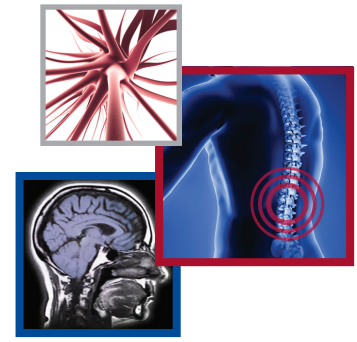
PERSPECTIVE

Pain Management



Re-branding cannabis: the next generation of chronic pain medicine?

Gregory T Carter*[1,2], Simone P Javaher[3], Michael HV Nguyen[2], Sharon Garret[4] & Beatriz H Carlini[4]

Practice Points

- Cannabis has been used for thousands of years by humankind as a safe and useful means of providing analgesia.
- Much of what has led to today's views on medicinal cannabis has been based on political and societal agendas rather than purely on the available science.
- There already exists in the available literature a strong evidence base supporting the use of cannabis to treat chronic pain, particularly neuropathic pain.
- There is a need for further research, particularly in to other forms of pain, using standardized cannabis preparations and protocols.
- There is a need for more rationale governmental regulations regarding the scheduling of cannabis and it's availability for clinical trials.
- Cannabis can be effectively used to treat chronic pain with appropriate patient screening and physician oversight.

SUMMARY The field of pain medicine is at a crossroads given the epidemic of addiction and overdose deaths from prescription opioids. Cannabis and its active ingredients, cannabinoids, are a much safer therapeutic option. Despite being slowed by legal restrictions and stigma, research continues to show that when used appropriately, cannabis is safe and effective for many forms of chronic pain and other conditions, and has no overdose levels. Current literature indicates many chronic pain patients could be treated with cannabis alone or with lower doses of opioids. To make progress, cannabis needs to be re-branded as a legitimate medicine and rescheduled to a more pharmacologically justifiable class of compounds. This paper discusses the data supporting re-branding and rescheduling of cannabis.

KEYWORDS
• cannabis • medical marijuana • pain • palliative care • re-branding

Background

Cannabis (marijuana) has been used by humankind for medicinal, religious, and recreational purposes for over 5000 years. Medicinal use has been noted in ancient Chinese texts written in 2800 BC, where it was recommended for analgesia [1–4]. Eastern Indian documents in the Athera Veda, dating to ~2000 BC, also refer to the medicinal use of cannabis for pain relief [3,4]. Archeological evidence has been found in Israel indicating that cannabis was used therapeutically during childbirth as an

[1]St Luke's Rehabilitation Institute, Spokane, WA 99202, USA
[2]University of Washington School of Medicine, Seattle, WA 98195, USA
[3]Health Policy Clinical Manager, Washington State Labor & Industries, Olympia, WA 98504–4321, USA
[4]Alcohol & Drug Abuse Institute, University of Washington, Seattle, WA 98105, USA
*Author for correspondence: Tel.: +1 509 473 6910; Fax: +1 509 473 6978; carterg@st-lukes.org

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analgesic [4]. In ancient Greece and Rome, both the Herbal of Dioscorides and the writings of Galen refer to the use of medicinal cannabis [4].

The medicinal use of cannabis arrived in the West much later when US Cavalry Army physician William O'Shaughnessy introduced a cannabis tincture used for analgesia and a wide array of ailments following his observations while travelling in India in the 1840s [3,4]. In that same era, Queen Victoria used cannabis for relief of dysmenorrhea [3,4].

Against the advice of the American Medical Society (now Association) and not on the basis of any scientific reasoning, all use of cannabis was criminalized in 1937 in the United States [3] and in 1942 it was officially removed from the US Pharmacopoeia. Due to fact that hemp, a non-medicinal form of the cannabis plant, grows so much faster and more efficiently than cotton, it was temporarily re-legalized and used productively in World War II to make rope and clothing. The hemp industry still thrives today in countries such as China and Hungary.

In 1972, the Nixon-appointed Shaffer Commission actually recommended that cannabis be re-legalized but this was ignored [5,6].

Today, the cultivation, possession and distribution of cannabis are strictly controlled by international narcotic regulations, though some states and nations interpret these regulations differently. For example, the Netherlands, Uruguay, and Portugal have completely decriminalized cannabis possession for any purpose. In the USA, at the time of writing, 23 states and the District of Columbia have passed voter initiatives and referenda to allow the medicinal use of cannabis. In addition, Colorado and Washington States have legalized cannabis for recreational purposes for individuals 21 and over.

Barriers to progress

Despite its rich history of therapeutic value, cannabis continues to be a controversial topic with many real and perceived barriers that have created a kind of cultural gridlock. This has limited progress in research, has resulted in confusing laws, and has caused even the most knowledgeable pain management specialists to be wary of using it. These barriers to progress center on negative societal perceptions and specific medical concerns [1]. Society's perceptions are mired in the near hysterical political and social campaigns of the past that branded cannabis as a dangerous recreational drug. Recreational use of a drug can cause legitimate concerns, but this is not a new phenomenon. Many currently used medications have the potential for misuse, however this does not diminish their effectiveness in treating patients when used as prescribed by a medical provider. Cocaine and morphine are addictive, but are still used medicinally as an anesthetic or to stop epistaxis, and in the management of acute pain respectively. It is important to distinguish the difference in how medicinal cannabis and recreational marijuana have been cultivated over time to meet specific needs. Recreational marijuana, grown for its psychedelic properties, contains Δ-9-tetrahydrocannabinol (THC) at much higher levels than is sought in medicinal cannabis, which tends to be rich in the non-psychoactive cannabinoid CBD, with relatively lower concentrations of THC.

The campaigns against cannabis started with the prejudicial treatment of Mexican farmworkers and the politically motivated media messages that sensationalized cannabis as causing psychosis, promiscuity, stunting of growth and addiction. This manufactured fear of *Reefer Madness* laid the groundwork for polarized social, economic, and geopolitical opinions, which have fomented controversy and confusion in the minds of both the lay public and the medical profession.

Hence, there remains much debate over what role, if any, cannabis should play in modern medicine, particularly in pain management. While medical professionals may also have negative perceptions about cannabis, more often they are reluctant to consider cannabis as a viable treatment modality because of practical and safety concerns. First there is the concern that the Federal United States Drug Enforcement Agency (DEA) has not rescheduled cannabis to recognize its medicinal value, thereby making it illegal to prescribe. Providers are concerned about their lack of control over the product in terms of consistency of the ingredients and the possible inclusion of unknown ingredients with unknown effects. They are unsure about correct dosing, the interactions of cannabis with other medications, and its effect on performance in the workplace. These concerns bolster the argument for rescheduling, regulating, and manufacturing pharmaceutical grades of cannabis. By eliminating barriers, research could happen more rapidly generating a better understanding of the plant's components, and regulation would allow for testing and labeling of the product as is occurring in Colorado and Washington State under the new regulations

that went into effect this year legalizing the use of recreational marijuana.

Lack of education and training is another barrier to progress. The medicinal use of cannabis is a frequently requested topic in lectures and seminars on pain management, yet paradoxically remains almost non-existent within the formal training of medical students, residents, fellows, and clinical pharmacists. An interesting paradox in the age of the internet and wide accessibility to databases like the National Library of Medicine (http://www.ncbi.nlm.nih.gov/pubmed/), is the increasing likelihood that pain specialists may be asked about potential or actual cannabis use for pain by their patients. Further, the patient may already have accessed and gained knowledge of the existing scientific knowledge base regarding cannabis. One of the authors (GTC) has, on a number of occasions, had a patient bring in copies of a published scientific paper in order to argue their case as to why cannabis use would be appropriate for their pain condition. The pain specialist who simply responds to a patient inquiring about cannabis use for their condition by saying "there is not enough evidence" is not practicing to the level of current knowledge. By summarily refusing to discuss or entertain the use of medicinal cannabis with a pain patient, the physician is undermining the doctor-patient relationship. This also encourages the patient to seek other, perhaps less qualified or legitimate, sources of authorization. This may include the so-called "doc in the box pot clinics" where the patient will likely receive a less than robust clinical evaluation and not likely establish a *bona fide* on-going relationship with the practitioner. In addition, patients may not share information about their use of cannabis with the provider who had dismissed the idea, leaving providers with incomplete information and limiting their ability to make well-informed clinical judgments.

Ultimately true progress can only be made when governments and the medical community allow legitimate clinical testing of cannabis for complete evaluation of its properties and therapeutic uses, including strains that are specifically cultivated for pain relief with minimal psychoactive effects.

Re-branding cannabis as legitimate medicine for the management of chronic pain

There certainly already exists a massive interest in cannabis use on behalf of the general public and media, centered primarily on recreational use. The medical community, including specialists in pain medicine, still appears to be holding onto a perception that cannabis may be effective for pain control, but poses too many dangers and risks. To break this juggernaut and allow chronic pain sufferers access to high quality, safely administered doses of medicinal cannabis, it must be re-branded in the minds of the public, health care regulators, and the medical community. This is not the re-branding of a product in the commercial sense, but a re-branding in terms of changing how we react to the thought of using medicinal cannabis; it requires a shift in its cultural meaning. "Brands, at their best, are, among other things, bundles of meanings, some of them robust, some of them delicate, all of them poised to speak to one or more segments and to deliver an understanding of not just what the product does, but what it means – its cultural meaning." [7]. This means changing how we talk about it, for example, using the term 'medicinal cannabis' for its therapeutic use versus 'marijuana' for recreational use, and discarding disparaging terms such as 'pot-heads'.

There are many examples of how our cultural thinking in the past is almost inconceivable to us now. To paraphrase German philosopher Arthur Schopenhauer, 'all truth passes through three stages, first being ridicule, followed by opposition, before ultimately becoming self-evident.' It wasn't that long ago that cigarette smoking was allowed everywhere in public places, including hospitals.

Cannabis has been around long enough for most clinicians to have had at least some experience with it either professionally, socially, personally, or otherwise; so the first step in re-branding cannabis would be for clinicians to examine their personal perspectives about its general and medicinal use, and the ramifications of those opinions [8–11]. This worthwhile reflective exercise may reveal previously unrecognized biases that have influenced their clinical judgment. Ultimately, treatment decisions should be based on current scientific evidence, clinical indications and need given the known risks and benefits, and in the context of a proper clinical evaluation and consultation. This presumably includes a full history with careful screening for past or current substance abuse, and following appropriate guidelines.

The opioid epidemic

There has been near epidemic increases in deaths related to prescription opioids. [12–25]. There

appear to be a a correlation between the risk of opioid overdose and increasing prescribed dosages [21–23]. Data from the Centers for Disease Control and Prevention (CDC) indicates that the number of opioid poisoning deaths in the USA nearly doubled, from approximately 20,000 to 37,000 from 1999 through 2006 [24].

This concerning scenario contrasts with the fact that cannabis has no known lethal dose [1,4,26]. If cannabis based medicines were more widely used to treat pain, potentially thousands of deaths from opioid toxicity could have been prevented. However, these problems with the use of opioids in the management of chronic pain may actually have served to increase physician sensitivity to issues of abuse, potential diversion, long term safety, patient screening and monitoring for functional outcomes, many of which are equally applicable to concerns around the medicinal use of cannabis.

The legal side of the equation

In the past decade many states have re-legalized cannabis for medicinal purposes. This is likely primarily based on political pressures placed on state governments by patients and their advocacy groups. Actual true acknowledgement of the growing scientific evidence base by governmental agencies has so far played a minor role. To date, laws still differ considerably from state to state, and even among countries, with much ambiguity regarding what constitutes acceptable medical use and guidelines for such usage. [27–30]

In the USA, the DEA laws, as determined by the Controlled Substances Act (CSA), still classifies cannabis as a Schedule I drug, the most tightly restricted category, reserved for drugs which have no currently accepted medical value and considered too dangerous for use even under medical supervision. Thus there is no uniform set of quality control standards in place to assure the quality, consistency, and availability of medicinal cannabis for patients with chronic pain. This is undoubtedly a barrier for health care professionals who may otherwise be willing to recommend cannabis use for their patients with chronic pain. While the scientific field of enquiry was expanding in the 1990s, the therapeutic potential for cannabis, coupled with prohibition on possession, became a source of patient-led legal challenges in several countries. This ultimately gave rise to compassionate access programs in Holland, Canada and Israel using a variety of regulatory mechanisms aimed at exempting *bona fide* patients from prosecution for the possession of cannabis and authorizing cannabis cultivation programs to provide access to a quality controlled and standardized herbal cannabis product. It is poignant to note that patient led efforts have been at the core of cannabinoid drug development. Past and present reports of the effects of cannabis on symptoms of, pain and spasticity triggered the clinical development and evaluation of cannabinoid drugs [31–37]. Pharmaceutical studies have, to a limited extent, validated these original claims, particularly for neuropathic pain [38–54].

The science behind THC & other cannabinoids

Israeli scientists Mechoulam and Gaoni identified THC as the primary psychoactive ingredient of cannabis in 1964 [55]. Originally THC was felt to be the main active ingredient in cannabis. However in the following decades, other compounds unique to cannabis ('cannabinoids') were isolated and characterized. Cannabis is now estimated to contain over 100 such compounds, some of which were further evaluated by pioneering scientists including E. A. Carlini, who elucidated the potential medicinal benefits of cannabidiol (CBD) [56–59]. Despite this basic science progress, the 1960s and 70s saw a resurgence in recreational use of cannabis, with it becoming a major part of the counterculture movement during that time period. By the early 1970s the medicinal use of cannabis began to be re-investigated, starting with a series of case reports from Harvard psychiatrist Lester Grinspoon [60].

• Dronabinol (marinol) & nabilone (cesamet)

In the early 1980s, the main focus of the pharmaceutical industry was on the THC molecule, primarily for the treatment of pain, loss of appetite, and intractable nausea. Dronabinol, more commonly known as Marinol, was initially produced as synthetic THC, became the primary cannabinoid based prescription medicine, followed later by nabilone (also a synthetic THC analogue), commercialized as Cesamet. These drugs remain as schedule III drugs today, with generic forms available worldwide. However, dronabinol is 100% THC and most patients find it too sedating at standard dosing, and associated with too many psychoactive effects [61,62]. Dronabinol and Nabilone are not appropriate substitutes for natural cannabis.

• Other cannabinoids

The cannabis plant is remarkably complex, with several subtypes of cannabis, each containing over 400 chemicals [63–65]. Cannabinoids, consisting of alkylresorcinol and monoterpene groups, are unique secondary metabolites that are found only in Cannabis. Cannabinoids may be broadly classified as terpenes and are biosynthesized predominantly via a deoxyxylulose phosphate pathway [66]. Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which may modify the pharmacology of THC, in addition to producing unique effects on their own [63]. Many cannabinoids are not psychoactive and this includes CBD, which has significant anticonvulsant and sedative properties and modulates the activity of THC [56]. Pre-treating mice with CBD will lead to threefold increases of brain THC levels [59].

Endocannbinoid system

Perhaps the biggest breakthrough in understanding the potential medicinal applications of cannabinoids was the the discovery of the endocannabinoid system in the early 1990s [65–69]. There are at least two distinct G-protein-coupled cannabinoid receptors type 1 and 2 (CB1 and CB2) which are widely expressed in the body [70–75]. The endocannabinoid system (ECS) plays a major physiologic role in maintaining homeostasis, as well as the modulating a number of functions in the central and peripheral nervous systems, the immune system, the gut, the cardiovascular system, among other critical physiological systems [76–81]. This includes modulating the degree and perception of pain. The ECS is arguably the most important newly discovered physiological pain moderating systems discovered in the past quarter century. The ECS forms the underlying physiological and pharmacological mechanistic basis to delineate the therapeutic actions of cannabinoid medicines.

Applications in the field of pain management

Studies already show that chronic pain is the most common reason for patients to report the medicinal use of cannabis [33,36]. Within chronic pain clinics, estimates of the prevalence of use range from 12–15%, with patients with fibromyalgia, degenerative arthritis, spinal cord injury and multiple sclerosis (MS) being among the main population who report using cannabis use for the relief of pain [36]. Data from medicinal cannabis programs suggest that self-reported pain conditions are responsible for up to 90% of cannabis authorizations [82]. Although the mechanisms by which cannabinoids treat pain, including chronic pain, are complex and remain to be fully elucidated, there is a growing evidence base to support its use in this setting [83]. The modulation of CB_2 receptors producing a decrease in the liberation of pro-inflammatory mediators has led some to propose that certain chronic pain conditions may represent abnormalities in the endocannabinoid system [84,85]. The immunomodulatory and neuroinflammatory properties, which would contribute to the antinociceptive properties of cannabinoids, would lend some credence to that hypothesis. Whether isolating agents that would selectively target peripheral CB_1 and CB_2 receptors would improve overall analgesia and improve quality of life for chronic pain patients remains to be studied. However bypassing the other, more subtle and complex analgesic properties that are seen in the cornucopia of cannabinoids that occur in the natural plant may not improve analgesia or safety. Indeed, there are even non-cannabinoid, terpenoid compounds that are purported to provide analgesia, which occur in the natural plant.

Conclusions & future perspective

There is an increasing evidence base supporting the use of cannabis for chronic pain disorders. Yet regulatory and funding limitations have led to trials that are generally small, and of short duration, particularly when compared with industry sponsored trials. Moreover, in the USA the only approved route of administration is smoking a cannabis cigarette that has been grown by the U.S. government. Overall, the limitations for doing clinical trials with cannabis are considerably more restrictive than those required in pharmaceutical industry trials. Yet the safety profile of cannabinoids remains a compelling force to move this area forward. Despite some conflicting and paradoxical reports, the overwhelming data, including large population-based studies of recreational cannabis use, indicate that the toxicity of cannabis is extremely low and adverse drug reactions are rare. The argument for allowing further clinical trials to be done, in a less restrictive, regulated fashion, would appear to be strong.

Whether it is necessary to make all reasonable efforts to try standard therapeutic

(pharmacological and non-pharmacological) approaches before cannabis is considered is often more a matter of legal statute than clinical indication. In other words, many laws require that all standard means of treating pain be tried and failed before cannabis can be offered. Arguably, any decision to offer medicinal cannabis as a treatment option will depend on the severity of the underlying pain condition and the extent to which other approaches have been tried. Simply relegating cannabis to a third or fourth line agent for chronic pain does not reflect the body of evidence showing that it could be a first line therapy for a condition like central neuropathic pain due to multiple sclerosis. The argument that dosing for herbal cannabis is difficult due to lack of standardized dose forms is easily removed by applying the universal principle of beginning therapy with low doses and gradually increasing the dose as tolerated to maximum benefit with minimum adverse events. The available data would indicate that most patients can get a beneficial analgesic effect by using average daily doses of under 5 grams per day [1]. However some patients may require a larger amount to obtain relief. As noted previously, the safety profile of cannabis is quite good and there is no hard evidence of significant toxicity at higher doses. For the most part the risk of developing tolerance to the therapeutic properties of cannabis is minimal, particularly when compared with drugs like opioids and benzodiazepines.

It should also be noted that cannabis, like many therapeutic medicines, has the potential for adverse effects. The literature contains many reports showing purported associations between recreational cannabis use and early onset psychosis, impairments in driving with potential increase in risk of accident, myocardial infarction, stroke, and risk of chronic bronchitis in those that smoke it [34,45,86]. There is also potential for abuse, cognitive impairment, and risk of dependency in susceptible patients. Yet from a harm reduction standpoint, these problems are less serious and less common than the potential risks and co-morbidities associated with opioid use. In a clinical setting, a patient using medicinal cannabis would not be smoking cannabis and the amount used would be monitored, as would the potential for any risk factor and comorbidity. The patient would presumably also be using a less psychoactive form of cannabis.

Of course, practitioners must carefully construct a treatment plan, as they would in any chronic pain management program, and diligently supervise the patient's medical care. A well-constructed treatment plan would include clinical monitoring, follow up, and mutually agreed upon treatment goals such as reduction in other medications, realistic expectations, functional outcomes and pain relief. These are essential yard sticks to measure therapeutic progress, and failure to demonstrate positive outcomes in a reasonable timeframe should prompt reconsideration and possible cessation of therapy. Cannabis dependency is possible and if a point arrives when a given patient's use of cannabis does not meet therapeutic standards, evaluation for possible cannabis abuse disorder may be needed, along with referral for treatment.

Using cannabis as a highly therapeutic analgesic treatment option does not mean that it is a panacea. Any recommendation to use cannabis as an analgesic agent should be based on clinical judgment and thorough knowledge of the available literature. However, using medicinal cannabis for pain expands the armamentarium of tools used to treat pain. Moreover, as opioid analgesic overdose mortality continues to rise in the United States, there is an increasing need for new and safer modalities to treat chronic pain. A recent study indicates that states in the USA with medical cannabis laws have significantly lower opioid overdose mortality rates [87]. Medicinal use of cannabis holds too much potential to be held back by laws that are not consistent or reflective of the science.

As our knowledge of the exogenous and endogenous cannabinoid system continues to grow, we better clarify the role and importance of this system and its therapeutic potential in chronic pain. It remains to be seen whether the future will lead solely to purified analogues or more highly refined extracts of natural cannabis. Regardless, purification and refinement do not always mean a safer drug or improved efficacy. There does remain a need for further clinical studies of inhaled (vaporized) and ingested forms of herbal cannabis. Ideally this would not be limited by restriction of access to high grade medicinal cannabis or concerns of intellectual property.

Pain medicine specialists should examine their attitudes and beliefs about cannabis to check for any bias, inform themselves about the most current literature and clinical guidelines, and embrace the scientific process, which continues to document the therapeutic effects

of cannabis. Practitioners must be willing to advocate for chronic pain patients who want to legitimately access a medicine that could potentially help them and safeguard them from the harmful effects of other options such as opioids. Using science and logic rather than societal and political posturing, we can bring our antiquated cultural conditioning about marijuana into the 21st century and help create safe, rational, and useful regulations for medicinal cannabis.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

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