A survey of the knowledge and perceptions of South African medical practitioners concerning the use of medical cannabis by patients.

by

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FIGURES

ABBREVIATIONS

WHO (World Health Organization)
UN United Nations
SAHPRA (South African Health Products Regulatory Authority)
QOL Quality of life
CBM Cannabimovone
THC Tetrahydrocannabinol
SAMJ South African Medical Journal
CBD Cannibidiol

ABSTRACT

Background: South Africa has recently legalized the cultivation, possession and use of cannabis by adults in South Africa. There has been much debate, discussion and controversy about cannabis as a treatment for pain and other symptoms and a demand for use of cannabis amongst patients. Medical personnel feel understandably uninformed and confused by the discrepancy between the available information and the increasing interest that patients and their families have demonstrated towards cannabis. They are therefore challenged to ensure they are equipped with knowledge to advise patients about the safe use of cannabis in the palliative setting.

Aim & Objectives: The aim of the study is to identify the knowledge and perceptions concerning medical cannabis for palliative care patients amongst South African doctors. The objectives are to survey South African medical practitioners with regards to their knowledge and perceptions concerning the use of medical cannabis. To review the current literature as to what is the recommendations regarding the use of cannabis and how to inform doctors regarding the possible benefit and harm. To draw on the evidence and regulatory statements to advise practitioners as to an approach for a palliative care patient with regards to the use of medical cannabis in the palliative setting.

Methodology: Physicians working in the field of oncology and palliative care completed an anonymous online questionnaire concerning the use of medical cannabis for palliative care patients. The survey assessed the participants demographic detail, as well as what their thoughts were regarding the use of cannabis. Also, what possible benefits as well as the concerns they had and the ease with which they speak to patients about the use of cannabis.

Results: The response rate was 33.3%. The respondents were 40 medical doctors, 21 men and 19 women. Among those medical doctors, the majority (62.5%) had more than 10 years of experience. Almost half of the doctors (45%) stated that patients asked for their opinion on use of cannabis at least weekly. The majority of medical doctors interviewed (77.5%) stated that they attempted to obtain information regarding the use of cannabis for palliative patients. While 70.5% of the practitioners considered cannabis as beneficial, only half would suggest it to patients for palliative care and chronic pain. When questioned about concerns, 60% were concerned about side-effects and 20% reported that cannabis could potentially do more harm than good. Need for more evidence.

Conclusion: Cannabis is not a registered medication for use in the medical setting due to lack of evidence. Patients and doctors are looking for information regarding the use of cannabis in palliative care, possible benefits as well as side effects. The use of cannabis is largely patient

driven and there is a need to overcome the legal and logistic barriers in order to do more research in the use of cannabis for palliative patients so that medical practitioners can advise their patients from evidence-based data.

CHAPTER 1

INTRODUCTION

Background

South Africa has recently legalized the cultivation, possession and use of cannabis by adults in South Africa (1). There has been much debate, discussion and controversy about cannabis as a treatment for pain and other symptoms for and a demand for use of cannabis amongst patients. Medical practitioners are challenged to ensure they are equipped with knowledge to advise patients about the safe use of cannabis in the palliative setting.

Patients commonly use cannabis. When seeking advice from their medical practitioner, they should be guided by and advised on scientific evidence regarding the use of cannabis.

Pain is one of the main reasons why many patients seek medical attention. Pain affects the daily life of the patient, especially when pain affects mobility. In palliative care, the management of acute and chronic pain is one of the most important aspects of improving a patient's quality of life (2). Medical cannabis is used in pain clinics in the USA, as well as other countries (3). In USA, the use of opioids are strictly controlled due to the high addiction rates and this has influenced the availability of opioids to patients who require pain control with opioids (4). Furthermore, according to a report from the International Narcotics Control Board in 2003 (and a similar trend was again confirmed in 2010), that 6 developed countries account for 79% of the world's consumption while only 6% of opioid use is in developing countries. In the worlds 6 richest countries, still only 24% of patients' pain is controlled (5). Due to the lack of effective pain management and difficult access to pain medication, patients turn to cannabis to treat their pain (4). Therefore, it is important for doctors to understand the medical uses of cannabis because many patients use cannabis as a substitute for opioids to control their pain. Cannabis and opioids are two different drugs, cannabis contains cannabinoids that bind to the cannabinoid receptors and opioids bind to opioid receptors.

Since there is no specific formulation of cannabis that is registered for medical use in South Africa, the term medical cannabis/cannabis in this dissertation will be referring to any form of cannabis that is being used as a medical treatment for a specific disease or symptom.

Medical personnel feel understandably uninformed and confused by the discrepancy between the available information and the increasing interest that patients and their families have demonstrated towards cannabis (6).

History of cannabis

For the past 4000 years, cannabis has been used for recreational and medical purposes. It has been the drug patients use when prescribed treatments appeared to be ineffective in the control of pain (7). United States passed a new law, the Cannabis Tax Act of 1937, this led to more legislation that eventually caused termination of the legal use of cannabis. In 1971, many European countries followed the USA and made the use of cannabis illegal in accordance with the UN Convention of Psychotropic Substances (7). The implementation of these laws meant that use of cannabis was criminalized and, in the process, also created barriers for further research to be done regarding the effects of cannabis (8). The implementation of these laws meant that use of cannabis was criminalized and, in the process, also created barriers for further research to be done regarding the effects of cannabis (9).

Cannabis use in spite of legal constraints

There are publications that examine the use of cannabis in palliative care (10,11)). Advice to nurses includes that they should support their palliative patients in their choice of pain medication, but to inform patients of up to date legal and pharmacological information while tending to their palliative care needs (10). In some contexts, it is also important to make patients aware of the possible penalties regarding cannabis use (11). Until cannabis is decriminalized there will be no treatment guideline (9, 12).

The fact that cannabis is being used for pain even though there is limited evidence of efficacy and potential for harm is noted in publications (13). The fact that the substance was illegal made it impossible to do randomized clinical trials and due to the side effects of the cannabis, even when trials were attempted very few people were willing to enrol once they heard that they were prohibited from driving for the duration of the trial due to the potential side effects(13). A cannabis related clinical trial in the USA, requires approval from 3 different government agencies and the drug used in the trials may only be supplied by the National Institute of Drug Abuse. These barriers make the gathering of scientific evidence even more difficult. The lack of phase III randomised controlled trials is not stopping the increasing use of the drug by the public for a variety of medical conditions (14).

According to the World Health Organization (WHO), the annual prevalence rate of cannabis is 2.5% of the world's population. No data is available as to how many people are using it for medicinal purposes. Cannabis has a high potential for abuse and dependence and has been

known as a gateway drug. There has however been continued acceptance of the drug by the public. In a survey done in 2016, 81% of Americans felt that cannabis should be legalized for medicinal purposes (9).

Cannabis has been scheduled as a Schedule I drug in the USA and schedule I drugs are not available for research, therefore making cannabis research impossible. Schedule 1 drugs in USA are drugs that have a high tendency towards abuse, no real medical treatment value and it is known to have adverse side effects. Therefore, there are little available studies on medical cannabis.

The drug cannot be prescribed in South Africa, but doctors may recommend the treatment or advice patients not to take the treatment. Cannabis is not covered by medical insurance, because it is not a registered medication (9). Cannabis has been legalised in many countries around the world, most countries have specific laws controlling the use (15).

Legal considerations of cannabis use in South Africa

Cannabis has been an illegal substance in South Africa since 1928 under the Medical, Dental, and Pharmacy Act. The Weeds Act (1937) was introduced that made occupants of property accountable to prevent the growth of cannabis on their property.
In 2016, following the international trend, the Alcohol, Tobacco and Other Drug Research Unit (ATODRU) of the South African Medical Research Council (SAMRC) assessed systemic reviews to assess the current evidence on the use of evidence to produce a policy. They found that there was moderate quality evidence for the treatment of chronic pain, chemotherapy-induced nausea, vomiting and multiple sclerosis. Their recommendations are limited due to the vast array of formulations, dosages and routes of administration(16).

The South African Medical Research Council met on 08 February 2017, they focused on research opportunities and possible clinical trials to assist the policy makers. Three major research priorities were identified: * To identify the best medicinal cannabis formulations, doses and clinical indications to conduct a trial on a national level and assist with future trial protocols. * To support research in order to guide the use of current available cannabis products to treat pain in the communities. * To identify barriers as well as facilitators to South African medical practitioners prescribing cannabis if it should become legal in the future(16).

The South African Constitutional Court decriminalised the use of cannabis on 18 September 2018. This pertains to the private use, cultivation, and possession of cannabis by adults. The act was amended in May 2019 to allow certain cannabis products to be sold. The SAHPRA

(South African Health Products Regulatory Authority) has not registered any commercial cannabis products for medical use. The cannabis products available are unregulated and unregistered, this makes any standard of care difficult.

Cannabis regulations in South Africa at present stipulate that Cannibidiol (CBD) products that contain 600mg or less and plant source materials the contain 0, 0075 % or less are schedule 0 (over-the-counter medication). Tetrahydrocannabinol (THC) products 0.2% or less for industrial use and 0.001% or less for ingestion are also schedule 0 (17).

In higher doses, CBD is a schedule 4 medication and THC is a schedule 6 medication. These would be therapeutic agents, but none of them has currently been authorized by the SAHPRA. There are a few medications already in use in other countries that could be eligible for registration: Dronabinol/Marinol (synthetic THC), Epidiolex (CBD) and Sativex (1:1 CBD:THC plant extract) (18).

In order to obtain these medications in South Africa a special permit application under Section 21 of the Medicines and Related Substances Act is required. This process is both time consuming as well as expensive and a doctor needs to sign and submit the request. Furthermore, medical aid will not cover these medications. In short, obtaining pharmaceutical cannabis in South Africa currently, is not an easy or cost-effective route to follow. The current legislation limits treatment with cannabis to lower schedule medication and no schedule 4, 5 or 6 products are currently registered or available legally (18).

Accessibility and availability of opioids

Opioids are the gold standard for pain control, especially cancer pain control (19). In the light of concerns about restrictions to access to opioids and opioid abuse, the WHO is developing a guideline for safe and effective use of opioids in chronic pain(20). However, global access to opioids to control pain remains a problem. According to the WHO in 2003, 79% of global morphine consumption was in by 6 developed countries. Barriers to the proper use of opioids are, physician training and perceptions, patient perceptions, health care system restrictions (5).

The opioid crisis in the US as well as other parts of the world started when opioids were over prescribed, leading to abuse and addiction (21). Opioids are the gold standard of pain management. However, opioids can cause respiratory failure due to respiratory suppression. Opioids are very effective in treating acute and chronic pain. However, from 1999 to 2016, there were an estimated 453300 deaths in America due to opioids. Over prescribing of opioids in the 1990 was seen as the cause of this rise in mortality rate. Approximately 4,3 % of patients that were prescribed opioids for post-operative pain or for an acute injury continued using opioids after the pain subsided. This caused opioids addiction. The Centre for Disease Control (CDC) developed a Guideline for prescribing opioids for chronic pain in 2016 (22). This guideline suggests stricter control to the access to opioids for patients with chronic pain as well as patients struggling with opioid addiction (23) and has resulted in patients with severe pain and legitimate need of opioids for pain control being denied pain relief.

The opioid crisis is not a purely American problem. In America drug overdose has a higher death toll than firearm and motor vehicle deaths in Americans under the age of 50. There are many countries that are battling with the same problems, including Canada and United Kingdom (24). Stricter regulation of opioid use creates restrictions in use for patients that really need the drug for pain control. Various guideline for the management of opioid dependence has been issued due to the magnitude of the problem (25).

The reason why the opioid crisis is relevant in the context of medical cannabis is that many medical practitioners in the US are much more guarded regarding prescribing opioids, due to legal restriction aimed at controlling the opioid crisis (5). This leaves the patients that need the pain medication without access to the much-needed drugs. In a recent article, Lucas states that cannabis could potentially reduce the use/need for prescription opioids and thus avoid adding to the opioid overdose crisis. In a large prospective study Lucas (4) found that patients who substituted traditional pain medication for cannabis showed a reduction in the use of prescription opioids and other drugs as well as improvement in quality of life over a period of 6 months (4).

Pharmacology of cannabis products

Cannabinoids are the active ligands of cannabis. There are three different kinds of cannabinoids and all of them can stimulate both the CB1 and CB2 receptors. Phytocannibinoids contains THC (mostly in flowers and leaves) and CBD (mostly in leaves and stems). THC is mostly responsible for the psychoactive effects of the drug and binds

strongly to CB1 receptors. On the other hand, CBD is more if an antagonist, making the ratio of these two active ingredients important in the clinical effect of the drug(1).

The endocannabinoid system has numerous CB1 and CB2 receptors in the body. The CB1 receptors are present in the central and peripheral nervous systems and helps to regulate appetite, sleep, nausea, emotion, cognition, memory and pain transmission. CB1 receptors are not that dense in the brain stem which is why there is a smaller incidence of respiratory suppression. CB2 receptors are found in the cardiovascular, gastrointestinal and reproductive systems (52).

About 480 different cannabinoid receptors have been identified. Cannabinoids can potentially interact with receptors in the opioid system and noradrenergic systems (52).

Pharmacokinetics and metabolism of the different routes of administration differs. (52).

Drug interactions can occur when cannabis is taken in conjunction with other medication. (83).

Research into the use of cannabis in palliative care

The medical community needs scientific data to back their treatment decisions. It is recognised that the use of that medical cannabis is a very controversial topic (13). In the 1990s, the medical cannabis movement was largely patient driven and the legal battle started in a few countries. Very few clinical trials were available at that point and even in 2014 the problem of what the clinician needs to know and how the clinician needs to approach a patient with questions about medical Cannabis was very real. Very few randomised clinical trials were done, and the concern remains possible harmful effects.

However, researchers recommend that the clinician should be able to advise the patient about cannabis since the patients will be driven into the hands of alternative practitioners and the doctor patient relationship could be compromised. Clinicians therefore need to be able to advise patients and research and more data is needed in this field (26).

Cyr and his co-authors (27), in ‘’Cannabis in palliative care: current challenges and practical recommendations’’ state that there is an urgent need and studies to address the many challenges that are delaying the appropriate integration of cannabis into clinical practice, formal usage and approval, notwithstanding the obvious need for a solid general knowledge of pharmacology, mechanism of action and available clinical evidence supporting the use of cannabis.

Cyr and his co-authors concluded that cannabis applications and usage will undoubtedly play a larger and more role in palliative care medicine in future. However, there are still concerns to the application, usage or preventing a safe and secure system of access for patients (27).

The major obstacle lies in the fact that cannabis products are still not considered as approved treatments for any condition for reasons mentioned. Large scale randomized control trials are still inaccessible to cannabis researchers for a variety of legal reasons.

Possible benefits vs risk of cannabis

Currently, there is insufficient evidence to guide or recommend the use of cannabis, either for or against use. In view of this finding, more research is needed to determine the effectiveness and safety of cannabinoids as adjunctive or complementary therapies, and to provide evidence-based recommendations on their clinical utility, and to provide unbiased recommendations for their use in palliative care. Researchers states that sound scientific evidence will be needed to answer controversial questions about cannabis(7,29).

There is an increased interest in the use of cannabinoids for adult cancer-related pain. Many countries are still getting their legislative processes in place. Some studies have been conducted to try and assess the benefits as well as adverse effects of cannabis compared with placebo. Boland et al. reported that the outcome of their study show that the addition of cannabis to opioids does not reduce cancer pain in patients with advanced cancer. The side effect profile of the cannabis was unfavourable and the drop out due to side effects was significant. Their recommendation was to not use at this point due to lack of evidence (30).

In palliative care, it is important to be able to guide patients with an advanced disease to make the best possible choices regarding their treatment to support patient autonomy. Since cannabis is currently available, it is important to be able to guide patients as to the possible benefits as well as adverse effects that could be expected from the drug. In a study by MacDonald (31), the authors were unable to provide precise research results due to the poor quality and quantity of the research of the use of medicinal cannabis in a palliative care setting. In a study by Imtiaz (4), results indicated that medical cannabis was found to be more effective compared to placebo for appetite and weight gain in palliative patients. However, in some cases mental health adverse effects were increased.

Balbin recommends discussing the benefits and harmful effects of cannabis in doctors training in order to provide advice and treatment to patients (32). This is however still subject to the availability of published evidence on the use of cannabis.

There are recommendations that reflect the known high risk of adverse events of medical cannabis, in connection with uncertain benefits for palliative care patients (9). The lack of the availability of other treatment options were also reported. It has also been suggested from the Canadian guidelines that it provides a strong recommendation against the use of medical cannabis as first or second-line option for pain in palliative care. This study does not provide an adequate description of patient involvement (31).

There is a need for a solid general knowledge of pharmacology, mechanism of action and available clinical evidence assessing the efficacy and side-effect profile of cannabis and comparing it to current available medications in palliative care (33). Arnsten recognises the gaps and plans to address these challenges in the future and strive to provide evidence, either for or against, the practical applications regarding patient assessment for the use of cannabis (3). As patients have more questions regarding these drugs due to its availability it is imperative that the medical community have updated, accurate studies available as reference (2).

Cannabis is currently available in various formulations that have not been standardized and have differing concentrations of active ingredient including Cannabidiol (CBD), Delta-9-tetrahydrocannabinol (THC) and other cannabinoids, different terpene formulations as well as whole plant extracts with different concentrations of active ingredient including highly purified extracts. Cannabis preparations that have the same active ingredient in the same dose will not have the same potency, due to varying absorption rates. The pharmacokinetics varies according to the different carrier oils, extraction methods and delivery systems. Therefore, any research needs to define the specific formulation and delivery system. In order to be registered, cannabis products and research should adhere to the same standard as other unregistered or unapproved medicines in the clinical trial process (34).

In the study ‘’Cannabis Use in Palliative Oncology: A Review of the Evidence for Popular Indications**’’,** Turgeman provides a summary of the available literature on the use of cannabis and cannabinoid-based medicines in palliative oncology. Some benefit is seen in chemotherapy-induced nausea and vomiting and cancer-related pain. There are indications that in the treatment of anorexia, insomnia and anxiety is also suggested. Short- and long-term side effects appear to be manageable and temporary. Medical personnel feel

understandably uninformed and confused by the discrepancy between the available information and the increasing interest that patients and their families have demonstrated towards cannabis (6).

Research facilities and practitioners receive little financial support to address the concerns or for further study support in this area. The need for health care professionals to be further educated on medicinal cannabis to understand the advantages or disadvantages for patients will also be assessed with the survey (2). Pain and symptom control challenges are common in palliative care (33).

Available guidelines and training for medical practitioners

Guidelines for cannabis are not common. In the study "Medical cannabinoids in palliative care" by Agar states that the treatment of palliative care patients needs to be evidence based. Palliative care is the treatment of patients with life threatening diseases to optimize quality of life. Clinical data has been inconclusive as to its effectiveness in this treatment. Unregistered medication should only be used if patients have refractory symptoms with optimal use of available registered medication. The use of medical cannabis should be done with informed consent and discussion as well as regular assessments to ensure that the patient benefits from the treatment in the broader sense. Public opinion seems to be shifting towards medical cannabis use, this means that medical practitioners need to have guiding principles as to how to implement these medications. The study contains a helpful guide to principles of palliative symptom management.(58).

In a critical review by MacDonald and Farrah, Medica Cannabis use in Palliative Care: Review of Clinical Effectiveness and Guidelines – An Update, some of the key findings include that cannabis effectiveness is unclear due to lack of evidence(35). Two evidence-based guidelines recommend that cannabis only be used once conventional methods have failed, taking into consideration the adverse effects and possible drug interactions(35). Nine randomised controlled trials gave low quality of evidence supporting the use of cannabis(35).

There are a few available cannabis guidelines internationally. The guidelines from Canada state that cannabis should not be used in the first line or second line setting pain in palliative patients due to the risk of harm and limited proof of benefit. Only after two pain medications have failed in refractory cancer pain cannabinoids can be considered. The benefits and harm/risks must be discussed with the patient(35).

Australia recommends the use of cannabis only after all other treatments have failed. Guidelines recommend that risks and possibly harm be discussed with the patient. In Australia level of evidence C (no clear evidence of effect) was given to Dronibanol in Alzheimer's and level of evidence D (Scientific evidence against the use) was given for Dronibanol and THC for treatment of poor appetite, nausea, insomnia, anxiety and depression, increased quality of life and weight gain (35).

These guidelines did not include specific products or dosing since it is not available or not registered and due to the lack of randomized clinical trials.

In South Africa, there has not been any official guideline published up to now. An article in the SAMJ by Van Rensburg was issued, "Medical Cannabis: What practitioners need to know." (36). This article points out that very few medical practitioners in South Africa have enough knowledge, clinical or legal, to be able to support the use of safe cannabis. Cannabis remains unregulated, so no standard of care is possible. There is little data to support the use and legislation will have to guide the use in the following years.

Conclusion

Medical practitioners have an obligation toward their patients to give them current and accurate medical information. Cannabis has been very prominent in the news due to the legalization of the drug. This has piqued the interest of the public more than before. Patients have questions regarding the efficacy and safety of cannabis and there is a discrepancy between the public interest and the available data. To maintain the trust relationship between medical practitioners and patients, medical practitioners should be willing to discuss the cannabis data, or the lack thereof with their patients.

CHAPTER 2

LITERATURE REVIEW

There are many controversies with regards to the use of cannabis, one of which is the use of Cannabis for medicinal purposes and the concerns about the pharmacology of cannabis. In preparation for this study the literature that was searched include studies on different aspects of cannabis.

Search

The literature search involved a systematic search and review of different databases including Medline through EBSCOhost, PubMed and other search engines, including Google Scholar.

The literature search was directed at answering a central research question.

"What are the applications of medical cannabis in palliative care?".

Keywords included were the following REVIEW / SURVEY / EPIDEMIOLOGY / MEDICAL CANNABIS / OPIOID CRISIS / PALLIATIVE CARE / ONCOLOGY / HEALTH PRACTITIONERS / ATTITUDES / KNOWLEDGE / ETICHS.
The following key search words and Boolean terms were used:
Firstly
Review OR systemic review OR survey OR overview
AND
Cannabis OR medical cannabis OR marijuana OR medical marijuana OR cannabinoids NOT recreational
AND
Palliative care OR end of life care OR oncology OR quality of life
AND
Attitudes OR knowledge OR confidence
AND
Medical practitioners OR doctors OR palliative care physicians
Secondly
Opioid crisis OR opioid mortality OR opioid availability
AND
Cannabis OR oncology OR pain management

Inclusion criteria

1 Medical cannabis studies
2 Palliative care studies
3 Studies from 2010-2021
4 Only English language publications
5 Studies with full text available

Epidemiology of cannabis

These studies are included to give a broader background to cannabis in the world today.

Anthony et al. conducted a selective review on the evidence from research conducted on the epidemiology of cannabis. They pointed out that cannabis has been widely used for recreational and medical purposes. This study looks at the general use of cannabis in the world and does not focus on medical cannabis. It does however state that, 1 in 7-8 cannabis users in the United States of America uses it for medical purposes (37).

According to the World Health Organization and the United Nations report on drug use cannabis (recreational and medicinal) people who have used cannabis or tried it at least one time in 2015 accounted for 4.9% of the world's population. No global estimate was available at the time as to how many patients used cannabis in the medicinal setting.

Another factor is the different forms of cannabis available; this includes smoking, vaping and consuming different parts of the cannabis plant. Inhaling includes smoking and vaping. This method is thought to be harmful to the lungs, but it has a very fast onset of action including both pain relief as well as side effects. Oral cannabis has the longest duration but the slowest onset of action. Sub-lingual cannabis has a fast onset of action (nearly as fast as inhalation) with long-acting effect. Topical formulations such as patches, sprays and creams are a new way of administering cannabis. Another way to administer cannabis is to use rectal or vaginal suppositories. The onset of action is rapid, and the effect is long-acting. Suppositories have a bio availability that is 2-3 times higher than that of oral administration (38).

The countries that are currently consuming the most cannabis in the world according to the United Nations (UN) and the World Health Organization (WHO) are the United States, Canada, Australia and New Zealand. Males seem to be more prevalent in using cannabis than

females. When looking at ethnicity, non-Hispanic whites in America are more prone to use of cannabis use than other ethnic groups (37).

There are challenges regarding the use, safety and recommendations for use of cannabis worldwide. Research is limited since cannabis is regarded as a harmful drug so there is not an adequate evidence base to address these questions. Some countries are moving towards legalizing cannabis. The following countries have started the process, Uruguay, Canada, Jamaica, the Netherlands, Portugal, Spain, France, Germany, 15 states in America, Mexico and United Kingdom (39).

One of the challenges in the use of cannabis is that governments are not prioritizing studies regarding a drug that has already been deemed harmful. Very few governments driven studies are being done, this makes it difficult to obtain strong evidence about the use of cannabis (37).

Zarrabi et al. looked the legislation research process in order to be able to conduct clinical trials on cannabis. The authors pointed out that in order to conduct a trial in America, approvals are needed by the Food and Drug Administration (FDA) as well as the Drug Enforcement Administration (DEA). This federal approval process alone can take a year or longer. Study cannabis in the USA can only be obtained from a single government approved farm in Mississippi. This farm cultivates cannabis for research purposes as per contract with the National Institute on Drug Abuse (NIDA). The products and formulations on this farm do not however, reflect what is obtained from commercial cannabis dispensaries and this limits the research potential. An opening statement during a U.S. House Committee on Energy and Commerce Subcommittee on Health hearing on cannabis policy on January 15, 2020, the opening statement that was made said that cannabis research is a “Catch-22” because cannabis needs to be proven to have medical use before it is approved for research, however researchers cannot prove medical use without research (40).

There are currently very few guidelines for use or scientific evidence of benefit or harm available (37). Despite the research limitations, patients have been using cannabis for symptoms relief. (37, 38, 40)

The opioid crisis

The studies about to be discussed relate the global opioid crisis to cannabis and why there is more interest in the possible role that cannabis could play in the treatment of patients and palliative care. The opioid crisis of over-prescribing of opioids in America (21) and other countries like Canada and United Kingdom is real (24). Although some studies claim that

there is sufficient evidence to support the use of cannabis in response to the opioid crisis, others believe that it is insufficient (24).

The opioid crisis has more than one perspective. Over prescribing of opioids led to patients overuse and opioid dependency that ultimately led to an increase in opioid death. This led to the next crisis namely that there was an increase in regulations regarding the prescribing of opioids, and this led to patient that are really in pain being unable to access the drugs needed to treat their pain. All of this is in the backdrop to the global problem that many countries have very limited access to opioids, and this translates into sub-optimal pain management for palliative care patients. (41)

Cleary et al. at the Pain Policy Studies Group address the issue of unrelieved pain globally. Cleary et al. states that the WHO has recognized morphine as an essential medication to relieve pain in cancer and AIDS. Cleary et al. comments that the International Narcotics Control Board (INCB), the United Nations Economic and Social Council and the United Nations Office on Drugs and Crime (UNODC) made statements to support improvement of the availability of opioids for pain relief. They have also started developing initiatives to improve opioid availability for pain relief. The International Narcotics Control Board (INCB) acknowledged that previously they focused more on restricting opioid abuse and misuse and neglected to ensure the availability of opioid for pain relief. The authors state that 75% of the world population lacks access to opioids for pain relief, this is often due to strict control of the drugs in a national level. These drug policies are the most significant barrier to the availability of opioids for palliative care. The Pain and Policy Studies Group (PPSG) is involved in initiatives to make opioids more accessible and available in different countries (41).

Cleary (42) has discussed restoring balance to cancer pain management. In his publication he describes that 1961 the United Nations Single Convention on Narcotics Drugs was adopted that would aim to ensure the availability of narcotics for pain management while reducing the risk of the abuse and misuse of these narcotics. The emphasis was more on waring against abuse than ensuring availability for pain control for cancer patients. Initially the abused drugs were prescription opioids, however it escalated to illicit heroin from Mexico and fentanyl imported from China. The increase in opioid consumption can be attributed to the following factors.

- Increased prescribing for acute pain
- Inadequate disposal
- Insurance regulated opioid use
- Fraudulent marketing for noncancer and non-palliative pain

- Fraudulent prescribing by physicians
- Opioid theft in the chain of supply

To address this problem, the US Centre for Disease Control and Prevention developed the CDC Guideline for Prescribing Opioids and Chronic Pain. The document makes recommendation for patients older than 18 years in the primary care setting with pain lasting longer than 3 months. The guidelines exclude end-of-life care, active cancer care as well as palliative care. The problem with this guideline is that it has been used by the state and insurance companies to set up very rigid dosing thresholds due to misapplication and over-interpretation. The misapplication of the guidelines has caused authorization for opioids in patients with severe chronic pain to take more than 10 days and dose titration are difficult due to limits on the number of tablets. The WHO Guidelines for the pharmacological and radiotherapeutic management of cancer pain in adults and adolescents' states that opioids are needed in the treatment of moderate to severe cancer pain (43). Cleary states that this message is important both for countries like USA where access to opioids has been impaired by over-regulation as well as 80% of the world's population that have no or very limited access to opioids. Opioids remains to be considered as the gold standard for cancer pain relief (43, 44).

In a study by Berterame et al. (45), the authors comment that despite opioid analgesics being deemed indispensable by the UN convention, 5 billion people worldwide had little or no access to opioids analgesia from 2011 to 2013. Use of opioids is much higher and it is growing faster in North America, Oceania and western and central Europe. There has been very little growth in the low- and middle-income countries like Africa, Asia, Central America, the Caribbean, South America, and eastern and south-eastern Europe. There needs to be specific strategies in order to increase the access of opioids in these countries. According to the authors there needs to be a balance between control of the drug and being too liberal with drug availability (45).

Cleary et al. looked at the availability and barriers to accessibility of opioids for cancer pain in Africa(46). Africa has 1.1 billion inhabitants and is the poorest and underdeveloped continent in the world. Africa has the lowest opioid consumption rate in the world. Only 15 of 52 countries have opioids available in oral immediate release, continued release as well as injectable formulations. Even if the drugs are on the government formularies, access is limited due to over-regulation. Over the past 30 years the consumption of opioids has increased in the rest of the world, it has not increased in Africa. The data represents 25/52 African countries. Very few opioids are available. No African country had all 7 different opioid

formulations available, while 6 countries had no oral immediate release opioids available. In half of the countries the medication was free while in the rest the patients had to pay in full or they had a significant co-payment. Availability with a valid script was inconsistent. Restrictions are in place in most countries. Special authorization is needed in most countries to acquire opioid prescription. The physicians in Africa had few restrictions on prescribing opioids, however in 3 countries even oncologists needed a special permit to prescribe opioids. Prescriptions need to be in duplicate and time limits of 2 days – 2 weeks were applied. Dispensing was also limited often only available at certain hospital pharmacies. Emergency opioids without script was only aloud in 3 countries. In nearly half the countries a pharmacist was unable to show any discretion if there was a minor fault on the script. Patients were prohibited from driving while on opioids in 40% of the countries. What is needed is to look at medication availability, education of patients and physicians and continued effort form organizations like the WHO to change opioid policies. Opioid access in Africa remains a concern that needs to be addressed on the levels of suppliers, regulators, education of patients and physicians, palliative care and oncology organizations. Opioid accessibility remains a crisis in Africa (46).

Lucas et al. conducted a prospective study that investigated the use of opioids and how the use of opioids was affected when they added cannabis to the treatment plan. The study showed that patients had improved quality of life as well as reduction in prescription drugs when adding cannabis. They found that older individuals were more willing to take the cannabis if it was administered in a tablet form that looked more like conventional medication. Although this study had a large number of participants, the samples were recruited in clinics that were convenient to approach and may not be representative of the general community. Lucas et al. acknowledges that is possible that participants could have been using additional medication to the drugs provided by the clinics. The authors recommend that further studies include control groups and that adverse effects of cannabis also be documented. (47).

A review by Manjiani et al. examined the reasons why opioids might not be available to or utilized for patients. The reasons stated include that a physician could have bias towards using opioids due to risk of addiction and death. Lack of training and confidence to prescribe opioids for pain. Patients on the other hand might fear that the use of opioids indicates their impending death, also they are often afraid of possible addiction and adverse effects, all these factors can make patients reluctant to use opioids. Health care systems can cause barriers with payments as well as strict legal requirements that also cause restrictions in terms of opioid administration to patients to treat their pain (48).

The International Narcotics Control Board (INCB) released a report on the following issues regarding narcotic drugs, specifically opioid analgesics: (a) There remains barriers and inequity in the access to opioid analgesics despite an increase in availability; (b) The increase in use of affordable morphine is less that the increase in synthetic opioids use (more connected to overconsumption); (c) Much of the available morphine is not utilized by pharmaceutical companies to prepare morphine preparations for palliative care; (d) Less available morphine translates into a negative effect on health care's ability to treat the pain in palliative care patients. The INCB states that opioid availability increased from 602 (1994-1996) to 2735 (2014-2016) in defined daily dose over a 20-year period, however the distribution of the increase was concentrated in high income countries. The authors state that most countries in Africa, Asia, Central and South America as well as the Caribbean and Eastern Europe the availability remains inadequate (49).

Bachhuber et al. conducted a study to assess the association between state cannabis laws and opioid overdose mortality by conducting a time series analysis of medical cannabis laws and state-level death certificates in 50 states of the United States. The study indicated that states where cannabis is legalized, there was a reduction in opioid overdose mortality. Limitations in this study are that the death certificates could have omitted opioid overdose as cause of death. If further studies show a definite correlation between legalization of cannabis and the reduction in opioid related death, cannabis policies should be re-evaluated (41, 50).

According to Imitiaz et al. in an editorial in the British Medical Journal, there is not enough evidence to suggest that legalising cannabis will remedy the opioid crisis. The US has implemented various policies to reduce the possibility of opioid overdose and related mortality. Cannabis legalisation could be seen as reducing opioid related harm. According to the authors, it was found that legalisation of cannabis was related to reduction in opioids related death. They did however state that before cannabis can be regarded as the solution for the opioid crisis, more evidence will need to be acquired (21).

Dasgupta et al. wrote a commentary on the 3 phases of the opioid crisis in the USA. Phase one was in 1990 as pain became more of a problem due to increased age, patients expecting more effective pain relief, increased surviving after cancer and injury and more surgeries being done. Pharmaceutical companies marketed a variety of opioids for chronic pain and toxicity of non-opioid drugs were under the spotlight. After 2010, the use and abuse of opioids became a concern due to the rising death, dependency as well as abuse of prescription opioids. The third phase is characterised by a sharp increase in elicit forms of opioids including heroin. The focus has been on medical treatments; however, this study

also points out that the root cause of addiction and abuse is social and that more focus should be put on prevention rather than trying to get a “quick fix” with another medical treatment (23).

The opioid crisis is really a delicate balance between regulating a dangerous drug and having the drug available to the patients that desperately need it. The absence of a perfect balance, can either lead to abuse or seeking alternative means for symptom control (41, 42, 44, 23)

Negative effects of cannabis

Boland et al. conducted a systematic review and meta-analysis about the use of cannabinoids for adult cancer related pain. According to the authors, there is an increased interest in the use of cannabinoids for adult cancer-related pain. This was a systemic review that looked at phase II and phase III studies done in the field. The review was conducted to assess the benefits as well as adverse effects of cannabis compared with placebo. The outcome was that studies show that the addition of cannabis to opioids does not reduce cancer pain in patients with advanced cancer. The side-effect profile of the cannabis was unfavourable and the drop out due to side effects was significant. The recommendation was to not recommend cannabis for cancer related pain (30).

Positive effects of cannabis

Bar-sela et al. conducted a prospective observation study evaluating the treatment of cancer patients in need of supportive or palliative care in Israel. Cannabis may be cultured, and patients may obtain a licence to take it in Israel. Patients who were enrolled in the study received counselling from a nurse on how to take the medication and what possible side effects to expect. Patients had two interviews, a baseline interview at the start of the study that was done in person and another interview six weeks later. According to the authors, a limitation of this study is that patients were self-reporting on their 6-week telephonic interview, rendering findings subjective. Patients self-reporting pain could be seen as a strength, since the pain remains a symptom that the patient is feeling (51). In patients that continued use of cannabis for 6 weeks, 32.1% reported improvement of their symptoms while 3.8% reported that the symptoms got worse. Overall, the study had a positive outcome as far as cannabis for symptom control. The symptoms that improved as reported by Bar Sela et al. include nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching and pain. The authors suggested that more studies should be done to get more objective information, preferably with a control group (8).

Dzierzanowski et al. conducted a review of the evidence for the use of cannabinoids in oncology and palliative care practice. They commented that there has been an increase in interest in cannabis and reviewed the evidence for cannabis in palliative care. The review concluded that although opioids are still the drug of choice for cancer-related pain, because of less respiratory depression**,** cannabis-related deaths are less than opioid-related deaths**.** They believe that for palliative care patients, the benefits outweigh the risks and should be regarded as an option for these patients. They noted that there were more arguments to support the use of cannabis in palliative care, but stated that there is a definite lack of evidence and that further randomized controlled trails should be done (52).

Lucas et al. conducted a prospective study on Canadian medical cannabis patients that investigated patients' quality of life, prescription opioid use and use of medical cannabis. The study was conducted over a six month period where the cannabis use, quality of life and opioid use was monitered at baseline and then at months 1,3 and 6. Opioid use dropped from 28% to 11%, morphine use dropped from 152mg morphine milligram equivalent per day to 32.2mg morphine milligram equivalent per day and the quality of life improved on all four domains evaluated when adding cannabis. Strengths of the study are the large number of participants longitudinal pre and post test repeat measured design and the fact that prescription medication was documented by the physicians and not the patients (4). According to the authors the limitations of the studiy include that patients self-reported on their drug use and pain experience. However, the fact that patients were self reporting could actully be seen as a strength, since pain is a subjective symptom that needs to be treated according to the patient's own perception. The fact that no control groups were used can be seen as another limitation. The measurment of quality of life is broad and it would have been more helpful if reference was made to specific symptoms that was measued.

Macari et al. conducted a survey on community haematology oncology patients about the use of medical cannabis in cancer patients According to the authors, 1 in 5 of oncology patients use cannabis. Symptoms that were reported to have improved on cannabis are, pain, poor appetite and anxiety. There were minimal reports of side effects, making it easier for haematologists and oncologists to talk to patients about the effects of cannabis. There was a minority of patients who were able to reduce their intake of other medications, however very few patients increased their other medications while on cannabis. The authors maintain that the survey adds to the growing body of evidence that cannabis can be beneficial to patients. This survey suggests that there are patients that are using cannabis whether the use is recommended by doctors or not (53). Macari et al. state that patients are driving the use of cannabis, up to 20% of patients are using cannabis, despite lack of

evidence and are putting pressure on the medical community to find the scientific data that will justify the use. The use of cannabis and drive for more evidence is patient-driven and doctors do not have enough scientific data to answer all the questions, as all the studies show lack of sufficient evidence for cannabis use.

Romero-Sandoval et al. published an article on cannabis for chronic pain where they analysed the available scientific evidence to address the challenges and considerations with regards to opioid use. They reported that current evidence suggests that cannabis is effective in chronic pain and to reduce opioid consumption. Opioids have high potential for dependence, 31 or more days of therapy has a 29.9% probability of long-term opioid use. Cannabis dependence after 10 years of use is 5.9%. Romero-Sandoval et al. recommends that scientific evidence in the use of cannabis is needed. To make these possible current legal restrictions should be addressed. Patients using cannabis should be monitored very strictly for side effects (54).

More studies indicating possible benefit are needed before real recommendations can be made, however cannabis remains less addictive than opioids and the fact that 1/5 of patients are using it indicates some benefit. (8, 53)

Studies showing lack of evidence

The following studies included in the research show lack of enough evidence to make recommendations about the use of cannabis.

Haroutounian et al. as part of the “International Association for the Study of Pain Presidential Task Force on Cannabis and Cannabinoid Analgesia” conducted a review of systemic reviews on the use of cannabinoids, cannabis, and cannabis-based medicines for pain management. They included any kind of pain, any form or route of administration for the purpose of pain reduction. Only randomized controlled trials were used. Haroutounian et al. found that the primary outcome was the proportion of patients with pain reduction was $\geq$30% or $\geq$50%. Secondary outcomes included improvement of pain intensity, better physical functioning, improvement of emotional functioning among others the primary outcome was that cannabis has efficacy in controlling pain. AMSTAR-2 and bias reduction techniques were used to assess the 54 included (out of 103 identified) studies. Confidence in the results was low and it was stated that current reviews lack the quality needed to make decisions regarding the use of cannabis for pain control. The conclusion was that high-quality randomized controlled trails are needed to make recommendations with confidence in the results (55).

In a review Henderson et al. conducted research about medical cannabis for the treatment of chronic pain, and they state that it should be considered as a treatment. There is much regarding the effects of cannabis that is not fully understood, including long term effects, drug interactions and the kind of pain most effectively treated. It is important to start with a very low dose and to gradually increase to give the minimum requirement for the symptom being treated, as to limit side effects. Even though the clinical evidence is of low quality, cannabis is being prescribed to patients with chronic pain. Doctors need to balance patient demand and the potential risks as well as lack of efficacy. Clinical trials of good quality are important to resolve the question of whether cannabis is an effective treatment for pain (56).

Pegram et al. assessed cannabis use in Seattle Cancer Care Alliance patients over a 6-week period by a cross-sectional anonymous survey. Questionnaires were distributed to all patients who presented to identify the patient's opinion about cannabis. Surveys were entered into the REDCap data base. Most respondents wanted more information about cannabis directly from their doctor, but they reported that most of their information was attained through sources outside the health care system. The study found that the patients used cannabis for symptom relief mostly for pain relief, including chronic neuropathic pain. The research findings indicate that use of cannabis reduces the use of opioids in chronic pain. However, there was insufficient evidence to make recommendations regarding the use of cannabis in cancer related pain. Limitations in this study include that only 34% of the surveys were returned, this could lead to over or under representation of certain use patterns. Possibly only patients that were interested in cannabis answered the survey, causing over reporting, or patients might have been intimidated due to cannabis not being a legal drug and this could have caused underreporting of use. Only English-speaking patients were included. This study concludes even though there is limited evidence to motivate the use of cannabis in cancer related pain, cancer patients are using it frequently. There is a need for more evidence as well as formal education of patients and physicians alike as to what the role of cannabis could be (26). Turgeman and Bar-Sela conducted a review that provides a summary of the available literature on the use of cannabis and cannabinoid-based medicines in palliative oncology. In their opinion some benefit is seen in chemotherapy-induced nausea and vomiting and cancer-related pain. There are suggestions that medical cannabis is also indicated in the treatment of anorexia, insomnia and anxiety. Short- and long-term side effects appear to be manageable and temporary. Medical personnel feel understandably uninformed and confused by the discrepancy between the available information and the increasingly interest in which patients and their families have demonstrated towards cannabis (6).

In a study of systemic reviews with meta-analysis on cannabis-based medicines for chronic pain conducted by Hauser et al., the difficulties with methodology in current studies was highlighted. Studies are small, pain is not specified as a variable, the type of cannabis is often not specified, other drugs used can influence outcomes and the short duration of studies could miss possible side effects. The study draws a comparison between the possibilities of abuse/dependency of cannabis as compared to opioids. More high quality evidence is needed to make informed decisions. (57).

In a systemic review and meta-analysis by Boland et al., the authors concluded that, in advanced cancer, pain is not reduced by the addition of cannabis to opioids. Strengths of the study are that the studies in the review are all from randomised controlled trails with a low risk of bias. The authors reported self-reporting of pain scores as a limitation due to it being less accurate. However, self-reporting of pain in palliative care is not seen as a limitation, since only the patient can assess the intensity and quality of pain that they are experiencing. According to Boland et al., there is an increased interest in the use of cannabinoids for adult cancer-related pain. The systematic review was conducted to try and assess the benefits as well as adverse effects of cannabis compared with placebo. The side effect profile of the cannabis was unfavourable and the drop out due to side effects was significant Their recommendation was to not use medical cannabis at present due to lack of evidence (30).

Agar wrote an article on medicinal cannabinoids in palliative care where he states that the treatment of palliative care patients needs to be evidence based. This is in line with general medical opinion that all medical treatment should be evidence based, however in medical treatment with cannabis there is a push from patients to include cannabis, regardless of the lack of evidence. Palliative care is the treatment of patients with life threatening diseases to optimize quality of life. Clinical data has been inconclusive as to the effectiveness of cannabis to improve quality of life in palliative care. Cannabis should only be used if patients have refractory symptoms with optimal use of available registered medication. The use of medical cannabis should be done with informed consent and discussion as well as regular assessments to ensure that the patient benefits from the treatment in the broader sense. Public opinion seems to be shifting towards medical cannabis use, this means that medical practitioners will be confronted with patient questions regarding cannabis. The study contains a helpful guide to principles of palliative symptom management which includes/excludes cannabis (58).

Kleckner et al. wrote an article on the opportunities for cannabis in supportive care in cancer described the possible advantages of cannabis. They also acknowledged the lack of scientific

evidence for the effectiveness of cannabis in treating these symptoms in patients. The literature at this point is not adequate to recommend cannabis for treatment of cancer patients. There is limited evidence with regards to cannabis applications for cancer- and treatment-related cognitive impairment, anxiety, depression and fatigue. Further research is required to confirm the mechanisms of action of cannabis, efficacy and to optimize cannabis preparations and doses for specific populations affected by cancer (59).

Mucke et al. conducted a systematic review and meta-analysis of cannabinoids in palliative medicine following the GRADE methodology and concluded that no recommendations can be made for the use of cannabis in palliative care treatment for cancer, HIV/AIDS or dementia. Sufficient evidence to guide or advice the use of cannabis is not currently available, either for or against the use. In view of this finding, further research is needed to identify the efficacy and safety of cannabinoids as adjunctive or complementary therapies and to provide evidence-based recommendations on their clinical utility and non-biased view for the use in palliative care. Although Mucke et al. (60) studied the applications of cannabis, it was found that efficiency, tolerability and safety could not be confirmed at that time. Similar observations were also reported and studied by Gilron, et al. (29) and on the risks related to the applications (29).

According to the final conclusion from Cyr and his co-authors (27), there is an urgent need for studies to address the many challenges that are delaying the appropriate integration of cannabis into clinical practice, formal usage and approval, notwithstanding the obvious need for a solid general knowledge of pharmacology, mechanism of action and available clinical evidence supporting the use of cannabis. Cyr and his co-authors concluded that cannabis applications and usage will undoubtedly play a larger and more role in palliative care medicine in future. However, there are still concerns to the application, usage and achieving a safe and secure system of access for patients (27). The major obstacle lies in the fact that cannabis is still not considered as approved treatment for any condition. Large scale randomized control trials are still not able to be conducted by cannabis researchers for a variety of legal reasons (28).

Van Rensburg et al. published a report on what practitioners in South Africa need to know about the use of medical cannabis. Since 18/09/2018 cannabis has been decriminalized in South Africa. Looking at the available evidence for use of cannabis the following key points were noted. Few practitioners have enough knowledge to safely advise cannabis use for their patients. As described in the previous chapter, cannabis is not standard in dosing and content of different active ingredients differ. No convincing evidence could be found for treatment of

pain, sleep and weight disorders. Significant adverse effects are present. Legal regulations will need to change in order to allow prescription use of cannabis in the future (1).

In an editorial in The Lancet, Horton stated that even though cannabis has been decriminalised in the USA, it has not been approved by the US Food and Drug Association FDA. There are two synthetic cannabis products approved, but no products from the plant itself. Cannabis research is highly restricted and regulated in the USA, making research very difficult and cumbersome. Research is needed in order to assess benefits and risk and to set up guidelines for the use of cannabis. Access, regulation and cost of medicinal cannabis needs to be handled appropriately (61).

Fisher et al. conducted a systemic review on pain management and the use of cannabis. Pain is the primary reason for most patients to visit the doctor. Pain remains a significant symptom impacting on quality of life. They found 36 trials investigating pain management with cannabis. The main reasons for use of cannabis were neuropathic pain and multiple sclerosis, but cancer pain was also reported as a reason for use of cannabis. No current evidence shows that a specific product, administered at a defined dose, using a specific route of administration, will reduce pain in any condition. There are many different kinds of cannabis, but very few have been enrolled in clinical trial to assess their treatment of pain. Clinical trails are needed for more definitive answers (2).

Hawley (62) conducted a survey to assess the reasons and patient opinions regarding the use of cannabis and the outcomes of this use. There is a definite concern that patients are putting themselves at risk by accessing and taking the drug inappropriately. In this study, 23% of responding patients was taking medical cannabis, 31% had medical authorization and the symptoms that they were treating were pain, insomnia, nausea and anxiety. Some of the patients were motivated by reports of possible anti-cancer effect. The conclusion was that physicians need to be able to advise patients about the possible benefits as well as harm of cannabis and to make this possible more research is needed (62).

Philpot et al. assessed the current knowledge of practitioners regarding medical cannabis. They recommended that clinicians be kept informed about the possible conditions for which medical cannabis can be used and that they consider medical cannabis to be a credible medical therapy. They recommended that practitioners should be aware of possible drug interactions with allopathic medicine In order to be able to do this there is a great need for clinical studies exploring the possible harm as well as benefits of cannabis in order to equip physicians to make the right choices of medication for their patients (63).

One of the earliest of the reviewed studies was 2010 by Green et al. The study states that at that time there was no medical support for the use of cannabinoids in palliative care in most clinical settings. They felt that the nurse had a professional responsibility to support patients in their choice of medication but also to be able to inform the patients of up-to-date legal and pharmacological information. However not all of which are available yet (64).

In 2013 a study was published by Johannigman (65) describing a case study to reveal the complexities of cannabis and the importance of knowing the benefits and side-effects of the drug. He states that possible benefits could be seen in chemo induced nausea and vomiting, cachexia, spasicity, pain and rhumatoid athritis pain. The side effects that he is concerned about include that smoking of the substance remains harmful to the lungs, as well as addiction and abuse is a potential threat and cannabis withdrawal. The conclusion however states that cannabis remains illegal under federal law and for patients with cancer to use it, it must be decriminalized on a state level (6).

Augustine et al. reported that, in 2016, the Alcohol, Tobacco and Other Drug Research Unit (ATODRU) of the South African Medical Research Council (SAMRC) assessed systemic reviews to assess the current evidence on the use of evidence to produce a policy. They found that there was moderate quality evidence for the treatment of chronic pain, chemotherapy-induced nausea, vomiting and multiple sclerosis. Their recommendations are limited due to the vast array of formulations, dosages and routes of administration. The South African Medical Research Council met on 08 February 2017, they focused on research opportunities and possible clinical trials to assist the policy makers. Three major research priorities were identified: * To identify the best medicinal cannabis formulations, doses and clinical indications to conduct a trial on a national level and assist with future trial protocols. * To support research in order to guide the use of current available cannabis products to treat pain in the communities. They planned to do this by, (1) doing surveys of the general public in person or online, (2) doing surveys of practitioners about their knowledge of patient use of cannabis. * To identify barriers as well as facilitators to South African medical practitioners prescribing cannabis if it should become legal in the future. Augustine et al. concluded that research is urgently needed on the use of cannabis and regarding the efficacy of locally sourced products(16).

There is a trend in the data that the sudies present that more high quality randomised controlled trials are needed in order to assess the possibly benefits of cannabis.The quality of the current studies are often not as good and control groups are lacking (55, 56, 57, 28) where as some of the trials indicate benefit, many trails shows lack of available evidence.

(30,61.29,1) All these studies show that more research is needed, preferably with randomised controlled trails that are placebo controlled.

Knowledge and attiudes of healthcare professionals

Karanges et al. conducted a cross-sectional survey on the attitudes of Australian general practitioners towards cannabis. Questionnaires were supplied to conference participants, and they could hand it is during the conference. This is the first Australian study to assess the attitudes and knowledge of general practitioners in Australia. Limitations are that the survey did not have established psychometric properties and the participants were self-selected from educational seminars. The Australian survey showed that practitioners are conservative and less than 60% of them think that cannabis should be available for patients. This is more than in 2012 when only 30% of practitioners felt that it should be available for patients. The survey concluded that general practitioners should be able to prescribe cannabis, possibly with a shared care arrangement with a specialist (66).

Szyliowicz et al. states that a survey of pharmacists in the USA revealed that they had very little (33%) or some (25%) knowledge of cannabis. Dosing was also a problem, with 70% having little or no knowledge regarding dosing. The majority (82%) of pharmacists were found to not discuss cannabis options with patients when they had the chance. Again, the majority (75%) of pharmacists said they would rather discuss cannabis with patients after it was approved by the FDA. The author states that the public move is towards use of cannabis. However, more research concerning the efficacy of cannabis to treat certain conditions is needed. Pharmacists agree that more research is needed (67).

Kruger et al. did an assessment on medical cannabis knowledge of health care providers at in a university affiliated health system and e mails them an online assessment. The authors stated that very little medical training regarding cannabis is given, and this makes it very difficult for physicians to make any recommendations to their patients. Most of the participants reported that they needed additional cannabis education. Many patients use cannabis without any physician oversight. The eighteen-item online questionnaire included demographical questions and then also questions pertaining the kind of education if any that the participants have had regarding cannabis. The questionnaire then had specific questions regarding cannabis dosing, the different available formulations as well as what effects and side-effects should be expected to assess the knowledge of the participants. The study showed that the actual knowledge and perceived knowledge of the participants correlated with their cannabis knowledge. The authors commented that physicians training has not

prepared them to educate patients on cannabis related questions. This makes physicians uncomfortable integrating cannabis into patient's treatment regimens. Therefore, patients often get cannabis related information from other sources. Physicians need more training to bridge the gap between policy and clinical care of their patients in this regard (68).

Caligiuri et al. looked at the curriculum and knowledge of pharmacology students. The authors sent out a one-time anonymous online questionnaire to first to third year pharmacology students. Overall, the results showed that the student lacked knowledge and confidence to identify conditions that would qualify to be treated by cannabis. Most of the students (84%) felt that cannabis studies should be part of the standard curriculum and 93% wanted training on the state law on cannabis. This study highlights the fact that medical training has not kept up with the legal system as far as cannabis in concerned (69).

Mirelman et al. studied the perceptions of Israeli oncologists on the use of medical cannabis. Israeli patients with cancer can receive cannabis permits since 2010, and >10 000 patients receive medical cannabis permits annually. An online survey was sent to the Israeli oncologists regarding their experience, perceptions and attitudes towards medical cannabis. Of the responding oncologists, 87% prescribed cannabis regularly. The most common reason for prescribing cannabis was loss of appetite 79%, nausea 77%, pain 75% and mood disorders 62%. Of the responding doctors most found that it was safe and 91% found cannabis to be effective to a certain degree and 42% commented that they found the patients to have mild to no side-effects. However, 50% stated that serious side effects did occur, but only in a few of their patients. Even though these oncologists extensively used cannabis, they admitted to relying on their personal experience rather than knowledge from training when prescribing cannabis. Of the participants, 36% favoured legislation and 62% opposed legislation. This however did not influence their views regarding safety, indications, knowledge and contra-indications. Oncologists in favour of legislation did recommend more permits per year compared to the oncologists that opposed the legislation. Of the participants, 26% felt that cannabis should be used for pain before opioids for patients, however 53% would use cannabis before opioids for cancer pain for their family members. The authors noted that demand for cannabis was patient driven, that get their knowledge from social networks that promotes cannabis as a potent treatment. The authors state that the experience of Israeli doctors could be of value in the absence of evidence-based studies. Guidelines are needed to enable a consistent rational approach to cannabis as opposed to attitudes of the prescribing physician (70).

Ali Murshid and Mohaidin reviewed models of what influences prescribing decisions of physicians, stating that it is a complex process involving numerous factors. The following

factors were found to be influencing factors, marketing efforts, patient requests and expectations as well as pharmacist expert power and collaboration. Drug characteristics, cost/benefit ratio and physician habits were also identified. The authors commented that little is known about the reasons why physicians prescribe certain medicines and that this warrants further studies (71).

Knowledge regarding cannabis has never been more needed as the legal system is progressing and more patient interest is sparked. The academic system or continued medical education on a professional level should keep medical practitioners up to date on the latest legal and clinically significant data. This would benefit both the physicians as well as the patients. (66, 67, 68, 69, 70, 71)

Cannabis guidelines

In a systemic review by MacDonald et al., key findings include that cannabis effectiveness is unclear due to lack of evidence. Two evidence-based guidelines recommend that cannabis only be used once conventional methods have failed, taking into consideration the adverse effects and possible drug interactions. Nine randomised controlled trials gave low quality of evidence supporting the use of cannabis. Limitations of the review include that there was no indication/guideline as to what the dose or choice of product of cannabis that was to be administered. This makes it very difficult to compare the effectiveness of different formulations and to get a standard dose that can be compared to different drugs. According to MacDonald (31), the authors of studies included in the review were unable to conclude evidence or to supply accurate findings on the research due to the poor quality and quantity of results and studies with regards to the use of medical cannabis in the palliative care environment. The recommendations by MacDonald reflect the known high risk of adverse events of cannabis, in connection with uncertain benefits for palliative care patients. The lack of the availability of other treatment options were also reported. MacDonald further suggested from the Canadian guidelines that there is a strong recommendation against the use of medical cannabis as first or second-line option for pain in palliative care. This study does not provide an adequate description of patient involvement (31).

Allan et al. wrote a guideline for the use of cannabis with the purpose of giving physicians in primary care in Canada a simplified guideline of how to approach prescribing medical cannabis. A systemic review of studies in four clinical areas, pain, nausea and vomiting, spasticity and adverse events was conducted, and the data was assessed by a team that made the recommendations. The recommendation was against first line use of cannabis in most medical conditions due to lack of evidence. In palliative care the recommendation was

against use in first and second line use due to lack of evidence and risk of harm. Cannabis can only be considered if the patient is well informed about the possible risks, the patient has pain despite more than two pain medications failing and medical cannabis must be used in conjunction with other medications. Limitations of the study include that in the studies that were investigated, many patients had a history of previous cannabis use and these patients with would have fewer side effects than naïve users. Unblinding was very common and occurred in up to 90% of the studies. Randomised controlled trials were small and the duration short which could lead to false positive results. There was also inconsistent inclusion and outcome reporting (72).

Guidelines are limited due to lack of information and studies in the field.

Patients want more information

Ware et al. states that the medicinal use of cannabis is a very controversial topic. In the 1990, the medical cannabis movement was largely patient driven. Very few clinical trials were available at that point and even in 2014 the issue of what the clinician needs to know and how the clinician needs to respond to a patient with questions about medical cannabis. Very few trials have been conducted and the concern remains that there are possible harmful effects from cannabis use. It was noted that the clinician should be able to advise the patient about cannabis since the patients will be driven into the hands of alternative practitioners and the doctor patient relationship could be compromised. Clinicians therefore need to be able to advise patients based on research. More data is needed in this field. Refusal to provide evidence based advice will undermine the doctor-patient relationship and drive patients away to other sources of information (13).

Kondrad et al. (73) conducted an American study using a survey where paired questionnaires were sent out to both the patients and their primary care physicians to assess the use of cannabis and patient communication. The surveys revealed that 22% of the patient's used cannabis in the past six months although cannabis was not licenced for use in the states in which they lived. The limitations of the study include that this survey was conducted in 2013 and at that time doctors were not able to recommend cannabis to their patients. The study however indicates that doctors are often not aware that their patients are using cannabis, when they are aware they are not aware who authorized the use. This could be a problem since some of the users had conditions contra-indicated to using cannabis that a different physician would not be aware of. Recommendations made are that physicians try

to specifically ask patients about the use of cannabis and engage in an open discussion about the possible risks and benefits as with any other medication (73) .

Abu-Amna et al. conducted a review of cannabis use in oncology. The authors identified several barriers to the use of cannabis. There is a lack of clinical research data for its use. Current legislation makes it very difficult to undertake any research, since it is an illegal drug. He reports that 24% of patients uses cannabis. The patients want evidence-based information about cannabis but are currently not receiving it from their doctors. According to the authors only 30% of doctors felt sufficiently informed to make recommendations about cannabis. (74) Abu-Amna et al. state that cannabis will **undoubtably** play a more significant role in oncology just after stating that there is a lack in clinical data. In the scientific approach to medicine the data should be followed by recommendations, but here it seems to be the other way around. It is impossible to empower clinicians with knowledge with current gap in evidence. How this gap is bridged will remain to be seen.

Patients receive information via media and social media, they do however have a need to be informed from their medical practitioners.

Glickman et al. looked at the ethical consideration of cannabis should be the same as any other medication, cost and benefit and patient centred decisions. Cannabis, however, does have unique challenges due to the legal and social status of the drug. It is important to note that, like with any other medication, the decisions should not be made on the grounds of social pressure and political decisions, but rather based on scientific evidence. Patients, however, also have the right to autonomy and primary care givers have an ethical obligation to acquire the expertise to be able to assist patients who may benefit from cannabis (75).

The American Society of Addiction Medicine made observations and recommendations regarding the prescribing of cannabis. The practice of modern medicine is evidence based, cannabis however lacks in information as basic as composition, dose, quality and randomised controlled evidence regarding benefits and safety (54).

Pharmaceutical and tobacco companies can be held responsible and accountable for harm done by products that they sell and, in the USA, the Food and Drug Administration controls and manages prescription medication regarding quality and risks, yet cannabis dispensaries are virtually unregulated. Cannabis is on the controlled substance list due to risk of abuse and dependence and physicians recommending cannabis should take great care to ensure patient safety. To ensure patient safety and benefit there should be the same standards applied to cannabis that is required from any other drug. Medical cannabis does not currently

meet these standards. The American Society of Addiction Medicine (ASAM) recommends that medical cannabis be subject to the same standards and control as any other prescription medication and that approval from the Food and Drug Administration should be obtained before market approval is obtained and the drug is distributed. The current process where the State and local ballot initiatives approve medication is not scientific and not done by people qualified for the task (76).

Nutt et al. looked at the UK's reluctance to prescribe cannabis despite it being legal. The majority of medical cannabis users (an estimated 1.4 million people). Cannabis based products for medicinal use has many patient driven testimonials, but very few randomised controlled trials. The authors state that patient reported outcomes and current evidence could be taken into consideration for peer review. The authors quote former NICE head saying that randomised controlled trials as evidence should be replaced by a diversity approach looking at all the different evidence. Nutt et al. states that between 1999-2014 more than 50 medications have been registered by the Food and Drug Administration and/or European Medicines Agency without any randomised controlled trials. Patient-reported outcomes (PRO) is one of the new approaches to that is now required as part of elements of outcome for clinical trials to register a medication (77).

Reasons for resistance include that demand for cannabis is patient driven and to register would be like an admission that patients are more knowledgeable than the doctor. The UK prefers data that was collected in the UK. The Department of Health and Social Care called into question the classification of cannabis as a "Special" since this makes it very difficult to prescribe due to bureaucracy as well as more responsibility for the doctor (78). The academic approach remains that medicine needs to be assessed only with randomised controlled trials, while patients seem to have a bigger influence on medication choices (77).

The process of medicine approval could be challenged by patient demands. (76, 77) The academic approach to medicine approval, however, needs to remain the process no matter what the drug or the public opinion dictates. (77) Medical approval remains a decision made on academic grounds with doctors advising patients, not a emotional process where patients are advising doctors. (77)

CHAPTER 3

RATIONALE FOR THE STUDY

The survey will obtain more information as to the opinions as well as approaches of palliative care physicians and oncologists regarding the use of cannabis in palliative care. The use of cannabis for pain control and symptom relief is patient driven. Medical personal are being asked what they think about the use of cannabis on a regular basis.

The research question to be answered is

What is the current knowledge and perceptions concerning medical cannabis among South African medical practitioners in palliative care patients?

Aim

The aim of the study is to identify the knowledge and perceptions concerning medical cannabis for palliative care patients amongst South African doctors.

Objectives

1. To survey SA medical practitioners with regards to their knowledge and perceptions concerning the use of medical cannabis and to provide information on medical cannabis according to current knowledge.
2. To assess the current literature as to what is the recommendations regarding the use of cannabis and how to inform doctors regarding the possible benefit and harm.
3. To draw on the evidence and regulatory statements to advise practitioners as to an approach for a palliative care patient with regards to the use of medical cannabis in the palliative setting.

Problem statement/rationale for the survey

The survey was done to assess the knowledge and perceptions of South African medical practitioners with regards to patient's questions and willingness and confidence to advise palliative care patients about the use of cannabis, whether it be advantages or disadvantages.

CHAPTER 4

METHODOLOGY

Study design

This is a prospective, descriptive cross-sectional study.

Study population

The study was conducted amongst South African medical practitioners working in the field of oncology and palliative care.

The study population was medical practitioners working with palliative care patients in South Africa. This included oncologists, hospice doctors, as well as doctors in general practitioners that have an interest in palliative care.

Selection criteria

Inclusion criteria:

1. Medical practitioners working in palliative care.
2. South African medical practitioners working in oncology and palliative care.

Exclusion criteria

1. Medical practitioners not working in oncology or palliative care.
2. Non-clinicians
3. Non-South Africa medical practitioners.

Sample size

Considerations regarding Sample size adequacy for the correspondence analysis.
Multivariate space reduction techniques, such as similarities, principal component and factor analysis, are performed to identify clusters of associations between variables and subjects. Basically, three factors determine the applicability of such techniques:

1) The sample size
2) The number of variables
3) The strength of the correlations between variables.

The number of participants should be at least equal to the number of variables that will be used, with better performances of the technique having several subjects of at least 1.5 to 2 times the number of variables. Given a 20-items questionnaire a sample size of 40-50 subjects appeared as suitable to apply the proposed analyses(79), as advised by Dr Christian Ricci, University of Leipzig, biostatistician for this study.

Data collection

Data collection tool was a questionnaire developed in REDCap.

Developing the questionnaire

The main objective of the questionnaire was to collect data regarding the knowledge and perceptions concerning medical cannabis of the South African medical practitioners working with palliative care patients.
The questionnaire was developed using the following resources.

- A literature review identified studies that used questionnaires on knowledge and perceptions concerning the medical use of cannabis and the questionnaire was further developed using these resources. (63), (80)
- Researcher's experience as a palliative care practitioner
- Discussions with supervisors.
- Discussions with peers was held to identify additional questions that may have been overlooked. The medical practitioners contacted were specifically selected from different backgrounds to get varied opinions.

The questionnaire was structured in such a way as to assess the medical practitioner's gender, age as well as years of experience to ascertain whether there is a trend between the age, gender or years of experience and attitude towards medical cannabis.

Questions were structured in such a way that there are identifying questions to know which sub-groups of medical practitioners are participating.
Dichotomous questions with yes/no answers were included. However, since this type of question is not the most accurate it was not the only type of question included even though it is the easiest to analyse (81).

Open ended questions were included to let the participants give a more detailed opinion. More information could be obtained in this manner and narrative content will be analysed using content analysis (82).

The questions were structured in such a way that they are simple to read, ask only one question at a time. Questions were limited to only the most essential as to not make the questionnaire too lengthy. The questionnaire was imported onto an electronic platform, REDCap, to be distributed by email.

The information about the research and questionnaire were included at the start of the questionnaire (see Appendix A) with a request to provide informed consent.
The option to get a copy of the findings of the study once the study concluded was offered.

The questionnaire

Face validity means that the questions should ask the intended question without any uncertainty. Discussions with peers as well as the pilot study assisted with face validity. Content validity was assessed by the pilot study as to assess whether the survey measures what it is intended to measure.

Criterion validity is the extent to which the measures agree with the gold standards, the biggest stumbling block is the general lack of gold standard. In this study criterion validity will not be assessed.

Reliability was assessed with the discussions through the pilot study. So that the same question posed to the same person will yield the same answer when done repeatedly.
The questionnaire was designed to start with identifying questions regarding the participant.

Pilot study

The questionnaire was sent out as a pilot study to 5-6 medical practitioners to assess the questionnaire in terms of face validity, content validity as well as criterion validity. After the pilot study the questionnaire was re-assessed and some of the questions were changed according to the feedback received. The final draft of the questionnaire was done according to the recommendations done by the pilot study.

Data collection method

The participants were identified as medical practitioners working in the field of palliative care in oncology, in general practice and palliative care practitioners. The questionnaire was sent to the doctors working in the A.B.J. Inc Clinical & Radiation Oncologists South Africa practice. An approach was made to the GVI practice. However, no response was received from the practice manager and the survey link was not distributed to oncologists in the GVI practice. The Association of Palliative Care Practitioners of South Africa (PalPrac) sent the REDCap questionnaire link to all their members via mail as well as WhatsApp.

The ABJ oncology medical practitioners were contacted via e mail addresses provided.

The sample size was set at 40-50 completed questionnaires.
Since medical practitioners are recognised as poor responders, 120 participants were approached to complete the questionnaire. The questionnaire remained open for 6 weeks, reminders were sent on weekly basis. The total number of responses was 40 questionnaires. The questionnaire was sent out as an electronical survey on the REDCap™ platform with the link being sent to potential participants via e mail and WhatsApp.

The data collected was pulled into EXCEL directly.

Data Analysis

The analysis was partly qualitative due to the fact there are open ended questions included in the questionnaire. Themes and sub-themes were explored and discussed once identified.

Continuous variables were described using median and interquartile range. Categorical variables, along with questionnaire's answers, were described by frequencies and percentages. Comparison of continuous variables between groups of interest (age classes, sex, SES status…) were conducted using parametric t-test or ANOVA for normally distributed variables, non-parametric tests such as Mann-Whitney U-test, or Kruskall Wallis test were considered elsewhere. The comparisons of categorical variables were conducted using chi-squared test or Fisher's exact test as adequate. Correlations between continuous or ordinal rank variables were performed using the Spearman's correlation coefficients and represented using heat-maps. The correspondence analysis of the questionnaire were conducted using the indicator matrix (a 1/0 coding of items' response according to a dichotomous paradigm). The visual inspection of the eigenvalues' scree-plot of were used to determine the number of

common factors to retain. The results from the correspondence analysis will be reported by means of biplot of subject and items coordinates.

Type-I error rate were set at 5% ($\alpha = 0.05$) and all statistical tests will be two tailed. The R software version 3.6 were used for all statistical evaluations, the correspondence analysis was conducted using the FactorMineR package.

CHAPTER 5

RESULTS

Demographic data

The analytical sample comprised 40 medical doctors, 21 men and 19 women. This was a response rate of 33.3%. Among these medical doctors, the majority (62.5%) had more than 10 years of experience. There were 12 palliative care physicians (35%), 10 general practitioners were (25%), 5 hospice care physicians (12.5%) and 11 oncologists (27.5%).
The majority (87.5%) of doctors stated they have more than 10 palliative patients per week. Almost half of the doctors (45%) stated that patients asked for their opinion on use of cannabis at least weekly. There are 30% of doctors who have more than 6 patients taking medical cannabis for therapeutic use. Sample characteristics are reported on table 1.

Table 1. Characteristics of the sample (40 medical doctors) and positive answers to the questionnaire.

Doctors' features	**Count (N)**	**Percentage (%)**
Men	21	52.5
Female	19	47.5
Less 10 years of practice	15	37.5
More than 10 years experience	25	62.5
Medical practitionaers		
Palliative care physician	14	35
General practice physician	10	25
Hospice care physician	5	12.5
Oncologist	11	27.5
Patient interactions		
Less 10 palliative patient in a week	5	12.5
More than 10 palliative patients in a week	15	87.5
At least weekly patients asking for opinion	18	45
More 6 patients currently taking medical cannabis	12	30
Questionnaire items	**Count (N)**	**Percentage (%)**
Ever attempted to access information regarding MCU	31	77.5
Feel confortable answering questions about MCU	17	42.5
Consider patients could benefit from MCU	28	70
Concerned about side effects of MCU	24	60
Consider MCU beneficial in palliative care	19	47.5
Opinion if MCU cause more harm than good	8	20
Open to answer when asked about MCU	26	65
Have you suggested MCU to patients	8	20
Refer patients enquiring about MCU to someone	9	22.5
Would suggest MCU for palliative care patients	20	50
Would suggest MCU for patients with chronic pain	20	50

Notes. **MCU**: Medical Cannabis Use

Results of content analysis of the qualitative questions

Four themes were identified Positive effects of cannabis, Concerns in the use of cannabis, Management of side effects, Recommendations.

Positive effects of cannabis

Pain was mentioned by 20/40 (50%) of the participants as a symptom that could improve, while 28.75% of the participants stated that nausea could be improved. Appetite was mentioned as a symptom that could improve by 7/40 (17.5%) of the participants with 1 participant stating that weight gain could be a benefit. Sleep was noted as a benefit for patients in 8/40 (20%)
of the participants. Psychological symptoms like anxiety, depression and stress were noted to improve and cause a general sense of wellbeing by 6.5/40 (16.25%) of the participants.

Concerns in the use of cannabis

Side effects were stated to be a concern by 6/40 (15%) of the participants. Overdose was noted as a concern by two participants, while one participant was concerned about withdrawal symptoms after stopping cannabis. Drug interaction was a concern for 6/40 (15%) of the participants and the fact that no standard dosing was available was of concern for 3/40 (7.5%) participants. Other concerns included patient exploitation due to the fact that there is no standard pricing available. Psychological effects like psychosis, confusion, delirium, hallucinations and dysphoria were a concern of six practitioners and sedation of two. One participant was concerned that cannabis might lead to death.

Management of side-effects

The most common answer (27.5%) as to how to manage side effects was to dose reduce the cannabis. Other comments included, one participant said to use approved medication, one said to treat symptomatically, five said to stop the medication altogether, two suggested to change the cannabis formulation, two suggested to educate the patients regarding the drug, three were uncertain how to manage it, two suggested using medication (one participant mentioned Haloperidol) to treat side effects and two suggested starting with a low dose.

Recommendations

Many recommendations were made. The need for more evidence was stated by five participants and one also pointed out the need for guidelines. There were two participants

stated that it should be legalised and one mentioned that the South African Health Products Regulatory Authority (SAHPRA) should approve cannabis.

Questionnaire evaluation of quantitative questions

The questionnaire responses show a degree of confidence regarding the use of cannabis for palliative patients. In the current sample, the majority of medical doctors interviewed (77.5%) stated that they attempted to obtain information regarding the use of cannabis for palliative patients while less than half of the sample (42.5%) identified that they were comfortable answering questions regarding the use of cannabis for palliative patients. A number of medical doctors (65%) declared to be open to answer questions regarding the use of cannabis for palliative patients. The majority of the medical doctors (70%) considered the use of cannabis for palliative patients as beneficial. More precisely, a sub-group of those medical doctors (47.5%) consider the use of cannabis as a valid approach for palliative care as well. In particular, half of the medical doctors, suggested the use of cannabis for both palliative care patients and patients with chronic pain.

A number of medical doctors (60%) declared to be concerned about possible side effects regarding the use of cannabis for palliative patients. A fifth of the medical doctors (20%) could be considered as hesitant regarding the use of cannabis for palliative patients, for they considered the use of cannabis for palliative patients having more harm than good. Frequencies and percentages of positive answers to the questionnaire are reported on Table 1.

Cross tabulations of sample characteristics and questionnaire items

Cross-tabulation of the physician's gender and answers to the questionnaire items show that men seem more comfortable to answering questions regarding the use of cannabis for palliative patients with respect to woman. More women than men seem to consider the use of cannabis for palliative patients as beneficial (Table 2). Years of experience influences the opinion towards the use of cannabis for palliative patients. Medical doctors that were in practise for more than 10 years more often attempted to access information regarding the use of cannabis for palliative patients, feel more comfortable to answer questions regarding the use of cannabis for palliative patients and consider that patients could benefit from the use of cannabis for palliative patients with respect to their less experienced counterparts. More experienced doctors more often have the opinion that the use of cannabis for palliative patients could cause more harm than good. Medical doctors with less than 10 years of experience

more often would suggest cannabis for both palliative care and chronic pain patients when compared to their more experienced counterparts (Table 3). More often, palliative care physicians suggest the use of cannabis for palliative and chronic pain patients when compared to other medical doctors (Table 4).

A number of associations did not reach a statistically significant value because of limited sample size.

Multiple correspondence analysis of item's questionnaire

Multiple correspondence analysis of item's questionnaire resulted in two latent factors explaining 22% and 20% of the total variance. A latent factor is a variable that cannot be directly observed, but the effects of the latent factor can be detected in other variables that can be observed.

The first latent factor, reported as the horizontal axe of figure 1, separates on the left positive answers to items related to attempts to gain information regarding the use of cannabis for palliative patients and feeling comfortable to answer question regarding the use of cannabis for palliative patients with the concern regarding the use of cannabis for palliative patients and their possible side effects.

Cluster A formed by the items Q1: Ever attempted to access information regarding the use of cannabis for palliative patients, Q2: Feel comfortable answering questions regarding the use of cannabis for palliative patients, Q4: Concerned about side effects of the use of cannabis for palliative patients, Q6: Open to answer when asked regarding the use of cannabis for palliative patients and Q7: Opinion whether the use of cannabis for palliative patients cause more harm than good). On the opposite site of the horizontal axe we observe a cluster of items more related to positive attitude towards the suggesting the use of cannabis for palliative patients. Cluster B formed by the items Q3: Consider patients could benefit from the use of cannabis for palliative patients, Q5: Consider cannabis beneficial in palliative care, Q8: Have you suggested the use of cannabis for palliative patients, Q10: Would suggest the use of cannabis for palliative patients for palliative care patients and Q11: Would suggest the use of cannabis for patients with chronic pain).

The second latent factor reported as the vertical axe of figure 1, seems more specifically related to the attitude towards patients enquiring regarding cannabis use to someone because they are concerned about possible side effects because it counterposes this two items (Q4:

Concerned about side effects of the use of cannabis for palliative patients and Q9: Refer patients enquiring regarding the use of cannabis for palliative patients to someone else) to the rest of the others.

Multiple correspondence analysis of item's questionnaire and plotting of sample characteristics.

When performing passive plotting of sex on the above-mentioned multivariate space we observed a specific pattern of association with women, palliative care physicians and medical doctors having more patients per week being more prone to a positive attitude towards the use of cannabis for palliative care patients while men, non-palliative care physicians and doctors having less patients per week having a more cautious approach (Figure 1a, 1c, 1d). A more cautious approach was also observed for less experienced doctors with respect to their more experienced counterparts (figure 1b). Finally, a more cautious approach was also observed for medical doctors having more patients using cannabis (figure 1f) and for medical doctors having weekly patients asking for opinion (figure 1e).

Tables 2-7. Cross tabulation between doctor's features and questionnaire items

Table 2 Cross tabulation of gender by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
Women	15 (78.9)	0.2884
Men	16 (76.2)	
Feel confortable answering questions about MCU		
Women	5 (26.3)	***0.0385***
Men	12 (57.1)	
Consider patients could benefit from MCU		
Women	14 (73.7)	0.2420
Men	14 (66.7)	
Concerned about side effects of MCU		
Women	13 (68.4)	0.1523
Men	11 (52.4)	
Consider MCU beneficial in palliative care		
Women	12 (63.2)	***0.0446***
Men	7 (33.3)	
Open to answer when asked about MCU		
Women	3 (15.8)	0.2564
Men	5 (23.8)	
Opinion if MCU cause more harm than good		
Women	13 (68.4)	0.2379
Men	13 (61.9)	
Have you suggested MCU		
Women	5 (26.3)	0.2011
Men	3 (14.3)	
Refer patients enquiring about MCU to someone		
Women	5 (26.3)	0.2545
Men	4 (19.1)	
Would suggest MCU for palliative care patients		
Women	11 (57.9)	0.1612
Men	9 (42.9)	
Would suggest MCU for patients with chronic pain		
Women	9 (47.4)	0.2364
Men	11 (52.4)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

Table 2 shows that cross-tabulation of the physician's gender and answers to the questionnaire items show that men seem more comfortable to answering questions regarding the use of cannabis for palliative patients with respect to woman. More women than men seem to consider the use of cannabis for palliative patients as beneficial.

Table 3 Cross tabulation of years of practice by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
More than 10 years of practice	24 (96.0)	***0.0006***
Less than 10 years of practice	7 (46.7)	
Feel confortable answering questions about MCU		
More than 10 years of practice	14 (56.0)	***0.0464***
Less than 10 years of practice	3 (20.0)	
Consider patients could benefit from MCU		
More than 10 years of practice	21 (84.0)	***0.0297***
Less than 10 years of practice	7 (46.7)	
Concerned about side effects of MCU		
More than 10 years of practice	17 (68.0)	0.2046
Less than 10 years of practice	7 (46.7)	
Consider MCU beneficial in palliative care		
More than 10 years of practice	13 (52.0)	0.5266
Less than 10 years of practice	6 (40.0)	
Open to answer when asked about MCU		
More than 10 years of practice	5 (20.0)	0.3143
Less than 10 years of practice	3 (20.0)	
Opinion if MCU cause more harm than good		
More than 10 years of practice	21 (84.0)	***0.0020***
Less than 10 years of practice	5 (33.3)	
Have you suggested MCU		
More than 10 years of practice	6 (24.0)	0.2418
Less than 10 years of practice	2 (13.3)	
Refer patients enquiring about MCU to someone		
More than 10 years of practice	4 (16.0)	0.2555
Less than 10 years of practice	5 (13.3)	
Would suggest MCU for palliative care patients		
More than 10 years of practice	8 (32.0)	***0.0036***
Less than 10 years of practice	12 (80.0)	
Would suggest MCU for patients with chronic pain		
More than 10 years of practice	8 (32.0)	***0.0036***
Less than 10 years of practice	12 (80.0)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

Table 3 reflects that years of experience influences the opinion towards the use of cannabis for palliative patients. Medical doctors that were in practise for more than 10 years more often attempted to access information regarding the use of cannabis for palliative patients, feel more comfortable to answer questions regarding the use of cannabis for palliative patients and consider that patients could benefit from the use of cannabis for palliative patients with respect to their less experienced counterparts. More experienced doctors more often have the opinion that the use of cannabis for palliative patients could cause more harm than good. Medical doctors with less than 10 years of experience more often would suggest

cannabis for both palliative care and chronic pain patients when compared to their more experienced counterparts.

Table 4 Cross tabulation of palliative care physician by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
Others	19 (73.8)	0.2189
Palliative care physician	12 (85.7)	
Feel confortable answering questions about MCU		
Others	12 (46.2)	0.2179
Palliative care physician	5 (35.7)	
Consider patients could benefit from MCU		
Others	18 (69.2)	0.2799
Palliative care physician	10 (71.4)	
Concerned about side effects of MCU		
Others	15 (57.7)	0.2461
Palliative care physician	9 (64.3)	
Consider MCU beneficial in palliative care		
Others	14 (53.9)	0.1473
Palliative care physician	5 (35.7)	
Open to answer when asked about MCU		
Others	3 (11.5)	0.0627
Palliative care physician	5 (35.7	
Opinion if MCU cause more harm than good		
Others	16 (61.5)	0.2291
Palliative care physician	10 (71.4)	
Have you suggested MCU		
Others	5 (19.2)	0.3113
Palliative care physician	3 (21.4)	
Refer patients enquiring about MCU to someone		
Others	7 (26.9)	0.2189
Palliative care physician	2 (14.3)	
Would suggest MCU for palliative care patients		
Others	16 (61.5)	***0.0386***
Palliative care physician	4 (28.6)	
Would suggest MCU for patients with chronic pain		
Others	16 (61.5)	***0.0386***
Palliative care physician	4 (28.6)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

Table 4 reflects that palliative care physicians suggest the use of cannabis more often for palliative and chronic pain patients when compared to other medical doctors.

Table 5 Cross tabulation of number of palliative patients in a week by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
More than 10 palliative patients/week	28 (80.0)	0.2459
Less than 10 palliative patients/week	3 (60.0)	
Feel confortable answering questions about MCU		
More than 10 palliative patients/week	16 (45.7)	0.2288
Less than 10 palliative patients/week	1 (20.0)	
Consider patients could benefit from MCU		
More than 10 palliative patients/week	22 (62.9)	0.1264
Less than 10 palliative patients/week	2 (40.0)	
Concerned about side effects of MCU		
More than 10 palliative patients/week	18 (51.4)	0.2349
Less than 10 palliative patients/week	1 (20.0)	
Consider MCU beneficial in palliative care		
More than 10 palliative patients/week	18 (51.4)	0.1728
Less than 10 palliative patients/week	1 (20.0)	
Open to answer when asked about MCU		
More than 10 palliative patients/week	8 (22.9)	0.3060
Less than 10 palliative patients/week	0 (0)	
Opinion if MCU cause more harm than good		
More than 10 palliative patients/week	24 (68.6)	0.1798
Less than 10 palliative patients/week	2 (40.0)	
Have you suggested MCU		
More than 10 palliative patients/week	7 (20.0)	0.4372
Less than 10 palliative patients/week	1 (20.0)	
Refer patients enquiring about MCU to someone		
More than 10 palliative patients/week	8 (22.9)	0.4304
Less than 10 palliative patients/week	1 (20.0)	
Would suggest MCU for palliative care patients		
More than 10 palliative patients/week	17 (48.6)	0.3292
Less than 10 palliative patients/week	3 (60.0)	
Would suggest MCU for patients with chronic pain		
More than 10 palliative patients/week	17 (48.6)	0.3292
Less than 10 palliative patients/week	3 (60.0)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

The associations in table 5 did not reach a statistically significant value because of limited sample size.

Table 6 Cross tabulation of doctors having at least weekly patients asking for opinions by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
Not having at least weekly patients asking for opinions	15 (68.2)	0.1489
Having at least weekly patients asking for opinions	16 (88.9)	
Feel confortable answering questions about MCU		
Not having at least weekly patients asking for opinions	8 (36.4)	0.1752
Having at least weekly patients asking for opinions	9 (50.0)	
Consider patients could benefit from MCU		
Not having at least weekly patients asking for opinions	15 (68.2)	0.2615
Having at least weekly patients asking for opinions	13 (72.2)	
Concerned about side effects of MCU		
Not having at least weekly patients asking for opinions	12 (54.6)	0.1910
Having at least weekly patients asking for opinions	12 (66.7)	
Consider MCU beneficial in palliative care		
Not having at least weekly patients asking for opinions	11 (50.0)	0.2351
Having at least weekly patients asking for opinions	8 (44.4)	
Open to answer when asked about MCU		
Not having at least weekly patients asking for opinions	2 (9.1)	0.0558
Having at least weekly patients asking for opinions	6 (33.3)	
Opinion if MCU cause more harm than good		
Not having at least weekly patients asking for opinions	12 (54.6)	0.0853
Having at least weekly patients asking for opinions	14 (77.8)	
Have you suggested MCU		
Not having at least weekly patients asking for opinions	3 (13.6)	0.1716
Having at least weekly patients asking for opinions	5 (27.8)	
Refer patients enquiring about MCU to someone		
Not having at least weekly patients asking for opinions	7 (31.8)	0.0954
Having at least weekly patients asking for opinions	2 (11.1)	
Would suggest MCU for palliative care patients		
Not having at least weekly patients asking for opinions	12 (54.6)	0.2053
Having at least weekly patients asking for opinions	8 (44.4)	
Would suggest MCU for patients with chronic pain		
Not having at least weekly patients asking for opinions	10 (45.5)	0.2053
Having at least weekly patients asking for opinions	10 (55.6)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

The associations in table 6 did not reach a statistically significant value because of limited sample size.

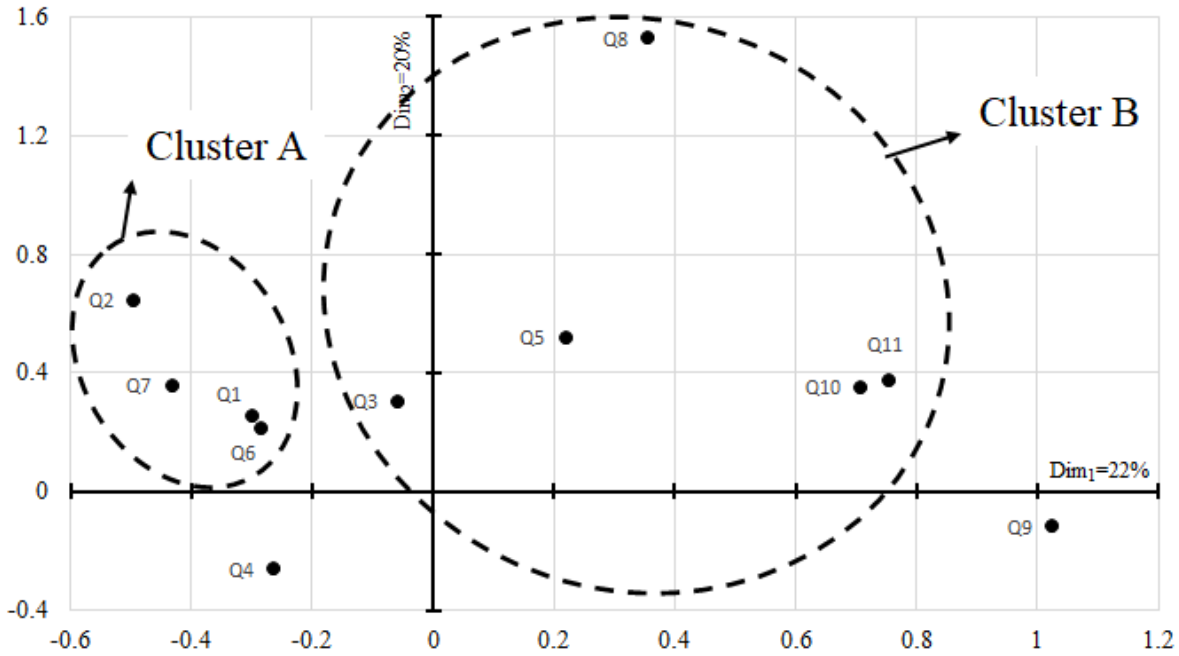
Table 7 Cross tabulation of number of patients currently taking medical cannabis by positive answer to questionnaire items

	Count (*%)	Pvalue
Ever attempted to access information regarding MCU		
Less than 6 patients currently taking medical cannabis	22 (78.6)	0.3031
More than 6 patients currently taking medical cannabis	9 (75.0)	
Feel confortable answering questions about MCU		
Less than 6 patients currently taking medical cannabis	13 (46.4)	0.2089
More than 6 patients currently taking medical cannabis	4 (33.3)	
Consider patients could benefit from MCU		
Less than 6 patients currently taking medical cannabis	21 (75.0)	0.1679
More than 6 patients currently taking medical cannabis	7 (58.3)	
Concerned about side effects of MCU		
Less than 6 patients currently taking medical cannabis	17 (60.7)	0.2706
More than 6 patients currently taking medical cannabis	7 (58.3)	
Consider MCU beneficial in palliative care		
Less than 6 patients currently taking medical cannabis	13 (46.4)	0.2635
More than 6 patients currently taking medical cannabis	6 (50.0)	
Open to answer when asked about MCU		
Less than 6 patients currently taking medical cannabis	6 (21.4)	0.3233
More than 6 patients currently taking medical cannabis	2 (16.7)	
Opinion if MCU cause more harm than good		
Less than 6 patients currently taking medical cannabis	18 (64.3)	0.2799
More than 6 patients currently taking medical cannabis	8 (66.7)	
Have you suggested MCU		
Less than 6 patients currently taking medical cannabis	7 (25.0)	0.1848
More than 6 patients currently taking medical cannabis	1 (8.33)	
Refer patients enquiring about MCU to someone		
Less than 6 patients currently taking medical cannabis	8 (28.6)	0.1364
More than 6 patients currently taking medical cannabis	1 (8.33)	
Would suggest MCU for palliative care patients		
Less than 6 patients currently taking medical cannabis	14 (50.0)	0.2689
More than 6 patients currently taking medical cannabis	6 (50.0)	
Would suggest MCU for patients with chronic pain		
Less than 6 patients currently taking medical cannabis	14 (50.0)	0.2689
More than 6 patients currently taking medical cannabis	6 (50.0)	

Notes. **MCU**: Medical Cannabis Use, * row percentage, P-value for two tail Fisher's exact test

The associations in table 7 did not reach a statistically significant value because of limited sample size.

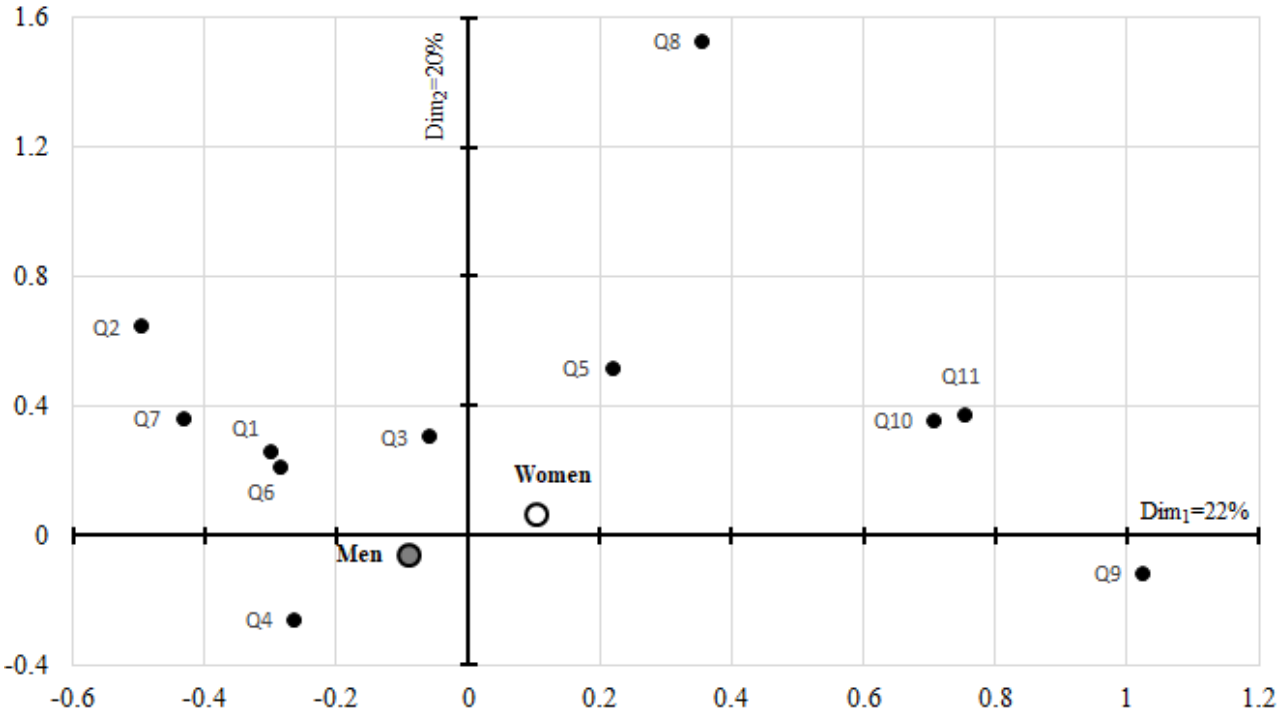
Figure 1 The latent factors



The first latent factor, reported as the horizontal axe of figure 1, separates on the left positive answers to items related to attempts to gain information regarding the use of cannabis for palliative patients and feeling comfortable to answer question regarding the use of cannabis for palliative patients with the concern regarding the use of cannabis for palliative patients and their possible side effects.

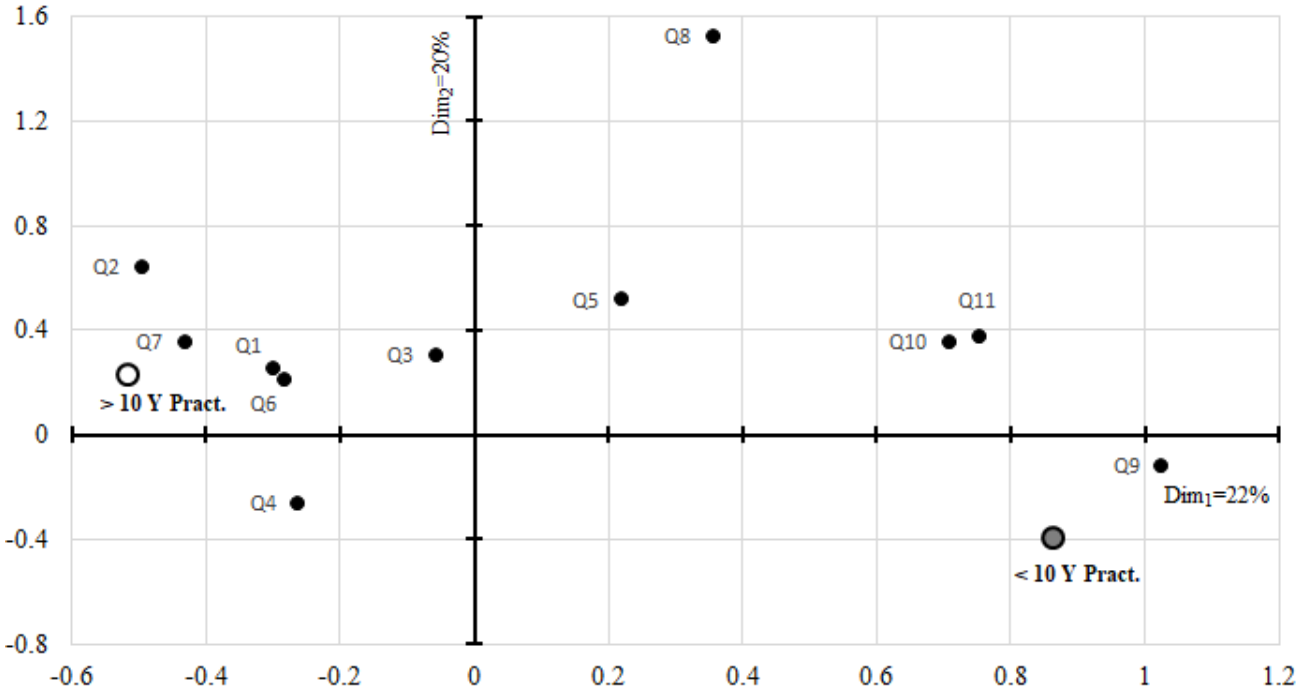
The second latent factor reported as the vertical axe of figure 1, seems more specifically related to the attitude towards patients enquiring regarding cannabis use to someone because they are concerned about possible side effects because it counterposes this two items (Q4: Concerned about side effects of the use of cannabis for palliative patients and Q9: Refer patients enquiring regarding the use of cannabis for palliative patients to someone else) to the rest of the others.

Figure 1a. Multiple correspondence analysis of questionnaire items. Gender reported as supplementary points.



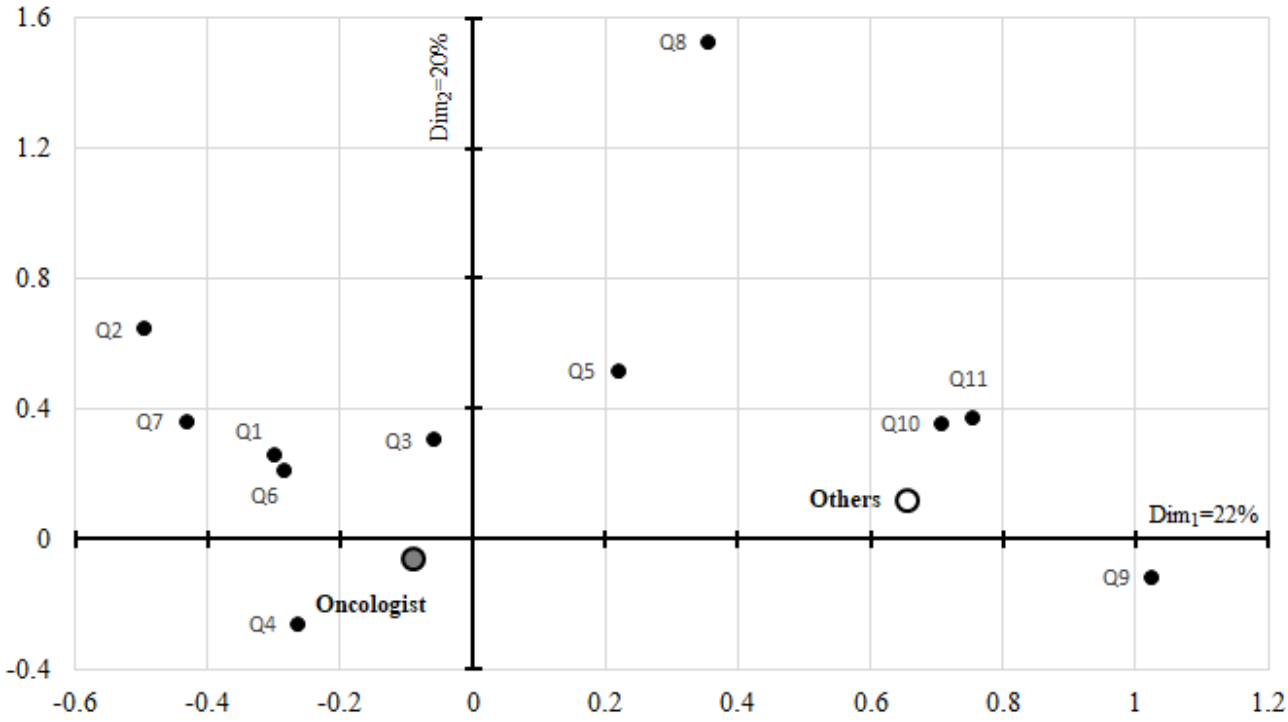
Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Figure 1b. Multiple correspondence analysis of questionnaire items. Years of practice reported as supplementary points.



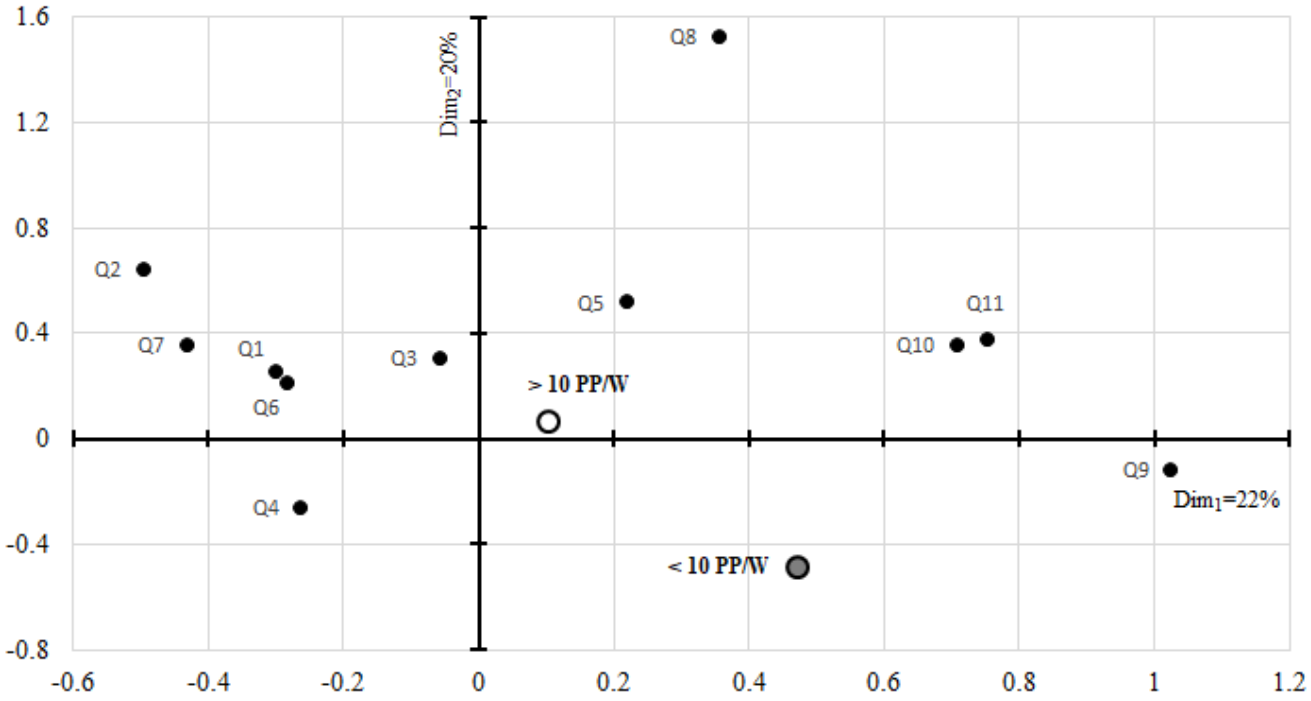
Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Figure 1c. Multiple correspondence analysis of questionnaire items. Oncologist and other medical doctors reported as supplementary points.



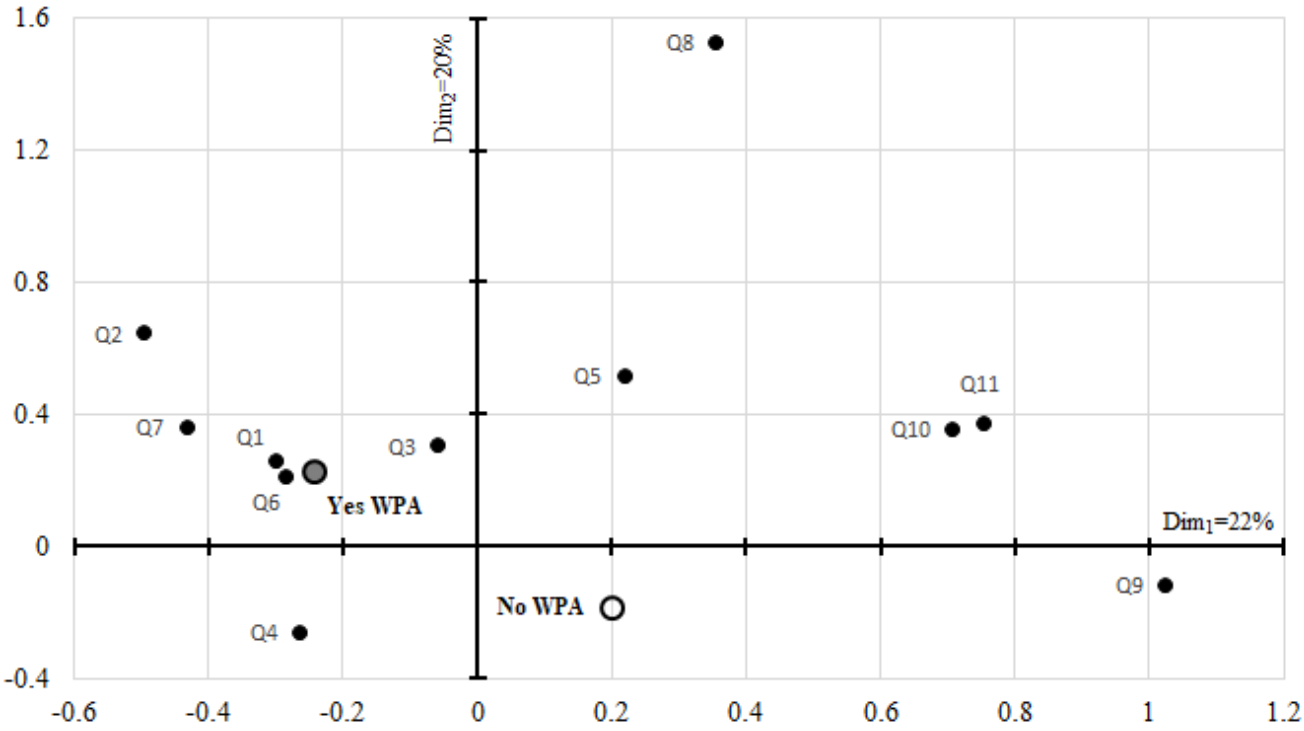
Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Figure 1d. Multiple correspondence analysis of questionnaire items. Number of patients per week reported as supplementary points.



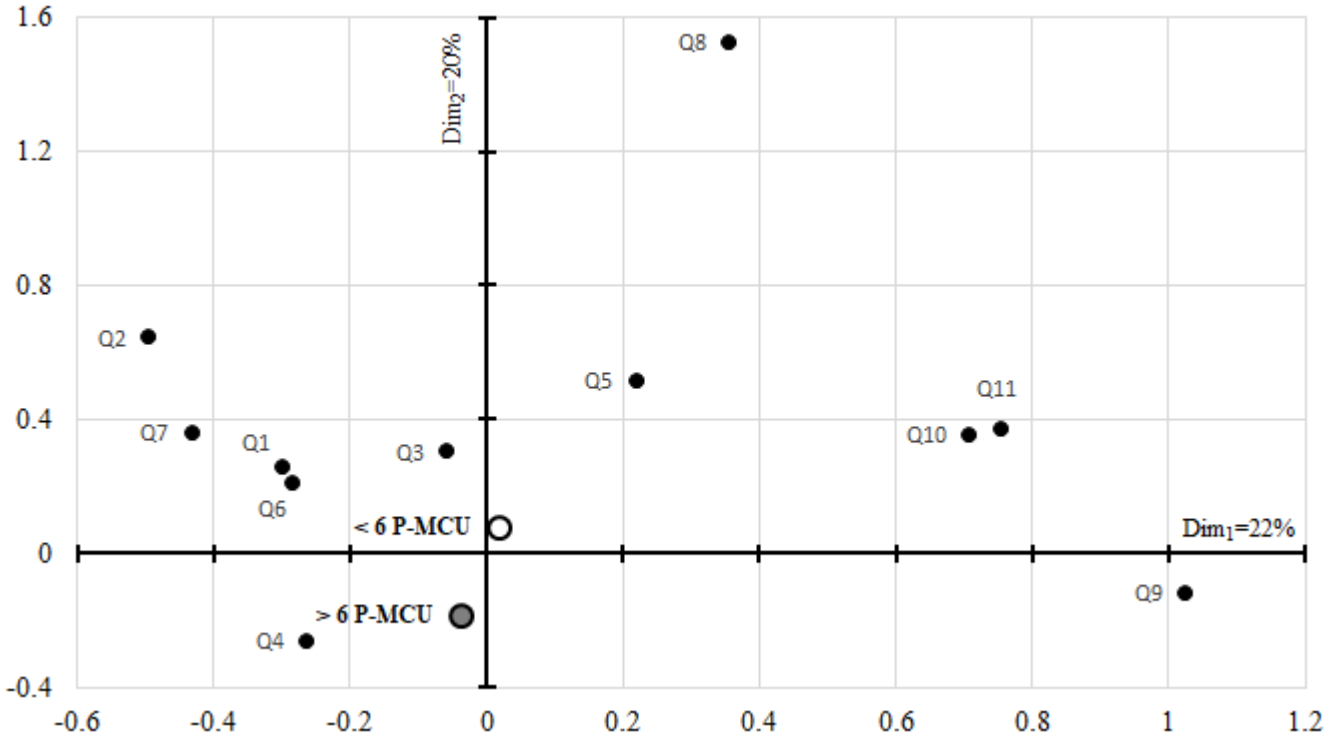
Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Figure 1e. Multiple correspondence analysis of questionnaire items. Weekly patients asking for opinion reported as supplementary points.



Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Figure 1f. Multiple correspondence analysis of questionnaire items. Number of patients taking medical cannabis reported as supplementary points.



Q1: Ever attempted to access information regarding MCU, Q2: Feel comfortable answering questions about MCU, Q3: Consider patients could benefit from MCU, Q4: Concerned about side effects of MCU, Q5: Consider MCU beneficial in palliative care, Q6: Open to answer when asked about MCU, Q7: Opinion if MCU cause more harm than good, Q8: Have you suggested MCU, Q9: Refer patients enquiring about MCU to someone, Q10: Would suggest MCU for palliative care patients, Q11: Would suggest MCU for patients with chronic pain.

Summary

In summary, according to the above-described multivariate space we may assume that medical doctor's characteristics may result in at least four generalized patterns of behaviours. Right to left of the biplot represents positive vs. negative indication for the use of cannabis in palliative care, while up to low of the biplot portray less vs. more cautious attitude towards the use of cannabis for palliative patients. Biplot of correspondence analysis of questionnaire's item was reported on figure 1.

CHAPTER 6

DISCUSSION

Cannabis is relevant in palliative care today

Cannabis has been a topic of many discussions regarding pain control and recreational use over the past few centuries. The outlawing of cannabis has created significant barriers for further research to be done on the drug. Even though use of cannabis was not legal at the time, studies still emerged about the use of cannabis in palliative care (10, 11). These publications advised nurses and doctors on how to administer cannabis for medical use, how to manage patients taking the drug, and cautioned them to warn patients about the possible penalties that they would face if they were caught taking the drug. This indicates that patients have been taking cannabis medicinally long before it was decriminalized. In one American and one Canadian study, it was found that 1 in 5 of patients use cannabis (62). In addition, patients are using cannabis whether the use is recommended by doctors or not (53). The medical use of cannabis was confirmed in this study as many doctors confirmed that they knew about patients currently using cannabis in their practices. The barriers in research mean that very little information about the drug to be available, due to the absence of randomised controlled trails. Thus, medical personnel have little or no formal pre-graduate training regarding the possible benefits as well as the potential harm that this substance has. In spite of this, there is a growing number of patients enquiring about the use of cannabis and the use of cannabis has been strongly patient driven. Medical personnel feel understandably uninformed and confused by the discrepancy between the available information and the increasing interest that patients and their families have demonstrated towards cannabis. Doctors are challenged to ensure they are equipped with knowledge to advise patients about the safe use of cannabis in the palliative setting as well as for chronic pain.

Questionnaire responses made it clear that cannabis is a relevant topic in the field of palliative care today. For example, in this survey, the response rate was 33%, with half being male and half female. In addition, almost all the doctors were seeing more than 10 palliative patients a week, and almost half of the doctors stated that patients enquire about cannabis use in palliative care at least weekly. This indicates that there is a definite interest in the possible place and use of cannabis for the palliative patient. For example, about a third of the participants were aware of patients actively using cannabis in their practices, while other reports have documented that 20% of palliative patients use cannabis (53). Patients are using cannabis with or without the directive of their doctors, however, most of the participants in the

survey have tried to access information regarding cannabis (73). Thus, the survey indicated that cannabis relevant to our everyday practice of medicine in palliative care today.

Cannabis and the law

Although no direct question was asked about the legal aspects of cannabis in South Africa, the participants of the study were aware that cannabis is not currently approved by SAHPRA, thus, doctors cannot prescribe cannabis to patients. Some participants felt that cannabis should be approved while most felt that it should not be approved. Cannabis was decriminalized in South Africa on 18 September 2018 for private, cultivation and possession, and in May 2019, the drug was allowed to be sold. This increased the interest in cannabis and opened up a market for cannabis sales in South Africa. One of the particular areas of interest is in the use of cannabis for adult cancer-related pain as seen in other countries (30). The cannabis currently available is however limited by the law to low concentrations and no cannabis medication formulations have been approved by SAHPRA. To use higher concentration medicinal cannabis, one would need to apply to SAHPRA under section 21.

The opioid crisis

Opioids remains the gold standard for pain control (19). In the study, participants stated that opioids still need to be the drug of first choice when treating severe pain in palliative care as over-prescribing of opioids led to overuse and opioid dependency. In particular, in North America, this ultimately led to an increase in opioid deaths due to respiratory suppression. This led to the next crisis namely that there was an increase in regulations regarding prescribing opioids, and this led to the inability of patient that are really in pain to access opioids needed to treat their pain. In certain countries the availability and access of opioids are limited and overregulated due to opioid prescriptions leading to abuse, addiction, and opioids overdose. Guidelines by the Centres for Disease Control in the United States suggests stricter control of opioid prescription for chronic pain, this resulted in pain relief being denied for many patients with severe pain in the USA, including legitimate need for opioids.

Africa has 1.1 billion inhabitants and is the poorest and underdeveloped continent in the world. As reported by Manjiani et al., Africa has the lowest opioid consumption rate in the world. Only 15 of 52 countries have opioids available in oral immediate release, continued release as well as injectable formulations (41, 42, 46). Even if the drugs are on the government formularies, access is limited due to over-regulation. Over the past 30 years, the consumption of opioids has increased in the rest of the world, however, it has not increased in Africa. What is needed is to review medication availability, education of patients and

physicians, and continued effort from organizations such as the WHO to change opioid policies. WHO is due to release new guidelines on balanced policies for access and safe use of controlled medicines in May 2022 (84).

Opioid access in Africa remains a concern that needs to be addressed on the levels of suppliers, regulators, education of patients and physicians, palliative care and oncology organizations. Opioid accessibility remains a crisis in Africa(46). For example, the INCB states that opioid availability increased from 602 (1994-1996) to 2735 (2014-2016) in defined daily doses over a 20-year period, however, the distribution of the increase was concentrated in high income countries.

This results in patients looking for alternative methods of pain relief, and cannabis was the next line of therapy that many patients experimented with. Certain studies state that cannabis could lower the dose of needed opioids and improve quality of life for palliative patients(4). The South African doctors responding to the study survey agree with these findings, half of the doctors stated that cannabis helped for pain relief. The British Medical Journal states that there is not enough evidence to suggest that legalising cannabis will remedy the opioid crisis. The US has implemented various policies to reduce the possibility of opioid overdose and related mortality. Cannabis legalisation could be seen as method of reducing opioid related harm. According to Imitiaz, it was found that legalisation of cannabis was related to a reduction in opioids related death. They did however indicate that before cannabis can be regarded as the solution for the opioid crisis, more evidence will need to be acquired (21).

Cannabis research

According to the results of the study amongst South African doctors, some participants were concerned because of the lack of standardized drug and delivery systems and that this translates into inability to advise patients regarding dosing or any prediction regarding drug effects and side effects. The literature confirmed these concerns as cannabis research is limited, and it is often regarded as a harmful drug. This limits the available data to address questions regarding efficacy as well as potential harmful side effects of cannabis. Another limiting factor in research is the lack of standard administration methods. There are various ways of taking cannabis, including smoking, vaping and different oral and sublingual formulations. Topical sprays, patches and creams as well as rectal or vaginal formulations are also available and each manufacturer has their own method and product, none of which are standard. This influences the availability of the drug, making research regarding dosing challenging and comparison between formulations as well as different drugs difficult. Cannabis preparations that have the same active ingredient in the same dose will not have the same

potency, due to varying absorption rates. The pharmacokinetics varies according to the different carrier oils, extraction methods and delivery systems (34). Pergam noted that the clinician should be able to advise the patient about cannabis since the patients will be driven into the hands of alternative practitioners and the doctor patient relationship could be compromised (26). There is however a need for studies to obtain more solid knowledge about pharmacology, mechanism of action and clinical evidence (27). The major obstacle lies in the fact that cannabis products are still not considered as approved treatments for any condition for reasons mentioned. Large scale randomized control trials are still inaccessible to cannabis researchers for a variety of legal reasons.

Need for data to support the use of cannabis

Some of the participants of the survey stated that cannabis should be approved by SAHPRA and others felt that cannabis should be legalised, without explaining the scope of the expectation for legalisation. The majority of the participants did not share this opinion and doctors stated that cannabis should not be approved and that more research is needed before approvals can be made. The majority of doctors in this study that were in practice for more than 10 years had at some point tried to gather more information regarding the use of cannabis for palliative care patients. They also felt more comfortable answering patients' questions this could be because they have more experience in general or because of the information that they gathered.

The American Society of Addiction Medicine made observations and recommendations regarding the prescribing of cannabis. The practice of modern medicine is evidence based, cannabis however lacks in information as basic as composition, dose, quality and randomised controlled evidence regarding benefits and safety. There is a need for data in order to make informed decisions. Pharmaceutical and tobacco companies can be held responsible and accountable for harm done by products that they sell and, in the USA, the Food and Drug Administration controls and manages prescription medication regarding quality and risks, yet cannabis dispensaries are virtually unregulated (74). Cannabis is on the controlled substance list due to risk of abuse and dependence and physicians recommending cannabis should take great care to ensure patient safety. Cannabis should be subject to the same standards and control as any other prescription medication and that approval from the Food and Drug Administration should be obtained before market approval is obtained and the drug is distributed. The current process in America where the State and local ballot initiatives approve medication is not scientific and not done by people qualified for the task (74). Cannabis based

products for medicinal use have many patient driven testimonials, but very few randomised controlled trials (75).

Current available data on cannabis

The survey results indicate that the participants are aware of the lack of research,
many research studies have been done. Large cohorts of randomized controlled trials with control groups are however not common. While some indicate that cannabis is in fact beneficial and others that it can cause real harm. Most studies advise more evidence is needed regardless of the outcome. Many of the participants were concerned about the possible side effects and negative effects that could be caused by cannabis use. Possible side effects that they were concerned about included psychosis, delirium, confusion, sedation, dysphoria and one participant was concerned about possible death. How to manage side effects was another very valid concern, this once again should be addressed by guidelines as well as courses and continued medical education to equip medical practitioners to manage patients. The management of cannabis is further complicated by the fact that the drug is not being prescribed by the practitioner, since there is no cannabis medication registered for use, so any “management” would have to be very general and the adjusted according to the specific drug. Due to the fact that the medication is nonstandard and different effects and side effects can be expected. Management includes reducing the dose, stopping the medication, starting at a low dose, treating the symptoms with drugs like haloperidol.

Boland et al. conducted a systemic review that confirmed these concerns, stating that the the side-effect profile of the cannabis was unfavourable and the drop out due to side effects was significant. Boland also commented that the outcome showed that the addition of cannabis to opioids does not reduce cancer pain in patients with advanced cancer. The recommendation was to not recommend cannabis for cancer related pain (30).

In spite of these concerns many participants also stated that cannabis does have positive outcomes. Half of the participants indicated that cannabis could help for pain, nearly a third that it would help for chemo induced nausea and appetite, anxiety as well as better sleep and overall psychological well being was named as some of the benefits. The majority considered cannabis to be beneficial and many referred patients to someone else for their cannabis needs, since currently in South Africa there is no cannabis formulation that can be prescribed by a doctor(67). There are published studies that confirm these findings and

comment on cannabis in a positive light. Symptoms that improved as reported by Bar Sela et al. includes nausea, vomiting, mood disorders, fatigue, weight loss, anorexia, constipation, sexual function, sleep disorders, itching and pain (52). Dzierzanowski et al. conducted a review of the evidence, they state that for palliative care patients (52), the benefits outweigh the risks and should be regarded as an option for these patients. They noted that there were more arguments to support the use of cannabis in palliative care, but stated that there is a definite lack of evidence and that further randomized controlled trails should be done (52). Maciri reported that symptoms that were reported to have improved on cannabis are, pain, poor appetite and anxiety (85). Romero-Sandoval et al. published an article on cannabis for chronic pain where they reported that current evidence suggests that cannabis is effective in chronic pain and to reduce opioid consumption (54).

Data from the study suggest that doctors that were in practice for longer than 10 years considered cannabis as beneficial but were also more concerned about the possible harmful effects of the drug than doctors in practice for less than 10 years. In spite of the fact that more doctors in practice for more than 10 years feel that cannabis could be beneficial, more doctors in practice for less than 10 years would suggest cannabis for use in palliative care patients as well as patients with chronic pain. This might be because doctors in practice for longer are more cautious/conservative or due to the fact that they were also more concerned about possible side-effects.

Lack of evidence

Participants in the study mentioned that more evidence was needed. Haroutounian stated was that high-quality randomized controlled trails are needed to make recommendations with confidence in the results(55). Pergram et al. commented that there was insufficient evidence to make recommendations regarding the use of cannabis in cancer related pain. There is a need for more evidence as well as formal education of patients and physicians alike as to what the role of cannabis could be (26). Hauser et al. conducted a systemic review and states that more high quality evidence is needed to make informed decisions (57). Boland et al. recommends to not use medical cannabis at present due to lack of evidence (30). Kleckner et al. also recommends that further research is required to confirm the mechanisms of action of cannabis, efficacy and to optimize cannabis preparations and doses for specific populations affected by cancer(59). According to Cyr and his co-authors (27), there is an urgent need for studies to address the many challenges that are delaying the appropriate integration of cannabis into clinical practice, formal usage and approval, notwithstanding the obvious need for a solid general knowledge of pharmacology, mechanism of action and available clinical evidence supporting the use of cannabis (27). Fisher et al. concluded that there are many different kinds of cannabis, but very few have

been enrolled in clinical trial to assess their treatment of pain. Clinical trails are needed for more definitive answers (2). Hawley also concluded that physicians need to be able to advise patients about the possible benefits as well as harm of cannabis and to make this possible more research is needed (62). Augustine et al. concluded that research is urgently needed on the use of cannabis and regarding the efficacy of locally sourced products in South Africa(16).

The survey results also indicate that some of the participants are concerned about the possible dangers of drug interactions. Philpot et al. recommended that practitioners should be aware of possible drug interactions with allopathic medicine. In order to be able to do this there is a great need for clinical studies exploring the possible harm as well as benefits of cannabis in order to equip physicians to make the right choices of medication for their patients (63).

Knowledge and attitudes of heathcare professionals

In spite of the limited data that is available on cannabis almost half the participants say feel comfortable answering questions about cannabis. According to Mirelman et al., this comfort is more often gained by personal experience in treating patients than actual intellectual scientific knowledge. Kruger et al. commented that physicians training has not prepared them to educate patients on cannabis related questions (68). This makes physicians uncomfortable integrating cannabis into patient's treatment regimens. Abu-Amna et al. found that only 30% of doctors felt sufficiently informed to make recommendations about cannabis (74).This contradicts the results of this study.

The study survey showed that men are more comfortable talking to patients regarding cannabis, however this does not indicate that they are more comfortable with the use cannabis. According to the findings, it appears that they are confident talking to patient due to the fact that they do not think it is beneficial and that negative information is easier to convey. Women are more prone to think that cannabis can be beneficial, and this results in a lot of questions that are more difficult to answer, which could explain why women are less comfortable explaining the risks and benefits to patients.

Even though half of the participants would suggest cannabis for use in palliative care as well as chronic pain, the majority expressed the need to read up more about the use of cannabis. For participants in practice for more than 10 years even more so, however participants that qualified more recently also felt the need for more information.

The data regarding the statistically significant findings comparing palliative care physicians' responses compared with other doctors involved with palliative care patients and the only two significant findings are that palliative care physicians are more likely to suggest cannabis for

palliative patients as well as for patients with chronic pain. This could be because palliative care physicians are often faced with patients with intractable pain that makes them more prone to try alternative medications like cannabis.

Cannabis guidelines

Some participants indicated that there is a need for cannabis guidelines. MacDonald et al. reports that one of the key findings of the systemic review shows that cannabis effectiveness is unclear due to lack of evidence. Available guidelines recommend that cannabis only be used once conventional methods have failed, taking into consideration the adverse effects and possible drug interactions (31). Allen et al. compiled a guideline about how to approach cannabis for pain and nausea and also to look at adverse events (72). The recommendation was against first line use of cannabis in most medical conditions due to lack of evidence. In palliative care the recommendation was against use in first and second line use due to lack of evidence and risk of harm. According to this guideline cannabis can only be used when at least two other medications failed, when the patient is informed about possible risks and when used in combination with other medication.

The quantitative data from this study revealed that many participants believe that cannabis could be beneficial for use in treatment of palliative patients for pain, nausea, poor appetite as well as to improve sleep and to improve psychological symptoms like anxiety and depression. This compares well to what some of the available guidelines propose as conditions that cannabis could possibly be used once the use of other more stated drugs have failed.

Guidelines are limited due to the lack of evidence-based data on the use of cannabis.

In South Africa, all cannabis products are privately sold and made from different parts of the plant with different concentrations and active ingredients and various delivery systems. So even if a doctor were to suggest cannabis there is no standardized product, dose or even manufacturer to refer the patient to. Specific guidelines regarding prescribing are therefore not applicable in South Africa currently.

The public's need for information

The survey shows that nearly half of the participants have enquiries about cannabis at least on a weekly basis. This indicates that patients want information about the drug.
Ware et al. noted that the clinician should be able to advise the patient about cannabis. Clinicians therefore need to be able to advise patients based on research. More data is needed in this field. Refusal to provide evidence based advice will undermine the doctor-patient relationship and drive patients away to other sources of information (13). Kondrad et

al. recommended that physicians ask patients about the use of cannabis and openly discuss the possible risks and benefits as they would with any other medication (73). Abu-Amna reported that patients want evidence-based information about cannabis but are currently not receiving it from their doctors (74). Glickman et al. commented that patients have the right to autonomy and primary care givers have an ethical obligation to acquire available data to be able to assist patients who may benefit from cannabis (75).

In South Africa, cannabis was only decriminalised less than 4 years ago, leaving very little time to implement new training programs by academic institutes for pre- as well as post graduate students. Doctors want more information and within the academic setting and there is very little information made available from the traditional academic society.

Most patients have a trust relationship with their medical practitioners, and we have an obligation towards our patients to be able to inform them what the available data is and what the guideline are recommending. However, medical personnel feel understandably uninformed and confused by the discrepancy between the available information and the increasing interest that patients and their families have demonstrated towards cannabis (6).

Limitations of the study

Limitations of this study include that the sample size is very small. Only a third of the doctors that were contacted responded to the questionnaire and it is possible that the authenticity of the results may have been affected by the fact that participants already interested in cannabis would be more open to answering questions regarding the topic than participants that had no interest in the topic at all. Questions regarding actual knowledge of cannabis were not included, so that there is no real way to assess what the scope knowledge that the participants have can be measured. This could have been helpful and assessed that actual knowledge instead of the perceived knowledge and confidence levels. It is beyond the framework of this research to make recommendations regarding the specific prescribing of cannabis, as there is no registered medication available in South Africa.

CHAPTER 7

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

The study was designed with the aim to identify the knowledge and perceptions concerning medical cannabis use for palliative care patients amongst South African doctors.

The first objective of the study was met by doing a survey amongst South African medical practitioners with regards to their knowledge and perceptions concerning the use of medical cannabis. This was achieved by asking the participants to complete a questionnaire about the topic. The study met the sample size of participants responding to the questionnaire. The majority of the participants indicated that they have previously sought information regarding the use of cannabis for patients. The survey further revealed that patients are asking questions about cannabis and that participants are aware that some of the patients they see are already using cannabis. Many of the doctors reported that patients could benefit from cannabis and that they felt comfortable talking to patients about cannabis. The questionnaire did not contain questions that tested the knowledge of the participants about the pharmacology of cannabis.

The second objective of the study was to assess the current literature and recommendations regarding the use of cannabis and how to inform doctors regarding the possible benefit and harm. This objective was met by reviewing current literature. The review revealed a lack of evidence supporting the use of cannabis as well as lack of training initiatives for medical doctors. There is also a lack of standardized delivery systems and bioavailability of the active ingredients causing difficulty in the study of the drug effects and side effects. There are limited guidelines available for the use of medical cannabis, and this, together with the lack of standardization of drug delivery and availability makes it more difficult to give specific advice. Advice given is usually an opinion based on limited amount of data available and personal experience. There is a lack of randomised controlled trials. However, since use of cannabis has been decriminalized in 2018 in South Africa, there is a need for medical practitioners to have enough knowledge to be able to give their patients advice regarding the use of cannabis even though cannabis cannot be prescribed by a medical practitioner. Many patients have a trust relationship with their doctors and therefore they want their guidance when contemplating the use of cannabis as part of their treatment regime. Doctors therefore have a responsibility to find out what the available guidelines says and what the legal implications are when taking cannabis to guide their patients in a responsible approach regarding the use of cannabis for their symptoms. If the medical practitioner fails to step into the conversation about cannabis the patient will obtain information via other possibly less responsible avenues. It is therefore

our responsibility to be able to give sound advice to maintain the doctor patient relationship of trust and care.

The third objective of the study was met by looking at guideline in the literature, drawing on the evidence and regulatory statements to advise practitioners as to an approach for a palliative care patient with regards to the use of medical cannabis in the palliative setting. Drawing from available guidelines in the literature reviewed, the only advice that can be given as to when cannabis can be considered under the following conditions:

When looking at available guidelines from Canada and Australia as seen in the literature reviewed, the following recommendations can be made as to how to approach the use of cannabis for medical purposes for palliative care patients.

Guidelines from literature regarding conditions where cannabis can be considered.

Conditions that could be considered for treatment with cannabis, if first- and second-line registered medication failed, are chronic pain, neuropathic pain, cancer pain and palliative pain and chemo induced nausea and vomiting and pain. Cannabis is not indicated for acute pain. Guidelines indicate that evidence for appetite stimulation, weight gain and mental health are very poor. These guidelines are based on the limited amount of data currently available and, as stated before, there remains a need for more evidence in the use of cannabis.

Guidelines from literature regarding the delivery system of the cannabis

The smoking of cannabis is not advised due to the risk involving smoking as well as the fact the drug availability is the most varied with this delivery system. There is no standard of care regarding delivery system.

Guidelines from literature when to consider adding cannabis for patients

Due to the risk and possibility of harm cannabis should not be use as first or second line treatment for pain in end-of-life care and should only be considered once other analgesics have failed. Cannabis can be considered under the following conditions. Chronic pain and end-of-life pain if two or more prescribed again medications have failed if the patient is aware of the benefits and possible risks and negative impact on quality of life of the unregistered medication. Cannabis should only be used in addition to other analgesics and not as a single agent.

Recommendation

Training

This research study shows that medical practitioners want more information with regards to cannabis as a drug. Training should start with undergraduate studies, to give students a basic knowledge regarding the background of cannabis that will equip them to advise patients as to the current available data and basic guidelines. Continued Professional Development (CPD) for qualified medical practitioners should also be available to keep practitioners up to date with regards to the available data and new legislation should it be revised. Since cannabis is a patient driven industry, consideration should also be given to providing patient training and giving the patients the information they need to make informed choices regarding the use of cannabis.

Courses for professionals and patients should be based on the available research and current guidelines.

Research

The barriers regarding research should be addressed on government level. Clear guidelines should be available on the use of cannabis. The lack of standardized dosing, delivery, bioavailability as well as the lack of price regulation in the current cannabis industry should also be highlighted and addressed.

Use of medical cannabis remains a patient driven industry and doctors need to be aware that patients are using cannabis, whether adequate research is available or not. Medical practitioners are there to protect and guide our patients to follow a path of least risk.

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APPEDICES

APPENDIX A

A survey of knowledge and perceptions concerning medical cannabis among South African medical practitioners.

Dear Doctor

My name is Dr Karlien du Plessis. I am conducting a study regarding the knowledge and perceptions of South African medical practitioners regarding the use of medical cannabis in palliative care.
I would appreciate your participation. This is an anonymous survey. All answers are confidential.

Cannabis has been decriminalized in South Africa and patients are asking more questions about whether to use and how to use medical cannabis. This placed the medical practitioner in a unique situation to assist and advise patients regarding effects, side-effects, possible helpful as well as harmful effects of medical cannabis.

The answers to your questions will assist in possibly compiling a guideline for palliative care physicians. The research is being done as part of a Masters in Palliative Care and a study report will be available to participants when the study is completed.

Do you consent to taking part in this study and answering the questions? YES / NO

Human Research Ethics Committee approval number HREC REF 296/2021

Human Research Ethics Committee contact number 012 406 6492

Questions

1. Gender? Male ___ Female ___
2. How long have you been in practice (years)? <5 ; 5-10 ; 10-20; >20
3. Are you a doctor working in general practice, palliative care, hospice care or an oncologist? Palliative Care / Oncology / General Practice / Hospice care
4. How many palliative care patients do you see in a week? <5 ; 5-10 ; 10-15 ; >20
5. Have you ever attempted to access information regarding medical cannabis? Yes/No
   Where did you access this information?_____
   _____
6. Do you feel comfortable answering your patient's questions about medical cannabis? Yes/No

Please explain your answer. _____

7. Do you consider that cancer patients could benefit from medical cannabis? Yes/No
   What benefits may be experienced by cancer patients using medical cannabis _____
8. Are you concerned about the side effect profile of medical cannabis? Yes/No
   What are your concerns? _____
   _____
   How might the side effects be managed? _____
9. Do you consider medical cannabis to be beneficial in palliative care patients? Yes/No
10. In your opinion, does medical cannabis cause more harm than good in palliative care patients? Yes/No
11. When people ask you about medical cannabis, are you open to answering their questions? Yes/No
12. Have you suggested the use of medical cannabis to a patient? Yes/No
13. Do you refer patients enquiring about medical cannabis to someone else? Yes/No
14. How frequently do you encounter patients asking for your opinion regarding the use of medical cannabis? Daily/weekly/monthly
15. Approximately how many patients in your practice are currently taking medical cannabis that you know of? <5 / 5-10 / 10-20 / >20
16. Would you suggest medical cannabis for palliative care patients? Yes/No
17. Would you suggest medical cannabis for patients with chronic pain? Yes/No
18. In your opinion what symptoms are considered to improve with medical cannabis?
    _____
    _____
19. Please provide any further comment or opinions regarding the use of medical cannabis.
    _____
    _____
    _____

If you would you like a copy of the findings when the dissertation is completed, please provide contact details for it to be sent to.

E mail _____

Contact number _____

ADDENDIX B

UNIVERSITY OF CAPE TOWN

Faculty of Health Sciences

Human Research Ethics Committee

Room G50- Old Main Building
Groote Schuur Hospital
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Telephone [021] 406 6492
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Website: www.health.uct.ac.za/fhs/research/humanethics/forms

10 May 2021

HREC REF: 296/2021

A/Prof L Gwyther
Division of Family Medicine
FHS
Email: Liz.Gwyther@uct.ac.za
Student: Kduplessis71@gmail.com

Dear A/Prof Gwyther

PROJECT TITLE: A SURVEY OF THE KNOWLEDGE AND PERCEPTIONS OF SOUTH AFRICAN MEDICAL PRACTITIONERS CONCERNING USE MEDICAL CANNABIS BY PATIENTS-MPHIL CANDIDATE-DR KARLIEN DU PLESSIS.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study, to adding the FHS HREC contact details to the info sheet.

This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, dated 17 March 2020 & 06 July 2020.

Approval is granted for one year until the 30 May 2022.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

The HREC acknowledge that the student: Dr Karlien du Plessis will also be involved in this study.

Please quote the HREC REF 296/2021 in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
NHREC-registration number: REC-210208-007

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.