Medical Marijuana for Failed Back Surgical Syndrome: A Viable Option for Pain Control or an Uncontrolled Narcotic?

CASE SCENARIO

M.J. is a 54-year-old woman with diffuse low back and bilateral leg pain. She has had 4 spinal surgeries over the past 12 years for her pain, including 2 laminectomies at L4-L5 and L5-S1, a fusion from L4-L5 to the sacrum, and a subsequent revision from L3 to the sacrum. The first surgery provided her 4 years of relief, but all other surgeries resulted in no measurable relief. Various interventional treatments have failed to help, including a spinal cord stimulator trial. She has no focal weakness on lower limb examination but has some subjective numbness in her lower extremities bilaterally and is areflexic in the Achilles tendon bilaterally. She sees a pain psychologist weekly for sessions that include pain coping skills and biofeedback. She denies any depression and scores well on standardized depression inventories. The apparent lack of depression may be due to the psychoaffective effects of opioids; she currently takes scheduled sustained release oxycodone 40 mg every 12 hours, with occasional oxycodone for breakthrough pain control. However, she believes that these medications only partially control her pain. She has had routine urine drug screens that show compliance with the treatment regimen. She has heard of people taking medical marijuana for pain control and wonders if that will be a viable option for her instead of escalating the dose of opioids. Sunil K. Aggarwal, MD, PhD, and Gregory Carter, MD, MS, will argue that medical marijuana is an appropriate treatment for this patient, and Sanjog Pangarkar, MD, Mark Miedema, MD, and Bianca Tribuzio, DO, will argue that medical marijuana is not a viable option for this patient.

Guest Discussants:

Sunil K. Aggarwal, MD, PhD
Rusk Institute of Rehabilitation Medicine, New York, NY
Disclosures outside this publication: stock/stock options, Co-Founder, Director, and Officer, C.H. (Cannabis Hemp) Revitalization Group Inc.

Sanjog Pangarkar, MD
Department of Physical Medicine and Rehabilitation, Inpatient Pain Service Veterans Health Service, Los Angeles, CA
Disclosure: nothing to disclose

Gregory T. Carter, MD, MS
St Luke's Rehabilitation Institute, Spokane, WA
Disclosure: nothing to disclose

Bianca Tribuzio, DO
Department of Physical Medicine and Rehabilitation, UCLA-WLA VA, Los Angeles, CA
Disclosure: nothing to disclose

Mark Miedema, MD
Department of Physical Medicine and Rehabilitation, UCLA-WLA VA, Los Angeles, CA
Disclosure: nothing to disclose

Feature Editor:

David J. Kennedy, MD
Stanford University, Redwood City, CA.
Address correspondence to: D.J.K.; e-mail: djkenned@stanford.edu
Disclosure: nothing to disclose

Sunil K. Aggarwal, MD, PhD, and Gregory T. Carter, MD, MS, Respond

Medical marijuana, or herbal cannabinoid preparations, have been used medicinally since ancient times and continue to be recommended by tens of thousands of contemporary physicians in multiple countries to provide patients with pain control. The pain-relieving ability of marijuana or cannabis' cannabinoid-rich resin-containing flowers, given in oral or inhaled forms, has stood up to the rigorous standards of evidence-based medicine, and is no longer controversial. The evidence runs the gamut from preclinical, to controlled clinical, to health service outcomes studies. In animal models, cannabinoids have been shown to relieve pain in "virtually every experimental pain paradigm" in supraspinal, spinal, and peripheral regions, that involve both ascending and descending pain pathways [1]. In humans, a 2012 review on cannabinergic pain compounds in *The Clinical Journal of Pain*, which surveyed randomized controlled trials (RCT) that involved all cannabinoid therapies (including cannabinoid herbals) for pain indications, showed that, of the 38 published clinical trials that met the inclusion criteria, 71% demonstrated a positive outcome for analgesia [1]. Pain syndromes studied in RCTs which showed a positive response to cannabinergic therapies were: chronic neuropathic pain with hyperalgesia and allodynia; chronic neuropathic pain related to human immunodeficiency virus, trauma, surgery, and complex regional pain syndrome (CRPS); and chronic pain secondary to upper motor neuron syndromes, cancer pain, multiple sclerosis, rheumatoid arthritis, and fibromyalgia [1]. The largest and longest-duration positive-outcome RCT with an oral and/or sublingually administered cannabis product for pain studied 630 subjects with multiple sclerosis who were enrolled from 33 different sites in the United Kingdom, and clinically monitored 80% of subjects in a double-blinded fashion for an extended duration of 12 months [2].

When turning to the specific diagnoses in this case, although there are no RCTs for cannabis in failed back surgical syndrome, there are some health outcomes data for

PM&R
1934-1482/14/$36.00
Printed in U.S.A.

Vol. 6, 363-372, April 2014
http://dx.doi.org/10.1016/j.pmrj.2014.03.006

patients with this diagnosis who are using physician-authorized medical cannabis as part of their pain management regimen. In 2009, we published a retrospective chart review on the characteristics of patients with chronic pain that accessed treatment with medical cannabis at a physiatric outpatient pain subspecialty clinic [3]. Of the 139 patient sample, 4 had the diagnosis of failed-back surgical syndrome. The patients were men in their 40s and 50s, and had been using cannabis while under medical authorization for up to 30 months. A summary of the data, taken from these 4 patients' medical records, with a standard pain syndrome classification system, are summarized in Table 1.

Cannabis has taken its place now more in line with complementary and alternative medicine offerings. Because there is no U.S. Food and Drug Administration (FDA) approval for cannabis use, in the absence of such a federal stamp of approval, physicians must take extra efforts to inform themselves about the risks and benefits of this therapy so that they can effectively use cannabis for the appropriate patients and monitor its effects. The safety profile of cannabinoids is relatively high. It is important to note that there is no risk of overdose death with cannabinoids, and no end-organ damage that would necessitate routine laboratory monitoring. A well-regulated state program can help to ensure the proper quality of herbal cannabinoids and ensure that the cannabinoids are free of contaminants and mold. We recommend the online free course, available for continuing medical education, accredited by the Massachusetts Medical Society, publishers of *The New England Journal of Medicine,* called "Medicinal Cannabis in the Treatment of Chronic Pain Syndromes" available at www.theanswerpage.com. Screenings used to stratify risk protocols for initiating patients on opioid therapy and monitoring protocols for adverse events could be used for this patient, who appears to be a suitable candidate for a medical cannabis empiric treatment trial based on the information provided.

There are several myths that are frequently touted by opponents of medical marijuana that need to be dispelled. The first is that one needs to be "high" to obtain a medical benefit from marijuana; this is clearly not true. Delta-9-tetrahydrocannabinol (THC) is now known to be the most psychoactive ingredient in cannabis [4]. Natural cannabis contains, at most, 10%-15% THC, and often much less. There are many therapeutic cannabinoids that do not produce a high or intoxication but yet hold tremendous medical and therapeutic value. Cannabis plants can be bred to have higher amounts of nonpsychoactive yet therapeutic cannabinoids [5]. Other major cannabinoids include cannabidiol (CBD) and cannabinol (CBN), both of which significantly modify the effects THC and have distinct effects of their own. CBD appears to modulate and reduce any untoward effects of THC [5,6]. CBN appears to have distinct pharmacologic properties that are quite different from CBD [5,6]. CBN has anticonvulsant, sedative, and other pharmacologic activities likely to interact with the effects of THC. CBD may induce sleep and may provide some protection against seizures in patients with epilepsy, in addition to being a powerful antioxidant with neuroprotective properties [6]. The ratios of the various cannabinoids differ according to the plant strain, and, to some extent, how the plant is grown. Oddly enough, one of the only forms of a cannabinoid-based medicine available in the United States is dronabinol, which is composed of 100% THC, the most intoxicating ingredient in natural cannabis. Choosing the right strain of cannabis can lead to significant medical benefits, including pain relief, without intoxication. Intoxication is not necessary to get a therapeutic medical effect or health benefit [5,6].

The second common myth is that you have to smoke marijuana, thereby resulting in unwanted secondary adverse health effects, for example, chronic bronchitis. This also is not true because there is no need to smoke cannabis. Effective and safer delivery systems are now available [7]. The route of administration is an important determinant in how fast cannabis is absorbed and metabolized [8]. Rapid onset of effect is the main advantage of smoking cannabis; however, smoking is clearly not healthy for the lungs and upper airway system. A better option may be to use a vaporizer, a device that aerosolizes the cannabinoids into a hot air mist without combusting the plant material [9]. Because cannabinoids are volatile, they will vaporize at a temperature much lower than combustion. Vaporization delivers the cannabinoids in a rapid manner similar to smoking, yet does not impose a health hazard to the airways and still provides excellent therapeutic effect [10]. Cannabis also can be ingested, although this has quite different pharmacokinetics than inhalation [8,11]. The onset of action is delayed, and adjustment of dosing is more difficult. Cannabis also can be used in concentrated tinctures placed under the tongue for more rapid absorption or even applied to this skin over painful or swollen areas. The basic advice for dosing is "start low and go slow." In other words, start with a small amount and monitor the effects.

Given this evidence, the question before the contemporary medical community now is, what shape or form is medicinal cannabis going to take in the practice of routine and high quality pain medicine today? How does a clinician proceed in the setting of federal regulations that officially deems cannabis a Schedule I drug devoid of medical utility and unsafe to use under medical supervision, while at the same time, state-level regulators, delegated the responsibility of issuing all medical licenses and regulating the practice of medicine, have acknowledged the medical utility of marijuana and have allowed its use under medical supervision? To add to the confusion, federal regulators who have long stymied cannabis research and empiric treatment trials domestically are now allowing private international pharmaceutical companies to import cannabis extracts produced overseas into the United States for large clinical trials, yet

Table 1. *Characteristics of failed back surgical syndrome patients accessing medical cannabis treatment in Washington state*

	Patient No.			
Characteristics	**1**	**2**	**3**	**4**
Age, y	41	44	52	51
Gender	M	M	M	M
Medical cannabis authorization duration, y	2.58	0.68	0.41	2.56
Primary diagnoses	Failed back surgery syndrome (13 spinal fusions; 1987 military accident + other later accidents)	Lumbar radiculopathy secondary to failed back surgery syndrome, including DDD at L4-L5 and microdiskectomy in 2004	Back, leg, bilateral shoulder DJD, and failed back surgery syndrome (history of diskectomy, multilevel fusion, rotator cuff repairs)	Failed back surgery syndrome; DJD + DDD throughout C- and L-spine, C- and L-spinal stenosis, herniated disk at L5/S1, OA; injury history; Chronic headaches secondary to underlying DJD, Oct 6, 1998, "Have been hit by Tree Top and two logs from about 8-feet high and Maple top all across low back. Hit on head and neck by top and fell on ribs bounced in air, land on ribs and many others."
Classified chronic pain syndromes	MPS, NPS, SCI, DP	MPS, NPS, DP	MPS, NPS, OA, DP	MPS, NPS, OA, DP
Chart notes about medical cannabis		"States quite forthrightly that he has used marijuana to treat his pain, and he gets better relief from that than most other medications." (Sept 25, 2007)	"He has been using marijuana on his own, as he feels it gives him the best pain relief of anything that he has used"; 2-3 inhalations on a MJ cigarette 2-3 times a day, and this improves his pain levels drastically without incapacitating him	MMJ daily; patient agreed to use less hydrocodone with MMJ
Chart notes about other medications	Uses morphine	Addiction to higher dose narcotics-pain specialists' referral to get him off; narcotics; uses oxycodone, APAP, carisoprodol (for muscle spasm), IBP	Taking MS contin	Does not tolerate narcotics due to N/V, and little success with other medications (eg, neurontin); uses hydrocodone and muscle relaxers
Chart notes about major access hurdles	Patient has a history of incarceration and forcible removal from Canadian emergency department with urinary catheter in place stemming from MC charges	Wanted to consider MMJ only after Labor and Industries claim was closed	"He is quite adamant, noting that he has never been a recreational marijuana user and is adamantly against recreational drug use. He stated a number of times during our visit that he is embarrassed to inquire about this."	

DDD = degenerative disk disease; DJD = degenerative joint disease; MPS = myofascial pain syndrome; NPS = neuropathic pain syndrome; SCI = spinal cord injury; DP = diskogenic pain syndrome; OA = osteoarthritis; MJ = marijuana; MMJ = medical marijuana; APAP = acetaminophen; MS = morphine sulfate; IBP = ibuprofen; N/V = nausea/vomiting; MC = medical cannabis.

ignoring data accumulated from such trials when it comes to national cannabis scheduling placement decisions [7,12]. This stance has produced significant barriers for both patients and researchers, with legitimate patients enduring unnecessary additional emotional and physical stress [13-15]. Moreover, federal scientists have filed and have been granted an applicability patent for the usefulness of cannabis-derived cannabinoids as antioxidants and neuroprotectants in humans, intellectual property that is ultimately held by U.S. Department of Health and Human Services, a federal agency.

Politics and private interest influence are not new when it comes to medical regulation and the pressures on the physician-patient relationship [16]. A proper historical frame is valuable to understand the clinical decision-making issues in the case. There is documentation from before 1937 that cannabis was part of more than 2000 different pharmaceutical products and preparations prescribed by physicians and stocked and dispensed in drug stores throughout the United States, including preparations intended for neuralgia and other forms of pain [7]. These cannabis medicines were prepared and sold by major pharmaceutical companies, for example, Parke Davis, Merck, Eli Lilly, Squibb. They were in the form of oral extracts, dried cannabis flowers ground into a powder, topicals, or rolled cigarettes, and they were produced both domestically and abroad. Leading physician-educators of the early 20th century, such as Sir William Osler, endorsed the use of cannabis as the most superior treatment for migraines [17,18].

Interestingly, as long as 120 years ago in medical journals, the debate about when cannabis versus opioids was appropriate for pain treatment appeared. A quotation from a physician's review article, "Cannabis India as an Anodyne and Hypnotic" published in *The St. Louis Medical and Surgical Journal* in 1891 is apropos, "With a wish for speedy effect, it is so easy to use that modern mischief-maker, hypodermic morphia, that they [young physicians] are prone to forget remote results of incautious opiate giving. Would that the wisdom that has come to their professional fathers through, it may be, a hapless experience, might serve them to steer clear of narcotic shoals on which many a patient has gone awreck. Indian hemp is not here lauded as a specific. It will, at times, fail. So do other drugs. But the many cases in which it acts well, entitle it to a large and lasting confidence. My experience warrants this statement: cannabis indica is, often, a safe and successful anodyne and hypnotic" [19].

When the FDA was founded in 1938 with the passage of the Federal Food, Drug, and Cosmetic Act, cannabis should have been grandfathered in for FDA approval at that time, just as aspirin, morphine, and other medicines were because no reading of medical history can support the position that cannabis was or is now an "investigational new drug" [7]. It was only after the federal government, led by the U.S. Department of Treasury, began a campaign to outlaw cannabis use and severely restrict its prescription use, which the major pharmaceutical houses began to reduce and eventually abandon the production of cannabis medicines. After having been used for nearly a century in the United States, cannabis was removed from the U.S. Pharmacopeia in 1942, where it had been since 1850, due to onerous restrictions on its prescription and dispensing [7].

Thus, it is not surprising when the use of cannabis as a medicine was "rediscovered" by the population in the 1960s and 1970s, due to its availability in underground markets rather than through pharmacies as in past eras, it was being administered in inhaled and home-prepared oral forms. The medical marijuana laws that are now in 20 states and the District of Columbia were prompted when the U.S. government, caught in the throes of culture wars, was unwilling to expand compassionate access to the federal cannabis supply and instead continued to strengthen a punitive regime for cannabis use. With the medical cannabis laws now in place for 17 years, these laws have become a part of the American health care system, with nearly 2.5 million patients enrolled. Consider this: The latest generation of medical school graduates in 2013, if they grew up in California, would had lived in a state with a medical cannabis program quite possibly since they were in the third grade.

The issues that this case raises are very similar to those that were discussed in the September 2013 issue of *PM&R* in "Balancing Burdens and Benefits: Ethical Issues of Off-Label Prescription Pharmaceutical Use" [20]. As was written there, "clinicians will need to balance ethical mandates to do no harm (nonmaleficence) with the need to try to do good and to alleviate suffering (beneficence)" [20]. As one of those authors passionately opined: "Medicine does not always have the luxury of waiting until the mountains of needed research on any given problem are completed centuries from now. We are tasked with treating real-world suffering today.…We must rise to a level of comfort with an intervention in building our theory as to where it may help and where it may not, and then we go forth and practice medicine with such tools as we have to deploy" [20].

PHYSIOLOGICAL BENEFIT AND ADVANTAGES OF CANNABINOIDS VERSUS OPIOIDS

Although a detailed discussion of all the complex physiological benefits of cannabinoids is beyond the intent and scope of this article, we will provide a brief overview. All species of cannabis contain hundreds of distinct chemical moieties, of which at least 100 are known cannabinoids [7]. There also are noncannabinoid terpenoid compounds that also have health benefits [5,7]. CBD and CBN, both significantly modify the effects of THC, essentially "taming" it [21]. In addition to analgesia, cannabinoids also provide

muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, anxiolysis, and anticonvulsant effects, among other pharmacologic activities [1,7,21]. These major benefits over opioids are all accomplished without any known lethal dose [7,21]. Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels [22-24]. There are data that strongly indicate that neurons in the rostroventral medulla and periaqueductal gray substance are involved in the brain-mediated analgesic effects of cannabinoids [2]. There also are spinal mechanisms of analgesia, including cannabinergic inhibition of γ-aminobutyric acid, glycine, and glutamate release [25].

FINAL THOUGHTS

We do not claim that cannabis is the answer to everyone's ills. Yet, despite being hampered by legal restrictions, the available medical research on cannabis indicates that cannabis is effective in treating a number of problems commonly encountered in a typical physical medicine and rehabilitation practice. Many patients in that care setting may be on long-term opioids for chronic pain. However, they could potentially be treated with either cannabis alone or in combination with a much lower, safer dose of opioids. From a pharmacologic perspective, cannabinoids are considerably safer than opioids and have broad applicability in palliative care. Had cannabis not been removed from our pharmacopeia 7 decades ago and had remained available to treat chronic pain, potentially thousands of lives that have been lost to opioid toxicity could have been prevented [11]. As physiatrists, we should embrace the scientific process, which continues to document the therapeutic effects of cannabis. We must be willing to advocate for our patients who want to legitimately access a medicine that could potentially be very beneficial for them and is safer than other options, such as opioids. The user of medicinal cannabis should not be considered a criminal in any state [16]. The U.S. Drug Enforcement Administration and our legal system should be using science and logic as the basis of policy making rather than political or societal bias.

REFERENCES

1. Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. Clin J Pain 2013;29:162-171.
2. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: Safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005;76:1664-1669.
3. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medicinal cannabis in Washington State. J Opioid Manag 2009;5:257-286.
4. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. From 32 ounces to zero: A medical geographic study of dispensing a cultivated batch of "plum" cannabis flowers to medical marijuana patients in Washington State. J Psychoactive Drugs 2013;45:141-155.
5. Carter GT, Flanagan A, Earleywine M, Abrams DI, Aggarwal SK, Grinspoon L. Cannabis in palliative medicine: Improving care and reducing opioid-related morbidity. Am J Hosp Palliat Med 2011;28:297-303.
6. Carter GT, Abood ME, Aggarwal SK, Weiss MD. Cannabis and amyotrophic lateral sclerosis: practical and hypothetical applications, and a call for clinical trials. Am J Hosp Palliat Med 2010;27:347-356.
7. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Medicinal use of cannabis in the United States: Historical perspectives, current trends, and future directions. J Opioid Manag 2009;5:153-168.
8. Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. Medical marijuana: Rational guidelines for dosing. IDrugs 2004;7:464-470.
9. Abrams DI, Vizoso HP, Shade SB, Jay C, Kelly ME, Benowitz NL. Vaporization as a smokeless cannabis delivery system: A pilot study. Clin Pharmacol Ther 2007;82:572-578.
10. Wilsey B, Marcotte T, Deutsch R, Gouaux B, Sakai S, Donaghe H. Low-dose vaporized cannabis significantly improves neuropathic pain. J Pain 2013;14:136-148.
11. Carter GT. The argument for medical marijuana for the treatment of chronic pain. Pain Med 2013;14:800.
12. Aggarwal SK, Kyashna-Tocha M, Carter GT. Dosing medical marijuana: Rational guidelines on trial in Washington State. MedGenMed 2007;9:52.
13. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Distress, coping, and drug law enforcement in a series of medical cannabis patients. J Nerv Ment Dis 2013;201:292-303.
14. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Prospectively surveying health-related quality of life and symptom relief in a lot-based sample of medical cannabis-using patients in urban Washington State reveals managed chronic illness and debility. Am J Hospice Palliat Care 2013;30:523-531.
15. Aggarwal SK, Carter GT, Zumbrunnen C, Morrill R, Sullivan M, Mayer JD. Psychoactive substances and the political ecology of mental distress. Harm Reduct J 2012;9:4.
16. Aggarwal S, Carter GT, Steinborn J. Clearing the air: What the latest Supreme Court decision regarding medical marijuana really means. Am J Hosp Palliat Care 2005;22:327-329.
17. Patterson R. The virtual Dr. Osler. CMAJ 1999;161:7.
18. Pelner L. Long road to nirvana. Dissertation on marijuana. N Y State J Med 1967;67:952-956.
19. Mattison JB. *Cannabis indica* as an anodyne and hypnotic. St Louis Med Surg J 1891;56:265-271.
20. Vox F, Capron AM, Kraus MF, Alexander GC, Kirschner KL. Balancing burdens and benefits: Ethical issues of off-label prescription pharmaceutical use. PM R 2013;5:882-889.
21. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 2011;163:1344-1364.
22. McAllister SD, Hurst DP, Barnett-Norris J, Lynch D, Reggio PH, Abood ME. Structural mimicry in class A G protein-coupled receptor rotamer toggle switches: The importance of the interaction in cannabinoid CB1 receptor activation. J Biol Chem 2004;279:48024-48037.
23. Burstein SH, Zurier RB. Cannabinoids, endocannabinoids, and related analogs in inflammation. AAPS J 2009;11:109-119.
24. Lichtman AH, Cook SA, Martin BR. Investigation of brain sites mediating cannabinoid-induced antinociception in rats: Evidence supporting periaqueductal gray involvement. J Pharmacol Exp Ther 1996;276:585-593.
25. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesic circuit activated by cannabinoids. Nature 1998;395:381-383.

Sanjog Pangarkar, MD, Mark Miedema, MD, and Bianca Tribuzio, DO, Respond

We agree that all available treatment options to manage her pain should be discussed with the patient who has failed back surgical syndrome. The treatments ideally should be holistic, evidence based, and comprehensive, all while acknowledging that likely no single treatment or therapy will offer a patient with complicated chronic pain complete relief. Rather, the goal for this patient would be to provide multimodal therapies, including cognitive behavioral treatments that address not only the physical aspects of pain but also the psychological aspects. Medical cannabis is now marketed as a novel treatment for pain. However, there are limited and inconsistent scientific data to support this claim. Presently, neither of the 2 FDA-approved prescription cannabinoids are indicated for pain relief. Instead, they are recommended for nausea related to chemotherapy and AIDS-related anorexia. A review published in 2006 by Amar [1] concluded the effects of synthetic cannabinoids on analgesia to be equivocal and found no controlled studies that evaluated smoked cannabis for the treatment of pain. The studies reviewed showed a mixed response to both nociceptive and neuropathic pain, with the most common adverse effects being drowsiness and dizziness [1,2]. An updated review in 2013 showed benefits in pain relief with smoked marijuana when compared with placebo, but conclusions were limited by small sample sizes, variable dosing of THC, adverse effects experienced by patients, and difficulty with blinding [2].

By contrast, medications that are approved by the FDA undergo meticulous testing to confirm bioequivalence, safety, and effectiveness. Cannabis has not gone through the same rigorous process, and there currently are no standards for quality, efficacy, dosing, or monitoring of adverse effects. There also is no recall available if public health concerns arise. A recent case in point is the fungal meningitis outbreak related to contaminated methylprednisolone used in epidural steroid injections. The FDA and U.S. Centers for Disease Control and Prevention were able to trace infected lots quickly through routine channels, which reduced morbidity and mortality [3]. Cannabis does not lend itself easily to this practice because of unclear provenance, legality issues, and variable suppliers. In addition, the lack of quality control and standardization could pose a challenge to public health should a similar concern arise.

Moreover, because of the lack of public health infrastructure to monitor the quality of cannabis, patients can unknowingly be exposed to contaminants such as molds and pesticides [4,5]. These contaminants, particularly fungal spores, are most concerning when exposed to patients who are immunocompromised [6]. Heather Miller Coyle, PhD, a botanist at the University of New Haven, has ongoing research about the contaminants in cannabis. Her laboratory uses DNA profiling and analysis that has demonstrated mold, mildew, and bacteria on cannabis plants [4]. There also are a variety of pesticides used when growing cannabis, with the amount absorbed by the individual varying based on heating method and inhalation amount. A study recently published in the *Journal of Toxicology* demonstrated that the common pesticides found on cannabis are transferred to the user when cannabis is inhaled [5].

Aside from the possible contaminants added to cannabis, the route of administration may also have an adverse effect on the patient. The most common route of administration is smoking. Inhaled cannabis smoke has a range of hazardous effects similar to tobacco smoke, including increased sputum production, dyspnea, bronchial irritation, and carcinogenic effects [7]. A filter may or may not be involved, depending on the method of inhalation. In addition, there usually is a longer, deeper inhalation associated with cannabis smoking, which increases the amount of inhaled tar by 3-fold [8]. Similar to long-term tobacco smoking, prolonged cannabis smoking is associated with symptoms similar to chronic obstructive pulmonary disease [7]. Although there is not a clear causal relationship between smoking cannabis and the development of lung cancer [9], there have been relationships established with other types of cancer. For instance, cannabis use also has been linked to testicular germ cell tumors. In a recent population-based, case-control study by Lacson et al [10], 163 male patients diagnosed with testicular germ cell tumors were matched with 292 controls. Cannabis use was associated with a 2-fold increased risk of developing nonseminomatous and mixed testicular germ cell tumors than with controls [10].

In terms of M.J., the physician is rightfully concerned about the psychotomimetic effects of opioids but should also be aware of the neurocognitive and psychological effects of cannabis. Results of many studies have shown a negative effect on reaction time, attention, learning, and working memory [11-13]. For instance, a retrospective study of 102 long-term users of cannabis demonstrated that chronic smokers recalled significantly fewer words on the Rey Auditory Verbal Learning Test and had impaired learning, retention, and retrieval of information compared with controls [11]. In addition, effects on executive function, including attention, decision making, and impulsivity, have also been demonstrated. These effects may linger beyond cannabis cessation [13], and the combination may reduce driving safety. One such study, that performed functional magnetic resonance imaging and measured motor skills after ingestion of cannabis, found that ingestion of cannabis decreased psychomotor skills and had a negative effect on cognition, attention, and saliency detection [14]. In fact, acute consumption was found to nearly double the risk of motor vehicle accidents that resulted in serious injury or death [15]. Psychological effects also may be present with

cannabis use, and analysis of the evidence suggests an association with psychosis. However, this association is more likely to exacerbate underlying psychotic disorders, for example, schizophrenia [16].

Finally, despite rapidly changing state laws, the federal government continues to label cannabis as a Schedule I substance. These substances are defined as drugs with no currently accepted medical use and a high potential for abuse. This poses hazards for both patient and physician alike. In *Gonzales v Raich* [17], the justices ruled that the federal government can arrest and prosecute patients and their suppliers even if the cannabis was permitted under state law. In *Conant v Walters* [18], the justices ruled that, although physicians could recommend marijuana under their First Amendment Rights, they violate federal law if they prescribe or dispense marijuana and may be charged with aiding and abetting.

To best assist M.J., the physician needs to provide safe and effective treatment options. Simply offering access to cannabis but not furnishing her with the proper information or monitoring does not benefit this or any other patient. Consequently, we cannot recommend the use of medical cannabis given its unclear safety profile, lack of evidence for treating nociceptive pain, imprecise dosing parameters, uncertain provenance, and possible contaminants. In addition, the psychomotor effects, psychological consequences, and potential legal ramifications make it less than suitable for a medical setting. Rather, we would recommend a multidisciplinary, multimodal approach that encompasses physical therapy and cognitive behavior therapy, and a focus on function.

REFERENCES

1. Amar MB. Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol 2006;105:1-25.
2. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy 2013;33:195-209.
3. Smith RM, Schaefer MK, Kainer MA, et al. Fungal infections associated with contaminated methylprednisolone injections. N Engl J Med 2013;369:1598-1609.
4. Collins D. University of New Haven researchers test marijuana for effects of contaminants. Huffingtonpost. Available at http://www.huffingtonpost.com/2013/12/01/university-of-new-haven-marijuana_n_4369402.html. Accessed December 1, 2013.
5. Sullivan N, Elzinga S, Raber JC. Determination of pesticide residues in cannabis smoke. J Toxicol 2013;2013:378168.
6. McPartland JM, Pruitt PL. Medical marijuana and its use by the immunocompromised. Altern Ther Health Med 1997;3:39-45.
7. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: Systematic review. Arch Intern Med 2007;167:221.
8. Wu TC, Tashkin DP, Djahed B, Rose JE. Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 1988;318:347.
9. Mehra R, Moore BA, Crothers K, Tetrault J, Fiellin DA. The association between marijuana smoking and lung cancer: A systematic review. Arch Intern Med 2006;166:1359.
10. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and nonseminoma risk. Cancer 2012;118:5374-5384.
11. Solowij M, Stephens RS, Roffman RA, et al. Cognitive functioning of long-term heavy cannabis users seeking treatment. JAMA 2002;287:1123.
12. Schweinsburg AD, Brown SA, Tapert SF. The influence of marijuana use on neurocognitive functioning in adolescents. Curr Drug Abuse Rev 2008;1:99-111.
13. Creen RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. J Addict Med 2011;5:1-8.
14. Battistella G, Fornari E, Thomas A, et al. Weed or wheel! fMRI, behavioural, toxicological investigations of how cannabis smoking affects skills necessary for driving. PLoS One 2013;8:e52545.
15. Asbridge M, Hayden JA, Cartwright JL. Acute cannabis consumption and motor vehicle collision risk: Systematic review of observational studies and meta-analysis. BMJ 2012;344:e536.
16. Pierre JM. Psychosis associated with medical marijuana: risk vs. benefits of medicinal cannabis use. Am J Psychiatry 2010;167:598-599.
17. *Gonzales v Raich*, 125 S. Ct. 2195, 2005.
18. *Conant v Walters*, (9th Cir 2002) 309 F.3d 629, cert denied Oct. 14, 2003.

Sunil K. Aggarwal, MD, PhD, and Gregory T. Carter, MD, MS, Rebut

Dr Pangarkar and colleagues raise some legitimate points, and we certainly agree that a holistic, biopsychosocial, multimodal evidence-based approach to these complex patients is most appropriate. However, we do take strong exception to the idea that medical cannabis is a novel treatment for pain [1-3]! There is reliable documentation that the cannabis plant was used as analgesic medicine more than 5000 years ago in China. In fact, cannabis is one of the 50 fundamental herbs of traditional Chinese medicine [1]. A 3000-year-old mummy of a shaman in a Chinese tomb was recently found with cannabis in an accompanying medicine pouch that still had active receptor binding properties [4]. Cannabis-based medicines were widely prescribed by U.S. physicians, and *Cannabis* was officially listed in the U.S. Pharmacopoeia from 1850-1942. Interestingly, a high-quality cannabis monograph was recently added to the nearly decade-old American Herbal Pharmacopoeia.

Dr Pangarkar and colleagues also cite outdated reviews such as Amar et al 2006 [5]. They do cite Borgelt et al [6], an updated nonsystematic narrative review from 2013 that did show benefits in pain relief with smoked marijuana compared with placebo, but, oddly, its scope did not include any of the published, large, multicenter positive-outcome RCTs that assessed oromucosally administered cannabis extracts for central pain, neuropathic pain, and allodynia [7-9]. We have provided much more timely and relevant references [7-14]. We agree that some trials are hampered by small sample sizes, variable dosing of THC, adverse effects experienced by patients, and difficulty with blinding, but this is due

to the considerable constraints that the U.S. federal government puts on research that uses cannabis. All medical cannabis studies done in the United States must be supported by the National Institute of Drug Abuse, which typically funds approximately $500,000 and requires that investigators use federally grown cannabis, which is of very poor quality and is provided as cigarettes. Randomly tested samples of this cannabis showed an average THC content of 6.34% ± 0.21% standard deviation [15]. Compare this with a leading California medical cannabis analytics laboratory that has reported that the average range of THC percentages found on testing of submitted samples to be in the teens [16].

As long as our U.S. federal government continues to hamstring cannabis research, our country will be left out of the enormous progress that is occurring by international pharmaceutical companies and health ministries. To help patients in our clinics and offices today, we should counsel patients on how to make the best of locally available medicinal cannabis and not avoid it all together because of federal missteps. It is incorrect to state that physicians are at risk for participating in such programs (by issuing recommendations, not official Schedule I drug "prescriptions"). The authoritative, nonpartisan Congressional Research Service noted in 2010 that "The federal government… may not initiate an investigation of a physician solely on the basis of a recommendation of marijuana within a bona fide doctor-patient relationship, unless the government in good faith believes that it has substantial evidence of criminal conduct" [17]. In addition, the U.S. Department of Justice has released federal guidelines that direct prosecutors not to target bona fide patients who use medical marijuana and state-licensed producers [18].

We are perplexed by Dr Pangarkar and colleagues' mention of the recent outbreak of fungal meningitis related to contaminated methylprednisolone used in epidural steroid injections because this would tend to illustrate the weakness of the FDA. Cannabis, without the intervention of the FDA, has a historically proven track record of safe medical use that dates back thousands of years. The arguments about mold, mildew, and bacteria on cannabis plants are overstated, as are the issues about smoking. *Aspergillus* is everywhere, and no one should smoke anything, including cannabis; smoking is not necessary to get a medical effect and benefit. We agree that the issue of pesticides is of some concern but, if growing cannabis were legitimized and taken out of hiding, as is happening in many state programs, then appropriate, safe supplies could be used.

Dr Pangarkar cites a study by Lacson et al [19], in which cannabis use was associated with certain forms of testicular cancer, but this study had serious limitations, which call into question any causality claims. For example, investigators were unable to demonstrate dose-dependency of effect. Cannabis researcher Donald Abrams, MD, chief of hematology-oncology at San Francisco General Hospital, stated in response to this study, "Young men use cannabis and get cancer. If they looked at video games and riding bicycles, that might also be associated. Is there an epidemic of testicular cancer in Jamaica where Rastafarians use cannabis religiously? I think that's all a trick of numbers, personally" [20]. Similarly, studies that Dr Pangarkar cites related to "neurocognitive and psychological effects of cannabis" are seriously confounded by the fact that chronic users studied all consumed under an environment of significant prohibition in which serious consequences to freedom and livelihood could result from discovered cannabis use. Such exposure to chronic psychosocial stress in itself can have neurocognitive effects and frankly do not apply to use in a medical system increasingly accepted in the mainstream. That being said, patients should be advised not to drive motor vehicles or operate heavy machinery if they are at all impaired.

What are some of the specific physiological benefits and advantages of cannabis versus opioids? All species of cannabis contain hundreds of distinct chemical moieties, of which there are at least 100 known cannabinoids. There also are noncannabinoid terpenoid compounds, which also have health benefits. Cannabinoids such as CBD and other terpenoids significantly modify the effects of THC, essentially "taming" it [21]. In addition to analgesia, cannabinoids also provide muscle relaxation, anti-inflammatory effects, neuroprotection in ischemia and hypoxia, enhanced well-being, anxiolysis, and anticonvulsant effects, among other pharmacologic activities [10]. These major benefits instead of opioids are all accomplished without any known lethal dose [21]. Potential analgesic sites of action for cannabinoids have been identified at brain, spinal cord, and peripheral levels [22-25]. There are strong data that indicate that descending pain modulation pathway neurons in the rostroventral medulla and periaqueductal gray substance are involved in the brain-mediated analgesic effects of cannabinoids [24]. There also are spinal mechanisms of analgesia, including cannabinergic inhibition of γ-aminobutyric acid, glycine, and glutamate release [25].

Again, we emphasize that we are not claiming that cannabis is a cure all for everything that ails humanity. We do claim, however, that cannabis is a reasonably safe and effective medicine to use in treating chronic pain and may be a considerably better option than opioids. As physiatrists, we are the "quality of life specialty" and, as a whole, we are known for embracing therapies that are not necessarily widely embraced by the general medical community. Here we offer you evidence of a very old medicine that is once again new. Embrace it!

REFERENCES

1. Touw M. Religious and medicinal uses of cannabis in China, India and Tibet. J Psychoactive Drugs 1981;13:23-34.
2. Butrica JL. Medical use of cannabis among the Greeks and Romans. J Cannabis Ther 2002;2:51-55.

3. Lozano I. Therapeutic use of *Cannabis sativa* (L.) in Arabic medicine. J Cannabis Ther 2001;1:63-65.
4. Russo EB, Jiang H, Li X, et al. Phytochemical and genetic analyses of ancient cannabis from Central Asia. J Exp Bot 2008;59:4171-4182.
5. Amar MB. Cannabinoids in medicine: A review of their therapeutic potential. J Ethnopharmacol 2006;105:1-25.
6. Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The pharmacologic and clinical effects of medical cannabis. Pharmacotherapy 2013;33:195-209.
7. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812-819.
8. Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. Pain 2007;133:210-220.
9. Serpell M, Ratcliffe S, Hovorka J, et al. A double-blind, randomized, placebo-controlled, parallel group study of THC/CBD spray in peripheral neuropathic pain treatment. Eur J Pain. 2014 Epub ahead of print.
10. Phillips TJ, Cherry CL, Cox S, Marshall SJ, Rice AS. Pharmacological treatment of painful HIV-associated sensory neuropathy: A systematic review and meta-analysis of randomised controlled trials. PLoS One 2010;5:e14433.
11. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: A randomized placebo-controlled trial. Neurology 2007;68:515-521.
12. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: A randomized, crossover clinical trial. Neuropsychopharmacology 2009;34:672-680.
13. Martín-Sánchez E, Furukawa TA, Taylor J, Martin JL. Systematic review and meta-analysis of cannabis treatment for chronic pain. Pain Med 2009;10:1353-1368.
14. Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; A systematic review of randomized trials. Br J Clin Pharmacol 2011;72:735-744.
15. RTI International. Annual report on the production, analysis and distribution of cannabis and marijuana cigarettes. Research Triangle Park, NC. November 17, 2003. Available at http://medicalmarijuana.procon.org/sourcefiles/RTI.pdf. Accessed March 16, 2014.
16. Raber J. Medical Cannabis Quality Control in California: Keeping a Weed Free Garden. Humboldt Institute for Interdisciplinary Marijuana Research. Annual Speaker Series. November 19, 2013. Available at http://humboldt-dspace.calstate.edu/bitstream/handle/2148/1628/HIIMR_Raber_video.html?sequence=5. Accessed March 16, 2014.
17. Eddy M. Medical Marijuana: Review and Analysis of Federal and State Policies. Congressional Research Service, RL33211. April 20, 2010. Washington, DC: Library of Congress. Available at https://www.fas.org/sgp/crs/misc/RL33211.pdf. Accessed March 16, 2014.
18. Cole J. Memorandum for all United States Attorneys: Guidance Regarding Marijuana Enforcement. August 29, 2013. Available at http://www.justice.gov/iso/opa/resources/305201382913275685746 7.pdf. Accessed March 16, 2014.
19. Lacson JC, Carroll JD, Tuazon E, Castelao EJ, Bernstein L, Cortessis VK. Population-based case-control study of recreational drug use and testis cancer risk confirms an association between marijuana use and non-seminoma risk. Cancer 2012;118:5374-5384.
20. Colliver V. Findings inspire medical pot researcher. San Francisco Chronicle September 18, 2012 Available at http://www.sfgate.com/default/article/Findings-inspire-medical-pot-researcher-3875582.php. Accessed March 16, 2014.
21. Russo EB. Taming THC: Potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. Br J Pharmacol 2011;163:1344-1364.
22. Walker J, Huang S. Cannabinoid analgesia. Pharmacol Ther 2002;95:127-135.
23. Meng ID, Manning BH, Martin WJ, Fields HL. An analgesic circuit activated by cannabinoids. Nature 1998;395:381-383.
24. Maione S, Bisogno T, de Novellis V, et al. Elevation of endocannabinoid levels in the ventrolateral periaqueductal grey through inhibition of fatty acid amide hydrolase affects descending nociceptive pathways via both cannabinoid receptor type 1 and transient receptor potential vanilloid type-1 receptors. J Pharmacol Exp Ther 2006;316:969-982.
25. Hohmann AG. Spinal and peripheral mechanisms of cannabinoid antinociception: Behavioral, neurophysiological and neuroanatomical perspectives. Chem Phys Lipids 2002;121:173-190.

Sanjog Pangarkar, MD, Mark Miedema, MD, and Bianca Tribuzio, DO, Rebut

Understanding the biology of pain conditions and how best to treat them continues to challenge the medical community. As issues of opioid abuse, diversion, and misuse continue to rise, physicians are faced with the difficult task of alleviating pain in a safe and effective manner. As such, the promotion of substances, for example, cannabis, has been encouraged as a potential solution to relieve suffering. Yet, in our review of the medical literature, we were unable to find any spine or pain society that actively incorporates cannabis into its treatment guidelines. In fact, The American Academy of Pain Medicine Chronic Pain Treatment Guidelines (2009) recommends against cannabis use for pain [1]. The cause for this is multifactorial and related to a lack of rigorous, controlled trials, the psychoactive effects of THC, and the effects on cognitive performance. In addition, cannabis continues to be listed as a Schedule I substance, which cannot be legally prescribed by a physician. It also implies that cannabis has a high potential for abuse, no currently accepted medical use, and a lack of safety data (*United States Code, 2006 Edition, Supplement 5, Title 21 - FOOD AND DRUGS*).

Although we applaud and encourage the efforts of the pro-cannabis investigators to bring rigorous science and healthy debate to the conversation, we respectfully disagree with the conclusions they have drawn. In their article, the authors provide an extensive history and framework on the topic of cannabis but fail to provide adequate evidence for use of this substance in this patient with failed back surgery syndrome. They admit "there are no RCTs for cannabis in failed back surgery syndrome" [2] and offer a 2009 retrospective chart review of 4 patients followed up in a pain clinic. These patients carried the failed back surgery syndrome diagnosis, but 2 patients were receiving concurrent morphine sulfate, one had been incarcerated due to issues with cannabis and another had a diagnosis of opioid addiction. From this chart review of 4 patients, it would be difficult to generalize any benefit perceived to the greater population.

In addition, the pro-cannabis investigators presented a recent publication from *The Clinical Journal of Pain* that reviewed 38 cannabis-related RCTs and concluded that "71% demonstrated a positive outcome for analgesia" [3]. What the pro-cannabis investigators did not highlight was the admonition contained in the discussions section, stating, "Little data are available on the risks associated with long-term medical use in published clinical trials" [3]. The article further clarifies that a "focused PubMed search was only targeted at determining the percentage of RCTs indexed in the National Library of Medicine showing efficacy of cannabinergic medications for pain and did not fully evaluate the pros and cons of each study" [3]. Without careful review of the content, accuracy, and validity of each RCT, the conclusions drawn by the investigators may be inaccurate.

Furthermore, the investigators present a 630 patient RCT [4] on the use of cannabis in patients with multiple sclerosis. The primary endpoint of this study was a reduced Ashworth score and not pain relief. On a series of 9 category-rating scales, pain relief being one of them, statistical significance was reached in the THC and cannabis extract groups. The investigators clarify, "Our results should be considered in the context of a degree of patient unmasking in the active treatment groups" [4], which means that the patients were aware they were receiving active drug, which may have influenced the data. Also, most patients in the active treatment group did not reach their target drug dose because of adverse effects, which included dizziness, light headedness, dry mouth, constipation, diarrhea, and increased appetite. Many of these adverse effects may be problematic in patients with a history of spine surgery and unnecessarily lead to motor difficulties, fall risk, and weight gain.

There are other problematic issues with cannabis for the treatment of pain disorders. To use cannabis as a medication, the health care provider must be able to prescribe the route of delivery, the particular dose to be prescribed, and the frequency of use. These prescription details have not been standardized with regard to treatment with cannabis or the various strains available. A similar analogy would be providing patients with a β-blocker for treatment of hypertension and having them self-titrate the medication as they feel necessary for symptom occurrence. As can be imagined, the lack of prescribing details may be unsafe in clinical practice. Despite the lack of clear evidence to promote cannabis for medical use, the shift in public opinion may lead to changes within state and/or federal laws. As such, we encourage rehabilitation physicians to be aware of the limitations and precautions associated with this substance. We also would advocate for our physical medicine and rehabilitation society to be involved in the development of evidence-based guidelines for management of pain in patients with disabling conditions.

REFERENCES

1. California Code of Regulations, Title 8, Section 9792.20-9792.26, Medical Treatment Utilization Schedule. Division of Worker's Compensation. Chronic Pain Medical Treatment Guideline. July 2009, 1-127.
2. Aggarwal SK, Carter GT, Sullivan MD, Morrill R, ZumBrunnen C, Mayer JD. Characteristics of patients with chronic pain accessing treatment with medicinal cannabis in Washington State. J Opioid Manag 2009;5:257-286.
3. Aggarwal SK. Cannabinergic pain medicine: A concise clinical primer and survey of randomized-controlled trial results. Clin J Pain 2013;29:162-171.
4. Zajicek JP, Sanders HP, Wright DE, et al. Cannabinoids in multiple sclerosis (CAMS) study: Safety and efficacy data for 12 months follow up. J Neurol Neurosurg Psychiatry 2005;76:1664-1669.

Web Poll Question

For the case scenario presented herein, is medical marijuana a viable option for pain control?

a. viable option
b. uncontrolled narcotic

To cast your vote, visit www.pmrjournal.org

Results of January's Web Poll

For the case scenario presented in Do Physiatric Procedures Represent a Value or Liability? would elimination of reimbursement for procedures represent a threat or an opportunity for PM&R?

62% - threat
38% - opportunity