allodynia, and changes in thermal pain threshold. Subjective measures were also evaluated with unipolar 0-100 point VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, like the drug effect, sedated, confused, nauseated, desire more of the drug, anxious, down, hungry, and bipolar 0-100 point VAS for sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, fearful/unafraid. Neurocognitive assessments measured attention and concentration, learning and memory, and fine motor speed.

Marijuana produced a reduction in pain compared to placebo, as measured by the pain VAS, the PGIC and on pain descriptors in the NPS, including sharp ($P < .001$), burning ($P < .001$), aching ($P < .001$), sensitive ($P = .03$), superficial ($P < .01$) and deep pain ($P < .001$). Notably, there were no additional benefits from the 7% THC strength of marijuana compared to the 3.5% THC strength, seemingly because of cumulative drug effects over time. There were no changes in allodynia or thermal pain responsivity following administration of either dose of marijuana.

Marijuana at both strengths produced increases on measures of any drug effect, good drug effect, high, stoned, impairment, sedation, confusion, and hunger. The 7% THC marijuana increased anxiety scores and bad drug effect (later in session) compared to placebo. Neither strength of marijuana affected the measures of mood. On neurocognitive measures, both the 3.5% THC and 7% THC marijuana produced impairment in learning and memory, while only the 7% THC marijuana impaired attention and psychomotor speed, compared to placebo. There were no adverse cardiovascular side effects and no subjects dropped out because of an adverse event related to marijuana.

The authors conclude that marijuana may be effective at ameliorating neuropathic pain at doses that induce mild cognitive effects, but that smoking is not an optimum route of administration. The limitations of this study include: inclusion of subjects with many forms of neuropathic pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. The authors compared pain score results by the type of pain condition, with no significant differences found; however, the sample size of this study was small thus a type II error may have been present. Thus, it is difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

The second study, conducted by **Ware et al. (2010)** in Canada is entitled, "Smoked cannabis for chronic neuropathic pain: a randomized controlled trial". The subjects were 21 adult patients with neuropathic pain caused by trauma or surgery compounded with allodynia or hyperalgesia, and a pain intensity score

greater than 4 on a 10 point VAS. All subjects maintained their current analgesic medication and they were allowed to use acetaminophen for breakthrough pain. Eighteen subjects had previous experience with marijuana but none of them had used marijuana within a year before the study.

The study design used a four-period crossover design, testing marijuana (2.5%, 6.0% and 9.4% THC) and placebo marijuana. The 2.5% and 6.0% doses of marijuana were included to increase successful blinding. Each period was 14 days in duration, beginning with 5 days on the study drug followed by a 9-day washout period. Doses were delivered as 25 mg of marijuana that was smoked in a single inhalation using a titanium pipe. The first dose of each period was self-administered using a standardized puff procedure: (1) inhale for 5 seconds, (2) hold the smoke in their lungs for 10 seconds, and (3) exhale. Subsequent doses were self-administered in the same manner for a total of three times daily at home on an outpatient basis for the first five days of each period.

The primary measure was an 11-point pain intensity scale, averaged over the 5 day treatment period, which was administered once daily for present, worst, least and average pain intensity during the previous 24 hours. Secondary measures included an acute pain 0-100 point VAS, pain quality assessed with the McGill Pain Questionnaire, sleep assessed with the Leeds Sleep Evaluation Questionnaire, mood assessed with the POMS, quality of life assessed using the EQ-5D health outcome instrument. Subjective measures included 0-100 point VAS scales for high, relaxed, stressed and happy.

Over the first three hours after smoking marijuana, ratings of pain, high, relaxation, stress, happiness and heart rate were recorded. During the five days of each study period, participants were contacted daily to administer questionnaires on pain intensity, sleep, medication and AEs. Subjects returned on the fifth day to complete questionnaires on pain quality, mood, quality of life and assessments of potency. At the end of the study, participants completed final adverse event reports and potency assessments.

The average daily pain intensity was significantly lower on 9.4% THC marijuana (5.4) than on placebo marijuana (6.1) ($p = 0.023$). The 9.4% THC strength also produced more drowsiness, better sleep, with less anxiety and depression, compared to placebo (all $p < 0.05$). However, there were no significant differences on POMS scores or on VAS scores for high, happy, relaxed or stressed between THC doses.

The most frequent drug-related adverse events reported in the group receiving 9.4% THC marijuana were headache, dry eyes, burning sensation, dizziness, numbness and cough. Reports of high and euphoria occurred on only three occasions, once in each dose of THC. There were no significant changes in vital signs, heart-rate variability, or renal function. One subject withdrew from the study due to increased pain during administration of 6% THC marijuana.

The authors conclude that smoked marijuana reduces neuropathic pain, improves mood and aids in sleep, but that smoking marijuana is not a preferable route of administration. The limitations of this study include: the lack of information on timing of assessments during the outpatient portion of the study and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own and that the actual AEs experienced during the study in response to marijuana are tolerable. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

Wilsey et al. (2013) conducted the most recent study entitled, "Low-Dose Vaporized Cannabis Significantly Improves Neuropathic Pain". This study is the only one in this review that utilized vaporization as a method of marijuana administration. The subjects were 36 patients with a neuropathic pain disorder (CRPS, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury) who were maintained on their current medications (opioids, anticonvulsants, antidepressants, and NSAIDs). Although subjects were required to have a history of marijuana use, they refrained from use of cannabinoids for 30 days before study sessions.

Subjects participated in three sessions in which they received 1.29% or 3.53% THC marijuana or placebo marijuana. The marijuana was vaporized using the Volcano vaporizer and a standardized cued-puff procedure: (1) "hold the vaporizer bag with one hand and put the vaporizer mouthpiece in their mouth" (30 seconds), (2) "get ready" (5 seconds), (3) "inhale" (5 seconds), (4) "hold vapor in lungs" (10 seconds), (5) "exhale and wait" before repeating puff cycle (40 seconds). Subjects inhaled 4 puffs at 60 minutes. At 180 minutes, the vaporizer was refilled with marijuana vapor and subjects were allowed to inhale 4 to 8 puffs using the cued procedure. Thus, cumulative dosing allowed for a range of 8 to12 puffs in total for each session, depending on the subjects desired response and tolerance. The washout time between each session ranged from 3-14 days.

The primary outcome variable was spontaneous pain relief, as assessed using a 0-100 point VAS for current pain. Secondary measures included the Patient Global Impression of Change (PGIC), the Neuropathic Pain Scale (NPS), a 0-100 point VAS for allodynia. Acute pain threshold was measured with a thermal pain model. Subjective measures included 0-100 point unipolar VAS for any drug effect, good drug effect, bad drug effect, high, drunk, impaired, stoned, drug liking, sedated, confused, nauseated, desire more drug, anxious, down and hungry. Bipolar 0-100 point VAS included sad/happy, anxious/relaxed, jittery/calm, bad/good, paranoid/self-assured, and fearful/unafraid. Neurocognitive assessments assessed attention and concentration, learning and memory, and fine motor speed.

A 30% reduction in pain was achieved in 61% of subjects who received the 3.53% THC marijuana, in 57% of subjects who received the 1.29% THC marijuana and in 26% of subjects who received the placebo marijuana ($p=0.002$ for placebo vs. 3.53% THC, $p=0.007$ for placebo vs 1.29% THC; $p>0.05$ 1.29% THC vs. 3.53% THC). Both strengths of marijuana significantly decreased pain intensity, unpleasantness, sharpness, and deepness on the NPS, as well as pain ratings on the PGIC, compared to placebo. These effects on pain were maximal with cumulative dosing over the course of the study session, with maximal effects at 180 minutes. There were no effects of marijuana compared to placebo on measures of allodynia or thermal pain. Subjects correctly identified the study treatment 63% of the time for placebo, 61% of the time for 1.29% THC, and 89% of the time for 3.53% THC.

On subjective measures, marijuana produced dose-dependent increases compared to placebo on ratings for: any drug effect, good drug effect, drug liking, high, stoned, sedated, confused, and hungry. Both strengths of marijuana produced similar increases in drunk or impaired compared to placebo. In contrast, desire for drug was rated as higher for the 1.29% THC marijuana compared to the 3.53% THC marijuana. There were no changes compared to placebo for bad effect, nauseous, anxiety, feeling down or any of the bipolar mood assessments. There was dose-dependent impairment on learning and memory from marijuana compared to placebo, but similar effects between the two strengths of marijuana on attention.

The authors conclude that vaporization of relatively low doses of marijuana can produce improvements in analgesia in neuropathic pain patients, especially when patients are allowed to titrate their exposure. However, this individualization of doses may account for the general lack of difference between the two strengths of marijuana. No data were presented regarding the total amount of THC consumed by each subject, so it is difficult to determine a proper dose-response evaluation. Additional limitations of this study are the inclusion of subjects with many forms of neuropathic pain and maintenance of subjects on other analgesic medication while being tested with marijuana. These limitations make it difficult to conclude that marijuana has analgesic properties on its own. It is also difficult to determine if any particular subset of neuropathic pain conditions would benefit specifically from marijuana administration. However, the study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for uncontrolled neuropathic pain.

3.2 Appetite Stimulation in HIV

Two randomized, double-blind, placebo-controlled Phase 2 studies examined the effects of smoked marijuana on appetite in HIV-positive subjects (Haney et al., 2005; Haney et al., 2007). Table 2 of the Appendix summarizes both studies.

The first study, conducted by **Haney et al. (2005)** is entitled, "Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood". The subjects were 30 HIV-positive patients who were maintained on two antiretroviral medications and either had clinically significant decreases in lean muscle mass[34] (low-BIA group, n = 15) or normal lean muscle mass (normal-BIA group, n = 15). All subjects had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5-6 times per week for 10-12 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 10, 20, and 30 mg dronabinol oral capsules and marijuana cigarettes with 0%, 1.8%, 2.8%, and 3.9% THC concentration by weight, using a double-dummy design (with only one active drug per session). The doses of dronabinol are higher than those doses typically prescribed for appetite stimulation in order to help preserve the blinding. There was a one-day washout period between test sessions.

Marijuana was administered using a standardized cued procedure: (1) "light the cigarette" (30 seconds), (2) "prepare" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), and (5) "exhale." Each subject smoked three puffs in this manner, with a 40-second interval between each puff.

Caloric intake was used as a surrogate measure for weight gain. Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day's administration of the test drug. Subjective measures included 0-100 point VAS for feel drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored.

The low BIA group consumed significantly more calories in the 1.8% and 3.9% THC marijuana conditions ($p<0.01$) and the 10, 20, and 30 mg dronabinol conditions ($p<0.01$) compared with the placebo condition. In contrast, in the normal BIA group, neither marijuana nor dronabinol significantly affected caloric intake. This lack of effect may be accountable, however, by the fact that this group consumed approximately 200 calories more than the low BIA group under baseline conditions.

Ratings of high and good drug effect were increased by all drug treatments in both the low-BIA and normal-BIA groups, except in response to the 10 mg dose of dronabinol. The 3.9% THC marijuana increased ratings of good drug effect, drug liking and desire to smoke again compared with placebo. Ratings of sedation were increased in both groups by 10 and 30 mg dronabinol, and in the normal BIA group by the 2.8% THC marijuana. Ratings of stimulation were increased in the normal BIA group by 2.8% and 3.9% THC marijuana and by 20 mg

[34] Lean muscle mass was assessed using bioelectrical impedance analysis (BIA). The low-BIA group was classified with having <90% BIA, and the normal-BIA group was classified with having >90% BIA.

dronabinol. Increases in ratings of forgetfulness, withdrawn, dreaming, clumsy, heavy limbs, heart pounding, jittery, and decreases in ratings of energetic, social, and talkative were reported in the normal BIA group with 30 mg dronabinol. There were no significant changes in vital signs or performance on neurocognitive measures in response to marijuana. Notably, the time course of subjective effects peaked quickly and declined thereafter for smoked marijuana, while oral dronabinol responses took longer to peak and persisted longer. Additionally, marijuana but not dronabinol produced dry mouth and thirst.

In general, AEs reported in this study were low in both drug conditions for both subject groups. In the low BIA group, nausea was reported by one subject in both the 10 and 20 mg dronabinol conditions, while an uncomfortable level of intoxication was produced by the 30 mg dose in two subjects. There were no AEs reported in this group following marijuana at any dose. In the normal BIA group, the 30 mg dose of dronabinol produced an uncomfortable level of intoxication in three subjects and headache in one subject, while the 3.9% marijuana produced diarrhea in one subject.

The authors conclude that smoked marijuana can acutely increase caloric intake in low BIA subjects without significant cognitive impairment. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Additional limitations in this study include not utilizing actual weight gain as a primary measure. However, the study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

A second study conducted by **Haney et al. (2007)** is entitled, "Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep". The design of this study was nearly identical to the one conducted by this laboratory in 2005 (see above), but there was no stratification of subjects by BIA. The subjects were 10 HIV-positive patients who were maintained on two antiretroviral medications and had a history of smoking marijuana at least twice weekly for 4 weeks prior to entry into the study. On average, individuals had smoked 3 marijuana cigarettes per day, 5 times per week for 19 years.

Subjects participated in 8 sessions that tested the acute effects of 0, 5 and 10 mg dronabinol oral capsules and marijuana cigarettes with 0, 2.0% and 3.9% THC concentration by weight, using a double-dummy design (with 4 sessions involving only one active drug and 4 interspersed placebo sessions). Both drug and placebo sessions lasted for 4 days each, with active drug administration occurring 4 times per day (every 4 hours). Testing occurred in two 16-day inpatient stays. In the intervening outpatient period, subjects were allowed to smoke marijuana prior to re-entry to the study unit for the second inpatient stay.

Marijuana was administered using a standardized cued procedure: (1) "light the cigarette" (30 seconds), (2) "prepare" (5 seconds), (3) "inhale" (5 seconds), (4) "hold smoke in lungs" (10 seconds), and (5) "exhale." Each subject smoked three puffs in this manner, with a 40-second interval between each puff.

Caloric intake was used as a surrogate measure for weight gain, but subjects were also weighed throughout the study (a measure which was not collected in the 2005 study by this group). Subjects received a box containing a variety of food and beverage items and were told to record consumption of these items following that day's administration of the test drug. Subjective measures included 0-100 point VAS for drug effect, good effect, bad effect, take drug again, drug liking, hungry, full, nauseated, thirsty, desire to eat. Neurocognitive measures and vital signs were monitored. Sleep was assessed using both the Nightcap sleep monitoring system and selected VAS measures related to sleep.

Both 5 and 10 mg dronabinol ($p < 0.008$) and 2.0% and 3.9% THC marijuana ($p < 0.01$) dose-dependently increased caloric intake compared with placebo. This increase was generally accomplished through increases in incidents of eating, rather than an increase in the calories consumed in each incident. Subjects also gained similar amounts of weight after the highest dose of each cannabinoid treatment: 1.2 kg (2.6 lbs) after 4 days of 10 mg dronabinol, and 1.1 kg (2.4 lbs) after 4 days of 3.9% THC marijuana. The 3.9% THC marijuana dose also increased the desire to eat and ratings of hunger.

Ratings of good drug effect, high, drug liking, and desire to smoke again were significantly increased by 10 mg dronabinol and 2.0% and 3.9% THC marijuana doses compared to placebo. Both marijuana doses increased ratings of stimulated, friendly, and self-confident. The 10 mg dose of dronabinol increased ratings of concentration impairment, and the 2.0% THC marijuana dose increased ratings of anxious. Dry mouth was induced by 10 mg dronabinol (10 mg) and 2.0% THC marijuana. There were no changes in neurocognitive performance or objective sleep measures from administration of either cannabinoid. However, 3.9% THC marijuana increased subjective ratings of sleep.

The authors conclude that both dronabinol and smoked marijuana increase caloric intake and produce weight gain in HIV-positive patients. However, it is possible that the low degree of cognitive impairment reported in this study may reflect the development of tolerance to cannabinoids in this subject population, since all individuals had current histories of chronic marijuana use. This study produced positive results suggesting that marijuana should be studied further as a treatment for appetite stimulation in HIV patients.

3.3 Spasticity in Multiple Sclerosis

Only one randomized, double-blind, placebo-controlled Phase 2 study examined the effects of smoked marijuana on spasticity in MS.

This study was conducted by **Corey-Bloom et al. (2012)** and is entitled, "Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial". The subjects were 30 patients with MS-associated spasticity and had moderate increase in tone (score $\geq$ 3 points on the modified Ashworth scale). Participants were allowed to continue other MS medications, with the exception of benzodiazepines. Eighty percent of subjects had a history of marijuana use and 33% had used marijuana within the previous year.

Subjects participated in two 3-day test sessions, with an 11 day washout period. During each test session they smoked a 4.0% THC marijuana cigarette once per day or a placebo cigarette once per day. Smoking occurred through a standardized cued-puff procedure: (1) inhalation for 5 seconds, (2) breath-hold and exhalation for 10 seconds, (3) pause between puffs for 45 seconds. Subjects completed an average of four puffs per cigarette.

The primary outcome measure was change in spasticity on the modified Ashworth scale. Additionally, subjects were assessed using a VAS for pain, a timed walk, and cognitive tests (Paced Auditory Serial Addition Test) and AEs.

Treatment with 4.0% THC marijuana reduced subject scores on the modified Ashworth scale by an average of 2.74 points more than placebo ($p < 0.0001$) and reduced VAS pain scores compared to placebo ($p = 0.008$). Scores on the cognitive measure decreased by 8.7 points more than placebo ($p = 0.003$). However, marijuana did not affect scores for the timed walk compared to placebo. Marijuana increased rating of feeling high compared to placebo.

7 subjects did not complete the study due to adverse events (two subjects felt uncomfortably "high", two had dizziness and one had fatigue). Of those 7 subjects who withdrew, 5 had little or no previous experience with marijuana. When the data were re-analyzed to include these drop-out subjects, with the presumption they did not have a positive response to treatment, the effect of marijuana was still significant on spasticity.

The authors conclude that smoked marijuana had usefulness in reducing pain and spasticity associated with MS. It is concerning that marijuana-naïve subjects dropped out of the study because they were unable to tolerate the psychiatric AEs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact. However, the current study produced positive results suggesting that marijuana should be studied further as an adjunct treatment for spasticity in MS patients.

3.4 Asthma

Tashkin et al. (1974) examined bronchodilation in 10 subjects with bronchial asthma in the study entitled, "Acute Effects of Smoked Marijuana and Oral Δ^9-

Tetrahydrocannabinol on Specific Airway Conductance in Asthmatic Subjects". The study was a double-blind, placebo-controlled, crossover design. All subjects were clinically stable at the time of the study; four subjects were symptom free, and six subjects had chronic symptoms of mild to moderate severity. Subjects were tested with 0.25ml of isoproterenol HCl prior to the study to ensure they responded to bronchodilator medications. Subjects were not allowed to take bronchodilator medication within 8 hours prior to the study. Previous experience with marijuana was not required for participation in the study, but 7 of the 10 subjects reported previous use of marijuana at a rate of less than 1 marijuana cigarette per month. No subjects reported marijuana use within 7 days of the study.

The study consisted of four test sessions with an interval of at least 48 hours between sessions. On two test sessions subjects smoked 7 mg/kg of body weight of either marijuana, with 2% THC concentration by weight, or placebo marijuana. During the other two test sessions, subjects ingested capsules with either 15mg of synthetic THC or placebo. Marijuana was administered using a uniform smoking technique: subjects inhaled deeply for 2-4 seconds, held smoke in lungs for 15 seconds, and resumed normal breathing for approximately 5 seconds. The author did not provide a description of the number of puffs taken at any smoking session. The authors state that the smoking procedure was repeated until the cigarette was consumed, which took approximately 10 minutes.

The outcome measure used was specific airway conductance (SGaw), as calculated using measurements of thoracic gas volume (TGV) and airway resistance (Raw) using a variable-pressure body plethysmograph. Additionally, an assessment of degree of intoxication was administered only to those subjects reporting previous marijuana use. This assessment consisted of subjects rating "how 'high' they felt" on a scale of 0-7, 7 representing "the 'highest' they had ever felt after smoking marijuana".

Marijuana produced a significant increase of 33-48% in average SGaw compared to both baseline and placebo ($P < 0.05$). This significant increase in SGaw lasted for at least 2 hours after administration. The average TGV significantly decreased by 4-13% compared to baseline and placebo ($P < 0.05$). The author stated that all subjects reported feelings of intoxication after marijuana administration.

The authors conclude that marijuana produced bronchodilation in clinically stable asthmatic subjects with minimal to moderate bronchospasms. Study limitations include: inclusion of subjects with varying severity of asthmatic symptoms, use of SGaw to measure lung responses to marijuana administration, and administration of smoke to asthmatic subjects. Smoke delivers a number of harmful substances and is not an optimal delivery symptom, especially for asthmatic patients. FEV1 via spirometry is the gold standard to assess changes in lung function, pre and post asthma treatment, by pharmacotherapy. SGaw has been shown to be a valid tool in bronchoconstriction lung assessment; however, since the FEV1 method was not utilized, it is unclear whether these results would correlate if the FEV1 method had been employed.

3.5 Glaucoma

Two randomized, double-blind, placebo-controlled Phase 2 clinical studies examined smoked marijuana in glaucoma (**Crawford and Merritt, 1979; Merritt et al., 1980**). In both studies, intraocular pressure (IOP) was significantly reduced 30 minutes after smoking marijuana. Maximal effects occurred 60-90 minutes after smoking, with IOP returning to baseline within 3-4 hours. These two studies were included in the 1999 IOM report on the medical uses of marijuana. Because our independent analysis of these studies concurred with the conclusions from the 1999 IOM report, these studies will not be discussed in further detail in this review. No recent studies have been conducted examining the effect of inhaled marijuana on IOP in glaucoma patients. This lack of recent studies may be attributed to the conclusions made in the 1999 IOM report that while cannabinoids can reduce intraocular pressure (IOP), the therapeutic effects require high doses that produce short-lasting responses, with a high degree of AEs. This high degree of AEs means that the potential harmful effects of chronic marijuana smoking may outweigh its modest benefits in the treatment of glaucoma.

3.6 Conclusions

Of the eleven randomized, double-blind, placebo-controlled Phase 2 clinical studies that met the criteria for review (see Sections 2.2 and 2.3), ten studies administered marijuana through smoking, while one study utilized marijuana vaporization. In these eleven studies, there were five different therapeutic indications: five examined chronic neuropathic pain, two examined appetite stimulation in HIV patients, two examined glaucoma, one examined spasticity in MS, and one examined asthma.

There are limited conclusions that can be drawn from the data in these published studies evaluating marijuana for the treatment of different therapeutic indications. The analysis relied on published studies, thus information available about protocols, procedures, and results were limited to documents published and widely available in the public domain. The published studies on medical marijuana are effectively proof-of-concept studies. Proof-of-concept studies provide preliminary evidence on a proposed hypothesis regarding a drug's effect. For drugs under development, the effect often relates to a short-term clinical outcome being investigated. Proof-of-concept studies serve as the link between preclinical studies and dose ranging clinical studies. Therefore, proof-of-concept studies are not sufficient to demonstrate efficacy of a drug because they provide only preliminary information about the effects of a drug. Although these studies do not provide evidence that marijuana is effective in treating a specific, recognized disorder, these studies do support future larger well-controlled studies to assess the safety and efficacy of marijuana for a specific medical indication. Overall, the conclusions below are preliminary, based on very limited evidence.

3.6.1 Conclusions for Chronic Neuropathic Pain

In subjects with chronic neuropathic pain who are refractory to other pain treatments, five proof-of-concept studies produced positive results regarding the use of smoked marijuana for analgesia. However, the subjects in these studies continued to use their current analgesic drug regime, and thus no conclusions can be made regarding the potential efficacy of marijuana for neuropathic pain in patients not taking other analgesic drugs. Subjects also had numerous forms of neuropathic pain, making it difficult to identify whether a specific set of symptoms might be more responsive to the effects of marijuana. It is especially concerning that some marijuana-naïve subjects had intolerable psychiatric responses to marijuana exposure at analgesic doses.

3.6.2 Conclusions for Appetite Stimulation in HIV

In subjects who were HIV-positive, two proof-of-concept studies produced positive results with the use of both dronabinol and smoked marijuana to increase caloric intake and produce weight gain in HIV-positive patients. However, the amount of THC in the marijuana tested in these studies is four times greater than the dose of dronabinol typically tested for appetite stimulation (10 mg vs. 2.5 mg; Haney et al., 2005). Thus, it is possible that the low degree of AEs reported in this study may reflect the development of tolerance to cannabinoids in this patient population, since all individuals had current histories of chronic marijuana use. Thus, individuals with little prior exposure to marijuana may not respond similarly and may not be able to tolerate sufficient marijuana to produce appetite stimulation.

3.6.3 Conclusions for Spasticity in MS

In subjects with MS, a proof of concept study produced positive results using smoked marijuana as a treatment for pain and symptoms associated with treatment-resistant spasticity. The subjects in this study continued to take their current medication regiment, and thus no conclusions can be made regarding the potential efficacy of marijuana when taken on its own. It is also concerning that marijuana-naïve subjects dropped out of the study because they were unable to tolerate the psychiatric AEs induced by marijuana. The authors suggest that future studies should examine whether different doses can result in similar beneficial effects with less cognitive impact.

3.6.4 Conclusions for Asthma

In subjects with clinically stable asthma, a proof of concept study produced positive results of smoked marijuana producing bronchodilation. However, in this study marijuana was administered at rest and not while experiencing bronchospasms. Additionally, the administration of marijuana through smoking introduces harmful and irritating substances to the subject, which is undesirable especially in asthmatic patients.

Thus the results suggest marijuana may have bronchodilator effects, but it may also have undesirable adverse effects in subjects with asthma.

3.6.5 Conclusions for Glaucoma

As noted in Sections 3.5, the two studies that evaluated smoked marijuana for glaucoma were conducted decades ago, and they have been thoroughly evaluated in the 1999 IOM report. The 1999 IOM report concludes that while the studies with marijuana showed positive results for reduction in IOP, the effect is short-lasting, requires a high dose, and is associated with many AEs. Thus, the potential harmful effects may outweigh any modest benefit of marijuana for this condition. We agree with the conclusions drawn in the 1999 IOM report.

3.7 Design Challenges for Future Studies

The positive results reported by the studies discussed in this review support the conduct of more rigorous studies in the future. This section discusses methodological challenges that have occurred in clinical studies with smoked marijuana. These design issues should be addressed when larger-scale clinical studies are conducted to ensure that valid scientific data are generated in studies evaluating marijuana's safety and efficacy for a particular therapeutic use.

3.7.1 Sample Size

The ability for results from a clinical study to be generalized to a broader population is reliant on having a sufficiently large study sample size. However, as noted above, all of the 11 studies reviewed in this document were early Phase 2 proof of concept studies for efficacy and safety. Thus, the sample sizes used in these studies were inherently small, ranging from 10 subjects per treatment group (Tashkin et al., 1974; Haney et al., 2007) to 25 subjects per treatment group (Abrams et al., 2007). These sample sizes are statistically inadequate to support a showing of safety or efficacy. FDA's recommendations about sample sizes for clinical trials can be found in the *Guidance for Industry: E9 Statistical Principles for Clinical Trials (1998).*[35] For example, "the number of subjects in a clinical trial should always be large enough to provide a reliable answer to the questions addressed. This number is usually determined by the primary objective of the trial. The method by which the sample size is calculated should be given in the protocol, together with the estimates of any quantities used in the calculations (such as variances, mean values, response rates, event rates, difference to be detected)." (pg. 21). Other clinical FDA *Guidance for Industry*[36] may also contain recommendations regarding the appropriate number of subjects that should be investigated for a specific medical indication.

[35] The *Guidance for Industry: E9 Statistical Principles for Clinical Trials* can be found at: *www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073137.pdf*
[36] Other Guidances for Industry can be found at: *www.fda.gov/Drugs/GuidanceComplianceRegulatory Information/Guidances/ ucm064981.htm*

3.7.2 Marijuana Dose Standardization

Dose standardization is critical for any clinical study in order to ensure that each subject receives a consistent exposure to the test drug. The *Guidance for Industry: Botanical Drug Products* (2004)[37] provides specific information on the development of botanical drug products. Specifically, this guidance includes information about the need for well-characterized and consistent chemistry for the botanical plant product and for consistent and reliable dosing. Specifically for marijuana studies, dose standardization is important because if marijuana leads to plasma levels of cannabinoids that are significantly different between subjects, this variation may lead to differences in therapeutic responsivity or in the prevalence of psychiatric AEs.

In most marijuana studies discussed in this review, investigators use a standardized cued smoking procedure. In this procedure, a subject is instructed to inhale marijuana smoke for 5 seconds, hold the smoke in the lungs for 10 seconds, exhale and breathe normally for 40 seconds. This process is repeated to obtain the desired dose of the drug. However, this procedure may not lead to equivalent exposure to marijuana and its constituent cannabinoids, based on several factors:

- Intentional or unintentional differences in the depth of inhalation may change the amount of smoke in the subject's lungs.
- Smoking results in loss from side stream smoke, such that the entire dose is not delivered to the subject.
- There may be differences in THC concentration along the length of a marijuana cigarette. According to Tashkin et al. (1991), the area of the cigarette closest to the mouth tends to accumulate a higher concentration of THC, but this section of the cigarette is not smoked during a study.

For example, Wilsey et al. (2008) used this standardized smoking procedure. The reported mean (range) of marijuana cigarettes consumed was 550 mg (200-830mg) for the low strength marijuana (3.5% THC) and 490 mg (270-870mg) for the high strength marijuana (7% THC). This wide range of amounts of marijuana cigarette smoked by the individual subjects, even with standardized smoking procedure and controlled number of puffs, supports the issues with delivering consistent doses with smoke marijuana.

In other marijuana studies that do not use a cued smoking procedure, subjects are simply told to smoke the marijuana cigarette over a specific amount of time (usually 10 minutes) without further instruction (Crawford and Merritt, 1979; Merritt et al., 1980; Ellis et al., 2009). The use of a nonstandardized procedure may lead to non-equivalent exposures to marijuana and its constituent

[37] The *Guidance for Industry: Botanical Drug Products* can be found at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070491.pdf.

cannabinoids between subjects because of additional factors that are not listed above, such as:

- Differences in absorption and drug response if subjects (especially marijuana-naïve ones) are not instructed to hold marijuana smoke in their lungs for a certain period of time.

- Prolonged periods between puffs may increase loss to side stream smoke.

- Subjects may attempt to smoke the marijuana cigarette in the way they would smoke a tobacco cigarette, which relies primarily on short, shallow puffs.

In both standardized and non-standardized smoking procedures, subjects may seek to control the dose of THC through self-titration (Crawford and Merritt, 1979; Merritt et al., 1980; Tashkin et al., 1974; Abrams et al., 2007; Ellis et al., 2009). Self-titration involves an individual moderating the amount of marijuana smoke inhaled over time in order to obtain a preferred level of psychoactive or clinical response. The ability of an individual to self-titrate by smoking is one reason given by advocates of "medical marijuana" in support of smoking of marijuana rather than through its ingestion via edibles. However, for research purposes, self-titration interferes with the ability to maintain consistent dosing levels between subjects, and thus, valid comparisons between study groups.

All of these factors can make the exact dose of cannabinoids received by a subject in a marijuana study difficult to determine with accuracy. Testing whether plasma levels of THC or other cannabinoids are similar between subjects following the smoking procedure would establish whether the procedure is producing appropriate results. Additionally, studies could be conducted to determine if vaporization can be used to deliver consistent doses of cannabinoids from marijuana plant material. Specifically, vaporization devices that involve the collection of vapors in an enclosed bag or chamber may help with delivery of consistent doses of marijuana. Thus, more information could be collected on whether vaporization is comparable to or different than smoking in terms of producing similar plasma levels of THC in subjects using identical marijuana plant material.

3.7.3 Acute vs. Chronic Therapeutic Marijuana Use

The studies that were reviewed administered the drug for short durations lasting no longer than 5 days (Abrams et al., 2007; Ellis et al., 2009; Ware et al., 2010). Thus all studies examined the short-term effect of marijuana administration for therapeutic purposes. However, many of the medical conditions that have been studied are persistent or expected to last the rest of a patient's life. Therefore, data on chronic exposure to smoked marijuana in clinical studies is needed. In this way, more information will be available regarding whether tolerance,

physical dependence, or specific adverse events develop over the course of time with continuing use of therapeutic marijuana.

3.7.4 Smoking as a Route of Administration

As has been pointed out by the IOM and other groups, smoking is not an optimum route of administration for marijuana-derived therapeutic drug products, primarily because introducing the smoke from a burnt botanical substance into the lungs of individuals with a disease state is not recommended when their bodies may be physically compromised. The 1999 IOM report on medicinal uses of marijuana noted that alternative delivery methods offering the same ability of dose titration as smoking marijuana will be beneficial and may limit some of the possible long-term health consequences of smoking marijuana. The primary alternative to smoked marijuana is vaporization, which can reduce exposure to combusted plant material containing cannabinoids. The only study to use vaporization as the delivery method was Wilsey et al. (2013). The results from Wilsey et al. (2013) showed a similar effect of decreased pain as seen in the other studies using smoking as the delivery method (Ware et al., 2010; Wilsey et al., 2008). This similar effect of decrease pain supports vaporization as a possibly viable route to administer marijuana in research, while potentially limiting the risks associated with smoking.

3.7.5 Difficulty in Blinding of Drug Conditions

An adequate and well-controlled clinical study involves double-blinding, where both the subjects and the investigators are unable to tell the difference between the test treatments (typically consisting of at least a test drug and placebo) when they are administered. All of the studies reviewed in this document administered study treatments under double-blind conditions and thus were considered to have an appropriate study design.

However, even under the most rigorous experimental conditions, blinding can be difficult in studies with smoked marijuana because the rapid onset of psychoactive effects readily distinguishes active from placebo marijuana. The presence of psychoactive effects also occurs with other drugs. However, most other drugs have a similar psychoactive effect with substances with similar mechanisms of actions. These substances can be used as positive controls to help maintain blinding to the active drug being tested. Marijuana on the other hand, has a unique set of psychoactive effects which makes the use of appropriate positive controls difficult (Barrett et al., 1995). However, two studies did use Dronabinol as a positive control drug to help maintain blinding (Haney et al., 2005; Haney et al., 2007).

When blinding is done using only placebo marijuana, the ability to distinguish active from placebo marijuana may lead to expectation bias and an alteration in perceived responsivity to the therapeutic outcome measures. With marijuana-experienced subjects, for example, there may be an early recognition of the more

subtle cannabinoid effects that can serve as a harbinger of stronger effects, which is less likely to occur with marijuana-naïve subjects. To reduce this possibility, investigators have tested doses of marijuana other than the one they were interested in experimentally to maintain the blind (Ware et al., 2010).

Blinding can also be compromised by differences in the appearance of marijuana plant material based on THC concentration. Marijuana with higher concentrations of THC tends to be heavier and seemingly darker, with more "tar-like" substance. Subjects who have experience with marijuana have reported being able to identify marijuana from placebo cigarettes by sight alone when the plant material in a cigarette was visible (Tashkin et al., 1974; Ware et al., 2010). Thus, to maintain a double-blind design, many studies obscure the appearance of plant material by closing both ends of the marijuana cigarette and placing it in in an opaque plastic tube.

While none of these methods to secure blinding may be completely effective, it is important to reduce bias as much as possible to produce consistent results between subjects under the same experimental conditions.

3.7.6 Prior Marijuana Experience

Marijuana use histories in test subjects may influence outcomes, related to both therapeutic responsivity and psychiatric AEs. Marijuana-naïve subjects may also experience a marijuana drug product as so aversive that they would not want to use the drug product. Thus, subjects' prior experience with marijuana may affect the conduct and results of studies.

Most of the studies reviewed in this document required that subjects have a history of marijuana use (see tables in Appendix that describe specific requirements for each study). However, in studies published in the scientific literature, the full inclusion criteria with regard to specific amount of experience with marijuana may not be provided. For those studies that do provide inclusion criteria, acceptable experience with marijuana can range from once in a lifetime to use multiple times a day.

The varying histories of use might affect everything from scores on adverse event measures, safety measures, or efficacy measures. Additionally, varying amounts of experience can impact cognitive effect measures assessed during acute administration studies. For instance, Schreiner and Dunn (2012) contend cognitive deficits in heavy marijuana users continue for approximately 28 days after cessation of smoking. Studies requiring less than a month of abstinence prior to the study may still see residual effects of heavy use at baseline and after placebo marijuana administration, thus showing no significant effects on cognitive measures. However, these same measurements in occasional or naïve marijuana users may demonstrate a significant effect after acute marijuana administration. Therefore, the amount of experience and the duration of abstinence of marijuana use are important to keep in mind when analyzing results

for cognitive and other adverse event measures. Lastly, a study population with previous experience with marijuana may underreport the incidence and severity of adverse events. Because most studies used subjects with prior marijuana experience, we are limited in our ability to generalize the results, especially for safety measures, to marijuana naïve populations.

Five of 11 studies reviewed in this document included both marijuana-naïve and marijuana-experienced subjects (Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010; Merritt et al., 1980; Tashkin et al., 1974). Since the number of marijuana-naïve subjects in these studies was low, it was not possible to conduct a separate analysis compared to experienced users. However, systematically evaluating the effect of marijuana experience on study outcomes is important, since many patients who might use a marijuana product for a therapeutic use will be marijuana-naïve.

Research shows that marijuana-experienced subjects have a higher ability to tolerate stronger doses of oral dronabinol than marijuana-naïve subjects (Haney et al., 2005). Possibly, this increased tolerance is also the case when subjects smoke or vaporize marijuana. Thus, studies could be conducted that investigate the role of marijuana experience in determining tolerability of and responses to a variety of THC concentrations in marijuana.

3.7.7 Inclusion and Exclusion Criteria

For safety reasons, all clinical studies have inclusion and exclusion criteria that restrict the participation of individuals with certain medical conditions. For studies that test marijuana, these criteria may be based on risks associated with exposure to smoked material and the effects of THC. Thus, most studies investigating marijuana require that subjects qualify for the study based on restrictive symptom criteria such that individuals do not have other symptoms that may be known to interact poorly with cannabinoids.

Similarly, clinical studies with marijuana typically exclude individuals with cardiac or pulmonary problems, as well as psychiatric disorders. These exclusion criteria are based on the well-known effects of marijuana smoke to produce increases in heart rate and blood pressure, lung irritation, and the exacerbation of psychiatric disturbances in vulnerable individuals. Although these criteria are medically reasonable for research protocols, it is likely that future marijuana products will be used in patients who have cardiac, pulmonary or psychiatric conditions. Thus, individuals with these conditions should be evaluated, whenever possible.

Additionally, all studies reviewed in this document allowed the subjects to continue taking their current regimen of medications. Thus all results evaluated marijuana as an adjunct treatment for each therapeutic indication.

3.7.8 Number of Female Subjects

A common problem in clinical research is the limited number of females who participate in the studies. This problem is present in the 11 studies reviewed in this document, in which one study did not include any female subjects (Ellis et al., 2009), and three studies had a low percentage of female subjects (Abrams et al., 2007; Haney et al., 2005; Haney et al., 2007). However, each of these four studies investigated an HIV-positive patient population, where there may have been a larger male population pool from which to recruit compared to females.

Since there is some evidence that the density of CB1 receptors in the brain may vary between males and females (Crane et al., 2012), there may be differing therapeutic or subjective responsivity to marijuana. Studies using a study population that is equal parts male and female may show whether and how the effects of marijuana differ between male and female subjects.

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Appendix (Tables)

Table 1: Randomized, controlled, double-blind trials examining smoked marijuana in treatment of neuropathic pain

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
Abrams et al. (2007) *HIV-Sensory Neuropathy; Neuropathic Pain*	Marijuana Group: 25/27 22 males 5 females Placebo Group: 25/28 26 males 2 females <u>Inclusion Criteria:</u> -documented HIV -documented HIV-SN -pain score ≥30mm VAS -prior marijuana use of six or more times in lifetime <u>Previous Marijuana Experience:</u> -marijuana group: 21 current users -placebo group: 19 current users <u>Exclusion Criteria:</u> -substance abuse (including tobacco) -family history of neuropathy due to causes not HIV related -use of isoniazid, dapsone, or metronidazole within 8 weeks of enrollment	NIDA marijuana, smoked 0%, 3.65% THC <u>Smoking Procedure:</u> -signal light cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs # of puffs not specified, only specified that subjects smoked the entire marijuana/placebo cigarette On 1st and last day of intervention period BID. For all other days TID	Parallel Group *5-day treatment period*	VAS daily pain score	-52% of the marijuana group showed >30% decrease in pain score compared to 24% of placebo group. -Marijuana group had significantly greater reduction in daily pain score than placebo group. -NNT=3.6	-Rating for adverse events of anxiety, sedation, disorientation, confusion, and dizziness were significantly higher in the marijuana group compared to placebo group. -Marijuana and placebo groups showed a reduction in total mood disturbance on POMS. <u>AEs</u>: -1 grade 3 dizziness in marijuana group -2 grade 3 anxiety, 1 in each group.
Ellis et al. (2009) *HIV Sensory Neuropathy; Neuropathic*	28/34 28 males <u>Inclusion Criteria:</u> -documented HIV -documented neuropathic	NIDA marijuana, smoked 0%, 1%, 2%, 4%, 6%, 8% THC <u>Smoking Procedures:</u>	Crossover Dose-titration (on 1st day)	Pain magnitude on DDS	-Pain reduction was significantly greater after marijuana compared to placebo.	-Mood disturbance, quality of life, and psychical disability improved for both marijuana and placebo. -Moderate to severe adverse events were more common with marijuana than placebo.

Author & Date ***Indication***	**Subjects (n) completed/randomized Subject characteristics**	**Drugs Admin. Methods**	**Study Type** ***Duration***	**Primary Outcome Measure**	**Primary Outcome Measure Results**	**Adverse events/AEs**
Pain	pain refractory to ≥2 analgesics -pain score ≥5 on pain intensity subscale of DDS <u>Previous Marijuana Experience:</u> -27 subjects had previous experience -63% of subjects had no exposure for >1 year before study <u>Exclusion Criteria:</u> -current DSM-IV substance abuse disorder -lifetime history of dependence on marijuana -previous psychosis with or intolerance to cannabinoids -concurrent use of approved cannabinoid medications -positive UDS for cannabinoids during wash-in week -serious medical conditions that affect safety -alcohol or drug dependence within 12 months of study	- Verbally cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs -unknown number of puffs QID	*2, 5-day treatment phase, with 2-week washout period*		-NNT=3.5	-HIV disease parameters did not differ for marijuana or placebo. -Adverse events included: concentration difficulties, fatigue, sleepiness or sedation, increased duration of sleep, reduced salivation, and thirst. These adverse events were more frequent in marijuana compared to placebo. <u>Withdrawals for drug related reasons:</u> -1 cannabis-naïve subject had acute cannabis-induced psychosis -1 subjects developed an intractable smoking-related cough during marijuana administration
Wilsey et al. (2008) *Neuropathic pain; Various Causes*	32/38 20 males 18 females <u>Inclusion Criteria:</u> -CRPS type I, spinal cord	NIDA marijuana, smoked 0%, 3.55%, 7% THC <u>Smoking Procedure:</u> Verbally cued	Crossover *3, 6-hour sessions, with 3-day between*	VAS spontaneous pain intensity	-A significant decrease in pain intensity for both strengths of marijuana compared to placebo	-7% THC marijuana significantly decreased functioning on neurocognitive measures compared to placebo. -Subjective effects were greater for 7% THC marijuana than 3.55%

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	injury, peripheral neuropathy, or nerve damage -previous marijuana use <u>Previous Marijuana Experience:</u> -median (range) time from previous exposure: 1.7 years (31 days to 30 years) -median (range) exposure duration: 2 years (1 day to 22 years). <u>Exclusion Criteria:</u> -no marijuana or cannabinoid medication use for 30 days prior to study; confirmed by UDS -severe depression -history of schizophrenia or bipolar depression -uncontrolled hypertension, cardiovascular disease, and pulmonary disease -active substance abuse	smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat procedure for desired number of puffs Cumulative dosing procedure: -escalate the number of puffs from 2 to 4 puffs over 3 smoking sessions with 1 hour between sessions TID	*sessions*			THC marijuana with significantly more ratings of good drug effect, bad drug effect, feeling high, feeling stoned, impaired, sedation, confusion, and hunger compared to placebo.
Ware et al. (2010) *Post-traumatic or postsurgical neuropathic pain*	21/23 11 males 12 females <u>Inclusion Criteria:</u> -neuropathic pain for ≥ 3 months caused by trauma or surgery -allodynia and hyperalgesia -pain score >4cm VAS -no marijuana use for 1	NIDA placebo; Prairie Plant System Inc. (Canada) marijuana, smoked 0%, 2.5%, 6%, 9.4% THC (25 mg of marijuana/placebo plant material was placed in opaque	Crossover *4, 5-day out-patient* treatment phase, with 9-day washout periods*	Pain intensity on 11-item NRS	-Average daily pain intensity was significantly lower after 9.4% THC compared to placebo.	-Anxiety and depression were significantly improved with 9.4% THC compared to placebo. -No significant difference between placebo and 9.4% THC for subjective effects. <u>AEs</u>: -248 mild AEs were reported -6 moderate AEs were reported: 2 fall, 1 increased pain, 1 numbness,

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	year prior to study -stable analgesic regimen -normal liver and renal function <u>Previous Marijuana Experience:</u> -18 subjects had used marijuana before <u>Exclusion Criteria:</u> -pain due to cancer or nociceptive causes -significant cardiac or pulmonary disease -current substance abuse or dependence (including marijuana) -history of psychotic disorders -current suicidal ideations	gelatin capsules) <u>Smoking Procedures:</u> -1) Break one capsule open and tip content into the bowl of a titanium pipe 2) light marijuana material 3) 5s inhale smoke 4) 10s hold smoke in lungs 5) Exhale 1 puff burned all 25 mg of plant material TID Intermediate doses were used to help maintain blinding				1 drowsiness, 1 pneumonia -Most frequently reported drug-related AEs for 9.4% THC: headache, dry eyes, burning sensation, dizziness, numbness, and cough. <u>Withdrawals for drug related reason:</u> -1 subject had increased pain after 6% THC administration -1 subject tested positive for cannabinoids in urine test during placebo treatment
Wilsey et al. (2013) *Neuropathic Pain; Various Causes*	36/39 28 males 11 females <u>Inclusion Criteria:</u> -CRPS type 1, thalamic pain, spinal cord injury, peripheral neuropathy, radiculopathy, or nerve injury -previous marijuana use <u>Previous Marijuana Experience:</u> - median (range) time from last exposure prior to	NIDA marijuana, vaporized 0%, 1.29%, 3.53% THC <u>Smoking Procedures:</u> - Verbally cued inhalation of vaporized material in the balloon with each puff consisting of: 1) 5s inhale vapors, 2) 10s hold vapors in lungs 3) 40s exhale and breath normally	Crossover *3, 6-hour sessions, with at least 3 days between sessions*	VAS spontaneous pain intensity	-Number of subjects that showed a 30% reduction in pain intensity was significantly greater for both strengths of marijuana compared to placebo. -Both strengths of marijuana showed a similar significant decrease in pain compared to placebo. -NNT=3.2 for 1.29% THC marijuana vs.	-Scores for feeling stoned, feeling high, like the drug effect, feeling sedated, and feeling confused were significantly greater for 3.53% THC marijuana compared to 1.29% THC marijuana, and for both strengths of marijuana compared to placebo. -Scores for feeling drunk and feeling impaired are significantly greater in both strengths of marijuana compared to placebo. -Scores for desired more of the drug were significantly greater for 1.29% THC marijuana compared to placebo, with no significant

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Primary Outcome Measure Results	Adverse events/AEs
	screening: 9.6 years (1 day to 45 years) -16 current marijuana users and 23 past users -# smoked daily: 6 current users, 5 past users -# used approx. once every 2 weeks: 8 current users, 6 past users -# used once every 4 weeks or less: 2 current users, 12 past users <u>Exclusion Criteria:</u> -no marijuana or cannabinoid medication use for 30 days prior to study; confirmed by UDS -severe depression -suicidal ideations -diagnoses of serious mental illness -uncontrolled hypertension, cardiovascular disease, or chronic pulmonary disease -active substance abuse	4) repeat procedure for desired number of puffs BID Cumulative & Flexible Dosing: -1st drug admin. consisted of 4 puffs from balloon. -Followed 2 hours later by 2nd drug admin. -2nd drug admin. consisted of 4 to 8 puffs from balloon; number of puffs taken was left up to the subject so they could self-titrate to their target does, which balanced desired response and tolerance levels.			placebo. -NNT=2.9 for 3.53% THC marijuana vs. placebo.	difference seen for 3.53% THC marijuana. -3.53% THC marijuana had significantly worse performance than 1.29% THC marijuana for learning and memory. -Both strengths of marijuana significantly reduced scores on attention compared to placebo.

*Out-patient: subjects were given enough doses of marijuana/placebo to last the 5-day treatment phase, and then were sent home for the remainder of the treatment phase.
AE=Adverse Event; BID=drug administered two times per day; CRPS=complex regional pain syndrome; DDS=Descriptor Differential Scale; NIDA=National Institute of Drug Abuse; NNT=Number Needed to Treat; NRS=Numeric Rating Scale; QID=drug administered four times per day; THC=delta-9-tetrahydrocannbinol; TID=drug administered three times per day; UDS=urine drug screen; VAS=Visual Analog Scale.

Table 2: **Randomized, controlled, double-blind trials examining smoked marijuana in treatment of appetite stimulation in HIV/AIDS**

Author & Date ***Indication***	**Subjects (n) completed/randomized** **Subject characteristics**	**Drugs** **Admin. Methods**	**Study Type** ***Duration***	**Primary Outcome Measure**	**Results (summary)**	**Adverse events/AEs**
Haney et al. (2005) *HIV+ with either normal muscle mass (Normal-BIA) or clinically significant loss of muscle mass (Low-BIA)*	Low-BIA: 15/17 12 males 3 females Normal-BIA: 15/18 15 males <u>Inclusion Criteria:</u> -21-50 years of age -prescribed at least 2 antiretroviral medications -currently under the care of a physician for HIV management -medically and psychiatrically stable -smoke marijuana ≥ 2x/week for past 4 weeks <u>Previous Marijuana Experience:</u> -mean (SD) # of days/week of marijuana use: Low-BIA= 6 (2); Normal-BIA=5 (2) -mean (SD) # marijuana cigarettes/day: Low-BIA=3 (2); Normal-BIA=3 (1) -mean (SD) years of marijuana use: Low-BIA=12.2 (8.3); Normal-BIA=10.8 (2.6) <u>Exclusion Criteria:</u> -diagnosis of nutritional	NIDA marijuana, smoked 0%, 1.8%, 2.8%, 3.9% THC Dronabinol, oral 0, 10, 20, 30mg Double-dummy drug admin. Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking <u>Smoking Procedures:</u> Verbally cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat for 3 puffs per smoking session	Crossover *8, 7-hour session, with at least 1 day between sessions*	No primary outcome measure is specified Related outcome measure was caloric intake	-In Low-BIA all dronabinol doses and 1.8% and 3.9% THC marijuana significantly increased caloric intake compared with placebo.	-Ratings of high and good drug effect were significantly increased for all strengths of marijuana and all doses of dronabinol except 10mg dronabinol. -3.9% THC significantly increased ratings of dry mouth and thirsty compared to placebo. -Low-BIA group showed no significant adverse event ratings, and in the normal-BIA group the only significant adverse events in response to marijuana included: diarrhea after 3.9% THC marijuana. -Dronabinol had more incidences of adverse events at all doses compared to marijuana.

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
	malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease -an opportunistic infection within past 3 months -obesity -use of steroids within past 3 weeks -drug dependence (excluding marijuana or nicotine)	QD				
Haney et al. (2007) *HIV+*	10 9 males 1 female <u>Inclusion Criteria:</u> -21-50 years of age -taking ≥ 2 antiretroviral medications -under the care of a physician for HIV management -medically and psychiatrically stable -smoke marijuana ≥ 2x/week for the past 4 weeks <u>Previous Marijuana Experience:</u> -mean (SD) # of days/week of marijuana use: 4.6 (0.6)	NIDA marijuana, smoked 0%, 2%, 3.9% THC Dronabinol, oral 0, 5, 10mg Double-dummy drug admin. Procedures: -only 1 active dose per session -one dronabinol/placebo capsule followed 1 hour later by marijuana/placebo smoking <u>Smoking Procedures:</u>	Crossover *2, 16-day treatment phases, with 5-10 days between phases* *Each 16-day treatment phase consisted of 2, 4-day active drug period with 4-day placebo period between active drug periods.*	No primary outcome measure is specified Related outcome measures were Caloric Intake & Body Weight	-Both strengths of marijuana significantly increased caloric intake compared to placebo. -3.9% THC marijuana significantly increased body weight compared to placebo.	-Both strengths of marijuana significantly increased ratings of: good drug effect, high, mellow, stimulate, friendly, and self-confident. Only 2% THC marijuana significantly increased ratings of anxious. -Both strengths of marijuana significantly increased subjective measures for satisfied sleep and estimated time of sleep.

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
	-mean (SD) # marijuana cigarettes/day: 3.2 (0.8) -mean (SD) years of marijuana use: 18.6 (3.3) <u>Exclusion Criteria:</u> -diagnosis of nutritional malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease -an opportunistic infection within past 3 months -obesity -use of steroids within past 3 weeks -drug dependence (excluding marijuana or nicotine)	Light cued smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 40s exhale and breath normally 4) repeat for 3 puffs per smoking session QID				

AE=Adverse Event; BIA=Bioelectric Impedance Analysis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; QID=drug administered four times per day; THC=delta-9-tetrahydrocannbinol

Table 3: **Randomized, controlled, double-blind trails examining smoked marijuana in treatment of spasticity in Multiple Sclerosis**

Author & Date ***Indication***	**Subjects (n) completed/randomized Subject characteristics**	**Drugs Admin. Methods**	**Study Type** ***Duration***	**Primary Outcome Measure**	**Primary Outcome Measure Results**	**Adverse events/AEs**
Corey-Bloom et al. (2012) *Multiple Sclerosis; Spasticity*	30/37 11 males 19 females <u>Inclusion Criteria:</u> -documented MS -spasticity -moderate increase in tone (score ≥ 3 on modified Ashworth scale <u>Previous Marijuana Experience:</u> -24 subjects had previous exposure to marijuana -10 subjects used marijuana within the year <u>Exclusion Criteria:</u> -no marijuana smoking for ≤1 month prior to screening -psychiatric disorder (other than depression) -history of substance use -substantial neurological disease other than MS -severe or unstable medical illnesses -known pulmonary disorders -using high dose narcotic medication for pain -using benzodiazepines to control spasticity	NIDA marijuana, smoked 0%, 4% THC <u>Smoking Procedure:</u> smoking of marijuana cigarette with each puff consisting of: 1) 5s inhale smoke, 2) 10s hold smoke in lungs 3) 45s exhale and breath normally 4) repeat for an average of 4 puffs per smoking session QD	Crossover *2, 3-day treatment periods, with 11 day washout period*	Spasticity on the Modified Ashworth Scale	-Smoking marijuana significantly reduced spasticity scores compared to placebo	-Marijuana reduced scores on cognitive measure compared to placebo. -Marijuana significantly increased perceptions of "highness" compared to placebo <u>Withdrawals for drug-related reasons:</u> -2 subjects felt uncomfortably high -2 dizziness -1 fatigue

AE=Adverse Event; MS= Multiple Sclerosis; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; THC=delta-9-tetrahydrocannbinol

Table 4: **Randomized, controlled, double-blind trails examining smoked marijuana in treatment of intraocular pressure in Glaucoma**

Author & Date ***Indication***	**Subjects (n) completed/randomized Subject characteristics**	**Drugs Admin. Methods**	**Study Type** ***Duration***	**Primary Outcome Measure**	**Results (summary)**	**Adverse events/AEs**
Crawford & Merritt (1979) *Hypertensive and Normotensive Glaucoma*	HT group: 8 4 males 4 females NT group: 8 4 males 4 females <u>Inclusion Criteria:</u> -documented glaucoma <u>Previous Marijuana Experience:</u> -all were marijuana naïve <u>Exclusion Criteria:</u> -coronary artery disease	NIDA marijuana, smoked 0%, 2.8% THC <u>Smoking Procedure:</u> -instructed to inhale 20 times deeply and retain smoke in lungs -smoke marijuana/placebo cigarette in 5 minutes QD	Crossover *4, 1-day sessions, no time between sessions*	No primary outcome measure is specified Related outcome measure was IOP	-Marijuana decreased IOP by 37-44% from baseline. -The maximal decrease in IOP was significantly greater in HT (-14mmHg) than NT (-9mmHg) after marijuana .	-Placebo marijuana increased heart rate for 10 minutes in both groups. -The maximal increase in heart rate was significantly greater in NT than HT after marijuana. -The maximal decrease in blood pressure was significantly greater in HT than NT after marijuana.
Merritt et al. (1980) *Glaucoma*	18 12 males 6 females (31 glaucoma eyes, analyzed results for each eye) <u>Inclusion Criteria:</u> -documented glaucoma <u>Previous Marijuana Experience:</u> -9 subjects had used marijuana at least once <u>Exclusion Criteria:</u> -cardiac, neurological,	NIDA marijuana, smoked 0%, 2% THC <u>Smoking Procedure:</u> -None described -smoked 1 marijuana/placebo cigarette over 10-20 minutes QD	Crossover *2, 1-day sessions*	No primary outcome measure is specified Related outcome measure was IOP	-Marijuana significantly decreased IOP compared to placebo	-Marijuana significantly increased heart rate compared to placebo -Blood pressure significantly decreased after marijuana -All subjects experienced hunger, thirst, euphoria, drowsy, and feeling cold -Observed adverse events were greater in marijuana naïve subjects than in subjects with prior marijuana experience. <u>AEs</u>: -5 subjects postural hypotension -8 subjects anxiety with

Author & Date *Indication*	Subjects (n) completed/randomized Subject characteristics	Drugs Admin. Methods	Study Type *Duration*	Primary Outcome Measure	Results (summary)	Adverse events/AEs
	and psychiatric dysfunction					tachycardia and palpitations

AE=Adverse Event; HT=Hypertensive; IOP=Intraocular pressure; NIDA=National Institute of Drug Abuse; NT=Normotensive; QD=drug administered one time per day; THC=delta-9-tetrahydrocannbinol

Table 5: **Randomized, controlled, double-blind trails examining smoked marijuana in treatment of asthma**

Author & Date ***Indication***	**Subjects (n) completed/randomized Subject characteristics**	**Drugs Admin. Methods**	**Study Design** ***Duration***	**Primary Outcome Measure**	**Results (summary)**	**Adverse events/AEs**
Tashkin et al. (1974) *Bronchial Asthma*	10 5 males 5 females <u>Inclusion Criteria:</u> -diagnosis of bronchial asthma -asthma relieved by bronchodilator medication -clinically stable <u>Previous Marijuana Experience:</u> -7 subjects had previous exposure to marijuana -amount of exposure <1 cigarette/month <u>Exclusion Criteria:</u> -no marijuana use ≤7 days of study -psychiatric illness	NIMH (NIDA) marijuana, smoked 0%, 2% THC Dronabinol, oral 0, 15mg Dosing is 7mg/kg of body weight of plant material <u>Smoking Procedure:</u> smoking of marijuana cigarette with each puff consisting of: 1) 2-4s deep inhale smoke, 2) 15s hold smoke in lungs 3) 5s exhale and breath normally 4) repeat till entire cigarette is smoked QD	Crossover *4, 1-day sessions, with at least 48 hours between sessions*	No primary outcome measure is specified Related outcome measure was sGaw	-Marijuana significantly increased sGaw (33-48%) compared to placebo and baseline	-Marijuana initially significantly increased pulse rate compared to placebo, and then at 90 minutes pulse rate was significantly decreased compared to baseline. -All subjects felt intoxicated after marijuana.

AE=Adverse Event; NIDA=National Institute of Drug Abuse; QD=drug administered one time per day; sGaw=Specific Airway Conductance; THC=delta-9-tetrahydrocannbinol