CANNABINOIDS FOR CHRONIC NONCANCER PAIN MANAGEMENT:
A FOCUSED LITERATURE REVIEW

by

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CANNABINOIDS FOR CHRONIC NONCANCER PAIN MANAGEMENT:
A FOCUSED LITERATURE REVIEW

Abstract

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July 2011

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The purpose of this literature review is to: 1. To determine if cannabinoid products are effective in treating chronic pain associated with HIV/AIDS, multiple sclerosis (MS), neuropathy, or other unspecified sources of chronic pain. 2. To ascertain if the form and route of administration of cannabinoid products is important in efficacy and safety (e.g. dronabinol versus whole-plant cannabis). 3. If efficacy has been established, are these medications available in a form that clinicians can safely recommend to their patients? 4. Lastly, to determine what the legal implications for clinicians and patients may be when working with a Schedule I drug.

Evidence from this review indicate that cannabinoid products can be highly efficacious in managing chronic noncancer pain, including pain caused by multiple sclerosis, HIV, antiretroviral therapies used in treating HIV and other sources of chronic pain. Cannabinoid therapies that bypass hepatic metabolism are better tolerated by patients and are the preferred route of administration. Additional large-scale randomized controlled trials are essential to elucidate appropriate forms of administration (whole plant, synthetic sublingual, etc.) for safe clinical management of cannabinoid products. Regarding the legal implications of working with a tightly regulated medication, to date no patients, providers, dispensaries or caregivers have been prosecuted for practicing within the bounds of their state’s legislation.

Providers need to familiarize themselves with the forms of cannabinoid products
available to patients within the state they practice in. Oral cannabinoids such as dronabinol (Marinol) can be helpful for many patients, but also have a side effect profile that limit therapeutic benefit for many more. Medical marijuana is available in 13 states at the time of this publication. It is the first time public initiative, rather than the FDA, is guiding the medications available to patients and preliminary research indicates that whole plant cannabis can be an effective analgesic for some patients. Consuming any product in a smoked form is never recommended, so clinicians should have conversations with patients regarding alternative methods of consumption (e.g. vaporization), or the harm versus benefit of smoking cannabis products.
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Cannabinoids For Chronic Noncancer Pain Management:

A Focused Literature Review

Chronic pain management is a challenging issue facing all primary care providers and pain in general is the most common reason patients seek medical attention (Joy, Watson, & Benson, 1999). Successful pain management combines the didactic training learned in formal education with the art of clinical expertise. No two patients are physiologically or psychologically similar in their reaction to pain, which makes achieving an acceptable level of pain relief very difficult in many cases. It has been estimated that chronic pain contributes more to serious morbidity in a patient’s life than other chronic diagnoses including lung, heart or kidney disease, and doubles the risk of suicide (Lynch & Campbell, 2011). Added to this, underlying addiction issues, refractory pain, access to care, other socioeconomic factors, and the overall picture of controlling pain becomes fairly grim. It is important that clinicians explore evidence-based options to optimize the quality of life of patients, and with medical marijuana and other cannabinoids garnering a great deal of media attention, this is an issue not only patients will bring to the attention of their providers, but one the providers should be considering as well.

Pathophysiology of Pain

Pain has many definitions but can be roughly described as an unpleasant sensory and emotional experience, which may or may not result in actual tissue damage. Pain is always a subjective measure (McCance & Huether, 2005). There is no objective measurement for pain, although there are many sensorineural pathways involved which biologically validate the subjective experience of pain.

Pain can be compartmentalized into three major classifications: visceral; neuropathic; and somatic (Joy et al., 1999). Visceral pain is the result of the activation of nociceptive receptors in
the intestine or gut (the viscera) and is usually described as an aching, cramping, poorly-localized pain. Visceral pain is commonly referred pain because there are far fewer nociceptors in the viscera and it can be difficult to ascertain the location of the painful stimulus (Joy et al., 1999; McCance & Huether, 2005). Neuropathic pain is a result of injury to either peripheral or central nerves or receptors, is particularly unpleasant, and is the most common form of chronic pain. It is characterized by burning, stabbing, shooting, tingling and/or numbness and can often have an element of allodynia (particularly painful sensation from a normally innocuous stimulus) (Joy et al., 1999; McCance & Huether, 2005). Lastly, somatic pain arises from painful stimuli applied to the peripheral nerves in connective tissue, muscle, skin or bone and is usually well-localized and characterized (Joy et al., 1999; McCance & Huether, 2005).

**Pain pathways and receptors.**

Nociceptors are the unspecialized, bare nerve endings that respond to mechanical, chemical, thermal or other noxious stimuli and begin the transmission of a pain impulse. The concentration of nociceptors in any area depends on the importance of receiving pain information in that area (e.g. the gut versus fingertips). Pain impulses and subsequent action potentials are transmitted via an array of voltage-gated channels, primarily potassium, calcium and sodium channels. A simplified explanation of how a pain impulse is transmitted is that at the onset of a noxious stimulus, for example a hammer blow to the thumb, the nociceptive receptors in the thumb transmit signals through the peripheral nerves of the hand and arm into the grey matter of the dorsal horn of the spinal cord. From there the signal is transmitted to the brain and the resulting pain information is processed by the medulla, thalamus, and the periaqueductal grey (PAG) matter of the midbrain. This information is then processed into a neuroendocrine response and relayed to the corresponding parts of the body (McCance & Huether, 2005).
Neurotransmitters play an essential role in the relay of pain information. There are both inhibitory and excitatory neurotransmitters. Excitatory neurotransmitters facilitate the processing of the nerve impulse up the nociceptive pathway, and examples of these neurotransmitters include glutamate, N-methyl-D-aspartate (NMDA) and Substance P. Inhibitory neurotransmitters interrupt (modulate) the nociceptive message and include γ-aminobutyric acid (GABA), 5-hydroxytryptamine (serotonin), norepinephrine, and endogenous opioids (McCance & Huether, 2005). It was not until the 1990’s that an additional form of inhibitory neurotransmitters was discovered and formal research on this family of compounds erupted: the endogenous cannabinoids (Joy et al., 1999).

Pain modulation is not only a matter of neurotransmitters. The receptors that these ligands bind to also play a critical role. Antagonists of excitatory neurotransmitter receptors will modulate the release of these ligands thus interrupting the nociceptive signal, and reducing pain (McCance & Huether, 2005). The muscle relaxant and analgesic medication baclofen acts on the GABA pathway. Baclofen is effective for treating spasticity for example in multiple sclerosis sufferers (Carter & Ugalde, 2004). Agonists of inhibitory receptors encourage the release of ligands that interrupt nociceptive signals, which is also effective for analgesia. All current opioid therapeutics work in this way by acting on μ, κ, and δ opioid receptors (McCance & Huether, 2005). Cannabinoid inhibitory receptors (CB1 and CB2) were discovered in the 1980’s, giving preliminary validation to the use and reported effectiveness of cannabis as an analgesic agent for millennia (Joy et al., 1999).

Cannabinoid receptors negatively regulate voltage-gated Ca-channels at synapses via retrograde signaling (Wilson & Nicoll, 2002). When cannabinoid ligands bind to cannabinoid receptors, this triggers an inhibition of further synaptic potentials, and thus modulation of the
pain signal by regulating the release of dopamine, norepinephrine, serotonin, GABA and glutamate (Carter & Ugalde, 2004; Fox et al., 2001; Rice, 2001). The inhibitory effect on the GABA pathway held promise for MS sufferers, since this is the mechanism in which baclofen and other antispasticity drugs are effective, and it was hoped that cannabis could replace or act synergistically with existing pharmaceuticals. This synergistic effect would be particularly exciting, since if cannabis was successful, it could work on both pain and spasticity.

CB₁ receptors, like opioid receptors, are membrane-bound receptors present at synaptic clefts. Initial proof of their importance of pain modulation was their high concentration in the PAG area, the dorsal horn of the spinal cord, dorsal root ganglia, rostroventral medulla and nucleus trigeminal caudalis (Fox et al., 2001; Joy et al., 1999; Napchan, Buse, & Loder, 2011; Rice, 2001). CB₂ receptors are still largely unknown, but are found in many peripheral tissues and are thought to play a large role in inflammation and immunity, including contributing to T-cell proliferation, proinflammatory cytokine secretion, humoral responses for B cells, and are the subject of research as anti-inflammatory agents. They can be found in lymphoid cells, the spleen, tonsils, bone marrow, the thymus and the pancreas (Croxford, 2003; Desroches & Beaulieu, 2010; Fox et al., 2001; Joy et al., 1999). There has also been recent research indicating there is likely at least one additional cannabinoid receptor type, although this has not yet been isolated (Karst & Wippermann, 2009).

The discovery of cannabinoid receptors lead to the conclusion that there must also be endogenous cannabinoids (endocannabinoids) that bind to them. Additional research revealed a handful of endocannabinoids and the ones known to date include anandamide (AEA), 2-arachidonyl-glycerol (2-AG), 2-arachidonyl-glyceryl ether, and N-arachidonyl-dopamine (NADA; Elkkottil, Gupta, & Gupta, 2009; Joy et al., 1999). See Figures 1 and 2. The exact role
that endocannabinoids play in the human body is still unknown and an area of active research (Joy et al., 1999).

Phytocannabinoids are a group of cannabinoids found in the cannabis plant. To date, there have been 66 cannabinoids isolated from cannabis. The four that have garnered the most attention are Δ⁹-tetrahydrocannabinol (Δ⁹-THC), Δ⁸-tetrahydrocannabinol (Δ⁸-THC), cannabidiol (CBD), cannabinol (CBN; Figures 1 & 2; Carter & Rosen, 2001; Desroches & Beaulieu, 2010; Grotenhermen, 2003; Joy et al., 1999). Each cannabinoid has a unique affinity for each receptor, so the therapeutic potential depends on the targeted receptor type. Δ⁹-THC has a higher affinity for CB₁ and has drawn a great deal of attention as an analgesic agent. So far, only one of the cannabinoids has shown potential affinity for CB₂ (see below), but it is likely there are cannabinoids with high affinity to CB₂ that have not yet been discovered.

Synthetic cannabinoids are deliberately designed to be used therapeutically and have historically been ligands of CB₁. Dronabinol (Marinol; Figure 2) and nabilone (Cesamet; Figure 2) are both synthetic cannabinoids and are used to treat pain related to multiple sclerosis as well as for their antiemetic, antinausea and appetite-stimulating properties. In a recent pilot study, 1',1'-dimethylheptyl-Δ⁸-tetrahydrocannabinol-11-oic-acid (CT-3; Figure 2) was found to have promise as a potent anti-inflammatory and analgesic agent (Karst & Wippermann, 2009), meaning it may have binding affinity for both CB₁ and CB₂.

Regardless of the origin of the cannabinoid (endogenous versus plant-derived), all cannabinoids are 21-carbon terpenes (Figure 2) and are volatile aromatics. They are highly lipophilic and will not dissolve in water. Δ⁹-THC has nine subspecies and the environmental pH and level of oxidation determines which chemical structure is present (Ben Amar, 2006; Croxford, 2003; Grotenhermen, 2003; Rice, 2001). Oxidation occurs primarily through the
addition of heat and with whole-plant cannabis this is most typically done through incineration of the plant material (i.e. smoking). This is important clinically because the oxidative product varies in its psychoactivity depending on the route of administration.

**Historical Types of Pain Treatment**

As long as humans have inhabited the earth, they have experienced pain, and utilized remedies to treat their pain. Some have been crude and rudimentary, such as trepanation (the practice of making burr holes to relieve headaches and evil spirits) dating as far back as the Bronze Age (Lorkiewicz, Stolarczyk, Śmiszkiewicz-Skwarska, & Żądzińska, 2005), to the current age of implanted pumps and epidural opioid infusions. There is also an array of pharmacological and physiological interventions that help patients combat both acute and chronic pain. These include: non-steroidal anti-inflammatories (NSAIDS), opioids, antispasmodics/ muscle relaxants, benzodiazepines, antidepressants, anticonvulsants, cannabinoids, transcutaneous nerve stimulation (TENS), physiotherapy, massage, biofeedback/relaxation, psychological treatment and acupuncture/ acupressure.

Opioid medications are the current staple of pain relief, and hydrocodone is now the number one most prescribed medication in the United States (Manchikanti & Singh, 2008). Opioids have not always been the mainstay of therapy however. It is believed that both opium poppies (Papaver somniferum) and cannabis (Cannabis sativa) have been cultivated since at least the third millennium BCE (Brownstein, 1993; Cohen, 2009a; Joy et al., 1999). Cannabis was used as an analgesic in ancient China as far back as 3000 BCE, India in 1000 BCE, and there are recorded historical documents and archeological findings associating its use in Egypt, Assyria, Ancient Israel/Palestine, the Greek and Roman Empires, the Islamic worlds, the United Kingdom, most of Europe and the United States (Bogdanoski, 2010; Cohen, 2009a; Elikkottil et
al., 2009; Russo, 2002). In fact, the U.S. added cannabis to its pharmacopeia as an over-the-counter medication in 1851 where it was listed into the 20th century (Elikkottil et al., 2009). Both opioid and cannabis products have been utilized in forms that have been either inhaled as a smoked product or eaten. It was not until the advent of the hypodermic needle that opium finally won the battle of the two analgesic agents. Opioid derivatives are soluble in water (Noyes, 1974) whereas cannabinoid products are extremely lipophilic making them harder to extract (Carter & Ugalde, 2004; Hosking & Zajicek, 2008; Robinson, 1986). Opioids are also fast-acting and potent (Noyes, 1974) making them appealing and easy to use as an analgesic. With the high rate of opiate abuse however, and the rate of patients with refractory pain, there is a growing need to find a different type of therapeutic pain relief.

**Societal Implications**

Marijuana has long been heralded as not only a dangerous drug but as a gateway drug that leads to further drug abuse (e.g. Kershaw & Cathcart, 2009). Despite at least 5000 years of documented therapeutic and recreational use, without one single verifiable lethality (Gretenhermen, 2003; Joy et al., 1999; Walker & Huang, 2002), a great deal of misinformation and hysteria still exists around this drug, in spite of the availability of more dangerous narcotics in use every day.

Americans constitute less than 5% of the world’s population, yet consume 80% of the opiate supply, including 99% of the global hydrocodone. From 1997 to 2006, sales of hydrocodone increased by 244%. In that same time period, oxycodone use increased ~900% and methadone use increased ~1130%. Between 1999 and 2002 poisoning by opioids increased to 91.2%, second in accidental deaths only to motor vehicle accidents (Manchikanti & Singh, 2008). With this increase in usage and prescribing, has come a very cavalier attitude toward opioids.
One survey of 7-12th graders revealed that 50% believed that there is no great risk in abusing prescription medications, and 30% believed that prescription pain medications are not addictive. Perhaps reflected in these data is the fact that opioids are now the most common drug for individuals initiating drug experimentation and abuse (Hernandez & Nelson, 2010), bringing into question of whether or not marijuana truly is still America’s gateway drug.

Providers are, of course, very familiar with the obstacles inherent with prescription opioid management, and many clinics now have strict policies regarding chronic pain management, pain contracts and the number of chronic pain patients their clinics will accept at any one time, if any. There are issues of patient management to provide safe pain relief without risking dangerous side effects such as respiratory depression, ensuring the patients and/or staff are not diverting medications, and managing each patient with regard to best evidence-based practice. Current data are murky at best with regard to the efficacy of opiate therapy for pain lasting longer than six months (Trescot, Glaser, et al., 2008; Trescot, Helm, et al., 2008). It remains unclear if long-term pain is even appropriate to treat with opioids, so if alternatives could exist (such as cannabinoids), this would be a worthwhile avenue to explore.

**Chronic Pain and Cannabinoids**

Chronic pain can be one of the most difficult types of pain to manage. Patients become frustrated with ongoing morbidity, with lack of success with previous therapies and ultimately just want to feel like they did prior to the onset of pain. With opioid therapy, the development of tolerance can occur, although some recent research has shown that this may be more a function of psychological changes or progressive disease rather than an actual tolerance to the medication (Watson, Watt-Watson, & Chipman, 2004). Regardless, many patients find their chronic pain to be refractory to most conventional pharmacological therapies. With the discovery of cannabinoid
receptors and their role in pain modulation, this may open a new avenue of analgesia for these patients. The scope of this literature review is to review the information available regarding the safety and efficacy of cannabinoids in treating chronic pain, particularly the areas currently covered by active medical marijuana legislation, and to give preliminary prescriptive guidance to primary care clinicians for incorporation into practice when indicated. The specific questions are:

- Are cannabinoids effective in treating chronic pain associated with HIV/AIDS, multiple sclerosis (MS), neuropathy, or other unspecified sources of chronic pain?
- Is the form and route of administration of cannabinoid important in their efficacy and safety (e.g. dronabinol versus whole-plant cannabis)?
- If efficacy has been established, are these medications available in a form that clinicians can safely recommend to their patients?
- What are the legal implications for clinicians and patients when working with a Schedule I drug?

One exclusion from this study is the area of oncogenic pain. The area of pain related to cancer (and its other side effects) and the efficacy of cannabinoids on treating pain are specialties that have been covered adequately by other reviewers (e.g. Hall, Christie, & Currow, 2005) and are not an areas that primary care providers manage often. Oncologists and their care teams typically oversee patients undergoing active cancer treatment, and pain management associated with these patients exceeds the scope of this paper.

**Methods**

To investigate these important questions about the medical usage of marijuana, a thorough and systematic review of the literature regarding cannabinoids and chronic pain
management was conducted using the following databases: PubMed/Medline, BIOSIS, CINAHL, Google Scholar and Cochrane Library. To perform the search, the following index of terms was used in a variety of combinations: analges*, cannab*, dronab*, hash*, HIV, marijuana, marihuana, MS, multiple sclerosis, nabilone*, neurop*, pain, Sativex, tetrahydrocannabinol, THC. References were utilized with parameters of peer-reviewed sources, or provided relevant information regarding the heated political climate surrounding this issue. Additional research was done for obtaining background information on this topic (e.g. on pain pathology, opioid therapy, legal matters, etc.) that is not outlined here. Only English language publications were used. If duplicate publications from identical authors or research groups that had been submitted to multiple journals during a similar time frame were found, the most thorough version was used. Although some publications greater than 15 years were used for historical perspectives, searches were typically restricted to more recent than 1995.

**Literature Review**

**Therapeutic and Political History of Cannabis**

Cannabis has been used as an analgesic agent for over 5000 years (Cohen, 2009a; Elikkottil et al., 2009; Grinspoon & Bakalar, 1997; Russo, 2002). In addition to analgesia, it has been utilized to alleviate a variety of types of suffering including: neuralgias, headache, syphilitic pain, gastrointestinal pain, pruritic disorders, migraine, snake bite, rabies, tetanus, gastric ulcer, urinary incontinence, dental pain, herpes zoster, diarrhea, venereal diseases, malaria, insomnia, depression, mania, insanity, hydrophobia, cholera, whooping cough, asthma, anemia, nausea, vomiting, convulsions, delirium, dysuria, to lower fever, to aid in childbirth, dysmenorrhea, appetite stimulation, eczema, delirium tremens, rheumatic pain, opium
withdrawal, glaucoma, gout, and as an aphrodisiac (Cohen, 2009b; Grinspoon & Bakalar, 1997; Russo, 2002). Clearly some of these conditions may have been treated more effectively with cannabis than others, but it was not until 1937 that the condemnation of marijuana began in the United States in earnest. That was the year the Marihuana [sic] Tax Act was passed which added hefty taxes to cannabis as a deterrent to its recreational use. At the same time a campaign organized by Harry Anslinger of the Federal Bureau of Narcotics, and the driving force behind the “public service” film *Reefer Madness*, transmitted information to the public that marijuana was highly addictive, would lead to violent behavior, mental deterioration and psychosis, despite no scientific evidence to support these claims. In 1942, the *American Journal of Psychiatry* published an article stating that cannabis is less addictive than either alcohol or tobacco and among its potentially important therapeutic uses, could include depression, appetite loss and opiate addiction. Not long after, the journal was pressured by Anslinger to print a statement denouncing the previous study (Grinspoon & Bakalar, 1997). The surge in recreational use of marijuana during the 1960’s actually brought more confirmation to the potential therapeutic uses of cannabis, but in 1970 Congress passed the Controlled Substances Act, which officially assigned all psychoactive drugs to a “schedule” and a subsequent level of legal control regarding their prescription. Marijuana was assigned to Schedule I, which is defined as without a medically therapeutic use and a high likelihood for abuse and addiction (Grinspoon & Bakalar, 1997).

It has been this Schedule I status that has restricted the ability of researchers to do meaningful investigation into the medicinal future of cannabis. They are trapped in a Catch-22 situation: research grants and requests for research-approved marijuana are routinely denied since marijuana is a Schedule I drug. On the other hand, researchers cannot evaluate the potential medical benefit, which could result in a change to Schedule II status. Abrams and colleagues
applied for over five years with a variety of research proposals, applications and creative ways to request for both funding and sources of marijuana (Dutch suppliers, U.S. government grown, DEA-seized) and were denied for years before finally reaching success (Abrams, 1998; Cohen, 2009b). A re-scheduling of marijuana would make it easier for researchers to do their studies, but if this cannot happen they need consistent access to research materials.

Prior to the legalization of marijuana for medical use in a handful of states, the only means for researchers to get whole-plant cannabis was through the National Institute on Drug Abuse (NIDA). This was fraught with problems. Firstly, it had been widely established that NIDA only grew and processed very poor-quality cannabis. It often contained seeds, stems and leaves in addition to the flower buds, which is considered contaminant material. Researchers also frequently reported getting extremely old, stale product, which for a botanical that relies on its volatile aromatic chemicals for its therapeutic benefit, was quite problematic. Additionally, even if it was not old, the concentration of $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), which is the primary psychoactive component in cannabis, was very low (about 2-4%; (P. Cohen, 2009b; Walker & Huang, 2002). The cannabis NIDA was supplying to researchers in no way resembled what patients receiving medical marijuana would obtain. These patients could often access a dispensary, obtain carefully cultivated whole-plant cannabis containing only flower bud material with no other contaminant plant products, with THC content ranging between 5-20% (Bogdanoski, 2010; Russo & McPartland, 2003). There is a clear discrepancy between research-grade marijuana and what patients have access to, which makes it difficult to draw parallels between scientific results and real world scenarios.

An additional obstacle included resistance within the federal government for research focused on the potential beneficial medical use of cannabis. Following the approval for research
by the Abrams group on the effects of using medical marijuana to assist with HIV/AIDS wasting, the researchers later found out that one of the major obstacles they were facing with NIDA was that NIDA had no interest in allowing any use of its marijuana be used for research that could later prove it had medical benefit (Abrams, 1998).

A further remarkable statistic is that the U.S. government has spent more money continuing the effort to keep marijuana illegal than on research into the therapeutic value of cannabis. In 2006, the FDA issued a press release stating that it continued support the premise that there was no sound scientific proof or data (in humans or animals) that marijuana had any medical or therapeutic role, ignoring the 1999 report by the Institute of Medicine and the ever-growing amount of peer-reviewed literature to the contrary (Bogdanoski, 2010).

**Routes of Administration and Safety**

The route of administration is a critical component in the efficacy of cannabinoid therapy. In whole-plant cannabis, THC exists as $\Delta^9$-THC. When smoked and inhaled, it directly enters the blood stream via the lungs and is ultimately metabolized into 11-nor-9-carboxy-$\Delta^9$-tetrahydrocannabinol or THC-COOH (Grotenhernlen, 2003; McPartland & Pruitt, 1999; Robinson, 1986). It is in this form that it is most effective as an analgesic and anti-inflammatory agent and has fewer psychotropic effects (Grotenhermen, 2003). Cannabinoids administered sublingually are also quickly available as this administration route avoids the first pass effect in the liver (Rog, Nurmikko, Friede, & Young, 2005). When smoked or administered sublingually, the onset of action is typically within 5-15 minutes (e.g. Robbins, Tarshish, Solomon, & Grosberg, 2009; Russo, Guy, & Robson, 2007).

Unfortunately, the burning of marijuana creates 200 additional compounds in the smoke, many of which are found in tobacco smoke and are known carcinogens (mutagenic polycyclic
hydrocarbons), and chemicals such as ammonia, benzene, carbon monoxide, hydrogen cyanide and toluene are present (McPartland & Pruitt, 1999; Walsh, Nelson, & Mahmoud, 2003). There are conflicting studies regarding the actual teratogenicity of marijuana smoke (Melamede, 2005; Tashkin, 2005; Walsh et al., 2003), but since smoking of any substance is something most healthcare providers denounce, there has been resistance to this form as a medication.

Vaporization is another form of administering the chemicals in whole plant cannabis. Since cannabinoids are volatile aromatics, the vegetative plant materials do not need to be combusted in order to volatize the targeted chemicals. Cannabinoids are volatized at temperatures between 180-200°C whereas the plant material combusts at 230°C, so the actual burning of plant material is not required. Additionally, when cannabis is administered in this way, there are no measurable amounts of carbon monoxide, benzene, toluene or naphthalene, which are all present in the smoked form (Abrams, Vizoso, et al., 2007). Vaporizing has also been shown to significantly decrease the amount of tar the patient is exposed to, whereas all forms of smoked administration (cigarette, water pipe, etc.) have high tar levels (Hazekamp, Ruhaak, Zuurman, van Gerven, & Verpoorte, 2006). In the studies that have been done to date, vaporization has been shown to be the fastest and most consistent and effective administration technique (regarding subsequent serum THC levels) for whole plant cannabis, when compared to all other forms of smoking. All of the studies also found patients who tried both delivery systems (smoking and vaporization), far preferred vaporization due to ease of use. Reasons for this included avoidance of smoke and perceived health risks, and many felt the consistency and titration of psychoactive of effects were easiest with vaporization (Abrams, Vizoso, et al., 2007; Hazekamp et al., 2006; Zuurman et al., 2008). The primary drawback to vaporization is the cost of the equipment. For example, the Volcano® vaporizer was used in all of the previous studies,
and costs approximately $550 (The Vapor Experts, 2011), compared to the nominal cost of cigarette rolling papers.

In contrast to smoking, vaporization or sublingual, cannabinoids that are administered via the oral route must be digested in the gut and undergo an extensive first-pass effect with a remaining 10-20% bioavailability. When ingested in an oral form, Δ⁹-THC in converted into 11-hydroxy-Δ⁹-tetrahydrocannabinol or 11-OH-THC. Figure 3. (Grotenhermen, 2003; McPartland & Pruitt, 1999; Robinson, 1986). This mechanism occurs through the inactivation of cytochrome P-450 in the liver (i.e. the grapefruit effect), specifically the 2C and 3A enzymatic subfamilies, which would have important implications for medications metabolized in the liver (McPartland & Pruitt, 1999). It is 11-OH-THC that is very psychoactive and weakly analgesic, and the etiology for the high side effect profile of oral cannabinoids. After Δ⁹-THC is metabolized into 11-OH-THC in the liver, it is then metabolized into THC-COOH. This metabolic process causes the long onset of action in oral cannabinoids; patients report an average onset of 1-2 hours with some as late as 4-6 hours. Another drawback is the variability in absorption. How the body metabolizes and absorbs oral medications can change on a daily basis; patients often report that on some days a given dronabinol dose may be ineffective in treating their symptoms, and the following day may be quite overpowering (Grotenhermen, 2003; McPartland & Pruitt, 1999). Oral forms of cannabinoids are also associated with a high side effect profile and are often reported as poorly tolerated due to this. Common side effects include somnolence, fatigue, irritability, anxiety, inability to concentrate, dysphoria and a sensation of the medication being too psychoactive (Attal et al., 2004; Russo, 2002; Russo & McPartland, 2003; Zajicek et al., 2003). One clear benefit of the oral medications (e.g. dronabinol, nabilone) is that they are readily available by prescription at most retail pharmacies.
Other routes of administration have been explored, such as inhaled aerosolized THC, intravenous and intramuscular. During clinical trials, aerosolized THC was too irritating on patients' airways, and the studies were terminated (McPartland & Pruitt, 1999). Intravenous THC administration has had largely ineffective results, but has also primarily been administered for immediate postoperative pain. The conclusions at this point are that cannabinoids are most effective for chronic analgesia rather than acute pain (Ben Amar, 2006). The exception to this was a study administering a synthetic cannabinoid intramuscularly, which improved postoperative pain control for up to six hours at a time (Ben Amar, 2006). There has also been a suggestion that intrathecal administration could be helpful for analgesia while bypassing systemic side effects (Hirst, Lambert, & Notcutt, 1998).

An additional benefit of cannabinoid compounds is the exceptionally low lethality. In the 5000 years of use of cannabis and its derivatives, there has not been one single documented lethal overdose (Grotenhermen, 2003; Joy et al., 1999; Walker & Huang, 2002). In fact, in clinical trials with dronabinol, lethal doses (LD50) were nearly impossible to establish, and would likely exceed the gastric capacity of the human stomach. In dogs they did not achieve an LD50 at as high a dose as 3000 mg/kg, in monkeys 9000 mg/kg was not lethal, and in humans it also has not been established (Grotenhermen, 2003). If assuming the dose used for monkeys could potentially be a lethal dose in humans, for a 75 kg human, this would entail consuming 67,500 10 mg dronabinol capsules; presumably the volume of capsules would be lethal well before the pharmacological dose. The explanation for the low lethality of cannabinoids is the very low concentration of cannabinoid receptors in the brain stem (Carter & Rosen, 2001; Carter & Ugalde, 2004). Unlike with opioids, there is no respiratory depression from high dose cannabinoid administration, so although there may be quite unpleasant side effects at high
Cannabinoid Use in Multiple Sclerosis

Multiple sclerosis (MS) is a degenerative, inflammatory, autoimmune disease affecting the central nervous system (CNS). The cause of MS is unknown and there is no cure, although there are some treatments available that slow the progression of the disease. In MS, the myelin sheaths of CNS neurons are attacked and stripped by the person's own T cells, with the additional formation of demyelinating lesions (sclerotic areas). This combination causes a slowing of nerve conduction and ultimately a complete block of nerve impulses in late-stage disease. There are four different types of MS: relapsing-remitting, primary-progressive, secondary-progressive, and progressive-relapsing. Relapsing-remitting MS the most common form of MS and is characterized by distinct relapses or exacerbations with periods of either complete recovery, or partial recovery with residual, permanent disability. Between attacks there is no advancement of disease. Primary-progressive MS is relatively uncommon and is typified by a steady progression of the disease process with infrequent periods of remission. Secondary-progressive starts similarly to relapsing-remitting, but over time there is a steady worsening in symptoms between attacks. In progressive-relapsing MS, there is a clear progression of disease from the onset, with overlying exacerbations as well. This is the most rare form of MS. In all forms of MS, as the disease advances, the progressive symptoms become quite troublesome and the sequelae are ultimately life-threatening. They are different for each patient and can include, but are not limited to: fatigue, weakness, ataxia, tremor, vertigo, spasticity, bladder dysfunction, pain, sensory sensations/dysfunction, heat intolerance, depression and cognitive issues (DiPiro et al., 2008; McCance & Huether, 2005). Up to 90% of MS patients will experience pain and spasticity and/or stiffness related to demyelination (Zajicek et al., 2003). This causes a
significant source of morbidity for these patients and requires a great deal of clinical intervention.

Pharmaceuticals are available to patients to help with pain and spasticity. Unfortunately, there are very few options that work well, are non-sedating, and have few side effects. These same medications may also not be adequate when addressing neuropathic pain, refractory pain or for patients that have drug allergies. Cannabinoid therapy has been particularly promising for MS pain and spasticity. Anecdotally, many MS patients have reported that for years they have found relief in their symptoms with cannabis (Zajicek et al., 2003), but were forced to obtain marijuana through illegal means. Upon the discovery of cannabinoid receptors, more emphasis was placed on the importance of both endocannabinoids and phytocannabinoids and their role in pain modulation, which would be important to those with MS, particularly with an emphasis on those regulating the GABA pathway.

In a large (n = 611), randomized, placebo-controlled trial, Zajicek and colleagues (2003) tested MS patients with either dronabinol, an oral pill containing 2.5 mg $\Delta^9$-THC:1.25 mg CBD, or placebo to see if cannabinoid products would objectively and subjectively improve spasticity. Doses of treatment medications were increased for the first five weeks of the study, and titrated to a maximum possible dose per body weight ($\leq$ 25 mg $\Delta^9$-THC total per day in divided doses), and adjusted for tolerance of side effects and therapeutic effect. The dose was then set at a plateau dose for an additional eight weeks before tapering off during week fourteen. Objective spasticity was measured with the Modified Ashworth Scale (Figure 4), a variety of secondary outcome measures, and subjective spasticity questionnaires. The researchers found that although treatment with a variety of combinations of cannabinoid therapies (dronabinol or THC:CBD) did not reduce objective measurements of spasticity, it did significantly improve patients’ perception of spasticity and mobility. An unexpected finding of the study was that across all treatment
groups, there was a decrease in hospital admissions for MS exacerbations during the treatment course, and the authors felt this could indicate a possible immune component to the therapy. Since MS is an autoimmune disease, an improvement of could be an indication of slowing disease advancement and a reduction in exacerbations. This was an area the researchers urged should be a focus of future studies. One limitation to the study, and possibility for a lack of therapeutic response in the patients, was a dose-limiting side effect profile of the medication. For the patients receiving dronabinol, as mentioned previously, it is often a poorly-tolerated medication due to side effects, and this proved to be the case in this study as well. Although no subjects dropped out of the study due to side effects, many were not able to maximize their therapeutic dose, which may have contributed to their negative findings. Fewer that 5% from each treatment group dropped out due to side effects, but it was unclear how suboptimal the dosing ended up being for the group of patients experiencing side effects. The most common side effect was dizziness and this was reported by about 50-60% of patients in both treatment groups. The authors are also analyzing serum samples from their subjects to determine if cannabinoid serum concentration is proportional to the clinical therapeutic effect, which could also help optimize the dosing regimen for dronabinol (Zajicek et al., 2003).

Central pain is pain originating from the CNS, rather than pain from spasticity or other sources, and affects over a third of MS sufferers (Svendsen, Jensen, & Bach, 2004). Svendsen et al. (2004) utilized dronabinol to ameliorate central pain in patients with MS. For this study patients may have also had spasticity, but would necessarily have been able to distinguish their central pain from their spasticity. This was a placebo-controlled crossover study (n = 24) with two treatment periods of 21 days and a washout period of 21 days in between. During the treatment portion, patients were given dronabinol and tapered onto a therapeutic dose, with a
daily maximum of 10 mg bid. A variety of tactile stimulation techniques (pain and cold sensation) were used to assess analgesic response. Dronabinol successfully reduced central pain by about 20% in patients, and some patients reported more than 30% pain reduction. Again, side effect rates were high with dronabinol treatment (nearly 60% reporting dizziness), but no patients withdrew from the study because of side effects, and by the final week of the study there was no significant difference in side effect profile between dronabinol and placebo (Svendsen et al., 2004).

The high side effect profile of both dronabinol and nabilone has lead to the development of a new medication, Sativex. Sativex is a proprietary blend of $\Delta^9$-THC and CBD but is approximately a 1:1 ratio, is an oromucosal spray and bypasses hepatic metabolism, and is designed in order to decrease the side effects from the medication and increase absorption. Sativex is approved for use in MS in the United Kingdom, Canada, New Zealand and Spain (GW Pharmaceuticals, 2011). In a six-week randomized controlled trial of Sativex, there was a significant improvement in spasticity and lower extremity muscle strength between treatment ($n = 124$) and placebo ($n = 65$). Strength was measured with the Ashford Scale and strength with the Motricity Index (Figure 4), and patient satisfaction and perception was measured subjectively. The only bothersome side effect was intoxication, and was typically with doses greater than 25 mg THC per day. There was a statistical improvement in both spasticity and muscle strength, meaning decrease in spasticity did not come with the cost of sacrificing strength. About 40% of test subjects had a $>30\%$ improvement in overall symptoms (Collin, Davies, Mutiboko, & Ratcliffe, 2007).

**Cannabinoids for Treating Pain Associated with HIV/AIDS**

Pain associated with HIV/AIDS has two different etiologies. It is believed that the HIV
virus may directly infect nerve cells. There are clear peripheral and central nervous system symptoms that are thought to be a result of this, and neuropathy is one symptom that can cause a great deal of pain for HIV-infected persons. The most common type of neuropathy is sensory neuropathy and it is often unresponsive to common pain treatment (Ellis et al., 2009; McCance & Huether, 2005). Highly active antiretroviral therapy (HAART) can also lead to neuropathy, and this is thought to be the result of mitochondrial toxicity caused by these medications. Some patients respond to the use of tricyclic antidepressants to treat HAART-neuropathy, but side effects and efficacy are often limiting factors (Carr & Cooper, 2000). The side effects of the disease process of HIV as well as the medication therapy associated with it are challenging to manage but it is important to do so effectively, particularly since the life span of these patients is now far greater than in years past.

In the United States, there are cannabinoid products available to patients with HIV/AIDS for the treatment anorexia, nausea/vomiting, AIDS-“wasting” and pain. Dronabinol is approved by the FDA for the nausea, vomiting and cachexia caused by HIV and/or antiretroviral therapies (ART). Utilization of dronabinol with other medications for pain associated with HIV is an area of interest, particularly since 30-88% of HIV patients experience some type of pain related to their disease (Ellis et al., 2009; Richardson et al., 2009). Unfortunately, as discussed for previous studies, side effects associated with dronabinol are an issue, and many HIV patients do not tolerate the maximal daily dose needed to achieve the benefits of the medication (Cohen, 2009b). The route of administration can also be an issue, since an oral medication can be impracticable if the patient is too nauseated to tolerate pills. This has lead to the investigation of alternative forms and routes of cannabinoids to treat HIV sensorineural pain.

Several studies have investigated smoked, whole-plant cannabis to alleviate sensorineural
pain associated with HIV. A randomized, placebo-controlled study \((n = 55)\) by Abrams and colleagues (2007) found that 30% to 50% of patients who smoked three cannabis cigarettes per day experienced significant reduction in sensorineural pain (as measured subjectively and by using thermal and capsaicin sensitization models) compared to patients who smoked THC-devoid placebo cigarettes. They also felt this was crucial since ART have many profound drug-drug interactions, particularly with medications that are commonly used to treat sensorineural pain (Abrams, Jay, et al., 2007). To find an alternative that could be effective in improving quality of life without causing drug interactions was an exciting development.

Ellis et al. (2009) also had a similarly-designed crossover study \((n = 28)\), although the patients were adding the marijuana cigarettes to their normal opiate regimen. The \(\Delta^9\)-THC content of the treatment cigarettes was between 1-8% and was tapered to the highest tolerable dose, to maximize pain treatment. Patients smoked cigarettes four times a day for five days. During the treatment portion, patients experienced significantly reduced HIV-related sensorineuropathic pain, mood disturbance, physical disability and while quality of life improved. There was no interaction (either positive or negative) between opioids and cannabis.

Despite difficulties with dronabinol and adverse side effects, there was one placebo-controlled study \((n = 7)\) that did show some promise with dronabinol and ART (considering they are both metabolized in the liver). Bedi et al. (2010) found that in HIV patients that were already self-medicating with marijuana, the addition of dronabinol (10 mg four times per day) initially improved appetite, mood and sleep quality, although it did not have any effect on pain. These patients did not experience any of the adverse side effects of dronabinol that have been previously reported, such as sedation, cognition effects, anxiety, and fatigue (e.g. Attal et al., 2004). By the second week of therapy however, none of the beneficial effects of the dronabinol
were apparent. It was thought that this might be due to the pre-existing exposure to cannabinoids, the fact that the patients had been required to stop using marijuana for the study, and either withdrawal symptoms or possible underlying tolerance, caused a decreased response. The authors suggested that an additional titration of dronabinol dosage would be required, although it would be necessary to exceed FDA-recommended daily maximums (Bedi et al., 2010).

**Chronic Pain, Neuropathy and the Use of Cannabinoids**

Since pain creates such a burden on the healthcare system, and is the most common reason patients seek medical attention (Joy et al., 1999), it is important to explore as many avenues of pain control as possible. Urine toxicology screens of chronic pain patients consistently find that marijuana is the number one illicit drug in their systems, and the patients often cite pain control as the reason they are using this substance (Heutink, Post, Wollaars, & van Asbeck, 2011; Narang et al., 2008; Ware, Doyle, Woods, Lynch, & Clark, 2003). Cannabinoids are now being investigated as a therapeutically important component in chronic pain management, particularly neuropathic pain.

Narang et al. (2008) designed a randomized, placebo-controlled study (n = 24) with chronic pain patients who were on stable doses of opiate therapy. These patients remained on their current regimens but the treatment groups added dronabinol therapy. The treatment group was able to dose themselves on a variety of dosing levels based on degree of pain relief and side effects, and the dosing range was between 5 mg once daily to 20 mg three times per day. The treatment groups experienced a greater degree of pain control and were very satisfied with the therapy. This shows potential for cannabinoids as adjuvant therapy in opioid pain control. Another promising element to this study was the side effect profile for dronabinol. Although side effects were reported, they were relatively mild, well-tolerated (since patients could modify their...
dosages), decreased over time, and the patients were pleased enough with the treatment effects that the side effects did not interfere with the overall treatment outcomes.

In a pilot study (n = 8) with contradictory results, Attal et al. (2004) did not find dronabinol effective in treating neuropathic pain. Only two patients were able to tolerate the maximum daily dose of 25 mg three times a day, and the rest found the side effects to be too severe to continue with therapy. Because of this, therapeutic and statistical effects of dronabinol were not reached. There were no patients at the end of this study who wished to continue dronabinol for adjuvant therapy.

Whole plant cannabis has had some promising results in preliminary studies for neuropathic pain. A randomized, controlled study (n = 21) looking at smoking cannabis with a variety of THC concentrations (2.5%, 6.0%, 9.4%) three times a day, found that cannabis containing 9.4% THC significantly reduced refractory neuropathic pain; cigarettes with lower concentrations and placebo were not effective. This reduction was comparable to that found with gabapentin and pregabalin. Euphoria was only documented in three instances, and was still at a level far lower than that reported by recreational users. In those three patients, serum THC concentration was <45 ng/mL, and in recreational users it is typically >100 ng/mL, again indicating the amount needed for a therapeutic response is far less than what is regularly used recreationally (Ware et al., 2010).

A handful of pilot or case studies have yielded mixed results. (Rintala, Fiess, Tan, Holmes, & Bruel, 2010) did not find significant results with their preliminary crossover study on neuropathic pain control using dronabinol (20 mg daily), but they cited poor experimental design and size (n = 7 due to drop-out rates), and felt they may have had significant results in a better-controlled environment (a longer washout period between treatments and larger sample size).
The patients in the placebo-controlled pilot study (n = 24) by (Wade, Robson, House, Makela, & Aram, 2003) were able to titrate their sublingual cannabinoid therapy to alleviate their intractable neuropathic symptoms (pain, spasticity, spasm), avoid adverse effects and were typically far below the maximum allowable dose. Three different cannabinoid combinations were used ($\Delta^9$-THC, CBD or 1:1 THC:CBD) in addition to the placebo. Patients could titrate within a range of 2.5-120 mg per day. Each treatment group had significant decreases in pain and/or spasticity compared to control.

In a group of 34 “n of 1” pilot studies, chronic pain patients with a variety of different types of refractory pain were chosen to undergo trials with sublingual cannabinoid therapy (Notcutt et al., 2004). Patients received either sublingual $\Delta^9$-THC, CBD or 1:1 THC:CBD and could dose themselves as needed throughout the day, although the maximum daily dosing was unclear. Patients receiving 1:1 THC:CBD treatments experienced the best symptom control and there were few adverse side effects. In fact, the side effects noted by several patients were beneficial since years of very poorly controlled pain had taken a heavy psychiatric toll, and they reported appreciating the heightened sense of well-being, relaxation and improved sleep from cannabinoid therapy. An additional benefit to the sublingual therapy was the route of administration; patients reported a high level of satisfaction with the discrete nature of administering the medication in public and the easy, familiar mode of delivery (Notcutt et al., 2004). Clearly conclusions attained from this study must be taken cautiously due to the lack of replication, but it does elucidate some interesting areas of future research using cannabinoids to manage refractory chronic pain.

**Medical Use of Cannabinoids and Legal Implications**

There are many areas of concern for providers and consumers surrounding the issue of
medical marijuana and other cannabinoid products. Providers have been justified in their concerns that their DEA licensure, livelihood and personal freedom could all be threatened when writing recommendations for medical marijuana. California was the first state to adopt medical marijuana laws in 1996 (Abrams, 1998). It was soon after that the federal officials began to send a stern message that they planned to prosecute and strip prescriptive licenses from doctors (the only authorized prescribers at the time) who provided even the most seriously ill patients with authority to get medical marijuana (Golden, 1996). For many years this environment persisted and prescribers were wary of authorizing medical marijuana, but slowly as evidence began to emerge, more vocal opposition to current laws and policies became apparent as well. Administrative Law Judge Francis L. Young, publically stated,

The evidence clearly shows that marijuana is capable of relieving the distress of great numbers of very ill people, and doing so with safety under medical supervision... it would be unreasonable, arbitrary and capricious for the DEA to continue to stand between those sufferers and the benefits of this substance.

(Carter & Ugalde, 2004, p. 9)

In 2009, the American College of Physicians released a lengthy position statement on medical marijuana and cannabinoids, and in it included thoughtful recommendations about the future of cannabis in healthcare. Of highest emphasis was the need to do more research in order to guide evidence-based practice for optimum patient care. See Figure 5. (American College of Physicians, 2008).

It has not always been as straightforward for healthcare providers to advocate for a role in the scientific debate surrounding cannabis however, and even the First Amendment protection of providers has been threatened. A Ninth Circuit Court case in the year 2000 received significant
attention regarding the protection the provider-patient relationship. In what was known as the Conant v. Walters case, the Ninth Circuit Court upheld providers’ First Amendment rights to discuss and recommend medical marijuana to their patients. Immediately after California passed the “Compassionate Use Act” in 1996, the White House Office of National Drug Control Policy was working to censure providers by revoking their DEA licensure if they provided patients with a means to obtain medical marijuana (i.e. a recommendation/prescription). In 1997, a group of physicians and other medical organizations filed and were awarded an injunction against the federal government in order to protect their First Amendment rights. The federal government appealed and the case went to the Ninth Circuit Court. This court upheld the lower court’s findings and in fact in their closing language, was quite critical of the federal government’s implication that providers would in some way contribute to illicit drug use. Further, the court was very clear that the DEA registration should never be at risk when providers are acting within the parameters of their state’s laws, and the actions of a patient (i.e. whether a patient uses illegal means to obtain marijuana), should not involve any consequence to the prescriber (Christenson, 2004).

In 2008, then presidential-candidate Barack Obama included in his campaign promises a more supportive environment for states with medical marijuana laws, and relatively early in his presidency he proposed a plan to have the DEA refrain from prosecuting dispensaries, patients, caregivers and providers who were acting within the laws outlined in their states (Johnson, 2009). States have also taken the opportunity to explicitly write in their legislation, protection for these same individuals from prosecution. For example, in 2011, Washington State passed an amended Senate Bill that the state’s health care professionals may not be arrested, prosecuted or subject to any other criminal sanctions or civil consequences for the proper authorization of the medical use
of cannabis by qualifying patients (as outlined in the bill) for whom the health care professional determined the use of cannabis would be beneficial (Senate Bill 5073, 2011). These bills and practices vary by state however, so care should be used when generalizing across all 13 states who have passed this legislation.

The semantics and logistics of the laws are not the only concern for patients and clinicians. There is often concern about the source of whole-plant cannabis and its extracts. There are now increased avenues patients can access to safely acquire cannabis, without having to use black market sources. In all 13 states in which medical marijuana is legal, there are provisions for either growing one’s own plants and/or having a proxy or “cooperative” growing situation if a patient’s situation is not amenable to cultivation (e.g. NORML, 2004). Many states have dispensaries that operate somewhat like a pharmacy, and provide a variety of different whole plant products, foods, tinctures, among other forms (e.g. The Green Cross, 2011). There are knowledgeable staff members that help the patient determine which products are most appropriate for them depending on which symptoms they are trying to treat and their previous experience with cannabis. Patients are only allowed entrance during normal business hours, with photographic identification and the prescriber’s recommendation letter or prescription, which is then verified at the time of entry by a telephone call to the provider. Often the dispensary will require an appointment to accommodate these requirements (SMMA, 2011). There are even not-for-profit dispensaries such as the Green Cross, and in some cases they will deliver medical marijuana or its constituent products to homebound patients (Carter & Rosen, 2001; The Green Cross, 2011). There are now also “farmer’s markets” that are gaining popularity and have proven to be an effective way for local cannabis providers to sell their products, and a safe and open environment for patients to support local businesses (e.g. Young, 2011).
Discussion

Most of human history and our relationship with pain has been spent treating symptoms with anecdotal or folk therapies. Cannabis has a central role in that, since it has been used medicinally for over 5000 years. Only within the last century or less has an emphasis been placed on evidence-based practice, and research is proving a scientific basis for many of the modalities that have existed for millennia.

The existence of cannabinoid receptors in the medulla, thalamus, and the periaqueductal grey area along with multiple endocannabinoid ligands indicates a role for cannabinoids in analgesia. Over the last decade, scientific research has confirmed the role of both endogenous and exogenous cannabinoids in modulating pain. The struggle is now how clinicians will assume their role in advocating for patients who battle life-long morbidity associated with chronic pain when faced with managing effective medications still bearing Schedule I status, and whether this struggle continues to be worthwhile when FDA-approved alternatives exist.

The results of this literature review clearly indicate that randomized controlled trials comparing orally digested cannabinoids and whole-plant cannabis (or other forms that bypass oral digestion) are essential when making clinical recommendations for the role of cannabinoid analgesia for treating all types of pain. Unfortunately, blinding of test subjects would be impossible, but a large-scale study could help reduce some study bias. Since some studies do indicate that oral forms cannot be completely discounted as a valuable therapeutic due to adverse side effects (Bedi et al., 2010), it is important to continue research regarding the role for this route of administration. No one type of medication or route of administration is right for all patients, and oral cannabinoids can be helpful for treating many different maladies, including chronic pain.
Preliminary studies indicate that cannabinoids may be quite effective in treating many of the debilitating symptoms associated with multiple sclerosis including central pain, spasticity, and muscle spasm, and may also help slow the autoimmune progression of the disease, although this is speculative at this point. Cannabinoids have been recognized for the symptom management role for MS, and have been given approval for this in many countries including the United States. The studies that used cannabinoids avoiding first-pass effect were able to optimize the therapeutic effects of the medications (Collin et al., 2007), so additional research into oromucosal and whole-plant cannabis for MS symptom control will be important.

The use of medical marijuana for controlling symptoms associated with HIV/AIDS was one of the first reasons it was legalized in the State of California in 1996 (Abrams, 1998). There is a debilitating set of symptoms associated with HIV/AIDS as well as with the ART used to treat the disease. Initially, control of AIDS cachexia, anorexia, nausea and vomiting were the targeted symptoms of interest with medical marijuana, but then it became clear that the painful neuropathy symptoms caused by ART were also effectively managed by the addition of cannabis. Protease inhibitors have an exhaustive list of medication interactions in addition to potent cytochrome P-450 effects. Finding effective medications that avoid this metabolic pathway in the liver is of critical importance for these patients. Although there has been some modest positive benefit with oral cannabinoids (e.g. Bedi et al., 2010), typically the side effects limit therapeutic response, and non-oral forms have yielded the best results (e.g. Ellis et al., 2009). Whether it is a combusted/inhaled or oromucosal form it is clear that with HIV/AIDS patients routes that bypass the liver are essential when administering cannabinoids, and additional research into which is most beneficial would be helpful for clinicians and patients alike.

Results for managing chronic neuropathic and non-neuropathic pain with cannabinoids
are mixed. Several studies have used dronabinol with conflicting data. The side effect profile in one study limited the dose patients were able to tolerate (Attal et al., 2004), whereas a contrasting study clearly showed benefit from the addition of dronabinol to stable opiate therapy (Narang et al., 2008). Like many of the previously mentioned studies, patients who received cannabinoids in either inhaled or oromucosal routes seemed to experience the most significant benefit with the lowest adverse side effects (Notcutt et al., 2004; Wade et al., 2003; Ware et al., 2010). Avoiding the highly psychotropic metabolite 11-OH-THC seems to be key in optimizing cannabinoid therapy for both pain control and minimizing side effects.

The route of administration is the basis for a growing area of attention in healthcare in the United States. Oral cannabinoids, as illustrated above, have high variability in absorption and tolerability due to adverse side effects, but there are no other routes of administration available to providers that are also FDA approved. Inhaled cannabis offers many therapeutic benefits to patients but puts providers in a potentially uncomfortable position. Anything that is smoked and subsequently inhaled is an irritant to the airway and a potential carcinogen. While there are no conclusive data regarding the teratogenicity profile of smoked cannabis, the presumed ill effects are clear. Healthcare providers simply cannot recommend ingesting any medication in this way, without a very clear cost-benefit analysis. Vaporization is a good option to avoid smoking but the price of equipment could be prohibitive for many patients.

An additional constraint with all medications can be cost. A month’s supply of dronabinol at even the lowest dose is about $260, and to dose at a more therapeutic level is closer to $2000 (Epocrates, 2011). Sativex is much more cost-effective, and an approximate month supply would be around $370 (Multiple Sclerosis Society of Canada, 2005). Sativex is not yet available in the United States, but is in Stage III clinical trials. If and when it is approved, it
would be released as a trade name medication and the cost to the consumer is unknown. Whether or not it is covered by insurance, and to what degree the cost will be covered, will remain to be seen. Whole plant cannabis is equivalent in price to dronabinol, but since whole-plant cannabis is a botanical and not FDA approved, it is not covered by insurance plans. In one case series, ranges of daily cannabis consumption were between 1-5 grams per day (Lynch, Young, & Clark, 2006). If using the highest amount noted, the patient would consume 150 grams, or about five ounces, of cannabis per month. Price varies considerably by region but in Washington State at the time of this publication, high-quality marijuana costs roughly $280 per ounce (Price of Weed, 2010), meaning a month supply would be about $1400. Fulfilling the legal maximum of 24 ounces for a 90-day supply in Washington State (Senate Bill 5073, 2011) would cost a patient approximately $2240 per month. This could certainly be a cost-prohibitive amount of money for many patients. The ability to grow one’s own cannabis could help alleviate the cost burden to the patient, but also creates a delay of treatment medication availability.

Concerns regarding legal issues with marijuana as a Schedule I drug are a frequent reason cited for avoiding using this as a medication, both from patients and providers. California was the first state to legalize marijuana for medical use, and as of 2009 had over 350,000 registered patients (MacDonald, 2009). Interestingly, in every state that has enacted medical marijuana legislation, there has been no rise in abuse rates or non-medical use (Aggarwal, Carter, & Steinborn, 2005; Carter & Ugalde, 2004). This indicates that patients are using their medication responsibly, and dispensaries and cannabis providers are also adhering to state guidelines for distributing cannabis. Many healthcare providers have also voiced concerns regarding their own liability in recommending a drug that is so strongly regulated by the DEA. Most states have incorporated into their legislation, explicit wording protecting healthcare providers and patients
and the First Amendment protects the provider-patient relationship when the provider recommends medical cannabis. When the controversy first began and providers were initially targeted, California Attorney General Bill Lockyer stated, "The federal government cannot force state officials to enforce federal laws," and this does appear to be an accurate statement. So far not a single provider has been prosecuted and/or lost his/her license for recommending or prescribing medical marijuana" (Aggarwal et al., 2005, p. 327).

Cannabinoid products are also minimally addictive when compared to many other compounds. National studies indicate that of regular recreational users of marijuana, only about 10% become addicted. This is compared to 15% of regular consumers of alcohol, 32% of those using nicotine and 23% using opioids (Cohen, 2009a). The reason that cannabis is thought to have low addiction potential is that although it does cause modest increases in dopamine, it is not enough to illicit a dopamine response in the “reward center” of the brain (McPartland & Pruitt, 1999). Although being highly addictive is a reason the FDA continues to leave marijuana as a Schedule I drug, scientific evidence continues to mount indicating this is unlikely to be accurate.

**Conclusion**

The current compendium of literature indicates that cannabinoids have an important and legitimate role in managing chronic noncancer pain. Healthcare providers have an obligation to familiarize themselves with the variety of available forms of cannabinoids and which of those may be most appropriate for their patients’ symptom management. With patients on high levels of opiates, attempts may be made to reduce opiate levels by adding adjuvant cannabis. Even if this is not something clinicians are comfortable with, decreasing the amount of opiates patients are on and that the general public has access to, is a public health concern. Part of ethical and responsible prescribing involves finding alternatives to opiates that are effective, safer and less
habit-forming. Cannabinoids qualify as all of these things, and finding the most appropriate way to prescribe them is ongoing.

Oral cannabinoids such as dronabinol or nabilone are not tolerated by numerous patients, but should also not be ruled out due to their difficult side effect profile. Low levels of these medications may be very successful in potentiating opiate medications and reducing the amounts of opiates required for the desired analgesic effect. Whole-plant cannabis (either smoked or vaporized) is generally more effective in treating pain, neuropathy and spasticity than oral cannabinoids, helps ameliorate the side effects associated with these oral medications, and may have a relevant role in primary care. And while inhaled or non-oral cannabinoids may be most appropriate for many patients, practical patient education and documented informed consent is critical. Many dispensaries and “cannabis-friendly” clinics are requiring signed informed consent prior to registration, and documenting informed consent would be sensible practice for any prescriber.

If the provider determines that a recommendation for medical cannabis is the next course of action, there are guidelines. The recommendation for medical cannabis should be written on tamper-resistant paper, with appropriate patient-identifying information, the relevant diagnosis, and an expiration date, so the patient will continue to follow-up with the provider. In Washington State, an expiration date is not mandatory, but a one-time order is not consistent with the principles of long-term pain management or a therapeutic relationship. Have the patient return for routine follow-up appointments would be essential in managing their chronic pain, and an expiration date would help facilitate return visits.

When whole-plant cannabis is considered, the provider’s recommendation, and goals of therapy are being discussed, a route of administration besides smoking should be encouraged
(eating if it is tolerated, or vaporization), since smoking of any substance is never recommended. Personnel in dispensaries may be very valuable for patients when making these decisions, particularly since equipment associated with vaporization can be cost prohibitive and they would be knowledgeable about what products are newly available on the market.

Ultimately, each primary care provider will have to navigate what they feel best reflects what is most appropriate for their own patients, scope of practice, and guidelines established for their clinic and state. Despite this, it is clear that cannabinoids have an important role in managing chronic noncancer pain. Healthcare providers have an ethical obligation to remain informed about the scientific evidence regarding the role they play in analgesia, so that they can help reduce one of the largest sources of morbidity their patients will face.
References


Fox, A., Kesingland, A., Gentry, C., McNair, K., Patel, S., Urban, L., & James, I. (2001). The


Rog, D., Nurmikko, T., Friede, T., & Young, C. (2005). Randomized, Controlled Trial of
Cannabis-Based Medicine in Central Pain in Multiple Sclerosis. Neurology, 65(6), 812 - 819. doi:10.1212/01.wnl.0000176753.45410.8b


doi:10.1136/bmj.38149.566979.AE


### Figures

<table>
<thead>
<tr>
<th>Endocannabinoids</th>
<th>Anandamide (AEA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2-Arachidonyl-glycerol (2-AG)</td>
</tr>
<tr>
<td></td>
<td>2-Arachidonyl-glyceryl ether</td>
</tr>
<tr>
<td></td>
<td>N-Arachidonyl-dopamine (NADA)</td>
</tr>
<tr>
<td>Phytocannabinoids</td>
<td>$\Delta^9$-THC</td>
</tr>
<tr>
<td></td>
<td>$\Delta^8$-THC</td>
</tr>
<tr>
<td></td>
<td>Cannabinol</td>
</tr>
<tr>
<td></td>
<td>Cannabidiol</td>
</tr>
<tr>
<td>Synthetic cannabinoids</td>
<td>Nabilone ($\Delta^9$-THC analogue)</td>
</tr>
<tr>
<td></td>
<td>Dronabinol (synthetic $\Delta^9$-THC)</td>
</tr>
<tr>
<td></td>
<td>CP-55940</td>
</tr>
<tr>
<td></td>
<td>WIN-55,212-2</td>
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</tr>
<tr>
<td></td>
<td>HU-211</td>
</tr>
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<td></td>
<td>JWH-133</td>
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</table>

**Figure 1.** Abbreviated list of endogenous, exogenous/phytocannabinoids and synthetic cannabinoids. While there are currently over 60 known phytocannabinoids, the four listed here are the four that are most clinically relevant. Adapted from Elikkottil et al. (2009).
Figure 2. Some example cannabinoid structures. a. generic THC (Grotenhermen, 2003), b. Δ⁸-THC (Ben Amar, 2006), c. AEA (Grotenhermen, 2003), d. CBD (Ben Amar, 2006), e. nabilone, a synthetic THC (Grotenhermen, 2003), f. dronabinol, an analogue of THC (Rice, 2001).
Figure 3. Metabolism of $\Delta^9$-THC. When $\Delta^9$-THC is metabolized orally, it first undergoes hepatic metabolism and is converted into 11-OH-THC before final metabolism into THC-COOH. Oxidation of $\Delta^9$-THC with heat or sublingual administration converts directly into THC-COOH. Chemical structure images (Wikipedia, 2011).
<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No increase in tone</td>
</tr>
<tr>
<td>1</td>
<td>Slight increase in muscle tone, manifested by a catch and release or minimal resistance at the end of the ROM when the affected part(s) is moved in flexion or extension</td>
</tr>
<tr>
<td>1+</td>
<td>Slight increase in muscle tone, manifested by a catch, followed by minimal resistance throughout the remainder (less than half) of the ROM</td>
</tr>
<tr>
<td>2</td>
<td>More marked increase in muscle tone through most of the ROM, but affected part(s) easily moved</td>
</tr>
<tr>
<td>3</td>
<td>Considerable increase in muscle tone, passive movement difficult</td>
</tr>
<tr>
<td>4</td>
<td>Affected part(s) rigid in flexion or extension</td>
</tr>
</tbody>
</table>

**Figure 4a.** Modified Ashworth Score

<table>
<thead>
<tr>
<th>ARM</th>
<th>RIGHT</th>
<th>LEFT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Pinch grip</td>
<td></td>
<td>0 = No movement</td>
</tr>
<tr>
<td>2 Elbow flexion (from 90°)</td>
<td></td>
<td>1 = Palpable flicker</td>
</tr>
<tr>
<td>3 Shoulder abduction</td>
<td></td>
<td>2 = Movement without gravity</td>
</tr>
<tr>
<td>LEG</td>
<td></td>
<td>3 = Movement against gravity</td>
</tr>
<tr>
<td>4 Ankle dorsiflexion</td>
<td></td>
<td>4 = Movement against resistance</td>
</tr>
<tr>
<td>5 Knee extension</td>
<td></td>
<td>5 = Normal</td>
</tr>
</tbody>
</table>

**Figure 4b.** Motricity Index

**Figure 4.** Tests used for objectively measuring strength and spasticity. 4a. Modified Ashworth Score. An objective measure of spasticity used by specially trained professionals. From (Cuccurullo, 2009). 4b. Motricity Index. A strength test originally designed to be used to test strength following a stroke (Collin & Wade, 1990).
<table>
<thead>
<tr>
<th>Position 1: ACP supports programs and funding for rigorous scientific evaluation of the potential therapeutic benefits of medical marijuana and the publication of such findings.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position 1a: ACP supports increased research for conditions where the efficacy of marijuana has been established to determine optimal dosage and route of delivery.</td>
</tr>
<tr>
<td>Position 1b: Medical marijuana research should not only focus on determining drug efficacy and safety but also on determining efficacy in comparison with other available treatments.</td>
</tr>
<tr>
<td>Position 2: ACP encourages the use of nonsmoked forms of THC that have proven therapeutic value.</td>
</tr>
<tr>
<td>Position 3: ACP supports the current process for obtaining federal research-grade cannabis.</td>
</tr>
<tr>
<td>Position 4: ACP urges an evidence-based review of marijuana's status as a Schedule I controlled substance to determine whether it should be reclassified to a different schedule. This review should consider the scientific findings regarding marijuana's safety and efficacy in some clinical conditions as well as evidence on the health risks associated with marijuana consumption, particularly in its crude smoked form.</td>
</tr>
<tr>
<td>Position 5: ACP strongly supports exemption from federal criminal prosecution; civil liability; or professional sanctioning, such as loss of licensure or credentialing, for physicians who prescribe or dispense medical marijuana in accordance with state law. Similarly, ACP strongly urges protection from criminal or civil penalties for patients who use medical marijuana as permitted under state laws.</td>
</tr>
</tbody>
</table>

**Figure 5.** American College of Physicians position statement regarding the role of medical marijuana in healthcare and research. Reproduced with permission (American College of Physicians, 2008).