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Standardized Cannabis and Pain Management

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1. Introduction

We began our journey researching cannabis as a medicine roughly twelve years ago and have been astounded time and time again at the profound effectiveness of the plant. In this chapter we will describe the usefulness of cannabis in pain management. In so doing we will be describing the *whole plant medicine* such as is dispensed in compassion clubs and medical marijuana dispensaries here in British Columbia, Canada and similarly in California and other parts of the world where cannabis has become legal as a medicine.

We treat cannabis as the herbal medicine that it is. What we do; is apply high tech instrument analysis of the plant and scientific method to members using cannabis therapeutically in attempts to unravel the truth of its efficacy and safety. We have set up research departments, collected membership data, run literally thousands of chromatograms and worked closely with persons with chronic pain at local dispensaries and cannabis clubs here in British Columbia for many years.

What we will describe in the chapter is primarily repeated observation of members of medical marijuana dispensaries who routinely use cannabis to deal with pain. Of the clubs we have worked with over the years most of their members are using cannabis for pain management. Often greater than 70% of the members surveyed will be using cannabis for this purpose. This holds true for medical dispensaries here in B.C. as well as for California, Holland and Switzerland (1). Simply put, most persons frequenting medical cannabis dispensaries are there for pain management.

Many of the people we have worked with over the years have been terribly broken up, either in car accidents, on the job injuries, infection (Reiter's syndrome), surgeries or cancer therapy, plus many other causes, that lead to 24/7 chronic pain. As if the pain isn't bad enough, often cycling with the pain is mood disorder, such as depression, attention deficit disorder and anxiety.

When it is difficult to put on a jacket, climb a flight of stairs or tie shoelaces, normal life is affected and the individual adjusts by changing their life style in attempts to relieve pain. These adjustments can often bring on anxiety (not being able to go out) or depression (relating to friends and family) since now the person's lifestyle is not as it used to be…now it is ruled by pain.

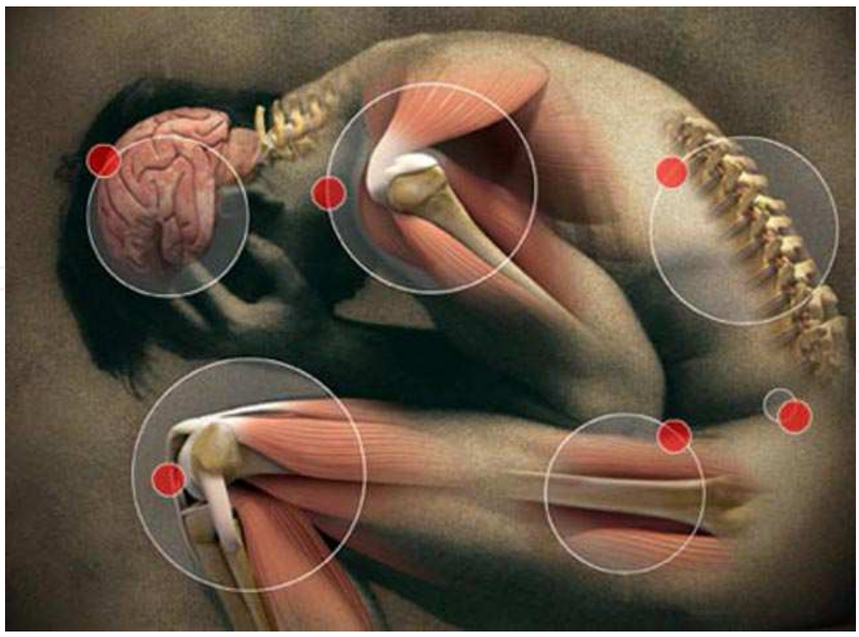


Fig. 1. Acknowledgement to: http://naturalbodyofflorida.webs.com/pain-map_alphachimp_com.jpg for this explicit graphic.

For those dealing with pain it often becomes a fulltime job: monitoring, medicating, resting, exercising, eating, going to bed, take on new meaning when one is in pain. Constantly seeking relief from "the banging drum," as quoted by Dr. Mel Pohl (2), being the top priority for those who suffer. Relief from pain leads to a new quality of life that, in turn, breaks the cycle of chronic pain syndrome.

Cannabis allows new quality of life for many suffering from chronic pain.

Having access to the member's data allows determination of; how much cannabis they're using daily, in what form (smoke able or edible), what strain is preferred, their ailment, etc. This accumulated data is used to take perspective on the cannabis use of the membership of the individual clubs and to track various individuals included in studies.

We have spent five years with our laboratory serving the quality control and standardization needs of one such dispensary, and the past two doing similar duties and research at a second. In all of this time we maintain close association with the members who use cannabis therapeutically for pain, tracking their symptoms with questionnaires, interviews, pain charts, emails, etc.

We have found a psychology that prevails at these dispensaries; they're friendly, non-violent, people whom all seem to be willing to take part in the scientific research that is being carried out. No shortage of volunteers. And many have sustained and continue to deal with disabling injuries that have dramatically affected their lives and families.

Currently we have joined with five medical dispensaries in our local area and are initiating Randomized Controlled Trials (RCT) with roughly one hundred volunteer subjects together taking part in the placebo controlled trial. Our focus will be arthritic pain and we look forward to publication before the end of 2012.

2. The legalities

Cannabis has been legal as a medicine, in Canada, since 2001, when a precedent setting court case ruled that Canadians had a constitutional right to the plant for medical purposes (3). The Medical Marijuana Access Regulations (MMAR) was established in that year allowing qualified individual's licenses to possess and produce their own cannabis for medical reasons.

Only persons who were terminally ill, with severe spinal cord injury, arthritis or multiple sclerosis and unresponsive to routine medical treatment were originally allowed a cannabis license. Often these people were too ill to grow their own, so designated growers were also assigned licenses to specific qualified persons for growing cannabis. An alternative to obtaining an MMAR license was to have a medical doctor fax a letter of acknowledgement of an individuals cannabis use to a local dispensary, releasing the dispensaries from some of the quasi-legal burden of distributing cannabis to members.

Overall the MMAR program has demonstrated itself to be lacking in meeting the needs of it's licensees, with long wait times for initial and renewal licensing and poor supply of government marihuana for those unable to grow for themselves or without a designate. Because of these shortcomings and yet another court case the program is about to be revamped once again to tighter government and industry control.

Nevertheless, most persons in Canada, at this time, with a legitimate complaint of chronic pain and a tenacious attitude can access medical marijuana. And most would do this with their own licensed grows or through dispensaries.

3. The endocannabinoids

As it turns out the receptor that binds THC is one of the most abundant binding sites in the human brain. Expressed at high levels in the hippocampus, cortex, cerebellum, and basal ganglia (4–6), the receptor, is virtually everywhere. An unusual receptor type in that binding occurs at the pre-synapse (upstream) side of the cleft, a type of receptor mechanism, called retrograde signaling. Different, in that depolarization at the post-synapse opens voltage-dependent Ca^{2+} channels, that in turn, activates enzymes that produce endocannabinoids from lipid precursors, in the cell membrane. See Figure 2, courtesy of Dr. Roger Nicoll (7), that illustrates retrograde signaling.

In the Hippocampus, for example, these highly fat-soluble compounds migrate back across the synapse to the pre-synaptic CB1 receptors where binding slows release of the inhibitory neurotransmitter, GABA. G-protein activation liberates Gbg (a receptor subunit), which then directly inhibits presynaptic Ca^{2+} influx, thus preventing release of neurotransmitter vesicles from the presynapse.

Until just a few years ago this type of receptor signaling was unheard of but today characterizes the endocannabinoid mechanism of neuromodulation, protection and plasticity.

In their review, Hohmann and Suplita state that: "Cannabinoid receptors are localized in neuroanatomical regions subserving transmission and modulation of pain signals, such as the periaqueductal gray (PAG), the rostral ventromedial medulla (RVM), (8,9) and the

dorsal horn of the spinal cord.(9) These findings suggest that endocannabinoids play a key role in central nervous system modulation of pain signaling.

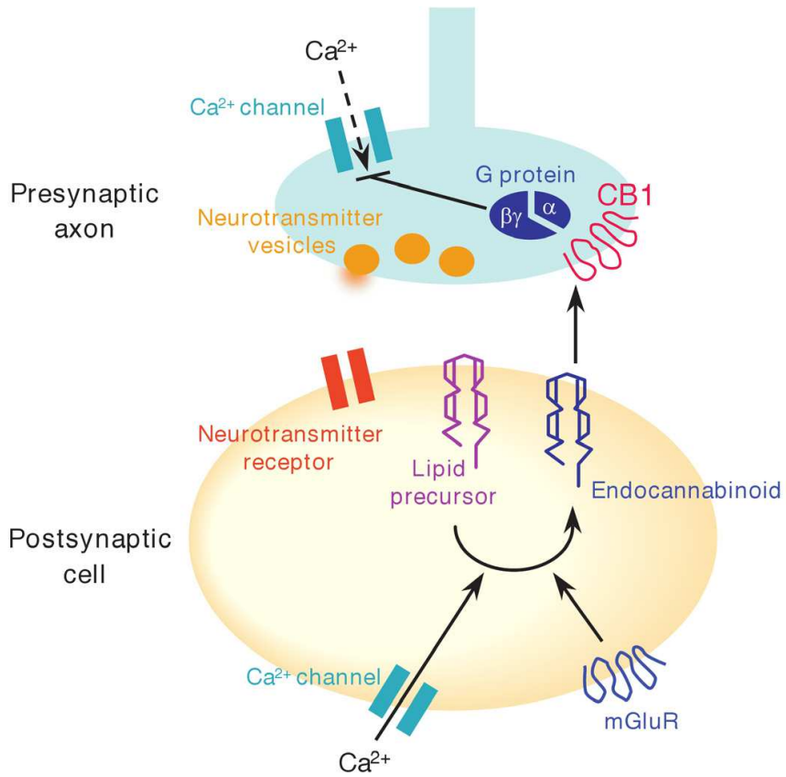


Fig. 2. Retrograde signaling by endocannabionids. Postsynaptic depolarization opens voltage-dependent Ca^{2+} channels; postynaptic Ca^{2+} then activates enzymes that synthesize endocannabinoids from lipid precursors. Activation of postsynaptic mGluRs can also generate endocannabinoids possibly by activation of phospholipase C, generating diacylglycerol, , which is then cleaved by diacylglycerol lipase to yield 2-arachidonylglycerol. Endocannabinoids then leave the postsynaptic cell and activate presynaptic CB1 receptors. G-protein activation liberates $G_{\beta\gamma}$, which then directly inhibits presynaptic Ca^{2+} influx. This decreases the probability of release of a vesicle of neurotransmitter.

Significantly, immunocytochemical studies have demonstrated FAAH expression in the ventral posterior lateral nucleus of the thalamus,(10-12) which is the termination zone of the spinothalamic tract. This pathway is the major source of ascending nociceptive information to the brain. Furthermore, FAAH has been identified in Lissauer's tract and in neurons of the superficial spinal cord dorsal horn (i.e., in close proximity to the termination zone of nociceptive primary afferents). These observations confirm that a mechanism for endocannabinoid deactivation is present in regions of the central nervous system implicated in nociceptive processing and further support the notion that endocannabinoids play a role in pain modulation."

Since the endocannabinoid system includes the G-protein receptors and subunits, the ligands that bind the receptors and the enzymes that make or breakdown the ligands, attention has been paid to all these components in relation to pain.

Mice bred with no CB1 receptors tend to hide in corners, die young and show high incidence of cataplexy and hypoalgesia, or decreased sensitivity to painful stimuli. It was experiments such as these that indicated the role of the endocannabinoid system in the modulation of nociception and pain. And, indeed, the tremendous abundance of the neuromodulatory CB1 receptor in the human central nervous suggests a regulatory role of neurotransmission, far greater than that commanded by the opiate system.

Research carried out between 2005 and 2010 indicates that synthetic cannabinoids and inhaled cannabis are effective treatments for a range of neuropathic disorders.[13] Smoked cannabis has been found to provide relief from HIV-associated sensory neuropathy.[14] This form of cannabis was also found to relieve neuropathy associated with CRPS type I, spinal cord injury, peripheral neuropathy, and nerve injury.[15]

3.1 CB2 receptor

Changes in endocannabinoid levels and/or CB2 receptor expressions have been reported in almost all diseases affecting humans [16]. CB2 receptors are found mostly in peripheral immune tissues such as the spleen, tonsils and thymus glands where they're primarily localized on immune cells such as monocytes, macrophages, B-cells, and T-cells.[17-20] Reducing intracellular levels of cyclic adenosine monophosphate (cAMP), leads to a series of down-regulatory events ultimately resulting in lowered immunity. Other types of cannabinoid receptors (CB3) are proposed and will undoubtedly more will emerge as research continues.

Several putative endocannabinoids have been isolated in the brain, including anandamide, 2-AG, noladin ether, virodhamine, and N-arachidonoyldopamine (NADA), the latter neurotransmitter decidedly involved with the vanilloid receptor and nociception.

4. Dosage

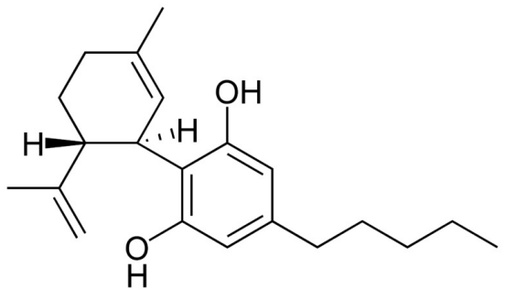
The first step in pain relief is accessing cannabis, once obtained…relief begins.

4.1 Oral vs. smoking

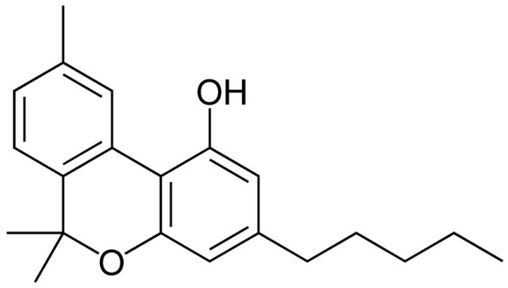
Often the initial use of cannabis for a person in chronic pain is the blessing they have been waiting for. Normally smoked the first time, the instant relief and general well being brought about from cannabis are greatly appreciated. But with smoking relief is short, roughly an hour or two before another dose is needed. With smoking the member of a dispensary or compassion club will cycle through their day with relief one hour, but not the next, for those with severe chronic pain, eating cannabis becomes a better solution. With oral ingestion the effects are often stronger and felt more "in the body than the mind" and pain relief is maintained for four to six hours in a plateau-like fashion rather the cyclical.

Indeed, oral ingestion of cannabis is most often indicated for those with chronic pain. But one cannot just pick a bud off the plant and eat it, since raw cannabis does not contain activated cannabinoids that bind a receptor. In nature the cannabinoids, such as Tetrahydrocannabinol (THC) and Cannabidiol (CBD) are present as acids with carboxyl groups at the 3′ or 5′ position on the aromatic ring of the molecule, (by the terpene numbering system) . With the carboxyl group in place the cannabinoid does not interact

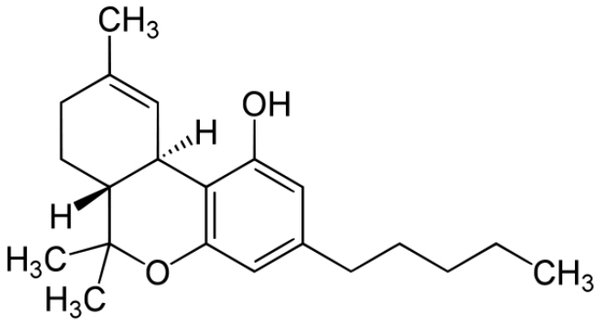
with the receptor; once decarboxylated, normally through heat, the carboxyl group is lost and THC, for example, can now bind. (see section 4.3 on smoking)



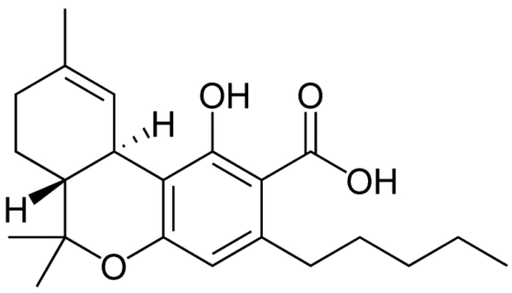
CBD



THC



CBN



THC-acid

Note that both CBD and CBN also have carboxyl groups as does THC-acid and most other cannabinoids at room temperature.

4.2 Decarboxylation

Decarboxylation of the major cannabinoids, tetrahydocannbinolic acid (THC-A), cannabidiolic acid (CBD-A) and cannabinolic acid (CBN-A), is important to understand particularly with oral administration of cannabis. With smoking de-carboxylation occurs by default with the high heat delivered through burning. With oral preparations the cannabinoids must be decarboxylated to produce an efficacious medicine. Most commonly baking the cannabis into a Brownie not only allows decarboxylation of the primary cannabinoids but also supplies a fatty medium, aiding in absorption of the medicine.

Since decarboxylation requires heating a particular strain of cannabis for a specified time at a specific temperature to achieve optimal release of the carboxyl group, often oral preparations of cannabis have incomplete decarboxylation, yielding only a percentage of the tetrahydorcannabinolic acid (for example) as THC and thus not allowing maximum utilization of the active compound.

Upon realizing the multitude of inefficient decarboxylation methods employed by many dispensary members preparing their own oral cannabis preparations, our research group set about standardizing cannabis into capsules, with known concentrations of the major actives (THC, CBD and CBN), for research purposes.

We also subjected the standardized oral capsules to routine quality control procedures such as screening for heavy metals, pesticides and pathogenic bacteria, yeasts and molds. It is with these standardized capsules that most of our research into the efficacy and safety of cannabis as a medicine as been studied.

4.3 Standardization

By standardizing cannabis into orally administered capsules that we are able to better determine dosage and efficacy and members were able to develop regimens for treating pain. The standardization process involves testing by High Pressure Liquid Chromatography (HPLC) the raw material prior to heating to determine the amounts of the various acids; currently in the heating step we are mostly concerned about the concentration of CBD-A in the raw material, since we consider CBD an extremely important medicinal cannabinoid and indeed it is the last of the three, to decarboxylate with heat.

To clarify, decarboxylation of THC-A occurs at a lower temperature than for CBD-A and since it is our quest to optimize the CBD concentration in a standardized prep, we must heat for long enough at a high enough temperature to fully decarboxylate the CBD-A. Once the heating step is finished the cannabis is re-ground to a fine powder and tested again by HPLC and encapsulated.

In each capsule the concentration of THC, CBD and CBN, is known and of course the ratios of these individual cannabinoids will change depending on the strain of cannabis used (strain specificity, discussed below), therefore there is no generic time or temperature that will optimally decarboxylate every cannabis strain …they're all different. An educated

guess for most strains available here in BC and in California would be 160ºC (325 ºF) for 45 to 60 minutes in a sealed environment. However it is only by pre-analysis of the raw material, and experimentation, that we are able to set a time and temperature for optimal decarboxylation of a specific strain.

The ratios of the three most abundant cannabinoids (excluding CBG), is a good indicator of the observed effects in an individual. For example, a ratio of roughly 1:10 CBD:THC proves useful for pain relief with sedation. Whereas increasing the CBN concentration relative to THC will bring about less pain relief and a more stimulatory effect. Point being, that the ratios of the individual cannabinoids one to t'other are an excellent indicator of efficacy for a given strain.

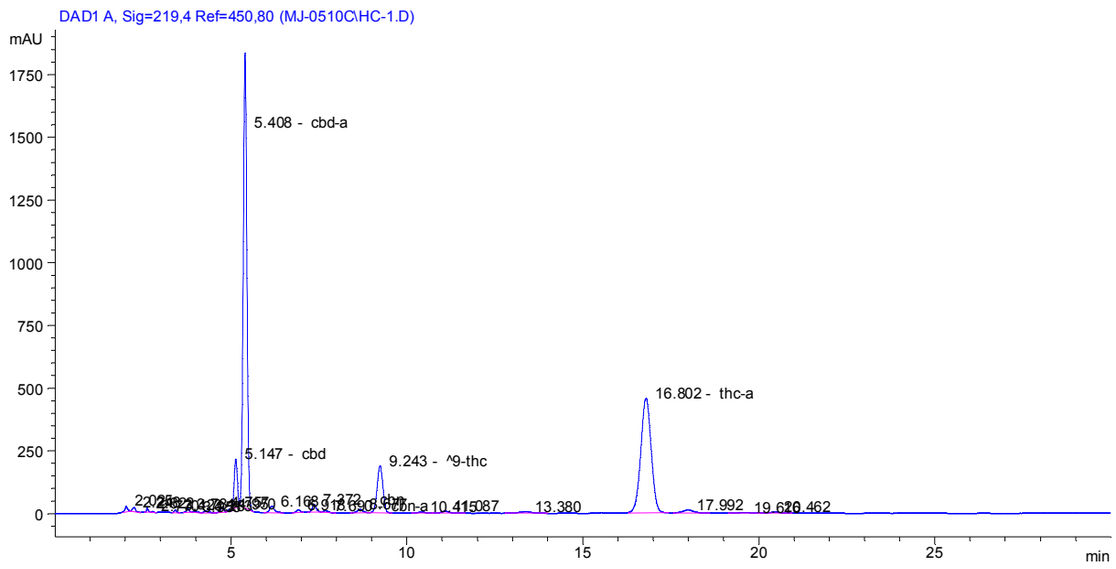


Fig. 3. HPLC (Cannabinoid) profile of a high Cannabidiol (CBD) Strain. Note the undecarboxylated THC-A and CBD-A, before heating.

In terms of dosing an individual there are some important considerations. The first being the individual's genealogy. It is our experience with roughly four thousand people over five years is that body weight is irrelevant to the effects experienced by a person using cannabis. Much more important is the individuals heritage or genetic background. Time and time again in working with persons using cannabis therapeutically it is the British Celtic (Irish, Scottish, Welsh) races that require more cannabis to relieve pain symptoms. Often three to five times more than middle Europeans, Asians or Africans, the latter, often not following theory as well as the former two.

Nevertheless, it is a common observation amongst cannabis users that different races have different tolerances with the Celts being the most tolerant. This phenomenon is important to recognize in sparing many from overdose, particularly with oral preparations and persons with lowered tolerance to cannabis.

Our first question in counseling an individual on cannabis use (particularly with oral administration) is what is their genealogy? Celts will frequently start with 50 to 100 mg of

THC without experiencing any of the effects of overdose, whereas Europeans will start with 20 to 40 mg of THC. We have recently reported two case studies (21,22) where the members being studied were both of Celtic origin, both dealing with pain issues and each required up to 500mg of THC as cannabis per day, to relieve their symptoms.

Now how does one determine THC concentrations in cannabis buds that are to be smoked or even prepped into an oral dose? We will present averages taken here in British Columbia that correlate with other areas of the world were cannabis is being used under medical license. Averages of BC cannabis that was provided to the members of one BC Compassion club is indicative of the concentrations of three cannabinoids found in most commercial cannabis available here and elsewhere.

THC + THC-A (total THC) 172 ($\pm$ 26) mg/gram

CBD + CBD-A (total CBD) 3.1 ($\pm$ 0.5) mg/gram

CBN + CBN-A (total CBN) 2.7 ($\pm$ 0.5) mg/gram

n = 30

Table 1.

Review of the literature on smoked cannabis provides an average ingestion of THC consumed when smoking. A good rule of thumb is that 20% of the available THC is ingested during smoking; the other 80% is lost to atmosphere or pyrolysis. Therefore, of the average 170-mg/gram of THC available, the patient would ingest roughly 34 mg from 1 gram of smoked cannabis, but since most cannabis cigarettes are normally in the 0.5-gram range, this would be approximately 17 mg per dose.

One will note that the concentration of total THC is far greater than CBD or CBN, since breeding, lighting and fertilizer regimens have all been designed to increase THC levels in commercial cannabis. We feel that this is unfortunate considering the growing evidence of the medical benefits of CBD. It is extremely rare to find strains that have anything above these averages for CBD or CBN.

Incidentally, dividing the mg/gram value by 10 provides the percent value.

And, since decarboxylation is a one to one conversion of the acid to the alcohol moiety, with complete loss of the carboxyl group it is possible to administer virtually 100% of the available THC, CBD and CBN, in an oral preparation.

For persons suffering from chronic pain, oral administration of cannabis is greatly preferred over smoking. By oral ingestion, dosing is normally every four to six hours, with the average in the range of 50 to 100 mg of THC, depending on genealogy, cannabis experience and term of use.

4.4 Overdose

An overdose on THC can be a terribly frightening experience. Feelings of fear, paranoia, confusion and vivid death thoughts can occur to a person with low tolerance and unfamiliar

with cannabis, who has overdosed on THC. Having done so, it is rare that an individual will want to repeat the event.

Therefore, overdose is to be avoided since a member may miss out on significant pain relief from correct dosing, because of fear of another overdose. This is one of the important aspects of standardized capsules, such that a member can start small and work up, to where relief is found. Important to people with chronic pain, is that low doses won't work, high doses can sometimes make the pain worse and medium doses are best. A medium dose being 50 mg for most, and 150 mg for a Scot. Sorry folks, the phenomenon of Celtic tolerance repeats itself too often to be ignored.

The good thing about overdose is that no one dies. There are no recorded deaths resulting from cannabis use (23). One estimate of THC's LD50 for humans indicates that about 1,500 pounds (680 kg) of cannabis would have to be smoked within 14 minutes.[24], to achieve toxic levels of THC. Cannabis can be considered an anti-toxin with constituents that offer neuroprotection, anti-oxidant activity and reduced stress.

Robert Kampia, Founder and Executive Director of the Marijuana Policy Project. House Subcommittee on Criminal Justice, Drug Policy, and Human Resources. Apr. 1, 2004: Stated that: "Regarding the claim that marijuana is too dangerous to be a medicine, it is interesting to note that there has never been a death attributed to an overdose of marijuana. Clearly, most prescription drugs are far more dangerous than marijuana."[25]

In summary, overdose can easily happen, particularly, when a person orally ingests unstandardized product and is not tolerant to the herb, often resulting in a feeling that one will die…but none do.

4.5 Strain specificity

Important too, when considering dosage is the strain of cannabis in question. There are two subspecies of cannabis, *Indica* and *Sativa*, and since they're the same species they interbreed creating thousands of strains of cannabis each with its own unique pharmacology. It is this latter understanding that holds many of us to it as an extremely useful herbal medicine with a very broad efficacy.

Firstly, correct strain selection is paramount for relief of chronic pain. In general the *Indicas* known as Kushs are widely used for pain relief, as are the Indicas as opposed to *Sativas*. The latter tend to be stimulatory and not as effective for pain. Indeed, Indica's tend to have higher levels of Cannabidiol (CBD), a cannabinoid with demonstrated powerful anti-inflammatory action (26). Our studies using HPLC to quantify cannabinoid concentrations in standardized capsules finds that a ratio roughly 1:10 CBD:THC, works well for pain relief in an oral preparation at doses of 20 to 100 mg (depending on tolerance) THC, every four to six hours (21,22).

Often members at dispensaries will use the term "different strains for different pains", to describe the effects of cannabis on their symptoms. Since high cannabidiol strains are rare, it has been difficult to study the effects of CBD on pain. Touted in the literature as being non-psychoactive we observe markedly different effects with cannabis both smoked and in oral preparations when high CBD levels are found in a strain. CBD brings about sedation at

moderate concentrations and shows efficacy with seizure disorder, tremor and neuropathic pain.

We have only discovered one re-producible strain in British Columbia that has a CBD count greater than 50 mg/gram dry, ground, flower weight and, indeed, this strain that has proven most useful in treating persons with chronic pain (patent app). The rarity of high CBD concentrations in B.C. cannabis and other parts of the world where cannabis is grown commercially is a result of selective breeding of high THC strains, over many years, such that cannabidiol has essentially been bred out of commercially available cannabis.

Cannabidiol is useful for a number of reasons…importantly its anti-inflammatory action (26). This property is fully utilized in treating rheumatoid arthritis, irritable bowel syndrome, and bacterial injury, to name a few. Also important is the anti-psychotic effects of CBD, when administered in conjunction with THC. CBD appears to 'buffer' the action of THC at the receptor, allowing less chance of overdose, further permitting higher THC doses, necessary for chronic pain management.

What this means is that CBD can be used to modulate and enhance the effects of THC, in pain management. We have previously discussed the differences in tolerance dependent on genealogy that many persons using cannabis therapeutically can easily overdose particularly on oral preparations. To avoid this we have provided members who are sensitive to cannabis, with high CBD capsules to take along with relatively high THC concentrations and thus prevent the fear and paranoia of overdose and ultimately allowing better pain relief.

5. Cross reaction and allergy

In all of our years studying cannabis effects on members of dispensaries or persons with an MMAR licenses, we have not observed cross-reaction with any other medications, including opiates (synergy observed, discussed below), anti-depressants, NSAIDS or steroids. The apparent neuroprotective, anti-oxidant and homeostatic properties of cannabis, no doubt, playing a role in the non-toxic events arising from combined drug interaction. What is observed occasionally is allergic response to cannabis. Although few in number, on rare occasions a member will present with hives, irritation of the nose, sneezing, itching, and redness of the eyes, symptoms of allergy.

6. Opiate reduction

Although we do not yet have hard data to present on the subject, repeated observation, plus a number of case studies demonstrate the phenomenon of significant reduction in opiate consumption when an individual begins using cannabis therapeutically, particularly by the oral route. In the case study on chronic pain (21) our subject, over the course of one year was able to set aside the following medications and is currently only using cannabis for pain management: Arthrotec, Flexeril, ketorolac, Tylenol 3 with codeine, Naprosyn, Percocet, gabapentin, Marinol, Lyrica, Supradol, oxycodin and Oxycontin for pain. Doxepin, Imovane, Cipralex, Trazadone, Elavil, Effexor XR for depression and HCTZ, Lipitor and ranitidine for a secondary hypercholesterolemia. Even the latter hypercholesterolemia has subsided since using cannabis.

Furthermore, other researchers have noted the same occurrence of opiate reduction or cessation with subsequent use of marijuana (27). And, others have found synergy with opiates, to which we fully agree. Pain relief is better realized when cannabis is used concurrently with opiate medications than with either, alone (28). Dr. Donald Abrams', Chief of Hematology-Oncology at San Francisco General Hospital research team found that plasma levels of opiates did not increase with concurrent use of cannabis, but surprisingly decreased in amounts, yet showed an increase in pain relief. This seemingly paradoxical effect was described as being pharmacodynamic rather than pharmacokinetic…the mechanism remains unexplained, but the finding is significant in that persons using opiates for pain relief could actually use less for equal or better pain relief if cannabis is included in the regimen (28).

The observed reduction in opiate consumption, plus dispensary's, repeatedly using cannabis to significantly reduce or eliminate other addictions suggests its role as a powerful harm reduction agent. Claims of the ability to de-rail crack cocaine and crystal meth addictions, plus reduce or eliminate heroin and methadone were frequently made by dispensary staff members. We believe this to be, once again, the ability of cannabis to lend homeostasis to the human CNS, allowing easier withdrawal and maintenance.

7. Natural supplements

As mentioned earlier in this document chronic pain often cycles with mood disorder. Anxiety and depression are close relatives to pain and although cannabis can help with the symptoms (provided the correct strain and dosage is selected), there are other natural supplements we have found useful for pain management. Taking the lead in popularity with our chronic pain population are free amino acids such as Tyrosine and DL-Phenylalanine, indeed GABA is found to be useful in treating pain as well as anxiety. Other mood enhancing natural products commonly used in pain management are phosphatidylserine (PS) and phosphatidylcholine (PC), S-adenosyl methionine and, of course, B-complex.

Frequently people using cannabis therapeutically, in time, want to eliminate synthetic pharmaceutical drugs from the repertoire entirely and therefore natural supplements fare well, and effectively, in their treatment.

8. Terpenes

It seems appropriate, at this time, to enter another realm of cannabis effects…the terpenes and aromatics contained in the flowers of the plant that are often misunderstood and not realized for medicinal importance. We've conducted experiments creating oral preparations for members that had equal amounts of THC. One, called the "bald" prep, had only THC, the other, termed the "hairy" prep, had an equal amount of THC as the "bald" prep, but also contained the sixty-odd other cannabinoids, plus the terpenes and other essential oils of marijuana. Members reported that the bald prep was boring…indeed it did help with pain, but not to the extent of the "hairy" prep, that provided euphoria and the full cannabis experience. Conclusions from this experiment, that the effects of cannabis are certainly not all about THC, as earlier literature tended to

suggest. We have often stated that there is a whole medicinal science called aroma therapy, that incidentally, has not had the use of cannabis essential oils, since they have been banned as long as the plant.

We believe the terpenes, as a result of their chemistry, to be brain active molecules, acting more like anesthetics than receptor binding agonists, playing their role by interacting with nerve cell membranes and modulating subsequent neurotransmission. Failure to include terpenes in cannabis medicine will leave much out of cannabis effects and, furthermore, we do not agree with ozonating cannabis medicine, for sterilization purposes, since we fear the formation of free radicals and reactive acid species (29).

And we do not believe euphoria should be left out of pain management, considering the therapy of laughter and smiles and the mood disorder that often cycles with chronic pain. Euphoria is medically recognized as a mental and emotional state defined as a profound sense of well-being. Technically, euphoria is an affect, but the term is often colloquially used to define emotion as an intense state of transcendent happiness combined with an overwhelming sense of contentment. The word derives from Greek, "power of enduring easily" (30). For those in chronic pain euphoria is welcomed as a break from “the banging drum” and although transient with cannabis it can lead to the preferred psychological state of a better quality of life.

Euphoria is more common to smoked cannabis than oral, since the terpenes enter the blood stream via the lung and are not metabolized first by the liver, as with oral ingestion.

9. Neuroimaging

The inverse agonist MK-9470 makes it possible to produce in vivo images of the distribution of CB1 receptors in the human brain with positron emission tomography.[31] This work, graphically illustrates the abundance of the receptor and its locations.

10. Conclusions

Since discovery of the cannabinoid receptor by Raphael Merchoulam of the Hebrew University in Jerusalem in the early 1990’s there has been an absolute explosion in research on what is now called the endocannabinoid system. The system, that is ubiquitous in human physiology is so prolific that it has been said that the human body is “wired for cannabis”. Indeed the most common G-protein receptor site in the human brain binds THC. Given the magnitude of this system and its influence of human biochemistry, it is certainly not “of no medical value”, yet remains as a Schedule 1 drug in the United States.

As stated a number of times in this Chapter we treat cannabis as a whole plant herbal medicine; we analyze it that way, standardize and quality control it, using the same QC parameters as set out by Health Canada for any other herbal medicine in the country. And we have studied its effects in humans for more than a decade.

Having, in this time observed thousands of persons, most of them in chronic pain, using cannabis therapeutically, in retrospect, we are also impressed by the apparent lack of adverse effects and events seen. We know that panic and anxiety attacks following cannabis

use can often be avoided with correct strain selection and dosage. And all of these adverse effects are transient.

After repeated observation, time and time again of desired effects in pain management with persons using cannabis we can only conclude it to be and extremely important and useful herbal medicine. Indeed, a witch's brew of phenolics, flavanoids, vitamins, terpenes, cannabinoids, and many other compounds of medical and human interest, we have always maintained that with sufficient instrumentation and resources, we could complete the story on the efficacy and safety of cannabis, *the whole plant herbal medicine*.

The fact that cannabis is illegal for most people often forces them to use synthetic painkillers that may prove harmful to liver, kidney and heart, with extended use. We have always promoted standardized, quality controlled, herbal cannabis medicine, and, as stated we do not highly purify or synthesize any of its components.

We have not observed any toxic events with any human subjects…not once. Noted on rare occasions are allergic responses to cannabis smoke or oral ingestion that may prevent a person from further use, but never more adverse or toxic reactions to the plant.

Having repeated this exhaustively, our team has concluded that marijuana is a safe and profoundly effective herbal medicine. So effective, in fact, that it has been banned across most of the world for almost 100 years. This is a tragedy, for those who suffer and could gain a new, extended quality of life, for those who do not know of the miracle of cannabis and for those who do.

Research has always been difficult with no government grants or similar resources to support labor or required equipment cost, we have essentially funded the work ourselves, with the help of the dispensaries and their members.

Apart from the occasional overdose, to which full recovery is made, we have only observed benefit in quality of life for those using cannabis therapeutically. Sometimes these benefits are alarming with members setting aside walkers and dancing in waiting rooms, after using marijuana. We have worked with members with crushed, metal impregnated and amputated limbs, addicted to pharmaceutical and street drugs, suffering from bipolar, ADHD, anxiety and depression…all find apparent benefit.

Seems astounding, maybe troubling, why this plant is illegal throughout most of the world, or maybe you've just figured it out too.

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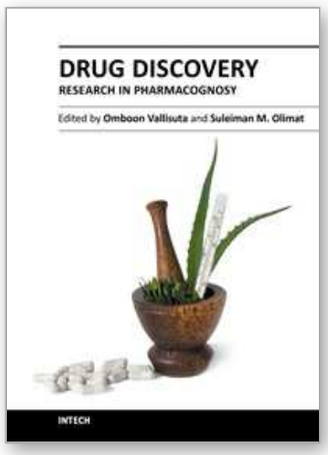
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This book, Drug Discovery Research in Pharmacognosy provides a full picture of research in the area of pharmacognosy with the goal of drug discovery from natural products based on the traditional knowledge or practices. Several plants that have been used as food show their potential as chemopreventive agents and the claims of many medicinal plants used in traditional medicine are now supported by scientific studies. Drug Discovery Research in Pharmacognosy is a promising road map which will help us find medicine for all!

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