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Cannabinoids in Pain Treatment: An Overview

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Abstract

The current landscape contains conflicting reports regarding the use of medical marijuana, creating fields of misinformation and lack of understanding by healthcare providers about cannabinoids. In this article we will provide a dispassionate look at medical marijuana, while providing a clinical overview focusing on pain management. We will examine the mechanisms of the endocannabinoid system (ECS), along with the pharmacology of cannabinoids. Current research on the use of marijuana for the treatment of pain will be reviewed. Finally, recommendations for pain management nurses on integrating research, clinical practice and U.S. drug policy will be made.

Introduction

There are conflicting reports regarding the use of medical marijuana, creating confusion, fear, and lack of understanding by health care providers about cannabinoids. In this article, we will provide a dispassionate look at medical marijuana, while providing a clinical overview focusing on pain management. We will examine the mechanisms of the endocannabinoid system (ECS), along with the pharmacology of cannabinoids. Current research on the use of marijuana for the treatment of pain will be reviewed. Pain management nurses are key health care providers to play a pivotal role on integrating research and education on the safety and utility of marijuana in pain management.

It is worthwhile to provide a framework of terms used in the discussion of medical marijuana. Throughout this article, the terms marijuana and cannabis are interchangeable. The differences between endocannabinoids, which are found within the body, are compared to phytocannabinoids, which are exogenous cannabinoids found in cannabis sativa herb (Lee, Grovey, Furnish, & Wallace, 2018). Even though over 100 phytocannabinoid compounds have been identified, only the two most explored phytocannabinoids, delta 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are discussed here. Additionally, cannabis sativa and cannabis indica are two species of cannabis that are studied for pharmacological use and discussed further in this manuscript (Piomelli & Russo, 2016).

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Endocannabinoid System

In the early 1990s, researchers discovered the ECS as a homeostatic regulatory system that regulates many physiological processes including cognition and behavior, immune and endocrine function, antinociception, appetite and digestion, inflammation, and the autonomic nervous system (Di Marzo, 2009; Janero & Makriyannia, 2009). The ECS regulates receptors and are referred to as cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2). The phytocannabinoids and endocannabinoids bind to these receptors to activate a response. CB1 receptors are found in the brain, such as the cerebellum, brainstem and limbic areas. They are also found in the spinal cord, the trigeminal ganglion, macrophages, mast cells and epidermal keratinocytes (Mackie, 2008; Sugawara, Zakany, Hudt, Emelianov, Tsuruta, & Schaefer, 2013). The CB1 receptors regulate the cannabinoid neurotransmitter effects within the central nervous system (Castillo, Younts, Chavez, & Hashimotodani, 2012). CB2 receptors are mostly found in the periphery in the hematopoietic stem cells, macrophages in the spleen, and other immune cells. These receptors function by 1) regulating neuroimmune interactions protecting neurons from pathogens, 2) interfering with inflammatory mediators that increase the sensitivity of sensory neurons to noxious stimuli, and 3) responding to peripheral nerve injury (Mackie, 2008; Guindon & Hohmann, 2009).

Endogenous cannabinoids.

Endocannabinoids are endogenous lipid-based retrograde neurotransmitters that bind to the cannabinoid receptors (CB1 or CB2). A retrograde neurotransmitter is a chemical that is part of a feedback loop and is released by the postsynaptic cell body and travels back across the synapse to bind to the presynaptic axon terminal. This feedback loop regulates the neurotransmitter (i.e. the endocannabinoids) by enhancing or disrupting the synthesis or release of the neurotransmitter. Anandamide and 2-arachidonoyl-sn-glycerol (2-AG) are the two most studied endocannabinoids. Anandamide responds to nerve injury and inflammation. It has a high affinity for the CB1 receptor site and plays a role in the processing of nociceptive information. 2 -AG is present in high levels in the central nervous system with great affinity and full agonist effect at the CB1 receptor, activates during tissue injury, and plays a prominent role in the descending modulation of pain during acute stress (Piomelli, Astarita, & Rapaka, 2007; Palazzo, Luongo, Novellis, Rossi, & Maione, 2010).

Exogenous cannabinoids.

Phytocannabinoids are exogenous cannabinoids. These exogenous cannabinoids also bind to the cannabinoid receptor. THC and CBD are the two phytocannabinoids that have undergone extensive research for medical and pharmaceutical use. THC is the cannabinoid most associated with cognitive side effects and abuse potential due to neuronal changes with elevated dopamine levels in the nucleus accumbens and prefrontal cortex. THC use can also produce hyperphagic behaviors (Bloomfield, Ashok, Volkow, & Howes, 2016). Tolerance and unpleasant withdrawal symptoms with abrupt cessation can occur (Hasin,O'Brien, Auriacombe\ et al., 2013; Vandrey, Budney, Hughes, & Liguori, 2008). In contrast, CBD has greatly reduced psychoactive properties and may inhibit the metabolism of THC.

Drug Pharmacology

An understanding of drug pharmacology is important to understand efficacy, drug to drug interactions and other safety parameters. In this discussion of drug pharmacology, we will discuss the pharmacokinetics and pharmacodynamics of THC and CBD, the bioavailability, metabolism, and elimination will be described. Additionally, the reader will be introduced to what products are commercially available by prescription and for which clinical indications.

Therapeutic pharmaceutical agents.

Currently, there are three synthetic pharmaceutical-grade THC products approved by the Food and Drug Administration (FDA) in the United States. These are dronabinol (Marinol®), dronabinol solution (5 mg/ml; Syndros®), nabilone (Cestamet®). Clinical indications in the United States are for antiemetic effects and appetite stimulation. Dronabinol is schedule III, and nabilone is schedule II (Wang & Henningfield, 2017). None of these products are FDA approved for pain management. Another cannabinoid-based pharmaceutical product is nabiximols (Sativex®), which is not approved in the United States. Nabiximol is an oromucosal spray of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids THC and CBD in a 1:1 ratio. It has been used for the relief of multiple sclerosis symptoms and the treatment of severe neuropathic-related cancer pain. The combination of THC and CBD may provide the best utility for pain management (Jensen, Chen, Furnish, & Wallace, 2015).

Proposed therapeutic effects.

Two sub-species of the cannabis plant, cannabis indica and cannabis sativa, are studied for pharmaceutical applications. Indica strains are horticulturally bred to enhance sedative effects, and recommended for symptoms of anxiety and insomnia. Sativa strains create more activating effects (Pearce, Mitsouras, & Irizarry, 2014). The potency of a variety of strains of the cannabis plant species is based on levels of THC, THC/CBD ratios, and presence of minor cannabinoids. There are more than 400 compounds including over 80 cannabinoids found in herbal cannabis. Additional chemicals, such as terpenoids, are yet to be understood for their role in the cannabis experience, and may play a role in treatment of pain and inflammation (Russo, 2011). Sequencing the cannabis genome can ultimately facilitate discovery of other major and minor cannabinoids for pharmaceutical and medical applications.

THC via oral route.—Oral use of THC creates a slow and erratic absorption. First pass hepatic metabolism reduces the bioavailability of oral THC because much of the THC is metabolized before it reaches the sites of action. The onset of action is 30 minutes to 1 hour with peak effect of 2–4 hours. The duration of the psychoactive properties are 4–6 hours and duration of the appetite stimulant effect is greater than 24 hours (Grotenhermen, 2003).

THC via inhalation.—When THC is inhaled, approximately 50% of the THC in an herbal cannabis cigarette is absorbed through the lungs, and rapidly enter the blood stream to affect the brain. The peak plasma concentration can be within 3–10 minutes. Ninety percent of THC is distributed to the plasma. The lipid solubility of THC causes the drug to rapidly

penetrate the fat tissues and highly vascularized tissues. This means that greater amounts of the drug are found in the tissue than circulating in the plasma (Sharma, Murthy, Bharath, 2012). THC is metabolized extensively in the liver through CYP450 complex using isoenzymes 2C9 and 3A4. There are around 100 metabolites, which continue to recirculate through the enterohepatic system so that most of the metabolites are excreted through the bile and feces. The half-life of THC is 25–36 hours depending on the dose of THC. For example, after a single dose of THC in a non-user, the metabolites can be detected in the urine on average of 3–5 days but can extend up to 12 days. In clinical practice, the urine toxicology testing would be negative in an average of 8.5 days for an infrequent user and 19.1 days for regular users (Grotenhermen, 2003). This delay in excretion is due to the enterohepatic recirculation of metabolites. A major metabolite is 11-hydroxy-THC which is possibly more potent than THC itself, creating some of the psychoactive effects of cannabis (Sharma, Murthy, & Bharath, 2012).

CBD.—The pharmacokinetics and pharmacodynamics of CBD are comparable to THC. The peak plasma concentration is dependent on route, with an average half-life of 24 hours during intravenous administration of CBD. There is similarity in metabolism except for a higher percentage of unchanged CBD excreted in the feces.

There are confusing dosing parameters for prescribed medical marijuana, and there is a lack of standardization. The L.E.S.S. Method is a measured approach to cannabis dosing: Start Low, Establish potency, go Slow, Supplement as needed (Erowid & Erowid, 2011). This method of dosing can enhance safety and efficacy in dose determination (Table 1). In the United States, only FDA-approved pharmaceuticals can be officially prescribed or furnished for medicinal use. If a prescribing clinician decides that a patient meets the qualifications to use medicinal marijuana for a determined diagnosis, they are required to complete a state medical necessity document following a comprehensive history and physical exam. The patient submits this document with other required documents and pays a fee to the state to receive a medical marijuana card. The medical marijuana card can be used at a local dispensary. Often, the employees at dispensaries guide the patient in decision making about which products to obtain and use. In most states the medical necessity document can only be completed by a medical doctor, in a few states this authority has been granted to nurse practitioners and physician assistants as well.

Regulations

Marijuana was placed in the Schedule 1 category since the Controlled Substances Act of 1970, indicating high potential for abuse and no accepted medical use in the United States. However, in 1992, California was the first state in the union to “legalize” the use of marijuana for medical purposes, and in 2012 Colorado was the first state to pass legislation to allow their residents to use marijuana for recreational purposes. This means that the federal law continues to supersede individual state laws, even though the federal government often chooses to respect the self-governance of states. At any time, regardless of state legislation, the federal government can decide to enforce federal policy and prosecute individuals who break federal laws. This has created much confusion for clinicians, lawmakers, and the public. There have been numerous legislative debates regarding access.

Currently, 29 states have legislation that allows eligible patients access to medical cannabis cards, and 7 states, and the District of Columbia have passed legislation for recreational use.

Despite recommendations from such groups as the American Medical Association, the World Health Organization, various patient advocacy groups, and state and federal legislators, a long history of regulations have restricted the use of cannabis in research and clinical practice. In the United States, scheduling marijuana products at the highest level of restriction, has created legal and practical barriers in obtaining product sufficient to conduct the safety and efficacy trials. Furthermore, from a legal perspective, the marijuana plant has been considered a single entity. As a single entity, isolated components of the marijuana plant, such as CBD or THC, are regulated as if it were the whole plant. Change in this area has been slow and has resulted in barriers to cannabinoid access for appropriate patient care. However, new knowledge of CBD and THC has improved understanding of the addictive potential and public safety profile of CBD compared with THC. This has led to recent Federal Drug Administration (FDA) approval of cannabidiol (Epidiolex®) for Lennox-Gastaut syndrome and Dravet syndrome (FDA, 2018).

Research on Clinical Applications for People in Pain

There is a need to improve and advance research on cannabinoid-based medicines for treatment of pain. Many groups including the American Medical Association and American Nurses Association have called for much-needed clinical trials on cannabinoids in pain management (American Medical Association House of Delegates, 2009; American Nurses Association, 2016). In a Canadian consensus statement, Moulin et al. (2014) recommended marijuana as third-line for treatment of pain. For analgesia, this consensus statement recommended the following analgesic agents for the treatment of pain: 1) first-line treatments are gabapentinoids (gabapentin and pregabalin), tricyclic antidepressants and serotonin noradrenaline reuptake inhibitors; 2) second-line treatments are tramadol and controlled-release opioid analgesics for moderate to severe pain; and 3) third-line treatments are cannabinoids. However, the majority of individual clinical trials looking at the efficacy of cannabis for pain management have involved small sample sizes, brief study durations, lack of heterogeneity in the formulations and delivery routes of study drugs, use of placebo rather than standard-of-care control groups, and the reliance on pain scores rather than functional outcome measures (Hill, 2015; Lynch & Campbell, 2011; Andreae, Carter, Shaparin et al., 2015). Given this, the recommendations of cannabis for neuropathic pain are based on the preponderance of the evidence through examination of metanalysis and systematic reviews (Aggarwal, 2013; Andreae et al., 2015; Aviram & Samuelly-Leichtag, 2017; Baron, 2015; Häuser, Petzke & Fitzcharles, 2018; Hill, Palastro, Johnson, & Ditre, 2017; Hill, 2015; Jensen et al., 2015; Lynch & Campbell, 2011; Martin-Sanchez, Furkawa, Taylor, & Martin, 2009; Meng, Johnston, Englesakis, Moulin, & Bhatia, 2017; Moulin et al., 2014). In a recent Cochrane Database review examining cannabis-based medicines for chronic neuropathic pain in adults, the authors concluded that potential benefit outweighs potential harm for its use in chronic neuropathic pain (Mücke, Phillips, Radbruch, Petzke, & Häuser, 2018). The authors stated that studies that included data collected from patients with a history of substance abuse were excluded. A research area that may have significant implications for patients with chronic pain is the opioid-sparing effects of cannabinoids. A

recent systematic review of 19 pre-clinical and 9 clinical studies concluded that pre-clinical studies provided robust evidence of the opioid-sparing effect of cannabinoids, whereas 1 of the 9 clinical studies identified provided very low-quality evidence of such an effect (Nielsen, Sabioni, Trigo et al., 2017). It was also concluded that future studies need to include prospective high-quality controlled clinical trials to determine efficacy in safety, dosing, diagnosis, and the opioid-sparing effect of cannabinoids.

Implications for Pain Management Nurses

The role of the pain management nurse is described below. These role includes research, clinical practice, education of patients and nurses, and policy regarding cannabis access.

Research.

As the field of cannabis research grows and gains national acceptance, nurse researchers have an growing role to play. Historically, nursing research has centered around patient care outcomes and educational needs (Thiel et al., 2008; Saunders & Vehviläinen-Julkunen, 2016; Lindsay et al., 2017). With the necessity for more patient-centered outcomes research, nurse researchers can design and implement studies within real-life daily practice that have practical implications for clinical practice (Newhouse, Barksdale, & Miller, 2015). Study designs focusing on needs assessment have been performed in Canada to assess the knowledge of advance practice nurses' knowledge and competence surrounding the use of medical cannabis (Balneaves, et al., 2018). These studies will need replication and validation in the United States, as the use of medicinal and recreation cannabis continues to grow.

Over the past several years there has been discussion regarding the use of medical cannabis as a solution to the opioid crisis. One study found an association between the decrease in opioid mortality and marijuana legalization in states that have medical marijuana legislation (Bachhuber, Saloner, Cunningham, & Barry, 2014). Another study found potential for decreased opioid use in patients with pain (Degenhardt, Lintzeris, Campbell, et al., 2015). Nurses are poised to rate the quality of the evidence, design symptom outcome studies on medical marijuana for pain management, and perform phenomenological studies regarding pain patients' experience with its use. Anne Dabrow Woods, Chief Nurse at Wolters Kluwer, writes:

> Nurses are an integral part of the interdisciplinary team fighting the opioid crisis …. Nursing is both an art and a science and using those principles can help guide our pain management practice through … using acupuncture, meditation, and other alternative or naturopathic techniques (Woods, 2017).

Nurses are already considering the use of cannabis as a response to the opioid crisis, and researching the possibility (Vyas, LeBaron, & Gilson, 2018).

Clinical practice.

Nurses are well positioned to lead the way in helping people effectively manage pain while minimizing risk for medication misuse. As leaders in the holistic view of patients, nurses continue to use a vast array of treatment modalities. Through the incorporation of the

biopsychosocial-spiritual model of pain, nurses understand the risk of undertreated pain as well as the risk of overmedicating pain with opioids (Matteliano, St. Marie, Oliver, & Coggins, 2014). Removing the barriers to access of medical cannabis for clinical care will provide options in managing pain while helping patients regain function.

Education of patients and nurses.

There are two distinct opportunities for nurses in areas of medical cannabis use, education of patients and education of other health care professionals including nurses. General considerations when counseling patients about the use of cannabis include legality, safety, side effects and drug to drug interactions. The cultivation, sale and use of cannabis, even with a state awarded medical marijuana card remains illegal in the eyes of the federal government. This means that some employers may choose to terminate employment of a patient who tests positive for marijuana on an employee drug screen. It is important to understand and be in full compliance with state marijuana legislation and realize that different states have different rules. Education about safe cannabis use includes but is not limited to informing patients about the possible cognitive side effects associated with THC use, such as euphoria, dissociation, anxiety, paranoia and psychosis (Karila et al., 2014). This discussion further includes withdrawal symptoms that may occur with acute cessation, such as sleeplessness, restlessness, irritability, and changes in appetite (Gorelick, Levin, Copersino et al., 2012; Karila et al., 2014). There is potential for interactions with other medications that interact with CYP450 isoenzymes such as 1A2, 3A4, 2C9, 2D6 (Lucas, Galettis, Schneider, 2018). These interactions may result in competitive or synergistic effects. Cannabis combined with central nervous system depressants can have synergistic effects (Grotenhermen, 2003). Cannabis combined with antidepressants or other sympathomimetic agents, may lead to worsening depression, anxiety and hypertension (National Library of Medicine, 2015). Serum levels of lithium, warfarin, antiretroviral agents, and protease inhibitors could be altered if cannabis is used with these medications. Patient education and working in partnership with patients can facilitate early identification of adverse effects, preventing morbidity or mortality through adverse medication interactions. Finally, patients must be educated about other aspects of safe use, including the physiological impact of using edibles versus vaporizing cannabis, driving safety, and keeping cannabis products away from children and animals.

Nurses have already taken a lead on peer education about topics surrounding use of cannabis. The American Cannabis Nurses Association has a website devoted to education and resources, and offers a Medical Cannabis Curriculum for Nurses certification (American Cannabis Nurses Association, 2018). Nurses in pain management, primary care, palliative care, and those who work with patients where the use of cannabis is a consideration, should be encouraged to implement or investigate outcome-oriented continuing education programs on the topic of cannabis to help dispel myths and misconceptions about this class of drugs. Curriculum topics could include mechanisms of the endogenous cannabinoid system, its interaction with the endogenous opioid system, safe dose determination, and attention to the side effect profiles of these drugs. The knowledge and skills gained can improve patient outcomes in the management of pain.

The utility of a treatment agreement to educate and outline each partners' responsibility, can serve as a guide for both patient and healthcare provider education, and peer to peer education. A treatment agreement, similar to what might be used for patients receiving chronic opioid therapy, is an excellent way of introducing the discussion about safety, and establishing guidelines and responsibilities of the clinician and the patient. The basics of a written treatment agreement include risks, benefits, side effects, patient responsibilities, clinician responsibilities, safety considerations, conditions of care/treatment, and consequences of non-compliance (Wilsey, Atkinson, Marcotte, & Grant, 2015). Nurses should be empowered to take a role in developing treatment agreements, monitoring for compliance, and reviewing best practice standards regarding implementation of treatment agreements.

Policy.

Nurses are well situated to contribute and lead the transformative changes that are occurring in healthcare. Through active participation in interprofessional teams and involvement in committees, city councils, and professional societies, nurses are influencing attitudes around wellness and population-based care with a renewed focus on patient-centered care, care coordination, data analytics, and quality improvement (Brokaw, 2016; Salmond & Echevarria, 2017). Nurses have a powerful voice to create policy and affect public opinion about cannabis use, and to help eliminate policies that currently restrict access to efficacy studies of cannabis products. Restrictive policies at federal, state, and payer levels must not hinder clinical judgment in the management of pain. Furthermore, policy is needed to support the following:

- Research focused on long-term effectiveness of cannabinoid use.
- Discovery of additional major and minor cannabinoids for pharmaceutical and medical applications.
- Methods to reduce addiction potential of not only cannabis but other addictive central nervous system drugs.

Conclusion

As the availability of medicinal and recreational marijuana increases, all health care providers must be provided with a basic education regarding the safety profile, efficacy, and science surrounding cannabis. The use of cannabis has been presented from a culturally biased framework for decades. The government and the medical community have sanctioned cannabis as an illegal substance without medical value, until recently. The current scientific understanding of cannabinoids, coupled with a better understanding of the endocannabinoid system, has activated patient advocacy groups and the medical community to reconsider legislative policy and reshape cultural bias. Concerned groups have called for quality research, outcome-oriented education, and dispassionate explorations of pain management options as essential to expand the field of analgesics. High-quality studies are needed to determine if cannabinoids are effective in many painful conditions and if there are opioid sparing effects.

The discovery of the endocannabinoid system as a modulator of nociception has expanded the wealth of research opportunities for modulating this system, and to expand the role of phytocannabinoids in health care. As patients continue to explore the utility of cannabinoid for the treatment of pain, healthcare providers need to be educated about the current state of research, policy, and ethical practice that intersects the use of cannabinoid. Nurses with enhanced knowledge of cannabinoid, can counsel patients on clinical indications, drug interactions, and safe use. Nurses play a fundamental role in research, education, and policy development surrounding the safeguard and use of medicinal cannabis in their patients. To prepare for this role, nurses need to be educated themselves or participate in education forums about the current science, in order to develop a true understanding about how the use of exogenous cannabinoids can best support the workings of the endocannabinoid system for the treatment of pain. Finally, nurses, like all healthcare providers, need to evaluate the evidence without bias and dispassionately prepare for discussion with their patients and colleagues as the topic arises.

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Table 1

Practical Dosing *

Average Adult Dosing of THC for:
• Cannabis-naïve individuals = 2.5–5mg
• Daily to weekly users = 10–20 mg
• Daily+ = 25 mg+

THC = tetrahydrocannabinol.

* Modified from lecture given at the California Association of Nurse Practitioners, 2017. National Education Conference, Burlingame, CA, March 16/16/2017.