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Meta-Analysis of Herbal Cannabis Therapy for Chronic Pain

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META-ANALYSIS OF HERBAL CANNABIS THERAPY FOR CHRONIC PAIN

by

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Dedication & Acknowledgements

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Abstract

Since the first so-called “medical marijuana” legislation was passed in California in 1996, a total of twenty states and the District of Columbia have passed laws permitting limited use of cannabis. Despite the changes in state laws, cannabis remains illegal for any purpose under federal law. Changes in state laws have coincided with a renewed interest in the substance for the treatment of a variety of conditions. There has been a significant increase in published data over the past twenty years examining the efficacy of cannabis as an appetite stimulant, antiemetic agent, and analgesic adjuvant. The purpose of this meta-analysis was to synthesize published data on cannabis use as an analgesic agent. Five studies meeting inclusion criteria were located through searches of online databases, review of reference lists, author correspondence, and review of clinical trials databases. Meta-analysis was conducted using fixed-effects modeling. The overall effect of mean reduction of pain intensity was -4.895 (Z-score) with an associated p value of 0.003. The combined standardized mean difference (SMD) was -0.362 (CI -0.507 to -0.217), indicating on average a moderate significant reduction in pain intensity for patients with chronic pain. As the legal status of the substance evolves, additional research is needed to establish evidence-based clinical recommendations regarding the use of medicinal cannabis in pain management.

Keywords: cannabis, marijuana, chronic pain, neuropathic pain

Chapter One: Introduction

Background

In the past decade, there has been a renewed interest in the use of cannabis for therapeutic purposes to treat a variety of ailments and conditions. Despite federal prohibition of the substance, so called "medical marijuana" laws have been enacted in the United States in twenty states and the District of Columbia over the last 16 years (Procon, 2013). The literature is replete with studies regarding clinically available synthetic cannabinoid agents. Given the legal ramifications, however, data regarding the clinical use of herbal cannabis is much more limited. The purpose of this project is to review the available literature and, using meta-analytic methodology, evaluate what is currently known regarding the effects of cannabis in the treatment of chronic pain.

Policy Influences

At the present time, the Drug Enforcement Administration (DEA) classifies cannabis as a "Schedule I" substance. According to the Comprehensive Drug Abuse Prevention and Control Act of 1970, categorization as a Schedule I substance means that the substance has been deemed to have no accepted medical use, a high potential for abuse, and a lack of any accepted margin of safety for usage. The placement of cannabis within this schedule remains controversial. All three of these requirements have been challenged through several formal petitions to the DEA over the past three decades (Gettman, 2004; Americans for Safe Access v. DEA, 2012). A total of twenty states and the District of Columbia have enacted legislation allowing for medical use of cannabis under a variety of conditions (Table 1). While this new legislation permits usage under state

laws, cannabis remains illegal for any purpose under federal law, except under very limited conditions for research purposes (Table 1).

Since the first medical marijuana legislation was enacted in California in 1996, there has been a significant increase in published data regarding the medical use of cannabis in the treatment of a variety of conditions. There is a considerable amount of published literature related to the ability of medicinal cannabis to promote appetite and minimize weight loss in chronic and terminal disease states such as AIDS and cancer (Machado Rocha, Stéfano, De Cassia Haiek, Rosa Oliveira, & Da Silveira, 2008; Tramér et al., 2001). The FDA-approved cannabinoid agonist dronabinol (Marinol) is labeled for use to promote appetite in chronic disease states and treat nausea and vomiting associated with chemotherapy ("New Drug Approvals," 1985).

While evidence of the analgesic properties of cannabis was published in the 19th century (O'Shaughnessy, 1843), the use of cannabis for this purpose diminished significantly into the early 20th century. The recognition of the analgesic potential of cannabis in Europe and the United States emerged around the same time as the invention of the hypodermic needle in 1857. During the middle and late 19th century, a variety of cannabis preparations were marketed in Europe and the United States for the treatment of discomfort related to numerous common ailments. At the turn of the 20th century, cannabis continued to be recommended by mainstream physicians and maintained a place on pharmacopeias in both the United States and Britain (Russo, 1998). Dr. William Osler, one of the founders of Johns Hopkins Hospital recommended cannabis for the treatment of migraine headaches as late as 1915 (Osler & McCrae, 1915). However, a number of factors contributed to a decreased prevalence of these preparations going further into the 20th century, including an association of the use of cannabis with certain classes

of people, vaccines for diseases that cannabis previously served to treat symptoms of, effective treatments for a number of diseases, the discovery of aspirin, increased opioid usage, and a preference for parenteral administration of medications (Grinspoon & Bakalar, 1993).

More recent research that has emerged in the last two decades has confirmed historical data and anecdotal evidence that cannabis is useful as an appetite stimulant, antiemetic agent, and analgesic adjuvant. In 1999, the United States Institute of Medicine (IOM) published an extensive report on the topic of medical marijuana, concluding that cannabinoids most likely play a role in pain modulation. Further, the 1999 IOM report suggested that cannabis has an acceptable margin of safety and recommended further research on the medicinal use of cannabis for a variety of conditions, including chronic pain states.

Abbreviated Literature Review

Mechanism of Action

It has long been recognized that cannabis possesses analgesic properties (O'Shaughnessy, 1843; Dixon, 1899). Recent studies have suggested that cannabis promotes analgesia through supraspinal modulation of nociception via the periaqueductal grey (PAG)-rostral ventromedial medulla (RVM)-dorsal horn (DH) axis (Palazzo, Luongo, Novellis, Rossi, & Maione, 2010). In addition to the role in central modulation of pain, there is also data to support a peripheral action of cannabis via peripheral cannabinoid type 1 (CB1) receptors (Richardson, Kilo, & Hargreaves, 1998).

Conflicting Findings With Hyperalgesia

The antinociceptive and antihyperalgesic properties of cannabis present in a delayed biphasic manner with a window of analgesia at lower doses and increased nociception at high doses (Wallace et al., 2007). The biphasic nature of the analgesic dose-response complicates

assessment of the analgesic properties of cannabis. A study by Kraft et al. (2008) actually demonstrated the development of a hyperalgesic state as a result of oral cannabis extract. Participants in the Kraft et al. study received controlled localized ultraviolet burns to their lower extremities to provide a model for evaluating heightened sensitivity to pain. Kraft et al. found that participants who received higher doses of oral cannabis extracts demonstrated heightened sensitivity to pain, or hyperalgesia, over a larger area. Comparison of the Kraft et al. findings with the findings by Wallace et al. is problematic for several reasons. Participants in the Kraft et al. study received capsules of cannabis extract rather than inhaled herbal cannabis, allowing for the possibility that first-pass metabolism and pharmacokinetic variability may have contributed to the different findings. When tetrahydrocannabinol (THC) is administered orally, only 10-20% of the compound reaches the systemic circulation unchanged (Agurell et al., 1986). An additional issue is that plasma levels of active compounds were not monitored in the Kraft et al. (2008) study, making direct comparison with the dosing in the Wallace et al. (2007) study problematic. Finally, cannabis extracts commonly contain one or two active compounds, such as tetrahydrocannabinol or cannabidiol. Herbal cannabis smoke is known to contain more than 525 components, at least 80 of which have been shown to be biologically active (Radwan et al., 2009; ElSohly & Slade, 2005). Generalizability of findings utilizing oral cannabis preparations that contain one or two active compounds with inhaled herbal cannabis is limited.

Experimental Trials Using Cannabis

Human research on the clinical benefits of cannabis has been limited by legal restrictions, but available data indicates a potentially beneficial effect of cannabis for a variety of pain states. Treatment of neuropathic pain in multiple sclerosis has been improved by the use of cannabis in clinical trials (Hosking & Zajicek, 2008). In a randomized controlled trial by Ware et al. (2010),

patients suffering from chronic neuropathic pain who smoked cannabis cigarettes experienced reduced pain intensity and improved sleep without significant side effects. The analgesic effects observed in the study by Ware et al. were absent in the control group, who received cannabis with a reduced quantity of active compounds. Research published previously indicated similar analgesic benefits to patients suffering from neuropathic pain. A randomized controlled trial conducted by Ellis et al. (2009) found that patients who received cannabis containing 8% THC experienced a significant reduction in HIV-associated neuropathic pain when compared with the placebo group (who received cannabis with THC removed). The 2009 Ellis et al. study replicated findings from an earlier study by Abrams et al. (2007a) that found a similar reduction in HIV-associated neuropathic pain in participants who received cannabis with THC present when compared with participants who received cannabis with THC removed.

Recent research has also demonstrated opioid-sparing properties of cannabis when it is used as an adjunct agent in pain management. Cannabis contributes to cumulative analgesia, reduces opioid consumption, and prevents or diminishes development of tolerance to and withdrawal from opioids (Lucas, 2012). An inpatient open trial conducted by Abrams, Couey, Shade, Kelly and Benowitz (2011) demonstrated that vaporized cannabis reduced pain by an average of 27% in chronic pain patients receiving twice-daily dosing of sustained-release morphine or oxycodone without altering plasma levels of opioids. Research findings of improved analgesia and reduced opioid consumption strongly suggest a beneficial role for cannabis as a potential adjunct agent in some patients experiencing chronic pain. A study by Wilsey et al. (2008) further supported the role of active cannabinoids in the analgesic benefits of cannabis with findings that both “high-dose” (7% THC) and “low-dose” (3.5% THC) produced significant reductions in neuropathic pain when compared with placebo.

Problem

Meta-analysis has been conducted on the much larger body of research investigating commercially produced THC pharmaceutical agents. A 2009 systematic review and meta-analysis conducted by Martín-Sánchez, Furukawa, Taylor, and Martin demonstrated a moderate analgesic effect of cannabinoid preparations that may be partially or completely offset by negative side effects. The review by Martín-Sánchez et al. evaluated eighteen clinical trials from 1975-2008. All of the studies included in the Martín-Sánchez et al. meta-analysis utilized THC preparations as the treatment intervention rather than herbal cannabis. Prior literature reviews such as the 2002 review by Bagshaw and the 2001 review by Campbell et al. described similar findings of modest analgesic effects mitigated by significant side effects. Both of these older reviews also suffer the same limitation of focusing solely on THC preparations rather than herbal cannabis preparations that contain a variety of active compounds. To date, no meta-analysis has been published regarding clinical trials of herbal cannabis.

As discussed in the abbreviated review of literature, several randomized controlled trials have been published recently that evaluated the effect of herbal cannabis as an analgesic adjunct agent in the treatment of neuropathic pain. Several of the cited studies were conducted at the University of California Center for Medicinal Cannabis Research (CMCR) with support from the Department of Health and Human Services (HHS), the National Institute on Drug Abuse (NIDA), and the Food and Drug Administration (Grant, Atkinson, Gouaux, & Wilsey, 2012). This series of studies is frequently cited in editorials related to the topic of medicinal marijuana. However, each of the published studies evaluating herbal cannabis as an adjunct analgesic agent has relatively small numbers of participants (n = 15-50). Compiling quantitative findings from these studies may demonstrate a greater effect size and provide better-powered data on the topic.

Project Purpose

The question to be addressed in this meta-analysis is whether the use of herbal cannabis by patients suffering from chronic pain provides a reduction in pain without an unfavorable side effect profile, as compared with currently available, FDA-approved medications and treatments. Inclusion criteria for studies to be reviewed and analyzed are randomized controlled trials of herbal cannabis in the treatment of chronic pain, limited to the English language. No date limitations were set for included studies, and any non-randomized trials were excluded. The participant population of included studies consisted of patients suffering from chronic pain, including pain resulting from comorbidities such as cancer, AIDS, and multiple sclerosis. Study interventions under evaluation included the usage of herbal cannabis, inhaled either through smoking or vaporization. Herbal cannabis will be compared against conventional therapies as well as against herbal cannabis that has been altered for reduced quantities of active compounds. Outcomes under evaluation include quantitative pain assessment utilizing visual analogue scales and 11-point numeric pain ratings.

Definition of Terms

Active Compound

The term active compound refers to all pharmacologically active substances found in cannabis, including all cannabinoids.

Cannabis

The term cannabis is used interchangeably with the term marijuana, and both terms refer to the plants *Cannabis Sativa* and *Cannabis Indica*.

Cannabinoid

The term cannabinoid refers to chemical compounds that interact with endogenous cannabinoid receptors, including tetrahydrocannabinol (THC).

Chronic Pain

Chronic pain is pain that is experienced, regardless of cause, for a duration of greater than three months.

Herbal Cannabis

The term refers to the dried flowers and top leaves from the plants *Cannabis Sativa* and *Cannabis Indica.*

Marijuana

The term marijuana is used interchangeably with the term cannabis, and both terms refer to the plants *Cannabis Sativa* and *Cannabis Indica*.

Neuropathic Pain

Neuropathic pain refers to pain resulting from damage to nerves. Common examples of neuropathic pain include diabetic neuropathy, postherpetic neuralgia, HIV-associated neuropathy, alcoholic neuropathy, diabetic neuropathy, and chemotherapy-related neuropathy.

Synthetic Cannabinoid

Any artificially synthesized compound or extract that interacts with endogenous cannabinoid receptor.

Chapter Two: Review of Literature

This chapter will review literature relevant to use of herbal cannabis in pain management. A literature search of Medline utilizing the keywords "cannabis" and "pain" in addition to the title phrases "systematic review" or "comprehensive review" returned nine results, of which four articles were relevant. An additional article was retrieved after a manual search of the list of publications from the Center for Medicinal Cannabis Research (CMCR) website. Additional searches utilizing the University of North Florida library "Onesearch" tool, as well as searches utilizing Pubmed and CINAHL did not return any additional unique relevant results. Five systematic reviews published between 2001 and 2012 were retrieved that were relevant to cannabis and pain management.

Systematic Reviews of Cannabinoids

The earliest systematic review relevant to the topic of cannabis and pain management was published in BMJ in 2001. By necessity, the 2001 review by Campbell et al. focused solely on oral cannabinoids, as no randomized controlled trials (RCTs) evaluating the effects of inhaled herbal cannabis as an analgesic had been published prior to this review. Campbell et al. performed a qualitative systematic review that included nine trials of oral cannabinoids with a total of 222 patients. The findings of this first review were that oral cannabinoids were only as effective as a single 60-milligram dose of codeine and were not beneficial in treating spasticity or neuropathic pain (Campbell et al.). In addition to poor analgesic efficacy, oral cannabinoids were found to often have undesirable psychotropic effects that worsened with increased dosages while not improving analgesic efficacy (Campbell et al.).

Bagshaw published a comprehensive literature review regarding the therapeutic effects of cannabinoids and herbal cannabis the following year in 2002 in the *Journal of Palliative Care*.

The Bagshaw review was very broad in scope and evaluated the effects of cannabinoids and herbal cannabis in the treatment of nausea and vomiting, anorexia-cachexia syndrome, spasticity, seizures and epilepsy, hiccups, and migraines in addition to their use as an analgesic. Similar to the prior review by Campbell et al., the Bagshaw review referenced studies that only used oral cannabinoids when evaluating analgesic efficacy. Bagshaw described similar findings that oral cannabinoids provided modest analgesia similar to weak opioids, with dosing limited by adverse effects such as somnolence, dizziness, blurred vision, and dysphoria.

In 2009, Martín-Sánchez et al. published a meta-analysis of cannabinoids in the treatment of chronic pain in the *Journal Pain Medicine*. Their review evaluated 18 RCTs that included a total of 809 participants. The work by Martín-Sánchez et al. is the first and, to date, only published meta-analysis of cannabinoid therapy for pain management. While the study makes reference to "cannabis treatment," all of the trials included utilized oral cannabinoids (Martín-Sánchez et al.). This study found cannabinoids reduced visual analogue scales (VAS) of pain by -0.61 (-0.84 to -0.37) but were offset by adverse effects such as altered perception, impaired motor function, and altered cognitive function (Martín-Sánchez et al.). Martín-Sánchez et al. concluded from their analysis that cannabinoids entailed more risk than benefits in the treatment of chronic pain.

Systematic Reviews of Herbal Cannabis

A systematic review published in 2011 in the *British Journal of Clinical Pharmacology* was the first to include analysis of RCTs of inhaled herbal cannabis (Lynch & Campbell). The review by Lynch and Campbell referenced "cannabinoids" in their study title, but their combined analysis looked at studies of both oral cannabinoids and inhaled herbal cannabis. They reviewed a total of 18 RCTs, with four of the trials evaluating inhaled herbal cannabis (Abrams et al.,

2007a; Ellis et al., 2009; Ware et al., 2010; Wilsey et al., 2008). All four of the inhaled herbal cannabis trials referenced by Lynch and Campbell are included in this meta-analysis. In their combined systematic review of both oral synthetic cannabinoids and inhaled herbal cannabis, Lynch and Campbell concluded that cannabinoids and herbal cannabis are safe and demonstrate modest effectiveness in the treatment of neuropathic pain as well as fibromyalgia and rheumatoid arthritis. A particularly significant finding from the Lynch and Campbell review was that all four of the trials that evaluated herbal cannabis found positive treatment effects without any serious adverse effects reported. Two of the four herbal cannabis trials evaluated by Lynch and Campbell found beneficial effects in the treatment of HIV neuropathy, a type of neuropathic pain that is often not responsive to traditional therapy (Phillips, Cherry, Cox, Marshall, & Rice, 2010).

An article published in 2012 by Grant et al. provided a comprehensive review of both oral cannabinoids and inhaled herbal cannabis. The review by Grant et al. included evaluation of several of the first of a series of studies on inhaled herbal cannabis that were conducted with funding provided by the CMCR. The Medical Marijuana Research Act of 1999 established the CMCR and provided a total of 8.7 million dollars of funding for research that was conducted from 2000-2012 (Hecht, 2012; Grant, 2012). The published studies on inhaled herbal cannabis for pain management conducted with funding from the CMCR, as reviewed by Grant et al. (2012), demonstrated a consistent reduction in pain intensity of 34-40 percent compared to 17-20 percent with placebo (herbal cannabis with active compounds removed). These findings are clinically relevant, as a reduction of chronic pain intensity by greater than 30 percent is associated with improved quality of life (Farrar, Young, LaMoreaux, Werth, & Poole, 2001; Grant et al., 2012).

Review of CMCR-Funded Research

The CMCR has provided funding for much of the research relevant to herbal cannabis that has been published since the turn of the century. Established by a California ballot initiative in 1999, the CMCR has stated research goals that transition through three stages: research on smoked cannabis, research on alternative cannabis preparations or delivery systems (such as vaporization), and research regarding molecules targeting the endocannabinoid system (CMCR, 2010). Clinical trials that have been conducted examining the efficacy of herbal cannabis as an analgesic agent will be discussed in subsequent chapters. A CMCR-funded RCT that investigated the pharmacodynamics of herbal cannabis through a model of neuropathic pain with healthy volunteers was discussed earlier (Wallace et al., 2007). The study by Wallace et al. found (similar to many pharmaceutical agents) that herbal cannabis likely has a therapeutic window of dosing. Subtherapeutic dosing of herbal cannabis provides no analgesia, while supratherapeutic dosing appears to potentially contribute to an increase in pain, or hyperalgesia (Wallace et al.). An earlier study conducted under similar laboratory conditions that evaluated a model of analgesia also found a dose-dependent antinociceptive effect (reduced sensation of pain) from herbal cannabis (Greenwald & Stitzer, 2000). The study by Greenwald and Stitzer also found that the analgesic effects of cannabis are not affected by opioid antagonists and likely are not derived from action at opioid receptors. Another CMCR-funded study discussed earlier was the open trial conducted by Abrams et al. (2011) with chronic pain patients in an inpatient setting. Abrams et al. (2011) found that vaporized cannabis inhaled three times daily augmented the effects of opioid therapy without altering plasma opioid levels. Patients in the Abrams et al. (2011) open trial experienced an average pain reduction of 27% (95% confidence interval 9, 46),

a clinically relevant reduction in pain that is consistent with the findings in CMCR-funded RCTs described by Grant et al. (2012).

Summary

Much of the highest-level evidence (systematic reviews) relevant to cannabis focuses solely on oral cannabinoid agents. High quality RCTs evaluating the role of herbal cannabis as an analgesic agent are largely limited to those conducted by the CMCR over the past few years, with systematic reviews prior to the past few years omitting these results. Results of the reviews by Lynch & Campbell (2011) and Grant et al. (2012) of inhaled herbal cannabis describe clinically relevant reductions in chronic pain intensity that is less limited by adverse reactions than prior reviews that focused solely on oral cannabinoids. While public funding for research through the CMCR is currently exhausted (Hecht, 2012), there are still additional study results pending publication. Currently published results on inhaled herbal cannabis suggest a potential beneficial role in pain management. It is possible that patients may experience less adverse effects with herbal cannabis than with currently available oral cannabinoids. With continued research, the CMCR may be able to continue into the latter stage of their stated research objectives and identify molecular targets in the endocannabinoid system that may balance clinical efficacy with minimal adverse effects.

Table 1

States That Have Enacted Medical Marijuana Legislation

State	***Year Passed***	***How Legislation Passed***
California	1996	Ballot (56%)
Alaska	1998	Ballot (58%)
Oregon	1998	Ballot (55%)
Washington	1998	Ballot (59%)
Maine	1999	Ballot (61%)
Colorado	2000	Ballot (54%)
Hawaii	2000	Senate Bill (32-18 in House; 13-12 in Senate)
Nevada	2000	Ballot (65%)
Montana	2004	Ballot (62%)
Vermont	2004	Senate Bill (22-7), House Bill (82-59)
Rhode Island	2006	Senate Bill (52-10 in House; 33-10 in Senate)
New Mexico	2007	Senate Bill (36-31 in House; 32-3 in Senate)
Michigan	2008	Ballot (63%)
Arizona	2010	Ballot (50.1%)
District of Columbia	2010	Amendment (13-0 vote)
New Jersey	2010	Senate Bill (48-14 in House; 25-13 in Senate)
Delaware	2011	Senate Bill (27-14 in House; 17-4 in Senate)
Connecticut	2012	House Bill (96-51 in House; 21-13 in Senate)
Massachusetts	2012	Ballot (63%)
Illinois	2013	House Bill (61-57 in House; 35-21 in Senate)
New Hampshire	2013	House Bill (284-66 in House; 18-6 in Senate)

Note. Adapted from "Summary Chart: 20 states and DC that have enacted laws to legalize medical marijuana" by procon.org

Chapter Three: Methods

This chapter will discuss methods utilized in evaluating and consolidating published data on herbal cannabis in pain management. Meta-analysis will be conducted on quantitative findings from published studies. The objective will be to provide organized results regarding the efficacy of herbal cannabis in pain management that are better powered than those found in individual studies.

Search Strategy

A literature search of Medline utilizing the keywords “cannabis” or “marijuana” and “pain” in addition to the title phrases “cannabis” or “marijuana” or “cannabinoid” or “cannabinoid-opioid” and “pain” or “painful” or “neuropathy” or “antinociceptive” or “nociceptive” or “analgesic” or “analgesia” or “hyperalgesia” and “trial” or “volunteers” or “humans” or “interaction” returned nineteen results. Inclusion criteria for study evaluation are RCTs of inhaled herbal cannabis in the treatment of chronic pain, limited to the English language studies. No date limitations were set for included studies. Exclusion criteria included any non-randomized clinical trials. Of the nineteen results, seven of the studies evaluated inhaled herbal cannabis. Two of the studies evaluated a model of pain in a laboratory setting and were discussed previously (Greenwald & Stitzer, 2000; Wallace et al., 2007). One study was an open (non-randomized) trial of opioid interaction with inhaled herbal cannabis (Abrams et al., 2011). Four of the results met the inclusion criteria of RCTs evaluating inhaled herbal cannabis in chronic pain patients. An additional article (Corey-Bloom et al., 2012) was retrieved after a manual search of the list of publications from the CMCR website. After email correspondence with the primary authors of all retrieved studies, an abstract for an additional article that was in press at

the time of the initial search was located (Wilsey et al., 2013), bringing the total of studies meeting inclusion criteria to six (see Appendix). Additional searches utilizing the University of North Florida library "Onesearch" tool, as well as searches utilizing Pubmed and CINAHL did not return any additional unique relevant results.

Further review of all study references also did not yield any additional unique relevant results. A search of the NIH database of registered clinical trials at ClinicalTrials.gov with the keyword "cannabis" yielded 264 studies, with no additional unique relevant results for completed studies, either published or unpublished. The last search was completed February 15, 2013. No unpublished studies were located through any source.

Study Selection

Five out of the six studies recruited patients with chronic neuropathic pain (Abrams et al., 2007a; Ellis et al., 2009; Ware et al., 2010, Wilsey et al., 2008; Wilsey et al., 2013). Two of these studies were specific to patients with Human Immunodeficiency Virus (HIV) neuropathy (Abrams et al., 2007a; Ellis et al., 2009). One study evaluated participants with multiple sclerosis (Corey-Bloom et al., 2012). All of the studies were limited to adult participants. The study by Abrams et al. (2007a) further limited participants to individuals with self-reported prior experience with smoked marijuana.

All six studies evaluated were double-blinded, randomized placebo-controlled trials. Sample sizes ranged from 23 to 50 subjects. One study utilizes a parallel design (Abrams et al., 2007a), with the other five studies utilizing crossover study designs (Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010, Wilsey et al., 2008; Wilsey et al., 2013). Treatment groups in all studies received inhaled herbal cannabis with concentrations of THC ranging from 1.29 to 7 percent. Placebos utilized in the studies were herbal cannabis provided by NIDA with active

compounds removed. Five out of the six studies utilized smoked herbal cannabis for drug delivery (Abrams et al., 2007a; Corey-Bloom et al., 2012; Ellis et al., 2009; Ware et al., 2010; Wilsey et al., 2008). One of the six studies utilized vaporized cannabis for drug delivery (Wilsey et al., 2013). With the exception of the 2010 study by Ware et al., which was conducted in the province of Quebec in Canada, all studies were conducted in the state of California in the United States.

Outcome Measures

All six studies evaluated pain intensity as an outcome. Five of the studies evaluated pain intensity as a primary outcome measure (Abrams et al., 2007a; Ellis et al., 2009; Ware et al., 2010; Wilsey et al., 2008; Wilsey et al., 2013). One study evaluated muscle spasticity as a primary outcome and pain intensity as a secondary outcome (Corey-Bloom et al., 2012). Four of the studies utilized a 100-millimeter visual analogue scale (VAS) as an instrument to measure pain intensity (Abrams et al., 2007a; Corey-Bloom et al., 2012; Wilsey et al., 2008; Wilsey et al., 2013). One study utilized an 11-point numeric rating scale (NRS-11) as an instrument to measure pain intensity (Ware et al., 2010). One study utilized a 20-point verbal rating scale (VRS-20) as well as a VAS as instruments to measure pain intensity (Ellis et al., 2009). All three of the instruments utilized to assess pain in the studies have been found to be reliable and valid in the measurement of pain intensity (Hjermstad et al., 2011). The frequency with which pain intensity was evaluated varied from study to study. Three of the studies evaluated pain intensity on a daily basis during the study period (Abrams et al., 2007a; Corey-Bloom et al., 2012; Ware et al., 2010). One study evaluated pain intensity on a weekly basis during the study period (Ellis et al., 2009). Two studies (Wilsey et al., 2008; Wilsey et al., 2013) evaluated pain intensity on an hourly basis for the six hours of each study arm.

Statistical Analysis

All included studies reported differences between baseline and final pain intensity ratings for each of the intervention groups. Difference (Cannabis - Placebo) in means of the pain ratings are reported and tested for significance. Differences in means (Cannabis - Placebo) were compiled, along with their standard errors, sample sizes, and p values. Meta-analysis was performed to quantify the effect of treatment (Cannabis) as the standardized mean difference (SMD) between treatment and control (Placebo) groups in each study as well to achieve an overall estimate of global effect size based on all studies. Weighting was carried out by reference to the degree of study precision using the method of the inverse of the variance. The 2013 study by Wilsey et al. did not report group means or standard errors of means or differences in means for pain intensity measures. It also used a different method of analysis (Factorial ANOVA) compared with the other studies. It was not possible to include this study in the meta-analysis and it was excluded from evaluation. The earlier 2008 study by Wilsey et al. included two treatment groups in a crossover design, and these were included as separate entries in the meta-analysis.

Heterogeneity between studies was statistically determined using the Q^2 test and I^2 statistic measures. The results of the Q^2 and I^2 were insignificant, providing evidence of homogeneity among the studies evaluated. It is possible to conduct meta-analysis with either random-effects or fixed effect modeling. Fixed-effect modeling assumes that there is one true effect size amongst all studies evaluated and that differences in effects are a result of sampling error (Borenstein, Hedges, Higgins, & Rothstein, 2010). Random-effects modeling allows for the possibility of different true effect sizes and is appropriate for meta-analysis of studies with significant variation in populations studied or interventions utilized (Borenstein et al.). After

ascertaining evidence of homogeneity amongst studies, it was determined that fixed-effect modeling was appropriate for this meta-analysis. However, meta-analysis was performed with both fixed-effect and random effects modeling, and both models produced the same results. Possible publication bias was ascertained by means of funnel plots. Specialized meta-analysis software, Comprehensive Meta Analysis version 2.2.064, was used to perform the complete analyses.

Chapter Four: Results

This chapter will present the quantitative meta-analysis data from five of the six studies that met the criteria for evaluation. One of the studies (Wilsey et al., 2013) was not included in the meta-analysis as a result of insufficient reported results that precluded inclusion in the meta-analysis.

Meta-Analysis Results

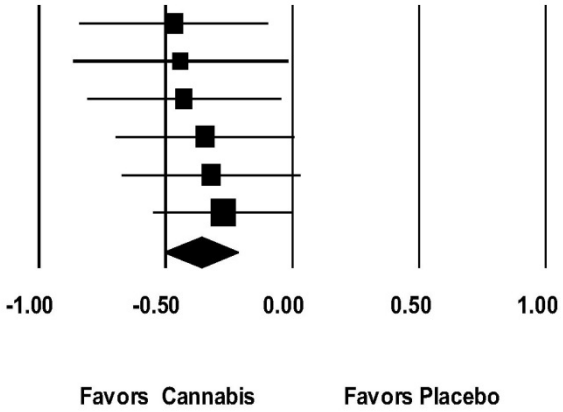
Results obtained from meta-analysis of efficacy herbal cannabis in reducing chronic pain intensity are reported in Table 2. The results show that all studies yielded standardized results in the same direction. The test statistic value of heterogeneity is obtained as 0.990 with a p-value of 0.963 implying between studies heterogeneity was almost certainly absent. This confirms that the variability between study estimates is too small to assume that they are estimating a different underlying treatment. The I^2 statistic is 0%, which implies that real heterogeneity is 0% to the total variance across the observed effect estimate.

The test value of overall effect of mean reduction of pain intensity is -4.895 with an associated p value of 0.003. At the 1% level of significance, this test is statistically significant. Based on these results, it can be concluded that there is a significant difference between the Cannabis and Placebo groups in pain intensity reduction. The combined standardized mean difference (SMD) is -0.362 (Confidence Interval -0.507 to -0.217). The negative SMD value ensured a greater reduction of pain intensity by Cannabis treatment than the Placebo. The 95% confidence interval around this estimate is not reasonably wide, indicating no uncertainty in the pooled result. According to Cohen's rules, a moderate impact of Cannabis on pain reduction can be concluded (Cohen, 1988). As a final finding, the funnel plot in Figure 1 shows no sign of asymmetry. Therefore, there is no evidence of possible publication bias.

Table 2

Meta-Analysis of Herbal Cannabis in Reduction of Pain Intensity

Study name	Statistics for each study							Standardized Mean Difference, Fixed Effects, 95% C.I.
	Std. diff. in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value	
Corey-Bloom et al., 2012	-0.467	0.192	0.037	-0.844	-0.090	-2.429	0.015	
Ware et al., 2010	-0.441	0.218	0.048	-0.869	-0.013	-2.019	0.043	
Ellis et al., 2009	-0.427	0.197	0.039	-0.814	-0.040	-2.165	0.030	
Wilsey et al., 2008 (3.5%)	-0.345	0.182	0.033	-0.702	0.012	-1.897	0.058	
Wilsey et al., 2008 (7%)	-0.320	0.181	0.033	-0.675	0.035	-1.765	0.077	
Abrams et al., 2007	-0.272	0.144	0.021	-0.555	0.010	-1.891	0.059	
Combined	-0.362	0.074	0.005	-0.507	-0.217	-4.895	0.000	



Test for Heterogeneity: Q = 0.990, p-value = 0.963, $I^2 = 0.00\%$

Test for overall effect: Z = -4.895, p-value = 0.000

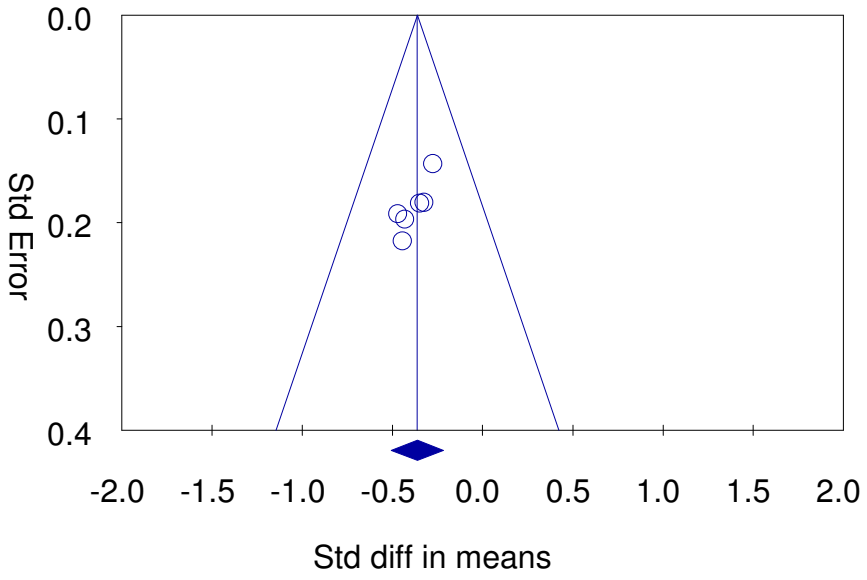


Figure 1: Funnel plot to assess publication bias.

Chapter Five: Discussion

The following chapter will discuss the results from the meta-analysis. Implications for practice will be discussed, as well as the limitations of this study and implications for future research.

Results of this meta-analysis demonstrate a statistically significant reduction in pain intensity in chronic pain patients receiving inhaled herbal cannabis. These findings are consistent with the findings discussed in a recent narrative review (Grant et al., 2012). The narrative review by Grant et al. included discussion of four (Abrams et al., 2007a; Ellis et al., 2009; Ware et al., 2010; Wilsey et al., 2008) of the six studies that met inclusion criteria, with the two most recent studies (Corey et al., 2012; Wilsey et al., 2013) not included in the discussion. The findings in the combined synthetic cannabinoid and herbal cannabis review by Lynch and Campbell (2011) were similar to the herbal cannabis discussion in the Grant et al. review, with the combined review describing modest reductions in pain and the herbal cannabis review describing significant reductions in pain intensity, both consistent with the findings in this meta-analysis. Additionally, results of this meta-analysis are consistent with the sole RCT that was excluded from data analysis (Wilsey et al., 2013). Compiled data from all available RCTs utilizing RCTs demonstrate moderate but statistically significant efficacy in reducing pain intensity in chronic pain patients. The data also lacked evidence of publication bias.

Implications for Practice

In states where regulations permit medical usage, herbal cannabis may represent an option for chronic pain patients as an analgesic adjuvant with opioid-sparing properties (Abrams et al., 2011). These findings present a number of implications for advanced nursing practice.

However, the direct relevance of these findings varies significantly between different practice settings.

Within the perioperative setting, the future therapeutic potential of the substance is essentially completely negated by practical limitations to administration as well as some potential concerns for pharmaceutical interactions and airway complications. For example, chronic cannabis usage has been shown to increase propofol dosage requirements for laryngeal mask airway placement (Flisberg et al., 2009). Although extremely rare, one case study documented an instance of acute uvulitis and partial airway obstruction that was thought to have resulted from recently smoked cannabis (Mallat, Roberson, & Brock-Utne, 1996). The authors of this single case study suggested that the higher combustion temperature of cannabis (relative to tobacco) paired with deeper and sustained inhalation might account for increased mucous membrane irritation in some cannabis smokers (Mallat et al.). Because of these concerns, recommendations in some anesthesia literature are that elective surgical procedures should be delayed for patients that have smoked herbal cannabis within 72 hours prior to surgery (Dickerson, 1980; Mallat et al., 1996). Other recommendations from anesthesia literature include simply treating patients with a history of smoking cannabis similarly to patients with a history of smoking tobacco due to potential similarities in airway hyperreactivity (Bryson & Frost, 2011).

Existing research demonstrates efficacy of herbal cannabis as an analgesic agent. However, a significant amount of additional research is needed to achieve the complete goals of the CMCR of establishing efficacy with inhaled cannabis prior to researching other delivery methods and eventually researching molecules that target the endocannabinoid system (Grant, 2012). It is possible that targeted delivery of cannabinoid agonists may eventually be feasible within the perioperative setting for acute pain management. However, current delivery methods

create a potential for adverse airway reactions that, in addition to potential drug interactions, make herbal cannabis unsuitable for the perioperative period.

Within the outpatient and primary care settings, patients may present who are using cannabis or (in jurisdictions where this is permitted) are seeking information and recommendations regarding the substance from practitioners. While further research is still needed to establish optimum dose and frequency, the findings of this meta-analysis support the recommendation of herbal cannabis as an adjunct analgesic agent for chronic pain patients.

In the palliative care setting, herbal cannabis provides the additional benefits of antiemetic properties and appetite stimulation (Machado Rocha et al., 2008; Tramér et al., 2001). Since the substance remains prohibited under federal law, providers do not "prescribe" herbal cannabis per se, but rather "recommend" it to patients, subject to state regulations that vary considerably. With the rapid pace of regulatory changes in this area, providers working in jurisdictions where medical cannabis initiatives are proposed or have passed may encounter questions from patients regarding the efficacy of the substance. The findings of this meta-analysis support the efficacy of herbal cannabis in reducing pain intensity in patients suffering from chronic pain.

Study Limitations

This meta-analysis had several limitations related to the available literature on this topic. There are a very limited number of RCTs from which to consolidate data. The RCTs that are available have small numbers of participants and vary somewhat in specific patient population and dosing regimen. As shown in the appendix, the RCTs included in this meta-analysis utilized herbal cannabis with concentrations of active compounds that varied somewhat from study to study. Additionally, the frequency of dosing and delivery method was not consistent across

studies. This meta-analysis was limited to English-language publications and did not evaluate any unpublished studies.

Some of these limitations are inherent to the technique of meta-analysis itself. A unique issue with studies utilizing herbal cannabis is the regulatory difficulty conducting such studies. Studies utilize herbal cannabis supplied by NIDA with uniform concentrations of active compounds (Grant, 2012). Research utilizing herbal cannabis has additional bureaucratic difficulties that may limit studies from being repeated to better confirm findings. Rather, what are available within the limited research that has been conducted are studies that evaluate the efficacy of herbal cannabis in slightly different and unique ways with slightly different participant populations.

Implications for Future Research

Trials utilizing herbal cannabis are very limited and involve considerable regulatory restrictions to conduct. There is a great deal that is not well understood regarding the therapeutic value of the substance. In regards to the efficacy of herbal cannabis in treating chronic pain, there is a need for clinical trials to determine optimum dosage, timing, and delivery methods. Additionally, larger studies that stratify specific chronic pain populations could be conducted to determine which patients might be most responsive to herbal cannabis therapy.

The sole RCT of herbal cannabis for chronic pain that was excluded from meta-analysis (Wilsey et al., 2013) did demonstrate similar findings of moderate analgesia in patients with treatment-resistant neuropathic pain. One unique aspect to the 2013 study by Wilsey et al. is that it is the first RCT to utilize vaporization as a delivery method for the inhaled cannabis. A prior open trial by Abrams et al. in 2011 used vaporized herbal cannabis and also found reduced pain intensity as well as reduced opioid consumption in chronic pain patients. Vaporization is able to

deliver similar levels of active compounds with patients experiencing lower plasma carbon monoxide levels and a general patient preference for vaporization over smoking (Abrams et al., 2007b). With the known pulmonary complications of smoked cannabis (Bryson & Frost, 2011), there is a need for further studies using the safer delivery method of vaporized cannabis to better establish analgesic efficacy of vaporized cannabis in chronic pain patients. Another possibility for future research might include a comparison of efficacy between different delivery methods such as smoked, vaporized, and ingested herbal cannabis. It is possible that first-pass metabolism may play a role in the lower efficacy seen with oral cannabinoids. However, research in this area relates primarily to oral ingestion of specific cannabinoid extracts rather than unaltered herbal cannabis. Further research might reveal the impact of other active compounds in herbal cannabis as well as the impact of first-pass metabolism that may possibly limit the efficacy of oral delivery of herbal cannabis for some uses.

Conclusion

Medicinal use of herbal cannabis is a controversial subject, but one that is in need of more evidence through objective, quality research trials. In light of the evolving attitudes regarding marijuana, it is an opportune time to investigate this substance further. More than half of Americans are now in favor of marijuana legalization, a statistic that is in stark contrast to attitudes towards the substance in prior decades (Pew Research Center, 2013). In the current sociopolitical environment, research can be conducted without as much concern for research findings disrupting the status quo.

The findings of this meta-analysis are consistent with all prior research on the subject, further demonstrating a moderate reduction in pain intensity with minimal side effects in chronic

pain patients with the use of herbal cannabis. Additional research is needed to better establish optimum therapeutic dosing regimens and factors related to safety and adverse reactions.

Appendix: Experimental Studies Investigating Herbal Cannabis and Chronic Pain

Author (Date)	Design	Sample	Outcome	Intervention	Results	Limitations
Wilsey et al. (2013, in press)	RCT (cross-over)	39 participants	VAS	Vaporized cannabis (or placebo cannabis)	Analgesic effects observed in both "high-dose" and "low-dose" groups. 30% reduction in pain intensity compared to placebo.	Potential for unmasking of blinding in crossover design
Corey-Bloom et al. (2012)	RCT (cross-over)	37 participants	VAS	Smoked cannabis (or placebo cannabis) daily x3 days, 11 day washout between treatment groups	VAS decreased by 5.28 points more than placebo (p=0.008)	Some participants prior cannabis users (self-selection bias, potential unblinding)
Ware et al. (2010)	RCT (cross-over)	23 participants	VAS	Random assignment to receive smoked cannabis three times a day at four potencies (0%, 2.5%, 6%, 9.4% tetrahydrocannabinol) over four 14-day periods in a crossover trial.	Single inhalation of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced pain intensity and improved sleep. In 0% vs. 9.4% groups, pain was 5.4 vs. 6.1 (95% CI, 0.02-1.4).	Small number of participants. Tetrahydrocannabinol concentration limited by legal availability. The use of smaller fixed dosing of herbal cannabis may have limited the effect size.
Ellis et al. (2009)	RCT (cross-over)	28 participants	Descriptor Differential Scale (DDS) & VAS	Random, double-blind assignment to smoke herbal cannabis with 8% tetrahydrocannabinol or 1% (placebo) herbal cannabis four times daily for five consecutive days in crossover trial with two-week washout period .	Pain relief was greater in active cannabis group vs. placebo (-3.3 points on DDS, effect size = 0.60; p= 0.016). Subjects achieving ≥30% pain reduction with active cannabis vs. placebo were 0.46 (95% CI 0.28, 0.65) and 0.18 (0.03, 0.32).	Potential placebo effects, as most subjects were able to differentiate between treatment and placebo groupings by the end of second crossover period.
Wilsey et al. (2008)	RCT (cross-over)	38 participants	VAS	Random assignment to either high-dose (7% tetrahydrocanna	Analgesic effects were observed in both "high-dose" and "low-dose" groups when	Brief observational period (6 hour sessions), possible placebo effect.

				binol), low-dose (3.5% tetrahydrocanna binol), or placebo cannabis. Patients inhaled smoked herbal cannabis during 3 separate 6 hour sessions, receiving each treatment group once, in random order.	compared with placebo (VAS difference per minute of -0.0035, 95% CI [-0.0063, -0.0007])	
Abrams et al. (2007a)	RCT	50 participants	VAS	Random assignment to 3.56% cannabis cigarettes or placebo (cannabinoids extracted) group, with cigarettes smoked three times a day for five days.	Cannabis significantly reduced pain vs. placebo. Daily pain was reduced by median of 34% (IQR = -71, -16) vs. median of 17% (IQR = -29, 8) for placebo.	Single tetrahydrocannabinol concentration may limit comparison of findings with other studies.

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