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Title: Gateway or exit drug? Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain, and implications for problematic substance use, public health, and drug policy

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Abstract: Abstract

Background: Cannabis has a long history as an analgesic and there has never been a death resulting from its use. Recent studies have shown that many of the chemicals found in cannabis display anti-inflammatory, anti-spasmodic and analgesic properties. Research suggests that when used in conjunction with opiates cannabinoids lead to a greater cumulative relief of pain, resulting in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting (Cichewicz et al. 1999). Studies also show that cannabinoids can prevent the development of tolerance to and withdrawal from opiates (Cichewicz and Welch, 2003), and can even rekindle opiate analgesia after a prior dosage has become ineffective (Cichewicz and McCarthy, 2003; Russo, 2008).

Methods: This paper examines the available evidence-base for the medical use of cannabis in the treatment of chronic pain and the consequential reduction of licit and illicit opiate use in patients suffering from this condition. I then explore the concepts of substitution effect in regards to cannabis access, and the relationship between harm reduction and benefit maximization in policies regulating cannabis and other substances.

Findings: There is a growing body of evidence to support the use of medical cannabis as an adjunct to or substitute for prescription opiates in the treatment of chronic pain. Additionally, novel research suggests that cannabis may be useful in the treatment of problematic substance use, either deliberately or through a process called substitution effect.

Conclusion: Increasing access to medical cannabis may reduce the personal and social harms associated with addiction, particularly in relation to the use of pharmaceutical opiates. Despite a lack of regulatory oversight by federal governments in North America, community-based medical cannabis dispensaries have proven successful at supplying patients with a safe source of cannabis within an environment conducive to healing.

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A Brief History of Cannabis as a Medicine

The medical use of cannabis can be traced back at least 5000 years. The oldest reports originate in China and Egypt. It appears in a medical context in the Vedas, India's oldest religious text, and there are reports of its use as a medicine from fragments of Assyrian texts dating back to 700 B.C. The famous Chinese doctor Hua T'uo (approx. 100 A.D.) reportedly made use of a wine and cannabis mixture as an anaesthetic for surgical operations (Fankhauser, 2002).

There are numerous reports of the medicinal properties of cannabis from early in the nineteenth century, the most famous of which is an 1839 report titled "on the Preparations of the Indian Hemp, or Gunjah" by the Irish doctor William B.

O'Shaughnessy in which he describes diverse applications for cannabis, including rheumatism, rabies, cholera, tetanus, cramps and delirium tremens. A few years later Ernst Freiherr von Bibra published the renown "Narcotics and the Human Being", devoting thirty pages to the therapeutic use of cannabis preparations and hashish (Von Bibra, 1855).

By the late 19th Century, cannabis-based preparations were manufactured and marketed by Burroughs-Wellcome & Co. In England; and Bristol-Meyers Squib, Parke-Davis, and Eli Lilly in North America. The development of vaccines to prevent the spread of common infectious diseases, the increased use of opiates (with the introduction of the hypodermic syringe), and the discovery of aspirin at the end of the nineteenth and early

twentieth century resulted in cannabis-based medicines losing their prevalence in the market place and Western pharmacopoeia (Grinspoon & Bakalar, 1993). The US Pharmacopoeia listed Cannabis until 1941, stating that cannabis can be used for treating fatigue, coughing, rheumatism, asthma, delirium tremens, migraine headaches, and the cramps and depressions associated with menstruation (Mikuria, 1973)

Although modern research into therapeutic applications for cannabis has been seriously stymied by its prohibition in most of the Western world, extensive anecdotal reports and a growing body of laboratory and clinical research suggest that it may have many medicinal uses, including hunger stimulation for wasting syndrome; anti-emetic and anti-nausea properties in AIDS or cancer chemotherapy; anti-spasmodic properties for MS, epilepsy and other neurological dysfunctions; reducing intra-ocular eye pressure in glaucoma; and analgesic properties in a large number of chronic pain conditions (Hazekamp & Grotenhermen, 2010; Ben Amar, 2006; Grotenhermen & Russo 2002).

Cannabis and Chronic Pain

Pain is one of the most common reasons for seeking medical treatment and for the prescription of pharmaceutical drugs. While numerous products are available for the relief of many different types of pain, there remains a significant group of patients for whom traditional pharmacological pain control is incomplete or ineffective.

Existing pharmacological treatments with known side effects are widely used for analgesia, but may show a lack of efficacy in certain conditions. These agents include:

- Non-opioid analgesics
- Opioid analgesics
- Anti-convulsants
- Anti-migraine drugs
- Tricyclic antidepressants

- Anti-inflammatories
- Steroids

Despite modern progress on the understanding and treatment of pain over the last century as well as a recent North American emphasis on treating pain stemming from other medical conditions, there still remain many problems in providing safe and effective analgesia for all those with a legitimate need for pain relief.

The Canadian Psychological Association (CPA) defines chronic pain as being pain that doesn't go away, last over six months, or extends beyond the expected recovery time after an accident or medical intervention. Additionally, they suggest that chronic pain is a highly variable condition with many different causes:

There are different types of chronic pain, many of which are not clearly understood. Chronic pain may be associated with an illness or disability, such as cancer, arthritis or phantom limb pain. Some types of chronic pain start after an accident. Others may start as acute episodes but then the pain becomes constant over time, such as low back pain. With some types of chronic pain, like migraine headaches, the pain is recurrent, rather than constant. There are many other kinds of chronic pain, such as chronic postsurgical pain, fibromyalgia, temporomandibular disorders, etc. While in some cases the cause of pain is known, in many other cases it is not clear why pain persists (CPA, 2007)

Although statistics regarding chronic pain are difficult to come by, the CPA website states that:

About one in ten Canadians has chronic pain. Chronic pain affects both sexes and while it is most common in middle age, it can occur at any age - from infancy to the elderly. Chronic pain can make simple movements hurt, disrupt sleep, and reduce energy. It can impair work, social, recreational, and household activities. People who have been injured in accidents may develop anxiety symptoms as well as pain. Chronic pain can have a negative impact on financial security, and can provoke alcohol or drug abuse. It can disrupt marital and family relationships... Given the impact pain can have on quality of life, it is no surprise that more than a quarter of all people who develop chronic pain also experience significant depression or anxiety (CPA, 2007).

Chronic pain is highly subjective in nature, and sufferers of the same chronic pain condition may experience very different symptomology. Fibromyalgia, a chronic pain syndrome of unknown origins associated with depression and chronic fatigue is a good example of this effect. It is interesting to note that Russo (2008b) has theorized that intractable and difficult to treat pain conditions like fibromyalgia may be related to a condition he terms *clinical endocannabinoid deficiency* (CECD), which is an imbalance in the body's own internal cannabinoid system (Russo, 2008; Russo 2008b). Furthermore there are numerous different origins for chronic pain – visceral, somatic, neurogenic, etc. – which may explain why so many sufferers report poor control with standard pharmaceuticals. Therefore chronic pain sufferers are in no way homogenous, indicating the need for variable and individual treatment regimens and dosages (Mersky & Bogduk, 1994).

In Europe, chronic musculoskeletal pain of a disabling nature affects over 25% of elderly people (Frondini et al. 2007). Responses to a 2005 poll indicate that 19% of adults (38 million) in the U.S. have chronic pain, and 6% (or 12 million) have utilized cannabis in attempts to treat it (ABC News Poll, 2005). Ware et al report that 25% of chronic pain sufferers in the U.K. use cannabis, and that medical cannabis was largely associated with “younger age, male gender and previous recreational use” (Ware et al, 2005). A further assessment of cannabis use and chronic pain by Ware and Beaulieu found that “there is increasing evidence that cannabinoids are safe and effective for refractory chronic pain conditions including neuropathic pain associated with multiple sclerosis, rheumatoid arthritis, and peripheral neuropathy associated with HIV/AIDS”, concluding that more research is needed (Beaulieu & Ware, 2007).

Cannabinoid Receptors and Analgesia

Over the last 15 years, CB1 and CB2 receptors have been identified (Pertwee, 2002). CB1 receptors are of particularly high concentration in the central nervous system, including several areas of the central nervous system that mediate the perception of pain (Walker et al, 1999). CB2 receptors are found mostly in immune tissue, such as leukocytes, the spleen and tonsils. These receptors are absent from the brain stem, thus explaining the lack of classic opioid side-effects such as respiratory depression. This may prove to be an advantage of cannabinoid-based drugs over opiates. Another similarity with the opioid system is the existence of endogenous cannabinoid receptor agonists, the most studied of which is anandamide (Pertwee, 2002). Evidence shows that this cannabinoid can serve as a neuromodulator or neurotransmitter (DiMarzo et al, 1998), and it has been found that cannabinoid receptors outside of the brain and spine are affected when skin or flesh is cut or injured; anandamide is released and helps modulates the pain associated with injury. Rats treated with a chemical blocker for anandamide showed an extended and more severe response to pain (Calignano et al, 1998). There is recent evidence that anandamide and methandamide can activate vanilloid receptors on sensory neurons. The extent to which exogenous or endogenous cannabinoids can modulate pain through vanilloid receptors that are known to be present on nociceptive sensory neurons has yet to be fully established (Pertwee, 2002).

Human Studies on Cannabinoids as Analgesics

Although human studies on the therapeutic effects of cannabis have been significantly limited by a restrictive legal regime and the unavailability of cannabis products to

conduct such studies, available research suggests that cannabis has strong potential as an analgesic.

An early study of synthetic delta-9-tetrahydrocannabinol (hereafter referred to as “THC” for the rest of this paper) administered orally in 10 to 25 mg doses was shown to relieve pain in cancer patients without significant effects on mood (Davies et al, 1974). A 2006 study by Blake et al examining the effects of Sativex, an oromucosal whole plant cannabis extract with a THC/CBD ratio of 50:50, on rheumatoid arthritis reported significant analgesic effect compared to placebo. Although some mild or moderate adverse effects like dizziness were reported by the active treatment group, Sativex was generally well-tolerated.

In a study to determine the effect of smoked cannabis on pain related to HIV-associated sensory neuropathy and an experimental pain model, researchers found that smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain (Abrams et al, 2007). A 2008 study by Wilsey on smoked cannabis and neuropathic pain compared the effect of high THC (7%) cannabis with low THC (3.5%) cannabis and placebo. The results showed that both active preparations were effective at reducing pain, with no apparent correlation between dose levels and pain relief. Although some moderate adverse effects were identified, the treatment was well-tolerated.

Ware et al (2010) recently published results from a randomized clinical trial on smoked cannabis and chronic pain, finding that 9.4% THC cannabis used three times daily for five days reduced the intensity of pain and improved sleep in patients compared to placebo, and was well tolerated by the 21 patients who concluded the study. Although

study participants reported mild or moderate adverse effects, these were comparable to the adverse effects of non-smoked pharmaceutical cannabinoid medicines.

Cannabinoids and Opioids in the Treatment of Chronic Pain

Opiates are amongst the most well-researched and widely prescribed treatments for chronic pain in the world. Evidence of the medical use of opiates dates back at least to the Ebers Papyrus from 1500 B.C. (Brownstein, 1993), and there is little doubt that despite the potential for serious side-effects, including death, and the ongoing development of alternative approaches to pain relief, pharmaceutical opiates will continue to be one of the most effective tools available for the treatment of chronic pain. However, a major personal and public health concern associated with the use of pharmaceutical opiates is dependence. In fact, according to US-based Substance Abuse and Mental Health Services Administration, the dependence on and abuse of pharmaceutical medications is currently the fastest growing form of problematic substance use in North America (SAMHSA, 2007). As a result of this increase in the use and abuse of prescription pharmaceuticals, Moore et al (2007) report that serious adverse events and deaths resulting from prescription drug use in the U.S. nearly tripled between 1998 and 2005 (Moore et al, 2007). Addiction to and abuse of pharmaceutical opiates has been identified as one of the main personal and public health concerns associated with this trend (Dhalla et al, 2009; Fischer et al, 2008; Compton & Volkow, 2006). The following research suggests that when used in conjunction with opiates, cannabinoids can lead to a greater cumulative relief of pain, which may in turn result in a reduction in the use of opiates (and associated side-effects) by patients in a clinical setting (Cichewicz et al. 1999). This may not only have positive impact on patient pain

levels and overall quality of life, but also on the overall morbidity and mortality associated with pharmaceutical opiates, and on the high levels of opiate addiction in both the patient and general population.

A randomized double-blind crossover placebo-controlled study of oral medication for pain in 10 terminal cancer patients comparing 5, 10, 15, and 20 mg of THC in single doses with placebo found a significant dose-related analgesic effect at the two higher doses (Noyes et al, 1975). A larger follow up study of 36 terminally ill patients with cancer pain was designed to compare 10 and 20 mg THC with 60 and 120 mg codeine and placebo. The results suggest that 10 mg THC was slightly less effective than 60 mg codeine, and that 20 mg THC was slightly more effective than 120 mg of codeine (Noyes et al, 1975b).

A later single-patient study examining the analgesic effects of oral doses of THC 5mg, codeine 50 mg, and placebo showed that both active preparations were significantly more effective than placebo at relieving MS-related pain. The only major reported difference between the active drugs was that THC relieved spasticity better than codeine (Maurer et al, 1990).

A study by Pinsger (2006) on the effects of nabilone (a synthetic cannabinoid) as an adjunct to existing chronic pain therapy resulted in reduced pain and improved quality of life. Although some mild to moderate side-effects were noted, the majority of patients reported overall benefits when compared to their usual chronic pain treatment.

A 2007 clinical study by Nurmikko examining the effects of Sativex as an adjunct to existing stable analgesia in patients suffering from peripheral neuropathic pain showed that 26% of participants reported more than 30% reductions in pain intensity, compared

with 15% using placebo. Adverse events were few and largely mild or moderate.

A 2008 randomized clinical study by Skrabek on nabilone as an adjunct treatment for 15 patients affected by fibromyalgia reported significant benefits in pain and overall function. Mild side-effects were reported, including weight gain, but participants indicated overall increases in quality of life.

Narang (2008) conducted a phase 1 and phase 2 study examining the efficacy of dronabinol as an adjunct to opioid therapy for the treatment of chronic pain. Both studies showed that dronabinol decreased pain intensity and increased quality of life compared to baseline opiate therapy. The findings also reported mild to moderate side-effects including drowsiness, but patients also reported an improvement in the quality of sleep and overall satisfaction with the treatment compared to placebo.

Additionally, studies also show that cannabinoids can prevent the development of tolerance to and withdrawal from opiates (Cichewicz and Welch, 2003), and can even rekindle opiate analgesia after a prior dosage has become ineffective (Cichewicz and McCarthy, 2003; Russo, 2008).

Gateway or Safer Substitute?

Despite its low potential for individual harm or abuse and minimal impact on public health and associated social costs, the medical use of cannabis remains controversial with police, physicians, and policy-makers. One of the main concerns cited by opponents is that it could lead to either dependence on cannabis, or potentially be a *gateway* to the use of and addiction to hard drugs. The premise of the *gateway* or *stepping stone* hypothesis is that the use of one substance may subsequently lead to the use of another. In regards to illicit substance use, this theory suggests that the use of cannabis may facilitate the use of

potentially more harmful/addictive substances such as opiates, cocaine, or amphetamines.

The evidential foundation for this theoretical construct is based on research indicating that most people who use so-called “hard” drugs such as heroin or cocaine report a prior use of cannabis. Lessem (2006) states that:

The “gateway theory” is comprised of two interrelated observations. The first is that marijuana use is associated with later, non-marijuana, illicit drug use, and the second is that there is a temporal ordering of substance experimentation in which lower order substances, which are more commonly used, precede the use of higher order substances. Thus, typically one licit substance such as alcohol or cigarettes is used first in a sequence. Marijuana is usually the first illicit substance used before progressing on to using other illicit substances. (p.499)

While most studies have focused on the social or economic determinants that could lead cannabis users to experiment with other substances (Wagner & Anthony, 2002; Pacula et al., 2000), some research suggests that this progression may be due to biological changes to individual exposed to cannabis (Lessem et al., 2006).

However, both social and clinical research has convincingly debunked the *gateway* or *stepping stone* hypothesis. The Senate Special Committee on Illegal Drugs final report on cannabis (Nolin et al, 2002) reviewed all of the available evidence on the topic and drew the following conclusions:

We feel that the available data show that it is not cannabis itself that leads to other drug use but the combination of the following factors:

- Factors related to personal and family history that predispose to early entry on a trajectory of use of psychoactive substances starting with alcohol;
- Early introduction to cannabis, earlier than the average for experimenters, and more rapid progress towards a trajectory of regular use;
- Frequenting of a marginal or deviant environment;
- Availability of various substances from the same dealers.

Thus, while it may be true that many people who use “hard” drugs have also used cannabis, the reasons range from social factors such as poverty, to the illegal status of the

substance, which results in black market control over its distribution. As the Canadian Senate discovered, drug use trends in Canada simply do not support the *gateway* or *stepping stone* hypothesis, concluding that “if we come back to trends in drug use in the population, while more than 30% have used cannabis, less than 4% have used cocaine and less than 1% heroin.” (p.126)

The counterpoint *gateway theory* is *substitution effect*, an economic theory that suggests that variations in the availability of one product (through changes in cost or social policy), may affect the use of another:

Within a behavioral economic framework, reinforcer interactions are classified into multiple categories; two commodities may be “substitutes” for one another (e.g., two forms of opioid drugs); they may be “complementary,” whereby the value of one is enhanced by consumption of the other; or they may be “independent,” such that the reinforcing functions of one are not altered by the presence or absence of the other (Hursh et al, 2005; p.24).

Changes in the use of cannabis, opiates, or other drugs - whether for medical or recreational use - can be the result of a) economic shifts affecting end-user costs; b) changes in policy which effect availability; c) legal risk and associated repercussions; or d) psychoactive/pharmacological substitution. In regards to psychoactive substitution, Hursh et al (2005) suggest that “pharmacological therapies for the treatment of drug abuse can also be conceptualized as alternative commodities that either substitute for illicit drug use (e.g., agonist therapy) or reduce the potency of illicit drugs directly (e.g., narcotic antagonist therapy)” (p.25). Perhaps the best example of the viability of psychoactive substitution is the now common prescription use of methadone as a substitute to injection heroin use. This substitution reduces some of the risks associated with injection drug use, including overdose and disease transmission, since drug levels are constant and predictable, and methadone is taken orally rather than injected.

Additionally, since methadone is less expensive than heroin (and is subsidized by provincial health registries in Canada), this substitution has the added potential benefit of reducing drug-related theft and crime. However, many methadone patients have reported health concerns associated with its use as well, and recent research suggests that prescription heroin or opiates may be a safer and more effective alternative for users than either black-market heroin or methadone (NAOMI Study Team, 2008).

As suggested earlier, not all psychoactive substitution is the result of a deliberate decision made on an individual basis. At the population level it is often the unintended result of public policy shifts or other social changes, such as cost, criminalization or availability. In an examination of hospital drug episodes in 13 U.S. states that decriminalized the personal recreational use of cannabis in the 1970s, Model (1993) found that users shifted from using harder drugs to marijuana after its legal risks were decreased. Findings from Australia's 2001 *National Drug Strategy Household Survey* (AIHW, 2002) specifically identify substitution effect, indicating 56.6% of heroin users substituted cannabis when their substance of choice was unavailable. The survey also found that 31.8% of people who use pharmaceutical analgesics for non-medical purposes reported using cannabis when pain-killers weren't available. This evidence strongly suggests that the increased availability of cannabis (through a reduction of penalties or actual regulated, legal access) might lead to a population level reduction in the licit and illicit use of opiates and pharmaceutical analgesics and the associated personal, social and public health harms and costs.

The illegal status of cannabis across most of the world has made clinical trials on cannabis as a treatment for problematic substance use nearly impossible, but a number of

studies on both humans and animals suggest that the cannabinoid system plays a role in dependence and addiction to both licit and illicit substances. Current research shows that behavioural effects and motivational responses induced by nicotine can be modulated by the endocannabinoid system (Balerio et al, 2006).

Additionally, a study by the New York State Psychiatric Institute on people with cocaine dependence with comorbid Attention-Deficit Hyperactivity Disorder has shown that cannabis users were more successful than other patients in abstaining from cocaine use (Aharonovich et al., 2006). An earlier study by Labigalini Jr. et al (1999) also noted this effect on people with a dependence on crack cocaine, reporting that 68% of the 25 subjects who self-medicated with cannabis in order to reduce cravings were able to give up crack altogether. Researchers theorized that this phenomenon is biological and psychological. Addiction to stimulants result in a decline in the cerebral activity involving serotonin transmitters, which is believed to result in increased impulsiveness and craving. Cannabinoids act as serotoninergic agonists, and as serotonin levels increase, impulsiveness and craving decline. Reports from study subjects also suggest that the ritual of preparing cannabis to smoke helped reduce the habituated psychological dependence associated with the preparation of crack cocaine.

Finally, a study by Reiman (2009) of 350 cannabis patients that purchase their medicine from a community-based dispensary in Berkeley suggests that many patients report using it as a substitute for other potentially more dangerous substances, particularly pharmaceuticals. Results show that 40% report using cannabis as a substitute for alcohol, 26% as a substitute for illicit drugs, and 66% as a substitute for prescription drugs. Patients cited a number of reasons to using cannabis instead of pharmaceutical drugs:

65% reported less adverse side-effects, 57% cited better symptom management, and 34% found that cannabis had less withdrawal potential than their other medications. A similar survey study of 400 patients is currently underway in four medical cannabis dispensaries located in British Columbia, Canada.

Maximizing the Potential Benefits of Medical Cannabis Use

While much of the research cited above suggests that cannabinoids can be safe and effective adjuncts or alternatives to pharmaceutical opiates, the illegality of cannabis and the associated stigma in patients that might benefit from its use has significantly hampered research into therapeutic potential of both whole-plant preparations and pharmaceutical cannabinoid treatments (Lucas 2009). As a result, the international prohibition on cannabis has not only lead to significant social costs with little impact on overall usage rates in the general population, it may also be inadvertently leading to increased suffering and addiction to patients suffering from chronic pain.

In light of recent evidence that cannabis not only helps relieve the symptoms of a number of serious conditions, but might also increases the success rate of both HIV/AIDS and Hep-C treatment (Sylvestre et al, 2006; Abrams et al, 2007), it can be argued that the governments throughout the world have a moral, ethical obligation to ensure that this medicine is legally available to patients who might benefit from its use. The same argument could be made if cannabis is shown to be effective in reducing the non-prescription use of other potentially more dangerous licit and illicit substances, including pharmaceutical opiates.

In an essay on the globalization of ayahuasca, which is an entheogenic plant-based medicine from the Amazon basin that, like cannabis, has a long history of traditional use, Tupper (2007) suggests that:

...a shift to a generative metaphor of drugs as “tools” offers a much more nuanced way to conceiving of the risks and benefits posed by ayahuasca practices. Rather than essentializing psychoactive substances as inherently dangerous, to regard them as tools – ancient technologies for altering consciousness...allows for a realistic assessment of their potential benefits and harms according to who uses them, in what contexts and for what purposes. (p.5)

Although this may appear reflective of a harm reduction approach to drugs, Tupper insists that conceptualizing drugs as “tools” necessitates a move beyond policies simply based on reducing potential harms, suggesting that benefits also need to be explored and where possible, maximized by government policies and practices. He states that:

The philosophy of harm reduction is also further illuminated by a shift to the generative metaphor of drugs as tools. To the extent that policy-makers or practitioners emphasize a behaviour’s potential risks, the harm reduction policy approach is justified. However, the tool metaphor for psychoactive substances warrants a corollary notion of “benefit maximization”, the other side of the harm reduction coin. Instead of approaching drug policy from a deficit perspective...the tool metaphor opens discursive avenues for realistic policy considerations of benefits as well as harms. (p.5)

As with ayahuasca, the concept of harm reduction may not be wholly appropriate to maximize the potential health benefits of medical cannabis. A great deal of research indicates that cannabis is far less dangerous than licit substances like alcohol and tobacco, and safer than many over-the-counter or prescription pharmaceuticals (Grotenhermen & Russo, 2002; Grinspoon, 1999; Grinspoon & Bakalar, 1998), and many have suggested that the greatest potential harms of cannabis use are based on its illegal status, including arrest or the vagaries of the black-market (Nolin et al, 2003). In this light, harm

reduction policies associated with the use of other substances that are designed to prevent the spread of infectious disease, reduce the likelihood of overdose and stem addiction and related crime – such as needle-exchange, safe consumption sites, heroin maintenance or opiate substitution — don't readily apply to the use and distribution of medical cannabis. Research suggests that community-based medical cannabis dispensaries appear to both reduce the potential harms and maximize the benefits of medical cannabis use by removing some of the social stigma associated with the therapeutic use of cannabis and by separating medical cannabis access from the potential dangers of the black-market (i.e. lack of safety and quality assurances, pressure to try other illicit substances, prohibition-associated harms such as arrest and prosecution) (Lucas 2010; Lucas 2009; Lucas 2008; Belle-Isle 2007; Reiman 2009; Reiman 2006). Additionally, they increase access to a safe consistent supply of medical cannabis at the community level within an environment conducive to health where patients can access important information on safe and effective use that isn't otherwise available from national health agencies, such as how to make a tincture or to bake with cannabis (Vancouver Island Compassion Society, 2009). Moreover, non-profit dispensaries like the VICS contribute to the overall social capital of their client-members through membership, joint knowledge creation, and inclusion and participation in a social movement informed by public health, harm reduction and human rights (Lucas 2009; Belle Isle 2007; Reiman 2006). As such this community-based, patient-centered model is growing in both legitimacy and popularity, and is now the predominant means for patients access in Canada and in many U.S. state-run medical cannabis programs (Lucas 2010; Lucas 2009; Reiman 2006).

DISCUSSION

Evidence is growing that cannabis can be an effective treatment for chronic pain, presenting a safe and viable alternative or adjunct to pharmaceutical opiates. Addiction to pharmaceutical opiates has been noted by the medical community as one of the common side-effects of extended use by patients (such as those suffering from chronic pain), and a growing body of research suggests that some of the biological actions of cannabis and cannabinoids may be useful in reducing this dependence. Therefore cannabis has the potential to both relieve suffering for those suffering from chronic pain, and to reduce morbidity and mortality often associated the use and abuse of pharmaceutical opiates.

Since both the potential harms of pharmaceutical opiates and the relative safety of cannabis are well established, research on ‘substitution effect’ suggests that cannabis may be effective at reducing the use and dependence of other substances of abuse such as illicit opiates, stimulants and alcohol. As such, there is reason to believe that a strategy aiming to maximize the therapeutic potential benefits of both cannabis and pharmaceutical cannabinoids by expanding their availability and use could potentially lead to a reduction in the prescription use of opiates and other potentially dangerous pharmaceutical analgesics, and thus a reduction in associated harms.

Therefore, it is reasonable to conclude from the available research that reducing or eliminating the penalties associated with non-medical cannabis use might increase opportunities for cannabis substitution at the population level, which may in turn result in reduced rates of problematic substance use, including alcohol and the non-prescription use of pharmaceuticals. The resulting public health benefits would include lower rates of

alcohol-related automobile accidents, less domestic violence, reductions in drug-related crimes such as break-ins and petty theft, and reduced drug and alcohol-related morbidity and mortality.

International experience appears to support this premise. A recent report by the European Monitoring Center for Drugs and Drug Addiction shows that the Netherlands long-time policy of de-facto cannabis decriminalization has resulted in some of the lowest drug-induced death rates in Europe, while countries with more severe cannabis laws and drug policies, such as Norway and Sweden, rank among the highest (EMCDDA, 2009).

Despite such compelling evidence, much of the world's current and long-standing prohibitionist approach to cannabis continues to act as a barrier to these potential personal and public health benefits, and to criminalize otherwise law abiding citizens as well as many critically and chronically ill patients.

Community-based dispensaries have emerged as a disjointed but effective social movement focused on the principles of harm reduction and human rights. Although they remain largely unregulated or even illegal in much of Canada and U.S., these dispensaries have been successful in establishing a safe and consistent supply of medical cannabis, advocating for patient rights, and adding to society's knowledge and understanding of the therapeutic potential of cannabis through scientific research. If we are to ever benefit from drug policies based on science, reason and compassion, national governments will need to abandon the misinformation that underscore drug prohibition, and to start promoting and supporting research into cannabis and cannabinoids as both a relatively safe and effective medicine in the treatment of chronic pain and other serious medical conditions, and as a potential 'exit drug' for problematic substance use.

5. REFERENCES

- ABC News Poll, (2005). Retrieved on August 19th, 2007 from <http://abcnews.go.com/images/Politics/979a1TheFightAgainstPain.pdf>.
- Abrams, D. et al. (2007). Cannabis in painful HIV-associated sensory neuropathy - A randomized placebo-controlled trial. *Neurology*; 68: pp.515–521.
- Aharonovich, E. et al. (2006). Concurrent cannabis use during treatment for comorbid ADHD and cocaine dependence: effects on outcome. *Am J Drug Alcohol Abuse*. 32(4): pp.629-35.
- Australian Institute of Health and Welfare, (2002). 2001 National Drug Strategy Household Survey: First results. *AIHW cat. no. PHE 35*. Canberra: AIHW (Drug Statistics Series No. 9). Retrieved on June 8th, 2007 from <http://www.aihw.gov.au/publications/phe/ndshs01/ndshs01.pdf>
- Balerio, G.N. et al. (2006). Role of the cannabinoid system in the effects induced by nicotine on anxiety-like behaviour in mice. *Psychopharmacology*. Jan 14; pp. 1-10.
- Beaulieu, P. & Ware, M.A. (2007). Reassessment of the role of cannabinoids in the management of pain. *Curr Opin Anaesthesiol*. Oct; 20 (5): pp.473-7.
- Belle-Isle, L. (2006). *Cannabis as Therapy for People Living With HIV/AIDS; Our Right, Our Choice*. Canadian AIDS Society. June 2006. Retrieved on October 10th, 2006 from <http://www.cdnaids.ca/web/casmisc.nsf/pages/cas-gen-0112>
- Belle-Isle, L. & Hathaway, A. (2007). Barriers to access to medical cannabis for Canadians living with HIV/AIDS. *AIDS Care*; 19(4): pp.500-506.
- Ben Amar, M. (2006). Cannabinoids in medicine: A review of their therapeutic potential. *J Ethnopharmacol*. 2006 Apr 21;105(1-2): pp.1-25.
- Blake, D.R., Robson, P., Ho, M., Jubb, R.W., McCabe, C.S. (2006). Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. *Rheumatology*. 45(1): pp.50-52.
- Brownstein, M.J. (1993). A brief history of opiates, opioid peptides, and opioid receptors. *Proc Natl Acad Sci*. 15; 90(12): pp.5391–5393.
- Calignano, A., La Rana, G., Giuffrida, A., Piomelli, D. (1998). Control of pain initiation by endogenous cannabinoids. *Nature*. 394: pp. 277-281.

- Canadian Psychological Association, (2007). Retrieved on October 25th, 2007 from www.cpa.ca/publications/yourhealthpsychologyworksheets/chronicpain
- Cichewicz, D.L., Martin, Z.L., Smith, F.L., Welch, S.P. (1999). Enhancement of mu opioid antinociception by oral delta9- tetrahydrocannabinol: Dose-response analysis and receptor identification. *J Pharmacol Exp Ther.* 289(2): pp.859-67.
- Cichewicz, D.L. & McCarthy, E.A. (2003). Antinociceptive synergy between delta(9)-tetrahydrocannabinol and opioids after oral administration. *J Pharmacol Exp Ther.* 304(3): pp.1010-5.
- Cichewicz, D.L. & Welch, S.P. (2003). Modulation of oral morphine antinociceptive tolerance and naloxone-precipitated withdrawal signs by oral Delta 9-tetrahydrocannabinol. *J Pharmacol Exp Ther.* 305(3): pp.812-7.
- Compton, W., Volkow, N. (2006). Major increases in opioid analgesic abuse in the United States: concerns and strategies. *Drug & Alcohol Dependence.* 81: pp.103-7.
- Davies, B.H., Weatherstone, R.M., Graham, J.D.P., Griffiths, R.D. (1974). A pilot study of orally administered delta-1-(trans)-tetrahydrocannabinol in the management of patients undergoing radiotherapy for carcinoma of the brohchus. *British Medical Journal of Pharmacology.* 1: pp.301-306.
- Dhalla, I., Mamdani, M., Sivilotti, M. (2009). Prescribing of opioid analgesics and related mortality before and after the introduction of long-acting oxycodone. *CMAJ.* 8;181(12): pp.891-6.
- DiMarzo, V., Melck, D., Bisogno, T., DePetrocellis, L. (1998). Endocannabinoids: Endogenous cannabinoid receptor ligands with neuromodulatory action. *Trends in Neuroscience.* 21(12): pp.521-528.
- European Monitoring Center for Drugs and Drug Addiction (2009). The State of the Drugs Problem in Europe; Annual Report 2009. Retrieved on Nov. 7th 2009 from <http://www.emcdda.europa.eu/situation/analysis>
- Fankhauser, M. (2002). In F. Grotenhermen & E. Russo (Ed.) *Cannabis and Cannabinoids*. New York: The Hayward Integrative Press. pp. 37.
- Fischer, B., Rehm, J., Goldman, B., et al (2008). Non-medical use of prescription opioids and public health in Canada: an urgent call for research and intervention development. *Can J Public Health.* 99: pp.182-4.
- Fronadini, C. et al (2007). Affective, behavior and cognitive disorders in the elderly with chronic musculoskelatal pain: The impact on an aging population. *Archives of Gerontology and Geriatrics.* 44, Supplement 1, pp.167-171.

- Grinspoon, L. (1999). Medical marijuana in a time of prohibition. *International Journal of Drug Policy*. 10, pp.145-156.
- Grinspoon, L., & Bakalar, J.B. (1993). *Marijuana the Forbidden Medicine*. New Haven, CT: Yale University Press.
- Grinspoon, L., & Bakalar, J. B. (1998). Missed Opportunities – Beneficial Uses of Illicit Drugs. From R. Coomber's *The Control of Drugs and Drug Users*. Harwood Academic Press.
- Grotenhermen, F., & Russo, E. (2002). e. *Cannabis and Cannabinoids*. New York: The Haworth Press.
- Hazekamp, A., Grotenhermen, F. (2010). Review on clinical studies with cannabis and cannabinoids 2005-2009. *Cannabinoids* 2010;5 (special issue): pp.1-21.
- Hursh, S. R., Galuska, C.M., Winger, G., Woods, J.H. (2005). The economics of drug abuse: a quantitative assessment of drug demand. *Molecular Interventions* 5: pp.20-28.
- Labigalini Jr., E. et al. (1999). Therapeutic use of cannabis by crack addicts in Brazil. *Journal of Psychoactive Drugs*; Oct-Dec; 31, 4; pp. 451.
- Lessem, J.M., Hopfer, C.J., Haberstick, B.C., Timberlake, D., Ehringer, M.A., Smolen, A., Hewitt, J.K. (2006). Relationship between adolescent marijuana use and young adult illicit drug use. *Behav Genet*. 2006 Jul; 36(4): pp.498-506.
- Lucas, P. (2008). Regulating compassion; an overview of Health Canada's medical cannabis policy and practice. *Harm Reduction Journal*. 5:5.
- Lucas, P. (2009). Moral regulation and the presumption of guilt in Health Canada's medical cannabis policy and practice. *International Journal of Drug Policy*. 20, pp. 296–303.
- Lucas, P. (2010). Patient-centered strategies to counter stigma, oppression and forced incarceration in the C/S/X and medical cannabis movements. *Interface*. 2 (2): pp.149 – 167.
- Maurer, M., Henn, V., Dittrich, A., Hoffman, A. (1990). Delta-9-THC shows antispastic and analgesic effects in a single case double blind trial. *European Archives of Psychiatry and Clinical Neuroscience*. 240(1): pp.1-4.
- Mersky, H., Bogduk, N., (1994). Classification of Chronic Pain. *Descriptions of chronic pain syndromes and definition of pain terms*. International Association for the study of Pain. Seattle, WA: IASP Press.
- Model, K., (1993). The effect of marijuana decriminalization on hospital emergency drug

- episodes: 1975–1978. *J. Am. Stat. Assoc.* 88, pp.423.
- Moore, T.J., Cohen, M.R., Furberg, C.D., (2007). Serious adverse drug events reported to the Food and Drug Administration, 199-2005. *Arch. Intern. Med.* Sep 10;167(16): pp.1752-9.
- NAOMI Study Team (2008). Reaching the hardest to reach – treating the hardest-to-treat: summary of the Primary Outcomes of the North American Opiate Medication Initiative (NAOMI). Retrieved on Nov. 7th 2009 from <http://www.naomistudy.ca/pdfs/NAOMI.Summary.pdf>
- Narang, S., Gibson, D., Wasan, A.D., Ross, E.L., Michna, E., Nedeljkovic, S.S., Jamison, R.N. (2008). Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. *J. Pain.* 9(3): pp.254-264.
- Nolin, P.C., Kenny, C., Banks, T., Maheu, S., Rossiter, E. (2002). *Report of the Senate Special Committee on Illegal Drugs*. Ottawa: Senate of Canada.
- Noyes, R., Brunk, S.F., Baram, D.A., Canter, A. (1975a). Analgesic effects of delta-9-THC. *Journal of Clinical pharmacology.* 15(2-3): pp. 139-143.
- Noyes, R., Brunk, S.F., Avery, D.H., Canter, A. (1975b). The analgesic properties of delta-9-tetrahydrocannabinol and codeine. *Clinical Pharmacology and Therapeutics* 1975. 18(1): pp.84-89.
- Nurmikko, T.J., Serpell, M.G., Hoggart, B., Toomey, P.J., Morlion, B.J., Haines, D. (2007). Sativex successfully treats neuropathic pain characterised by allodynia: a randomised, double-blind, placebo-controlled clinical trial. *Pain.* 133(1-3): pp.210-220.
- Pacula, R.L. et al, (2000). Marijuana and Youth. *NBER Working Paper No. 7703*. Retrieved on May 31st, 2007 from <http://econpapers.repec.org/paper/nbrnberwo/7703.htm>
- Pertwee, R.G. (2002). Sites and mechanisms of action. In Grotehermen F, Russo E, e. *Cannabis and Cannabinoids*. New York: The Hayworth Press. ch.7, pp.73-83.
- Pinsger, M., Schimetta, W., Volc, D., Hiermann, E., Riederer, F., Pölz, W. (2006). Benefits of an add-on treatment with the synthetic cannabinomimetic nabilone on patients with chronic pain; a randomized controlled trial (original in German). *Wien Klin.* 118(11-12): pp.327-335.
- Reiman, A. (2006). Cannabis Care: Medical cannabis facilities as health service providers. Dissertation. School of Social Welfare/Alcohol Research Group: University of California, Berkeley.

- Reiman, A. (2009). Cannabis as a substitute for alcohol and other drugs. *Harm Reduction Journal* 2009, 6:35
- Russo, E.B. (2008). Cannabinoids in the management of difficult to treat pain. *Therapeutics and Clinical Risk Management*. 4(1) pp.245–259.
- Russo, E.B. (2008b). Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? *Neuro Endocrinol Lett*. (2): pp.192-200.
- Substance Abuse and Mental Health Services Administration, (2007). *Results from the 2006 National Survey on Drug Use and Health: National Findings*. Office of Applied Studies, Rockville, MD. NSDUH Series H-32, DHHS Publication No. SMA 07-4293.
- Sylvestre, D. et al (2006). Cannabis use improves retention and virological outcomes in patients treated for hepatitis C. *Eur J Gastroenterol Hepatol*. Oct; 18(10): pp.1057-63.
- Tupper, K.W. (2007). The globalization of ayahuasca: harm reduction or benefit maximization? *International Journal of Drug Policy*. doi: 10.1016/j.drugpo.2006.11.001
- Von Bibra, E. (1855) *Die Narkotischen Genussmittel und der Mensch*. Nuremberg. pp.290.
- Wagner, F.A., & Anthony, J.C. (2002). Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, and cocaine. *Am J Epidemiol*. 2002 May 15; 155(10): pp.918-25.
- Walker, J.M. et al, (1999) The neurobiology of cannabinoid analgesia. *Life Sciences*. 65(6-7): pp. 665-673.
- Ware, M.A., Adams, H., Guy, G.W. (2005). The medicinal use of cannabis in the UK: results of a nationwide survey. *International Journal of Clinical Practice*. 59 (3), pp.291–295.
- Ware, M. A., Wang, T., Shapiro, S., Robinson, A., Ducruet, Huynh, T., Gamsa, A., Bennett, G.J., Collet, J-P., (2010). Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. *CMAJ*; 182 (14).
- Wilsey, B., Marcotte, T., Tsodikov, A., Millman, J., Bentley, H., Gouaux, B., Fishman, S. (2008). A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J. Pain*. Pp.506-521.