

**A REVIEW OF THE EVIDENCE SURROUNDING THE SAFETY OF
MEDICAL MARIJUANA AUTHORIZATION FOR ADULTS WITH
NEUROPATHIC PAIN IN PRIMARY CARE**

by

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ABSTRACT

Chronic neuropathic pain (NeP) is a complex condition that is commonly seen in primary care and is often refractory to current recommended treatments. Novel approaches to pain management are increasingly being studied to address this issue including the use of cannabis, a plant that has been used medicinally for thousands of years. The aim of this project was to review the current literature to determine if medical marijuana can be authorized safely by primary care providers (PCPs) to treat NeP in adults. Rational prescribing guidelines were used as the foundation for determining safety. Background knowledge of pain, chronic pain, neuropathic pain, analgesia, the history of medical marijuana, marijuana licensing, pharmacology of cannabis, including what is known about the efficacy on NeP, medical marijuana and society, nurse practitioner prescriptive authority and safe prescribing practices formed the basis of this review. The 12 studies utilized in this review do not provide enough data to support the safe use of medical marijuana for NeP in adults. It may be considered after guideline recommended prescription treatments have failed in specific clients taking into account the limitations of the evidence and associated risks. For those PCPs who are considering authorizing dried cannabis for their clients recommendations for practice will be discussed. Areas for future research and limitations of the review will also be acknowledged.

Keywords: cannabis, medical marijuana, neuropathic pain, nurse practitioner, safe prescribing

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INTRODUCTION

The dried plant form of cannabis is a preparation from the *Cannabis sativa* species and is acknowledged for its psychoactive, medicinal, and analgesic properties dating back thousands of years (ElSohly & Slade, 2005; Greenwell, 2012). The therapeutic potential of cannabis has been historically supported by anecdotal reports and more recently by experimental animal and human studies (Fontelles & Garcia, 2008; Greenwell, 2012). It is being used for a variety of conditions including chemotherapy induced nausea and vomiting, anxiety, depression, migraine, osteoporosis, glaucoma, spasticity, wasting syndrome, multiple sclerosis, spinal cord injury, epilepsy, anorexia nervosa, sleep disorders and pain syndromes (Health Canada, 2013a). The extensive preclinical research has revealed analgesic properties of both exogenous and endogenous cannabinoids on the endocannabinoid system; this has prompted an increase in dedicated clinical studies to evaluate the safety and efficacy of dried cannabis. This increase also comes from a recognized need to develop new strategies for pain conditions that respond poorly or are refractory to current treatment regimens and public pressure (Abrams et al., 2007a; Finnerup, Sindrup, & Jensen, 2010; Wilsey et al., 2013).

One condition commonly seen in primary care that often responds poorly to currently recommended treatments is neuropathic pain (NeP) (Finnerup et al., 2010; Gilron et al., 2006). Neuropathic pain results as a complication of diabetes, alcoholism, herpes zoster, HIV, amputation, multiple sclerosis, chemotherapy, spinal cord injury and facial nerve problems (Canadian Neuropathy Association, 2013). The synthetic cannabinoid nabilone and dried cannabis derivative Sativex have demonstrated some efficacy for the treatment of NeP in clinical trials and are available by prescription in Canada (Karst et al., 2010; Lynch & Campbell, 2011; and Martín-Sánchez, Furukawa, Taylor & Martin, 2009).

Current indications include for multiple sclerosis and cancer induced pain, nausea and vomiting (Government of Canada, 2012a) though off-label use of nabilone is not uncommon.

Dried cannabis is not legally approved for use as a therapeutic agent in Canada but the *Marihuana for Medical Purposes Regulations* legislation permits the limited sale of cannabis for medicinal purposes (Health Canada, 2013b). Individuals are given a medical document by their physician that authorizes a license for legal access to buy and use the dried cannabis plant for a specific medical condition. However, physicians have expressed concern with the lack of literature and evidence to provide guidance on how to authorize this licensure safely (College of Family Physicians of Canada [CFPC], 2014). Nurse practitioners (NPs), as primary care providers (PCPs), are also concerned regarding the lack of evidence for dried medical marijuana authorization, because they have recently become another group of PCPs that have been granted authority by federal legislation to authorize its use, with final regulation resting with the provinces. The medico-legal implications of utilizing this substance in practice, when ambiguity surrounds its appropriate use and safety, is a concern for PCPs.

Rational clinical decision-making incorporates the principles of safe prescribing using a standardized method that evaluates the risks, benefits, potential complications and drug interactions associated with the use of a medication (College of Physicians and Surgeons of British Columbia [CPSBC], 2014). An authorization for medical marijuana is not a true prescription because it does not include all the key elements of traditional controlled drugs and substance (CDS) prescriptions including the use of a numbered, personalized PCP duplicate prescription pad that has the date, patient name and address, name of drug, strength, dose, route, quantity, directions for use and practitioner signature (College of Pharmacists of British Columbia, 2010). Further, CDS prescriptions are void if not filled within five days of date

written (College of Pharmacists of British Columbia, 2011). However, though dried cannabis is not regulated by Health Canada, PCPs are expected to use the same standards when assessing the suitability and safety of a prescription medication for a client when authorizing medical marijuana (CPSBC, 2014). Thus, the aim of this project is to review the current literature to determine if dried cannabis can be authorized safely by PCPs to treat NeP in adults. The World Health Organization (WHO) published a guideline, *Guide to Good Prescribing: A Practice Manual* (de Vries et al., 1994) that identifies six key steps in the process of rational prescribing (see Appendix A). All of the steps are important to follow but for the purpose of this project, step three of the guideline will be highlighted as it focuses on the suitability and safety of prescribed medications. The efficacy in meeting the therapeutic objective, the drug's adverse and toxic effects, contraindications, drug-interactions, proper dosing and method of delivery, client mental status, presence of comorbidities and cost to the client are evaluated in this step (de Vries et al., 1994).

This review begins with an in depth discussion of the pathophysiology of pain, chronic pain, neuropathic pain, the endocannabinoid system, the pharmacology of cannabis, medical marijuana licensing, NP prescriptive authority legislation in Canada, and the guidelines and principles that define rational prescribing. The methods section will detail how the literature search was completed. The findings will provide an analysis of the studies presenting key themes for further examination. The discussion section will provide a synthesis of the current evidence from the literature that will be followed by recommendations for practice and future research.

CHAPTER 1

Background

Neuropathic pain is a complex condition that responds sub-optimally to the current recommended treatments. Thus, the objective of this review is to determine if dried cannabis can be authorized safely by PCPs to treat NeP in adults. This section will provide the reader with the necessary background information on neuropathic pain, dried medical marijuana, and the principles of safe prescribing.

Pathology of Pain

Pain is a subjective sensory symptom that is invisible and difficult to measure. It also has physical, psychological and emotional components (Baron, Binder & Wasner, 2010). It occurs as a result of a variety of pathological conditions and is generally divided into two types: nociceptive and neuropathic (King et al., 2013). Nociceptive pain, which has both visceral and somatic varieties, is typically associated with a direct response to tissue damage from noxious stimuli that happens with injury, inflammation or cancer. Neuropathic pain occurs with damage to the neural tissue of the central nervous system (CNS) and peripheral nervous system (PNS) (Rang et al., 2012).

At the microscopic level, peripheral sensory neurons, called polymodal nociceptors, in visceral and somatic tissue respond to noxious chemical, mechanical, or thermal stimuli by activating sodium channels in the cell membrane. Sodium channels generate electrical impulses that are transmitted along afferent nerve fibers from the PNS to the CNS where the stimuli are received (Rang et al., 2012). Areas of the CNS involved in pain processing include parts of the thalamus, somatosensory cortex, periaqueductal gray, basal ganglia, cerebellum, amygdala, and

hippocampus (Aggarwal, 2013). Pain is inhibited when these impulses leave the brain and travel along descending efferent pathways (Rang et al., 2012).

Chemical mediators are also released that act on these peripheral sensory neurons to induce pain and include bradykinin, protons, adenosine triphosphate (ATP), histamine and transient receptor potential channels (TRP) (Rang et al., 2012). In addition, bradykinins release prostaglandins that enhance pain production by increasing nociceptor pain sensitivity.

Acute pain stimulation is typically self-limiting as it disappears when the original insult has resolved. However, prolonged insult to these pain receptors can result in a continuation of pain signalling past the normal point of termination, resulting in the initiation of a chronic pathological state process that produces chronic pain.

Chronic pain. Chronic pain that is not due to cancer or cancer related conditions. It is defined as pain that lasts beyond the duration of time that the original injury would normally take to heal; this is generally longer than three to six months (Canadian Psychological Association, 2014). Many clinical pain states fall under this category of chronic non-cancer pain and may include phantom limb pain, fibromyalgia and neuropathic pain. Chronic pain is a major issue in Canada and results in a reduced quality of life and productivity. It is estimated that 15% to 19% of Canadians over the age of 15 have chronic non-cancer pain, with 11.4% to 13.3% reporting a negative effect on their daily activities (Reitsma et al., 2011). One type of chronic pain that differs in its pathophysiology when compared to nociceptive chronic pain is neuropathic pain.

Neuropathic pain. Neuropathic pain (NeP) is a type of pain that is induced by several pathological mechanisms that result from neuronal damage. Inflammatory mediators are released when a nerve is injured with resulting peripheral and central sensitization. Overexpression and hyper-excitability of the voltage gated sodium channels leads to over firing of nerve impulses in

injured and neighbouring non-injured afferent pain pathways (Baron et al., 2010). CNS immune modulators are also released during inflammation and contribute to the sustainment of pain without any external stimulus. Further, descending efferent nerve pathways are responsible for pain inhibition but lesions on these nerves directly impair their ability to inhibit the pain signal (Baron et al., 2010).

The sympathetic nervous system (SNS) also plays a role in NeP. Sympathetic neurons can grow into the injured dorsal root neurons. Sympathetic fibers also grow into the injured dermis. This results in both an increased number and activity of calcium ion gated channels sensitive to circulating catecholamines (Gilron et al., 2006). This pathology produces allodynia, which is, the initiation of pain without a noxious stimulus (Gilron et al., 2006). Medications that target these calcium ion channels, such as the antiepileptic gabapentin, can be effective for relieving NeP.

NeP is generally differentiated on the basis of pathology involving the PNS or CNS (Moulin et al., 2007). Causes of central NeP include post-stroke pain, multiple sclerosis, fibromyalgia, and spinal cord injury (Moulin et al., 2007). Causes of peripheral NeP include diabetic neuropathy, post-herpetic neuralgia, HIV distal sensory polyneuropathy, amputation and chemotherapy (Canadian Neuropathy Association, 2013; Moulin et al., 2007). Symptoms of NeP are divided into spontaneous pain and stimulus-evoked pain (Moulin et al., 2007). The burning, shooting and lancing pain with a feeling of tightness is characteristic of spontaneous pain whereas the symptoms of allodynia and hyperalgesia are associated with stimulus-evoked pain (Moulin et al., 2007). There are specific validated screening tools including the “Douleur Neuropathique en 4 questions” (DN4) (Bouhassira et al., 2005) and the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (Bennett, 2001) that help to diagnose NeP in order to tailor treatment.

Individuals differ in their response to treatments and this is partially the result of the underlying complexity of NeP and individual genetic variability (Baron et al., 2010). New research is uncovering more details explaining the neural mechanisms of pain. As a result, new targets for pain management and analgesia are being developed (Rang et al., 2012).

Analgesia

Analgesia is the inability to feel pain and is a result of endogenous opioids and the neurotransmitters serotonin and norepinephrine (Bauldoff et al., 2011). An analgesic is a class of drug that relieves pain without blocking nerve impulse conduction or sensory function. This includes two drug classes, the opioids and the non-steroidal anti-inflammatory medications (NSAIDs) (Rang et al., 2012). There are other classes of drugs, including antiepileptics and antidepressants, which also exhibit analgesic qualities but work differently from opioids and NSAIDs. Acute pain responds more favourably to those medications that exert their action on normal pain pathway receptors seen with nociceptive pain. NSAIDs are effective for mild and moderate nociceptive pain arising from muscles and vessels seen in arthritis, bursitis, toothaches, painful menses, and bone cancer (Rang et al., 2012). They exert their effects by decreasing the production of prostaglandins in the PNS and inhibiting the release of prostaglandins from the spinal cord. Prostaglandins sensitize nociceptors to inflammatory mediators such as bradykinin (Rang et al., 2012). Acetaminophen exhibits a similar pharmacological activity to NSAIDs but with fewer anti-inflammatory effects (Bauldoff et al., 2011)

Opioids are a group of substances that target the opioid receptors located on neurons of the PNS and CNS (Rang et al., 2012). Their action results in the inhibition of nociceptive impulse transmission through the dorsal horn of the spinal cord, the suppression of neurotransmitter release presynaptically and response postsynaptically, and the release of serotonin from the

descending inhibitory pathways (Rang et al., 2012). They are generally quite effective for the management of acute nociceptive pain and for some types of chronic pain (Rang et al., 2012).

Opioids are commonly prescribed for NeP but have shown only a small or modest benefit (National Opioid Use Guidelines Group [NOUGG], 2010). They are third line agents in the Canadian neuropathic pain guidelines (Moulin et al., 2007). Those with NeP are thus likely prescribed higher opioid doses to improve efficacy; however, higher doses of opioids are associated with higher rates of adverse effects, dependence and abuse (NOUGG, 2010). A balance between effective pain management and preventing harms with opioid use is a challenge for PCPs. As a result, alternative therapies are being sought that target other receptors (NOUGG, 2010).

Medications that are indicated for non-pain conditions that target the PNS and CNS have shown some efficacy for chronic pain like NeP. Tricyclic antidepressants (TCAs) act centrally to inhibit noradrenaline reuptake whereas the antidepressant venlafaxine inhibits both serotonin and norepinephrine reuptake (Rang et al., 2012). Antiepileptic drugs, gabapentin and pregabalin, reduce neurotransmitter release by inhibiting calcium channel function; their action is enhanced in the presence of damaged sensory neurons (Rang et al., 2012). These classes of drugs are first and second line agents in the national and international NeP pain treatment guidelines (Attal et al., 2010; Moulin et al., 2007). The complexity of NeP is being increasingly studied and new research into the role of the endocannabinoid system for analgesia has revealed some interesting findings.

Endocannabinoid System

The endocannabinoid system is a lipid signalling system with two main receptors, cannabinoid one (CB1) and two (CB2). These are activated by the endocannabinoid mediators,

anandamide and 2-arachidonoyl glycerol (2-AG) (Rang et al., 2012). This system is found in all vertebrates and has important regulatory functions.

CB1 receptors are found throughout the PNS and CNS encompassing the areas of the brain responsible for memory, coordination, appetite, body temperature, psychological “reward”, and in central and peripheral pain pathways including peripheral nociceptors (Rang et al., 2012). They are also found in adipocytes, leukocytes, the spleen, heart, lungs, gastrointestinal tract, kidney, bladder, reproductive organs, skeletal muscle, bone, joints, and skin (Health Canada, 2013a). They are involved in many processes including stimulation of the immune system (Greineisen & Turner, 2010), lipogenesis (Rang et al., 2012), and reproductive system suppression (Brown & Dobs, 2002). They are also involved in the pathogenesis of nonalcoholic fatty liver disease and progression of liver fibrosis in chronic liver disease (Mallat & Lotersztajn, 2008).

CB2 receptors are expressed in the tissues and cells of the immune system including leukocytes, the spleen, tonsils, thymus, liver, bone and some nerve cells (Rang et al., 2012). The activation of these receptors results in immune suppression (Greineisen & Turner, 2010), atherosclerosis (Rang et al., 2012), and the regulation of pain (Fontelles & Garcia, 2008).

Components of the cannabis plant and its derivatives exert their effect on the endocannabinoid system receptors, key therapeutic targets in the management of N&P.

Medical Marijuana

History of use. Dried marijuana has been used for over a thousand years for medicinal purposes; however, its therapeutic value has only been supported by anecdotal evidence and less rigorously designed scientific studies (Greenwell, 2012). In 1997, the United States Institute of Medicine (IOM) was tasked to analyze the existing research on the potential health benefits of dried cannabis and its isolated cannabinoids (Joy, Watson & Benson, 1999). These early studies

identified cannabis and its derivatives as potential therapeutic agents for several neurological conditions. From this preliminary data recommendations were made to conduct further research using rigorous clinical trials.

Canadians have had access to dried medical marijuana since 1999 through an exemption created under section 56 of the *Controlled Drugs and Substances Act* (Government of Canada, 2014). In 2000, the Ontario Court of Appeal (*Regina. vs Parker*) ruled that an individual has the right, as set out under the *Canadian Chart of Rights and Freedoms*, to reasonable access to a legal source of marijuana for medical purposes (Government of Canada, 2012a). Thus, in 2001, the Marihuana Medical Access Regulations (MMAR) were established (Government of Canada, 2001). Medical cannabis was approved for use in clients who had significant nausea, anorexia, weight loss, persistent muscle spasms, seizures, severe pain cancer, AIDS, multiple sclerosis, spinal cord injury, epilepsy, and severe arthritis (Government of Canada, 2001). However, with the increasing numbers of Canadians accessing marijuana under the MMAR, there have been stakeholder concerns over how the MMAR creates barriers to access. There were concerns that the current system threatens public safety because of unregulated growing operations. Thus, in March of 2014, significant amendments were made. The new *Marihuana for Medical Purposes Regulations* (MMPR) were created with the following objectives: to produce quality controlled dried marijuana, to require only licensed producers with an unencumbered process of medical marijuana licensing, and to only permit direct sale of marijuana to individuals in possession of a license (Government of Canada, 2012a). Health Canada claims the aim of the regulation is to treat medical marijuana like any other controlled substance for medical purposes and for licensed producers to be subject to regulatory requirements including proper security, packaging, labelling, shipping, distribution, record keeping and reporting (Government of Canada, 2012a).

The intention is also to reduce the risk for and incidence of diversion among distributors. However, a document for medical marijuana does not follow the same standards as a CDS prescription as previously discussed (College of Pharmacists of British Columbia, 2011). Further, this increase in regulatory oversight will likely increase the cost of dried cannabis to consumers which may deter some from obtaining a license and instead use illegal sources of cannabis that are not quality controlled (Government of Canada, 2012a).

Medical marijuana license. Health Canada does not regulate or approve of medical marijuana; thus, a medical marijuana document given to a client from a PCP is not a prescription but an authorization that provides the patient with a license to possess dried cannabis for medical purposes. However, despite the lack of pharmaceutical regulation and intrinsic safeguards seen with traditional prescriptions of medications, it is still the responsibility of the PCP to demonstrate proper evaluation of clients for the risks, benefits, potential complications and drug interactions of cannabis, in addition to screening for risks of abuse and addiction (College of Physicians and Surgeons of British Columbia [CPSBC], 2014). The current limited research available surrounding the safety of medical marijuana has made it difficult for PCPs to embrace it as a therapeutic option, particularly with the ambiguity surrounding efficacy, dosing and frequency.

Composition. Marijuana, or *Cannabis sativa*, is a hemp plant that grows in temperate and tropical climates. It contains over 400 distinct chemical compounds (ElSohly & Slade, 2005). The leaves and flowering tops contain over 70 exogenous phytocannabinoids (Aggarwal, 2013; ElSohly & Slade, 2005). These act on the CB1 and CB2 receptors and cause effects similar to the endogenous mediators, anandamide and 2-AG. The most studied and abundant cannabinoid in cannabis is delta-9-tetrahydrocannabinol (THC) and is responsible for most of the physical and

psychotropic effects (Rang et al., 2012). The highest concentration of THC is found in the mature flowering heads and it is this part that is cultivated and used to produce the desired therapeutic and recreational psychoactive properties (Health Canada, 2013a). Currently, Health Canada provides dried marijuana with a THC concentration of $12.5 \pm 2\%$ and less than 0.5% of the other cannabinoids including cannabidiol (CBD), cannabigerol (CBG), and cannabichromene (CBC) (Health Canada, 2013a). It is estimated that illegal forms of marijuana contain THC concentrations in the range of 1% to 30% with an average of 10% (Health Canada, 2013a). One of the main objectives of the revised MMPR was to establish quality controlled marijuana with known cannabinoid concentrations by licensed producers (Government of Canada, 2012a). Knowing the THC concentration of a given strain contributes to safety by providing a consistent dose. Health Canada (2014) also provides an updated list of authorized licensed producers for access by the public.

Clinical pharmacology. THC is a partial agonist and cannabidiol (CBD) an antagonist at the CB1 and CB2 receptors (Izzo et al., 2009). Cannabidiol also targets calcium ion channels; 5-lipoxygenase and phospholipase A2 enzymes; and the tryptophan, 5-HT1A, adenosine, glycine, and opioid receptors which produces the anti-inflammatory, analgesic, anti-nausea, antipsychotic and anxiolytic effects (Izzo et al., 2009). It also demonstrates anti-convulsant activity and induces hepatic drug metabolism (Rang et al., 2012). Preliminary research has shown that CBD appears to mitigate THC's psychoactive effects but enhance its analgesic effect. An important relationship to consider when prescribing different strains of cannabis since the therapeutic effects will vary somewhat. They produce analgesic effects through their action on both ascending and descending pain pathways where they suppress calcium ion conduction that is responsible for nerve firing and transmission (Aggarwal, 2013).

The pharmacological effects of cannabis are numerous. Age, immune status, concurrent use of other medications and substances, method of delivery, dose, previous cannabis experience, and composition of cannabis plant used influence the effects experienced by a given individual (Hunault et al., 2009). Many of the effects of cannabis occur biphasically with lower doses causing effects that are opposite to effects seen with higher doses (Mechoulam & Parker, 2013); this is a characteristic shared with opioids (NOUGG, 2010). Further, some studies have shown cannabis to have a narrow therapeutic window for analgesia with hyperalgesia occurring at high doses (Wallace et al., 2007; Wilsey et al., 2008). These characteristics stress the importance of careful titration to avoid adverse effects.

Physiological effects measured in animal and human studies include pharmacological activity on most body systems. CNS effects include the impairment of short-term memory and learning, subjective feelings of confidence and heightened creativity, impairment of motor coordination, catalepsy, hypothermia, analgesia, antiemetic action and increased appetite (Rang et al., 2012). Peripheral effects include tachycardia, vasodilatation, reduction of intraocular pressure and bronchodilation (Rang et al., 2012).

Pharmacokinetics. There are several routes for cannabis administration. Each route has a distinct mode of absorption and time to onset of activity (Aggarwal, 2013). The plant material can be ingested orally, absorbed through the lungs via smoking or inhalation of vapors, applied topically, or absorbed through the oral mucosa (Health Canada, 2013a).

Smoking. The onset of action of smoked cannabis occurs within seconds to minutes with peak effects reached at 30 minutes and duration of two to three hours (Rang et al., 2012). Smoking cannabis results in a higher plasma level of cannabinoids and a shorter duration of action compared to oral administration. This rapid entry into CNS contributes to the intense

pleasure experienced by some users. This rapid euphoria also contributes to its abuse potential (Huestis, 2007). Factors that impact levels of absorption of THC and the other cannabinoids include the source of the plant material, composition of the cigarette, and the efficiency and method of smoking by the person such as the depth of inhalation, puff duration and breath hold (Health Canada, 2013a). THC bioavailability with smoking ranges from $23\pm16\%$ (Lindgren et al., 1981) in experienced users and $10\pm7\%$ in occasional users (Grotenhermen, 2003). Also, as the marijuana cigarette shortens in length the concentration increases (Carter, Weydt, Kyashna-Tocha, & Abrams, 2004).

Vaporization. Vaporization is an alternative method of drug inhalation. Cannabis is heated to a temperature between 180 and 200 and vapors are inhaled. It is theorized that these cannabinoid vapors form below the temperature of combustion where toxic compounds, such as tar, are released, making this a safer route of administration (Abrams et al., 2007b; Wilsey et al., 2013). However, studies have shown that carbon monoxide, tar, and other carcinogenic compounds including polycyclic aromatic hydrocarbons are released and absorbed in the lungs, though in smaller amounts compared to the smoking route (Health Canada, 2013a). This has led to the belief that the risks of respiratory disease and cancer are lessened with this method. However, there is not enough data to confirm this finding. The onset of action, peak plasma levels, and subjective effects of vaporized cannabis are similar to the smoked form in clinical studies (Abrams et al., 2007b; Wilsey et al., 2013).

Oral ingestion. Cannabis can be consumed orally in butters, oils, brownies, teas, and cookies. There is variability of the amount of THC absorbed when ingested orally because of individual differences in rates of absorption, metabolism and excretion (Huestis, 2007). Peak plasma levels are reached between one to six hours (Grotenhermen, 2003) and duration of action

is between five to eight hours (Huestis, 2007) though cognitive function can be impaired for up to 24 hours in some cases (CFPC, 2014). The oral form results in lower bioavailability and plasma levels compared to the smoked form because of the first pass hepatic effect (Grotenhermen, 2003); one study showed only a range of $6\pm3\%$ (Ohlsson et al., 1980).

Other forms of cannabis administration includes oromucosal, rectal and topical but will not be discussed further in this review as the current literature reviewed discusses the smoking, vapor and oral ingestion routes only, as these are the most common routes of ingestion for dried cannabis.

Distribution. THC is absorbed by the fatty tissues, heart, lungs, liver and brain (Health Canada, 2013a). The blood brain barrier slows the crossing of THC that results in a delay between peak plasma levels and psychoactive effects (Health Canada, 2013a). This effect on the brain is a concern for users who titrate their dose of cannabis based on a subjective “high” that occurs after peak plasma levels have been reached. This has the potential to put the client at risk for more serious adverse effects. THC accumulates and is retained in fatty tissue, which may explain why adverse effects are observed in organs that contain this type of tissue, including the reproductive organs and the brain (Huestis, 2007).

Metabolism and excretion. THC and cannabidiol are metabolized in the liver to active metabolites by the xenobiotic cytochrome P450 enzymes, CYP2C9 and CYP3A4 (Watanabe et al., 2007). With oral cannabis, metabolism by the liver results in the formation of higher levels of the psychoactive metabolite, 11-hydroxy-THC, which results in increased sedation compared to the inhalation route (Grotenhermen, 2002).

More than 65% of cannabis is excreted in the feces and 20% is excreted by the kidneys with no differences between the sexes (Wall et al., 1983). Excretion also occurs through the hair,

sweat and oral fluids (Huestis, 2007). Cannabis is highly lipophilic; thus, complete elimination from the body occurs slowly over several days due to its slow release from body fat (Aggarwal, 2013). The terminal half-life of dried cannabis varied among studies due to variations in lab test measurement sensitivities in the measurement (Huestis, 2007). One study that measured urinary excreted cannabis metabolite determined the half-life to be three to four days (Johansson & Halldin, 1989).

Adverse effects. Reported adverse effects from cannabis are based mainly on studies of recreational users; there is a lack of data with non-recreational cannabis users. The short-term effects in clinical trials demonstrate a peak effect at 30 minutes that lasts for several hours (Grotenhermen, 2003). The time frame considered long term has been mainly based on studies evaluating subjects who have used marijuana for several years; it is unclear at what point long-term effects start to appear initially (Gordan, Conley & Gordon, 2013).

Physical effects. Short-term adverse effects include tachycardia, bronchodilation (Tashkin, 2013), arteritis, hypotension, and multifocal vasoconstriction. Multifocal vasoconstriction may lead to reversible ischemic stroke (Wolff et al., 2011). Long-term adverse effects include hyperemesis, reproductive and immune system alteration, and increased rates of chronic bronchitis and lung infections. Long-term chronic heavy users of cannabis demonstrate lung changes that include mutagenic changes, suppressed activity of alveolar macrophages, and increased airway resistance induced by airway inflammation (Tashkin, 2013). An association between cannabis use and lung cancer was recently confirmed in data collected from a 40 year cohort study, even accounting for baseline tobacco and alcohol use, pre-existing respiratory conditions and socioeconomic status (Callaghan, Allebeck, & Sidorchuk, 2013). Tolerance, physical dependence and psychological addiction occur in both infrequent and heavy users of

cannabis. This occurs as a result of CB1 receptor down regulation and desensitization (Health Canada, 2013a). Withdrawal symptoms include depressed mood, anger, aggression, cravings, headache, restlessness, anxiety, irritability and decreased appetite (Budney, Hughes, Moore & Vandrey, 2004). Symptoms begin within one to two days of discontinuation with peak symptoms occurring between two and six days. Resolution occurs within one to two weeks (Budney et al., 2004).

Cognitive effects. Short-term effects on cognition include impaired learning, sedation, memory, attention, judgment, concentration, executive function, and psychomotor coordination (Rang et al., 2012; Volkow, 2014). Impaired driving and increased risk for motor vehicle accidents have been associated with cannabis use (Calabria et al., 2010). Long-term effects include impaired fetal neurocognitive development, impaired brain development, lowered IQ in frequent users during adolescence, and addiction (Volkow, 2014). One prospective study found that persistent cannabis users who started in adolescence had impaired neuropsychological functioning even after one year of abstinence; a finding not found in persistent users who had started in adulthood (Meier et al., 2012).

Psychological effects. Short-term effects include anxiety, paranoia and psychosis (Volkow, 2014). Long-term effects include diminished life satisfaction and achievement, chronic psychosis, depression and addiction (Volkow, Baler, Comptom & Weiss, 2014). Evidence has shown cannabis use to be a trigger for earlier age onset of schizophrenia and bipolar disorders in genetically susceptible individuals (Volkow et al., 2014).

Addiction. Up to 9% of those who experiment with cannabis will become addicted (Anthony, 2006) based on the criteria for cannabis use disorder recognized by the DSM-V (American Psychological Association, 2013). Higher rates are seen in those who initiate cannabis

use in adolescence with one out of six becoming addicted (Anthony, 2006) and 25% to 50% becoming addicted who smoke it daily (Hall & Degenhardt, 2009). In Canada, statistics from 2012 showed a lifetime prevalence rate for cannabis abuse or dependence of 6.8% (Statistics Canada, 2013). The presence of withdrawal symptoms makes cessation more difficult and results in higher relapse rates (Volkow et al., 2014). In 2009 to 2010, statistics from Ontario showed 38.2% of men and women who went to Ontario treatment centres identified cannabis dependence as their primary reason for admission (Rotondi & Rush, 2012). It is the most commonly used illegal substance in Canada with the most recent statistics reporting a prevalence rate of 10.2% in Canadians over the age of 15 (Health Canada, 2012).

Toxicity. The cannabis dose that induces intoxication is variable among users though doses greater than 5 grams per day are associated with greater risk for dependence and adverse effects (Health Canada, 2007). Toxic effects include tachycardia, hyperemesis, hypotension, psychosis, anxiety, and impaired motor coordination, memory and concentration (Weinstein & Gorelick, 2011). Most effects are self-limiting and mild though there have been two reported cases of death directly attributable to cardiovascular complications caused by smoking cannabis in two young adults (Hartung, Kauferstein, Ritz-Timme & Daldrup, 2014).

Drug-interactions. THC and cannabidiol are metabolized in the liver by the cytochrome P450 CYP2C9 and CYP3A4 enzymes. These enzymes are also involved in the metabolism of other drugs. Limited studies have shown THC to inhibit the metabolism of haloperidol and induce the metabolism of phenytoin, indinavir and nelfinavir (Mozayani & Raymon, 2011). Medications that inhibit THC metabolism include fluoxetine, nicotine and tricyclic antidepressants (Mozayani & Raymon, 2011). Cannabis also interacts with substances that act on

the central nervous system including alcohol and lorazepam; increased sedation is observed when these are combined with marijuana (Canadian Pharmacists Association, 2014a).

Contraindications. Dried cannabis use is contraindicated or cautiously used in populations that are vulnerable to the adverse effects discussed in the previous text (Health Canada, 2013a). The brain remains in an active state of development into young adulthood (Lebel & Beaulieu, 2011) and is more vulnerable to environmental insults (Volkow et al., 2014). THC affects neural connections in the brain that manifests as impaired learning, memory, self-awareness, alertness, and inhibitory control (Volkow et al., 2014). Thus, those under 25 should not be prescribed cannabis. Further, it is advisable to avoid use in those with severe cardio-respiratory, liver, renal, severe mental illness including schizophrenia or psychosis, and pregnant or breastfeeding (Health Canada, 2013a). Caution or avoidance is also warranted if prescribing for clients with history of active or remote substance abuse, mania, depression, or on concurrent anti-psychotic or sedative-hypnotic medications (Health Canada, 2013a).

Dosing. The optimal dose of medical marijuana should improve pain relief and function while causing minimal euphoria or cognitive impairment (CFPC, 2014). However, therapeutic dosing of cannabis is complex due to several factors: the pharmacological complexity of cannabis, the inconsistent and variable concentration of active ingredients due to conditions of plant growth, harvesting practices, heterogeneity of THC concentrations used in clinical studies, individual genetic variability in the physiological response to the drug, individual variability with method used for delivery, and varying pharmacokinetics among the different ingestion methods (Carter et al., 2004). Health Canada has made recommendations for the daily dose of cannabis based on the results from surveys in peer-reviewed literature. In any form of ingestion, with a THC concentration of $12.5 \pm 1.5\%$, the daily dose should be limited to between 1 and 3 grams of

dried plant (Health Canada, 2013a). More recent guidelines released by the CFPC (2014) advise a daily inhaled dose of 100 mg to 700mg of a THC concentration up to 9%. This dose is similar to that found in one retrospective study done in the Netherlands (N=5540) where the average daily dose of cannabis used for therapy, of varying potencies, was 0.68 grams per day (Hazekamp & Heerdink, 2013). This narrower daily dose suggested by CFPC will likely contribute to a better safety profile and lower incidence of adverse effects although the dosing is not as refined as prescription oral cannabinoids.

Frequency of dosing differs between methods of ingestion. Health Canada (2013a) advises users to wait a few minutes between puffs of smoked cannabis. The evidence from clinical studies demonstrates a shorter time period between puffs at an average of 45 to 55 seconds though most of these subjects were not cannabis naive. For a client who has never used cannabis or is trying a new strain, the lowest concentration of THC available is recommended as a single slow inhaled puff. Then, the individual should wait four hours to assess the efficacy (CFPC, 2014). For oral ingestion, the user should wait at least 60 minutes between bites of oral ingestion to determine strength of effect due to the slower achievement to peak plasma levels (Carter et al, 2004).

Cost. Medical marijuana is not covered under any provincial or federal prescription drug plan so the entire cost is left to the client. The new MMPR anticipates an increase in cost from the current \$1.80 to \$5.00 per gram to \$7.60 per gram this year with a further increase to \$8.80 per gram (Government of Canada, 2012a). For clients who require treatment long term, this is a significant expense. For example, a client that uses one gram per day would expect to spend from \$1825.00 to \$2774.00 per year; this is a conservative estimate. This is in comparison to nabilone, which costs \$2.73 per 1mg tab (London Drugs Pharmacist, personal communication, November

10, 2014). If a person takes the standard dose (one to two tabs twice daily) this amounts to \$10.92 per day or \$3985.80 per year not including the pharmacy dispensing fee. However, many provincial drug plans cover the partial cost of this medication; for example, in BC Pharmacare pays for \$1.67 of the cost of each 1mg nabilone tab (British Columbia Ministry of Health, 2014). Sativex costs \$662.24 for a 30 ml bottle (London Drugs Pharmacist, personal communication, November 10, 2014) or \$2.21 per spray. The normal dose is four to eight sprays per day, the cost of which equals approximately \$8.84 to \$17.68 per day and this medication is not covered by provincial drug plans though it may be covered by private insurance. Thus, the use of medical marijuana and other cannabinoids is limited to those who can afford it.

Prescription Cannabinoids

Health Canada regulates and approves the use of two types of cannabinoid medications available by prescription. Nabilone is an oral synthetic cannabinoid used for nausea and vomiting associated with cancer therapy and Sativex is an oromucosal spray made from cannabis plant extracts used for multiple sclerosis and cancer pain (Government of Canada, 2012a). Both of these medications have standardized concentrations and dosing that follow traditional medical prescribing protocols with better efficacy and safety profiles than dried cannabis. Sativex, for instance, combines two chemical extracts, THC and cannabidiol, from the plant in a fixed ratio ensuring a precise concentration for a metered, recordable dose (Brownjohn & Ashton, 2012). Both of these medications have adverse effect profiles and contraindications similar to the natural plant form (Canadian Pharmacists Association, 2009; 2014b).

Medical Marijuana and Society

Marijuana remains a controversial substance due to several societal and clinical concerns. It is an illegal substance often involved in diversion (Government of Canada, 2012a) and its use

can lead to abuse and addiction (Lucas, 2012; Volkow, 2014). There is also a prevailing view called the “gateway drug” theory that its use leads one to use more dangerous illicit substances (Lucas, 2012; Volkow et al., 2014). Indeed, epidemiological (Agrawal, Neale, Prescott & Kendler, 2004) and animal (Panlilio et al., 2013) studies have confirmed that THC primes the brain for addiction and enhances the responses to other drugs in susceptible individuals. However, the alternative theory is that people who are already more susceptible to drug use start with marijuana because of ease of accessibility and their social interactions with other drug users increases the likelihood of trying other drugs (Volkow et al., 2014). Further, reports of its therapeutic value have been mainly based on personal testimony and not on the results of rigorous scientific research trials (Bostwick, 2012). The CFPC (2014) report a keen interest in medical marijuana by patients often accompanied by less interest in the available evidence. The two dominant Canadian political parties are divided in their view of the legalization of marijuana. The Liberal Party of Canada is in favour of the decriminalization and legalization of medical marijuana whereas the Conservative Party opposes the decriminalization (Kennedy, 2014). A Canadian opinion poll by Ipsos Reid (N = 3000) found 37.3% in favour of marijuana legalization and 33.4% in favour of less punitive penalties for possessing small amounts, preferring fines instead of a criminal record (Kennedy, 2014). It is clear that a significant majority of Canadians in this poll do not support legalization nor the relaxed penalties for possession.

Current legislation and public opinion has likely contributed to pressure for researchers to gain support and funding to conduct scientific trials evaluating the therapeutic value of dried cannabis. Further, PCPs are taught to base clinical decision-making on evidence-based information. The lack of scientific evidence supporting the therapeutic value of dried cannabis,

the ambiguity around appropriate dosing, and the lack of regulatory oversight put PCPs in an uncomfortable position. Further, synthetic cannabinoids are already available and regulated by Health Canada. They also have a greater body of evidence for efficacy with lower rates of both adverse effects and addiction risk (CFPC, 2014). They are approved for use in a few conditions including multiple sclerosis and cancer related pain, nausea and vomiting. Off-label use for other conditions, however, is common (Government of Canada, 2012a). Finally, high rates of abuse and recreational use, supported by the current evidence, makes it difficult for the PCP to ensure that the prescribed marijuana will be used only for its intended therapeutic purposes.

Guidelines on Cannabis for Neuropathic Pain

The CFPC released preliminary guidelines, *Authorizing Dried Cannabis for Chronic Pain or Anxiety*, in September 2014 to assist prescribers by providing suggested approaches for the authorization of dried cannabis for medical purposes. This literature review evolved in September 2013 out of a lack of clinical guidelines on the objective but has included all relevant and current literature up to January 2014 with periodic evaluation for new studies. Thus, the results at the initiation of this review are based on a paucity of clinical guidelines at that period in time. New guidelines have been recently released and there will be further comment on those recommendations.

The College of Physicians and Surgeons of British Columbia (CPSBC) released a brief position and guidance on what should be assessed and documented when authorizing a medical marijuana license. Most notably, it was suggested that trials of unsuccessful therapies be documented. It was also suggested that the dose and frequency of marijuana use be specifically stated and that a one year expiration date be included as well (CPSBC, 2014).

Prior to the release of these two guidelines the Canadian Pain Society released the *Pharmacological Management of Chronic Neuropathic Pain - Consensus statement and Guidelines from the Canadian Pain Society* with the recommendation that cannabinoids be considered fourth line treatment in the management of NeP when other treatments have failed or are not available (Moulin et al., 2007). There were only two studies used to support this recommendation and they utilized the synthetic and medicinal extract forms of cannabinoids available by prescription. In 2010, the European Federation of Neurological Sciences (EFNS) Task Force issued guidelines for NeP treatment with the recommendation to use synthetic cannabinoids as second or third line treatment for central pain in multiple sclerosis. There was also one recommendation to use the dried plant form of smoked cannabis for HIV-associated polyneuropathy (Attal et al., 2010).

Nurse Practitioners and Prescriptive Authority

The introduction of the NP as a PCP has increased access to primary care for many Canadians (Canadian Nurses Association, 2008). Patients commonly present with acute and chronic pain in primary care; this is the most common reason for analgesic and or narcotic prescriptions (Gerhardt, 2004). As PCPs, NPs are educated in pain and pain management. This includes both non-pharmacologic and pharmacologic treatments and moreover, the judicious use of CDS. In 2012, the federal *Controlled Drugs and Substances Act* included NPs as health care providers with the authorization to prescribe CDS, though final regulation, standards, and processes rest with the provinces and territories (Government of Canada, 2012b). In jurisdictions where NPs controlled substance prescriptive authority has not yet been completed, a physician's signature is required. The College of Registered Nurses of British Columbia (CRNBC) is currently working with the Minister of Health to establish policy that will ensure public safety

for NPs who will be prescribing CDS. The first phase of CDS prescribing legislation will not include medical marijuana; CRNBC (2014a) states that after NPs have had experience with prescribing CDS will they consider what needs to be in place for medical marijuana authorization. Safe prescribing for NPs requires a strong foundation of education and policy support. Safety in medication prescribing is paramount to protect the public and avoid ineffective or harmful treatments, the prolongation or worsening of illness, needless suffering and excessive health care system costs (de Vries et al., 1994). A license to authorize medical marijuana warrants the same consideration for safety that is given to the writing of a traditional prescription. And, the use of guidelines, such as the one developed by the WHO, will help clinicians do this.

Medication Prescription Safety

The practice of rational prescribing seeks to avoid ineffective and unsafe treatments, illness exacerbation or prolongation, higher costs, and prescriber vulnerability to patient, colleague or industry pressure (de Vries et al., 1994). The WHO's *Guide to Good Prescribing: A Practice Manual* (de Vries et al., 1994) was developed to help the prescriber avoid the above with identification of six key steps for HCPs to follow in the process of rational prescribing (see Appendix A). Step three considers the suitability and safety of the drug for a particular client with evaluation of the efficacy on the therapeutic objective, adverse effects, contraindications, drug-interactions, proper dosing, appropriate method of delivery or formulation, client's mental status and cost (Devries et al., 1994). It is this step that formed the basis of this literature review. The evaluation of the evidence concerning the suitability and safety of medical marijuana was highlighted in this review, although the author acknowledges that all six steps are essential to rational prescribing.

Several factors influenced the development of this review including: federal government legislation granting access to medical marijuana, patient requests for it, anecdotal evidence and limited clinical studies that indicate it may relieve NeP, potential future legislation granting NPs to authorize its use, and a lack of clinical guidelines for how to use it safely. There are legitimate concerns surrounding the health risks associated with the use of dried cannabis since most people will opt for the smoked method of ingestion. The objective of this is to determine if medical marijuana can be authorized safely by PCPs to treat NeP in adults.

CHAPTER 2

Methods

A literature review was carried out to determine if dried cannabis can be authorized safely by PCPs to treat NeP in adults. The methodological process for reviewing the literature was completed in four stages.

Stage One: Identification of Issue and Search Strategy

Stage one started with identification of key terms related to the objective. The dried cannabis plant is the compound available through the *Marihuana for Medical Purposes Regulations* (Government of Canada, 2013). Therefore, the initial terms used in the literature search included *cannabis* and *medical marijuana* in combination with the term *neuropathic pain* on Google and Google scholar. These terms were further used in health-related research databases to determine MeSH headings when applicable. The databases used to conduct the searches included those with relevancy to medicine, nursing, clinical studies, and Canadian content though the search was expanded to international sources because of the limited local and national information. The Cochrane Database of Systematic Reviews, EBM reviews, Database of Abstracts of Reviews of Effects, ACP Journal Club, Cochrane Central Register of Controlled Trials, CINAHL, Medline ovid, Medline with full text, Pubmed, Psychinfo, Biomedical reference collection, and Longwoods were searched. An online search was completed using government and professional websites such as Health Canada, the Government of Canada, the National Guidelines Clearinghouse, the Canadian Medical Association, and the American Psychiatric Association. In addition, journals associated with the Canadian Pain Society, International Association for the Study of Pain and the American Pain Society were also explored. Figure 1B details the initial search that resulted in 360 articles for further evaluation using an inclusion and exclusion criteria

(see Table 1). A ten year time frame was utilized to obtain the most current and relevant evidence as the initial cursory search revealed no observational or experimental studies dated earlier than 2004.

Table 1: *Inclusion and Exclusion Criteria*

Inclusion Criteria	<ul style="list-style-type: none"> • quantitative and qualitative human studies that evaluated the efficacy of the cannabis plant on neuropathic pain • any method of cannabis used including smoking, vaporization, oral ingestion, topical, rectal or oromucosal ingestion • literature published between 2004 and up to January 2014 • Canadian literature was the main focus of the search due to the applicability of the literature to Canadian NP practice but the search was expanded to American, European, and Asian sources in an effort to ensure all key research data applicable to cannabis on neuropathic pain was included • English language literature or sources that were translated into English
Exclusion Criteria	<ul style="list-style-type: none"> • studies that used animals as subjects as data from these is not easily transferred to humans or to clinical practice (Karst et al., 2010) • studies that evaluated other forms of pain or disability • synthetic or prescription medicinal extracts of cannabis such as dronabinol, nabilone or nabiximols

Stage Two: Focused Search

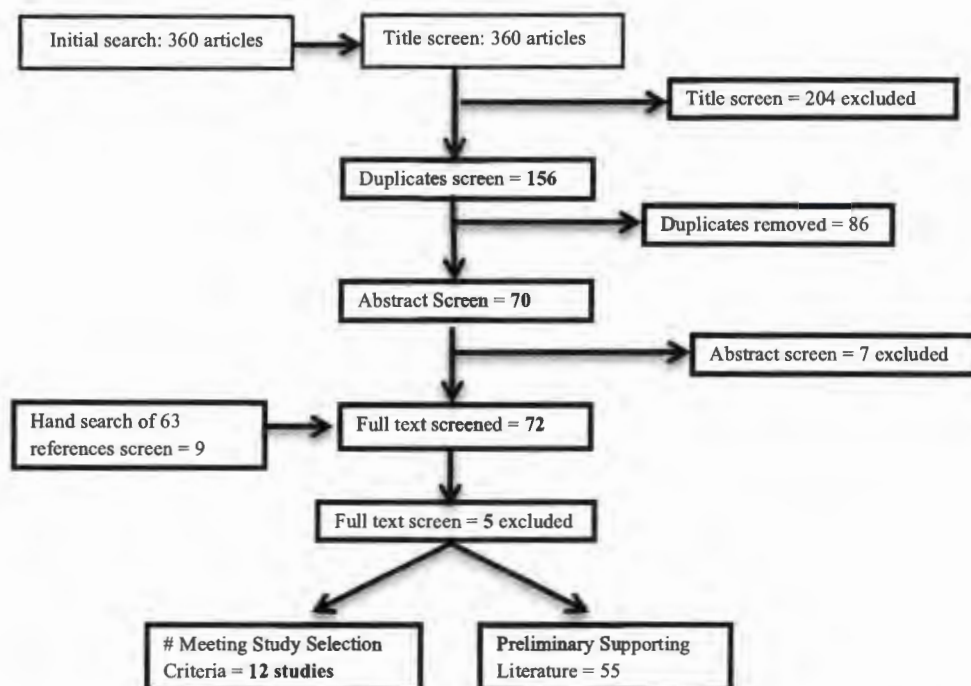
Stage two of the search strategy involved the use of Refworks as a citation manager for collecting the articles. Figure 1 details the narrowing down of articles through the removal of duplicates, evaluation of the titles, abstracts and full text systematically until key articles were revealed. The references of these key articles identified by the initial search were reviewed for additional literature; 12 studies met the inclusion and exclusion criteria and were found to be relevant to the objective.

Stage Three: Study Quality Analysis

Stage three involved a detailed analysis of the chosen articles for quality of evidence using a modified checklist tool by Downs and Black (1998) (see Table C1). It gives a score out of 28 and

is based on evaluation of the reporting, internal validity, external validity, and power of randomized and non-randomized studies.

Figure 1: *Literature Search Flow Chart*



There were 12 clinical studies that consisted of both experimental and observational quantitative research designs. The experimental studies included seven randomized controlled trials (RCTs), an open-label pilot study, and an open-label clinical trial. The observational studies included a sub-analysis of a RCT, a case series, and a cross-sectional questionnaire study. The inclusion of both experimental and observational studies was deliberate so the strengths of each type of study would be complementary to the other in order to provide a synthesis of evidence for application in clinical practice.

Stage Four: Identification of Key Themes

Stage four involved a detailed evaluation of these 12 studies with identification of key themes related to the research question. Themes identified in the literature included: examination

of the efficacy of dried cannabis on NeP compared to current guideline recommended medications, the relationship between adverse effects, drug-interactions and contraindications to specific client groups, dried cannabis dosing and appropriate method of delivery. The following findings section will provide a critical analysis of the quality of evidence presented in each study.

CHAPTER 3

Findings

The following section will provide a critical analysis of the research findings, organized by the key themes and will include a specific focus on step three of the WHO *Guide to Good Prescribing: A Practice Manual* (de Vries et al., 1994). The themes identified include: the efficacy of cannabis in comparison to currently recommended treatments for NeP; the relationship of adverse effects, drug interactions and contraindications associated with specific client groups, and the recommended dose and method of delivery of dried cannabis. Table C1 details the evaluation of the studies using the “*Checklist for Measuring Quality*” tool by Downs & Black (1998) to identify the internal and external validity and the reliability of the studies’ results. The quality of the experimental studies ranged from 22 to 27 out of 28; one open label trial rated the lowest at 13 out of 28. The observational studies scores ranged from 18 to 21. Studies with scores below 14 are considered poor quality, 15 to 19 as fair quality, and greater than 20 as good quality. Thus, the methodological quality of the studies in this review are acknowledged to have flaws that will be discussed and analyzed further.

Efficacy of Cannabis on Neuropathic Pain Compared to Current Treatments

When selecting a medication for a client it is important to know how effective it is in terms of the therapeutic objective (de Vries et al., 1994). In this case, the literature was evaluated to determine the efficacy of cannabis as a treatment for NeP in comparison to current guideline recommended medications. All 12 studies reported improvement in NeP after the use of dried cannabis. Seven of the RCTs showed statistically significant pain relief when compared to the placebo with five of these studies reporting a clinically significant 30% reduction in pain from the baseline (see Table C2). Three of the clinical studies acknowledged the difficulty with

blinding due to the psychoactive effects of cannabis (Corey-Bloom et al., 2010; Ellis et al., 2007; Wilsey et al., 2013). However, the authors of two of these studies (Ellis et al., 2007; Wilsey et al., 2012) reported that the effect of cannabis still provided superior pain relief to placebo even taking into consideration the effects of unblinding and the placebo effect. The data, when treated to compensate for the lack of blinding, did not appear to influence the results when evaluating cannabis efficacy. The fact that the data had to be treated however could be a source of significant concern with respect to reliability. The open-label trial that evaluated the interaction between cannabis and opioids had a small sample size but saw a 27% (95% CI 8.9 to 45.5%) reduction in pain from baseline, though this study was not placebo-controlled (Abrams et al., 2011). In the observational studies, the cross-sectional questionnaire by Woolridge et al. (2005) reported that 37% ($n = 53$) of subjects used cannabis for nerve pain with 91% ($n = 48$) reporting either “much” better or “a little” better compared to only 9% ($n = 5$) reporting no change ($p < 0.001$). However, the degree of improvement from baseline was not numerically reported making it difficult to gauge the efficacy of cannabis in comparison to other medications used for NeP. This is also a significant limitation in terms of validity. The gold standard for research in pain control is the use of the visual analogue scale as a quantitative measurement and this method was not used in this study. The case series by Lynch et al. (2006) reported a 60% reduction in baseline pain in 93% ($n = 28$) of those who used cannabis for pain control. However, the percentage of these subjects with NeP was not reported. The study, unfortunately, lacked a control group, which constitutes a significant weakness in design. The sub-analysis of a RCT by Corless et al. (2007) on self-care strategies for HIV symptom management failed to show significant differences between the effect of cannabis versus over-the-counter medications ($n = 15$, $p = 0.472$), prescribed analgesics ($n = 15$, $p = 0.465$), or antiepileptics ($n = 13$, $p = 0.636$) on

NeP. These studies are limited by their small sample size. However, participants subjectively rated cannabis as more effective than unspecified over-the-counter or antiepileptic medications (Corless et al., 2007) though self-reports of effect are a known source of bias. Long-term efficacy was not evaluated in the clinical trials and the two open-label studies (see Table C2). Further, two of the observational studies that assessed the use of marijuana for symptoms associated with HIV did not report the length of time the subjects had used marijuana, thus making it difficult to determine long term effects (Corless et al., 2009; Woolridge et al., 2005). This makes it difficult for the PCP to endorse a treatment when the long term efficacy and safety is not known.

Number needed to treat. The NNT value reflects the number of people needed to be treated with a medication or intervention for one person to see a benefit and is the value obtained from the inverse of the absolute risk reduction (Rang et al., 2012). For example, a NNT value of 2 means that for one person to see a statistically significant benefit from taking a medication or treatment two people have to be treated. This value represents the clinical significance of a medication or treatment. In this review, NNT values for dried cannabis were calculated to reflect the number of people needed to be treated before one person would achieve a clinically significant 30% reduction in pain (Rang et al., 2012). Abrams et al. (2007) calculated a 3.6 NNT value from 52% ($n=13$) of those who smoked cannabis versus 24% ($n=6$) who smoked placebo (95% CI 2% to 54%, $p<0.04$). Ellis et al. (2009) calculated a 3.5 (95% CI 1.9 to 20.8) NNT value from 46% ($n=13$) who smoked cannabis versus 18% ($n=5$) who smoked placebo ($p=0.043$). Wilsey et al. (2013) calculated a 2.9 NNT value from 61% ($n=22$) who smoked a medium dose (3.53%) of cannabis and a 3.2 NNT value from 57% ($n=37$) who smoked a low dose (1.29%) of cannabis versus 26% ($n=10$) who smoked placebo ($p=0.0023$ and $p=0.0069$, respectively). These same authors also used their NNT values to compare cannabis efficacy against the NNT

values of current medications used for treating NeP. This will be discussed in the text to follow. However, significant limitations in the method used to analyze the results and calculate the NNT value were found. Only two studies used the intention-to-treat method, which includes all subjects who were initially randomized in the final analysis even if there were subjects that dropped out before finishing the trial (Corey-Bloom et al., 2012 and Ellis et al., 2009). Five studies used the per-protocol method where only those subjects who complete the entire trial are included in the analysis of effect and one used the modified intention-to-treat method where the authors modify who they include in the analysis (see Table C2). As will be discussed further, these analysis methods impact the validity of the outcomes and applicability to practice.

Time period to effect. There was heterogeneity among the studies evaluating at what point in time cannabis was most effective at relieving pain. Abrams et al. (2007a) observed the greatest decrease in chronic pain scores occurred at 15 minutes post cannabis inhalation with a continued but less marked decrease in pain at the 55 and 95 minute marks. Jay et al. (2004) observed the greatest effect on pain to occur between 15 to 55 minutes post cannabis inhalation. Wallace et al. (2007) evaluated the effect of cannabis on pain induced by a capsaicin injection; no analgesic effect occurred at 20 minutes post exposure but did occur at 55 minutes post exposure. Wilsey et al. (2008) observed the greatest pain decrease between the 60 and 120 minutes post cannabis exposure and Wilsey et al. (2013) reported the greatest decline in pain between 120 and 180 hours. It is difficult to directly compare these two studies (Wilsey et al., 2008; Wilsey et al., 2013) with the first two since Jay et al. (2004) and Abrams et al. (2007a) assessed the cannabis effect after only one dose while the other two assessed the cannabis effect after each subsequent dose increase. These differences in onset of action make it difficult for HCPs to provide an evidence base that will effectively inform the prescription of the appropriate dosing frequency.

Adverse Effects, Drug Interactions and Contraindications to Client Groups

Identifying the safety issues is a key step in the process of prescribing (de Vries et al., 1994). The studies reported adverse effects, risk of toxicity, and contraindications but limited data was available to describe the incidence. All of the experimental studies were short in duration ranging from a few days to a few weeks. Lynch et al. (2006) provides some information on the potential long-term effects as they evaluated subjects who had been using medical marijuana for one to five years; however, the major limitations of this study was that it was simply observational. In addition, the small sample size and presence of self-selection bias was also limiting as the clients interviewed all had prior recreational use of cannabis experience.

Adverse effects. The severity and frequency of adverse events increased as the cannabis dose increased with adverse effects reported in a concentration as low as 1% (Ellis et al., 2009). In all seven RCTs, adverse effects were more common in the active THC versus placebo arms (see Table C2). The most common adverse reactions identified by frequency in subjects are detailed in Table 2.

Physical effects. Physiological effects seen that were directly attributed to smoked cannabis included dizziness ($n=1$, Lynch et al., 2006), tachycardia and an intractable cough ($n=2$, Ellis et al., 2009). Other physiological effects observed are detailed in Table 2.

Cognitive effects. The most frequently reported adverse effects involve the CNS (Health Canada, 2013a). In this review, three studies calculated significant effects of smoked cannabis on cognitive function compared to placebo ($p < 0.04$) (Corey-Bloom et al., 2012; Wilsey et al., 2008; Wilsey et al., 2013). Woolridge et al. (2005) found that subjects with pre-existing HIV-related memory loss (26%, $n=38$) experienced a greater deterioration of memory (47%, $n=18$). An improvement in memory loss was reported after using cannabis in a smaller cohort (18%, $n=$

7) ($p = 0.043$) (Woolridge et al., 2005). Wallace et al. (2007) reported no statistically significant cognitive impairment (6%, $n=1$) and the other two studies only reported no subject withdrawals due to adverse cognitive effects (Ellis et al., 2009; Ware et al., 2010).

Table 2: *Frequency of Adverse Effects (% of Subjects)*

Physiological	
Dizziness	5.9% to 23% ^{abcf}
Headache	2% to 33% ^{bfg}
Fatigue	5% to 30% ^{bdfg}
Cough	3% to 14% ^{cf}
Increased pain	10% to 14% ^f
Weight gain	23% ^d
Throat irritation	3% to 18% ^{bf}
Increased heart rate	13% to 46% ^{cd}
Nausea	4% to 11% ^{abefg}
Asthenia	5% to 15% ^{fg}
Dyspnea	5% to 6% ^{cf}
Dry mouth	6% ^c
Cognitive	
Sedation	54% ^a
Concentration difficulties	9% ^f
Sensation of being “impaired”, “stoned” or “high”	5% to 6% ^{bf}
Slowed thoughts	23% ^d
Decline in learning and memory	47% ^g
Confusion	7% to 16% ^a
Psychological	
Psychosis	3% ^c
Paranoia	7% to 13% ^{ad}
Anxiety	4% to 25% ^{adg}

Note: ^aAbrams et al. 2007a. ^bCorey-Bloom et al., 2012. ^cEllis et al., 2009.

^dLynch et al., 2006. ^eWallace et al., 2007. ^fWare et al., 2010. ^gWoolridge et al., 2005.

The degree of neurocognitive impairment was related to the dose of cannabis; higher doses showed greater impairment (Wallace et al., 2007; Ware et al., 2010; Wilsey et al., 2008; Wilsey et al., 2013). For instance, in one study, cognitive decline worsened as the concentration of THC increased from 0% (placebo) to 1.29% to 3.53% (Wilsey et al., 2013).

It is interesting to note that in the Corless et al. (2009) study those subjects who reported using marijuana for symptoms associated with HIV had significantly lower rates of adherence to their HIV medications when compared to subjects who did not use marijuana. The authors reported that this finding might not be related to the cognitive effects of marijuana or higher symptom intensity scores. Instead, they suggest that it may be due to the length of time the subjects had HIV since this issue with adherence was seen in those who had lived with HIV longer (Corless et al., 2007). It is worth noting this issue since adherence problems with the use of medical marijuana may also be a factor in clients who have had other chronic conditions, including neuropathic pain. Indeed poor adherence to any prescribed drug remains a prevalent issue in Canada (British Columbia Pharmacy Association, 2013).

Psychological effects. Twelve studies that evaluated changes in mood associated with cannabis use reported a general improvement. Three studies showed no statistically significant changes in mood (Wallace et al., 2007; Wilsey et al., 2008; Wilsey et al., 2013) while six of the studies showed an improvement in both anxiety and depression (see Table C2). Ellis et al. (2009) reported a subject withdraw due to psychosis. Three studies reported anxiety as an adverse effect of cannabis use with one withdrawal due to this effect (Wallace et al., 2007). It is interesting to note that the relief from anxiety and depression was cited as a major reason for cannabis use in three of the observational studies (Corless et al., 2007; Lynch et al., 2006; Woolridge et al., 2005).

Toxicity. Evidence of toxicity in the studies was low overall but there was a clinically significant event with one subject withdrawal due to psychosis ($n=1$, $N=34$) (Ellis et al., 2009); however, it is acknowledged that the dose used (4% THC by weight) was below the expected dose range (5 grams per day) when toxicity usually occurs.

Cannabis effects on naïve users. Of the 10 clinical studies that evaluated cannabis use on NeP seven excluded cannabis naïve subjects. Further, only 4% and 20% in the other two studies had prior cannabis experience (Ellis et al., 2009 and Corey-Bloom et al., 2012, respectively). This raises the concern that the studies have not fully investigated the effects on naïve users, which could potentially result in different clinical outcomes and adverse events. One study attempted to address this issue through the inclusion of non-experienced users of cannabis in the study; their findings did not show any increased adverse effects on non-experienced users versus experienced users (Ware et al., 2010).

Drug interactions. Cannabis is metabolized by the same hepatic xenobiotic cytochrome P450 enzymes (CYP2C9 and CYP3A4) (Watanabe et al., 2007) that are involved with the metabolism of many other medications. Hence, there is a potential for drug interactions. All of the studies except one (Wallace et al., 2007) reported their subjects were taking other medications while using dried cannabis but there was a lack of objective analysis on potential drug interactions of cannabis with concomitant medications except in only one study (Abrams et al., 2011). Ellis et al. (2009) did not report any synergistic drug interactions between opioids and cannabis. Abrams et al. (2011) evaluated the interaction between vaporized cannabis and opioids and found that cannabis augmented the analgesic effect of opioids without significantly altering the opioid plasma levels. No adverse effects were observed in this study. Morphine absorption was slowed when cannabis was ingested and there was no effect on oxycodone absorption (Abrams et al., 2011). This may have implications for the safety profile in persons using morphine as once the cannabis is discontinued, a higher serum value may be reached to which the individual is not tolerant. The authors interestingly, concluded that this study presents some evidence that cannabis used in conjunction with a lower dose of opioid results in fewer side

effects than the use of a higher dose of opioid without cannabis. This conclusion is supported by the findings in Lynch et al. (2006) where the majority of subjects ($n = 15$, 70%) reported the use of marijuana allowed them to decrease the use of other medications that were causing side effects including NSAIDs, opioids and antidepressants. However, this study is limited by self-selection bias and the small sample size. Marijuana users reported improved efficacy of their non-cannabinoid medications when compared to non-marijuana users in the study by Corless et al. (2007). However, this finding was not significant using an independent t test calculation (-0.039 , $p = 0.969$).

Contraindications. The risks associated cannabis use provides some guidance in determining which patient populations are inappropriate for medical marijuana. All of the experimental studies excluded subjects with active substance abuse. Five of the RCTs and one open-label study excluded subjects with a history of (a) mental illness including major depressive disorder, schizophrenia, bipolar, and psychosis, and (b) pulmonary disease including tuberculosis, asthma, emphysema and bronchitis (Abrams et al., 2011; Corey-Bloom et al., 2012; Ware et al., 2010; Wallace et al., 2007; Wilsey et al., 2008; Wilsey et al., 2013). In the three observational studies, the underlying medical or psychiatric conditions of the clients were not addressed (Corless et al., 2007; Lynch et al., 2006; Woolridge et al., 2005). Additional exclusion criteria that varied in the studies included those with uncontrolled hypertension, cardiovascular disease, pregnancy or breastfeeding, history of cannabis dependence, abnormal kidney and liver function, any serious medical condition not specified, epilepsy, head trauma, or tobacco dependence. The observational studies presumably included subjects with a variety of underlying medical conditions in addition to chronic pain but these were not addressed in the evaluation.

The exclusion criteria in the experimental studies were extensive which makes it difficult to apply the findings of the studies to the general population seen in practice.

Cannabis Dosing and Method of Delivery

Another concern with the use of dried cannabis is the lack of data surrounding appropriate dosing and method of delivery to minimize adverse effects while achieving the desired therapeutic outcome. The studies provided useful but only provided limited information on how to address this issue.

Cannabis dosing. In the studies that evaluated smoked cannabis a range of 1% to 9.4% was used (see Table C2). Four studies reported no difference in pain reduction when a lower dose of THC (range of 1.29% to 3.5%) was directly compared to a higher dose (range of 3.5% to 9.4%). One study found that a higher dose of THC (7%) had a greater effect on superficial pain than a lower dose (3.5%) (see Table C2).

In the observational studies, Lynch et al. (2006) evaluated information from clients who used a range of 1g to 5g of cannabis per day with the average dose of the oral form being less than 1g per dose (Lynch et al., 2006). In this study, the number of doses per day ingested was not differentiated to include the methods used. Two of the studies in this review evaluated a self-titrating dosing schedule (Ellis et al., 2009; Wilsey et al., 2013) that allowed the subjects to balance the analgesia against adverse effects.

In the studies that reported time between inhalations there were similarities with three studies waiting 40 seconds (Wallace et al., 2009, Wilsey et al., 2008, Wilsey et al., 2013) and two studies waiting 45 seconds (Abrams et al., 2011; Corey-Bloom et al., 2009). The other four trials did not report time between inhalations. Only two studies reported the time between doses at 60 minutes (Wilsey et al., 2008; Wilsey et al., 2013). Corey-Bloom et al. (2009) and Wilsey et

al. (2008) reported that doses of smoked cannabis in their trials ranged from two to four puffs. This variation in frequency of dosing makes it difficult to apply these findings for practice recommendations. The following discussion on the method of delivery also provides conflicting information for use in practice.

Method of delivery. The majority of study subjects utilized the smoking method. There were no experimental clinical trials that evaluated the oral form of cannabis on NeP and one study did not clarify what method their subjects used (Corless et al., 2007). Lynch et al. (2006) found that all of their subjects (N= 30) used the smoking route with only 37% ($n = 11$) using the oral route only or in combination with smoking. Likewise, the majority of subjects ($n = 101$, 71%) who completed the questionnaire by Woolridge et al. (2005) used the smoking route only; only 2% ($n = 3$) reported using the oral route only. Vaporization was utilized in two studies with efficacy outcomes similar to the studies that utilized smoked cannabis (Abrams et al., 2011; Wilsey et al., 2013).

In summary, this literature review identified 12 studies relevant to the objective and was critically evaluated. The data identified provides some decision making guidance for PCPs in the authorization of a medical marijuana license. The following section will discuss the findings with an analysis for making recommendations for practice and future research.

CHAPTER 4

Discussion

This integrative literature review was undertaken to determine if dried cannabis can be authorized safely by PCPs to treat NeP in adults. Step three of the WHO guidelines formed the basis for evaluating the literature. Some data was unavailable or incomplete limiting the validity of the results. The nine clinical trials and three observational studies utilized in this review do not provide enough data to support the safe use of medical marijuana for NeP in adults. Medication prescribing, however, is always a balance of risks versus benefits and when standard treatment fails, some health care providers may consider alternate therapies. Some PCPs are providing or are considering providing their patients authorization for dried cannabis, this may be due to many factors including federal legislation granting access, patient requests, and anecdotal evidence of its efficacy. In future, when provincial regulations are in place, NPs, as primary care providers, may also be considering the authorization of dried cannabis in certain patients. A synthesis of the evidence will provide the necessary foundation to support the recommendations and conditions for those PCPs who are considering authorizing its use.

Efficacy of Cannabis on Neuropathic Pain Compared to Current Treatments

An important step in selecting a treatment is to determine the efficacy of the medication for the desired therapeutic objective. In this case, the review centered on the efficacy of medical marijuana as compared to current medications used for the treatment of NeP. All of the studies used in this review demonstrated a potentially modest analgesic effect for NeP but were limited to a large degree by flaws in design. One particular area of bias is common to many clinical efficacy studies where only those study subjects who completed the entire trial were included in the final analysis. Thus, a study is inherently biased because those who dropped out from

intolerance or ineffectiveness are not included in the analysis. This may give the mistaken impression that a drug is potentially more effective than it actually is. Therapeutic failures were excluded in the literature examined and thus, the studies do not represent the most accurate description of efficacy.

Three studies calculated the NNT values with a range of 2.9 to 3.6 for a THC concentration range of 1 to 9.4% (see Table C2). Cannabis has NNT values that are higher than the first line medications for NeP and these values were calculated from a 30% reduction in pain whereas the NNT values for the guideline recommendations were calculated from a 50% reduction in pain from baseline. Further, only one study calculated the NNT value based from a sufficient sample size and the intention-to-treat method (Ellis et al., 2009). The other two studies (Abrams et al., 2007 and Wilsey et al., 2013) used biased outcomes to calculate the NNT so these values cannot be considered reliable. Tricyclic antidepressants (TCA) and antiepileptics are first line medications, the serotonin-norepinephrine-reuptake inhibitor (SNRI), venlafaxine, is second line, the opioid tramadol is third line, and cannabinoids are fourth (Moulin et al., 2007). NNT values for these medications are presented in Table 3. A NNT value for nabilone on neuropathic pain was not found in the literature search. The cannabis trials' authors used their NNT values to compare cannabis efficacy against the NNT values of current medications used for treating neuropathic pain but it is important to acknowledge the differences between the degree of pain reduction from baseline used to calculate the NNT values in the cannabis studies used in this review. The NNT for the first, second and third line medications used the more stringent requirement of a 50% change from the baseline while the cannabis trials only required a 30% reduction. Hence, a real comparison cannot be made with the data provided between these medications. The WHO prescribing guidelines advise clinicians to choose medications with the

largest data concerning the efficacy, safety, suitability and cost (de Vries et al., 1994). It is best practice to start with medications that demonstrate the safest profile with the highest level of efficacy first.

Table 3: *NNT Values for Medications Used to Treat Neuropathic Pain*

Medication	NNT using 30% change from baseline	NNT using 50% change from baseline	Author
TCAs ^a		1.2 (95% CI 1.2 - 1.5)	Saarto & Wiffen, 2007
TCAs ^b		2.7 (95% CI 2.0– 4.0)	Saarto & Wiffen, 2007
Amitriptyline (up to 125mg/day) ^{abd}		4.6(95% CI 3.6 - 6.6)*	Moore et al., 2012
Venlafaxine (ER 150-225mg/day)		4.5	Rowbotham, Goli, Kunz, & Lei, 2004.
Pregabalin 600mg/day ^a		4.0 (95% CI 3.1 – 5.5)	Wiffen et al., 2013
Pregabalin 600mg/day ^b		6.3 (95% CI 4.6 – 10)	Wiffen et al., 2013
Gabapentin (600 - 3600mg/day) ^a		5.8 (95% CI 4.3 – 9)	Wiffen et al., 2013
Tramadol		3.8 (95% CI 2.8 - 6.3)	Duehmke, Hollingshead, & Cornblath, 2009
Sativex ^c	8.6	8.5	Nurmiikko et al., 2007
SC 3.56% THC ^c	3.6		Abrams et al., 2007
SC 1-8% THC ^c	3.5		Ellis et al., 2009
SC 1.29%	3.2		Wilsey et al., 2013
SC 3.53%	2.9		Wilsey et al., 2013

Note: CI = confidence interval. SC = smoked cannabis. ^adiabetic neuropathy. ^bpostherpetic neuralgia. ^cHIV-associated sensory neuropathy. ^dpost-stroke pain. ^eunilateral peripheral NeP. *NNT calculated with data from NeP and fibromyalgia.

Adverse Effects, Drug Interactions and Contraindications to Client Groups

Adverse effects. It is important to minimize adverse drug reactions and to avoid harmful drug interactions. The studies revealed dose related adverse effects from dried cannabis. The main ingredient of medical marijuana, THC, exerts its greatest effects on the CNS through its action as a partial agonist on the CB1 and CB2 receptors of the endocannabinoid system (Rang et al., 2012). It is therefore not surprising that neurocognitive and psychological effects are reported with the highest frequency. Anxiety, dizziness, euphoria, impaired cognition, fatigue, confusion,

and paranoia were reported in the studies with varying frequency and severity. Four of the studies reported subject withdrawals due to adverse effects (see Table C2). Two of these studies did not include subjects who withdrew from adverse effects in the final analysis (Ware et al., 2010; Wallace et al., 2010). This places bias on the outcomes making it seem more efficacious on the intended population than it actually is. However, it is also valid to consider that the outcomes of these two trials are applicable to clients who will tolerate dried cannabis in practice.

The acute cognitive effects on learning and memory seen with cannabis use is concerning. Wilsey et al. (2013) states the effect observed in their study was minimal and not likely to have a major impact on daily functioning. However, Wilsey et al. (2008) observed the same effect but cautioned the prescribing of cannabis to those who require intact cognitive processing for their work. Indeed, the risk of and incidence of impaired driving and motor vehicle accidents is correlated to impairment from cannabis use (Volkow et al., 2014). The Office of the Superintendent of Motor Vehicles (OSMV) in BC requires the disclosure of psychotropic medication use on the driver fitness form (BC Ministry of Justice, 2014). Cannabis is not specifically identified in the guidelines but it is important to acknowledge the evidence that indicates cannabis effects driving ability. PCPs have the responsibility to inform the OSMV if a client is using cannabis to ensure public safety.

How cannabis use affects the user cognitively over the long term is one of the major concerns for PCPs also (Corey-Bloom et al., 2012) but was not assessed in this review because the studies were conducted over short periods of time. Evidence from other studies has shown impairment in neurocognitive development in fetuses exposed in utero, altered brain development, and lowered IQ in frequent users during adolescence with evidence of impairment even after one year of abstinence (Huestis, 2007; Volkow, 2014). Indeed, one study recorded a

six-point reduction in IQ in adult subjects who initiated cannabis use in adolescence, which may be more detrimental to the overall cognitive function in an individual who already has lower baseline intelligence (Meier et al., 2012).

The effects on subjects mental health was conflicting in this review since cannabis induced anxiety and depression in some subjects (see Table 2) and relieved it in others (see Table C2) though the studies that evaluated these symptoms were short term. Chronic NeP itself is associated with higher rates of depression and anxiety (Choinière et al., 2010). Long-term effects from other studies have shown evidence of diminished life satisfaction and achievement, chronic psychosis, depression and addiction (Volkow et al., 2014). The long-term effects of tolerance or addiction to cannabis were not evaluated in these studies but are important to consider because it is likely in practice that cannabis will be prescribed for long-term chronic pain management. Up to 25% to 50% of those who smoke it daily will become addicted (Hall & Degenhardt, 2009). Screening clients for addiction and avoiding use in those with a history of addiction prior to prescribing cannabis is one method to address this concern. The study by Lynch et al. (2006) evaluated 30 people who have been using cannabis for one to five years for refractory pain. All of the subjects reported the benefits of dried cannabis outweighed any negative effects experienced even though 76% of subjects reported cognitive side effects including confusion, anxiety and paranoia. This is an interesting finding and one to consider in a client who has refractory pain and impaired quality of life or functioning in addition to depression or anxiety.

Toxicity from cannabis use is not common and sometimes difficult to differentiate it from an adverse effect because of the lack of measured plasma cannabis levels; however, ingestion of greater than 5 grams per day increases the risk for toxicity (Health Canada, 2013a). Psychosis is considered a toxic effect and was experienced by one subject (Ellis et al., 2009). A positive

aspect of cannabis is that it shares some similarities with opioids but it lacks the ability to suppress the respiratory system (Carter et al, 2004). However, as the background literature reveals, there have been reports of death attributable to the toxic effects of cannabis (Hartung et al., 2014). A key part of the discussion with the client includes disclosure of these toxic and adverse effects that may outweigh any benefits derived from cannabis use.

Cannabis-drug interactions. The potential for cannabis to interact with other medications and cause adverse effects is high because THC and cannabidiol are metabolized in the liver by the cytochrome P 450 enzymes CYP2C9 and CYP3A4 (Watanabe et al., 2007) that metabolize many other common drugs.

Abrams et al. (2011) provided objective data on the effect that cannabis had on plasma opioid levels with encouraging results. The two observational studies by Corless et al. (2007) and Lynch et al. (2006) provide evidence that cannabis (1) augments the efficacy of other medications without increased side effects and (2) leads to the decrease in use of these other medications, as reported by the subjects. However, self-reports of effects are subject to bias when interpreting the results for use in practice. The objective data collected from Abrams et al. (2011) and subjective from Corless et al. (2007) and Lynch et al. (2006) provide support for the use of cannabis on clients who are using other medications. In addition, it provides reassurance that in the other clinical trials most of the clients were on concurrent medications throughout the study without apparent increase in adverse effects other than that already associated with cannabis; however, any possible interactions between cannabis and other medications were not objectively measured in these studies. One potential problem is that of concurrent use of street drugs, most notably opiates. Since the studies exclusion criteria included those with addiction histories, it is not known how this population is affected. However, it remains important to

monitor clients on concurrent medications for any change in therapeutic effects. Cannabis acts on the CNS and the use of alcohol or benzodiazepine could increase sedation (Canadian Pharmacists Association, 2014a). The studies in this review did not evaluate cannabis and these other medications but the background literature provides evidence to make the recommendation that cannabis should not be licensed to those who are taking concurrent benzodiazepines, alcohol or other sedatives. The identified adverse effects from this review and known drug interactions provide some guidance on who should not be prescribed medical marijuana.

Contraindications. The client demographic is an important consideration when choosing a therapy. A major limitation of the clinical trials was the exclusion criteria since all of the studies excluded individuals who had mental illness including depression, bipolar, schizophrenia, and anxiety; therefore, there is no clinical data observing the effect of cannabis on these groups. The observational studies by Corless et al. (2007), Lynch et al. (2006), and Woolridge et al. (2005) evaluated subjects who used cannabis to relieve a variety of symptoms including anxiety and depression; however, the underlying baseline mental status of these clients were not evaluated and so one cannot draw conclusions about the safety of cannabis for use with those who have mental health conditions from these studies either. In addition, none of the studies looked at the impact on long-term mental health as they were all short term studies. It has been shown that the adverse psychoactive effects of cannabis may aggravate underlying mental health symptoms as evidence points to cannabis use may be a trigger for the earlier age of onset of bipolar and schizophrenia in genetically susceptible individuals (de Hert et al., 2011). Groups known to be at higher risk for experiencing adverse effects of medications include children, the elderly, those who are pregnant or breastfeeding, those who have liver or renal failure, or individuals with multiple comorbidities (de Vries et al., 1994). Cannabis should not be used in those under the

age of 25, with active or remote substance use, schizophrenia, history of psychosis, or bipolar disorder (Health Canada, 2013a). Further, the smoked form should not be used in those with cardiovascular or respiratory disease.

Cannabis Dosing and Method of Delivery

Cannabis dosing. The aim of medication dosing is to maintain the plasma level of the drug within the therapeutic window (de Vries et al., 1994). The dosing of cannabis in practice remains a concern for PCPs because there has been no standardized formula. Many variables affect THC and cannabinoid absorption (Carter et al., 2004). Health Canada acknowledges that quantifying the amount of THC absorbed in a single puff through smoking is difficult due to factors such as prior experience and smoking technique. And, further, the concentration of cannabinoids in each supply of dried cannabis varies with growing conditions (Health Canada, 2007). However, based on data from the WHO (1997) and peer reviewed literature, Health Canada (2007) recommends that the daily dose of dried cannabis ingested in any form be kept between 1 and 3 grams, or three to six joints per day with a concentration of $12.5 \pm 1.5\%$. In this review, Lynch et al. (2006) showed the average dose used by their subjects was less than 1 gram, which is consistent with the Health Canada and CFPC recommendations.

The clinical studies that evaluated different doses on analgesic efficacy provides little guidance for the PCP except to advise that clients will likely derive benefit with a low dose and should be advised to start with the lowest dose possible which is in keeping with the principles of good prescribing for any drug.

In terms of frequency of dosing there was heterogeneity among the studies evaluating at what point in time cannabis was most effective at relieving pain. Therefore, clients should be instructed to titrate very slowly. Health Canada (2007) advises clients to wait a few minutes

between each puff of smoked or vaporized cannabis; the studies in this review had clients wait 40 or 45 seconds between inhalations providing limited but helpful information for use in practice. The CFPC (2014) advises those new to cannabis or those trying a new strain to inhale one puff and wait four hours before the next one to determine strength of effect since the observed duration of action of each dose is two to four hours (Health Canada, 2013a). There was no data on the frequency of oral dosing utilized by subjects in the trials and it is acknowledged that the main recommendations for frequency between doses is based on anecdotal reports and limited information regarding the rates of absorption (Health Canada, 2013a). The oral method is preferred over the inhalation route so the recommendations made are based on the background literature. Since peak plasma levels are reached between one and six hours it is advisable for clients to wait at least 60 minutes between doses to gauge the strength of effect (Carter et al., 2004). In summary, this review confirms the ongoing issue with dosing and does not provide clear guidance to the PCP on how to calculate accurate dosing or provide information on the actual amount of cannabis the client is actually absorbing.

Method of delivery. The most common method of cannabis delivery is smoking (Tashkin, 2013); a finding also confirmed by the subjects from the observational studies in this review. Smoked cannabis is acknowledged to be an efficient method for self-titration in order to achieve a balance between analgesia and side effects (Wilsey et al., 2008). However, the known adverse effects seen with smoking including chronic bronchitis (Volkow et al., 2014) and association with lung cancer (Callaghan et al., 2013) make it particularly difficult for the PCP to promote this method.

The vaporized form of ingestion is thought to be safer than smoking but there is not enough clinical data to determine if this is true. Some of the data suggest that this method may be more

efficacious for neuropathic pain. The inhaled method though cannot be endorsed as a safe route by PCPs when authorizing dried cannabis use.

Studies on the characteristics of the oral form of cannabis are lacking with no high quality clinical studies found in the literature search. It is acknowledged that the oral form of cannabis is complicated by a long five to eight hour half-life and lower bioavailability (Health Canada, 2013a). Thus, it remains harder to self-titrate and has a slower onset of action compared to smoking. The oral route does not have the same adverse effects on the respiratory and cardiovascular system compared to the smoking and vaporized form making it theoretically more appropriate for clients with respiratory and cardiac disease. However, due to the greater amount of metabolization to active metabolites, this route has a greater sedative effect compared to the smoking route. It is advisable for the clinician to limit or avoid its use in those who need to be mentally alert for work or other activities including driving or operating heavy machinery.

Cost. Cost is an important consideration surrounding the suitability of a medication for a client (de Vries et al., 1994) but was not addressed in the literature review either in the clinical trials or observational studies. The new MMPR acknowledges that the increase in regulation of medical marijuana is also likely to result in an increase in the cost to consumers. This will represent a hardship for some clients, eliminating it as a therapeutic option.

Review Limitations

There are limitations present in this literature review. The evaluation of the data was completed by only one person potentially leading to errors in data analysis. PCP concerns surrounding the issue of diversion of dried cannabis impacts the willingness to utilize it in practice but it was beyond the scope of this review to explore this issue; it is acknowledged by the author to be an important part of safety in prescribing.

It is acknowledged that not all aspects of rational prescribing, as described in the six steps of the WHO guidelines were explored in depth in this review. Monitoring the response to therapy is an important step in the process of rational prescribing as it enables the clinician to determine if the medication has been successful or whether further action is needed (de Vries et al., 1994). It is also important to incorporate information about the drug, instructions for administration and warnings, which will help to enhance patient adherence and give them the best possible outcome.

The next section will discuss conclusions derived from the literature with recommendations for practice based on the synthesis and analysis of the findings. Recommendations for future research will also be included.

CHAPTER 5

Recommendations and Conclusion

Dried cannabis is not regulated by Health Canada the same way that prescription medications are. However, PCPs are expected to use the same standards when assessing the suitability and safety of a prescription medication when authorizing medical marijuana (CPSBC, 2014). Thus, it was the intention of this review to analyze and synthesize the literature to determine if dried cannabis can be authorized safely by PCPs to treat NeP in adults using the principles of safe prescribing by the World Health Organization. The following discussion is a summary of the findings to answer the objective, make recommendations to inform practice, and make suggestions for future research.

Recommendations for Practice

Over one million Canadians suffer from NeP (Moulin et al., 2007) and in many cases the current treatments show limited effectiveness (Abrams et al., 2007a; Wilsey et al., 2013). NPs who address NeP in practice have a responsibility to be educated in the available therapeutic options and are accountable for the treatments they utilize in practice. A survey done by the CRNBC (2013) showed that 31% of NPs would incorporate dried medical marijuana in their practice with 40% feeling unsure. This survey speaks to the significant need for NP education as evidence based guidance should inform all prescribing. Evidence based guidelines were not in place at the time of this survey.

It is the finding of this integrative review that dried cannabis cannot not be authorized safely by PCPs to treat NeP in adults based on the WHO safe prescribing guidelines. Further, the efficacy of dried cannabis has not been established to warrant its use as a treatment for neuropathic pain. However, as NP authority to authorize dried cannabis has been included in

federal legislation and is currently being considered at the provincial level by the CRNBC, it is important that NPs be well informed of the evidence surrounding this substance. In future, NPs as primary care providers, considering authorizing dried cannabis under the MMPR should do so with a full understanding of the evidence, associated risks, and a clear awareness that the short and long term medico-legal implications for those who authorize dried cannabis is currently unknown. It is recommended that dried cannabis not be prescribed in general. As PCPs are currently authorizing dried cannabis, and some NPs surveyed in BC have reported planning to authorize dried cannabis into their practices, the findings of this integrative review will provide recommendations for safer prescribing. For those providers that are considering its use in a small minority of clients who have severe NeP refractory to all other non-pharmacological treatments and more effective medications, a decreased quality of life, have no contraindications, and who understand and accept the associated risks, a systematic and thoughtful approach to authorization should be adopted. A thorough review of the risks and benefits of dried cannabis must be carried out with each patient. Further, a thorough history, health and pain assessments, and utilization of evidence-based care for those with NeP is required. The following recommendations, taken from the current evidence, provide some guidance to PCPs, including NPs, for safer authorization (see Table 4).

Table 4: *Recommendations for Safer Authorization of Medical Cannabis*

Efficacy
Dried cannabis has not been proven more effective for NeP than prescription medications. If planning on authorizing its use, only consider its use in clients with proven severe, refractory NeP. Document that all guideline recommended medications and treatments have failed. Clients should be fully informed regarding the lack of efficacy of dried cannabis.
Synthetic cannabinoids should be tried before dried cannabis as they are regulated and approved for use by Health Canada with established dosing and safety profiles
Evaluating Safety and Communicating Risk
Clients should be fully informed regarding what is known and not known about short and long term adverse effects and risks
Clients should be aware of the high rates of addiction in those who use cannabis daily

Complete careful assessments of all clients being considered for authorization of dried cannabis to identify those patients with contraindications, such as anyone who: <ul style="list-style-type: none"> • is younger than 25 • needs intact cognitive processing or operates or drives complex machinery for work • has past or active substance use disorder including alcohol, cannabis, or other illicit drug • has a history of schizophrenia, bipolar, or psychosis • is pregnant or breastfeeding • has severe liver, kidney, cardiovascular, or respiratory disease • are currently taking other sedative-type medications including benzodiazepines
Perform careful additional screening and assessment of clients with mental health conditions including anxiety and depression
Advise clients that cannabis impairs driving ability and to refrain from driving when using or wait for several hours before driving. Disclose cannabis use when completing a driver fitness form
Identify possible cannabis-drug interactions with concurrent medications
Dosing
Accurate dosing remains unclear in the literature; however, it is clear the lowest possible dose should be used. Clients should be authorized to use 1 gram or less per day and wait at least one hour between doses of orally prepared dried cannabis to gauge effects
Method of Delivery
Educate clients that the inhalation method is associated with long term negative changes in the lungs including COPD and lung cancer and should not be utilized
Advise clients to use the oral route and advise that it may result in increased sedation compared to the inhaled route
Cost
Clients should be aware of the potential long term costs associated with cannabis use and that it is not covered by any medical plan

Recommendations for Future Research

The review of the literature identified that dried cannabis cannot be safely authorized for clients with NeP in primary care as identified by the WHO rational prescribing guidelines. Future studies should ideally consider the long-term effects, as there is a paucity of data in this regard. Issues with regards to dose and frequency are also a concern. The study that revealed decreased adherence to HIV medications on those clients using cannabis warrants further exploration. The NNT data is clinically helpful but the data for the number needed to harm (NNH) was lacking which is also important when evaluating for prescriptive safety. The new regulations are intended to treat marijuana like other controlled substances. However, the

document for medical marijuana authorization is not written on a duplicate form or numbered. It also has a one year expiration date (CPSBC, 2014); a length of time not standard with traditional prescribing. Research is needed to determine if this difference from a CDS prescription will contribute to issues of reduced safety and security for the individual and the population at large. Related to this is the need for future research on the medico-legal implications for PCPs who authorize its use despite the paucity of evidence relating to its safety, as defined by the WHO prescribing guidelines. The results of the studies also are difficult to apply to the general population because of the exclusion criteria.

However, those subjects excluded were in client groups that are already acknowledged to be at higher risk for experiencing adverse effects from cannabis. The results of the observational studies did not exclude clients with underlying mental health or physical conditions but the degree to which cannabis positively or negatively affected these conditions were not analyzed and could arguably be quite significant. Future studies that include clients with mental health conditions are preferred as there are high prevalence rates in the general population.

Smoking cannabis remains the most popular method of cannabis delivery and was the most studied method in the studies despite the concerns over long-term effects on the lungs. Therefore, other methods of delivery including oral ingestion, mucosal and topical forms should be evaluated.

Addiction to cannabis is a prevalent consequence for many people who use cannabis recreationally and future studies should evaluate the risk of addiction in those who use it therapeutically since it is likely that they will be using it daily and over the long term. Addiction to any substance tends to result in less optimal outcomes. There was a lack of data concerning whether cannabis-naïve subjects experience increased rates of adverse effects; thus, this is

important information for the NP who may be considering using this as a treatment for clients who have refractory NeP but have not used cannabis before.

There was a lack of research data on other manifestations of NeP including allodynia and hyperalgesia. Future studies on the impact of cannabis on these other characteristics of NeP should be explored.

Conclusion

Under treatment of chronic pain can have serious economic, societal and health impacts including the inability to work and decreased quality of life. As researchers and clinicians our concern is with providing our patients with the most efficacious therapies to promote and maintain best health outcomes. Chronic NeP is a complex condition common in primary care that is often refractory to currently recommended treatments. Novel approaches to pain management are increasingly being studied to address this issue including the use of cannabis. Government legislation, public and patient pressure, anecdotal evidence of efficacy and refractory pain has made medical marijuana an alternative treatment that requires consideration and evaluation of the evidence. Thus, it was the intention of this review to determine if dried cannabis could be safely authorized by PCPs, including NPs, for the treatment of NeP in adults using step three of the WHO prescribing guidelines. It was determined that at this time, dried cannabis cannot be prescribed safely based on the current evidence. However, for those PCPs who still may consider using it in clients with severe refractory NeP the evidence provides some guidance on what should be considered to at least be *safer* when authorizing its use. This review made it clear that further research is needed to establish consistent and valid information surrounding the efficacy, dosing, method of delivery, and long-term adverse effects. Further, the PCP has to consider the medico-legal implications of using a medication with limited reliable

evidence to support its use based on rational prescribing guidelines. It is the responsibility of the clinician to work within evidence-based guidelines in order to ensure the safety of their clients and the public.

Glossary

All citations from Medical Dictionary (Merriam-Webster, 2014) unless otherwise indicated.

2-arachidonoyl glycerol (2-AG): an endogenous agonist endocannabinoid present in high levels in the CNS with action at the CB1 receptors

5-lipoxygenase enzyme: inflammatory mediator derived from phospholipid (Rang et al., 2012)

11-hydroxy-THC: an active metabolite of THC (Aggarwal, 2013)

absolute risk reduction: the absolute arithmetic difference in rates of bad outcomes between experimental and control participants in a trial, calculated as the experimental event rate (EER) and the control event rate (CER), and accompanied by a 95% CI. Depending on circumstances it can be reduction in risk (death or cardiovascular outcomes, for instance, in trials of statins), or an increase (pain relief, for instance, in trials of analgesics) (Bandolier, 2007)

adenosine triphosphate (ATP): an ester of adenosine and triphosphoric acid, formed aerobically by a chemical reaction during oxidation. It serves as a source of energy for physiological reactions, especially muscle contraction

adipocyte: fat cell

adrenergic receptors: any of a group of receptors that are present on cell surfaces of some effector organs and tissues innervated by the sympathetic nervous system and that mediate certain physiological responses (as vasoconstriction, relaxation of intestinal muscle, contraction of smooth muscle) when bound by specific adrenergic agents

afferent nerve fibers: nerve cells that convey impulses toward the central nervous system

C fibers: unmyelinated (C) fibers are associated with the dull, diffuse, and burning type pain

A fibers: myelinated (A) fibers convey a sharp and well-localized pain (Rang et al., 2012)

agonist: a chemical substance (as a drug) capable of combining with a receptor on a cell and initiating the same reaction or activity typically produced by the binding of an endogenous substance

allodynia: pain resulting from a stimulus (as a light touch of the skin), which would not normally provoke pain

anandamide: a derivative of arachidonic acid that occurs naturally in the brain and in some foods (as chocolate) and that binds to the same brain receptors as the cannabinoids (as THC)

antagonist: a chemical that acts within the body to reduce the physiological activity of another chemical substance (as an opiate); *especially:* one that opposes the action on the nervous system of a drug or a substance occurring naturally in the body by combining with and blocking its nervous receptor

antiretroviral medications: drugs used to treat retroviruses, namely HIV

asthenia: lack or loss of strength

atherosclerosis: atheromatous deposits in and fibrosis of the inner layer of the arteries

bias: bias is an asystematic error or deviation in results or inferences. In studies of the effects of healthcare bias can arise from systematic differences in the groups that are compared (selection bias), the care that is provided, or exposure to other factors apart from the intervention of interest (performance bias), withdrawals or exclusions of people entered into the study (attrition bias) or how outcomes are assessed (detection bias) (Bandolier, 2007)

bioavailability: the degree and rate at which a substance (as a drug) is absorbed into a living system or is made available at the site of physiological activity

bipolar disorder: any of several mood disorders characterized usually by alternating episodes of depression and mania or by episodes of depression alternating with mild nonpsychotic excitement

blinding: that act of having no knowledge of information that may cause bias during the course of an experiment or test <researchers *blind* to whether the investigational drug is administered>

blood brain barrier: a naturally occurring barrier created by the modification of brain capillaries (as by reduction in fenestration and formation of tight cell-to-cell contacts) that prevents many substances from leaving the blood and crossing the capillary walls into the brain tissues

bradykinin: a polypeptide hormone that is formed locally in injured tissue, acts in vasodilation of small arterioles, is considered to play a part in inflammatory processes, and is composed of a chain of nine amino acid residues

cannabinoid: cannabinioids are a class of drugs that take their name from the cannabinoid botanical *Cannabis sativa* from which they were first isolated and include herbal preparations of cannabis as well as synthetic, semisynthetic, and extracted cannabinoid preparations (Aggarwal, 2013)

carcinogens: substances or agents that cause cancer

cannabidiol: a crystalline diphenol $C_{21}H_{28}(OH)_2$ obtained from the hemp plant that is physiologically inactive but is rearranged by acids into THC

catecholamines: any of various amines (as epinephrine, norepinephrine, and dopamine) that contain a dihydroxy benzene ring, that are derived from tyrosine, and that function as hormones or neurotransmitters or both

catalepsy: a trancelike state of consciousness (as that occurring in catatonic schizophrenia) that is marked by a loss of voluntary motion and a fixed posture in which the limbs remain in whatever position they are placed

chemotherapy: the use of chemical agents in the treatment or control of disease or mental disorder

clinical significance: refers to the practical or applied value or importance of the effect of an intervention and whether it makes a practical and noticeable difference in everyday life (i.e. improvement in quality of life and overall functioning) (Kazdin, 1999).

combustion: a rapid chemical process that produces heat and light

dependence, physical: a state of adaptation manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist (Chou et al., 2009)

dermis: the sensitive vascular inner mesodermic layer of the skin

descending efferent pathways: pathways of the PNS that conduct nerve impulses away from the brain to the effector

desensitization: to decrease a response (as of a cell receptor) progressively following prolonged exposure to a stimulus

diversion: the intentional transfer of a controlled substance from legitimate distribution and dispensing channels (Chou et al., 2009)

dorsal root neurons: the one of the two roots of a spinal nerve that passes posteriorly to the spinal cord separating the posterior and lateral funiculi and that consists of sensory fibers

down regulation: the process of reducing or suppressing a response to a stimulus; *specifically:* reduction in a cellular response to a molecule (as insulin) due to a decrease in the number of receptors on the cell surface.

emphysema: a condition of the lung that is marked by distension and eventual rupture of the alveoli with progressive loss of pulmonary elasticity, that is accompanied by shortness of breath with or without cough, and that may lead to impairment of heart action

endocannabinoid: endogenous cannabinoids that are biosynthesized as needed, usually triggered by increased intracellular calcium ion concentrations. Have many roles including functioning as retrograde mediators passing information from postsynaptic to presynaptic neurons. Influence nociception, cardiovascular, respiratory and gastrointestinal functions (Rang et al., 2012)

evidence-based medicine: the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. Evidence-based medicine does not mean "cook-book" medicine, or the unthinking use of guidelines. It does imply that evidence should be reasonably readily available in an easily understood and useable form (Bandolier, 2007)

experimental study: a procedure carried out under controlled conditions in order to discover an unknown effect or law, to test or establish a hypothesis, or to illustrate a known law

fibromyalgia: a chronic disorder characterized by widespread pain, tenderness, and stiffness of muscles and associated connective tissue structures that is typically accompanied by fatigue, headache, and sleep disturbances

first past hepatic effect: the metabolism of orally administered drugs by gastrointestinal and hepatic enzymes, resulting in a significant reduction of the amount of unmetabolized drug reaching the systemic circulation (Medical Dictionary for the Health Professions and Nursing. (2012)

glycine: a sweet crystalline nonessential amino acid $C_2H_5NO_2$ that is a neurotransmitter which induces inhibition of postsynaptic neurons, is obtained by hydrolysis of proteins

half-life: the time that a living body requires to eliminate one half the quantity of an administered substance (as a radioisotope) through its normal channels of elimination

histamine: a compound $C_5H_9N_3$ especially of mammalian tissues that causes dilatation of capillaries, contraction of smooth muscle, and stimulation of gastric acid secretion, that is released during allergic reactions, and that is formed by decarboxylation of histidine

hyperalgesia: increased sensitivity to pain or enhanced intensity of pain sensation

lipogenesis: formation of fat in the living body especially when excessive or abnormal

metabolism: the sum of the processes in the build-up and destruction of protoplasm; *specifically:* the chemical changes in living cells by which energy is provided for vital processes and activities and new material is assimilated

nociceptor: a receptor for injurious or painful stimuli: a pain sense organ

neurons: one of the cells that constitute nervous tissue, that have the property of transmitting and receiving nervous impulses, and that are composed of somewhat reddish or grayish protoplasm with a large nucleus containing a conspicuous nucleolus, irregular cytoplasmic granules, and cytoplasmic processes which are highly differentiated frequently as multiple dendrites or usually as solitary axons and which conduct impulses toward and away from the nerve cell body—called also *nerve cell*

neurotransmitter: a substance (as norepinephrine or acetylcholine) that transmits nerve impulses across a synapse

norepinephrine: a catecholamine $C_8H_{11}NO_3$ that is the chemical means of transmission across synapses in postganglionic neurons of the sympathetic nervous system and in some parts of the central nervous system, is a vasopressor hormone of the adrenal medulla, and is a precursor of epinephrine in its major biosynthetic pathway

noxious stimuli: physically harmful or destructive to living beings

nurse practitioner: an advanced practice nurse with a graduate education whose legislated scope of practice includes diagnostic and prescriptive authority (CRNBC, 2014b)

observational studies: in research about diseases or treatments, this refers to a study in which nature is allowed to take its course. Changes or differences in one characteristic (e.g. whether or not people received a specific treatment or intervention) are studied in relation to changes or differences in other(s) (e.g. whether or not they died), without the intervention of the investigator. There is a greater risk of selection bias than in experimental studies (Bandolier, 2007)

opioids (endogenous): any of a group of endogenous neural polypeptides (as an endorphin or enkephalin) that bind especially to opiate receptors and mimic some of the pharmacological properties of opiates—called also *opioid peptide*

cytochrome P450 enzymes: haem proteins, comprising a large family of enzymes, but differ in reactions they catalyze. CYP1, CYP2 and CYP3 are involved in drug metabolism of the liver (Rang et al., 2012)

pharmacodynamics: a branch of pharmacology dealing with the reactions between drugs and living systems

pharmacokinetics: the study of the bodily absorption, distribution, metabolism, and excretion of drugs

phospholipase A2 enzymes: an enzyme activated by the cannabinoids involved in prostaglandin synthesis and release (Evans, Formukong & Evans, 1987)

physical dependence: compulsive physiological need for and use of a habit-forming substance (as heroin, nicotine, or alcohol) characterized by tolerance and by well-defined physiological symptoms upon withdrawal

phytocannabinoids: any plant-derived natural product capable of either directly interacting with cannabinoid receptors or sharing chemical similarity with cannabinoids or both and include THC and cannabidiol (Gertsch, Pertwee & Di Marzo, 2010)

polymodal nociceptors: responding to several different forms of sensory stimulation (as heat, touch, and chemicals) <unmyelinated *polymodal* nociceptors>

post-herpetic neuralgia: pain that occurs along a nerve that persists for more than three months after the rash of herpes zoster (shingles) resolves (Venes, 2013).

prostaglandins: any of various oxygenated unsaturated cyclic fatty acids of animals that are formed as cyclooxygenase metabolites especially from unsaturated fatty acids (as arachidonic acid) composed of a chain of 20 carbon atoms and that perform a variety of hormone like actions (as in controlling blood pressure or smooth muscle contraction)

presynaptic: relating to, occurring in, or being part of a nerve cell by which a wave of excitation is conveyed to a synapse <*presynaptic* terminals><*presynaptic* inhibition><a *presynaptic* membrane>

primary care: essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families through their full participation and at a cost that the community and country can afford... It is the first level of contact of individuals, the family and community with the national health system, bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process.

psychological addiction: persistent compulsive use of a substance known by the user to be physically, psychologically, or socially harmful

psychomotor behaviour: of or relating to motor action directly proceeding from mental activity

psychosis: a serious mental disorder (as schizophrenia) characterized by defective or lost contact with reality often with hallucinations or delusions

postsynaptic: relating to, occurring in, or being part of a nerve cell by which a wave of excitation is conveyed away from a synapse <*postsynaptic* dopamine receptors>

schizophrenia: a psychotic disorder characterized by loss of contact with the environment, by noticeable deterioration in the level of functioning in everyday life, and by disintegration of personality expressed as disorder of feeling, thought (as in delusions), perception (as in hallucinations), and behavior

sensitization: increased response of peripheral and central neurons to painful stimuli as a result of nociceptive insult and inflammation that follows the injury (Bauldoff, Burke, & LeMone, 2011)

serotonin (5-HT_{1A}): a phenolic amine neurotransmitter C₁₀H₁₂N₂O that is a powerful vasoconstrictor and is found especially in the brain, blood serum, and gastric mucous membrane of mammals—called also *5-HT*, *5-hydroxytryptamine*

somatic pain: somatic nociceptive pain arises from injury of tissue including skin and muscle, is well localized and varies in character (Bauldoff, Burke, & LeMone, 2011)

sympathetic nervous system: the part of the autonomic nervous system that is concerned especially with preparing the body to react to situations of stress or emergency, that contains chiefly adrenergic fibers and tends to depress secretion, decrease the tone and contractility of smooth muscle, increase heart rate, and that consists essentially of preganglionic fibers arising in the thoracic and upper lumbar parts of the spinal cord and passing through delicate white rami communicates to ganglia located in a pair of sympathetic chains situated one on each side of the spinal column or to more peripheral ganglia or ganglionated plexuses and postganglionic fibers passing typically through gray rami communicates to spinal nerves with which they are distributed to various end organs

synthetic: of, relating to, or produced by chemical or biochemical synthesis; *especially:* produced artificially <synthetic drugs>

terminal half life: or biological half-life, the time that a living body requires to eliminate one half the quantity of an administered substance (as a radioisotope) through its normal channels of elimination

thalamus: the largest subdivision of the diencephalon that consists chiefly of an ovoid mass of nuclei in each lateral wall of the third ventricle and serves to relay impulses and especially sensory impulses to and from the cerebral cortex

tolerance: the capacity of the body to endure or become less responsive to a substance (as a drug) or a physiological insult especially with repeated use or exposure <developed a *tolerance* to painkillers>

toxicity: refers to adverse effects that can be caused by the principal pharmacological action of the drug (bleeding with anticoagulant) or unrelated to the effects of the pharmacological action (liver damage from paracetamol) (Rang et al. 2012)

transient receptor potential channels (TRPs): ion channels present on sensory neurons that are activated by thermal stimuli and chemical agents. Capsaicin, the substance in chili peppers, activates TRPV1, resulting in pain and heat (Rang et al. 2012)

tryptophan: a crystalline essential amino acid $C_{11}H_{12}N_2O_2$ that is widely distributed in proteins

visceral pain: visceral nociceptive pain occurs with stimulation of stretch receptors in visceral tissue typically located in organs; the pain is poorly localized, deep, dull and cramping (Bauldoff et al., 2011)

xenobiotic: a chemical compound (as a drug, pesticide, or carcinogen) that is foreign to a living organism

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Appendix A

WHO Guidelines for Rational Prescribing (deVries et al., 1994)

Step 1: Define the client's problem	<ul style="list-style-type: none"> • Perform history, physical and evaluate labs/diagnostic tests • Establish diagnosis
Step 2: Specify the therapeutic objective	<ul style="list-style-type: none"> • Determine what you and the client want to accomplish with the medication
Step 3: Verify suitability of the p(ersonal)-drug	<ul style="list-style-type: none"> • What is the <i>efficacy</i> of the drug on therapeutic objective • <i>Safety of drug</i>: adverse and toxic effects, safety margins, contraindications (i.e. in high risk group) and drug-interactions specific to client • <i>Suitability</i> of dosing, formulation to age, mental status, concurrent medications, food interactions, comorbidities • <i>Cost of drug</i> to client
Step 4: Write a prescription	<ul style="list-style-type: none"> • Include strength, dose, route, total amount to be dispensed
Step 5: Give information, instructions and warnings	<ul style="list-style-type: none"> • Give <i>information</i> on drug, administration, and warnings
Step 6: Monitor treatment	<ul style="list-style-type: none"> • Establish regular follow-up visits to determine if medication meeting therapeutic objective

Appendix B

Initial Search: Google and Google Scholar	"cannabis" "medical marijuana" "neuropathic pain" 2009-2014	110
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Database	Search terms (MeSH unless otherwise written with " term ")	Result
Cochrane Reviews	"Cannab*" OR "THC" OR "marijuana" AND "neuralgia" OR "neuropathic pain" OR "neuropathy"	80
CINAHL	cannabis OR	24
Medline Ovid	medical	15
Medline full text	marijuana AND neuralgia OR neuropathy	10
Pub Med	cannabis OR cannabinoids OR medical marijuana OR "THC" AND neuralgia	31
PsychInfo	cannabis OR cannabinoids OR marijuana AND neuralgia OR neuropathic pain	6
Biomedical ref	"cannabis" AND "neuropathy"	18
Longwoods	"cannabis", "marijuana"	1

Hand Search	Search terms	Result
Pain Research and Management	"cannabis" AND "neuropathic pain"	1
The Journal of Pain and PAIN Journal		41
National Guidelines Clearinghouse		2
Health Canada Information for Health Care Professionals: Cannabis (marijuana, marijuana) and cannabinoids	"neuropathic pain"	11
Websites	Search Terms	Result
Health Canada	"cannabis" OR "medical marijuana" AND "neuropathic pain"	4
Gov't of Canada		3
Canadian Medical Assoc.		3
American Psychiatric Assoc.		1

**Total Articles = 366
(see Figure 1)**

Appendix C

Table 1: *Study Quality Checklist*

Reporting	
1. Is the hypothesis/aim/objective of the study clearly described? Yes – 1 No - 0	6. Are the main findings of the study clearly described? Yes – 1 No - 0
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section? Yes – 1 No - 0	7. Does the study provide estimates of the random variability in the data for the main outcomes? Yes – 1 No - 0
3. Are the characteristics of the patients included in the study clearly described ? Yes – 1 No - 0	8. Have all important adverse events that may be a consequence of the intervention been reported? Yes – 1 No - 0
4. Are the interventions of interest clearly described? Yes – 1 No - 0	9. Have the characteristics of patients lost to follow-up been described? Yes – 1 No - 0
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described? Yes – 2 Partially – 1 No - 0	10. Have actual probability values been reported(e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001? Yes – 1 No - 0
External Validity	
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited? Yes – 1 No – 0 Unable to determine - 0	13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive? Yes – 1 No – 0 Unable to determine - 0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited? Yes – 1 No – 0 Unable to determine - 0	
Internal Validity - Bias	
14. Was an attempt made to blind study subjects to the intervention they have received ? Yes – 1 No – 0 Unable to determine - 0	18. Were the statistical tests used to assess the main outcomes appropriate? Yes – 1 No – 0 Unable to determine - 0
15. Was an attempt made to blind those measuring the main outcomes of the intervention? Yes – 1 No – 0 Unable to determine - 0	19. Was compliance with the intervention/s reliable? Yes – 1 No – 0 Unable to determine - 0
16. If any of the results of the study were based on “data dredging”, was this made clear?	20. Were the main outcome measures used accurate (valid and reliable)? Yes – 1 No – 0 Unable to determine - 0

Yes – 1 No – 0 Unable to determine - 0	
17. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls ?	
Yes – 1 No – 0 Unable to determine - 0	
Internal Validity – Confounding (Selection Bias)	
21. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	24. Was the randomised intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable?
Yes – 1 No – 0 Unable to Determine - 0	Yes – 1 No – 0 Unable to determine - 0
22. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	25. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
Yes – 1 No – 0 Unable to determine - 0	Yes – 1 No – 0 Unable to determine - 0
23. Were study subjects randomised to intervention groups?	26. Were losses of patients to follow-up taken into account?
Yes – 1 No – 0 Unable to determine - 0	Yes – 1 No – 0 Unable to determine - 0
Power	
27. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%? (modified)	
Yes – 1 No - 0	

Note. From “The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions,” by S. H. Downs & N. Black, 1998. *Journal of Epidemiology and Community Health*, 52(6), 377-384. Reprinted with permission.

Table 2: Study Outcomes

	Research Question	Methodology	Quality Rating # / 28 (Downs & Black, 1998)	Analysis/ Results	Conclusions	Implications for future research	Implications for practice
Abrams et al. (2007)	To determine the efficacy of smoked cannabis (SC) on HIV-assoc. sensory neuropathy (HIV-SN)	Prospective randomized placebo-controlled trial THC: 0% vs 3.56% N=55 (n=50 finished)	25	SC pain by 34% vs 17% placebo (p=0.03) 52% > 30% pain reduction vs 24% placebo (p=0.04) Hyperalgesia 34% SC vs 11% placebo (p0.05) no withdrawal from A/E NNT 3.6 mITT method of analysis	-SC was more effective in HIV-SN vs placebo -Results are consistent with pre-clinical pain model studies with systemic cannabinoids -acceptable safety margin -no apparent reaction with other medications taken	- studies using people who have not used cannabis before -studies on smoked or oral cannabis for neuropathy not associated with HIV	-NNT and pain reduction not better than current treatments -possible 3 rd line agent -use for patients with hyperalgesia -caution with cannabis naïve clients
Abrams et al. (2011)	Does cannabis augment the analgesic effects of opioids?	Open-label clinical trial, nonplacebo controlled N=24 (n=21 finished) Vaporized cannabis (VC) 3.56%	22	Pain by 27% from baseline after vaporized cannabis (95% CI 9,46) No withdrawal from A/E anxiety/depression per-protocol method analysis	VC augments the analgesic effects of opioids without significantly altering plasma opioid levels.	- further controlled studies of the synergistic interaction between cannabinoids and opioids are warranted. -evaluation of other forms of cannabinoids	The combination may allow for opioid treatment at lower doses with fewer side effects. -caution for use in cannabis naïve patients
Corey-Bloom et al. (2012)	Assess the safety and efficacy of smoked cannabis vs placebo in pts with MS (tx-resistant) spasticity	Randomizeddouble-blind, placebo controlled crossover design THC 0 vs 4% N=37(n=30 finished study)	27	SC of 4.28 more points on VAS vs placebo (p 0.009). PASAT 6.981 SC vs placebo (p 0.003) n=5 w/d because of a/c Intention-to-treat analysis	-SC was superior to placebo in pain reduction -w/d because of cognitive effects -no serious effects -SC does effect cognition (though clients still within range for their age and education)	-larger, longer term studies to determine if lower doses still work with less cognitive effects -people with more intense baseline pain -to do study on other patient populations (mentally ill, major medical conditions) -long term cognitive effects	-SC could be offered to MS patients with refractory spasticity and minor pain -expect cognitive effects -can't generalize to all patients -caution with cannabis naïve patients -caution for use in patients that need mental alertness for their work (driving et)
Corless et al. (2009)	Is it effective for symptom relief in HIV? Subanalysis compared MJ to other meds for neuropathy	Subanalysis of a RCT N=768	20	MJ rated as more effective for relieving NeP Not stat signif. anxiety/depression	MJ was rated more effective than other meds for NeP	-Need larger sample size -basis for future clinical trial -effect of MJ on plasma levels of other meds	-cannot draw conclusions for use in practice other than reported positive correlations with MJ use for HIV symptoms

	Research Question	Methodology	Quality Rating # / 28 (Downs & Black, 1998)	Analysis/ Results	Conclusions	Implications for future research	Implications for practice
Ellis et al. (2009)	To ascertain a safe, clinically useful and efficacious dosing range for smoked medicinal cannabis as a short term analgesic in the tx of refractory NeP in HIV DSPN	Phase II, double-blind, placebo-controlled, crossover trial THC 1-8% (self-titrated dosing) N=34 (n=28 finished)	27	Cannabis >placebo pain relief DDS pain intensity scale (p 0.016) 46% had 30% reduction in pain compared to placebo 0.46 (95%CI 0.28, 0.65) vs 0.18 (95%CI 0.03, 0.32), p = 0.043). anxiety/depression NNT= 3.5 ITT analysis	-SC did pain compared to placebo -there were 2 subjects with S/E that had them drop out (psychosis and cough) -no change on CD4 or viral loads	-need longer term study to determine if S/E will be more pronounced -can it be applied to those with other types of NeP	-smoking is effective but not for everyone – some cannot tolerate, assoc, with COPD -may be good for those with refractory pain -can be used with other drugs with no concern for interactions -those with lung conditions or mental health conditions may not be candidates
Jay et al. (2004)	Assessed the effect of SC on NeP and experimentally-induced pain in individuals with painful neuropathy due to HIV or ARVs	Open-label pilot inpatient study conducted over 9 days THC 3.56% N=16	13	> 30% reduction in baseline pain for 10/16 clients >30% reduction of hyperalgesia for 14/16 patients No CI or P value calculated	Smoked THC decreased pain and hyperalgesia in HIV-associated neuropathy	A 50 subject 7-day randomized placebo-controlled trial has been initiated in an attempt to confirm these preliminary findings.	-again no substance use included -may be used as adjunct for refractory NeP for HIV clients -caution with use in cannabis naïve patients -use in clients on other medications
Lynch et al. (2006)	What is the effect on pain for clients using MM under the program?	Descriptive survey on case series 11-point pain rating scale 1-5g/day N=30	18	-93% reported reduction in pain 6/10 points (>30%) -use of other OTC meds anxiety/depression	There is evidence that MM may be an alternative for refractory pain	Need to have larger, placebo controlled studies to determine safety and effect of use with other medications	-consider use for clients with refractory NeP
Wallace et al. (2007)	Used a human exp, pain model and a dose-response design to evaluate the effects of SC on acute nociceptive processing and the facilitated pain state	randomized, double-blinded, placebo-controlled, crossover trial THC 2.4, 8% N=19 (n=15 completed)	24	Low dose no effect Medium dose dec. pain (SS compared to placebo delayed) High dose pain No effect on hyperalgesia Per-protocol method of analysis	Medium dose relieved pain without adverse effects -narrow therapeutic window for pain	-short term, small sample size -evaluate other compounds in cannabis that may have contributed to increase pain at higher doses	-concerns about smoking as delivery system -they did not advocate use of cannabis for pain at this time due to abuse potential, tolerance, efficacy and safety issues

	Research Question	Methodology	Quality Rating # / 28 (Downs & Black, 1998)	Analysis/ Results	Conclusions	Implications for future research	Implications for practice
Ware et al. (2010)	safety and efficacy of smoked cannabis in outpatients with chronic NeP.	Randomized double-blind, placebo-controlled, four-period crossover design THC 0, 2.5, 6, 9.4% N=23 (n=21 finished)	22	9.4 vs 0% (p=0.023, CI 0.02-1.4) No serious A/E expected, A/E with THC dose No difference in sleep/quality of life anxiety/depression Per-protocol analysis	-SC improved pain, sleep, anxiety -one withdrawal d/t pain.	-future trial to use vaporizer instead of smoke -need higher potencies and flexible dosing strategies -determine effect of cannabis on other medication plasma levels	-use for clients as adjuvant therapy -not for use with cardiac/pulm. Disease -okay for use with clients who take other medications
Wilsey et al. (2008)	To evaluate the analgesic efficacy of smoking cannabis for NeP	RCT crossover trial of cannabis (high, low, no doses) N=38 (n=33 0% n=36 3.5% n=34 7% finished)	25	Allodynia (n=23) no SS with different concentrations of cannabis (p=.40) or cumulative dose (p=.29) Per-protocol analysis	Cannabis was effective for NeP Low dose worked as well as high dose with less psychoactive effects	Larger, longer studies Alternative to smoking	Low dose may help with less diversion risk, for clients with jobs that require cognition intact
Wilsey et al. (2013)	evaluating the analgesic efficacy of low dose THC with vaporization cannabis refractory NeP -vaporize not smoke	double-blind, placebo-controlled, crossover study 1.29% THC 3.53% THC N=39 (n=38 0%, n=37 1.29%, n=36 3.53% finished)	24	30% pain for low/mod doses -no dropouts due to S/E -tolerated S/E with good pain relief -no sig diff between med and low dose NNT: 3.2 (low); 2.9 (med) Per-protocol analysis	-present study adds to growing literature of cannabis use for NeP -vaporizing low dose worked well -quantitative prescribing not feasible at present time	-larger longer studies regulated/standard plant use to be able to quantify dosing -to do studies with clients that were excluded (mentally ill, substance use, severe medical illness)	-low dose, nonsmoke delivery system worked may make it easier for prescribers -can only generalize to study demographics
Woolridge et al. (2005)	To investigate HIV-symptom management with cannabis	anonymous cross-sectional questionnaire study. Varied forms of delivery N=143 used cannabis for symptom mx (n=61 nerve pain)	21	90% reported improvement of NeP (n=53) (p=0) anxiety/depression	-cannabis is used by many HIV clients for symptom control -effective for NeP	-for use in other client demographics and illnesses -clinical trials evaluating cannabis on NeP -longer study evaluating cannabis on HIV viral loads/CD4	-for use in clients with HIV-associated symptoms -use in patients with NeP -use in clients taking other medications