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The Medicinal Cannabis Treatment Agreement: Providing Information to Chronic Pain Patients via a Written Document

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Abstract

Over 20 states now approve medical marijuana for a long list of "indications," and more states may well offer access in the near future. Surveys have demonstrated that pain is the most common indication for medical use of cannabis. As more individuals gain access to this botanical product through state ballot initiatives and legislative mandate, the pain specialist is likely to be confronted by patients either seeking such treatment where permitted, or otherwise inquiring about its potential benefits and harms, and alternative pharmaceuticals containing cannabinoids. Whether or not they are in the position to prescribe medical cannabis, pain physicians would seem to have an obligation to understand and inform their patients on key issues of the evidence base on cannabinoid therapeutics. One way to fulfill this obligation might be to borrow from concepts developed in the prescription of opioids: the use of a written agreement to describe and minimize risks. Regrettably, the widespread adoption of opioids was undertaken while harmful effects were minimized; obviously, no one wants to repeat this misstep. This article describes a method of educating patients in a manner analogous to other treatment agreements. Undoubtedly, the knowledge base concerning risks will be an iterative process as we learn more about the long-term use of medicinal cannabis. But we should start the process now so that patients may be instructed about our current conception of what the use of medicinal cannabis entails.

INTRODUCTION

When prescribing opioid therapy, written informed consent via treatment agreements are implemented to minimize abuse liability. (1) These agreements commonly specify that one prescribing physician will provide the opioids, with subsequent follow-up of efficacy,

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adverse events, and functional status. A corollary to the one physician rule is that controlled substance prescriptions should be filled at the same pharmacy. In addition, random urine drug screens and state prescription drug monitoring reports may be alluded to in the agreement. They are designed to help determine if the patient is taking other substances and to monitor the patient's medication use patterns. (2) A drug screen may provide the first indication that a patient is using cannabis. Subsequently, a confrontation between the clinician and patient may ensue as to whether or not opioids should be continued concurrently with cannabis. This is probably not an uncommon event; the prevalence of cannabis use among patients prescribed chronic opioid therapy ranges from 6.2% to 39%; compared with 5.8% in the general population. (3)

Despite the potential for negative consequences, there is also support for the use of medical cannabis as an adjunct to or substitute for prescription opioids in the treatment of chronic pain in both the preclinical (4,5) and clinical (6-9) literature. In a recent interactive web-based poll, physicians in favor of medicinal cannabis often emphasized their responsibility as caregivers to alleviate suffering. (10) Many pointed out the known hazards of prescription opioids, supported patient choice, or described personal experience with patients who were helped by the use of cannabis. Those who opposed medicinal cannabis spoke of the lack of evidence regarding treatment efficacy, the absence of an identified mechanism of action, inconsistency regarding dosage and THC levels in privately sold products, and concern about side effects, including psychosis. A common theme in this debate was the issue of whether cannabis even belonged within the purview of physicians or whether it should be legalized and patients be permitted to decide for themselves whether or not to use it as a medicine. This laissez faire approach is not implausible. In 2012, ballot measures approved by voters in Colorado and Washington led to the most liberal cannabis laws in the nation. They permit citizens to use this psychotropic agent for recreational purposes, while stipulating legislative participation in establishing regulations for its commercialization analogous to that for alcohol. (11) However, if we assume that physicians may be placed in a position to advise on cannabis as a medicine, it is important that patients be provided with information regarding benefits, risks, and responsible medicinal use. (12-15) This can be accomplished through dialogue during a clinic visit, and if the physician elects, a written treatment agreement.

MATERIALS AND METHODS

The material presented was drawn from influential sources of current and past medical literature, including a published guideline to avoid harm from recreational cannabis. (13) PubMed searches were conducted using the following keywords: cannabis guidelines, harmful effects of cannabis, medical marijuana, medicinal cannabis, opioid cannabis interaction, cannabis dependence and cannabis abuse. The authors selected individual tenets a medicinal cannabis patient would be asked to review and acknowledge via signature. The intent would be to provide information and, potentially, minimize adverse effects. The precepts of the agreement are enumerated in Appendix 1. The rationale of each tenet (i.e., principle) is presented sequentially in the Results Section.

RESULTS

Tenet #1 I must prevent children and adolescents from gaining access to medicinal cannabis because of potential harm to their well-being. I will store cannabis in locked cabinets to prevent anyone else from using it.

Cannabis is one of the most widely used illicit drugs among adolescents. (16) Almost half of adolescents in one substance abuse treatment setting reported obtaining cannabis from someone with a medicinal cannabis license. (17) In another program, almost three quarters of the adolescents diverted medicinal cannabis a median of 50 times. (18)

Adolescence is known to be a critical phase for brain development, during which time neuronal rearrangement processes occur (e.g., myelination and synaptic pruning). Changes in endocannabinoid activity induced by cannabis can lead to subtle but lasting neurobiological changes that can affect brain functions and behavior. (16) Preclinical data seems to support the presence of deficits as well as psychotic-like signs in adult rodents after exposure to cannabinoids in their “adolescence”, suggesting that this exposure may trigger a complex behavioral phenotype closely resembling a schizophrenia-like disorder. (19) In humans, the available data suggests that adolescent cannabis exposure induces significant protracted effects suggestive of enhanced vulnerability to addiction and psychiatric disorders in later life, in certain subsets of individuals. (20) Several longitudinal cohort studies have shown a statistical association between psychotic illness and self-reported cannabis use. However, these results are difficult to interpret due to methodological problems, particularly the unknown reliability of self-reported data, and the difficulty of disentangling cause and effect (e.g., is earlier onset of cannabis use a symptom of underlying psychiatric disorders, rather than their cause). (21) Thus, it has not been possible to establish a causal relationship of cannabis to schizophrenia, because of these methodological limitations. Whether or not cannabis causes long term physiological harm to adolescents, it is clear that youth who are intoxicated are less likely to learn in an optimal manner, and that those who are under the influence of cannabis have problems with memory, attention, and psychomotor performance. Furthermore, they may refocus their energies from desired scholastic, athletic, and interpersonal pursuits, and thus impair psychosocial maturation.

Another risk to adolescents is a general reduced level of function, the so-called amotivational syndrome, characterized by a state of apathy. (22) Complicating the picture is the fact that the cannabis available to the current generation of adolescents is more potent, with higher levels of THC, the psychoactive component in cannabis. This information is derived from the Potency Monitoring Program, which provides analytical data on cannabis preparations confiscated in the United States. (23) The data show an upward trend in the mean THC content of all confiscated cannabis preparations, increasing from 3.4% in 1993 to 8.8% in 2008.

Therefore Tenet #1 needs to be a cornerstone of any Cannabis Written Agreement.

Tenet #2 I know that some people cannot control their use of cannabis. One example is using cannabis for reasons other than for the indication for which it was prescribed; like

getting stoned. This may lead to not going to work, or not doing my household chores. I agree to discuss this with my doctor if this happens.

Cannabis poses less addictive risk than many other substances. It has been estimated that 32% of tobacco users, 23% of heroin users, 17% of cocaine users, 15% of alcohol users and 9% of cannabis users become addicted. (24) Though cannabis might be less dangerous, addiction to this substance represents a significant health concern. In 2010, it was the most widely used illicit substance in the United States. (25) Presumably related to this ranking, the number of individuals with a diagnosis of dependence or abuse of an illicit drug in the past 12 months was highest for cannabis (4.5 million). The magnitude of the problem was greater than the combined total for prescription opioids (1.9 million), and cocaine (1.0 million). (25) Therefore, special precautions should be taken by physicians to a) identify patients with substance use problems before recommending medicinal cannabis; b) in cases where addiction is a concern, be certain to articulate any recommendation for medicinal cannabis with expert evaluation and treatment for substance abuse disorders. An example of a decision path is presented in Figure 1.

The evolving use of cannabis for medicinal purposes has contributed to diminishing the perceived risk and increased acceptability of cannabis as a safe agent. (26) Full legalization, as is being implemented in Washington and Colorado, could increase non-medicinal cannabis use and thereby increase the incidence of cannabis substance use disorder. By way of precedent, the increased availability of opioids for the treatment of chronic pain occurred without adequate prospective studies concerning the long-term risks or optimal structure of treatment. (27) The regrettable lesson learned from the effort to improve outcomes for patients with pain was that the potential for opioid misuse and abuse is high, as in the possibility of diversion to vulnerable individuals. Whether such trends will develop as both medicinal and non-medicinal cannabis become more legitimized remains to be seen.

Tenet #3 I realize that unless specifically recommended by my doctor, I should abstain from medicinal cannabis if:

- **a.** I am pregnant or am of child-bearing age
- **b.** I am middle-aged or older and have a heart disease or heart rhythm problem
- **c.** I have a history of serious mental illness (e.g., schizophrenia, mania, or a history of hallucinations or delusions)

As with all medications, the benefits and risks need to be weighed when recommending cannabis to patients. (28) The following conditions present relative contraindications (13):

Pregnancy

Two extended longitudinal cohort studies, the Ottawa Prenatal Prospective Study and the Maternal Health Practices and Child Development Study, have measured the cognitive functions of children born from mothers who consumed Cannabis sativa preparations during pregnancy. (29-35) These studies showed the consequences of prenatal exposure to cannabis are rather subtle. Immediately after birth, there was little evidence of an effect either upon growth or behavior. (36) However, beyond 3 years of age, there were findings suggesting an

association between prenatal cannabis exposure and aspects of cognitive behavior that fall in the domain of executive functions. For instance, exposure to one or more cannabis joints per day during the first trimester was associated with deficits in reading and spelling scores and a lower rating on the teachers' evaluations of the children's performance. (37) Similarly, second-trimester cannabis use was associated with reading comprehension underachievement.

Developmental exposure to cannabinoids induces changes in central nervous system patterning in structures relevant for mood. (38) Human studies have demonstrated that prenatal exposure to cannabis predicts levels of self-reported anxiety and depressive symptoms in 10 year old children. (30,37,39) The long-term consequences of in-utero cannabis exposure on the emotional reactivity of the offspring is also supported by preclinical studies. In experimental animals, even low to moderate doses of cannabinoids, when administered during particular periods of brain development, can have profound consequences for brain maturation, leading to long-lasting alterations of cognitive functions and emotional behaviors. (38) Although the human data on intrauterine exposure are not conclusive, and extrapolation from animal models can be problematic, it would be optimal to avoid medicinal cannabis during pregnancy. However, if a pregnant woman needs neuropharmacologic management, we need also to be mindful that other medications, including antidepressants, neuroleptics, and various potent analgesics may also have unknown impacts on the fetus; it is therefore possible that in some select circumstances medicinal cannabis might be deemed safer than its alternatives.

Psychosis

A history of cannabis misuse is common in patients who have schizophrenia; 25% of patients with schizophrenia have a comorbid cannabis use disorder. Cannabis use disorders are very common in first-episode schizophrenic samples and in samples with high proportions of males. (40) Patients commonly report that their reasons for cannabis use are relief of dysphoria and improved ability to socialize.

The extent to which cannabis use might alter the clinical course of schizophrenia remains a point of contention within the literature. A study associated daily cannabis use with an increased risk of psychosis by a factor of 1.6-1.8, and suggested that cannabis causes psychosis in this relationship. (41) However, others offer the opposite direction of causality, and believe cannabis use appears to be neither a sufficient nor a necessary cause for psychosis. Rather, it is a component cause, part of a complex constellation of factors leading to psychosis. (42)

Many researchers at least partially attribute the correlation between cannabis use and mental illness to self-medication. Indeed, as many as 60% of the mentally ill are suspected to be substance abusers, and many seem to prefer cannabis and alcohol. (43) Others point out that the hypothesis that cannabis causes schizophrenia is not supported by the data on trends in the incidence of this psychosis. (44) The argument is that if cannabis is causally related to schizophrenia, then initiation of widespread exposure to cannabis that began in the late 1960s in industrialized societies should have been reflected in rise in schizophrenia rates in these societies some decades later. However, there is no evidence for such global rise. The

more salient point, however, is that those with severe mental illnesses could experience worsening; for this reason any decision to recommend medicinal cannabis to a person with a major mental illness must be done cautiously, and in close coordination with expert psychiatric services.

Coronary Heart Disease

Cannabis can result in a rapid and substantial dose-dependent increase in heart rate by as much as 20–100%, as well as supine hypertension and orthostatic hypotension. (45,46) Such hemodynamic responses are believed to be mediated through sympathetic stimulation and reduced parasympathetic activity, with the maximal increase generally seen within 15 min after a peak plasma THC concentration. Cannabis can be associated with frequent premature ventricular beats, sinus tachycardia, atrial fibrillation and more significant cardiac arrhythmias. (47-53)

The hemodynamic effects of cannabis are generally not problematic for most young, healthy users. In middle-aged users, the cardiovascular risk of cannabis is less benign. In a case-crossover study, the risk of myocardial infarction was 4.8 times higher in the hour after cannabis use than at baseline. Furthermore, middle-aged users increase their annual absolute risk of a cardiovascular event by 1.5%-3%. (46) Occasionally, the orthostatic hypotension induced by cannabis can be symptomatic and incapacitating. (48)

There appears to be little public awareness of the vulnerability of patients with cardiovascular disease to the effects of cannabis. Although a rare trigger of myocardial infarction, patients with coronary artery disease should be warned that medicinal cannabis may aggravate ischemia. (49)

Tenet #4 In order to reduce the risk of lung disease, I will avoid smoking medicinal cannabis with tobacco; avoid deep inhalation or breath-holding; and use a vaporizer rather than smoke joints or use a water pipe.

Acute inhalation of cannabis produces bronchodilation, but chronic use is associated with central airway inflammation and increased large airway resistance to airflow. Cannabis increases cough, sputum production, hyperinflation, and upper lobe emphysematous changes. (54,55) Although regular cannabis smoking leads to bronchial epithelial ciliary loss and impairs the microbicidal function of alveolar macrophages, evidence is inconclusive regarding possible associated risks for lower respiratory tract infection. (56) Nor do changes in pulmonary function testing occur with low levels of cannabis use. The latter is defined as 7 joint-years of life (with 1 joint-year equivalent to 365 joints or filled pipe bowels). With increasing levels of exposure (more than 10 joint-years of lifetime exposure), FEV1 declined but was not statistically significantly different from baseline in a cohort over a 20-year time period. (57) These findings are consistent with the opinion that cannabis does not hasten the development of chronic obstructive pulmonary disease. (57,58)

There are several reports of emphysematous bullous disease in heavy cannabis smokers. The majority of the disease is seen on computed tomography (CT) in the upper lobes. Despite CT findings, pulmonary function testing and chest radiographs in these patients tend to be

normal. (59) The clinical relevance of the hyperinflation is uncertain. (55) Several case reports have implicated cannabis smoking as an etiologic factor in pneumothorax and pneumomediastinum, although evidence of a possible causal link from epidemiologic studies is lacking. (56)

Although cannabis smoke contains a number of carcinogens, findings from a limited number of well-designed epidemiological studies do not suggest an increased risk for the development of either lung or upper airway cancer from light or moderate use, although evidence is mixed concerning possible carcinogenic risks of heavy, long-term use. (56) With regard to the latter finding, in one recent report "heavy" cannabis smoking (lifetime use of more than 50 times) was significantly associated with more than a twofold risk (hazard ratio 2.12, 95 % CI 1.08-4.14) of developing lung cancer over a 40-year follow-up period, even after statistical adjustment for baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status. (60)

The potential hazards of smoking has promoted a quest for alternative systems of administration. Oral synthetic THC is a legally marketed medication (dronabinol). While plasma concentrations may be variable due to inter-individual pharmacokinetic variation and first pass metabolism (i.e., in liver), dronabinol may offer a greater safety margin because of slower onset of action and lower potency. As an inhalational alternative to smoking, there are devices that vaporize cannabis by heating the plant product to below the temperature of combustion (175-225 degrees C), permitting inhalation of volatilized gases minus harmful pyrroles produced by incineration. This has a number of advantages over smoking cannabis, including formation of a smaller quantity of toxic by-products and a more efficient extraction of THC from the cannabis material. (61) Preliminary work using plant material with a range of THC content (e.g., 1% - 7% THC) suggests that there is rapid onset, with peak concentrations and six-hour area under the plasma concentration curves comparable to those achieved by smoking. (62) Vaporization is not a perfect solution since carbon monoxide is formed, but levels are significantly lower than with smoking. (62)

Tenet #5 I will not drive a car or operate heavy machinery for 3-4 hours after use of medicinal cannabis, or longer if large doses are used or the effects of impairment persist. I will use a designated driver for automobile transportation if I have to go out sooner than 3-4 hours after taking this medicine.

The role of medicinal cannabis in driver impairment and motor vehicle crashes has been scrutinized in experimental and epidemiological studies. In experimental studies involving driving simulation, detrimental effects of THC were more prominent in certain driving tasks than others. Highly automated behaviors, such as road tracking control, i.e., lane weaving, were more affected compared to more complex driving tasks requiring conscious control. (63) Combining cannabis with alcohol enhances impairment, especially lane weaving. (64) Although drivers attempt to compensate by driving more slowly after smoking cannabis, control deteriorates with increasing task complexity. (64) And while cannabis can impair skills required to drive motor vehicles in a dose-related fashion in driving simulation studies, epidemiological data are inconclusive with regard to the association of traffic accidents and use of cannabis. (65) Nonetheless, the National Safety Council (NSC) developed a position

paper and unequivocally stated that it is “unsafe to operate a vehicle or other complex equipment while under the influence of cannabis (marijuana), its primary psychoactive component, delta-9-tetrahydrocannabinol (THC) or synthetic cannabinoids with comparable cognitive and psychomotor effects, due to the increased risk of death or injury to the driver and the public”. (66)

Evidence suggests recent smoking and/or blood THC concentrations 2-5 ng/mL are associated with increased driving impairment, particularly in occasional smokers. (67) Performance impairment after THC is usually highest during the first hour after smoking and declined to baseline over 3–4 h after THC use. (63) This information has led to the recommendation that either the patient be advised to wait at least 3 hours after exposure of medicinal cannabis before operating a motor vehicle or use a designated driver to provide safe transit. (65)

Tenet #6 As the potency of cannabis varies widely I will use the minimum amount of medicinal cannabis needed to obtain relief from pain or other symptoms. When trying a new strain of cannabis, I will start with a very small amount and wait at least 10 minutes to see how it affects me.

Under Colorado's new recreational-cannabis law, all retail cannabis products will have to be labeled according to their potency starting in January 2014. (68) The labels are intended to inform consumers on the nature of the product they are buying, not unlike alcohol-content labels on beer or wine. Reputable dispensaries in other states have already instituted this service; for instance, the Harborside Health Center in Oakland, California lists products enabling patients to choose types of cannabis with various potencies and constituent cannabinoids. (69)

Human laboratory experiments in neuropathic pain patients have demonstrated that very low percentages of THC provide analgesia. In a recent study, cannabis grown under the supervision of the National Institute of Drug Abuse was studied using a placebo controlled cross-over design. Cannabis containing low dose (1.3%) THC was as effective as a sample containing a medium dose (3.5%) THC. (70) In a previous study performed by the same authors, the same cannabis containing medium dose (3.5% THC) was as effective as cannabis with a high dose (7.0% THC). (71) To place these concentrations into perspective, cannabis with a THC concentration below 1.0 percent is believed not to be capable of inducing a psychoactive effect. (72) By comparison, THC levels in samples of cannabis seized by law enforcement officials in 2008 averaged 10.1%. (73) On average, subjects in these human laboratory experiments experienced dose related drug effects from THC. Compared to placebo, psychomimetic effects were more evident with active study medication. In general, the effect sizes on cognitive testing were consistent with the minimal doses of Δ9-THC employed, with the greatest dose effects seen on learning and memory, where effect sizes compared to placebo were in the small to medium range (range 0.00 to −0.28 for 1.3% Δ9-THC). (70)

The implication of the above is that patients should be advised to use as low a dose as possible when using medicinal cannabis to bring about pain relief, or, for that matter,

amelioration of any disease. Whether or not they develop analgesic tolerance to low doses remains to be seen; long term clinical trials will be necessary to evaluate this phenomenon. Nonetheless, it is heartening that responders participating in an open label extension phase of a controlled trial of nabiximols (Sativex®) appeared to have maintained analgesia at one-year follow-up. (74)

Tenet #7 If thought advisable by my health care provider, I might want to substitute one of the Food and Drug Administration (FDA) approved medicines containing THC rather than take natural cannabis.

It is conceivable that one of the constituent cannabinoid molecules in cannabis, or some combination of them, will be therapeutically effective, and either more effective, safer, or just simpler to administer than the more variable mixture in herbal cannabis. (75) Pure THC is currently available as dronabinol (Marinol®), and is used as an appetite stimulant, anti-emetic, and analgesic. As a result of the rescheduling of Marinol from Schedule II to Schedule III in 1999, refills are now permitted for this substance. Interestingly in this regard, oral dronabinol has recently been found to have similar psychoactive effects to smoking marijuana. (76) Nabilone (Cesamet®), is a synthetic cannabinoid and an analog of dronabinol that is a Schedule II controlled substance. Many individuals will insist that the crude material is 'much better' than these FDA approved compounds. (77) As testament to this belief, dronabinol and nabilone have been on the market in the United States for many years and not widely used. Their chemical composition and oral delivery mechanism (1.5 – 2 hour delay in onset) are probably both disadvantages for most patients compared to inhaling the vapor of crude cannabis. At present, however, European and Canadian guidelines place nabilone as a second to fourth line drug for neuropathic pain. (78,79) Nabiximols, a liquid containing THC and cannabidiol (CBD) extracted from the cannabis plant (in roughly a 1:1 ratio), is designed for use as a nasal or mouth spray. At present, it is approved for use in the treatment of neuropathic pain and spasticity in over twenty countries including England, Canada and Spain. (80)

Although cannabis was commonly used in the US in the 19th century for a myriad of indications, it lost favor after President Roosevelt signed the Food and Drugs Act in 1906. This legislation was designed to regulate product labeling; drugs were to be defined in accordance with the standards of strength, quality, and purity. As it is easier to label pure compounds as opposed to plant materials, a decline in the use of prescribed cannabis followed. As a warning of the risk of allowing herbal medicines to be substituted for pharmacology, the history of the nutritional supplement industry, with its dearth of reliable information, stands as an example. (75) Still, it is entirely possible that the mixture of dozens of different cannabinoids in the natural plant might outperform any one or two or three cannabinoids in isolation. Witness the fact that the synthetic THCs, dronabinol and/or nabilone, have not been sought after by patients as replacements for the crude plant. (75) Yet we still do not have the answer as to whether cannabis or one or two cannabinoids in isolation would the most effective treatment with the lowest side effect profile. (75) We will need controlled trials comparing constituent molecules directly with crude cannabis to answer this question.

Tenet #8 I might notice a withdrawal syndrome for two weeks if I stop cannabis abruptly. Trouble getting to sleep and angry outbursts might require that I withdraw from the cannabis slowly.

A potential consequence of recurring medicinal cannabis intake is a withdrawal syndrome. Because the withdrawal symptoms are time-limited, occur shortly after cannabis cessation, and are ended by resuming cannabis use or administration of THC, they represent a true withdrawal syndrome. (81) The effects and symptoms observed during the abstinence period included anger and aggression, decreased appetite, irritability, nervousness, restlessness, shakiness, sleeping difficulty, stomach pain, strange dreams, sweating, and weight loss. (82) Onset of most symptoms occurs primarily on the first day of abstinence, and peak effects are observed between day 2 and day 6. Most symptoms return to baseline levels within two weeks.

Compared with alcohol or benzodiazepine withdrawals, cannabis withdrawal does not typically cause significant medical or psychiatric problems. Prominent side effects may include nightmares; but the ensuing strange dreams result in relatively little distress. On the other hand, trouble initiating sleep and angry outbursts are sometimes significant enough to warrant treatment. (83) The most successful demonstration of withdrawal suppression was observed in a clinical trial involving oral THC,10 mg administered five times daily. This dose significantly reduced ratings of anxiety, misery, sleeping difficulties, chills, and cannabis craving compared to placebo. (84)

Tenet #9 I understand that the course of treatment will have to be regularly re-evaluated after I start the medicinal cannabis

Existing pharmacologic treatments for all types of neuropathic pain, one of the most extensively studied chronic pain syndromes, are somewhat limited, with no more than 40–60% of patients obtaining even partial relief. (85) This is consistent with a substantial heterogeneity of treatment effects, implying significant variation across patients as to which treatment works best. Many pain therapies display this type of varied response. (86) When treatment variability is large, average effects may be misleading, calling for a more personalized approach that emphasizes individualized treatment effects. The expectation that medicinal cannabis will be universally effective is likely to be incorrect. Consequently, neuropathic pain patients, as well as those with other types of chronic pain, must be periodically re-evaluated and managed empirically over time.

Tenet #10 I will not use medicinal cannabis in public places unless the law specifically permits this.

Many state medicinal cannabis laws specify that they do not allow cannabis to be smoked in public or possessed in correctional facilities. (87) Two states have explicit language. Connecticut’s medicinal cannabis law prohibits ingesting plant material anywhere in public, in a workplace, in any moving vehicle, in the line of sight of a person under 18, or on any school or university grounds, including in dorm rooms. New Hampshire’s law stipulates that cannabis cannot be smoked or vaporized in a public place, including a public bus, any other public vehicle, a public park, a public beach, or a public field. These attempts to limit the

use of medicinal cannabis to locations behind closed doors are consistent with the intent of the US Department of Justice to prevent the distribution of cannabis to minors. (88)

Tenet #11 I know there is no legal precedent to help me if I am terminated from employment if a urine toxicology screen is positive for cannabis

Case law does not support an employer accommodating the medical use of cannabis in the workplace. In Ross v. Ragingwire, the California Supreme Court ruled that the law does not protect patients from firing for testing positive for metabolites. (89) It noted that the legislature could enact such protections. The legislature did so in 2008, passing AB 2279, but the bill was vetoed. Likewise, the Colorado Court of Appeals ruled against a medicinal cannabis patient who was denied unemployment after he was fired for testing positive for cannabis (Beinor v. Industrial Claim Appeals Office). (ibid) In April 2013, the Court also ruled against Brandon Coats, a paralyzed patient who sued his employer for terminating him for off-hours medicinal cannabis use. (ibid) In 2009, the Montana Supreme Court upheld the dismissal of a patient who tested positive for cannabis metabolites in Johnson v. Columbia Falls Aluminum. (ibid) In April 2010, the Oregon Supreme Court ruled in Emerald Steel v. BOLI that patients are not protected from being fired for testing positive for metabolites. (ibid) On Sept. 19, 2012, the federal appellate court for the sixth district ruled against sinus cancer survivor Joe Casias, who sued WalMart for terminating his employment for failing a drug test. (ibid) Other states and appellate courts have not posted rulings in this matter. Clearly this will be an evolving area of law, but at this time Tenet 11 represents a provident warning

Tenet # 12 I know that I may be asked to reduce or stop my intake of opioids (narcotics), sedative-hypnotics (benzodiazepines), and/or alcohol. This will be done to reduce the risk of side-effects from a combination of medications that affect the central nervous system.

Rather disconcerting, cannabis use in chronic opioid patients shows statistically significant associations with present and future aberrant opioid-related behaviors. (3) Such misuse would unambiguously be an indication to discontinue prescribing an opioid medication and recommend cessation of cannabis.

On the other hand, there are hints that opioids and cannabis can work synergistically. A sampling of 1,746 patients from a network of nine medicinal cannabis evaluation clinics in California found that the most common indications for cannabis were pain relief, spasms, headache, and anxiety, as well as to improve sleep and relaxation. (90) Half of those surveyed indicated that they used cannabis as a substitute for prescription medication, suggesting that medicinal cannabis may, in select instances, be exchanged for opioids and sedative-hypnotics.

In animal studies, there is confirmatory evidence that the interaction between cannabinoid and opioid receptors may result in enhanced analgesia in both chronic and acute pain models. (91-95) There is confirmatory evidence from a human laboratory experiment involving adjuvant cannabinoid therapy in individuals on opioids for chronic pain. (8) Over several days, participants inhaled vaporized cannabis while pain scores and serum levels of analgesics were obtained. Pharmacokinetic investigations revealed no significant change in

the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9%, 46%) after the addition of vaporized cannabis. The authors concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. It was posited by the authors that the combination may allow for opioid treatment at lower doses with fewer side effects. But this was not a controlled study. In the future, a randomized, placebo-controlled trial will be necessary to provide an evidence-based determination whether cannabis enhances the analgesic effects of opioids.

The contribution of the combined use of benzodiazepine and/or other sedative agents to opioid-related morbidity and mortality is underappreciated. (96) Patients with chronic pain who use opioid analgesics along with benzodiazepines and/or alcohol are at higher risk for fatal/nonfatal overdose and have more aberrant drug-seeking behaviors. (96) In such circumstances, the medical use of cannabis may contribute to improved patient safety.

There is also the potential of emphasizing alternative cannabinoids such as cannabidiol (CBD) a patient selects a category of crude cannabis. CBD is abundant compound in Cannabis sativa, constituting approximately 40% of the plant's active substances. (97,98) In an animal study, the effects of CBD were similar to those of FDA approved drugs to treat anxiety. (99) Congruently, CBD (600 mg) was shown to reduce apprehension in a placebo controlled social anxiety disorder human laboratory experiment that involved simulated public speaking. (100)

Sativex®, a whole plant cannabis extract with equal levels of CBD and Δ9-THC, is a sublingual spray produced by GW Pharmaceuticals. Experience to date in numerous studies demonstrate marked improvement in subjective sleep issues in patients with chronic pain. (101) No tolerance to the benefit of Sativex® on pain or sleep, nor need for dosage increases have been noted in safety extension studies of up to four years, wherein 40-50% of subjects attained good or very good sleep quality, a key source of debility in chronic pain patients. (101)

DISCUSSION

At this point in time, the liability and legal implications of a cannabis agreement are unknown. In the future, such issues may be decided by court cases, if and when litigation arises. However, we have experience with opioid agreements and, despite any legal issues they may engender, their acceptance in medical practice is well documented. (102-104) Although the efficacy of opioid agreements have yet to be proven, they have been endorsed by the Federation of State Medical Boards (105) and utilized in several treatment guidelines for chronic opioid therapy. (106) For instance, the Veterans Administration and Department of Defense commissioned an expert panel to perform a systematic review of the medical literature. In their evidence-based clinical practice guidelines published in 2010, they determined that opioid treatment agreements are a standard of care when prescribing chronic opioid therapy. (107)

Others have pointed out the negative aspects of agreements stating there is often too much focus on prohibited behaviors, associated risks, and abuse monitoring; setting a negative tone. (108) This may have an undesirable impact on the provider-patient relationship by conveying the provider's lack of trust and reducing the patient's autonomy. The controversial nature of medicinal cannabis makes this type of undesirable outcome even more likely. Although the authors have attempted to provide non-judgmental tenets, it is doubtful that an unbiased interpretation will always follow.

In clinical research, many subjects sign consent documents without understanding the study purpose, procedures, risks, benefits, and their rights. (109) In both research consents and patient-provider agreements, substantiation of understanding is not required and rarely obtained. There have been some investigations concerning improving the informed consent process in clinical trials that might be useful in the future to refine the medicinal cannabis agreement. The use of an interactive system with the option for viewing and reading the consent at a relaxed pace before or after the face-to-face interview is now being utilized with the use of a tablet based presentation. Combining an introductory audiovisual presentation, non-technical language, and an interactive quiz on a tablet- or internet based system might improve comprehension of a cannabis agreement as has been demonstrated with research consents. (109) For the present, however, we offer a paper version for use by the clinician interested in providing edifying material to patients concerning medicinal cannabis.

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Appendix 1 Medicinal Cannabis Agreement (modified from Lower Risk Cannabis Use Guidelines for Canada: A Narrative Review of Evidence and Recommendations (13))

Date: _____

I understand that _____(clinician name) is helping me with the treatment of my chronic pain.

In considering the possibility of using medicinal cannabis, it is important to recognize that the risks of medicinal cannabis may be impacted by specific medical conditions and patterns of use. I understand what has been explained to me and agree to the following conditions of treatment:

1. I must prevent children and adolescents from gaining access to medicinal cannabis because of potential harm to their well-being. I will store cannabis in locked cabinets to prevent anyone else from using it.
2. I know that some people cannot control their use of cannabis. One example is using cannabis for reasons other than for the indication for which it was prescribed; like

getting stoned. This may lead to not going to work, or not doing my household chores. I agree to discuss this with my doctor if this happens.

3. I realize that unless specifically recommended by my doctor, I should abstain from medicinal cannabis if:
   a. I am pregnant or am of child-bearing age
   b. I am middle-aged or older and have a heart disease or heart rhythm problem
   c. I have a history of serious mental illness (e.g., schizophrenia, mania, or a history of hallucinations or delusions)
4. In order to reduce the risk of lung disease, I will avoid smoking cannabis with tobacco; avoid deep inhalation or breath-holding; and use a vaporizer rather than smoke joints or use a water pipe.
5. I will not drive a car or operate heavy machinery for 3-4 hours after use of medicinal cannabis, or longer if larger doses are used or the effects of impairment persist. I will use a designated driver for automobile transportation if I have to go out sooner than 3-4 hours after taking this medicine.
6. As the potency of cannabis varies widely I will use the minimum amount of medicinal cannabis needed to obtain relief from pain or other symptoms. When trying a new strain of cannabis, I will start with a very small amount and wait at least 10 minutes to see how it affects me.
7. If thought advisable by my health care provider, I might want to substitute one of the Food and Drug Administration (FDA) approved medicines containing THC rather than take natural cannabis.
8. I might notice a withdrawal syndrome for two weeks if I stop cannabis abruptly. Trouble getting to sleep and angry outbursts might require that I withdraw from the cannabis slowly.
9. I understand that the course of treatment will have to be re-evaluated regularly after I start the medicinal cannabis.
10. I will not use medicinal cannabis in public places unless the law specifically permits this.
11. I know there is no legal precedent to help me if I am terminated from employment if a urine toxicology screen is positive for cannabis.
12. I know that I may be asked to reduce or stop my intake of opioids (narcotics), sedative-hypnotics (benzodiazepines), and/or alcohol. This will be done to reduce the risk of side-effects from a combination of medications that affect the central nervous system.

Signed: _____

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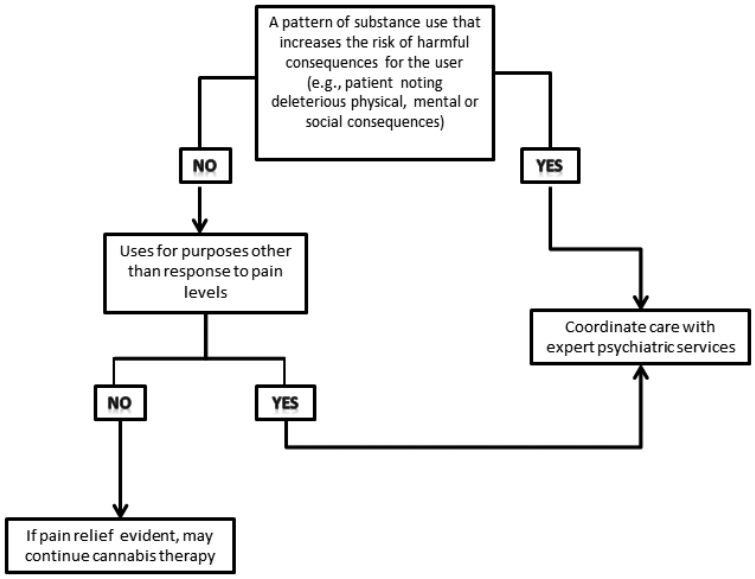

Figure 1. Decision Tree for Cannabis Substance Use Disorder

Identification of patients with problematic use of cannabis and need for expert evaluation and treatment for cannabis substance use disorder.