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Prescribing cannabis for harm reduction

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Abstract

Neuropathic pain affects between 5% and 10% of the US population and can be refractory to treatment. Opioids may be recommended as a second-line pharmacotherapy but have risks including overdose and death. Cannabis has been shown to be effective for treating nerve pain without the risk of fatal poisoning. The author suggests that physicians who treat neuropathic pain with opioids should evaluate their patients for a trial of cannabis and prescribe it when appropriate prior to using opioids. This harm reduction strategy may reduce the morbidity and mortality rates associated with prescription pain medications.

Keywords: cannabis, cannabinoids, opioids, neuropathic pain, chronic pain, harm reduction, ethics

Neuropathic pain (NP) is defined as pain caused by a lesion or disease of the central or peripheral somatosensory nervous system [1]. NP affects between 5% and 10% of the US population [2] and examples include diabetic neuropathy, complex regional pain syndrome, radiculopathy, phantom limb pain, HIV sensory neuropathy, multiple sclerosis-related pain, and poststroke pain [3]. Neuropathic pain is difficult to treat and opioid analgesics are often prescribed [4]. Recent science has demonstrated efficacy in treating NP with cannabis, [5-7] a safer drug than opioids [8]. This paper suggests that physicians who treat neuropathic pain should prescribe cannabis prior to using opioids as a harm reduction (HR) strategy. Topics covered include how harm reduction applies to prescription opioid substitution, the legality of medicinal cannabis, a comparison of cannabis to opioids, the science on treating NP with cannabis and cannabinoids, and the ethics of prescribing a drug which is deemed illegal on the federal but not the state level.

Medicine relies upon the principle of, "First, do no harm," and one might supplement the axiom to read - "First, do no harm, and second, reduce all the harm you can." "Harm reduction" or "harm minimization" can be defined in the broadest sense as strategies designed to reduce risk or harm [9]. Those harmed may include the individual, others impacted by the harmed person, and society [9]. The substitution of a safer drug for one that is more dangerous is considered harm reduction [10]. Specific examples of HR include prescribing methadone or buprenorphine to replace heroin, [11] prescribing nicotine patches to be used instead of smoking tobacco, [12] and prescribing intranasal naloxone to patients on opioid therapy to be utilized in case of overdose [13]. Substituting cannabis for prescribed opioids may be considered a harm reduction strategy.

Under the Federal Controlled Substance Act "marihuana" is illegal and classified as a schedule I substance-meaning it has a high potential for abuse and no accepted medical use [14]. However, sixteen states and the District of Columbia have legalized cannabis for medicinal use and these include Alaska, Arizona, California, Colorado, Delaware, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington [15]. Each state law differs but all allow physicians to "authorize" or "recommend" cannabis for specific ailments [16]. This "recommendation" affords legal protections for patients to obtain and use medicinal cannabis, and may be considered the "prescription."

Cannabis (*Cannabis sativa*) and the opium poppy (*Papaver somniferum*) are both ancient plants that have been used medicinally for thousands of years [17,18]. The natural and synthetic derivatives of opium, including morphine, are called "opioids." [19] "Cannabinoids" is the term for a class of compounds within cannabis of which delta-9-tetrahydrocannabinol (THC) is the most familiar [20]. Besides THC, approximately 100 other cannabinoids have been identified [21,22] including one of special scientific interest called "cannabidiol" (CBD) [23]. The human body produces both endogenous cannabinoids (endocannabinoids) and opioids (endorphins)

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and contains specific receptors for these substances [24,25]. There is an extensive literature on opioids but far less on cannabis/cannabinoids (CC).

Adverse effects from opioids include respiratory depression, sedation, sleep disturbance, cognitive and psychomotor impairment, delirium, hallucinations, seizures, hyperalgesia, constipation, nausea, and vomiting [26-28]. Adverse events from cannabis/cannabinoids include psychotic episodes, anxiety or panic reactions, memory impairment, reduced concentration, disorientation, lowered blood pressure and increased heart rate [7,29-31]. In a systematic review Wang and colleagues found most adverse events for short-term cannabis use were not serious, and there was a lack of evidence to determine adverse effects for long-term use [32]. Opioids and cannabis share issues of addiction, physical dependence, tolerance and withdrawal [5,33,34].

Between 1999 and 2006 approximately 65,000 people died from opioid analgesic overdose [35]. Regarding fatal overdose from cannabis, Carter and colleagues write, "... this well documented fact: no one has ever died from an overdose of cannabis." [8] In addition, there is insufficient data to demonstrate smoking cannabis causes lung cancer [36] but long-term use is associated with an increased risk of respiratory problems [37]. Although, eating cannabis [38] avoids the respiratory issues. In 2001 the total cost of prescription opioid abuse was estimated at $8.6 billion [39]. Unfortunately, there are no comprehensive studies on the total cost of cannabis abuse. However, enforcing the prohibition on cannabis costs an estimated $7.7 billion per year [40]. Since the federal and most state governments view any use of cannabis as abuse - including medicinal use - one might include this cost. According to a report from the Substance Abuse and Mental Health Services Administration between 1999 and 2009 admissions for treatment of nonheroin opioid abuse increased approximately 516% while admissions for cannabis saw a 53% rise [41].

Nerve pain can be refractory to treatment [42] and opioids are often used as a second-line therapy while antidepressants and anticonvulsants are commonly used first [4,43]. Moreover, opioids may provide only limited pain relief and as Henry McQuay writes, "...you may be able to decrease neuropathic pain with strong opioids, but the decrease is often slight and is achieved with an adverse effect burden that will not be tolerable over weeks to months." [44] Cannabis and cannabinoid research is in its relative infancy and many studies are of short duration and with small sample sizes [6]. However, a number of review articles suggest that treating neuropathic pain with cannabis/cannabinoids is efficacious and with moderate adverse effects [5-7]. The most thorough of the systematic reviews was of randomized controlled trials (RCTs) of CC therapy [6] which looked at nine studies [45-53] whose focus was on treating different types of neuropathic pain with either smoked cannabis, [45-48] a synthetic cannabinoid similar to THC, [49,50] or a whole plant extract of THC and CBD in a 1:1 ratio [51-53]. CBD may moderate the psychoactive effect of THC and have analgesic properties [24]. Seven of the nine studies demonstrated efficacy for using CC for neuropathic pain [45-49,52,53] while two had mixed results, [50,51] and eight of the nine studies found no serious adverse events [45-51,53].

A closer look at the four RCTs which evaluated smoked cannabis for neuropathic pain [45-48] reveals some common and contrasting elements (Table 1). Two of the studies, Ware et al. [45] and Wilsey et al., [47] examined cannabis in treating a variety of NP conditions; while the other two, Ellis et al. [46] and Abrams et al., [48] explored the effects of cannabis on HIV-related neuropathic pain. Both Wilsey et al. [47] and Abrams et al. [48] required participants to have previously used cannabis in order to reduce the risk of adverse reactions from psychoactive effects. The RCTs used cannabis with a variety of THC strengths ranging from 0% for placebo [45-48] to 9.4% in Ware et al. [45] Each study required participants to continue taking their regular medications during the cannabis trials and all found a significant decrease in pain compared to placebo [45-48]. In addition, adverse events were tolerable for the vast majority of participants [45-48].

Commentators have suggested that patients should use whole plant cannabis, as opposed to chemical derivatives, because of other potentially beneficial compounds [8,19]. In addition, a number of articles have reported on interactions between cannabinoid and opioid receptors which may result in enhanced analgesia and a synergistic effect when CC is added to opioids [54,55]. This may translate into patients being able to reduce their opioid intake with adjuvant cannabinoid therapy [5,29].

Although prescribing cannabis is legal in 16 states and the District of Columbia, it remains illegal at the federal level. Portions of the American Medical Association's Code of Medical Ethics, Opinion 1.02 - The Relation of Law and Ethics reads, "Ethical values and legal principles are usually closely related, but ethical obligations typically exceed legal duties. In some cases, the law mandates unethical conduct." "In exceptional circumstances of unjust laws, ethical responsibilities should supersede legal obligations." [56] An "exceptional circumstance of unjust laws" may be interpreted as the federal ban on cannabis for medical use. Sixteen states and the District of Columbia found the federal government's prohibition on prescribing and using medicinal cannabis so unjust as to create laws in direct violation of federal statute. Therefore, one could surmise that

Table 1 Comparison of Randomized Controlled Trials of Smoked Cannabis for Neuropathic Pain

	Ware et al. [45]	Wilsey et al. [47]	Ellis et al. [46]	Abrams et al. [48]
Purpose of Study	"... explore the safety and efficacy of smoked cannabis in outpatients with chronic neuropathic pain."	"... examine whether smoking cannabis produces dose-dependent analgesia on both spontaneous and evoked pain in patients with neuropathic pain."	"... ascertain a safe, clinically useful, and efficacious dosing range for smoked medicinal cannabis as a short-term analgesic in the treatment of refractory neuropathic pain in HIV DSPN."	"... determine the effect of smoked cannabis on the neuropathic pain of HIV-SN, and to determine if cannabinoids have a more general analgesic and anti-hyperalgesic effect."
Study Design	randomized, double-blind, placebo-controlled, crossover	randomized, double-blind, placebo-controlled, crossover	randomized, double-blind, placebo-controlled, crossover	randomized, double-blind, placebo-controlled
Sample Size	21	38	28	50
Pain Conditions	NP caused by trauma or surgery, with allodynia or hyperalgesia	spinal cord injury, peripheral NP, and multiple-sclerosis	HIV infection, refractory NP	HIV infection, HIV-SN
Exclusion Criteria	active substance abuse, pain due to cancer or nociceptive causes, history of psychosis, cardiac or pulmonary disease, pregnant	active substance abuse, major depressive disorder, schizophrenia, bipolar disorder, cardiovascular or pulmonary disease, never having used cannabis	active substance abuse, history of psychosis or intolerance to cannabinoids, serious medical conditions	active substance abuse, serious medical conditions, never having used cannabis
Cannabis Potency (%THC)	2.5%, 6%, 9.4%; 0% placebo	3.5%, 7%; 0% placebo	ranging from 1% to 8%; 0% placebo	3.56%; 0% placebo
Length of Study	4 phases over 8 weeks	3 sessions over ~ 4 weeks	5 study phases over 7 weeks	4 phases over 3 weeks
Findings	The 9.4% THC dose significantly decreased pain as compared to placebo. Patients also experienced improved sleep, decreased depression and anxiety as compared to placebo.	Both the 3.5% and 7% THC cannabis produced equal and significant analgesia compared to placebo. Pain was more tolerable at higher doses compared to placebo. Both doses had no effect on evoked pain or allodynia.	Pain reduction was significantly greater compared to placebo. Mood, physical disability, quality of life and sleep improved during all study treatments. The majority of patients titrated to the highest THC dose of 8%.	Patients experienced a significant decrease in pain compared to placebo. Cannabis decreased induced hyperalgesia but had little impact on heat stimulation.
Adverse Events	AE increased with potency. The most frequent complaints from the highest dose cannabis was headache, dry eyes, burning sensation, dizziness numbness and cough.	Both doses produced a general cognitive decline with the highest dose causing the greatest impairment. Both groups felt "high" or "stoned."	2 patients dropped out due to AE; 1 had a psychotic episode, 1 had respiratory irritation. AE was greater for cannabis than placebo and included cognitive impairment, fatigue, sedation, sleepiness, dry mouth, thirst.	2 patients had AE (1 dizziness; 1 anxiety) which were treated with a one-time dose of lorazepam. AE included anxiety, disorientation, confusion and dizziness.

HIV-DSPN, HIV distal sensory polyneuropathy; HIV-SN, HIV-associated sensory neuropathy; NP, neuropathic pain; AE, adverse events

prescribing cannabis for the purpose of harm reduction is ethical even though it violates federal law. In addition, Hayry suggests that the idea of "freedom" also provides an ethical reason for prescribing cannabis and he writes, "... whatever the legal situation, respect for the freedom of the individual would imply that requests like this (for medicinal cannabis) should be granted, either by health professionals, or by society as a whole." [57]

In states where medicinal cannabis is legal, physicians who treat neuropathic pain with opioids should evaluate their patients for a trial of cannabis and prescribe it when appropriate prior to using opioids. There is sufficient evidence of safety and efficacy for the use of CC in the treatment of nerve pain relative to opioids and as Carter et al write, "From a pharmacological prospective, cannabinoids are considerably safer than opioids..." [8] Prescribing cannabis in place of opioids for neuropathic pain may reduce the morbidity and mortality rates associated with prescription pain medications and may be an effective harm reduction strategy.

[The subject of cannabis dosing is beyond the scope of this paper but those interested should consider reading Carter GT, Weydt P, Kyashna-Tocha M, Abrams DI. **Medicinal cannabis: rational guidelines for dosing**. *IDrugs* 2004;**7**:464-70.]

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