Reduction in Methadone Consumption and Withdrawal Symptoms with Ingestion of Standardized Oral Cannabis. An Observational/Feasibility Study.

Dr. Paul Hornby and Adolfo Gonzalez C.
(Research Coordinator)

Abstract

A short (3 month) study was undertaken to determine the feasibility of a larger scale clinical trial designed to determine the efficacy and safety of standardized oral cannabis in withdrawal from methadone addiction. The study population was composed entirely of medical cannabis users that regularly access the services of the Eden Medicinal Society, (Vancouver, Canada) a non-profit, natural medicine & social wellness organization. Participants were monitored through daily questionnaires, pain charts and prescription records. Of the 11 members originally selected for the study, 5 completed, all showing marked reduction in methadone consumption over the three-month period.

Cannabis was administered in capsules as a standardized product, at a dosage of 40mg THC per capsule (as determined by HPLC). Study participants reported better sleep, less pain and significantly reduced methadone consumption after receiving the capsules. Additionally, one-on-one support was found to be a critical factor in participant retention as well as success in decreasing methadone use.

Introduction

Methadone (also known as Symoron, Dolophine, Amidone, Methadose, Physeptone, Heptadon and many other names) has an extensive history in modern medicine, used primarily as a maintenance drug for opiate withdrawal and more recently for managing chronic pain. The German chemical conglomerate, I.G. Farben, best known for their production of Zyklon B during WW2, introduced the drug in 1937; it was then brought over to America in 1947, with continued marketing and sales by the Eli Lilly Pharmaceutical Company. In 2009, there were over 4 million methadone prescriptions written in the United States alone, despite US Food and Drug Administration (FDA) warnings about the risks associated with it (1).

According to a recent CDC Vital Signs report, in America, more than 16,000 people die every year from prescription drug overdoses. With nearly one-third of those overdoses involving methadone. In the United States, researchers found that while methadone accounts for only 2 percent of analgesic prescriptions, it is involved in more than 30 percent of prescription painkiller overdose deaths. One study found that in cases of single prescription painkiller overdose deaths, four in ten involved methadone. This figure is twice as high as any other prescription painkiller (2).

Used for harm reduction purposes as well as pain management, methadone often poses a greater danger to the user than other opiates in terms of overdose risk, particularly when used for chronic pain. Due to the side effects, which include: slowed breathing, disruption to heart rhythm, cold sweats, dry mouth (causing gum disease and tooth loss), anxiety, bone aches, lack of energy and negative cross reactions with other medicines, methadone has many risks and often fails as a harm reduction agent. The extreme level of dependency that methadone users develop is perhaps the most crippling of all the negative side-effect. Often referred to as "liquid handcuffs", methadone will often times severely limit a patient's ability to travel even a short distance within a region, as missing even a single dose of this highly controlled substance causes intense withdrawal symptoms. This effect is particularly damaging in the social context of Vancouver's Down Town East Side (DTES), where methadone users are faced with a social environment that is highly conducive to illicit drug use.

Based on mounting anecdotal evidence indicating that reductions in opiate consumption are common when therapeutic cannabis is used as an adjunct(particularly when consumed orally), Eden Medicinal Society (EMS) has developed and implemented programs that support opiate substitution. As part of their ongoing efforts to learn how to best support community members in the struggle to reduce their opiate use, EMS, a non-profit natural medicine & social wellness center, conducted a three-month observational study to gather more data on the subject. The main goal was to determine whether there is a real need for further investigation into the subject matter, as well as probing the feasibility of a larger clinical study of this nature within the unique social context of the DTES.

EMS is located in the heart of the DTES, where a large proportion of the population (including the participants of this trial) come from a demographic with a very high rate of drug addiction, HIV and hepatitis C infection (3). As with many compassion clubs, a high percentage of the EMS clients deal with chronic pain management issues arising out of trauma associated with accidents, falls, on-the-job injuries, disease or arthritis; many of the patients have a sever dependence to pharmaceutical painkillers, including methadone.

To determine feasibility, throughout the study a number of quality of life parameters were monitored as well as the reduction in Methadone consumption over a three-month period. As mentioned, this trial was undertaken in order to illustrate the need for a full observational/clinical study with a larger population in a double blind, placebo controlled protocol using a standardized oral cannabis adjunct, in the hopes of producing hard evidence that cannabis can be helpful in battling methadone addiction and withdrawal symptoms.

Methods

The selection criteria was volunteer based, using an advertisement posted at EMS that asked for participants who had experience with long term methadone use. Out of the volunteers that came forward, a further selection process was implemented, based on the patient's answers to a general questionnaire regarding their drug history, medical conditions, compliance probability, and willingness to take part.

All participants were regular cannabis users (mostly smokers) previous to partaking in the research. Low-income patients were given preference in the selection processes since they already could only afford low-doses of cannabis for their daily pain management. However, none of the participants had any experience with the unique high-potency standardized cannabis capsules used in the study. Cannabis was administered in capsules as a standardized product, at a dosage of 40mg THC per capsule (as determined by HPLC). This method of ingestion was chosen because edible cannabis is widely accepted as the most health conscious form of ingesting cannabinoids. The capsules, made from fully organic raw materials sourced from a unique strain, are designed specifically for fighting pain.

Ethics protocols were followed according to International Review Board (IRB) services, however no ethics committee approval was sought for the feasibility study since it was a survey-based protocol where there was no risk of physical harm.Answering questions on drug history and emotional and physical well-being, did pose minimal risks. Participants were given a full description of what was required of them and were asked to sign an informed consent document, prior to the commencement of the study.

Initially, 25 patients showed interest in the study and were interviewed as outlined above. Due to limited resources, in terms of available cannabis capsules, the trial was limited to 11 of the most likely and compliant candidates and the trial duration was limited to three months. Beginning in early February and running until the end of April, provided the researchers with sufficient time to observe various parameters that had been set for study feasibility. These parameters included: compliance (attendance and participation), the proper administration of the capsules, the patient's response to oral cannabis ingestion as well as their dosage levels. The reduction in methadone consumption and pain, any increase/decrease in sleep or appetite and the general well-being of the participant were all recorded as well.

Four research assistants were involved in the study, their duties were to query after the participant's well-being and conduct routine interviews 2-3 times per week. Research assistants were also tasked with providing the participants with a safe and friendly environment to further facilitate compliance. Since the participants would check in on a daily basis, tracking of general well-being was relatively easy for study researchers.

Subjects were routinely interviewed, with the same questions:

- Have you observed any changes in how you experience pain?
- Have you experienced any change in your craving or need for any drugs or medication you may be taking (either legal or illegal)?
- What is your dosage routine (i.e. when do you take your pills, in what quantity, etc.)
- Have you made any changes to your methadone dosage?
- Have you observed any discomfort or adverse side effects from taking the cannabis pills?

In addition to the routine questions, patients were asked to fill out pain charts, initial for pick-up records and to supply their methadone prescription records before, during and after the trial.

HPLC methods: Appendix 1.

Results

Prior to the commencement of the study, the 11 participants selected were queried on their age, years of both methadone and cannabis use as well as the amount of each drug ingested daily. The query produced an average age of 43 years, with an average of 106.7 mg/day over 12.2 years of methadone use and a mean of 6.5 grams per day over 27.1 years of cannabis use. Ten of the subjects were male and all stated that they used cannabis for both pain and as mood enhancer. All participants also stated that they use methadone for pain and/or to prevent withdrawal (see table 1).

Table 1. Summary of subject ages, years and daily amounts of consumption of methadone and cannabis.

Subject No.	*Age*	*Methadone Use (yrs)*	*mg/day*	*Cannabis Use (yrs)*	*Grams/day*
1	52	2	75	20	1
2	32	6	115	15	2
3	47	16	49	20	1
4	48	22	130	39	3
5	54	25	120	40	1
6	39	18	160	10	20
7	29	4	45	15	3
8	48	5	160	30	4
9	40	15	140	30	2
10	34	3	100	20	1
11	51	9	90	39	3.5
Mean	*43*	*12.5*	*106.7*	*27.1*	*6.5*

Further questioning illustrated that 8 of 11 study subjects used other painkillers besides methadone, three of whom were also using pharmaceutical psychotropics for mood. In regards to cannabis consumption, 4 of 11 preferred sativa strains over indica strains (a figure anomalous to earlier findings implying that those in chronic pain prefer indica strains) (4); 6 of 11 used both sativa and indica strains, modulating between daytime with the former and evening with the latter; finally and surprisingly one patient consumed only indica strains. For methods of ingestion it was found that 6 of 11 subjects both ate and smoked cannabis, 4 only smoked it and one ate, smoked and vaporized the plant.

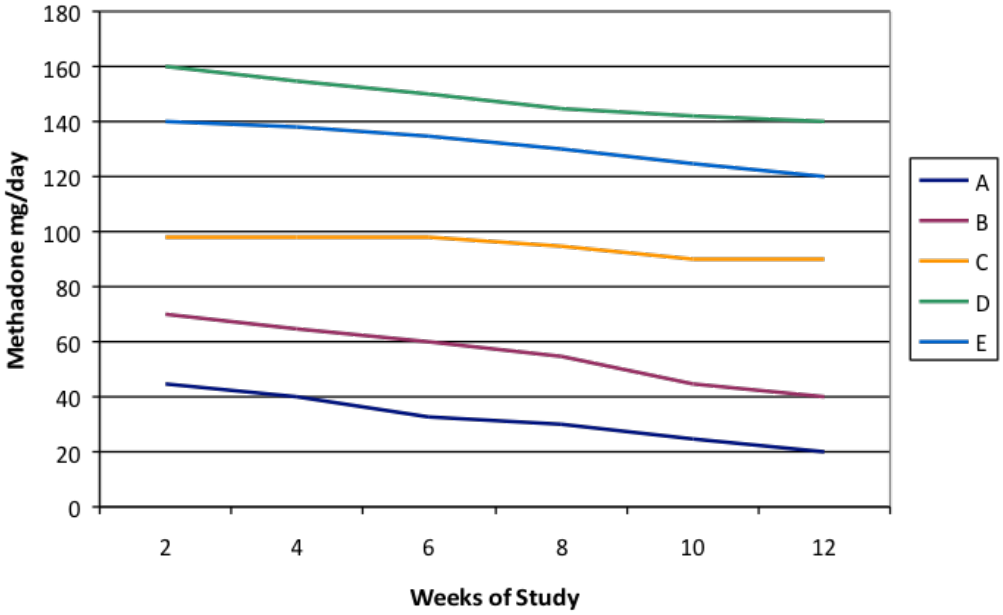
With an expected daily pickup of cannabis capsules over the study's 89 days, the participant's compliance ranged between 85% and 16%. The subjects who were unable to drop in daily were allowed to take capsules home for the days that they could not be present. Study subject/researcher interaction lent credibility to allowing subjects to take dosages without a researcher's observation, since the patients would be interviewed every few days. Pain chart results and prescription records collected showed no drastic difference in those taking doses home more frequently than others. The average number of cannabis capsules required per day was 7 equaling 280 mg of THC per day. Once optimal dosage rates were achieved, participants reported many benefits from the oral cannabis capsules, with eating, sleeping and bowel movements greatly improved (see table 2).

Table 2. Summary of daily capsule pick-up and amounts of THC consumed

Subject No.	*No. of Pickups*	*% compliance*	*Caps/pickup*	*Caps/day*	*mg THC/day*
1	2	0	1-2	1	-
2	76	85	3-10	6	240
3	54	61	3-8	5	200
4	46	52	2-12	9	360
5	69	78	2-10	5	200
6	14	16	3-10	7	280
7	36	46	4-12	8	320
8	20	22	3-12	8	320
9	23	26	3-10	7	280
10	47	53	2-8	6	240
11	6	0	3-6	6	-
Mean	*43*	*48*	*3-10*	*7*	*280*

Of the two subjects who did not comply at all with the study (0% compliance), one was lost due to financial reasons (unable to travel) and one did not respond at all to the cannabis capsules (no effect with 8 capsules administered at once). Those that did comply with the program all showed a downward trend in methadone use, with a more significant change observed amongst those who began with a lower dosage methadone prescription. As an example, Subject A reduced intake by 13% whereas, subject D reduced intake by over 50%, though it is important to note that both participants reduced their methadone intake by similar amounts (see graph 1). The patients with the highest compliance were those that developed closer relationships with the study researchers, showing that the personal rapport and the perception that they were not alone against what they were facing was a significant factor to their success.

Graph 1: Individual Subject Reduction in Methadone consumption over weeks of study.



Discussion

Since members would have to come to the wellness centre on a daily basis to administer cannabis capsules in front of a research assistant, compliance was considered to be a major obstacle to be investigated for feasibility.

Methadone users most often visit and pick up their doses daily at the same clinic, hence such an exercise is not foreign to them. It is this requirement that brings about the term "liquid handcuffs", since missing a daily dose will lead to pain, nausea and other withdrawal symptoms that cause extreme discomfort.

We predicted non-compliance issues in terms of participants showing up for daily pick ups and had therefore selected study participants also in terms of how regular their attendance was to the establishment before the commencement of the study. Clients who were already well familiar to EMS staff members (who acted as research assistants during the study) achieved a personal understanding of the authentic nature of each participants struggle, establishing sufficient trust to allow participants to take a second dose home. In any case, the number of capsules a participant would be allowed to take home would have been no more than 4. One dose was always administered in front of a research assistant with only one more dose given to take home.

Most of the study participants demonstrated a surprising sameness in their daily activities as well as in their methadone related ailments. Inability to sleep, constipation, low-energy constant dry mouth (causing tooth loss) were common complaints within the study group. However, the most resounding complaint throughout the entirety of the study was that participants literally felt like prisoners, forever bound to their methadone clinics. Many had not seen family for years, and many participants chose to vocalize the belief that the cycle poverty and drug use only becomes further entrenched when mobility from the DTES is so limited.

This unfortunate set of circumstances likely contributed to the high compliance rates observed throughout the study(as high as 85%), as EMS is located near the majority of methadone clinics in the DTES. However compliance rates for this study are still far below the near 100% compliance seen at a methadone clinics. A joint investigative study conducted between a medical cannabis provider and a registered methadon clinic could fully take advantage of this high compliance rate as well as many other advantages in daily data collection.

Patients reported feeling benefits within 90 minutes of ingesting the cannabis capsules, with less pain, less anxiety, lowered cravings for tobacco, alcohol, prescription and street drugs, as well as improvements in sleep patterns and bowel movements. It appears that the effects of oral cannabis ingestion are perfectly matched to alleviate the associated discomforts of regular methadone use and in particular methadone withdrawal (pain, anxiety, relapse, lack of appetite and lack of sleep).

Taking a brief detour into the mechanism by which cannabis takes effect in the human body, we can hypothesize the effects experienced from oral cannabis ingestion as follows: following metabolizing by the liver, the principle active biochemical of cannabis (Delta 9 tetrahydrocannabinol or THC) into an even more potent metabolite (Delta 11 THC) that binds to the receptor (one of the most common binding sites in the human brain) called CB1 that is positioned at an unusual site at the nerve synapse, it is located up-stream of the nerve junction where binding causes a general slow-down in neuron transmission from the individual nerve cell.

It is this slow-down in transmission that brings about the calming, balancing and neuroprotective qualities of cannabis and allows significant reduction in withdrawal symptoms. This may hold true not only for Methadone, but for virtually all other addictive drugs, including heroin, crack cocaine, crystal meth, pharmaceutical opiates, alcohol and tobacco. Though participants did not set out with the intention of lowering their alcohol or tobacco use, this effect was reported by several participants. This remains one of the most important pieces of peripheral data collected during the trans-course of the study, something that certainly warrants further study.

Four of the 11 study volunteers were able to achieve significant methadone reduction throughout the course of the study (from more than 100 mg per day down to 20 mg per day). A catch phrase that evolved was "the first half is the easy part; it's the last half, that gets really hard". Although none of the participant where able to completely come off Methadone during the study, our four 'successes' continued to be subsidized for cannabis capsules and carried on beyond the three month study, at relatively low levels of Methadone. As of August 2013, one of the test participants has managed to completely quit methadone and move out of the DTES to rejoin his family in the interior of BC.

Although the average dosage of 280 mg/day of THC as cannabis may seem high considering recommended dosages of synthetic THC (Marinol, Nabilone), it is important to note that natural product cannabis also contains other receptor agonists/antagonists that modulate the effect of THC at the receptor, thus requiring larger doses of natural THC. This level of dosage corresponds with earlier observations of persons using standardized natural cannabis orally to treat chronic pain. (5).

The observed side effects were mostly the result of an individual taking too much in the early phases of the study. An overdose of THC presents with anxious discomfort, paranoia and fear; however, there are no recorded deaths from THC overdose.
Since all of the study participants were experienced cannabis users (average 27 years), adjusting to dosage happened quickly and with little discomfort.

As mentioned briefly in the results section an interesting finding was that the participants that were the most successful in reducing methadone and maintaining compliance were the ones that perceived a caring researcher on their team. This means that the more a research assistant befriended a participant, the greater their chance at success. Although merely a repeated observation, it is one that is not uncommon in the field of addiction; one-on-one support is key to success.

Conclusions

The purpose of this study was to go a step beyond the repeated anecdotal evidence that cannabis can be significant aid in methadone withdrawal as well as that from other opiates. The results reveal that designing a full clinical study that considers the effects of high-dose standardized de-carboxylated cannabis capsules on methadone withdrawal is something that can and should be effectively undertaken, especially within the context of the Vancouver Down Town East Side.

Periphery data collection and personal notes also showed that compliance and success rates where highest amongst those that built strong interpersonal relationships with researchers. This indicates the need to consider social and psychological support as important factors in the development of substitution therapies.
All participants reported struggling with a surprisingly similar set of health issues before commencing the study(tooth loss, bone aches, constipation, lack of sleep, lack of energy, cold-sweats, random onsets of anxiety). This was unanimous amongst participants, regardless of how large or small the daily dose of methadone.

An important understanding that developed from this study is that traditional perspectives on methadone side-effects may not give enough consideration to the negative social impact felt by methadone users who are bound to make visits to the same city location everyday. The high compliance rate of methadone programs indicates that perhaps the best place for conducting a larger scale study would ideally be done out of a methadone clinic instead of a medical cannabis dispensary.

Considering the epidemic in addiction to opiates and the growing recognition of the medicinal value of cannabis, it greatly warrants the utilization of cannabis preparations for opiate substitution. This study concludes that cannabis (specifically oral) is highly indicated as an effective natural remedy for methadone withdrawal. The findings of this feasibility study clearly show that conducting further studies on the subject is possibled and likely to yield meaningful results.

Acknowledgements

The authors would like to thank the Eden Medicinal Society for providing vital resources and allowing access to the medical cannabis users necessary to make this study possible.

We would also like to thank the participants, for their diligence and cooperation and to our research assistants Keegan Seeburger, Jordin Woodbeck and Rohan Gardiner for their hard work and dedication in collecting and processing data.

A big thank you to our sponsor Leafly.com for paying for the transportation to Cologne!

Dedicated to my father, who always believed in my cause.
A. Paul Hornby, Ph.D.

References

1) METHADONE-ASSOCIATED OVERDOSE DEATHS: Factors Contributing to Increased Deaths and Efforts to Prevent Them. GAO-09-341, Mar 26, 2009
2) Center for Disease Control and Prevention CDC Vital Signs report
3) Drug Situation in Vancouver. Report prepared by the Urban Health Research Initiative of the British Columbia Centre for Excellence in HIV/AIDS October 2009 http://uhri.cfenet.ubc.ca
4) In: Drug Discovery Research in Pharmacognosy (ISBN 978-953-51-0213-7) Chapter title: Standardized Cannabis and Pain Management Authors: A. Paul Hornby
5) Standardized natural product cannabis in pain management and observations at a Canadian compassion society: a case report A Paul Hornby1*, Manju Sharma2 and Bree Stegman3 18 May 2009, Cases Journal 2009, 2:7487

Appendix 1.

HPLC (Capsule Standardization Methodology)
Chromatography, using a Hewlett-Packard (Agilent) 1090 Series II binary pumping system with a 79883a diode array detector, with primary absorbance at 219 nm, was conducted. Mobile phase at 1 ml/min was isocratic with 14% aqueous (1:25:974 phosphoric acid: acetonitrile: distilled water) and 86% organic phase (acetonitrile). The column was a Zorbax C18 reverse phase 4.6 mm × 25 cm. Samples were prepared by the method modified from Health Canada for the preparation of hemp flowers for HPLC analysis [2]. Calibration curves were run for a number of commercial standards (Sigma) and averages made. 0.1 gram of dry (dryness determination appendix 1) cannabis was suspended in 10 ml THF and sonicated for 3 minutes then passed through a 0.45 micron nylon syringe filter into a 1 ml HPLC sample vial. Under these conditions suitable chromatography is achieved for the three most abundant cannabinoids present in the capsules provided to EMS clients. These capsules were prepared by proprietary method involving clean, dry cannabis flowers which are heated in a sealed container by a convection oven for a specific time and temperature. Decarboxylation efficiency is determined byHPLC analysis, after the THC and CBD concentration of the raw material was recorded. Further quality control testing for heavy metals, pesticides and pathogenic microorganisms, yeasts and molds are performed to ensure safety. The raw material is then ground to a fine powder and encapsulated.