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Therapeutic Benefit of Smoked Cannabis in Randomized Placebo-Controlled Studies

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Abstract

The medicinal use of marijuana has been legalized in 28 states, with a wide range of specificity for approved medical conditions. Even with the emergence of non–combustion-based delivery systems, in 2014, 90% of marijuana users used smoked marijuana. The purpose of this review is to summarize the data available on use of smoked marijuana for medical purposes. A literature search was performed to retrieve randomized controlled trials exploring the efficacy of smoked cannabis for treatment of a medical condition. Studies with the primary endpoint listed as the effect of smoked cannabis on a disease-specific characteristic were included. Open-label studies and studies using other administration methods were excluded. Seven studies met these criteria and were included in this review. Cannabis did not outperform placebo on experimentally evoked pain or times walk test. There is clear evidence that smoked cannabis reduces intraocular pressure, but the effect is too brief (< 4 hours) to be of therapeutic benefit for this chronic disorder. There was also consistent evidence that smoked marijuana, even at lower concentrations of tetrahydrocannabinol, increased total daily calorie intake and number of eating occasions. Neither of the studies with quality of life as secondary outcome measures revealed statistically significantly improved outcomes with cannabis use.

MeSH Key Words

cannabis; medical marijuana; neuropathic pain; glaucoma; pain; spasticity; anorexia

Background

Early physicians, monks, and healers used plants as medicine in the form of vapors, tinctures, poultices, and salves. As scientific knowledge has progressed, the active ingredients of natural products have been isolated and have led to the development of

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aspirin, digoxin, and morphine (1). Europeans brought cannabis with them when they colonized North America(2). The plant grew well and was used primarily for its fiber, seeds, and oil. By the third edition of the *United States Pharmacopeia*, cannabis was included (3).

In the 1916 *United States Pharmacopeia*, instructions can be found for preparing extracts of cannabis for medicinal use as well as discussion of the difficulty of standardizing the chemical assay (2). At the time, standardization was recommended based on animal testing prior to human consumption(4). Smoked cannabis was not described in the pharmacopeia or dispensatory. Recommendations were given for the use of cannabis extracts to treat "neuralgia, gout, rheumatism, tetanus, hydrophobia, epidemic cholera, convulsions, chorea, hysteria, mental depression, delirium tremens, insanity, and uterine hemorrhage, with cautions regarding consistency of dosing and "alarming effects" associated with overdose (5).

Many individual states restricted cannabis use in the early 20th century prior to Congress passing the 1937 Marihuana tax act that placed prohibitive tariffs and registration requirements on physicians prescribing and pharmacists dispensing cannabis. Physician testimony at the time revealed that medicinal use of cannabis was already on the decline due to uncertainty regarding its effects and potency (6). Congress was urged not the pass the law, as it would curtail further research into its efficacy (6). Decades later, in 1970, the Controlled Substances Act was passed, and cannabis was assigned Schedule I status signifying that it was a drug "with no currently accepted medical use and a high potential for abuse" (7). Other examples of Schedule I drugs include heroin, lysergic acid diethylamide (LSD), 3,4-methylenedioxymethamphetamine (Ecstasy), methaqualone, and peyote. (7). Since the classification of cannabis as a Schedule I substance, groups have lobbied to change this designation so that there would be fewer barriers to research to determine safety parameters, risks, and possible areas of treatment efficacy (8).

In its 1999 report, the Institute of Medicine (IOM) noted that the evaluation of the use of smoked marijuana was of focal concern (1). At that time, the IOM report concluded that "the future of cannabinoid drugs lies not in smoked marijuana but in chemically defined drugs that act on the cannabinoid systems that are a natural component of human physiology" (1). Since this report, the political landscape regarding the use of marijuana has changed. Currently, medicinal marijuana is legal in 28 states and Washington, DC, and recreational marijuana is legal in eight states and Washington, DC. According to the most recent data from the National Survey on Drug Use and Health, 22.2 million people aged 12 years or older were current users of marijuana in 2015 (9). Most of those users were administering marijuana through a combustion format. In 2014, a nationally representative sample revealed that 90% of current users reported use of smoked marijuana (10). However, there is still a dearth of information about the efficacy of smoked marijuana for the medical purposes. The purpose of this review is to summarize the data available to date on smoked marijuana for medical purposes and to discuss research needs on this topic.

Literature Search

A literature search was performed to retrieve randomized controlled trials exploring the efficacy of smoked marijuana for medical purposes. The Scopus, PubMed, Cochrane Library, and ClincalTrials.gov databases were searched from December 2016–February 2017 using the terms medical, medicinal, therapeutic, cannabis, cannabinoid, marijuana, smoke, efficacy, and trial. A total of 266 articles were identified. Bibliographies were searched for additional relevant studies. Studies with the primary endpoint listed as the effect of smoked cannabis on a disease-specific characteristic were included. Open-label studies and studies using other administration methods were excluded. Seven studies evaluating the therapeutic benefit of smoked cannabis met these criteria and were included in this review (Table 1).

Neuropathic Pain

Human immunodeficiency virus (HIV)-associated peripheral neuropathy affects 30–67% of patients with advanced HIV (11). Abrams studied the ability of smoked cannabis to improve this neuropathic pain as well as pain induced through thermal stimulation and any antihyperalgesia effect in a prospective, randomized, placebo-controlled trial (12). The study was limited to those who had prior exposure to THC and directly compared pre-rolled cannabis cigarettes with 3.56% THC and placebo cannabis cigarettes. The primary outcome was each patient's subjective measurement of 24-hour pain on a 100-mm visual analog scale (VAS). The predetermined criteria for clinically significant pain relief was set at a 30% reduction. Patients were allowed to continue their non-study pain medications. Fifty-two percent of the intervention arm and 24% receiving placebo had a clinically significant reduction in pain from baseline to end of treatment. Cannabis did not outperform placebo in long thermal stimulation tests or heat/capsaicin secondary hyperalgesia, but it reduced the area to brush and von Frey hair stimuli compared to placebo. The number of adverse events requiring treatment was low, but there was a statically significant increase in self-report of adverse effects among the cannabis group, specifically anxiety, sedation, disorientation confusion, and dizziness. Limitations to the study included low THC concentration, brevity of the intervention, and lack of cannabis naïve participants.

Ellis also explored the use of smoked cannabis to decrease pain intensity associated with HIV neuropathy using the Descriptor Differential Scale as the primary measure (13). This double-blind, placebo-controlled crossover trial compared placebo versus active cannabis exposing each participant to both arms. During the initial treatments of each arm, participants could titrate active and matched placebo cannabis to dose between 1% and 8% (THC in the active phase and no THC in the placebo phase) with a goal of symptom control without adverse effects. Most participants titrated to 8% during the placebo phase but remained at 2% or 4% during the active phase. The median difference in pain reduction was 3.3 DDS points (effect size 0.60; p=0.016). Although pain was significantly reduced, concomitant use of other analgesics did not decrease during the 5-day active phase. The most significant adverse event involved a treatment-naive patient who was unable to continue the study due to onset of psychosis deemed to be related to the study. Limitations in

addition to the short active phase included difficulty with preserving the blind, as most participants noted being able to guess which treatment arm they were in at any given time.

Wilsey explored the effect of smoked cannabis on neuropathic pain in a randomized double-blind, placebo-controlled, crossover design comparing 0%, 3.5%, and 7% THC (14). Each treatment day included a total of 9 puffs over the course of 3 hours. The primary outcome was pain relief as measured by a VAS. Other dynamics of pain and of the cannabis use experience were measured as well as alterations in pain threshold and neurocognitive assessments. Participants were recruited from pain clinics as well as through advertisements. Candidates with complex regional pain syndrome type I, spinal cord injury, peripheral neuropathy, or nerve injury were enrolled. Previous cannabis exposure was required for inclusion, but participants were required to abstain from cannabis and oral cannabinoids for 30 days prior to the procedures. Both study treatments decreased pain intensity versus placebo, but no statistically significant difference was noted between 3.5% and 7% THC. Subjective effects of “feeling high,” feeling impaired, and feeling stoned also correlated with treatment versus placebo and may have led to the conclusion that the blind was not maintained. Neuropsychological impairment was greater with 7% than 3.5 % THC, with the low dose demonstrating a decreased level of impairment. It was noted that greater than three quarters of the participants had impaired performance at baseline. Cannabinoid blood levels were measured in this group, and they did not correlate with analgesia. THC levels only correlated with one of the tests within the neurocognitive battery.

A 2010 study explored the ability of smoked cannabis (0%, 2.5%, 6%, and 9.4%) to treat posttraumatic or postsurgical neuropathic pain (15). This randomized, placebo-controlled, crossover study set the level of clinical significance at 10 mm on the 100-mm VAS and administered only a single inhalation 3 times daily with the first day of each cycle including 3 hours of outpatient monitoring. There was a statistically significant difference in average daily pain, and participants reported improved perceptions of time to sleep when administered the highest doses. The study did not report improvement in mood, quality of life, mobility, or self-care. Adverse events were consistent with the other studies and increased with potency. There was also an increase in anxiety or depression as queried by the EQ-5D quality-of-life instrument.

HIV-Associated Anorexia

Haney investigated the effect of dronabinol and marijuana versus placebo on calories consumed and sleep in a group of 10 HIV-positive marijuana smokers (16). The study design involved two 16-day inpatient sessions. Participants experienced all three marijuana (0%, 2%, and 3.9%) and dronabinol (0 mg, 5 mg, and 10 mg) treatments with 4-day washout periods between treatments. Participants completed a range of questionnaires as well as cognitive tasks batteries and physiologic measurements. Dronabinol and marijuana at both doses produced a statistically significant increase in calories consumed. Higher-strength marijuana and dronabinol increased body weight. Only the highest dose marijuana provided statistically significant improvement in sleep satisfaction. There was no significant difference in objective measures of sleep between dronabinol and marijuana. The results of the cognitive batteries did not reveal any alterations in performance with use of either

substance. Most reported adverse events were mild and associated with higher potencies or cannabis nonsmokers. Higher-dose dronabinol increased ratings for marijuana liking for placebo marijuana administered the same day, leading to the assumption that the blind was maintained.

Spasticity

Spasticity is a common symptom of multiple sclerosis and significantly affects quality of life. A 2012 study compared smoked cannabis (4% THC) with placebo on change in spasticity as the primary outcome (17). In the cohort of participants studied, spasticity, as measured by the modified Ashworth scale score, was reduced by an average of 2.74 (95% confidence interval 2.20–3.14) points more than placebo and 2.95 points overall (with a change of 2 points considered to be clinically significant). Visual analog pain score improved by an average of 8.27 points compared with placebo. Tests of physical performance (timed walk) did not improve. Cognitive performance on the Paced Auditory Serial Addition Test decreased within each session after administration of cannabis but improved visit to visit as expected. The study did not report any serious adverse events but noted that participants withdrew due to feeling “uncomfortably high,” dizziness, and fatigue. Although raters were blinded to treatments, test of the blind revealed that participants guessed the phase of treatment at a rate greater than chance.

Glaucoma

Merritt studied smoked cannabis for the treatment of intraocular hypertension (18). Marijuana cigarettes with THC content of 0% or 2% were administered, and each patient’s blood pressure, heart rate, and intraocular pressure were monitored for 4 hours. Marijuana inhalation led to tachycardia and decreases in systemic blood pressure, as well as decreases in intraocular pressure as rapidly as 30 minutes with maximal effect at 90 minutes of 6.6 ± 1.5 mm Hg. Intraocular pressure returned to baseline by 4 hours after administration. The team noted that marijuana was not an ideal therapy due to frequency and severity of adverse effects. In their study, symptomatic postural hypotension occurred in 5 of 18 patients.

Discussion and Conclusion

Marijuana has long been considered to have potential health benefits, but few trials have addressed its efficacy in smoked form, and studies of other methods of administration have limited generalizability due to differences in drug metabolism. Generalizability is also hampered by differences in the relative distributions of phytocannabinoids and terpenoids in whole plant and concentrated plant abstracts, which provide a synergistic effect (19). The most recent Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine report reveals that these research gaps continue to exist despite the changing legal landscape and hundreds of studies being funded each year (8). The studies described above report that smoked cannabis can provide subjective improvements in pain and spasticity. There was no evidence that patients reduced use of other prescribed pain medications when using cannabis during the study time frames. Cannabis did not outperform placebo on experimentally evoked pain or timed walk test. There was clear evidence that

smoked cannabis reduced intraocular pressure, but the effect was too brief (< 4 hours) to be of therapeutic benefit for this chronic disorder. There was also consistent evidence that smoked marijuana even at lower concentrations of THC increased total daily calories and number of eating occasions. Neither of the studies with quality of life as secondary outcome measures revealed statistically significant improved outcomes with cannabis use.

The studies of smoked cannabis above demonstrated the tolerability of smoked cannabis and its acute effects primarily on current and historical smokers of cannabis. Smoked cannabis was generally well tolerated with mild to moderate adverse effects. Of the 208 participants, few (2) were reported to experience severe adverse effects. Experienced cannabis smokers (n=170) were less likely to report adverse effects and more likely to tolerate higher concentrations of THC than cannabis-naïve participants. This is concerning considering the low doses of THC administered, as these effects may be dose dependent. These studies were not designed to address long-term risks of smoking cannabis.

Limitations include small sample sizes, brevity of treatment, and inability to blind patients to the psychoactive effects of cannabis. The highest THC concentration studied was 9.4%, with a median concentration of 3.75%. When given the opportunity to self-titrate in a 2009 pain study,(13) most chose 2–4%. This level of THC exposure differs from the average concentration currently available in the marketplace: 12% on the illegal market (20) and 20% in the Washington state legal market (21). The concentrations of cannabidiol and other cannabinoids were not reported in these studies, and these also differed between National Institute on Drug Abuse cannabis and that available in the marketplace(19). Other limits to generalizability are that these studies excluded patients with clinical depression, however depression and pain are highly comorbid.

This review included only randomized placebo controlled clinical trials, the scarcity of which highlights the barriers to systematic research posed by the current classification of marijuana. It is noted that due to the limited number of randomized placebo controlled clinical trials, open-label studies currently represent the preponderance of evidence related to the efficacy and safety of cannabis as a medicinal plant (8, 22, 23). Cultural change continues to outpace research, with ever higher-potency cannabinoids reaching the market and an increasing array of administration methods. Work is being done to set a standard unit of cannabis content—the “standard joint unit”—to establish common language describing consumption (24). Adoption of a standard would enable clearer evaluation of dosing for medicinal use as well as a common language for discussing parameters to limit risks associated with recreational use. Clear guidance on effective doses as well as doses associated with increased risk of adverse events is needed for physicians, pharmacists, and marijuana dispensary staff. Future research is also needed to ascertain whether higher concentrations of THC have greater efficacy and what risks they may pose.

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References

1. Joy, JE., Watson, SJ., Jr, Benson, JA, Jr. Medicine Io. Marijuana and Medicine: Assessing the Science Base. Washington, DC: The National Academies Press; 1999. p. 288
2. Hemp & Flax in Colonial America. 2017.
3. United States Pharmacopea. 2017. Available from: http://antiquecannabisbook.com/Appendix/AppendixC.htm
4. Full text of "The Pharmacopeia of the United States of America (The United States pharmacopeia)" [Available from: https://archive.org/stream/pharmacopeiaofun09unit/pharmacopeiaofun09unit_djvu.txt.
5. The dispensatory of the United States of America. 1868. Available from: https://archive.org/stream/dispensatoryofun00bachuoft - page/382/mode/2up
6. Statement of Dr. William C. Woodward, Legislative Council, American Medical Association 2017 [Available from: http://www.druglibrary.org/Schaffer/hemp/taxact/woodward.htm.
7. DEA / Drug Scheduling. 2017. Available from: https://www.dea.gov/druginfo/ds.shtml
8. National Academies of Sciences E, Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. Washington, DC: The National Academies Press; 2017. p. 440
9. Quality CfBHSa. Key substance use and mental health indicators in the United States: Results from the 2015 National Survey on Drug Use and Health). 2016. Available from: http://www.samhsa.gov/data/
10. Schauer GL, King BA, Bunnell RE, Promoff G, McAfee TA. Toking, Vaping, and Eating for Health or Fun. American Journal of Preventive Medicine. 50(1):1–8. [PubMed: 26277652]
11. Evans SR, Ellis RJ, Chen H, Yeh T, Lee AJ, Schifitto G, et al. Peripheral neuropathy in HIV: prevalence and risk factors. AIDS. 2011; 25(7):919–28. [PubMed: 21330902]
12. Abrams DI, Jay CA, Shade SB, Vizoso H, Reda H, Press S, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology. 2007; 68(7): 515–21. [PubMed: 17296917]
13. Ellis RJ, Toperoff W, Vaida F, Van Den Brande G, Gonzales J, Gouaux B, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology. 2009; 34(3):672–80. [PubMed: 18688212]
14. Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain. Journal of Pain. 2008; 9(6):506–21. [PubMed: 18403272]
15. Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: A randomized controlled trial. CMAJ. 2010; 182(14):E694–E701. [PubMed: 20805210]
16. Haney M, Gunderson EW, Rabkin J, Hart CL, Vosburg SK, Comer SD, et al. Dronabinol and marijuana in HIV-positive marijuana smokers: Caloric intake, mood, and sleep. Journal of Acquired Immune Deficiency Syndromes. 2007; 45(5):545–54. [PubMed: 17589370]
17. Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. Smoked cannabis for spasticity in multiple sclerosis: A randomized, placebo-controlled trial. CMAJ. 2012; 184(10): 1143–50. [PubMed: 22586334]
18. Merritt JC, Crawford WJ, Alexander PC, Anduze AL, Gelbart SS. Effect of marihuana on intraocular and blood pressure in glaucoma. Ophthalmology. 1980; 87(3):222–8. [PubMed: 7053160]
19. Russo EB. Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol. 2011; 163(7):1344–64. [PubMed: 21749363]
20. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC. Changes in Cannabis Potency Over the Last 2 Decades (1995–2014): Analysis of Current Data in the United States. Biol Psychiatry. 2016; 79(7):613–9. [PubMed: 26903403]

21. Smart R, Caulkins JP, Kilmer B, Davenport S, Midgette G. Variation in cannabis potency and prices in a newly legal market: evidence from 30 million cannabis sales in Washington state. Addiction. 2017

22. Bachhuber MA, Saloner B, Cunningham CO, Barry CL. Medical Cannabis Laws and Opioid Analgesic Overdose Mortality in the United States, 1999–2010. JAMA Intern Med. 2014; 174(10): 1668–73. [PubMed: 25154332]

23. Haroutounian S, Ratz Y, Ginosar Y, Furmanov K, Saifi F, Meidan R, et al. The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study. Clinical Journal of Pain. 2016; 32(12):1036–43. [PubMed: 26889611]

24. Casajuana C, Lopez-Pelayo H, Balcells MM, Miquel L, Colom J, Gual A. Definitions of Risky and Problematic Cannabis Use: A Systematic Review. Subst Use Misuse. 2016; 51(13):1760–70. [PubMed: 27556867]

Table 1

Summary of the Seven Placebo-Controlled Trials

Author	Design	Study treatments	No. of patients	No. of patients with previous or current cannabis experience	Primary outcome measures	Secondary outcome measures
Abrams 2007(12)	Randomized, placebo-controlled	0% and 3.56% THC cannabis	Cannabis group: 27 Placebo group: 28	55	Neuropathic pain intensity rating on a visual analog scale and achievement of > 30% reduction in pain intensity	Long thermal stimulation and heat/capsaicin sensitization
Ellis 2009(13)	Randomized, placebo-controlled, crossover	1–8% THC and matching placebo (containing 0% THC)	34	31	Neuropathic pain intensity change using the Descriptor Differential scale	Mood, disability, and quality of life
Wilsey 2008(14)	Randomized, placebo-controlled, crossover	0%, 3.5%, and 7% THC cannabis	38	38	Neuropathic pain intensity rating on a visual analog scale	Other pain dimensions, evoked pain, mood, and cognition
Ware 2010(15)	Randomized, placebo-controlled, crossover	0%, 2.5%, 6%, and 9.4% THC cannabis	23	18	Neuropathic pain intensity rating on a visual analog scale	Mood, sleep, and quality of life
Haney 2007(16)	Randomized, placebo-controlled, within-subject	0%, 2%, and 3.9% THC; dronabinol 0, 5, and 10 mg	10	10	Caloric Intake	Cognition and sleep
Corey-Bloom 2012(17)	Randomized, placebo-controlled	0% and 4% THC cannabis	30	24	Change in spasticity as measured by modified Ashworth scale	Pain, mobility, and cognition
Merritt 1980(18)	Randomized, placebo-controlled	0% and 2% THC Cannabis	18	9	Intraocular pressure	Heart rate and blood pressure

THC = tetrahydrocannabinol.