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Research Article

Medical Marijuana for the Management of Chronic Pain: Issues for Consideration

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Abstract

Patients with chronic pain often request information related to the use of non-traditional therapies. The reasons for these requests are varied. Some patients simply prefer using complementary therapies (e.g., herbal remedies). Others may have experienced issues related to poor analgesic response or significant adverse effects (e.g., nausea with opioids) with traditional therapies. In recent years the potential for use of medical marijuana has become increasingly of interest. Published reports indicate both positive and negative experiences associated with the use of cannabinoid-based analgesic therapies. The management of chronic pain for patients is often challenging. The use of the cannabis plant as a cannabinoid based strategy presents additional challenges for clinicians. This article provides a balanced perspective on the use of medical marijuana as a therapeutic strategy. Further research evaluating clinical outcomes associated with this treatment strategy is warranted.

Introduction

Pain treatment is a significant concern for modern society with many patients reporting poor pain control [1]. This crisis exists even in the face of significant efforts by entities such as the Joint Commission on Accreditation for Healthcare Organizations, who added pain assessment and treatment to their accreditation process more than a decade ago [1]. Another significant example of an attempt to improve pain assessment and treatment is evidenced by the Veteran's Administration promotion of pain as the "fifth vital sign." Despite these admirable efforts, more people in the United States are living with chronic pain today than are living with cancer, diabetes, and heart disease combined [1]. Managing chronic pain continues to challenge health care professionals and limit patients' wellbeing. This issue is substantial since chronic pain has a dramatic impact on the quality of life in these patients, including physical, emotional and psychological effects.

A major component of treatment for many chronic pain presentations involves the use of prescription and over-the-counter pharmacologic agents (e.g., acetaminophen, NSAIDs, and opioids) [1]. Pharmacotherapy may provide direct effects on pain pathways as well as target symptoms associated with comorbid disease states frequently encountered in chronic pain patients (e.g., anxiety, depression). At the same time, a significant number of patients may not be able to tolerate the adverse effects associated with analgesics. Commonly encountered analgesic adverse events include nausea, constipation, itching, and sedation. In some cases rational polypharmacy (e.g., stimulant laxatives for opioid induced constipation) may be able to assist an individual patient in managing the analgesic induced adverse effects. Unfortunately, this is not always true and may lead some patients to consider unconventional methods for pain relief.

The use of marijuana (also known as cannabis) is an alternative approach that has become increasingly of interest. Although illegal on a federal level, 20 states plus Washington DC authorize medical marijuana. This paradigm places the health care community in the middle of a difficult controversy, often without a thorough understanding of the facts surrounding this emotionally and politically charged issue. The purpose of this review is not to support or oppose the use of medical marijuana, but to present a balanced perspective on this alternative method of pain management that appears to be gaining popularity.

Mechanism of Action

The mechanism of action for cannabis was unclear until 1988 when researchers identified a cannabinoid receptor system composed of two, potentially three, receptor subtypes [2]. CB1 receptors are found in many parts of the human body and are mainly responsible for the euphoric, analgesic, and anticonvulsant qualities of cannabinoids. Activation of the CB_1 receptor decreases presynaptic intracellular calcium concentrations and activates inward-rectifying potassium channels thereby depressing neuronal excitability and reducing transmitter release. CB_2 receptors are found primarily in the immune system [3]. These CB_2 receptors are also thought to play a role in controlling inflammation and pain [4].

Another important finding was the discovery of endogenous cannabinoids (endocannabinoids), mainly anandamide and 2-arachidonylglycerol (2-AG), which act at cannabinoid receptors similar to endorphins interacting with the body's opioid receptors [5]. This finding has sparked increasing interest in the potential uses of cannabinoids for chronic pain. Phytocannabinoids are plant-derived cannabinoids whereas synthetic cannabinoids are manufactured

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in the laboratory setting. Tetrahydrocannabinol (THC) is the most widely known phytocannabinoid and is responsible for many of the psychotropic effects of cannabis. Two commercially available oral synthetic cannabinoids are currently available in the United States, dronabinol (Marinol®) and nabilone (Cesamet®).

Studies examining the effectiveness of cannabis for treating chronic pain have examined the use of phytocannabinoids and synthetic cannabinoids, as well as comparing different routes available for the drug's delivery. It is theorized that the combination of the more than 100 different cannabinoids found in the marijuana plant itself are responsible for providing pain relief. A meta-analysis of 18 studies on medical marijuana showed improvement in pain scores over placebo, but could not prove statistical significance because of study design issues such as small inclusion numbers, concurrent opioid usage, and prior exposure to cannabis [6]. Animal experimentation has clearly demonstrated that synthetic and endogenous cannabinoids not only produce analgesia but also interact in some manner to potentiate opioids [7].

The route of administration also appears to be an important consideration, as oral cannabinoids are not well absorbed and have unpredictable effects. THC undergoes extensive first-pass liver metabolism, which reduces the systemic bioavailability to less than 20% [8]. Oral cannabinoids have been examined in a few studies and have shown modest effects on pain, but optimal dosing of these agents for pain may lead to unpleasant psychological side effects [8]. Systemic bioavailability from inhaled cannabinoids is also unpredictable and can range from two to 56%. This range is due to a variety of dynamics, including intra- and inter-subject variability and exposure time of the cannabinoid to lung tissue. This approach can also cause a rapid on-off effect, producing an effect within minutes. The peak effect occurs in about 30 minutes and may last up to four hours [8].

Inhaling cannabinoids by way of smoking cannabis may cause significant intoxication and coughing, especially in patients naive to cannabinoids. However, some studies have observed acute bronchodilatory effects in chronic marijuana smokers; perhaps leading to increased lung capacity [9]. Vaporizing cannabinoids reduces the irritation of inhalation on the lungs by reducing the toxic byproducts in the cannabis smoke and has been shown to possess equal analgesic properties to smoking cannabinoids [10,11]. THC is extensively metabolized in the liver via the cytochrome P450 isoenzymes CYP2C, 2C19, 2D6 and 3A4 and is highly protein bound to plasma proteins. Even though no drug-drug interactions were reported during clinical trials of commercially available synthetic cannabinoids, patients should be monitored for changes in dosage requirements due to potential drug interactions [8,12].

While no commercially available cannabinoid products for the treatment of pain are currently licensed in the United States, nabiximols (Sativex®) is an oromucosal spray approved and marketed in Canada, UK, Spain, Germany, New Zealand, Denmark, Czech Republic, and Sweden. Sativex® is indicated for adjunctive treatment for symptomatic relief of spasticity in adults with multiple sclerosis in addition to conditional use as adjunctive treatment for neuropathic pain and as an adjunctive analgesic for patients with advanced cancer and moderate to severe pain with concurrent high doses of opioids. Cannabinoids appear as adjuvant agents in guidelines for pharmacological management of neuropathic pain in Europe and Canada [13,14].

Advantages

Smoking cannabis may not necessarily cause lasting damage to lung function according to the CARDIA study [9]. Pletcher and colleagues looked at the association between cannabis exposure and pulmonary function over a 20-year period [9]. One finding from the study supports the benefit of inhaled marijuana in light smokers. "Marijuana use was associated with higher FEV1 and FVC at the low levels of exposure defined as up to 7 joint-years of lifetime exposure (i.e., 1 joint/day for 7 years or 1 joint/week for 49 years)" [9]. The increase in lung function is theorized to be due to the strengthening and training effects of the deep inspiratory maneuvers practiced by marijuana smokers [15,16].

Another potential benefit of cannabis use is the clinically significant synergy with opioids shown at both the preclinical and clinical levels [7]. Due to the wide-spread concern about opioid misuse in our nation and the detrimental adverse effects associated with the amplified need for dose increases with opioid therapies, cannabinoids may find a place in chronic pain therapy as "opioid-sparing drugs" [17].

One recent study examined the effects of THC and cannabidiol on regional brain function in fifteen healthy men which indicated a surprising, yet additional benefit of cannabis use in psychosis [18]. Specifically, the cannabidiol component was shown to have an opposite effect of THC on the brain by decreasing the incidence of psychotic episodes. Cannabidiol increased the response of the left caudate area of the brain, which is normally weakened by THC. Cannabidiol may have a potential place in therapy as an antipsychotic due to its inherent ability to counteract the psychomimetic effects of THC [18].

Disadvantages

Cannabis is the most commonly used illegal substance worldwide [19]. Approximately four percent of the world's population used cannabis at least once in 2004 and cannabis use appears to be increasing. Cannabis is more commonly used in the United States than any other illicit substance with a lifetime prevalence rate of 46%. Among those that have ever used marijuana, nine percent also have a lifetime history of dependence [20]. Concerning statistics show that cannabis use at an early age is associated with use of other illicit substances at a later age [21]. Adults who use cannabis are significantly more likely to use, abuse, and be dependent upon alcohol, sedatives, stimulants, and opiates [22]. This information leads to the gateway theory of drug abuse, which many opposed to medical marijuana use as support for their argument.

Another concerning element involves patients with co-morbid mood disorders such as depression and anxiety who may be at higher risk of cannabis use disorder [23]. Published data appear to implicate marijuana as the culprit for cannabis-induced psychotic disorders. This is certainly a concern voiced by psychiatrists who question the potential therapeutic benefit of medical marijuana. In a study by Arendt and colleagues, 535 case reports of cannabis-induced psychosis were followed over three years to determine their

progression to a schizophrenia-spectrum disorder. The results showed almost half of the patients in the study developed a schizophrenia-spectrum disorder, with the most common type being paranoid schizophrenia [24]. It is well established that the younger age of onset of schizophrenia is correlated to more severe outcomes. The study suggests the patients suffering from cannabis-induced psychosis were more likely to develop schizophrenia at a significantly younger age compared to schizophrenic patients without a history of cannabis-induced psychosis [24].

According to a national survey by the Substance Abuse and Mental Health Services Administration, marijuana continues to increase as the drug of choice amongst young adults [25]. Marijuana use increased from 14.4 million Americans in 2009 to 17.4 million Americans in 2010 [25]. SAMHSA also reported an increase in marijuana use from 2009 to 2010 in persons ages 18 or older in correlation to a mental illness, which showed increased use in those with a serious mental illness as defined by the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders (*DSM-IV) [26].

In contrast to the CARDIA study, smoking marijuana has been shown to result in a greater respiratory injury than smoking a similar amount of tobacco according to Tzu-Chin and colleagues [27]. THC causes short-term bronchodilation, increased oxidative stress, rise in the carboxyhemoglobin level and approximately three times the amount of tar inhaled when compared to tobacco [28]. This is thought to partly be due to the differing manner in which marijuana is smoked (e.g., larger puff volume, greater inhalation depth and longer breath-holding time) [27,28]. Vaporizing THC may decrease irritation to the lungs but it does not completely eliminate contaminates (e.g., pesticides, mold, and bacteria) contained in the cannabis plant.

Discussion

In view of the growing interest in medicinal marijuana, it is important for healthcare professionals to be educated on the positives and negatives of this clinical debate. Most traditional medical and pharmacy education programs do not require training in illicit substances, leaving many clinicians unprepared to adequately answer patients' questions. As patients travel from state to state, they may be confused and unaware of the current legislation allowing or denying medicinal cannabis use, and may worry about potential incarceration for possession of a cannabis product. Currently, there are 20 states and the District of Columbia that have enacted laws to legalize medical marijuana [29]. These legal medical marijuana states include Alaska, Arizona, California, Colorado, Delaware, Hawaii, Illinois, Maine, Maryland, Massachusetts, Michigan, Montana, Nevada, New Hampshire, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington.[29] Each state has varying laws, fees, and possession limits.

Researchers have shown cannabis affects receptors that could play an important role in pain management. Currently, marijuana is one of a handful of agents that may reduce pain from activity at these receptors. Conversely, marijuana use may lead to various negative sequelae and is illegal in many parts of the United States. It has respiratory effects that could put the patient at risk for chronic obstructive lung disease and cancer. Oral absorption is unpredictable. THC's metabolism by the P450 enzymes and protein binding may cause changes in other drug concentrations putting patients at even greater risk. Abuse potential and psychoactive side effects are not something clinicians should take lightly especially in a patient population that already has a high incidence of comorbid psychological disorders. Pain patients could be at higher risk of abuse and/or dependence.

Studies have demonstrated that cannabinoids have a synergistic effect on opioids[7], theoretically enabling practitioners to lower patients' opioid doses. Moreover, a recent study showed that use of marijuana in addition to opioids did not increase systemic concentrations of circulating opioids [17]. Similarly, studies have shown that cannabinoids have moderate effects on both neuropathic and nociceptive pain types, making it a unique tool for pain management, as very few medications possess this quality [30].

Conclusion

More than 116 million American adults are living with chronic pain [1]. Surveys have shown a $635 billion cost the nation spends annually in medical treatments and lost productivity. The Institute of Medicine has challenged our health services to implement a prevention and management strategy for assessing and treating chronic pain patients and has charged pain relief as a national priority [1]. A tailored plan by healthcare providers for each individual suffering from chronic pain is highly recommended. Medicinal marijuana may be one treatment option, even if considered a last-line choice for patients suffering from treatment-refractory pain.

Not only is it important to consider the legal ramifications of medical marijuana, but also the medical concerns. Abuse potential, psychotic exacerbations, mood disturbance, breathing impairment with chronic use, and decreased response times are just a few of the potential concerns associated with its use. As a nation, we have put the topic of medical marijuana on the "hot seat", as it continues to be a primary focus of debate.

The intent of this article is not to justify the legality of medical marijuana, but to analyze its place in the treatment of patients suffering from chronic pain. As clinicians, we need to be sensitive to the debilitating effects chronic pain can have on our patient's lives but also be aware of potential harmful risks of traditional and nontraditional therapies. In an ideal future, well-designed controlled clinical trials will answer many of the questions concerning the use of marijuana for pain.

References

1. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Institute of Medicine Report Brief. 2011.
2. Di Marzo V, Petrocellis LD. Plant, synthetic, and endogenous cannabinoids in medicine. Annu Rev Med. 2006; 57: 553-574.
3. Pertwee RG. The pharmacology of cannabinoid receptors and their ligands: an overview. Int J Obes (Lond) 30 Suppl. 2006; 1: S13-18.
4. Malan TP Jr, Ibrahim MM, Vanderah TW, Makriyannis A, Porreca F. Inhibition of pain responses by activation of CB(2) cannabinoid receptors. Chem Phys Lipids. 2002; 121: 191-200.
5. Hohmann AG, Suplita RL 2nd .Endocannabinoid mechanisms of pain modulation. AAPS J. 2006; 8: E693-708.
6. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med. 2009; 10: 1353-1368.

7. Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid-opioid interaction in chronic pain. Clin Pharmacol Ther. 2011; 90: 844-851.

8. Huestis MA. Human cannabinoid pharmacokinetics. Chem Biodivers. 2007; 4: 1770-1804.

9. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M. Association between marijuana exposure and pulmonary function over 20 years. JAMA. 2012; 307: 173-181.

10. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME. Vaporization as a smokeless cannabis delivery system: a pilot study. Clin Pharmacol Ther. 2007; 82: 572-578.

11. Cichewicz DL. Synergistic interactions between cannabinoid and opioid analgesics. Life Sci. 2004; 74: 1317-1324.

12. Marion DW. Tetrahydrocannabinol and cannabidiol: Drug information. In: UpToDate, Basow DS (Ed), UpToDate, Waltham, MA, 2012.

13. Attal N, Cruccu G, Haanpää M, Hansson P, Jensen TS. EFNS guidelines on pharmacological treatment of neuropathic pain. Eur J Neurol. 2006; 13: 1153-1169.

14. Moulin DE, Clark AJ, Gilron I, Ware MA, Watson CP. Pharmacological management of chronic neuropathic pain - consensus statement and guidelines from the Canadian Pain Society. Pain Res Manag. 2007; 12: 13-21.

15. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR. Effects of cannabis on lung function: a population-based cohort study. Eur Respir J. 2010; 35: 42-47.

16. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A. Effects of cannabis on pulmonary structure, function and symptoms. Thorax. 2007; 62: 1058-1063.

17. Ware MA. Clearing the smoke around medical marijuana. Clin Pharmacol Ther. 2011; 90: 769-771.

18. Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S. Induction of psychosis by Î"9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Arch Gen Psychiatry. 2012; 69: 27-36.

19. Leggett T; United Nations Office on Drugs and Crime. A review of the world cannabis situation. Bull Narc. 2006; 58: 1-155.

20. Anthony JC, Warner LA, Kessler RC. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances and inhalants: basic findings from the National Comorbidity Survey. Exp Clin Psychopharmacol. 1994; 2: 244.

21. Lynskey MT, Heath AC, Bucholz KK, Slutske WS, Madden PA. Escalation of drug use in early-onset cannabis users vs co-twin controls. JAMA. 2003; 289: 427-433.

22. Degenhardt L, Hall W, Lynskey M. The relationship between cannabis use and other substance use in the general population. Drug Alcohol Depend. 2001; 64: 319-327.

23. Conway KP, Compton W, Stinson FS, Grant BF. Lifetime comorbidity of DSM-IV mood and anxiety disorders and specific drug use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J Clin Psychiatry. 2006; 67: 247.

24. Arendt M, Rosenberg R, Foldager L, Perto G, Munk-Jørgensen P. Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases. Br J Psychiatry. 2005; 187: 510-515.

25. Merikangas KR, McClair VL. Epidemiology of substance use disorders. Hum Genet. 2012; 131: 779-789.

26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV). Washington, DC: American Psychiatric Association; 1994.

27. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med. 1988; 318: 347-351.

28. Tashkin DP. Smoked marijuana as a cause of lung injury. Monaldi Arch Chest Dis. 2005; 63: 93-100.

29. ProCon.org. "20 Legal Medical Marijuana States and DC". Dec 13, 2013. Web. Available at: http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881. Accessed December 16, 2013.

30. Campbell FA, Tramèr MR, Carroll D, Reynolds DJ, Moore RA. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ. 2001; 323: 13-16.

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