

Do-It-Yourself medicine. Exploring the use of cannabis as medicine in Denmark

PhD dissertation

Sinikka L. Kvamme



Centre for Alcohol and Drug Research
Department of Psychology
Aarhus BSS
Aarhus University
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© Sinikka Lehmann Kvamme
Centre for Alcohol and Drug Research, Aarhus University, Denmark
Email: slk.crf@psy.au.dk

Supervisor:

Associate Professor Birgitte Thylstrup
Centre for Alcohol and Drug Research, Aarhus University, Denmark

Co-supervisor:

Associate Professor Kristine Rømer Thomsen
Centre for Alcohol and Drug Research, Aarhus University, Denmark

Assessment committee:

Professor Dr. Tom Decorte, Faculty of Law and Criminology, Institute for Social Drug Research (ISD), Ghent University, Belgium.

Senior researcher Carsten Hjorthøj, MSc, Ph.D., Mental health services in the Capital Region of Denmark, Associate Professor, University of Copenhagen, Denmark.

Associate Professor Adriana del Palacio Gonzalez (chair), Centre for Alcohol and Drug Research Aarhus University, Denmark.

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Abbreviations

ADHD (Attention Deficit Hyperactivity Disorder)

CBD (Cannabidiol)

CaM (Cannabis as Medicine)

CBM (Cannabis-Based Medicines)

DCGP (Danish College of General Practitioners)

DPA (Danish Psychological Association)

(IASP) (International Association for the Study of Pain)

MCPP (Medical Cannabis Pilot Program)

MS (Multiple Sclerosis)

NSAIDs (Nonsteroidal Anti-Inflammatory Drugs)

NASEM (National Academies of Sciences, Engineering and Medicine)

PTSD (Post-Traumatic Stress Disorder)

RCTs (Randomized Controlled Trials)

RWD (Real World Data)

THC (Delta-9-Tetrahydrocannabinol)

U.S. (United States)

Terminology

Cannabis as medicine (medical cannabis and medicinal cannabis)

Medical cannabis (cannabis prescribed by a doctor)

Medicinal cannabis (non-prescribed cannabis used with a medical motive)

Cannabis-based medicines (Plant derived or synthetically produced THC or CBD, or a combination of THC and CBD)

Whole-plant cannabis (Cannabis preparations containing a spectrum of cannabinoids and non-cannabinoids)

Overview of the thesis.

The basis for this thesis is the three following studies exploring the use of cannabis as medicine (CaM) in Denmark

Study	Data and methods	Main findings
<p>1. Beyond the high: Mapping patterns of use and motives for use of cannabis as medicine. Published in Nordic Studies on Alcohol and Drugs.</p>	<p>Survey of a self-selected convenience sample of users of CaM, both prescribed and non-prescribed (n=3.021).</p>	<p>Who: Predominantly women, mean age of 49 yrs. Only ¼ in full-time occupation. What: Most use cannabis oil high in CBD. ¼ use smoked plant material. Only 8.4% hold a prescription for cannabis. Why: to treat pain, sleep, stress, arthritis, anxiety, and depression. Users of CaM report substantial symptom relief and few side effects. Conclusion: The use of CaM may be a growing trend among Danes. Some users seek effects beyond the high conventionally associated with cannabis.</p>
<p>2. Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample. Published in Harm Reduction Journal.</p>	<p>Survey of a self-selected convenience sample of users of CaM, both prescribed and non-prescribed cannabis (n=2.841).</p>	<p>Who: Substitution use is more common among women, people with reduced working capacity, and people who treat chronic pain or other somatic conditions. What: Pain medication and anti-depressants are the classes of drugs most commonly substituted with CaM. Why: Most users indicate better effects and fewer side-effects of CaM compared to prescription drugs. Conclusion: Substitution is a leading motive for the use of CaM. Users may perceive CaM to be the lesser of two evils.</p>
<p>3. With medicine in mind? Exploring the relevance of having recreational experience when becoming a medicinal cannabis user. Published in Contemporary Drug Problems.</p>	<p>Survey of a self-selected convenience sample of users of medicinal cannabis, i.e., only non-prescribed cannabis (n=2.281).</p>	<p>Who: Medicinal cannabis users who were either novices or had occasional or regular recreational experience (RE) prior to medicinal cannabis use. What: Novices are more likely women who treat somatic conditions and use CBD oil. Previous RE is associated with being male, using smoked cannabis products, and treating mental health conditions. Why: Medicinal use is discovered in public media, on social media, or suggested by friends or family. ¼ develop a medicinal cannabis use on a gradual transition from recreational cannabis use. Conclusion: Medicinal cannabis users are a heterogeneous group, and this heterogeneity is related to previous RE and whether users have medicine in mind from the onset of cannabis use.</p>

Chapter 1. Background

In this section, I describe the development regarding medical cannabis use in Denmark that led to the initiation of a Medical Cannabis Pilot Program (MCP) and describe the program and the reactions to it. Also, I describe the multiple indications of a large use of “Do-It-Yourself-medicine” with cannabis from the illegal market.

1.1. Medical cannabis in Denmark

1.1.1. The push for a medical cannabis policy

“For me, a cookie when I was at my worst meant a world of difference. I got my appetite back so I could eat and gain energy and strength. I could sleep at night, because I was able to relax... I did not care at all that I broke the law - they could just take me straight to jail for all I cared because it helped!” (Hansen, 2017, p. 1).

This patient report on illegal cannabis used as a medicine during advanced lymph node cancer treatment belongs to the Danish actor and comedian Søs Egelind. Her report illustrates commonly reported reasons for the use of *medicinal cannabis* (non-prescribed cannabis use with a medical motive) and is comparable to reports from other cancer patients who experience relief through the use of cannabis during cancer treatment (Buchwald et al., 2020; Pergam et al., 2017). However, what is extraordinary about Søs Egelind’s report is how well known it became to the general public in Denmark. After surviving lymph node cancer, Søs Egelind became vocal about patients’ rights to *medical cannabis* (cannabis prescribed by a physician). In June 2015, she was on the cover of the largest tabloid newspaper in Denmark with a headline that read: “Saved by cannabis (Reddet af cannabis)” (Hansen, 2015b). In the article, she encouraged researchers and politicians to take cannabis as medicine (CaM) seriously and find a solution so that people did not have to choose between criminalization and unnecessary suffering (Hansen, 2015a).

At the time of Søs Egelind’s statement, all cannabis products in Denmark were illegal to sell, and possession was punished with confiscation of the product, a fine, and a criminal record (Houborg et al., 2011). Søs Egelind was not the only one addressing a need for reform, as other Danish celebrities and politicians - among them, a former Danish minister – were vocal about their use of illegal cannabis with a medical motive and problematized the current Danish

law prohibiting all cannabis use (Bundgaard, 2017; Elabdi et al., 2017; Jørgensen, 2017). Moreover, several documentaries were produced from 2014 to 2017 by the National Broadcasting corporation Denmark's Radio, exploring the medicinal use in Denmark (Dr1, 2016, 2017; Dr2, 2014), one in which aforementioned Søs Egelind detailed her personal use of medicinal cannabis and interviewed other medicinal cannabis users (Dr1, 2017). Another documentary focused on a seller of cannabis, Claus "Moffe" Nielsen, who started producing cannabis oil in his basement when his daughter fell ill with cancer (Dr1, 2016), and ended up being convicted of producing 6,7-liters of cannabis oil and 52.000 chocolates containing cannabis, supplying some 6.000 Danes with cannabis for medicinal use (Toft, 2017). Yet another documentary called "Sick Danes on hash medicine" documented the increased popularity of medicinal use of cannabis oil among various patient groups and the illegal market that had emerged to accommodate this demand (Dr2, 2014). Overall, there was increased attention towards the topic of medical and medicinal cannabis use, and a content analysis on cannabis in Danish newspapers from 1989 to 2016 shows that the term "medical cannabis" had been virtually absent for a decade until it rose in 2013 and peaked in 2015 (Houborg et al., 2018). At the same time, a strong push for a medical cannabis policy was manifesting as public opinion overwhelmingly favoured legalization of medical cannabis, with a poll from 2016 showing that 80% of Danes supported permanent legalization of medical cannabis (Blackman, 2017) and a poll from 2017 showing that 85% supported legal, medical cannabis for "seriously ill" patients with cancer or chronic pain (Gottschalck, 2017). Also, several patient organizations were vocal about their demand for changes in policy that would give legal access to medical cannabis to their specific patient group (Epilepsiforeningen, 2016; Færch, 2014; Scleroseforeningen, 2014). Altogether, there were multiple actors articulating issues related to medicinal cannabis use and calling upon political action on the issue.

1.1.2. The Medical Cannabis Pilot Program

The salience of the topic of medical cannabis did not go unnoticed by politicians. In November 2016, a large majority of parliament agreed on a four-year Medical Cannabis Pilot Program (MCP) effective from January 2018 (Ministry of Health, 2016). The purpose of the MCP was to create a "*safe framework for the use of medical cannabis within the healthcare system (...) providing a legal alternative for some of the patients who self-medicate with illegal products*" (Ministry of Health, 2016, p. 1). With the MCP, it became possible for doctors to prescribe cannabis products that did not meet the standards conventionally required for prescribed medication, i.e., authorization for use either by the Danish Medicines Agency or the European Medicines Agency (Danish Medicines Agency, 2020). Such authorization is

contingent on large scientific studies providing sufficient evidence of the medicine's quality, efficacy, and safety (Danish Medicines Agency, 2020).

Before the MCPP, it had been possible for doctors to prescribe cannabis-based medicines containing one or two of the active components of cannabis, *cannabinoids*. Still, the MCPP saw the introduction of the whole cannabis plant with its more than 125 active components (*cannabinoids*) and some 400 passive components, such as flavonoids and terpenes (Bonn-Miller et al., 2018; Radwan et al., 2021). According to the acting Danish health minister, Ellen Trane Nørby, exempting from the standards conventionally applied to medicine was necessary in the case of whole-plant cannabis, as the plant was difficult to standardize (Nørby, 2018). Moreover, Ellen Trane Nørby argued that the pharmaceutical industry lacked incentives to produce the relevant research on whole-plant cannabis, as they could not patent the entire plant (Wang, 2018).

The Danish Medicines Agency was tasked with identifying patient groups that could be treated with whole-plant cannabis in the MCPP and chose patients with multiple sclerosis, spinal cord injury, chronic pain (with a neuropathic component) or side effects from chemotherapy (Ministry of Health, 2016). Additionally, the MCPP allowed for the production of medical cannabis on Danish soil (The Danish Parliament, 2017), intended to supply both the Danish patients in the MCPP and other European countries with medical cannabis (Danish Ministry of Health, 2018a). Thus, according to Ellen Trane Nørby, the MCPP was not only an important tool for helping patients in Denmark who did not experience relief from conventional therapies but also an important opportunity to make Denmark a pioneering country in medical cannabis (Nørby, 2018), ensuring a competitive edge for investments and jobs related to a booming medical cannabis market (Danish Ministry of Health, 2018a).

The initiation of the MCPP was met with heavy criticism from the Danish medical community. In a hearing on the MCPP, the head of the Danish College of General Practitioners (DCGP), Anders Beich, criticized the decision to use whole-plant cannabis products as medicine, as no such product met the current standards for drug approval (Beich, 2017). In addition, Anders Beich argued that the MCPP would put physicians in a difficult position, as they were to take full responsibility for prescribing products for which the necessary information and documentation were lacking. Anders Beich further noted: *"It seems that the state is now trying to partially legalize cannabis – but only as a medicine. DCGP believes that this makes a legal and moral problem concerning the large illegal consumption of cannabis into a medical problem"* (Beich, 2017, p. 2). Similarly, the chair of the Danish Medical Association, Andreas Rudkjøbing, argued that the MCPP would expose patients to the risk of harm due to lack of evidence on the long-term effects and side effects of medical cannabis use (Schmidt, 2017).

The critique of the MCPP from the medical community did not resonate with the acting health minister. In an interview in 2018 on the topic of medical cannabis, Ellen Trane Nørby said that she believed that doctors and science were lagging behind the public and global trends (Støttrup, 2018). This comment sparked further critique from the medical community, with doctors arguing that the minister's comment weakened the public faith in science and the medical institutions (Eienstand, 2019; Wang, 2018). Moreover, the DCGP advised their members not to prescribe cannabis through the MCPP. Several Danish practitioners issued official statements to their patients, declaring that they did not prescribe medical cannabis (Hjort, 2018). Despite the reluctance among some doctors to take part in the MCPP, within the first 2,5 years that the MCPP has been active, more than 10.071 prescriptions for medical cannabis have been made and distributed among 2.550 patients (Danish Ministry of Health, 2020).

1.1.3. The medicinal cannabis use

In concert with the intensified debate surrounding medical cannabis in the media and the initiation of the MCPP, there were several indicators of an increased interest in self-medicating with cannabis among the public. In particular, there was an emergence of networks on the social media platform Facebook offering guidance in medicinal cannabis use, where experienced users guided newcomers in everything from effects of medicinal cannabis on various conditions, how to supply cannabis, to dosing and form of intake. The Danish Broadcasting Cooperation covered one such Facebook group called "Cannabis Recovery – Håb, Støtte, Erfaringsudveksling (in English: Cannabis Recovery - Hope, Support, Experience



Oils by Simpson - Cannabis Recovery - Håb, Støtte, Erfaringsudveksling

Privat gruppe · 22,9 tusind medlemmer

Figure 1. Screenshot of the front page of the "Cannabis Recovery" Facebook page

exchange (see figure 1)", established in 2013, interviewing an administrator of the group, who said that they had seen a rapid increase in the number of group members who had a great variety of conditions they wished to treat with cannabis (Bechgaard, 2014). At the time that this Ph.D. project was proposed, the three largest medicinal cannabis groups on Facebooks collectively held 59.058 members (Association for Medicinal Cannabis Denmark, 2017; Cannabis Oil and CBD, 2017; Cannabis Recovery, 2017), altogether suggesting a considerable interest in medicinal cannabis use in Denmark.

A few years after the emergence of large networks on social media related to medicinal cannabis use, a poll in 2016 by Epinion for the Danish Broadcasting Cooperation estimated that 4% of Danes used cannabis as medicine, which would be at least 50.000 users when accounting for the statistical uncertainty of the poll (Damløv, 2016). Coupled with the described indications of increased interest in self-medicating with cannabis among Danes, large indications of the growth in the development of the illegal cannabis market in Denmark to accommodate this interest have emerged. For example, reports from 2013 already described the changes in the illegal open cannabis market in Christiania, where cannabis oil had become a standard commodity to accommodate a new customer group who did not seek cannabis for recreational use but for treatment of medical conditions (Færch, 2013; Jensen, 2013). When the people living in Christiania closed down the organized cannabis trade in Pusher Street following a deadly shooting (Svaneborg, 2016), they left a "self-service" stand with cannabis oil (like the ones you see in the countryside for fruit and vegetables) to accommodate the medicinal cannabis users (see figure 2).



Figure 2. "Self-service" cannabis oil left for medicinal users at Christiania Private photo by Julie Loui Grundtvig. Permission to print the photo has been obtained.

Moreover, a growing number of web shops have been selling cannabis oil in recent years; in May and June of 2017, Danish customs seized almost 1000 containers of cannabis oil, which is more than double the amount that was seized in all of 2016 (Sørensen et al., 2017b). Particularly, cannabis products high in the non-psychoactive cannabinoid *Cannabidiol* (CBD) and a low level of the main psychoactive cannabinoid *Tetrahydrocannabinol* (THC) appear to have become more prevalent (Damløv, 2016; Sjöberg et al., 2016). Another indication of the growth in prevalence of these products is the list¹ made by the Danish Medicines Agency of illegal medicines on the market, where 39% of the products contain the letters CBD (Danish Medicines Agency, 2021). In conclusion, from around 2013 and onward, there were multiple indications of a large and growing trend in Denmark of “Do It Yourself-medicine” with cannabis from the illegal market.

1.2. Knowledge on the use of CaM (cannabis as medicine)

In this section, I explore the state of the art related to research on use of CaM, both in Denmark and internationally, up to when data collection for my Ph.D. project was initiated in February 2018. The main focus in this section is on the state of the art related to the key areas that I chose to study; motives for the use of CaM, patterns of use and user experiences with CaM, as well as substitution use of CaM and paths to becoming a user of CaM. Afterwards, in section 1.2.5. *Efficacy of cannabis and cannabinoids*, I review what was known about the efficacy of cannabis and cannabinoids at the time.

1.2.1. Use of CaM in Denmark

At the time when my Ph.D. project was initiated, the use of whole-plant cannabis in the formal medical treatment had been in effect for one month in Denmark through the MCPP, allowing the use of medical cannabis for selected patient groups (See section 1.1.2. *The Medical Cannabis Pilot Program*). Before the medical use of whole-plant cannabis was initiated through the MCPP, treatment with cannabis-based medicines, such as Sativex and Marinol, was possible within the Danish healthcare system. Sativex is a plant-derived mouth spray containing standardized doses of both THC and CBD, whereas Marinol contains synthetically produced THC (Danish Ministry of Health, 2018b). Beyond these drugs, doctors could prescribe magistral preparations of plant-derived THC or CBD produced by Glostrup Apotek, which had been the most used cannabis-based medicine (Danish Ministry of Health, 2018b); the product was used by 5 patients in 2015 and by some 500 patients in 2017 (Damløv, 2017;

¹ last updated in May 2021

Damløv et al., 2016). However, no systematic data on the experienced effects of this use was available at that time.

Beyond the legal, medical use of whole-plant cannabis and cannabis-based products, there were growing indications of a large medicinal use of cannabis in Denmark. However, scientific studies on this type of use were scarce, except for a qualitative study from 2011 that explored 19 small-scale non-profit home growers of cannabis who expressed a medicinal motive for use (Dahl et al., 2011). All but four medicinal cannabis users in this study were men, and all had smoked cannabis as teenagers and perceived themselves as experienced recreational users. For all but two of the 19 respondents, growing cannabis was described as a strategy for supplying their recreational use before medical problems became an additional motivational factor for use. The 19 respondents detailed their current use of cannabis as a means to manage pain related to various somatic conditions such as migraine, whiplash, ruptured discs, arthritis, and sclerosis, or to soothe emotional distress related to mental health conditions such as depression, anxiety, panic attacks, and ADHD. The effects of cannabis use that they most frequently mentioned as helpful and relieving were analgesic, sedative, and sleep-inducing effects. Aside from this study, not much was known about the use of medicinal cannabis in Denmark, besides the increasing indications of a growing medicinal cannabis use (see section 1.1.3. *The medicinal cannabis use*).

1.2.2. Use of CaM internationally

Compared to Denmark, the focus on the use of CaM internationally had been considerably bigger when my Ph.D. project was initiated. In the 1990'ies, seismic shifts had already happened with respect to changes in cannabis policy in several countries. While Israel was the first country to initiate a medical cannabis program in 1992 (Aguilar et al., 2018), the state of California followed in 1996, as it voted to pass the Compassionate Use Act that allowed cannabis to be recommended by a physician for any condition for which cannabis provides relief (Compassionate Use Act, 1996; Nunberg et al., 2011). Not long after, Canada initiated a medical cannabis program in 1999 in response to a court ruling in favour of the legal rights of a person living with AIDS to use and possess cannabis (Lucas, 2008).

By the time when my Ph.D. project was initiated, cannabis policy had shifted rapidly around the globe, and medical cannabis laws had been adopted in most European countries, Israel, Thailand, the Philippines, Peru, Brazil, Chile, Colombia, Argentina, Australia, New Zealand, Mexico, Canada, and 29 states in the U.S. (Abuhasira et al., 2018; Aguilar et al., 2018). However, these medical cannabis programs vary widely, both in terms of eligible conditions,

the number of patients in the programs, and in terms of available cannabis products. In general, the medical cannabis programs have been more liberal in the Americas with respect to patient access and use of whole-plant cannabis, while European countries have taken a more cautious approach, implementing pilot programs with whole-plant cannabis for a narrow range of medical conditions or relying solely on the use of cannabis-based medicines (Aguilar et al., 2018; Krcevski-Skvarc et al., 2018).

Due to the changes in cannabis policy globally, a great number of studies have explored the use of CaM with the aim of mapping user demographics, motives, and experiences. Some studies include only legal, medical cannabis users, while others include both medical and medicinal users, and yet others explore a medicinal sample of users or use among specific patient groups. In this section, for simplicity, I focus on the literature on users of CaM in general and on the use of CaM among specific patient groups, but for one review (Park et al., 2017), which also included specific patient groups. Cross-sectional surveys of self-selected legal, medical cannabis users from the U.S. (Bonn-Miller et al., 2014; O'Connell et al., 2007; Reinerman et al., 2011; Troutt et al., 2015) and Canada (Lucas et al., 2017; Walsh et al., 2013), ranging from a few hundred to over a thousand respondents, have found similar demographic profiles, with a majority of males, typically between 30 to 45 of age. These medical cannabis patients report use cannabis for a great variety of conditions, of which the most prominent is pain management followed conditions such as depression, anxiety, sleep disturbances, nausea, and stress (Bonn-Miller et al., 2014; Lucas et al., 2017; Reinerman et al., 2011; Troutt et al., 2015; Walsh et al., 2013). In fact, some medical cannabis users report relief from conditions for which cannabis is not specifically prescribed or allowed in their jurisdiction (Bonn-Miller et al., 2014). So, for instance, a patient might hold a recommendation for medical cannabis to treat neuropathic pain but will also report relief from a co-morbid depression or anxiety condition, even though medical cannabis is not indicated for such conditions. Another common finding from these studies is that patients generally self-report that medical cannabis helps them manage their condition(s). Yet another commonality across the findings from the U.S and Canada studies is that most medical cannabis users consume cannabis on a daily basis and report inhalation as the most frequent form of use.

The use of CaM has also been explored in two cross-national surveys that included both medical and medicinal cannabis users in self-selected samples. One study included 953 participants from 31 countries, primarily the US (38,5%), and in this sample, there was a mean age of 40.7 years, a majority of men (64%), and the most frequent conditions treated with CaM were back pain (11.9%), sleeping disorder (6.9%), depression (6.7%), pain resulting from injury or accident (6.2%), and multiple sclerosis (4.1%) (Hazekamp et al., 2013). With respect to patterns of use, inhalation was most prevalent, with (94.8%) of users having tried at least

one form of inhaled administration. The other study included 1429 participants from 18 countries, again primarily the U.S. (77.8%), and again there was a majority of men in the sample (54.6%), however with a slightly lower mean age of 36.3 years (Sexton et al., 2016). The most frequent conditions treated were pain (61.2%), anxiety (58.1%), depression (50.3%), headache/migraine (35.5%), nausea (27.4%), and muscle spasticity (18.4%), and in this study, users reported an 86% reduction in symptoms from the use of CaM on average. Also, with respect to patterns of use, inhalation was again most prevalent, with 84,1% of users reporting inhalation as the most common mode of intake (Sexton et al., 2016). Similar trends in motives for use and self-reported effects are found in an international review from 2017 based on 25 surveys with a variety of study populations such as medical and/or medicinal cannabis users in either specific patient groups or among CaM users in general (Park et al., 2017). The review found that pain management was the most frequently endorsed reason for use across all studies and that most users self-reported that cannabis relieved various symptoms, particularly chronic pain and other pain conditions, sleep disturbances, and anxiety, but not cluster headache symptoms.

Lastly, at the time that my Ph.D. project was initiated, there had been a growing international scientific interest in the use of CaM in contexts where medical cannabis was not legal or restricted to limited use of cannabis-based medicines, resulting in samples of almost exclusively medicinal cannabis users. These studies were conducted as national survey studies in the UK (Ware et al., 2005) and New Zealand (Pledger et al., 2016), as anonymous self-selected surveys in Germany (Grotenhermen et al., 2003; Schnelle et al., 1999) and Australia (Swift et al., 2005), and as a large qualitative study in Norway (Pedersen et al., 2013). Overall, these studies align with the findings described for medical cannabis users. In the nationwide surveys, medicinal cannabis use was associated with being male and younger, and in the self-selected sample of medicinal cannabis users, there was a majority of men and a wide age range. Moreover, in all studies, medicinal cannabis was used for a great variety of conditions, most commonly chronic pain conditions, depression, anxiety, arthritis, multiple sclerosis, nausea and sleep-related issues. Likewise, a majority of users in general perceived cannabis to be effective in managing their conditions. As an example, of 948 British medicinal cannabis users, 68% reported that cannabis reduced their symptoms considerably and 27% that cannabis use reduced their symptoms a little (Ware et al., 2005). Similarly, of 128 Australian medicinal cannabis users, 86% reported: "great relief" overall from the use of cannabis. In the studies that explored patterns of use, all respondents reported that a majority used inhalation as route of administration, with 92% of Australian users (Swift et al., 2005), 82 % of British users (Ware et al., 2005) and 86% of German users (Schnelle et al., 1999).

In all, there are several commonalities between medical use and medicinal users, with a majority of men, a wide age range and inhalation as the most common form of intake. Also, users of CaM report using cannabis for a great variety of conditions, of which the most prominent are pain management, mental health conditions such as depression and anxiety, multiple sclerosis, sleep, stress and appetite/nausea. Overall, these self-selected self-report data show that most users experience cannabis to be effective in managing their conditions.

1.2.3. Substitution of prescription drugs with cannabis

In the following, I provide an overview of what was known at the time of the initiation of my Ph.D. project about the use of cannabis as a substitute for prescription drugs in practice, combining research from Denmark with international research.

There were some indications that the rising use of both medical and medicinal cannabis in recent years may have had a substitution effect on prescription drug use, meaning that the use of CaM may have replaced or reduced the use of prescription drugs. In the U.S., the introduction of legal, medical cannabis programs has been associated with a significant reduction in state-wide use of prescription medication (Bradford et al., 2016), particularly opioid prescriptions (Bradford et al., 2018; Vigil et al., 2017; Wen et al., 2018). Furthermore, cross-sectional surveys from the US and Canada show that patients often report a reduction in the use of other medications when using medical cannabis (Lucas et al., 2016; Nunberg et al., 2011; Reiman, 2007; Reinerman et al., 2011), with opioids, anxiolytics, and anti-depressive drugs being most commonly substituted (Corroon et al., 2017; Lucas et al., 2016; Piper et al., 2017; Reiman et al., 2017). Some survey studies have also explored motives for substitution use, both among medical (Lucas et al., 2013; Reiman et al., 2017) and medicinal (Ware et al., 2005) users and have found that cannabis is often reported to be more effective and have more tolerable side effects when compared to prescription drugs. The before mentioned Danish qualitative study on medicinal cannabis use among 19 cannabis growers also found a substitution motive for use, where some users contrasted the effects and side-effects of cannabis to prescription drugs, particularly opioids, and indicated that they had found cannabis superior in managing their conditions (Dahl et al., 2011). However, at the time, there was no research exploring substitution use of medicinal cannabis in Denmark after the increased salience of the topic (see section 1.1. *Medical cannabis in Denmark*). In sum, some ecological studies have found a negative association between medical cannabis programs and opioid prescriptions and some users of CaM report using cannabis as a substitute for prescription drugs, particularly opioids.

1.2.4. Paths to becoming a user of CaM

In the following, I provide an overview of what was known at the time of the initiation of my Ph.D. project about the paths to becoming a user of CaM, combining research from Denmark with international research.

There was some research that focused on the process of initiating use of CaM and the factors and circumstances that lead to use. Qualitative research from the U.S. and Canada has found that medical cannabis use is often initiated at the individual user's initiative and that use is often evoked by information found online or by advice from friends or family members, while the advice from general practitioners play a minor role (Athey et al., 2017; Lankenau et al., 2018). Cross-sectional survey studies exploring the use of CaM have found that users of both medical and medicinal cannabis, for the most part, have previous experience with recreational cannabis use (Park et al., 2017; Reinerman et al., 2011) and that many report discovering self-identified therapeutic effects of cannabis in a recreational setting (Cohen, 2015; Dahl et al., 2011; Pacula et al., 2016; Reinerman et al., 2011). The impact of previous recreational experience with cannabis use has also been explored in some qualitative studies, finding that motives for use of CaM were related to the process of becoming a user of CaM (Cohen, 2015; Dahl et al., 2011). For instance, in the qualitative study on 19 Danish medicinal cannabis users (Dahl et al., 2011), the researchers noted that the users fell into two distinct groups, where the users treating a mental health condition were more likely to have developed medicinal use on a gradual transition from recreational use, while users that treated pain conditions were more likely to have had a period of cessation between recreational and medicinal use. Another study exploring paths to use of CaM among Canadian medical cannabis users noted a similar trend, where individuals with a period of cessation between recreational and medical cannabis use were more likely to treat pain conditions, while those with no period of cessation were more likely to use cannabis to manage mental health conditions (Cohen, 2015). Taken together, these studies show that there are different paths to becoming a user of CaM. However, more research is needed that explores these paths and user patterns further and, to my knowledge, no research has explored the process of becoming a user of CaM among users without recreational experience.

In sum, survey studies have consistently found that most medical and medicinal cannabis users have recreational experience with cannabis use, and qualitative studies have found differences in motives for use depending on whether use happened on a sliding scale for recreational use.

1.2.5. Efficacy of cannabis or cannabinoids

In this section, I outline state of the art within studies on the efficacy of cannabis or cannabinoids at the time my Ph.D. project was initiated, with a summary of findings from reviews of the available randomized controlled trials.

Despite the massive shift in policy worldwide towards legal use of medical cannabis, as well as a growing number of studies that report findings on positive experiences with the use of CaM reported from both medical and medicinal cannabis users (described in section 1.2 *Knowledge on use of cannabis as medicine (CaM)*), there was limited evidence regarding both the short- and long-term health effects of using cannabis or cannabinoids as a medical treatment at the time of the upstart of my Ph.D. project. Thus, the efficacy of cannabis or cannabinoids had not been explored in high-quality research for most of the conditions for which CaM was being used around the globe, both medically and medicinally. However, there was some research. A systematic review and meta-analysis conducted in 2015 on 79 randomized controlled trials (RCTs) (Whiting et al., 2015) showed that the majority of trials had evaluated the following conditions; nausea and vomiting due to chemotherapy (n=28), chronic pain (n=28), or spasticity due to multiple sclerosis and paraplegia (n=14). The review concluded that there currently was moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain and spasticity due to multiple sclerosis. Moreover, the authors found low-quality evidence suggesting that cannabinoids were associated with improvements in nausea and vomiting due to chemotherapy, weight gain in HIV, sleep disorders, and Tourette syndrome. The review also highlighted great knowledge gaps and reported a lack of RCTs exploring the effects of cannabis or cannabinoids on depression or anxiety as primary endpoints, despite the fact that these conditions were frequently reported as reasons for using CaM. Likewise, a later systematic review from 2017 also found a relative dearth of high-quality evidence for medical cannabis in the treatment of mental health conditions, although such conditions were reported as a frequent motive for use (Walsh et al., 2017).

While there was virtually no evidence base for evaluating the efficacy of medical cannabis in mental health conditions, there was more available research exploring cannabis or cannabinoids in pain management, albeit with contested interpretations. In an overview of 10 systematic reviews exploring cannabis-based medicines for chronic pain management that included the before mentioned review by Whiting et al. 2015, Häuser et al. 2018 showed that of four systematic reviews, that there were inconsistent findings with respect to the efficacy of

cannabis-based medicines compared to placebo in chronic neuropathic pain. Thus, the authors demonstrated that not all systematic reviews reached the same conclusion as Whiting et al. 2015. Also, Häuser et al. 2018 showed that three of the systematic reviews had found insufficient evidence for the use of cannabis-based medicines in pain management for rheumatic disease, while two of the other systematic reviews found insufficient evidence for the use of cannabis-based medicines in cancer pain. As a consequence, Häuser et al. 2018 criticized Whiting et al. 2015 for having a bias toward a positive evaluation of cannabis products. In particular, Häuser et al. point to the fact that Whiting et al. state that there is moderate-quality evidence for the efficacy of cannabis-based medicines for multiple sclerosis, despite providing a non-significant finding. Also, Häuser et al. 2018 critique Whiting et al. 2015 for including single-dose studies, short-term studies, and studies with small sample sizes that could overestimate positive treatment effects (Häuser et al., 2018). Further, Häuser et al. 2018 pointed out that while two reviews besides the review by Whiting et al. 2015 had found that cannabis-based medicine may provide short-term relief from neuropathic pain, these reviews had also cautioned that the benefits of cannabis-based medicines might be outweighed by their harms in terms of adverse events (Häuser et al., 2018).

While the overview from Häuser et al. 2018 was conducted (January 2009 - January 2017), another overview was published by the National Academies of Sciences, Engineering and Medicine (NASEM), exploring the health effects of cannabis and cannabinoids, including publications from January 1999 to August 2016. While reviewing much of the same evidence base, this overview reached a markedly different conclusion compared to Häuser et al 2018, namely that there was *substantial evidence that cannabis is an effective treatment for chronic pain in adults* (National Academies of Sciences Engineering and Medicine, 2017, p. 44). Of note, the authors specifically referred to cannabis and not cannabinoids and based their evaluation on the review by Whiting et al. 2015 and on positive findings with relative strong effect sizes from 7 short-term (1 day – 2 weeks) RCTs exploring the efficacy of smoked whole-plant cannabis for neuropathic pain. However, while the conclusion made by the NASEM may be valid, one could also argue that it is imprecise, as the evidence reviewed pertains to neuropathic pain only and therefore is not generalizable to treating chronic pain in general (Deshpande et al., 2015). Also, the findings that NASEM refers to are limited to short term effects, which is not specified in their conclusion. In Chapter 4, I will elaborate on the critique that subsequently has been raised of the review by the NASEM (see section 4.2.4. *Efficacy of cannabis and cannabinoids*). However, the overviews that I have described in this section illustrate that researchers had reached conflicting conclusions about the efficacy of cannabis or cannabinoids in managing pain condition at the time of the upstart of my PhD project. Further, beyond the limited research into cannabis or cannabinoid for the management of

multiple medical conditions, there was also limited research exploring the role of cannabis or cannabinoids as a substitute for opioids. A systematic review from 2017 found nine clinical studies exploring opioid and cannabinoid co-administration with a total of 750 participants (Nielsen et al., 2017). The review found mixed results with respect to analgesia and few studies measuring opioid sparing as an endpoint. Only one case series (n=3) provided very low-quality evidence of a reduction in opioid requirements, and no randomized controlled studies were identified that provided evidence of an opioid-sparing effect of cannabinoids. Thus, beyond the indications of a substitution effect of cannabis on opioids discussed in section 1.2.3. *Substitution of prescription drugs with cannabis*, there was also limited high-quality evidence to support that cannabis functions as a substitute for opioids.

In sum, the available evidence at the time of the upstart of my PhD project illustrates that the evidence base for the efficacy of cannabis or cannabinoids was rather small and limited to a set of relatively rare conditions, such as multiple sclerosis, paraplegia, nausea, and vomiting due to chemotherapy, while studies exploring cannabis or cannabinoids for mental health conditions were virtually non-existent. Moreover, there was limited evidence that cannabis functioned as a substitute for opioids. Consequently, at the time of the initiation of my Ph.D. project, there were conflicting opinions on how to evaluate the limited evidence available, especially with respect to pain management.

1.3. The conflict over cannabis in medicine

While there has been a popular agenda for legalizing medical cannabis in several countries, the introduction of cannabis into medicine has generally been met with hesitance and criticism from the medical community. In the following section, I will outline the medical community's reaction to illustrate that the main concern is related to the lack of research into the medical effects of cannabis. The causes for concern and hesitance among physicians regarding medical cannabis are a relevant contrast to the enthusiasm among politicians, patient organizations, and the users of CaM themselves. I outline them to elucidate the conflict over cannabis in medicine. I then proceed to outline the barriers to conducting whole-plant cannabis research to illustrate the relevance of exploring the use of whole-plant cannabis as medicine in practice.

1.3.1. "Is the Cart Before the Horse?"

As described in section 1.1.2. *The Medical Cannabis Pilot Program*, the introduction of

cannabis as a formal medical treatment in Denmark, was met with heavy criticism from the Danish medical community, arguing that no such product met the current standards for drug approval and that the long-term effects and side effects of medical cannabis use were largely unknown. This critique was parallel to the critique raised by the medical community in Canada and the U.S, where both medical associations and several researchers raised similar concerns related to the popular agenda of legalizing cannabis for medical use (American Medical Association, 2019; Cairns et al., 2017; D'Souza et al., 2015; Fletcher, 2013; Janus, 2014; Owens, 2018; Spurgeon, 2001; Wilkinson et al., 2014).

In an editorial by D'Souza et al. (2015) titled *“Medical Marijuana. Is the Cart Before the Horse?”*, the authors give a thorough summary of concerns that had been raised (D'Souza et al., 2015). One of the main concerns is that drug approval should rely on evidence from at least two adequately powered RCTs, which is far from the case for some of the conditions for which medical cannabis has already been approved. Further, D'Souza et al. 2015 stress that results from the available studies on the efficacy of individual cannabinoids (THC or CBD) cannot be extrapolated to the whole-plant cannabis products used in several medical cannabis programs. Also, the authors point out that individual cannabinoid products are already commercially available in the form of synthetic THC, with better dosing guidelines than what exists for smoked whole-plant cannabis. They also highlight the potential harms of cannabis use, pointing out that there are well-known risks associated with cannabis used recreationally, as approximately 1 in 10 adult users of cannabis develop cannabis addiction and use of cannabis is associated with a small but definite risk of psychotic disorders. Lastly, the authors stress that potential interaction effects between cannabis and other drugs call for more research and that careful consideration should be given regarding the use of medical cannabis in adolescence and early adulthood due to the effect of cannabinoids on brain maturation processes. Overall, the reaction from the medical establishment can be understood in the context of the available research on medical cannabis, described in section 1.2.5. *Efficacy of cannabis or cannabinoids*, or rather in the lack thereof. In an interview with CTVNews, The head of the Canadian Medical Association, Dr. Louis Hugo Francescutti, described the situation that medical professionals are faced with due to the legalization of medical cannabis; *“It’s just bad medicine to be asked to authorize a product that we don’t know how it works, we don’t know when it works, for who it works,”... “Where are the studies? We try to base what we do on evidence.”* (Janus, 2014, p. 1). Consequently, survey studies show that both Canadian (Fitzcharles et al., 2014; Ziemianski et al., 2015) and American (Carlini et al., 2017; Hwang et al., 2016; Luba et al., 2018) physicians were reluctant to recommend/prescribe medical cannabis to patients, citing lack of research on risks and benefits, as well as lack of clinical guidelines, as the main reasons for their hesitance.

Another area of concern has been the use of medical cannabis as a tool to combat the opioid epidemic, which has been suggested in both the U.S. (Collen, 2012; Hurd, 2017) and Canada (Corroon, 2017; Lucas, 2017). Opponents of this suggestion argue that the evidence for such use is weak, as it is based almost entirely on self-reported outcomes from medical cannabis users and on ecological data showing a correlation between medical cannabis laws and a reduction in prescription opioid use and opioid-related deaths (D'Souza et al., 2015; Hall et al., 2018). Also, beyond the fact that there was very weak evidence to support a substitution effect of cannabis or cannabinoids on opioids (Nielsen et al., 2017), there was some research indicating that medical cannabis users were more likely to use prescription drugs (Caputi et al., 2018) and that cannabis use may lead to worse outcomes in people with chronic non-cancer pain (Campbell et al., 2018).

In sum, the overall hesitant reaction from the medical establishment in Denmark to the initiation of the MCPP echoes the reaction from medical communities in the U.S. and Canada. The hesitation is founded in the fact that research on the medical use of cannabis is scarce for most conditions. Therefore, prescribing medical cannabis before having sufficient evidence for its indication puts “the cart before the horse”. Thus, there appeared to be a great divide between the popular perception of the medical utility of cannabis and the perception held in the majority of the medical community.

1.3.2. Barriers to whole-plant cannabis research

While there were great disputes over the medical utility of cannabis, there was also a widespread agreement on the need for more research. However, as I will elaborate on in this section, there were several barriers to conducting cannabis research. Consequently, most studies focused on single cannabinoids and not the complex cannabis plant, making it difficult to translate findings from available RCTs to the use of CaM in practice, where the whole plant is used.

One of the main barriers to cannabis research is that cannabis remains a Schedule I substance in the U.S, despite multiple campaigns to reschedule the plant. Schedule I is the most heavily restricted category designated for drugs with “a high potential for abuse,” “no current accepted medical use,” and “a lack of accepted safety for use” (Schedules of controlled substances, 2011). Because of this scheduling, substantial layers of bureaucracy discourage researchers from pursuing the topic (Nutt, 2015; Nutt et al., 2013; Piomelli et al., 2019), ironically preventing the research necessary for a potential rescheduling (Campbell, 2015), all within the country with the largest funding available for cannabis research (Hudson, 2020).

Further, suppose all regulatory approvals are met. In that case, there are additional barriers to securing the cannabis supply. It is often difficult for researchers to access the quantity, quality, and type of cannabis product necessary to address specific research questions (National Academies of Sciences Engineering and Medicine, 2017).

Another significant barrier is that the financial support for studying the positive health effects of cannabis is inadequate, as funding is predominantly allocated to explore the negative health effects of cannabis use (National Academies of Sciences Engineering and Medicine, 2017). Neither the cannabis industry nor the pharmaceutical companies are adequately incentivized to invest in clinical research (Bonn-Miller et al., 2018). While funding has increased in the last two decades in the U.S, Canada, and the UK, research that focus on the harms of cannabis use has received twenty times more funding compared to explorations of the medical potential of cannabis (Crossney, 2020; Hudson, 2020). Yet another barrier to whole-plant cannabis research is that modern medicine refrains from working with plant extracts and prefers single molecules that can be described and studied (Mechoulam, 2007). Indeed, *“with each increase in the number of ‘active’ substances in a medicine, the challenges with respect to clinical evaluation and manufacturing precision increase exponentially”* (Bonn-Miller et al., 2018, p. 282), making the RCT framework an unrealistic avenue for generating evidence on the potential medical benefit of cannabis (Fitzcharles et al., 2019). Thus, medical cannabis challenges the conceptualization of drugs in modern medicine, where single-component drugs are preferred over multi-component drugs. Concluding on the many barriers to cannabis research, Politico summarized the state of affairs in the U.S. perfectly with the headline of their article: *“Legal weed is everywhere – unless you’re a scientist”* (Owermohle, 2018).

The consequences of the research barriers are evident in the massive report on the Health Effects of Cannabis and Cannabinoids, reviewing more than 10.000 studies in 2017. Due to the difficulty of obtaining cannabis for research purposes, most of the current evidence relates to pharmaceutical cannabinoids (dronabinol, nabilone, and nabiximols) (Abrams, 2018), meaning that they study only the cannabinoid THC or THC in combination with CBD. The distinction between single cannabinoids and whole-plant cannabis is important, as the results of studies with individual cannabinoids (e.g., THC or CBD) cannot be extrapolated to whole-plant cannabis and vice versa (D’Souza et al., 2015). Some cannabis researchers have theorized a so-called “entourage effect” of cannabis, where the effect of active compounds is mediated by the “entourage” of each other and the presence of other compounds that are not themselves inherently pharmacologically active (Ben-Shabat et al., 1998; Mechoulam et al., 1999). Some researchers believe there is sufficient evidence for the relevance of an entourage effect (Russo, 2018); others argue that proponents of the theory are overstating the evidence (Cogan, 2020). Some evidence does suggest that the effects of one or two components are

different from the synergistic effects of the more than 500 components present in whole-plant cannabis (McPartland et al., 2014; Russo, 2018). For instance, several animal studies have demonstrated enhanced therapeutic effects of single cannabinoids when other components of the cannabis plant are added (Berman et al., 2018; Blasco-Benito et al., 2018; Gallily et al., 2015; LaVigne et al., 2021; McPartland et al., 2014). These findings are echoed in anecdotal evidence from clinicians treating forms of severe epilepsy with CBD, reporting better treatment outcomes of high-CBD cannabis extracts compared to pure CBD preparations (Goldstein, 2016; Russo, 2017; Sulak et al., 2017; Zafar et al., 2021). Moreover, patient ratings from medical cannabis patients in the Netherlands (Hazekamp et al., 2013) and Germany (Grotenhermen et al., 2003) also indicate that whole-plant cannabis is superior to pharmaceutical cannabinoids, as herbal cannabis receive higher appreciation scores compared to pharmaceutical products containing single cannabinoids.

The vast majority of scientific exploration into the efficacy of “medical cannabis” reflects what was manageable, available, and economically feasible to study. However, although it produces important insight into the effects of cannabinoids and expands the potential of pharmaceutical cannabinoids, it does not address the contested question societies are grappling with today; “what (if any) is the medical utility of cannabis?”. As the plant is already present in society and in light of the increasing normalization (Järvinen et al., 2011; Sznitman et al., 2015) and medicalization (Taylor, 2010) of cannabis, addressing barriers to whole-plant research is vital for clarifying the distinction between cannabis as a medicine, cannabis as a recreational substance and cannabis as a problematic substance of abuse (Duff, 2016).

In sum, there are multiple barriers to whole-plant cannabis research, despite research indicating that whole-plant cannabis could be a superior therapeutic tool compared to single cannabinoids. Also, the current barriers to whole-plant cannabis research are problematic because we need more knowledge on the effects and side-effects of the “Do-It-Yourself” medicating with cannabis that is already occurring and this use involve whole-plant cannabis.

Both the medical and medicinal cannabis use have in many cases outpaced the current scientific knowledge and in light of the multiple barriers to whole-plant cannabis research described above, it is highly relevant to explore the use currently occurring with medicinal use of whole-plant cannabis. An exploration of this use can provide ‘real world data’ on user experiences with whole-plant cannabis products (Ware, 2018). While such ‘real world data’ cannot inform us about the efficacy of medical cannabis, it can potentially inform public health policy, complement RCTs trials and provide important insights into safety and adverse events related to use.

1.4. Relevance of exploring the use of cannabis as medicine

In this section, I describe the relevance of exploring the use of CaM in Denmark, involving several indications of a large medicinal use of cannabis, indications of a diversification in the cannabis market with the emergence of novel cannabis products and the need for understanding the motives for use of CaM.

Beyond the challenges related to the lack of whole-plant cannabis research, there are several other rationales for exploring the use of CaM in Denmark. At the time of initiation of the Ph.D., there was no scientific inquiry into the phenomenon for Danish users except for the before mentioned qualitative study from 2011 exploring the medicinal use of cannabis among 19 cannabis growers (Dahl et al., 2011). However, there were multiple testimonials from users with positive experiences with medicinal cannabis use scattered on social media and several cases presented in the media with successful medicinal cannabis users (Askgaard, 2017; Dalin, 2017; Nielsen, 2017; Sørensen et al., 2017a), but they were merely the visible testimonials and cases, and no one knew what this trend looked like in the aggregate. In addition, much had transpired since the qualitative study by Dahl et al. (2011), with increased interest in medical cannabis in the media, the initiation of the MCPP in January 2018, and indications of extensive unregulated use of medicinal cannabis among Danes. Moreover, apparent changes in the illegal cannabis market indicated an increased availability of cannabis oils, particularly the so-called “CBD-oils,” low in the main psychoactive cannabinoid THC and high in the other main cannabinoid CBD, which is non-psychoactive (Bergamaschi et al., 2011).

The apparent changes in the market increased the relevance of exploring patterns of medicinal cannabis use. The last decades of cannabinoid research have shown that the risks associated with cannabis use are related to the composition of these two main cannabinoids, as CBD and THC have been found to have opposing neural, cognitive, and behavioural effects (Colizzi et al., 2017; Rømer Thomsen et al., 2017). Risk factors related to cannabis use such as cannabis dependence (Curran et al., 2019; Freeman et al., 2015; Freeman et al., 2018), cognitive impairment (Colizzi et al., 2017; Morgan et al., 2018), and psychosis (Di Forti et al., 2019; Di Forti et al., 2014), are all associated with consumption of high THC-products. Conversely, CBD has a superior safety profile (Bergamaschi et al., 2011; Iffland et al., 2017) and limited abuse potential (Schoedel et al., 2018) compared to THC. Also, CBD may mitigate some of the harmful effects of THC (Freeman et al., 2019a). This novel scientific insight does not mean that we can conclude that “THC is bad” and “CBD is good,” as therapeutic effects of THC have

been demonstrated (National Academies of Sciences Engineering and Medicine, 2017). However, we can conclude that the complexity of the cannabis plant makes it hard to treat cannabis as a monolith and generalize presumed effects of use without knowledge of the subtype used. Therefore, to evaluate the public health effects of this trend of “Do-It-Yourself”-medicating with cannabis, it is imperative to explore the subtypes of cannabis used and other patterns of use, such as dose, frequency and mode of intake. Such an exploration could potentially guide policymakers and health care practitioners in further addressing the trend of medicinal cannabis use in order to mitigate its adverse public health effects.

Beyond exploring patterns of use, it is equally important to explore what motivates Danes to use cannabis as medicine, particularly those who do so without a prescription, as they risk several hazards related to such use. Users of medicinal cannabis engage with an unregulated illegal market and risk the hazards of engaging with such a market, with the potential for violence, deception and criminalization. Moreover, the use of unregulated products without medical supervision likely increases the risk of adverse events related to use, such as hazards related to the untested products themselves (Dryburgh et al., 2018; National Academies of Sciences Engineering and Medicine, 2017) or potential interaction effects with prescription drugs used (Qian et al., 2019). Additionally, medicinal users potentially face social risks related to stigma and marginalization (Bottorff et al., 2011; Satterlund et al., 2015) if use is exposed to others who disapprove. Despite these multiple risks, it appears that many thousand Danes disregard advice from medical authorities and solicit the illegal market for medicine. Thus, factors that motivate such behaviour is relevant to explore, and answers to such a question could potentially inform policymakers and healthcare practitioners about patient groups experiencing poor treatment within the health care system. Lastly, it is important to explore the contextual factors related to the use of cannabis as medicine. At the time of initiation of the project, there were growing indications of substitution effects of cannabis use on prescription drug use reported in the U.S. and Canada, which had not been explored on a large scale in Europe. However, qualitative studies are suggesting that substitution is an important motive for the medicinal use of cannabis in Scandinavia (Dahl et al., 2011; Pedersen et al., 2013). Indeed, exploring a substitution motive in the context of a Scandinavian country is relevant in order to elucidate whether a substitution motive for medicinal cannabis use is distinct to North America or ubiquitous. In addition, it is relevant to explore to what extent Danes seek medicinal cannabis in order to decrease or discontinue existing prescription drug use, as this could potentially signal broader issues related to existing treatment options for some patient groups. Another area that is underexplored is the process of initiating medicinal cannabis use, as such research has primarily focused on the process of becoming a user of legally prescribed medical cannabis (Athey et al., 2017; Lankenau et al., 2018). In the context

of medicinal cannabis use, advice from formal medical authorities is absent, and we lack knowledge about who or what guides the Danish medicinal cannabis users. Knowledge about these processes can inform politicians and health care professionals about the engines driving health trends in the public unguided by the medical institutions. Overall, concerning motives, patterns of use and contextual factors related to use, systematic scientific knowledge on the basics of this trend in Denmark was needed.

Chapter 2: Aim of the thesis

2.1. Research questions

In this thesis, I examine the use of cannabis as medicine in Denmark. The central research questions I ask throughout the thesis are “who, what, and why”: *Who are the users of cannabis as medicine in Denmark, what are their patterns of use, and why do they use cannabis as medicine?*

The “who” is rather straightforward, as it refers to the sociodemographic characteristics of medicinal cannabis users’ age, gender, educational background, and occupational status. The “what” refers to patterns of use, i.e., which subtypes of cannabis are being used, in what dosage and forms of intake, as well as the frequency and duration of use. Finally, with respect to “why,” the aim of the thesis was to cover the motives for the use of cannabis as medicine, the conditions treated with cannabis, the experienced effects and side effects, and the potential substitution of prescription drugs. However, the “why” also covers a broader sociological context and addresses ‘how’ use arose in the first place, i.e., exploring the processes involved in becoming a medicinal cannabis user in the absence of formal medical guidance.

2.2. Cannabis. A drug or construct – on paying attention to research paradigms

When I initiated my Ph.D. project, I was interested in contributing with a comprehensive outlook on the use of cannabis as medicine in Denmark via my research questions. As a part of this, I was interested in examining how the current trends related to use of cannabis as medicine could be explained by understanding cannabis both as a drug and as a construct. Obviously, cannabis can be understood as a drug; that is, cannabis can be explained from epidemiological and bio-medical perspectives that focus on exploring the prevalence of cannabis use, the doses and modes of intake used, as well as the use of the compounds within cannabis called cannabinoids and the combination of these compounds. The perception of cannabis as a drug is evident in randomized controlled trials (RCTs) that explore the effects and side-effects of cannabinoids and the emerging research on the functions of the endogenous cannabinoid system. However, I was equally interested in examining cannabis as a construct. From this perspective, understanding the use of cannabis must incorporate historical and sociological perspectives on how cannabis has been perceived and used as multiple different phenomena. The range of these phenomena is wide, and includes

understanding and using cannabis as a crop for food and clothing, religious tool, as a formalized medicine, and as a recreational drug and a menace to society. Thus, besides collecting data on user characteristics as well as patterns and motives for the use of CaM, I was also interested in collecting data on the users' narratives related to their use of CaM, especially with regard to examining the lived experiences of medicinal cannabis users and how they constructed their medicinal cannabis use. Further, I was interested in examining to what extent these user narratives were influenced by how medical cannabis use had been presented (and constructed) by the Danish media and social media.

At times, the two perspectives felt antagonistic. During my Ph.D. project, I have often felt that by acknowledging one of these perspectives, I somehow would risk diminishing the other perspective. This was particularly the case concerning my interest in examining and understanding the subjective user experiences with medicinal cannabis. I must admit that I have often wondered whether user experiences would best be understood through the perspective of cannabis as a drug and tied to empirical knowledge about the effects of cannabis or cannabinoids - or whether user experiences should be understood through the lens of cannabis as a construct, and thus be tied to the context and narrative related to medicinal cannabis.

This antagonism led to reflections on where the drug *actually* is situated? Is the effect of the use of cannabis already there to be discovered (cannabis as a drug), or do we produce the effect of using cannabis (cannabis as a construct)? I believe that such questions are indicative of much broader issues related to the research paradigm, a term introduced by philosopher of science Thomas Kuhn in 1962 in the book *The Structure of Scientific Revolutions*, where he discusses the shared beliefs and assumptions regarding the nature of reality and knowledge that exist within various fields of research (Kuhn et al., 2012). The term paradigm refers to variations in ontology, i.e., assumptions about the nature of reality, as well as in epistemology, i.e., assumptions about how we can know the world, variations that often result in differences in research methodology, i.e., the means chosen for gaining knowledge (Lincoln et al., 2011). One could argue that the schism between "cannabis as a drug" and "cannabis as a construct" aligns with the "paradigm wars" between positivism and constructivism, which can be understood as two opposite ends of a continuum. Thus, in line with the positivist ontology, there is a "real" reality that exists separate from our understanding of it. This reality can be approximated through methods that prevent human contamination (Guba et al., 2005). In this perspective, the matter is superior to the mind. However, in constructivist ontology, there may be a real world out there, but it is beyond our direct apprehension. Since all knowledge about the world can only exist as a construct of human consciousness, "reality" is understood as

something we produce as we attempt to make sense of the world. Thus, in this perspective, the mind is superior to matter.

As the two paradigms have mutually exclusive axioms, following either paradigm can lead to different conceptions about what to explore when trying to make sense of CaM. The focus on “cannabis as a drug” aligns with a positivist paradigm, with essentialist conceptions about substances, where drug effects are inherent to the substance itself. The focus on “cannabis as a construct” aligns with a constructivist perspective, where drug effects are not discovered but produced. In the former, the drug is already there, and we simply have to discover its effects through observation while reducing noise from the outside world, such as placebo effects and other biases. In the latter, the drug in itself becomes less interesting. The focus is rather on the subjective and intersubjective experiences of the drug and on discourses and social structures in which the drug is entangled.

The focus on cannabis as a drug is evident in studies exploring the biomedical and clinical effects of cannabinoids in RCTs (Häuser et al., 2018; National Academies of Sciences Engineering and Medicine, 2017) or the surveys exploring the subtype of cannabis used, the dose, mode of intake, conditions treated, experienced effects and demographics of users (Park et al., 2017). Traditionally, such studies pay less attention to the political and historical context of use, stigma and marginalization, and the processes that lead to medicinal use. Conversely, the focus on “cannabis as a construct” is evident in the qualitative studies exploring the process of becoming a medicinal cannabis user and the narratives related to medicinal use (Athey et al., 2017; Lankenau et al., 2018; Pedersen et al., 2013; Pedersen, 2014) or in the policy analyses exploring the re-medicalization of cannabis (Fischer et al., 2015; Lancaster et al., 2017). Traditionally, such studies pay less attention to the biomedical effects of the drug. An illustration of how these foci may exclude each other is the otherwise excellent analysis by Duff detailing how cannabis is “breaking apart” ontologically due to diversification in the social and material relations to the drug (Duff, 2016), barely mentioning cannabinoid research and thereby missing one of the primary ways in which cannabis is truly “breaking apart” in recent years, namely in terms of the opposing nature of its two main components; THC and CBD (Rømer Thomsen et al., 2017).

During my Ph.D. project, I have attempted to employ both ways of thinking about the world because I regard both perspectives as essential for understanding the trend of using cannabis as medicine in Denmark. Inspired by objectives often articulated in mixed methods research, I have thus sought to stimulate a dialogue between different ways of seeing, interpreting, and knowing the object of interest (Greene, 2007; Maxwell, 2010), both in my choice of research

methods and objectives for the three studies (papers). My attempt to stipulate a dialogue between the two perspectives described above is also inspired by Dewey's critique of dualisms, such as the dualism between mind and matter being opposite sides of the same coin (Dewey, 2008). From this perspective, the positivist (cannabis as a drug) and the constructivist paradigms (cannabis as a construct) can be recognized as equally important to the nature of human experience (Morgan, 2014). As explained by Morgan, "*On one hand, our experiences in the world are necessarily constrained by the nature of that world; on the other hand, our understanding of the world is inherently limited to our interpretations of our experiences*" (Morgan, 2014, p. 1048). I also draw on the Zizekian notion of a parallax view, where a change in observational position results in the displacement of the observed object (Zizek, 2009). Zizek explains that the subject gaze is always-already inscribed into the perceived object and therefore, "*the reality I see is never "whole" – not because a large part of it eludes me, but because it contains a stain, a blind spot, which indicates my inclusion in it*" (Zizek, 2009, p. 17). In my view, there is a "parallax gap" between looking at "cannabis as a drug" and "cannabis as a construct", thus the drug is both already there AND we produce it, depending on point of observation.

As mentioned above, my interest was to take on both observational positions when studying my research topic. I have thus been interested in examining cannabis as a drug, for example by describing the subtypes of cannabis that is used as medicine in Denmark, and in how this use is correlated with experienced effects. However, I have also been interested in examining cannabis as a construct and the processes by which cannabis becomes medicine to the users. In the following, I will elaborate on why I find these positions relevant for my research topic.

2.3. Cannabis as a drug

2.3.1. Medical cannabis in history

The cannabis plant has co-evolved with humans since the beginning of agriculture (Schultes et al., 1974), and as a consequence, it is likely unrivalled with respect to its biochemical diversity (Russo, 2007). The medical use of cannabis is as old as the history of medicine, with *Ma-fen* (i.e., 'fruit' of hemp) listed in the world's oldest pharmacopeia, the *Pen-ts'ao ching*, dating back to 2.700 B.C, documenting use of cannabis for pain, constipation and malaria (Touw, 1981). From 1.000 B.C. and onward, there was a vast use of medical cannabis in India (Aldrich, 1997) and clay tablets from the same era, show the use of cannabis for pain, inflammation, epilepsy, but also anxiety, sorrow and depression, among the Akkadians and



Figure 3. Cannabis extract sold under the name "Cannabisol" at a pharmacy in Copenhagen. Photo: Dansk Farmacihistorisk Fond

Sumerians, in what is now modern-day Iraq (Russo, 2017). Europe and North America were late to this practice, as medical cannabis was discovered in 1839 by way of British colonialism in India, and introduced in the west as a cure for cholera (O'Shaughnessy, 1843). However, use spread quickly, and between 1840 and 1900, European and American medical journals published more than 100 articles on the therapeutic use of cannabis (Grinspoon et al., 1995) and widespread use of medical cannabis from the second part of the 19th century up to the first decades of the 20th century is well-documented (Aldrich, 1997; Earleywine, 2002; Mikuriya, 1973; Mikuriya, 1969; Pisanti et al., 2017; Zuardi, 2006). Here, cannabis was used as a treatment of several conditions such as pain, whooping cough, asthma, cholera, epilepsy, rheumatic diseases and tetanus, as well as being used as a withdrawal agent for opiate and alcohol addiction (Aldrich, 1997; Fankhauser, 2002; Mikuriya, 1973). At the height of its use, cannabis tinctures and extracts were available over the counter. They were mass-produced in Germany (Merck), England (Burroughs Wellcome & CO.) and the U.S. (Bristol-Meyers Squibb, Eli Lilly and Company), with commercial names such as "Dr. Browns Sedative Tablets" and "The One Day Cough Cure" (Fankhauser, 2002, 2008). Likewise, at the beginning of 20th century, cannabis extracts and tablets were produced in Denmark (see figure 3), available from pharmacies and promoted in newspapers and magazines for multiple medical purposes (Dahl et al., 2011). This vast and widespread medical use of cannabis diminished in the 20th century due to; 1) the invention of other types of medication with

analgesic and sedative properties, 2) issues related to the standardization of cannabis products and unwanted psychoactive effects, and 3) legal restrictions brought on by prohibitionist tendencies in the U.S. (Dahl et al., 2011; Pisanti et al., 2017; Zuardi, 2006). Eventually, cannabis was prohibited in countries that signed the Single Convention on Narcotic Drugs of 1961. By that time, several legal restrictions had already put an end to formal medical cannabis use (Mikuriya, 1969; Zuardi, 2006).

2.3.2. Cannabis and the endocannabinoid system

In the last century, there have been seismic shifts in our understanding of cannabis and its effects on the human body. The cannabis plant has been a “black box” scientifically until the early sixties. While the active component in opium (morphine) and coca (cocaine) had been discovered more than half a century earlier, the chemical structure of the main components of cannabis, the cannabinoids *tetrahydrocannabinol* (THC) and *cannabidiol* (CBD), were first

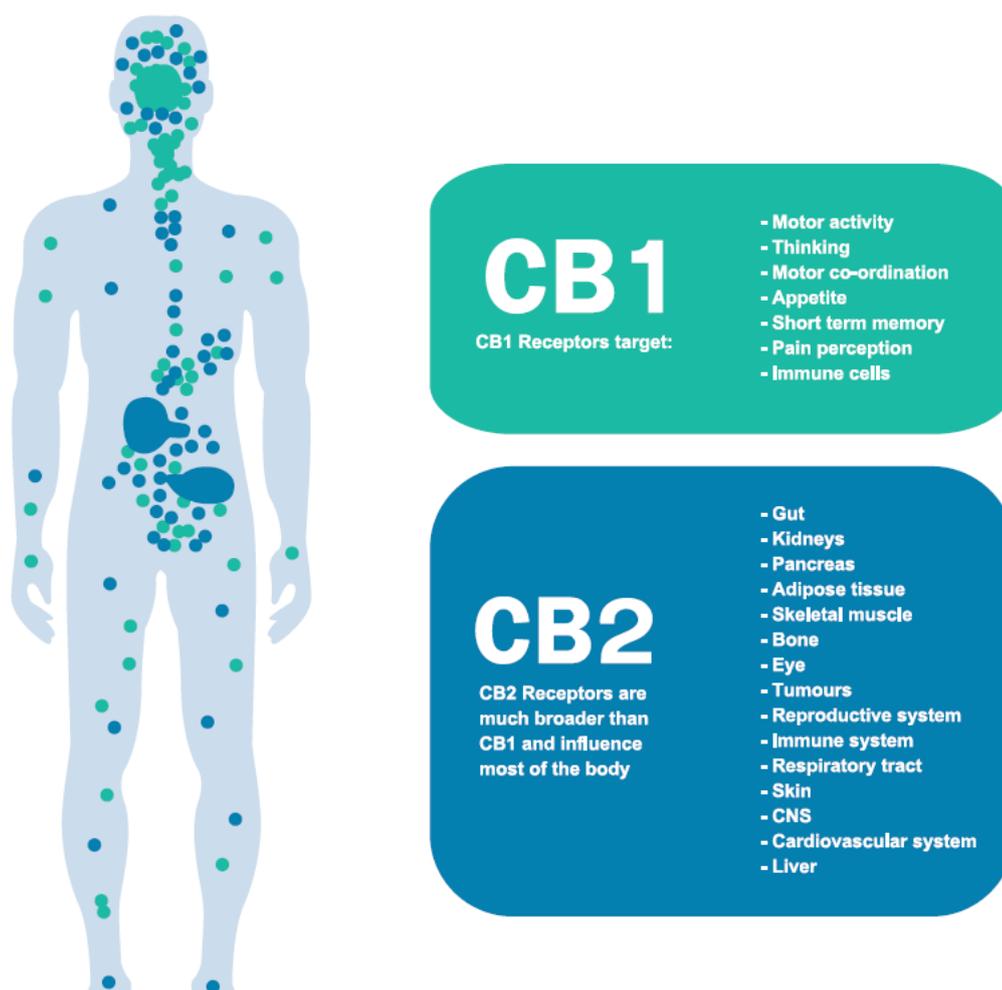


Figure 4. An overview of the endocannabinoid system. Photo acquired from Shutterstock.

described in the sixties by Israeli chemist Rafael Mechoulam (Mechoulam, 2007). At present, more than 500 constituents have been identified in the complex cannabis plant, out of which 125 are classified as cannabinoids, the active components in cannabis, while the rest are passive components such as phenols, flavonoids, terpenes and alkaloids (Radwan et al., 2021). It has been hypothesized that all these components, both active and passive, function in synergy with each other, which has been termed “the entourage effect” (Ben-Shabat et al., 1998), a theory that has gained momentum in recent years (Anand et al., 2021; Russo, 2018). The uncovering of THC and CBD in the sixties sparked a search for the binding site of cannabinoids in humans. In the late eighties, the endogenous cannabinoid system was discovered. This system consists of cannabinoid receptors (the main ones being CB1 and CB2), endocannabinoids (the cannabinoid molecules that we produce ourselves), and substances that break down these cannabinoid molecules (Lu et al., 2020) (see figure 4). The endocannabinoid system is ubiquitous and is involved with the regulation of numerous processes in the body, such as pain, appetite, blood pressure, digestion, immune response, inflammation, memory, stress response, reproduction, etc. (Meccariello, 2020; Moreno et al., 2021; Skaper et al., 2012). The endocannabinoid system exerts its effects on the body through retrograde signalling, where endogenous cannabinoids are produced on demand in the postsynaptic synapse, as a response to neuronal activity, in order to give feedback on neural activity. The goal of this feedback is to maintain homeostasis in the body and brain. Therefore, the system has been described as a “dimmer switch,” a device that allows for the fine-tuning of light, as it protects the brain from being overwhelmed by excessive excitatory or inhibitory activity (Ashton et al., 2011). As the system is involved in maintaining homeostasis in almost all neuronal communication throughout the body, this system is essential in establishing and maintaining human health (Alger, 2013; Kaur et al., 2016). The complexity of the system is immense, but it has been summarized as a system that helps us relax, eat, sleep and to forget and protect our cells (Alger, 2013; Di Marzo, 1998; Russo, 2016).

The discovery of the endocannabinoid system has made cannabinoid research one of the most active fields in neuropharmacology and has led to many patents on cannabinoids or other methods related to targeting the system (De Fonseca et al., 2008; Zuardi, 2006). At present, cannabis or cannabinoids have been found to be effective in treating some medical conditions (see section 1.2.5. *Efficacy of cannabis or cannabinoids*) and targeting the endocannabinoid system holds a potential for the treatment of other somatic and mental health conditions (Cascio et al., 2017; Cohen et al., 2019; Scherma et al., 2020).

2.3.3. Cannabis composition matters

Beyond the increased scientific interest in the medical utility of targeting the endocannabinoid system, research into the main components of cannabis, THC, and CBD, has also informed our understanding of the harmful effects associated with cannabis use. A growing body of evidence suggests that THC and CBD display opposing neural, cognitive, and behavioural effects (Colizzi et al., 2017; Englund et al., 2017; Rømer Thomsen et al., 2017). For instance, THC can produce psychosis-like symptoms and be anxiogenic, while CBD has been shown to produce anti-psychotic and anxiolytic symptoms (Blessing et al., 2015; Scherma et al., 2020). Also, a meta-analysis has found that CBD is well tolerated and has few serious side effects (Chesney et al., 2020), and CBD may mitigate some of the adverse effects of THC (Bonaccorso et al., 2019; Freeman et al., 2019a). Thus, there are great differences between consuming high THC cannabis products and high CBD cannabis products, to the extent that they may be considered as two different types of drugs or at least as opposite ends of a continuum.

At the biomedical level, cannabis products appear to have diversified in recent years, with some subtypes of cannabis becoming drastically more harmful to health while other subtypes are emerging that may be relatively harmless. The relevance of the improved understanding of the complexity of cannabis is apparent in the recent developments in the illegal cannabis market, where the THC content in seized cannabis resin (hash) and herbal cannabis has increased markedly in Europe and in the U.S. (EISOhly et al., 2016; Freeman et al., 2019b; Freeman et al., 2020a) in the last decades. This development has also been documented in Denmark, where I, along with colleagues, showed that the THC concentration in seized hash rose three-fold from 2000 (mean: 8.3%) to 2017 (mean: 25.3%), while CBD levels remained stable (mean around 6%) (Rømer Thomsen et al., 2019). From a public health perspective, the increase in THC content is highly problematic, as a growing body of evidence suggests that exposure to cannabis with high concentrations of THC is associated with a higher risk of cannabis-related harms, such as psychosis (Di Forti et al., 2019; Di Forti et al., 2014), cognitive impairment (Colizzi et al., 2017; Morgan et al., 2018), and cannabis dependence (Curran et al., 2019; Freeman et al., 2015; Freeman et al., 2018).

Meanwhile, another development has also taken place in recent years, where cannabis products high in CBD rapidly have become popular for medicinal use and general well-being, both in Europe (Carrieri et al., 2020; Manthey, 2019) and the U.S. (Corroon et al., 2018; Hazekamp, 2018). As discussed in section 1.1.3 *The medicinal cannabis use*, there are multiple indications that this is also the case in Denmark. Thus, the cannabis market (both illegal, quasi-legal, and legal) is rapidly diversifying, making identification of the sub-types of

cannabis used relevant for the evaluation of the public health implications of medicinal and medical cannabis use.

In sum, the last decades of cannabis and cannabinoid research have greatly improved our understanding of the complex cannabis plant, and this development warrants the perspective on “cannabis as a drug” and the view of medicinal and medical use through an epidemiological, biomedical perspective.

2.4. Cannabis as a construct

2.4.1. Placebo. A meaning response?

A constructivist approach to use of CaM is relevant both at the micro-level of the individual experience of the effect of cannabis use and at the societal level with historically fluctuating understandings of the nature of cannabis. Concerning the experienced effect of drug use, there has long been an understanding of the importance of “non-drug parameters” (Feldman, 1963) shaping drug effects, often conceptualized as *set* (personality, preparation, expectation of and intention for use) and *setting* (the physical, social and cultural environment of use) (Hartogsohn, 2017; Zinberg, 1984) (see figure 5). Research suggests that “non-drug

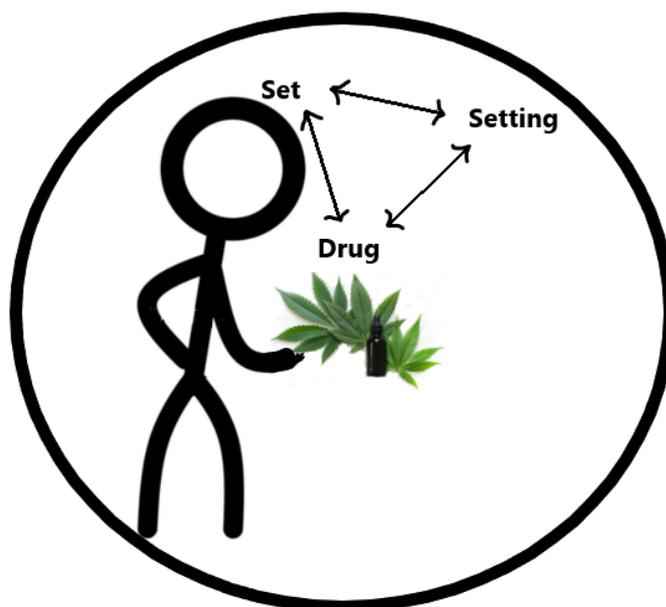


Figure 5. Visualisation of drug, set and setting

parameters” related to *set and setting* make up a substantial part of the therapeutic effects of standard medications (Kirsch et al., 1999; Moerman, 2002), suggesting that drug effects are influenced by various non-drug factors, conventionally categorized as placebo effects. For instance, the effects of a medication have been significantly associated with the branding or labelling of such medication (Branthwaite et al., 1981), with whether the treatment was open or hidden (Amanzio et al., 2001; Colloca et al., 2004) and with the demeanour of the health care provider (Howe et al., 2017). Also, studies have demonstrated the effect of an open-label placebo, where the participants are aware that they receive an inert treatment, on conditions such as pain, IBS, and depression (Charlesworth et al., 2017; Schaefer et al., 2018), suggesting that the act of taking an inert medication can function as a conveyer of meaning, by serving as a repeated reminder to the participants of an encounter with a caring medical professional. Furthermore, some interdisciplinary work on placebo effects has underlined the importance of the meaning that is created in the context of drug use (Moerman, 2002), which has led to the suggestion that the term “meaning response” is more appropriate than “placebo response” (Moerman, 2013). Also, experimental studies on placebo have begun to unravel the underlying mechanisms that link the expectation of relief from pain to descending pain modulatory pathways in the brain (Bingel, 2020). Thus, while placebo effects are conventionally understood as something that should be held constant and eliminated to explore the “true” drug effect, the concept of *set and setting* reminds us that both mind and context are always present when a drug is consumed (Hartogsohn, 2017). As an example, in a comparison of clinical trials with methadone as substitution for heroin in the U.S. and France opposing effects of methadone are found, where in the US the effect of methadone is found to be similar to heroin, while it is found to be different from heroin in France (Gomart, 2002). Through her analysis of these trials, Gomart argues that these opposing drug effects of methadone are not merely differences in interpretation of the measured effects, but that the effects of methadone are produced through particular relations within the trials, as they are “folded into” the practices of observation (Gomart, 2002).

In sum, an essentialist conception of pharmaceuticals, assuming distinct drug effects inherent to the chemical composition of that drug that is stable over time and place, is challenged by the undeniable relevance that *set and setting* play in shaping the drug effect.

2.4.2. The political pharmacology of cannabis

Beyond the importance of the *set and setting* of the individual drug experience, drugs can also be viewed as cultural entities, reflecting specific societal norms and ideas (Cohen et al., 2001; Whyte et al., 2002). In this perspective, drugs are inherently ambivalent multi-functional

phenomena, where we rely on cultural practices when drawing distinctions between drugs as “benevolent cures” and “dangerous toxins.” For instance, through rigorous dosing schedule and medical discourse discarding any pleasurable effects, a stimulant drug (methylphenidate) has become a prescription medication (Ritalin) (Keane, 2008). Conversely, through socialization and distinct consumption practices, euphoric effects can emerge from the non-medical use of prescription drugs (Bundy et al., 2017).

Cultural practices also shape the use of CaM. Within the last 200 years, medical cannabis has gone from being discovered in the West and used widely, falling from grace, and is now being rediscovered (Pisanti et al., 2017). In its relatively brief history in the West, cannabis has oscillated between panacea and menace, substantiating the Foucauldian notion that knowledge, meaning, and “truth” are confined within specific historical contexts (Hall, 2001). Houborg (2012) suggests the term *political pharmacology* denotes such cultural aspects of drugs, noting that the constitution of drugs as particular kinds of entities does not only rely on their biomedical effects but “*also involves the constitution of social identities and social relations, the sanctioning of certain forms of knowledge, and the distribution of power*” (Houborg, 2012, p. 159). Therefore, such factors are relevant to consider when trying to understand why policies and programs for the use of medical cannabis have become more widespread at this current point in time. As an example, Taylor (2008) identified three forces driving the process of re-medicalize cannabis in her exploration of how cannabis came to be understood as medicine in the last decades; 1) The discovery of the endogenous cannabinoid system in the 1980s; 2) The pharmaceutical industry and its interest in the endogenous cannabinoid system, which led to the development and licensing of cannabis-based medicines; 3) The user demand for safe access to medical cannabis (Taylor, 2008). Thus, the medicalization of cannabis has been contingent upon both the production of knowledge related to the endocannabinoid system and the social power relations of the claim makers demanding access to medical cannabis.

In sum, besides focusing on the chemical structures and biological effects of a drug, it is also relevant to focus on the social life of a drug and how it is enacted as a medication (Whyte et al., 2002). Thus, it could be argued that the essentialist conception of drugs as something inherent to only the substance itself risks overlooking the influence that the mind-set of the user and the socio-cultural setting have on the effect of the consumed drug and that *set and settings* constitute important contributing factors that shape drug-related experiences and broader societal trends in drug use. The rationales for studying cannabis as a drug and as a construct played a major role in my initial choice of methods in my Ph.D. project, which I will describe in the next section.

Chapter 3. Method

In this section, I describe my initial choice of methods in my Ph.D. project, the limitations related to the method, as well as reflections and rationale for the methodological choices that I have made throughout the Ph.D. project.

3.1. Research method

3.1.1. Rationale for choosing a web-based survey

A descriptive and analytical cross-sectional survey design was chosen as it is an apt tool for profiling a population or group of interest, providing “*a slice of life at a particular point in time*” (Aday et al., 2006, p. 31). A cross-sectional survey design is advantageous for reaching a large and geographically diverse sample and thus providing large-scale quantitative data on a topic of interest. In this study, an internet-mediated research method was chosen in the form of a web-based survey, as this is cost-effective and less time consuming compared to postal or telephone interviews and has the potential to reach more respondents, as they do not need to be identified beforehand (Heiervang et al., 2011; Kays et al., 2013). Also, the nature of the web-based survey, where responses are captured directly in electronic format, allows for faster and cheaper data collection (Wyatt, 2000) and reduces errors in data entry (Callegaro et al., 2015). Data capture in an electronic format also allows for customization of the survey with build-in skip patterns to hide non-relevant follow-up questions (Van Gelder et al., 2010), making it possible to explore a subsample within the sample without lengthening the survey for all respondents. Moreover, respondents often prefer completing surveys online, as they can answer the survey at their own pace and convenience (Callegaro et al., 2015).

Sensitive topics in hidden populations

However, the primary rationale for using a web-based survey is that the topics of interest, drug use, and personal health status are sensitive. The population of interest is a so-called “hidden population,” where it is difficult to establish who constitutes the population. Questions are sensitive when they ask for a socially undesirable answer, in effect, an answer where the respondent admits to have violated a social norm (Tourangeau et al., 2007). A population is termed “hidden” when no sampling frame exists, when public acknowledgement of membership in the population is potentially threatening and where strong privacy issues are at stake due to illegal behaviour and risk of stigmatization (Ellard-Gray et al., 2015;

Heckathorn, 1997). Indeed, no sampling frame exists for users of cannabis as medicine, as this population does not appear in any register as a whole and no research exists profiling Danish medicinal users in general. Also, public acknowledgement of medicinal cannabis use could potentially lead to criminalization, social stigma (Newhart et al., 2018; Satterlund et al., 2015), and loss of employment. The latter was exemplified by a Danish case, where openness about using low potency cannabis oil cost one nurse her job and jeopardized her authorization (Christensen, 2019). In the case of the current research project, considerations related to privacy and anonymity are particularly relevant, as the focus is drug use and personal health status, which are sensitive topics. Thus, a method that creates an atmosphere of privacy and anonymity will be more likely to produce accurate and less biased data (Kalogeraki, 2011).

Privacy, anonymity and convenience

Internet-mediated research methods, such as web-based surveys, hold several advantages when researching sensitive topics in hidden populations, as they offer enhanced anonymity, privacy, and convenience (Barratt et al., 2015a). Web-based surveys have been shown to promote more honest responses and self-disclosure (Heiervang et al., 2011; Joinson et al., 2007), as an electronic survey that is filled out in privacy on a personal laptop or smart-phone creates perceived anonymity that reduces the vulnerability associated with answering sensitive questions (Joinson et al., 2008). As an example of this dynamic, a recent experiment found that estimates of non-heterosexual prevalence in the U.S. increased as the privacy and anonymity of the survey administered increased (Robertson et al., 2018). Web-based surveys have increasingly been used to successfully access hidden populations of illicit drug users (Duncan et al., 2003; McCabe, 2004; Miller et al., 2010), exploring the use of ecstasy (Scholey et al., 2004), non-medical opioids (Katz et al., 2008), cannabis (Barnwell et al., 2006) and drug use in general (Miller et al., 2007). Based on more than a decade of experience, it has been argued that web-based surveys are the best available method for effectively targeting hidden populations of illicit drug users (Kalogeraki, 2011; Miller et al., 2010).

Further, to preserve an atmosphere of privacy and anonymity, it was decided not to collect IP addresses, which is a conventional method for excluding potential repeated participation (Eysenbach, 2004). International research on growers of cannabis has found that the inclusion of a statement alluding to the issues of digital surveillance caused suspicion among respondents (Barratt et al., 2015b). Consequently, a decision was made not to mention IP addresses to respondents. IP addresses were available to Ramboll, the company hosting the software tool SurveyXact, in which the survey was created (Ramboll, 2014), and they could have been made available to the researcher. Choosing not to have them available meant forgoing an opportunity to identify potential repeated participation; thus, preserving an

atmosphere of anonymity was deemed more important than avoiding this risk. Also, it is following the ethical guidelines of the Helsinki Declarations with respect to anonymity, to limit the amount of potentially identifiable data collected when possible. With respect to repeated participation, it is unlikely that someone would be incentivized to answer a 15 minutes survey multiple times. If someone with sophisticated programming skills (i.e., a hacker) designed software to make multiple responses, they would also be able to vary their IP address (Bowen et al., 2008), making collecting them less effective. Nonetheless, the risk of repeated participation was mitigated by the decision not to offer reimbursements or other financial incentives for participating in the survey, as this can increase the prevalence of repeated participation (Teitcher et al., 2015). Also, a previous study on medicinal cannabis use has found that this demographic was highly motivated to share information on use (Ware et al., 2005), suggesting that the use of financial incentives to increase participation may be superfluous when recruiting medicinal cannabis users.

In conclusion, an anonymous web-based survey was found advantageous because it is a cost-effective method for reaching a large hidden population and is an apt tool for exploring a sensitive topic. It provides an atmosphere of privacy and anonymity which produces less biased data. However, there are also some disadvantages to using a web-based survey concerning external and internal validity and reliability of the data produced, which I will now explore.

3.1.2. Limitations of the chosen method

External validity

The concept of validity refers to the accuracy and trustworthiness of instruments, data, and findings in research (Bernard, 2017), thus addressing whether we measure what we aim to measure. External validity assesses the generalizability of the study, i.e., how well the subsample collected infers to the targeted population (Ball, 2019).

When using a web-based self-selected survey to explore the use of CaM, there are some limitations to consider with respect to external validity. Limitations associated with non-random sampling may inhibit valid inference from the sub-sample collected to the population of interest (Bernard, 2017; Kalogeraki, 2011). Indeed, when the respondents are self-selected, and data is collected online, there is a high probability of non-random sampling or selection bias, as some users of CaM may be more inclined to participate compared to others, and those eager to participate may differ systematically from the population of interest. Such potential differences may be multiple; first, the respondents may weigh towards those with internet

access, familiarity with online surveys, and the resources to answer such surveys (Bernard, 2017; Wyatt, 2000), which may bias the sample toward upward socioeconomic status (Aday et al., 2006). I sought to mitigate such limitations by allowing someone next of kin to answer the survey on behalf of some who cannot answer due to illness or old age. Also, research from the year that the survey data was collected shows that Danes are fairly “tech-savvy,” ranking among the highest in Europe, as 93% of Danish households had an internet connection and 74% of Danes between 16-89 years used social media (Tassy et al., 2018).

Second, the respondents may weigh towards those with positive experiences with medicinal cannabis use, as such users will be more likely to identify as “users of cannabis as medicine.” In contrast, users with negative or neutral experiences may have disengaged from the topic and may be less interested in answering a survey on the use of CaM. Third, respondents will weigh towards those who become aware of the survey’s existence at the time of recruitment. In my project, I cannot rule out that exposure to information about the survey may not have been randomly distributed, and thus may weigh towards users with a connection to social networks where the survey was distributed or towards users that were open about their medicinal use and therefore were made aware of the survey by next of kin. Fourth, respondents may weigh towards users who trust academic institutions to handle their personal data, protect their anonymity, and towards users who appreciate the value of exploring the topic.

In sum, when using a web-based survey to explore a self-selected convenience sample, subsamples of the targeted hidden population may be systematically excluded, thus limiting the external validity of the study, as oversampling from socially advantaged groups characterized by trust in institutions and internet access cannot be ruled out, as well as oversampling of users with positive experiences engaged with the topic online.

Internal validity

The term internal validity refers to the trustworthiness of the data produced, and *concerns the degree to which we actually measure the concept we truly wanted to measure* (Callegaro et al., 2015, p. 234). Certain types of response biases may increase the discrepancy between the answers given in the survey and the true value, as self-reported data may be prone to social desirability bias (Althubaiti, 2016; Krumpal, 2013). Despite the atmosphere of privacy created through anonymous web-based surveys, respondents may still be inclined to report the answers that they perceive to be socially desirable, which can skew data systematically. Social desirability bias is not only motivated by impression management, where respondents

bias their answers to gain social approval, but also by self-deception, where answers are biased to enhance self-perception and preserve a positive self-image (Stocké et al., 2007). Also, respondents may perceive themselves to be stakeholders in the outcomes of potential survey findings and may consequently exaggerate the effects of cannabis and underreport adverse effects or dose of cannabis used. To reduce social desirability bias, all questions in the survey used in the present study were framed with respect to their sensitivity in wording (Näher et al., 2012). For instance, the wording of all questions was kept neutral and non-judgmental, and the list of potential conditions treated with cannabis was exhaustive and in alphabetical order, signalling the inclusion of all types of use. Also, a decision was made to exclude screening tools for problematic use (for more see section 3.3. *Reflections on screening for problematic use*).

Reliability

The concept of reliability refers to the consistency of the results produced, i.e., the stability of the responses across repeated measures (Callegaro et al., 2015). Some aspects of the chosen method may decrease the reliability of the data produced. When the researcher does not observe the data collection process, the environmental factors (noise, interruptions, respondent's mood, etc.) are out of the researcher's control, which can challenge the consistency of the data produced. For instance, web respondents may be multitasking, and involved in other activities that disturb their concentration when answering the questionnaire, causing them to give superficial answers to survey items. Naturally, a paper questionnaire does not alert the respondent that their friend just sent them a cat video, but their smartphone might do just that. Also, while online surveys offer privacy and convenience for respondents, such conditions may also lower the commitment to complete the survey, as respondents can "break off," i.e., leave prematurely, before answering the last question of the survey (Callegaro et al., 2015; Heiervang et al., 2011; Sue et al., 2012). Indeed, a meta-analysis has shown that administered surveys have a higher response rate than web-based interviews (Manfreda et al., 2008). Moreover, the absence of an interviewer when the survey is completed also forgoes the opportunity to clarify survey questions, thus trading reliability for the validity of the data produced, as the presence of an interviewer could potentially increase the risk of social desirability bias (Bernard, 2017). Another challenge to reliability can be multiple interpretations of the same survey question. In order to mitigate this challenge, the items in the survey exploring patterns of use and motives for use were designed with inspiration from previous surveys exploring the use of cannabis as medicine (Grotenhermen et al., 2003; Hazekamp et al., 2013; Schnelle et al., 1999; Sexton et al., 2016; Swift et al., 2005; Ware et al., 2005). To improve the reliability of the survey, all items were framed to avoid ambiguity; however, I

cannot rule out that some of the wordings of the items may have resulted in multiple interpretations and thus decreased the reliability of the survey (Ball, 2019). However, to avoid this, the survey was tested through pilot interviews with medicinal users, others with knowledge about the field, and lay people (see section 3.3.3 *Testing the survey*) to ensure that all questions related to the items were perceived clearly by respondents. Given that the purpose of my Ph.D. project was exploratory in nature, that is, interested in mapping a new area related to drug use in Denmark; the survey did not make use of large batteries of validated items exploring background variables or concepts, such as political opinions or social status. An exception was using the VAS-pain score, which has been validated (Delgado et al., 2018).

In conclusion, the method of a cross-sectional design using a web-based survey was chosen as it is cost-effective, expedient and convenient for covering a large and geographically dispersed sample, but most prominently because it is the most effective way of exploring sensitive topics in hidden populations. The chosen method presents some issues related to validity, particularly concerning problems of generalizability of survey findings to the population of interest and the potential for social desirability bias among respondents.

3.2. Further method reflections

3.2.1. Reflections on external validity

An estimate of the prevalence of use of CaM in Denmark, and the possibility of making inferences from a sub-sample of users to the population of users, would have required drawing a probability sample from the general population (Dawson et al., 2004). However, this method was not desirable given the purpose of the study. Firstly, it should be noted that an estimate of the number of medicinal cannabis users in Denmark was less relevant at the initiation of the project, as one such estimate already existed at the time (Damløv, 2016), showing that 4% of Danes used unregulated cannabis as medicine, reported as at least 50.000 persons given the statistical uncertainty related to the poll conducted by the polling company Epinion. Secondly, the use of probability sampling methods in the investigation of hidden populations is limited, particularly when the behaviour of interest is less prevalent (Barratt et al., 2015a), and using this method would have likely resulted in a lower subsample of the target population; users of cannabis as medicine. Thus, in the current project, a greater volume of data on the use of CaM was preferred over prevalence estimates and inference to the population, as the experiences of a large number of self-selected respondents were valued over the experiences of a smaller number of respondents whose experiences were inferable to the population. This

is due to the research questions, where the object of interest is the experiences and practices of users of CaM.

Consequently, the present Ph.D. project was projected to unveil some aspects of the phenomenon in greater detail while failing to explore other aspects. For instance, the method chosen will likely lessen the focus on those that may have tried CaM and discontinued use, as they may be underrepresented in the convenience sample. Moreover, this project is less interested in estimating the prevalence of the phenomenon of using cannabis as medicine and more interested in the practices and experiences of a large subsample of the population of users. Therefore, the sample is both a convenience sample, as it is a sample convenient to the researcher, and it is also a purposive sample (Bernard, 2017), as it is based on characteristics that are deemed relevant for the study. Purposive sampling techniques have been used frequently in drug studies with hidden populations, where a combination of snowballing or network sampling and advertisement online on websites, forums, and chat-rooms, has resulted in the successful recruitment of large subsamples of illicit drug users (Barratt et al., 2010; Borodovsky et al., 2018; Miller et al., 2010). Also, when little is known about the phenomenon of interest, exploratory methods are relevant for generating hypotheses that can inform future confirmatory studies of pre-set hypotheses (Tukey, 1977). Therefore, when exploring the topic use of CaM in Denmark, where much is unknown, the use of a web-based survey exploring a purposive self-selected sample was considered the best method.

3.2.2. Reflections on screening for problematic use.

Much consideration was given to whether to include a screening tool for cannabis use disorder (CUD) in the survey. When given access to a population of cannabis users, it is relevant to monitor potential adverse consequences of use, including CUD. This focus is particularly relevant in relation to cannabis used with a medicinal purpose, as the use of cannabis with the purpose of controlling adverse symptoms of a medical condition may make cannabis more rewarding, and the lack of formal medical guidance in dosing in a clinical setting may increase the risk of uncontrolled use. In particular, the “The Cannabis Use Disorders Identification Test-Revised” (CUDIT-R), an 8-item self-report measure of problematic or harmful cannabis use within the past six months, was considered a screening tool, as it is frequently used and has been validated for population surveys of adult cannabis users (Adamson et al., 2010; Anaheim et al., 2008). However, recent confirmatory factor analysis indicates that the CUDIT-R has a poor fit when applied to a sample of medicinal cannabis users (Loflin et al., 2018),

which raises questions about the appropriateness of its use for this population. As an example of this poor fit, the second item in the CUDIT-R asks how many hours the user is “stoned” on a typical day when using cannabis, ranging from “less than 1” hour to “7 or more” hours. Thus, intoxication when using cannabis is presumed in each possible response, as the CUDIT-R was designed to explore problematic use among recreational cannabis users. Several other items also assume intoxication or inebriating effects of cannabis use. However, research shows that medical cannabis users report dosing regimens with small controlled doses and timed intake to avoid intoxication, in order to accommodate other activities, and maximize role functioning (Newhart et al., 2018).

Also, with the apparent popularity of low-potency cannabis products, it is likely that a proportion of the medicinal users in Denmark do not experience any intoxication when using cannabis. Including a screening tool with items that assume intoxication could potentially damage the trust between respondents and the researcher, which is important for the willingness to participate (Bosnjak et al., 2002; Fang et al., 2012), as it would display a lack of knowledge about the target population and their patterns of use. Moreover, conventional screening tools for problematic cannabis use generally give considerable weight to the frequency of use and patterns of use, where daily use and use before midday are seen as indicators of problematic use. However, such patterns of use may not be problematic when the motive for use is medicinal (Sznitman, 2017). Thus, using such a tool could potentially produce invalid findings suggesting a higher degree of CUD among medicinal users than is the case. Also, introducing a battery of questions that is a poor fit for the population could potentially increase break-offs, as it may damage the respondent’s confidence in the study and the researchers’ understanding of the topic, if presented with questions that assume intoxication. In sum, it was decided not to include a screening tool for cannabis use problems, as it was not a primary focus of the project and inclusion of screening tools lacking sensitivity to medicinal use could potentially overestimate adverse outcomes.

3.2.3. Reflections on adjusting the scope of the Ph.D.

In the initial Ph.D. proposal, my plan was to conduct a web-based survey as well as 25 interviews with medicinal cannabis users, thus making the project a mixed-methods approach (see also section 2.2. *Cannabis. A drug or construct – on paying attention to research paradigms*). A decision was made to conduct the quantitative part of the study first, as this would access the “hidden population” of users and enable recruitment for the qualitative interviews. The purpose of the 25 interviews was to explore cannabis as a construct, primarily

by exploring paths to becoming a medicinal cannabis user, potential challenges and stigma related to use, as well as motives for use and experienced effects of medicinal cannabis use. This part of the study planned to recruit the 25 interviewees from two different groups of medicinal users; novices and those with extensive recreational experience who had developed medicinal use on a gradual transition from recreational use. However, I conducted and transcribed four interviews before the decision was made to adjust the scope of the Ph.D. to focus on the available survey data only. This decision was made for three reasons. Firstly, the quantitative study generated an impressive amount of data, thus making it possible and compelling to do more than three articles on this data alone. Secondly, collecting intimate details about a person's life, medical history, and drug use face to face was problematic when it was uncertain if there was enough time in the Ph.D. period to make good use of this data also, particularly when more than 3.000 people had already spent time sharing personal information in the survey. Thirdly, while discontinuing qualitative data collection meant foregoing the opportunity to explore the lived experience of Danish users of medicinal cannabis anno 2019, I found that it was important to prioritize the publication of quantitative data on the topic. While some, but rather scarce, qualitative data already existed from Norway (Pedersen et al., 2013) and Denmark (Dahl et al., 2011), no quantitative studies in Europe had explored the substitution of prescription drugs or the role of recreational experience when becoming a user of medicinal cannabis. In sum, the considerations above led to prioritizing the survey data that was already collected. As a consequence the qualitative method is not described in detail in the thesis.

However, my decision to adjust the scope of the Ph.D. project and discard the qualitative part of my initial Ph.D. project has had implications for the project and its ability to address certain aspects of my research questions. Qualitative research uses non-numerical data to explore individual experiences and how these individuals make sense of their experiences (Strauss et al., 1998; Zohrabi, 2013). By doing this, one may argue that qualitative research allows for a more complex and multi-layered reality of the lived experience of these individuals (Polkinghorne, 2005) and thus the "how's and "why's" of a social phenomenon (Mohajan, 2018). Consequently, without the planned qualitative data, it has been difficult to explore certain aspects of my research questions with regard to why people use cannabis as medicine, especially in terms of the individual and social processes involved in becoming a medicinal cannabis user in the absence of formal medical guidance. Moreover, the use of qualitative methods allows for a more exploratory approach that could have contributed to more knowledge on other relevant aspects of the use of CaM in terms of motives for use, challenges or dilemmas related to use, and perhaps identification of sub-groups of CaM users that were not "visible" through analysis of the survey data. Finally, using a mixed-method approach could

have allowed for an exploration of the validity of the quantitative data on experienced effects and side-effects of use. For instance, through the four interviews that I did conduct, I found that two of the interviewees mentioned potential side effects from the use of CaM, while having reported experiencing no side effects from use of CaM in the survey. Lastly, foregoing qualitative data limited the possibility of exploring the paths to becoming a medicinal cannabis user and how the meaning attributed to the use of cannabis may have changed over time. Consequently, the thesis does not explore cannabis as a construct in the way that was initially planned; however, I have aimed to include the perspective on cannabis as a construct, specifically concerning the paths to becoming a user of medicinal cannabis, in some of the analyses of the quantitative data, see section 4.1. *Key findings from the three studies.*

3.3. Survey design

3.3.1. Inspiration for the survey

A literature search was conducted to explore existing research on both medical and medicinal cannabis use, utilizing qualitative and quantitative methods. To explore the use of cannabis as medicine in Denmark, a novel survey was designed, drawing inspiration from several existing quantitative studies, utilizing surveys when exploring either medicinal or medical cannabis use or both (Grotenhermen et al., 2003; Hazekamp et al., 2013; Reiman et al., 2017; Reinerman et al., 2011; Sexton et al., 2016; Swift et al., 2005; Ware et al., 2005; Webb et al., 2014). These studies inspired the items related to patterns of use, conditions treated, experienced effects, symptoms relieved, and side effects experienced when using cannabis as medicine. For instance, the item exploring the experienced effects of cannabis on symptoms was inspired by Sexton et al. 2016. The item exploration of frequency of use was inspired by Ware et al. 2005. However, with respect to subtype of cannabis used, the available answers were tailored to the Danish population of users according to knowledge about available products in the unregulated market and generic terms for such products in online discussion forums and at the open illegal drug scene Christiania (see figure 2). Consequently, “THC-oil” and “CBD-oil” were added as potential reply categories to capture nuances in subtypes of oil used. However, they were rarely included in the existing literature. The relevance of distinguishing between subtypes of oil products reflects a rapid change in the illegal cannabis market in recent years (Hazekamp, 2018; Manthey, 2019), which may explain the absence from previous surveys of earlier date and could limit the ability to compare survey findings to other countries.

The list of potential conditions treated with cannabis was made from overlapping all surveys mentioned above. Also, the survey was inspired by reading multiple testimonials on use from medicinal cannabis users online and unofficial guidelines for medicinal cannabis use on social media. Other conditions were added to the list of potential conditions treated with cannabis from the observations made here. Through observations of medicinal users online arose the idea to quantify experiences with improved sleep, as many testimonials underscored the positive effects of medicinal cannabis on sleep patterns, often noting improvements in numbers of hours slept. Testimonials from users on social media also inspired items inquiring into the positive aspects of using cannabis as a medicine in daily activities, as testimonials often highlighted experiences of cannabis use increasing their ability to handle practical chores or partaking in social events. Thus, the project was inspired by an approach called Netnography, drawing together the terms Internet and ethnography (Kozinets et al., 2014), as social media allows researchers to approach cultural phenomena in their local context. Here, vast amounts of content are created which can be searched through and utilized as a window into a naturalistic setting, allowing the researcher to “lurk” non-intrusively at the population of interest (Kozinets, 2010; Kozinets et al., 2014).

Further, the survey was informed by the opportunity to interview a Danish pain specialist who had become known in Denmark for her willingness to prescribe cannabis-based medicines. Here, I was able to query her prescribing practices with medical cannabis and her perceptions about the user demographic in her consultation and her knowledge on the users experiences with navigating the illegal cannabis market, as many were already medicinal cannabis users when they sought a prescription for medical cannabis. In this context, I was inspired to include a VAS-pain score (Jensen et al., 2003), exploring the pain intensity without and with the use of cannabis among the medicinal users who indicated relief of pain. Lastly, the survey was inspired by qualitative studies on medicinal and medical cannabis use, exploring stigma (Satterlund et al., 2015), gender differences (Bottorff et al., 2011), the process of initiating use with a medical motive (Athey et al., 2017; Lankenau et al., 2018), or the phenomenon of medicinal cannabis use in general (Dahl et al., 2011; Pedersen et al., 2013). These studies inspired questions exploring access and stigma related to cannabis and the construction of an ordinal scale exploring the degree of previous recreational experience.

3.3.2. Content of survey

The survey consisted of 42 structured questions and 21 follow-up questions, answered in a yes/no format, multiple-choice response, or rating scales. The questions were divided into six

thematic sections; 1) Motives for use, 2) Substitution of a prescription drug, 3) Patterns of use, 4) Becoming a medicinal cannabis user, 5) Access and stigma, 6) Attitudes and demography (See Appendix 4). As the survey was self-administered, the text in the survey was the main communication tool in the researcher-respondent interaction, making it an important avenue for conveying the importance of the survey, providing instructions, and ensuring motivation (Callegaro et al., 2015). Consequently, meta-communication was used to inform respondents of the survey's progression and the upcoming section's topic, such as *“That was the first part of the questionnaire. Thank you for helping us uncover the use of cannabis as a medicine. The next part contains questions exploring the paths to becoming a user of cannabis as medicine”*.

Forced responses, i.e., where respondents cannot move further through the survey until an answer is given to a specific question, were only used for questions on conditions treated and evaluation of potential effects of use. Connecting the use of cannabis to a specific condition was considered essential for defining respondents as “medicinal users,” and with the evaluation of effectiveness, the intent was to force respondents to give their best estimate. While forced responses may eliminate missing data, it may also increase break off rates (Décieux et al., 2015; Stieger et al., 2007), and it is arguably in violation of the participant's right not to give answers to specific questions, as consent to participate is an ongoing process (Mahon, 2014). Therefore, all other questions included the option of a non-substantive response (e.g., “Do not know” or “Do not wish to answer”).

Beyond the conditions listed in previous surveys and conditions mentioned by users in testimonials online, treatment of types of addiction and several mental health conditions were added to the list to explore users' perception of cannabis as medicine for such conditions. Much consideration was given to the length of the list of conditions treated with cannabis, as it was long and could therefore be overwhelming for respondents to orient themselves in. The purpose of having many conditions represented in the response categories was to create a non-judgmental atmosphere signalling inclusiveness of all types of medicinal cannabis use. Qualitative research shows that users of cannabis as medicine are at times uncomfortable with claiming legitimacy as a medical user in cases where the condition treated is not immediately visible and have a certain severity (i.e., MS, cancer, epilepsy, etc.) (Lankenau et al., 2018; Newhart et al., 2018). Thus, having an extensive list of conditions was considered a tool for increasing comfort related to reporting on the use and experienced effects. Breaking the list up into categories of somatic and mental health conditions for a better overview was considered; however, that could make respondents aware of the distinction between somatic and mental health conditions and thus self-aware of legitimacy issues related to their use.

3.3.3. Testing the questionnaire

Testing of a questionnaire is essential for identifying whether the respondents understand the questions and whether the meaning of the questions is the same for all respondents (Kelley et al., 2003) to improve the reliability of the questionnaire. Testing allows for the discovery of issues related to question wording, question order, and questionnaire length to mitigate potential sources of measurement errors and non-response bias (Callegaro et al., 2015). When using web-based surveys, additional attention must be given to technical issues related to the web mode, such as digital appearance, consistency across devices, and proper branching (Callegaro et al., 2015). Previous international research exploring cannabis growers shows that pilot feedback from individuals in the targeted population can greatly improve the validity and acceptability of the questionnaire among respondents (Barratt et al., 2015b).

Prior to launching the survey, it was tested through nine pilot interviews with users of medicinal cannabis and through feedback from others who reviewed the survey; fellow drug researchers, lay people, and selected others with insight into the topic of cannabis as medicine. Interviewees for pilot interviews were recruited through word of mouth and through a network of medicinal cannabis users in central Aarhus (discovered via Facebook), which was also present in other large towns in the country (Canna-cafe, 2021). This network consisted of several experienced medicinal cannabis users who had taken it upon themselves to guide novices in use and supply them with cannabis products for medicinal use. Recruiting through this network allowed for great diversity in users concerning age, gender, and experience with medicinal use. While completing the survey, the interviewees were encouraged to “think out loud” when reading, thinking about, and answering each question, inspired by cognitive interviewing techniques (Miller et al., 2014) and give the researcher feedback on both content and form of the survey. The interviews were about an hour long and were conducted at a place selected by the interviewees themselves, either at Aarhus University, in the users’ private home, or in the community centre, where the network of users would meet regularly.

Based on the testing and feedback, the survey was modified mostly related to the clarity of the questions and the inclusion of response categories or items suggested by the interviewees. For instance, the conditions “Stress,” “Chronic nerve inflammation,” “Endometriosis,” and “Psoriatic arthritis” were added to the list of conditions treated with cannabis. Also, the item exploring whether the users had asked their doctor for medical cannabis was added after the realization that some of the medicinal users that were interviewed were eligible for the Medical Cannabis Pilot Program. Still, they preferred the

illegal market to avoid stigma and potentially a rejection from their general practitioner. Modifications to the inclusion criteria of the survey and mode of survey response were also made due to insight from pilot interviews. The possibility of proxy response, i.e., letting a relative fill out the survey, was included, as an older user (<80 years), who taught computers to the elderly, estimated that only some 20% of the elderly would be able to answer the survey.

The decision to include legal, medical cannabis users was made following a pilot interview with an experienced medicinal user, who guided others in the use of medicinal cannabis and provided them with cannabis. They had personally obtained legal, medical status while continuing to use illegally sourced cannabis. They had sought a prescription for medical cannabis, not intending to fill it out but intending to justify the presence of small amounts of THC in their body as they were subjected to random workplace drug testing. Hence, including legal medical users made it possible to explore such potential overlaps of legal status with co-occurring unregulated cannabis use. Fellow drug researchers provided comments about the wording of the survey, suggestions to explore the purpose for use (symptom treatment, cure, or mitigating side effects of other treatment), and comments on the item exploring the degree of previous recreational experience.

Other experts provided valuable objections; Professor Lene Vase, a pain researcher at Aarhus University, guided the wording accompanying the VAS scale. Cannabis Denmark, an organization in contact with many medicinal users, advised on several items and estimated the average user's knowledge on items such as dosing and potency of products. Further, lay people reviewing the survey commented on the wording. They also found inconsistencies in the survey layout and setting, such as issues with skipped questions or errors in multiple single reply options. Before launching the survey, it was piloted with 20 non-users to identify remaining errors and estimate an average length of completion (15,3 minutes, range 6-28). Thus, the survey did not exceed the recommended length of 20 minutes for web-based surveys, after which response quality is known to decline (Callegaro et al., 2015; Revilla et al., 2017), which is understandable as it corresponds with the amount of time an adult can concentrate on a task without becoming distracted (David Cornish et al., 2009).

3.4. Inclusion criteria and Ethics

Inclusion criteria were having experience with the use of cannabis for medical purposes, i.e., both prescription cannabis and illegally sourced cannabis. Thus, the term CaM (cannabis as

medicine) used in articles 1 and 2 covers both medical and medicinal cannabis use. It was possible to answer on behalf of someone next of kin.

Data collection for this project was reported to a publicly accessible database before initiating recruitment (Danish Data Protection Agency), which is a requirement when collecting data involving human subjects. The data gathered from the respondents was stored on secured servers at Aarhus University. Under Danish law, no Ethics approval is required for conducting a survey. Still, procedures for developing the survey, as well as recruitment, data management, and dissemination of findings, were guided by the Declaration of Helsinki regarding medical research with human subjects, including research on identifiable human material and data, developed by the World Medical Association (World Medical Association, 2013). The articles of the Helsinki Declaration are developed in the context of medical studies, but they are relevant for all research involving human participants, as they stress the responsibility and duty of the researcher with respect to issues such as; privacy and confidentiality, informed consent, risks, burdens and benefits of participation, research in vulnerable groups and research registration and dissemination of results. Throughout the thesis, I will point to considerations where these ethical principles have guided my decision-making process.

3.5. Recruitment of respondents

3.5.1. Recruitment strategy

Survey data was collected from July 14th to November 1st, 2018. To create awareness of the survey, material was made describing the survey in terms of purpose and scope of the study, and practical information about where to find the survey (see Appendix 3). A shortened URL (crf.au.dk/cannabis) and QR-codes that could be scanned with a smartphone directing potential respondents to the survey were made in order to give potential respondents easy access to the survey. The material was distributed via flyers, posters at targeted locations, and digital versions of the material online. The recruitment strategy was based on targeting four different populations (see figure 6).

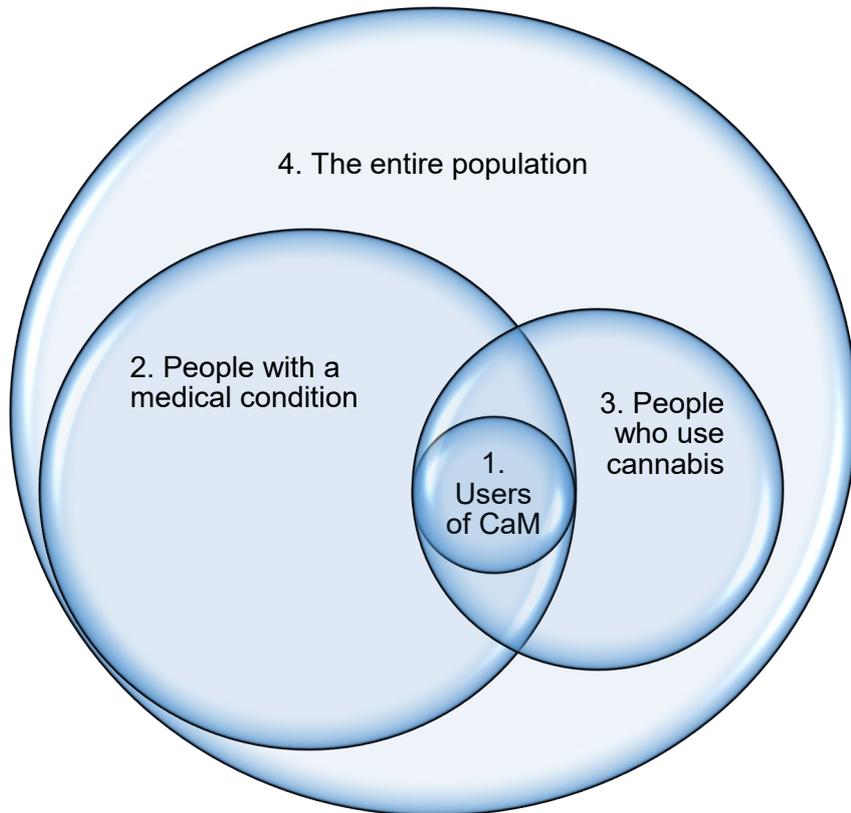


Figure 6. Overview of the four populations targeted for recruitment

1. Users of cannabis as medicine

The first target for recruitment was the users of cannabis as medicine, the primary target population of the survey. These respondents were targeted on social media in multiple groups where medicinal cannabis use was a theme. They were also targeted through the organization Cannabis Danmark, a patient organization formed in 2017 dedicated to helping Danish patients gain access to legal, medical cannabis. Cannabis Denmark shared the survey multiple times on their social media pages and sent it to their members via their newsletter. Also, users of cannabis as medicine were targeted at places where medicinal users buy their cannabis; in physical stores (head-shops) selling cannabis oil and cannabis paraphernalia (grow equipment, seeds, paper for joints, etc.), through an online seller of cannabis oil marketed for medicinal purposes and in the open illegal drug scene Christiania in Copenhagen. In physical stores, posters were hung, and flyers were distributed to customers. One online seller of cannabis oil assisted with recruitment, as they sent information about the survey in their newsletter (Oils by Simpson, 2018), reaching 10.000 subscribers by their

account, which is plausible as they have 3.600 reviews on Trust pilot (Truspilot, 2021). The survey was also shared in the network on Facebook of medicinal users created by Claus Mofte, the man convicted of selling cannabis oil and other cannabis products to some 6.000 Danes (Toft, 2017). Another online seller approached me with an offer of sending information about the survey to 20.000 users of cannabis as medicine, which they claimed to be in contact with, provided that the Center for Alcohol and Drug Research advertised their online shop selling cannabis products. This was declined, and the seller was encouraged to share information about the survey on their own accord.

Moreover, medicinal users were targeted at the open illegal drug scene Christiania, a place where users of cannabis with medicinal purposes have been reported to frequent in recent years (Færch, 2013; Jensen, 2013), where posters were hung and flyers distributed and left for users to find them at cafes. Two sellers were approached, and during the conversation with them, I was told that the “mood” among sellers in the market was not good due to frequent police raids. They advised against contacting other sellers but agreed to distribute flyers to customers and pass them on to other sellers at Christiania. Lastly, medicinal users were recruited at a Cannabis exhibition named North Grow Expo. The project was given a stand from which information about the survey could be presented, and I was invited to give a talk on the background of the project. Also, posters and flyers were distributed throughout the Expo (see figure 7). This North Grow Expo was held for the first time in 2018 in Copenhagen and again in 2019 in Herning. It was a three-day event with an entrance fee (15-40 €) exploring everything in cannabis, with stands of sellers of cannabis paraphernalia from all over Europe and a program of speakers, entertainers, and debates (Krog, 2018; Nielsen, 2018).



Figure 7. Photo taken by me of a recruitment poster hung at the North Grow Expo, just below a poster advertising cannabis gum.

2. People with a medical condition

The second population targeted with information about the survey was people with a medical condition, as they could potentially be users of cannabis as medicine. This population was targeted in the relevant doctors' offices and hospitals with the help of doctors from Clinical Cannabis Forum, an organization founded in 2018 dedicated to sharing medical cannabis research (Cuculiza, 2018). Systematic distribution of posters and flyers to waiting rooms, hospitals and general practitioners was considered, but eventually rejected due to the negative opinions that many doctors had expressed. Also, the waiting room setting at the general practitioners was deemed inappropriate for recruitment due to the ethical considerations on privacy for potential respondents, as recruitment in a waiting room setting leaves them potentially vulnerable to the exposure of their medicinal cannabis use to medical professionals. Parallel to this, Danish patient organizations were contacted and asked to aid in distributing survey material. While all patient organizations were positive about the topic and willing to help, some organizations merely allowed posting information on their social media pages. Other organizations posted the survey themselves, thereby giving it a broader reach and

lending the organization's trust to the project (see figures 8 and 9). Some patient organizations (Danish Cancer Society, Danish MS Society, Danish Epilepsy Association, and the Danish Fibromyalgia and Pain Association (Epilepsiforeningen, 2018; Fibromyalgi- og Smerteforeningen, 2018)) went further and took it upon themselves to distribute the survey, writing about the survey in their newsletter, or posting it to their members on internal forums.



Figure 8. Screenshot of recruitment from the Danish cancer society



Figure 9. Screenshot of recruitment from SIND - the association for mental health

3. People who use cannabis

The third recruitment strategy was to target users of cannabis in general, as some of them may perceive their use to be medicinal. These users were naturally also targeted in growth shops at Christiania and the Cannabis Exhibition. Moreover, information about the project was dispersed on social media in groups related to cannabis use and/or cultivation (Afkriminaliser Cannabis, Doctorens Drivhus, and Legaliser Hash I Danmark). Also, the survey was distributed through an app called SmokeBuddy, an application to smartphones that was designed to help cannabis users monitor police presence at Christiania. The app host agreed to send a push notification to all those who had the app downloaded on their smartphone, encouraging them to participate in the survey (see figure 10).

4. The entire population

The fourth population targeted for recruitment was the entire Danish population, as they may be users of cannabis as medicine or may know someone who is and make them aware of the survey's existence. Danmarks Radio, the National Broadcasting Corporation in Denmark, was

contacted with a suggestion for an article covering the topic of the survey, which they posted on their website (Worup, 2018), accompanied by a segment on their morning radio show where I was interviewed about the survey and the background for doing the study. The online article featured a description of the survey and its link. Later in the recruitment process, I was invited to comment on medicinal cannabis use in a “fact-checking” article on the efficacy of cannabis, and here I managed to make them link to the survey again (Aagaard, 2018).

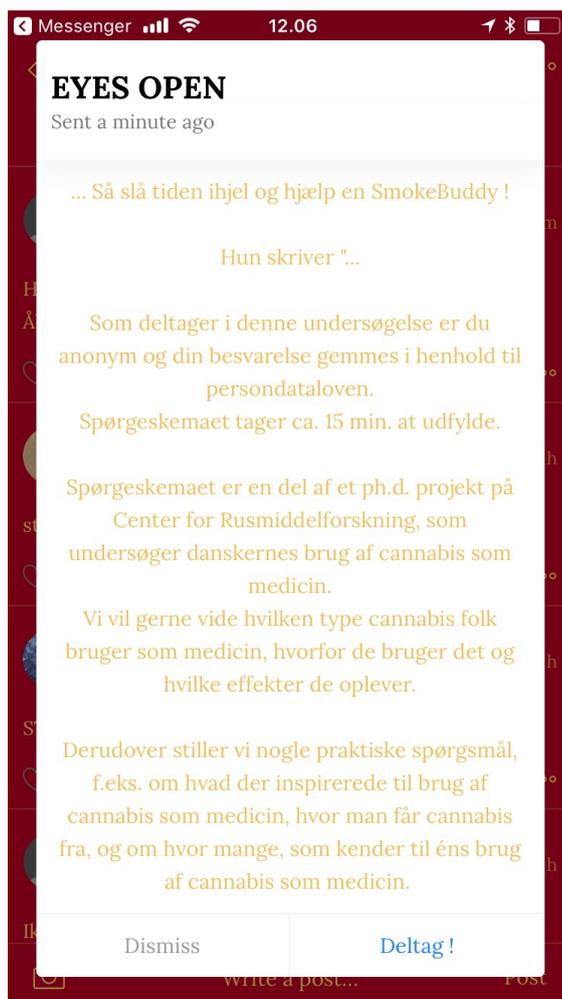


Figure 10. Screenshot of recruitment from SmokeBuddy
It reads: Kill time and help a smokebuddy! She writes:...(followed by my recruitment text)

Throughout the recruitment process, the greatest number of respondents came through, targeting the entire population in Denmark, as some 800 respondents filled out the questionnaire on the day or the day after that the survey was covered in the national media, which amounts to almost a quarter of the total responses (3.021). Additionally, increases in

the number of respondents were seen on days when the survey was shared heavily on social media and when the survey was promoted in the newsletter of an online seller of cannabis.

3.5.2. Potential recruitment bias

A successful recruitment strategy is, to a large extent, predicated on researcher knowledge about the targeted population, particularly when researching “hard to reach” or hidden populations (Shaghghi et al., 2011), as knowledge about the targeted population can inform the recruitment process in terms of where and how to recruit. Therefore, the knowledge acquired when designing the survey was utilized in the following recruitment process. For example, through the pilot interviews and observations of user communication online, I gained insight into the various sources of supply that medicinal cannabis users utilizes and could thus target all such channels, such as Christiania, online sellers and physical shops with information about the survey.

The recruitment strategy described above (section 3.5.1. *Recruitment strategy*) was intended to approximate a probability sample of the targeted hidden population of users of CaM. To meet this end, in the recruitment process, I drew inspiration from a mix of specialized sampling methods for hard to reach populations. For one, I utilized snowballing or network sampling (Callegaro et al., 2015), where respondents are encouraged to share the survey with other people that they know within the same target population or refer me to other relevant networks. Thus in this case, I asked respondents to share the survey with or refer me to other users of CaM. Further, inspired by time-location sampling techniques (Karon et al., 2012), I mapped out locations that users of CaM may frequent in order to obtain cannabis (grow shops, cannabis fair, Christiania, online sellers, online support groups) and distributed information about the survey in these locations. I also recruited users of CaM through the national media in order to not rely on venue or peer contact alone, as a national approach would be more likely to reach a more varied population of users of CaM.

However, as users of CaM can be described as a hidden population because no sampling frame exists, it is difficult to know if the recruited sample in my Ph.D. represents a probability sample of the entire population of users of CaM in Denmark. It is likely that there may be other sub-groups of CaM users that are underrepresented in the final sample, making it more aptly defined as a convenience sample, where the sample may not be fully representative of the population of interest (Aday et al., 2006). This is due to the limitations already described (in section 3.1.2. *Limitations of the chosen method*). However, these limitations may be further exacerbated by the potential for recruitment bias in the study. For one, in some cases, the

used recruitment material may have been skewed towards attracting current users of CaM as the material read either “Do you use cannabis as medicine” or “Do you have experiences with the use of cannabis as medicine”. Here, one may argue that the former sentence may be read as less inclusive by some in the population of interest, as it implies a current use. Moreover, users with negative or neutral experiences with the use of CaM may be underrepresented in the final sample, as such users may be less likely to self-identify as a CaM user and to engage with the topic of medical cannabis, as a positive experience may lead to more engagement with a cannabis-positive subculture. If users with negative or neutral experiences have disengaged from the topic of CaM, they may be less likely to be the target of recruitment material. Moreover, users with negative or neutral experiences may also be less interested in investing the time to answer the survey.

Conversely, users with positive experiences with the use of CaM may be enthusiastic about answering a survey on their experiences and user patterns; due to the stigmatized and criminalized nature of medicinal cannabis use, users with positive experiences with the use of CaM may perceive themselves to be important stakeholders in the survey findings, as such findings could potentially shape public perceptions on the use of CaM. Thus, this group of users may have been more inclined to participate in the study. Finally, I cannot rule out that this user group may be inclined to overreport positive experiences from use for the same reason. In all, the recruitment process and material may be more likely to capture the attention of active users of CaM and users with positive experiences with CaM, which may have skewed the sample in their favour.

Some recruitment venues, such as the Facebook support groups, Christiania, and the cannabis fair, may have attributed to the oversampling of a sub-group of users of CaM. For instance, users who visit Christiania or pay to take part in the cannabis fair could potentially have a more positive view on cannabis use in general and may therefore be more likely to overreport positive experiences from the use of CaM. Likewise, the members of Facebook support groups may also represent a sub-group of CaM users that have traits that differ from the overall population of users of CaM. Indeed, users of CaM who chose to be members of medical cannabis groups on identifiable social media are likely to differ from users of CaM who do not wish to disclose an interest in the use of CaM online. However, it is not entirely clear which parameters differ. In general, the disclosure of private personal information online has been associated with loneliness and being younger (Błachnio et al., 2016). Moreover, membership of a Facebook support group is predicated on the gatekeeper of these groups and Facebook group administrators can have a personal agenda and may exclude users who question the benefits of CaM, resulting in a biased sample of CaM users in these groups. Also, respondents recruited through Facebook support groups may have a perspective on use of

CaM that is shaped not only by their personal experiences but also by their participation in these online communities. Indeed, the process of self-disclosure online can function as a tool to cultivate a shared group identity (Joinson et al., 2007). It is possible that some Facebook group members have cultivated a shared understanding of the utility of CaM and that this understanding may shape their perceptions of their personal use, thereby affecting the internal validity of the findings from the survey. In all, recruitment from Facebook support groups may have led to an overrepresentation of a subgroup of CaM users that are younger and have positive perceptions on cannabis use and the medical utility of cannabis.

Moreover, the utilization of network sampling may have further skewed the sample towards users with positive experiences with the use of CaM. Through the recruitment process, I encouraged potential respondents to share the survey with other users of CaM, thereby utilizing the networks of users to recruit respondents beyond my reach. Some researchers argue that a probability sample can be attained from a hidden population through network sampling methods; however, this is predicated on a practice where the initial respondents chosen for referrals (“seeds”) are chosen non-randomly with a probability proportional to their network degree (Salganik et al., 2004; Volz et al., 2008). In the current study, I did not control which respondents made referrals to other potential respondents, and therefore any initial bias from “seeds” may have been exacerbated with respondents only recruiting other respondents who have favourable perceptions of the use of CaM. This fact is yet another argument for describing the final sample as a convenience sample, where the sample may not be representative of the population of interest.

In conclusion, due to the recruitment biases described in this section and the limitations described in section 3.1.2. *Limitations of the chosen method*, it is fair to say that this Ph.D. project does not explore the use of CaM in Denmark; it explores the use of CaM in a convenience sample, represented by those who knew about the survey and were interested in answering the survey.

3.6. Online recruitment

3.6.1. Reflections on online recruitment

In the age of the internet, particularly with the emergence of social media, researchers can access hidden populations and recruit the population of interest in large numbers through online tools such as web-based surveys (Miller et al., 2010). It is now also possible to engage

with the targeted population throughout recruitment as social media has made many hidden populations semi-visible, including people who engage in illicit drug use. Online discussion forums have created a permanently open two-way communication channel between participants and researchers, allowing for a dialogue that is not restricted by time and situation or driven by the research agenda, allowing the participants to “talk back” to the researcher at their convenience (Bakardjieva et al., 2000). Lessons from previous online research on hidden populations of illegal drug users show that it is important that the researcher takes an active role in online recruitment, as merely dispersing information about the survey is not necessarily sufficient (Bakardjieva et al., 2000; Barratt et al., 2010; Barratt et al., 2015b; Curtis, 2014; Mendelson, 2007; Temple et al., 2011). Gaining trust with potential research participants can be a challenge in general and maybe more so in hidden populations, where mistrust in the research process can be more pronounced (Ellard-Gray et al., 2015). In addition, the nature of an online discussion forum or group can foster a sense of privacy and intimacy where members share intimate details about their personal life (Curtis, 2014). Posting information about participating in research can appear as an intrusion to some group members. It can breach the sense of privacy and remind members of the group that they are visible to “outsiders.” As noted by Illingworth (2001, p. 86), *“The researcher cannot simply ‘step’ into a virtual community and must establish commonality and trust through the computer interface alone.”* Even when the researcher is a well-known member of a secret online group, requesting to utilize such a group for research purposes can be met with fierce negativity and challenges to the authenticity of the researcher (Johnson et al., 2018). Consequently, when recruiting hidden populations for online research, it is critical to have a researcher active throughout the recruitment process who can monitor the data collection process and engage with the online communities of interest (Barratt et al., 2015a; Mendelson, 2007). A researcher's active role throughout the recruitment process is crucial to address potential critical comments (Barratt et al., 2015b) and monitor potential misinformation about the research project (Curtis, 2014). As internet-mediated recruitment *“can take on a life of its own, snowballing in online communities beyond those targeted by researchers”* (Barratt et al., 2015b, p. 247), the researcher must remain aware of the bifurcation of the shared information, as far as possible. Engaging actively and addressing potential questions or objections can increase trust and increase the posts' reach. Trust and rapport between the researcher and participants is built over time through interaction with potential respondents raising objection or concerns (Ellard-Gray et al., 2015; Temple et al., 2011), and all questions and objections should ideally be addressed as it has a potential impact beyond recruiting the person asking a question. As pointed out by Mendelson (2007), most members of online forums are not active “posters” but passive “lurkers” who read discussions but rarely or never post themselves, and many of these lurkers may be influenced in their decision to participate by discussions in the online forum.

Moreover, previous research on both cannabis users (Temple et al., 2011) and cannabis growers (Barratt et al., 2015b) has shown that it is critical for successful recruitment that the researcher forms a partnership with the moderators of the online communities, as they function as gatekeepers to the population of interest. It may be more expedient for researchers to utilize derived reports, where recruitment messages are disseminated via people, organizations, or communities that have an existing relationship with potential participants (Temple et al., 2011). Indeed, ethnographic research exploring drug sellers found that successful recruitment rested upon the right contacts and locating trusted “go-betweens” to explore this hidden population (Dunlap et al., 1998). Moderators of online platforms with potential participants are likely far more successful in recruitment than the researcher, as they have the trust of the members in the group and their position in the network makes their posts visible to more group members, increasing the reach of the information. Furthermore, an alliance with moderators and other activists within the targeted demographic can be helpful, as this will increase the number of eyes on the recruitment process and engage others who can be “case markers” for participation, and reduce negative attitudes towards the research project (Mendelson, 2007; Temple et al., 2011). Such an alliance is predicated on the researchers' ability to adjust their tone and speech to the individuals they are engaging with. It may be important to avoid asserting dominance as a researcher in some groups, as posts with advanced vocabulary and academic credentials can be interpreted negatively as signals of presumed superiority and outsider status (Kozinets, 2015). Indeed, as with all other spaces that one can enter for research purposes, humility and respect for the territory that one is requesting to enter are essential (Kozinets, 2015). The online encounter between participants and the researcher can pose additional challenges to the researcher's authority. This online encounter is far removed from a classic research setting, with the researcher as an authority figure in a white lab coat, *“as subjects remain protected by the relative anonymity of their e-mail addresses or avatar names, while the researcher exposes herself in all relevant detail when communicating with subjects”* (Bakardjieva et al., 2000, p. 238).

3.6.2. My experiences conducting an active online recruitment

Throughout the recruitment process, I utilized the lessons detailed above. As many large networks for sharing advice on medicinal cannabis use had emerged on Facebook, I decided to “donate” my personal Facebook profile to the project. From that profile, I contacted 25-30 moderators through direct message, detailing information about the project and asking them to share information about the survey or permit me to do so. This was mostly successful; none

were critical about the survey, most permitted me to post, others posted themselves, and a few never replied. One group that I found during the recruitment had an intense discussion among themselves about whether to allow me into the group, weighing the risks and benefits to them of the research into their medicinal use in terms of privacy issues and the potential outcome of the research concerning policy and public perception. Eventually, there was a vote among members, and I was allowed to post information, which may be attributable to the moderators making a case for the importance of the research. In several other instances, some users met my recruitment with initial scepticism, raising similar issues as those debated in the before-mentioned group. Still, it was usually reversed into an appreciation for the study once a moderator or I had elaborated on the nature of the survey. Few instances of anger and contempt for both research and authority in general occurred, which I calmly contained and took the opportunity to reiterate the study's relevance.

Overall, I experienced overwhelmingly positive feedback on the survey, with both online group members and medicinal cannabis users I met in person expressing gratitude that people in academia were taking an interest in their experiences with medicinal cannabis use. Many examples of my interactions with potential participants are still accessible online today, and my initial thought was to include examples in this thesis. However, I have decided not to share screenshots of these interactions. Although they occurred in a semi-public space, I assess these conversations to be private, and no individual consent was given to use such data for research purposes (Golder et al., 2017). Therefore, I find that using these screenshots would be a breach of ethics related to consent to participate in research (World Medical Association, 2013). All moderators were contacted again two weeks before the survey closed, asking them to share information about the survey closing with their members. In addition, when the National Broadcasting Cooperation covered the survey, it was shared once more in many of the same forums that it had already been shared in previously.

Beyond contacting moderators, I identified several other actors on the medicinal cannabis scene who had been vocal about their support for increased access to medical cannabis, such as actors, musicians, comedians, former and current politicians, and activists within the cannabis community. This meant contacting people who had expressed positive views on medical cannabis, such as actor Søs Egelind, musician Søren Rasted, ex-minister Manu Sareen, and radio host Dan Rachlin and encouraging them to share information about the survey to their followers on social media, thereby utilizing the networks that had emerged when medical cannabis was heavily debated from 2013 and until the time of recruitment in the fall of 2018.

Besides the abovementioned, my strategy was to remain passive but vigilant and active once directly addressed or when questions or comments arose. I never invited any of the activists/moderators to be my Facebook friend, as this would breach their privacy and the ethical guidelines of the Helsinki Declaration. Article 24 of the declaration clearly states that *“every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information, with respect to preserving privacy and confidentiality”* (World Medical Association, 2013, p. 2192). Still, I accepted all friendship invitations and got some 30 new cannabis-related Facebook friends throughout the process. However, I did encourage users to alert other medicinal users to the existence of the survey. When appropriate, I asked moderators and respondents to point me in the direction of other groups where potential respondents could be reached. This led to the realization that, while I had been aware of some medicinal cannabis groups before the project's initiation, a large majority of groups had been unknown to me. The suggestions of other groups from both moderators and respondents led to a snowballing of recruitment. Finding one new group would lead me to another and yet another secret online group of medicinal cannabis users. Sometimes groups were suggested to me. Other times the medicinal users took it upon themselves to share information in networks that had previously been unknown to me.

In many cases, questions or criticism had been addressed by moderators or other members before they came to my attention. In other instances, one of my newfound cannabis-related Facebook friends would “tag” me in the thread so that I became aware of the question/criticism, underscoring the value of building trust with selected insiders when doing online research. I considered building an additional platform for recruitment where I could present information about the survey. However, I decided against creating such a platform, because it would be a breach of the Helsinki Declaration with respect to privacy and anonymity (World Medical Association, 2013), if I encouraged potential respondents to become members of such a platform, as their relation to the topic of medical cannabis could inadvertently be exposed to others in their social network. I also considered boosting content using internet advertising. Still, I decided against buying an advertisement for the survey, as I was more interested in cultivating organic and authentic reach, because, while sponsored content can increase overall reach, it can also significantly negatively impact organic reach (Varga et al., 2016). Also, recruitment would have been restricted by the shadow ban of anything cannabis-related on social media (Esposito, 2018). “Organic advertising” was made as some moderators decided to boost the information and “pinned” it to their pages, making it the first thing group members would see when entering the group.

Recruiting from the online communities of Facebook, some of which I had been a member of myself, acquiring inspiration for both my masters and the current Ph.D., meant giving up my role as a member of those communities and becoming an observer and researcher of them. I had mostly been a “lurker” in these groups. However, I still had to reorient myself and reflect on my communication with people in these groups differently, as I suddenly represented an academic institution. For instance, at the beginning of the recruitment process, I experienced the challenges of finding a balanced and neutral approach as a researcher; while I was interested in making a case for potential respondents to participate in the survey, I was not interested in encouraging them to view themselves as stakeholders, as this could further the risk of social desirability bias. Instead, I used arguments about the neutrality of explorative research and the value of uncovering hidden populations for society. Still, it is possible that an active online recruitment strategy can make the researcher more visible to the respondent in a manner that potentially compromises the atmosphere of privacy and secrecy created by the online survey (Heiervang et al., 2011; Joinson et al., 2007), thus diminishing the honest responses and self-disclosure that the method conventionally creates. Further, recruiting through Facebook, with my own personal profile, made me visible and somewhat vulnerable as a researcher. I could potentially be subject to online harassment (Marwick et al., 2016), which luckily did not happen. The recruitment period was interesting and exciting because I learned much about my targeted population that I did not already know. It was also exhausting at times because people could contact me both privately and online, with everything from their life story, to suggestions for recruitment, to criticism of politicians, to requests for access to clinical trials, to business ideas, to requests for medical advice, to accusations about my relation to big pharma, to express their gratitude for the study and so on and so on. However, I believe that much of this interaction was likely necessary for building rapport and gaining trust within the population of interest (Temple et al., 2011).

The permanently open two-way communication channel between participants and researcher had interesting feedback loop consequences both for the survey structure and the structure of the online networks. The survey was changed as multiple respondents expressed concern that their response was unsuccessful. Having designed the survey myself, I had not experienced what happened after the survey was finalized. Apparently, it went to a white page with small letters that said:” Testindtastningen er afsluttet” (Test entry completed), which left many users in doubt about whether their responses had gone through to the researcher. After encountering several of these concerns from respondents, I added some meta-text to the final page of the survey:” *This is the last page. When you click "Finish", your answer will be sent.*

Click "Finish" to submit your answer. Thank you very much for your participation!". After this adjustment, no more confusion was expressed by respondents online.

Through the two-way communication channel, I may have accidentally provoked changes to some group names. A group member sent me a direct message with suggestions for other groups that could be relevant for recruitment, only when I searched for them I could not find anything. I realized that there were multiple indications that Facebook had created a so-called "shadow ban" on all cannabis-related words, meaning that searching such words would not produce any results (Shackford, 2018). This was later confirmed by Facebook themselves in the context of the Canadian legalization of cannabis use for adults (Somerset, 2018). Researchers in Australia have experienced similar issues in their recruitment process (Esposito, 2018). The group member I was messaging with had been puzzled by the fact that I could not find the groups, so I shared it with them when I found this potential explanation. Almost immediately after, discussions about a potential shadow ban on all cannabis-related terms broke out in several groups, and consequently, some of the groups changed their names to avoid terms that could not be found. This experience made me more aware of the potential feedback that I, as a researcher, could have on these online networks.

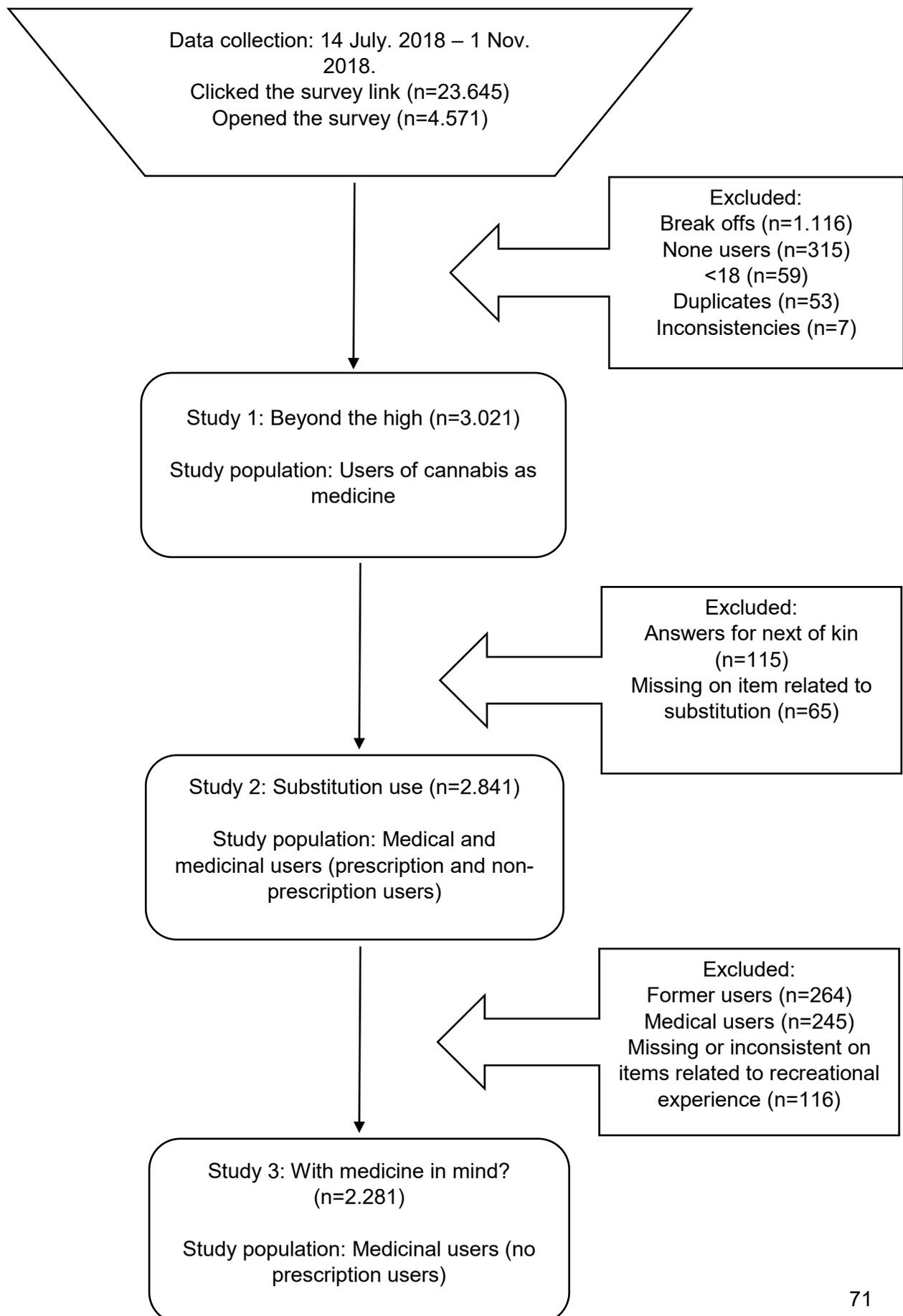
In sum, a recruitment strategy was made, distributing material with information about the survey to 1) users of cannabis as medicine, 2) people with a medical condition, 3) people who use cannabis, and 4) the general population. Inspired by recent lessons from conducting online research, an active online recruitment strategy was undertaken. The researcher builds rapport and trust with moderators and other actors within the community, which is critical for targeting various online communities of potential respondents with information.

3.7. Data management

In the course of recruitment, 23,645 potential respondents opened the link that led to the page with informed consent that preceded the actual survey. 4,571 proceeded from this site and began filling out the questionnaire, of which 315 were excluded as they answered negatively on the first question, “Do you use cannabis as medicine?”. 1,116 were excluded as they broke off before completing the entire survey, and these break-offs are analysed below (in section 3.8. *Analysis of break-offs*). Fifty-nine were excluded as they were under 18; all but three of these were parents answering on behalf of their children. Fifty-three were identified as duplicate entries, either through an overlap in the contact information given (n=44) or through analysis in Stata (Hamilton, 2012) (n=9) and thus excluded. Seven respondents were excluded for giving inconsistencies in data, i.e., reporting amounts of cannabis use that were highly unlikely or answering on behalf of multiple people.

In total, 3,021 were included in the study population for the first article, “Beyond the high: Mapping patterns of use and motives for the use of cannabis as medicine.” For the second article, “Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample,” those answering on behalf of someone next of kin (n=115) and those missing on items related to substitution (n=65) were excluded, leaving a total study population of 2,841 respondents. For the third article, “With medicine in mind? Exploring the relevance of having recreational experience when becoming a medicinal cannabis user”, former users (n=264) and medical users (prescription holders) (n=245) were excluded in order to explore current users outside the MCPP. Respondents who had missing (n=45) or inconsistent answers (n=71) on items related to recreational experience (i.e., indicating no previous recreational experience while responding that medicinal use had occurred on a gradual transition from recreational use) were also excluded, leaving a study population of 2,281 current medicinal users (see also Figure 11. Flow chart of data management).

Figure 11: Flowchart of data management.



3.8. Analysis of break-offs

Of the 4.571 that opened the survey, 1.116 were break-offs, meaning that they began filling out the survey but then broke off before completing it. A sub-analysis was made of these 1.116 partial responses to identify potential reasons for break-off. A meaningful distinction can be made between introduction break-off (respondents that break off early in the survey, i.e., after the first question) and questionnaire break-off (respondents that breaks off later in the survey. Introduction break-off likely represents respondents that were reluctant to participate in the first place for various reasons, e.g., the salience of the survey topic, opinions about the host of the survey, or time pressure (Callegaro et al., 2015). On the other hand, questionnaire break off represents respondents who were initially intent on participating but broke off either due to situational factors (e.g., fatigue, distractions, etc.) or to questionnaire characteristics (e.g., design, length, content, question types, etc.) (Callegaro et al., 2015).

Of the 1.116 partial responses, 97 were introduction break-offs, and 1.019 were questionnaire break-offs, indicating that few of the respondents who broke off were reluctant to participate. While most breakoff (61%) occurred within the first 20% of the survey, there was no indication of any item eliciting reasons to break off in particular, as the break-offs occurred steadily throughout the survey with decreasing intensity. A sub-analysis was conducted comparing the 1.116 partial responses to the 3.021 full responses on motives for use and patterns of use. Demographic characteristics were not compared, as the demographic section was placed last, and only 20 partial responses were left at the beginning of that section. The sub-analysis comparing full responses to partial responses showed that partial responses were significantly less likely to treat mental health conditions (36,7% vs 32,0%, $p < 0.01$), sleep disturbances (27,5% vs 22,3%, $p < 0.01$) and stress (23,5% vs 20,5%, $p < 0.05$), while no significant difference was found for treating somatic conditions (79,3% vs 80,4%). Also, no significant differences were found related to patterns of use, having a prescription for medical cannabis, or having previous recreational experience with cannabis. However, a statistically significant difference was found between the mean experienced effect of cannabis on symptoms (M 2,82 (SD 0.96) vs M 2,54 (SD 1.72), $p < 0.01$), indicating that those that experienced a smaller effect were more likely to break off when answering the survey. This finding shows that interest in participating in the study is related to the experienced effect of cannabis on symptoms and thus substantiates a potential limitation of the study, namely that the study sample may skew towards users of CaM who experience positive effects from use. No partial responses were included in the final analysis, due to ethical considerations, as consent to participate in

research is an ongoing process (Mahon, 2014), and break-offs could indicate respondents withdrawing their consent to participate.

3.9. Data analysis

Statistical analysis of the data was conducted in Stata SE/15 (Hamilton, 2012), exploring simple proportions and means with standard deviations related to demographic variables, motives for use, patterns of use, and items related to the initiation of medicinal use and social control factors, to produce descriptive statistics of the sample. To reduce complexity, the 52 conditions respondents could choose from when reporting conditions treated with cannabis as medicine were categorized as either somatic conditions ($n = 36$) or psychiatric conditions ($n = 13$), based on ICD 10 classification (World Health Organization, 1992), except for “chronic pain,” “sleep disturbances,” and “stress,” which were kept as independent categories.

Dichotomized variables were coded, distinguishing between; CBD-only use vs use of other cannabis products, substitution users, and non-substitution users. These dummy variables were used as dependent variables. Other dummy variables were made for educational level and recreational experience. A trichotomized variable was coded on the item exploring the degree of previous recreational experience, distinguishing between users with no recreational experience (no experience), users with occasional recreational experience (lesser degree of experience and some degree of experience), and users with regular recreational experience (high degree of experience and very high degree of experience). This trichotomized variable was made to conform to Becker's terminology on the career of a cannabis user. To explore the association between various categorical variables, multivariate analyses were conducted between the variable of primary interest and other categorical variables while controlling for demographic variables (age, gender, education, etc.). Logistic regression models were made to assess CBD-only users, substitution users, and the users with a gradual transition from recreational use on key variables. These models were made to explore associations between variables without assumptions of causality or direction of potential causality. Odds ratios were used to estimate the strength of associations and presented with confidence intervals, allowing the reader to evaluate the statistical power of the association. Before the comparison of means, a Shapiro-Wilks test was used to assess normality. As none of the variables were normally distributed, the Wilcoxon signed-rank test was used to assess the potential significance of differences between means. The distribution of the qualitative responses for brands of prescription drugs was quantified using the data analysis software Nvivo 12 (Bazeley et al., 2013).

Chapter 4. Key findings, contextualization and conclusion

In this chapter, I present key findings from the three studies of the Ph.D. project, contextualize the key findings with the relevant literature and conclude on the Ph.D. project.

4.1. Key findings from the three studies

In this thesis, I have explored the use of CaM in a convenience sample of Danes through an anonymous online survey. The aim of the thesis was to explore the who, what and why related to the use of CaM in Denmark. The study focus has been on the following three areas: In study 1, I have explored the demographics of users, their patterns of cannabis use and their motives for the use of CaM. In study 2, I have explored the use of cannabis as a substitute for prescription drugs and the motives and patterns of this type of use. In study 3, I have explored the sources of information that users draw on when becoming a medicinal cannabis user and the role that recreational experience plays in that process. The thesis view cannabis as both a drug and a construct. Therefore, the focus of the thesis is on the biomedical effects of cannabis and the public health consequences of medical cannabis use while still reflecting on how cannabis is constructed as medicine, exploring the process of becoming a user of unregulated CaM.

Study 1: Beyond the high. Mapping patterns of use and motives for use of cannabis as medicine.

This paper concerns an exploratory mapping of demographics, patterns of use, and motives for use among Danes who use CaM, both medical cannabis prescribed by a doctor and self-prescribed cannabis from the illegal market.

This study aimed to gain an overview of the use of CaM in Denmark, mapping the basics of this trend in terms of demographics, patterns of use, and motives for use. The primary focus of this study is on the public health implications of the emerging trends among Danes and the policy implications of the study findings. The perspective on cannabis in this study is mainly on “cannabis as a drug,” that is, on the biomedical drug effects of certain subtypes of cannabis and the health implications of patterns of use. The study findings show that while the study sample can be described as a heterogeneous group with a great range within both motives of use and patterns of use, some interesting trends emerged; a majority of women, users of older age, and users of cannabis oil high in CBD and low in THC, users in this study sample differ

from the typical users of recreational cannabis and from users in previous studies on medicinal cannabis use, where users are more likely to be men, younger and use smoked cannabis products.

The findings on patterns of use suggest that most users of CaM in this study sample are interested in effects beyond the high that is conventionally associated with smoked cannabis used for recreational purposes; that is, the users in the current sample are more likely to use cannabis products with limited amounts of the psychoactive component THC. Moreover, the study indicates that most users of CaM in the sample use cannabis for a wide variety of conditions, many of which are not included in the Medical Cannabis Pilot Program (MCP), with the most frequent motives being chronic pain, sleep disturbances, stress, arthritis, anxiety, and depression. This finding resembles motives for use in other studies surveying the use of CaM. In this study, most users report substantial symptom relief from CaM, limited or no side effects, and a positive impact on daily life functions. Further, results from this study indicate that most users of CaM in Denmark remain outside the “safe and legal framework” established within the MCP, as the vast majority of users in the study reported not having a prescription for medical cannabis. The public health consequences of this use are discussed in light of the subtypes of cannabis used and the risks inherent to self-medicating with cannabis products from an illegal market.

Study 2: Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample.

This article concerns an exploratory mapping of the use of cannabis as a substitute for prescription drugs among users of cannabis as medicine, both medical cannabis prescribed by a doctor and self-prescribed use of cannabis from the illegal market. This study aimed to explore to what extent substitution use is a motive among Danish users of cannabis as medicine and to map the motives and patterns related to substitution use. The perspective is mainly on “cannabis as a drug,” focusing on the bio-medical effects of subtypes of cannabis and types of prescription drugs substituted. However, this study also reflects on “cannabis as a construct,” as cannabis is contextualized with prescription drugs and the contemporary problematization of opioid use. It is described how cannabis is perceived by some users as a “lesser of two evils” compared to opioids because cannabis is non-lethal. Thus, the medical value of cannabis is determined not only based on what cannabis *is*, in terms of the available evidence of efficacy but on what cannabis *is not* in the context of problematic opioid use.

The study shows that substitution of prescription drugs is a leading motive among users of cannabis as medicine in the sample and that pain medication is by far the most common prescription drug substituted with cannabis, followed by anti-depressants and arthritis medication. The findings reflect findings in other studies on cannabis substitution. In this study, most substitution users used CBD oil except those who substituted antipsychotics, where hash, pot or skunk was the most common cannabis product used. A large majority of substitution users reported either termination or substantial reduction of prescription drug use due to their use of cannabis as medicine. In addition, most substitution users found cannabis more effective than prescription drugs, and a large majority reported that the side effect profile of cannabis was preferable to prescription drugs, a finding also reflected in other studies on cannabis substitution. The public health effects of substitution use are discussed in the contexts of potential barriers in the health care system, the health effects of subtypes of cannabis, and trends in the use of prescription opioids in Denmark.

Study 3: With medicine in mind? Exploring the relevance of having recreational experience when becoming a medicinal cannabis user.

This article utilized the theoretical framework of Howard Becker on becoming a cannabis user to explore how a person becomes a medicinal cannabis user in Denmark in the absence of formal medical guidance. Thus, this study only includes users of unregulated cannabis as medicine from the original study sample. The study explores the sources of inspiration that users draw on when becoming medicinal cannabis users and to what extent the users have overcome various forms of social control factors that Becker identified as barriers to becoming a regular user of cannabis. Also, the study explores the role of having previous recreational experience with cannabis and how such experiences are related to patterns of medicinal cannabis use and social control factors related to use. In this study, the focus is primarily on “cannabis as a construct” and the factors that inspire the users to construct cannabis as medicine. Moreover, the article explores how the construct of cannabis as medicine is shaped by the presence (or absence) of previous recreational experience, exploring to what extent the construct of cannabis as medicine is influenced by *recreational learning*. However, the focus on “cannabis as a drug” is also present, as the study seeks to relate the paths that users take when becoming a medicinal user to their patterns of cannabis use, thus merging the thinking of both “cannabis as a construct” and “cannabis as a drug.”

The study finds that users of medicinal cannabis are a heterogeneous group in terms of demography, motives for use, and patterns of use and that this heterogeneity is related to the

degree of previous recreational experience with cannabis. Also, the study shows that inspiration for use and social control factors were significantly related to the degree of previous recreational experience. Compared to users with recreational experience, medicinal users with no recreational experience are more likely to be women, older, to treat somatic conditions, and to have a more medicalized approach to cannabis use with daily use of products that seek to exclude intoxication. Medicinal users with no recreational experience also draw more on social networks for information during their initiation of medicinal use and they are also more successful in overcoming social control factors related to use. The emergence of medicinal cannabis use among users without recreational experience is discussed in the context of surveillance capitalism, with social media potentially inspiring new drug users. The use of medicinal cannabis among users with recreational experience is discussed in the context of the self-medication hypothesis for problematic cannabis use, Foucault's concept of governmentality, and whether a medicalized perspective on problematic cannabis use is preferable both for the individual user and in the interest of public health. Lastly, with respect to the differences in overcoming social control factors between the two groups of medicinal cannabis users, it is discussed why some users might find it easier to convince others about the legitimacy of their medicinal cannabis use compared to others.

4.2. Contextualization of the findings

4.2.1. Demographics and patterns of use

Since I started my PhD project, more data from survey studies on medicinal cannabis use in Denmark has emerged. One survey study explored the use of cannabis to alleviate symptoms related to Multiple Sclerosis (MS), and found that of 2.009 Danish MS patients, 21% had used cannabis within the past year, and only 21 % of those users had received medical cannabis prescribed by a doctor (Gustavsen et al., 2019). A later survey study from 2021 on cannabis use among cancer patients showed that 13% of 2.839 cancer patients had used cannabis for self-treatment during their cancer treatment (Nielsen et al., 2021). Also, a survey study done by the Danish umbrella organisation for patients named Danske Patienter explored cannabis use among seven large patient organizations² and found that out of 4.548 patients, 13% were current users of CaM, while 14% were previous users of CaM, and an additional 37% were currently considering using CaM (Danske Patienter, 2020). Furthermore, in the same study,

² Danish Epilepsy Association, Danish Cancer Society, Danish Multiple Sclerosis Society, Accident Patient Association, Danish Spinal Cord Injuries Association, Danish Rheumatisms Association and the Danish Fibromyalgia and Pain Association.

only 20 % of the current users of CaM had received a prescription for medical cannabis. Of note, the prevalence of previous users of CaM in both the study of MS patients (Gustavsen et al., 2019) and the study of the seven patient organizations (Danske Patienter, 2020) was almost equal to that of current users, which differs substantially from the findings in Study 1 in the thesis, where current users outnumber previous users by 10 to 1. This discrepancy could indicate that the recruitment process of my PhD project may have oversampled current users of CaM. However, in general, the three subsequent survey studies from Denmark echo several of the findings from Study 1 in this thesis. For one, they also indicate that most users of CaM in Denmark remain outside the “safe and legal framework” established within the MCPP, and that use of CaM to treat a great variety of conditions, appears to be a growing trend among Danes. The study of the seven patient groups showed that most of the CaM users had initiated use within the last couple of years, and that 37% of the non-users were currently considering using CaM (Danske Patienter, 2020). Similarly, the study of MS patients showed that 44% of non-users would consider use of CaM if it was legal (Gustavsen et al., 2019) and taken together, these findings indicates that the trend in the use of CaM could potentially increase. Secondly, the studies on the use of CaM among cancer patients and MS patients show similarities to Study 1 in terms of the demographics of users of CaM with a majority of women and in terms of age, indicating that the use of CaM is primarily a phenomenon among older adults. In the study from 2021, users of CaM among cancer patients were 58.9% female, with a median age of 63 (Nielsen et al., 2021), while users of CaM among MS patients were 62,4% female, with a mean age of 47,9 years (Gustavsen et al., 2019). These findings are also in congruence with the demographics of the legal, medical cannabis users within the MCPP, where a majority are women (60,2%) and 83% where older adults (defined as 42 years or older) (Danish Ministry of Health, 2020). Interestingly, these two studies also found that CaM users reported cannabis oil as the most frequent form of intake (88% of CaM using cancer patients and 64,3% of CaM using MS patients)³. Since these findings echo findings on patterns of use found in Study 1, it is likely to support the emergence of a novel subtype of cannabis use that goes “beyond the high”, that is, a type of use that is distinct from the conventional practices of recreational cannabis use, where cannabis is smoked with the purpose of producing a high.

The prevalent use of illegally sourced cannabis tinctures and extracts with a medicinal motive found across the studies is highly interesting because it bears some resemblance to the formal medical cannabis use that existed in the west from 1840 to 1930, where extracts and tinctures were sold over the counter for the treatment of a variety of ailments (see section 2.4.1. *Medical*

³ The study among the seven patient groups did not detail demographics of CaM users or their forms of intake

cannabis in history). It is curious to see this type of cannabis use revived, this time not so much from the top down via the medical establishment, but from the bottom up by vigilante activists/opportunists producing great amounts of cannabis oil in order to meet a demand that is, in many cases, inspired by the media and guided by laymen on social media. As shown in Study 3, cannabis novices, in particular, seemed to draw inspiration from the media and social media and were most likely to use low potency CBD oils, which could indicate that these online cannabis-positive sub-cultures shape the patterns of medicinal cannabis use among novices. This development where online social networks inspire and shape drug use points to the relevance of internet-driven social mobilization in the emergence of the medical cannabis movement (Pedersen et al., 2013) and underscore the relevance of further exploring online drug-positive sub-cultures and online inspiration for health-related behaviour.

4.2.2. Motives for use

After the initiation of my Ph.D. project, more data has emerged on motives for medicinal and medical cannabis use in the U.S (Mahabir et al., 2020), Canada (Eurich et al., 2019) and Australia (Lintzeris et al., 2020), adding to the notion that pain management is the most common reason for the use of CaM, followed by mental health conditions (Eurich et al., 2019; Kosiba et al., 2019; Lintzeris et al., 2018; Lintzeris et al., 2020; Mahabir et al., 2020; Schlag et al., 2021). For instance, using prescription registers from November 2018 to March 2020 in the U.S., the study by Mahabir et al. found that of 61.379 medical cannabis patients, the primary medical conditions reported were unspecified chronic pain (38.8%), anxiety (13.5%) and post-traumatic stress disorder (PTSD) (8.4%) (Mahabir et al., 2020). In comparison, of all the prescriptions made for whole-plant cannabis through the MCPP in Denmark with a registered indication (n=6.797), the vast majority were for neuropathic pain (93%) (Danish Ministry of Health, 2020). This finding illustrates that the formal use of medical cannabis in Denmark has been in greater congruence with the available scientific literature indicating efficacy of cannabis or cannabinoids, compared to the U.S., as most of the evidence for the efficacy of cannabis or cannabinoids for pain relates to neuropathic pain only (Häuser et al., 2018). However, the before-mentioned survey studies documenting predominantly medicinal cannabis use in Denmark and the findings from Study 1 indicate that cannabis is used medicinally to treat a great variety of conditions, for which there is currently limited evidence. Effects on pain and sleep are frequently cited as reasons for the use of CaM among both MS and cancer patients, along with condition-specific ailments such as spasticity for MS patients and nausea for cancer patients (Gustavsen et al., 2019; Nielsen et al., 2021). In the study of the seven patient organizations (Danske Patienter, 2020), 54% of the current and former users of CaM reported a reduction in pain, 44% improved sleep, 40% and relaxation from the use of

CaM. In the study of the seven patient organizations, 22% indicated that they had not experienced any positive effects from the use of CaM (Danske Patienter, 2020). The findings on no experienced effect of the use of CaM is a far greater proportion than the 3.3% reporting no effect of CaM found in Study 1, and could indicate that the sample in my PhD involves a greater selection bias towards users with positive experiences with the use of CaM. However, with respect to reported side-effects from use, the CaM users in the study by Danske Patienter (Danske Patienter, 2020) were more likely to report no side-effects from the use of CaM (65%) compared to the CaM users in Study 1 (52.3%), indicating a more positive evaluation of side-effect profile of CaM from these respondents. Thus, one could argue that overall, the data that has emerged since the initiation of my PhD echo the findings from Study 1, where pain, sleep and stress were the most reported motives for use of CaM and were most users reported positive effect from use. Taken together, this indicates that most medicinal cannabis users, use cannabis to manage conditions for which there is currently limited or insufficient evidence for efficacy and nonetheless a majority of users report experiencing positive results from this use.

4.2.3. Potential biases of user-reported outcomes

These user-reported outcomes described above are highly relevant to mention because they in part may explain why some people use medicinal cannabis, despite stigma and illegality, and that is likely because a number of people experience a positive effect from this use. However, these user-reported outcomes cannot inform us whether cannabis is an effective treatment option for the conditions for which it is currently being used. For one, it is important to consider all the potential biases related to survey findings on user experiences described in section 3.1.2. *Limitations of the chosen method* and section 3.5.2 *Potential recruitment bias*, such as recall bias, social desirability bias and selection bias. In the survey studies of user-reported outcomes, there is no separation of cannabis as a drug from cannabis as a construct, as the drug effects experienced are difficult to disentangle from the meaning that has been produced in the contexts of cannabis positive subcultures or by the predominantly positive narrative presented in the media at the time. Indeed, the setting of using an illegal drug as medicine might be a potent narrative for the creation of strong placebo effects, as this setting arguably differs from the setting of a doctor's office. When initiating use, there are differences in what effects the user can be told to expect, where doctors are bound to adhere to the existing knowledge on the known effects of the drug, while laymen on social media are not. Indeed, positive expectations play a great role in the outcome of interventions for pain, with positive expectations producing large clinically significant effects comparable to the drug effects (Bingel, 2020; Vase et al., 2015). Also, hope can be a therapeutic tool (Bressan et al.,

2017) that could enhance a placebo response, and notably, it is front and center in one of the largest medicinal cannabis support groups on Facebook: "Cannabis Recovery – Håb, Støtte, Erfaringsudveksling (in English: Cannabis Recovery - Hope, Support, Experience exchange) (Cannabis Recovery, 2017). There may also be differences with respect to empowerment, i.e. the patient control and/or involvement in their healthcare, a concept that is associated with positive health outcomes (Pekonen et al., 2020). A journey into a semi-secret illegal setting may be wholly uncomfortable and evoke feelings of stigma (Satterlund et al., 2015), but it could also evoke a feeling of empowerment, as it involves personal action, and such a feeling could also be entangled in the experienced drug effects. Indeed, the concept of *set and setting* reminds us that both mind and context are always present when a drug is consumed, and these factors can mediate the drug experience. Further, beyond the potential for a sizable placebo effect or meaning effect, there is the issue of regression towards the mean, i.e. the fact that unusually large or small measurements tend to be followed by measurements that are closer to the mean, which can make natural variation appear as real change (Barnett et al., 2005). If an intervention is introduced when symptoms peak, this intervention may be followed by a period of symptom reduction, but this does not necessarily mean that the intervention caused the symptom reduction.

All the limitations of survey studies on user-reported outcomes discussed above illustrate the necessity of exploring the efficacy of cannabis in randomized placebo-controlled studies, because such a setting is the best available method for exploring cannabis as a drug while controlling for the profound effects that mindset of the user and social setting can have on the drug experience (i.e. cannabis as a construct). However, as I will now show, the evidence base remains limited for most of the conditions for which cannabis is used medicinally.

4.2.4. Efficacy of cannabis or cannabinoids

Since the initiation of my PhD project, there have been some developments with respect to our understanding of the efficacy of cannabis or cannabinoids. For example, the drug Epidiolex containing the cannabinoid CBD, has been approved for the treatment of severe forms of epilepsy (Wise, 2019). However, for the most prevalent conditions for which CaM is currently being used, reviews show that there is currently still insufficient evidence to support treatment. For sleep, a systematic review of 14 preclinical and 12 clinical trials investigating the effect of cannabinoids on sleep disorders found that there was insufficient evidence to support routine clinical use of cannabinoid therapies for the treatment of any sleep disorder (Suraev et al., 2020). For mental health conditions, a review included 13 studies and concluded that there is *encouraging, albeit embryonic, evidence for medical cannabis in the treatment of a range of*

psychiatric disorders (Sarris et al., 2020, p. 1). Another review, published in the same month as the review by Sarris et al., included 23 studies and concluded that there was *moderate recommendation supporting the use of CBD for the treatment of schizophrenia, social anxiety disorder (SAD), autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD)* (Khan et al., 2020, p. 1). The review by Khan et al. also cautioned that the recommendations should be considered in the context of a limited number of available studies, but the two simultaneous reviews illustrate that reviewers reached different conclusions on how to interpret the available literature.

For pain conditions, the efficacy of cannabis or cannabinoids remains a contested topic. In 2018, the International Association for the Study of Pain (IASP) established a task force on the use of cannabinoids, cannabis, and cannabis-based medicines (CBM) for pain management. This task force conducted a systematic review of 36 studies (7,217 participants), exploring the analgesic effects of cannabinoids (8 studies), cannabis (6 studies), and CBM (22 studies). The task force concluded that they had little confidence in the estimates of effects in the studies reviewed, that the interventions were associated with more adverse events than controls, and that the evidence neither supported nor refuted claims of efficacy and safety for cannabinoids, cannabis, or CBM in the management of pain (Fisher et al., 2021). Moreover, in an overview of systematic reviews of cannabis and cannabinoids for pain, the IASP task force criticized the review by the NASEM (National Academies of Sciences Engineering and Medicine, 2017) for concluding that there is substantial evidence that cannabis is an effective treatment for chronic pain in adults (Moore et al., 2021). In their critique, they point to the fact that the NASEM committee consists of experts in several fields, but not pain and they point to the fact that they have given the review on which the NASEM base much of their findings (Whiting et al., 2015) a critically low confidence rating. As mentioned in section 2.1.5. *Efficacy of cannabis and cannabinoids*, the conclusion made by the NASEM is arguably imprecise, as most of the evidence reviewed pertains to neuropathic pain only. A recent Danish register-based study exploring use in the context of the MCPP, further indicates that the analgesic effect of cannabis or cannabinoids may be confined to neuropathic pain. When matching users of cannabis-based medicine or medical cannabis via the MCPP (n=2,741) with controls, the study found that use was associated with some positive effects for patients with neuropathic pain (n=1,817) but not for patients with other pain disorders (n=924) (Hjorthøj et al., 2022). Interestingly, in another study comparing 96 Danish pain patients using cannabis-based medicine or medical cannabis to controls, the 96 cases reported having higher levels of pain when compared with controls, but also higher levels of satisfaction with treatment and an indication of lower scores on depression (Kudahl et al., 2021). It is difficult to tease out if the greater satisfaction with treatment is due to other positive effects of the treatment that is not captured in this study or could be explained by potential positive expectations related to

medical cannabis (see more in section 4.2.3. *Potential biases in user reported outcomes*). Overall, the use of cannabis or cannabinoids in pain management remains controversial. The IASP taskforce does not endorse the general use of cannabis or cannabinoids for pain relief, due to a lack of evidence from high quality research (IASP Presidential Task Force, 2021). Conversely, others have argued that when combining the conclusion from NASEM, the clinical experience of clinicians and patients, and real-world evidence from observational studies on opioid substitution and patient reported outcomes of positive effects, there is high strength of evidence to support the use of cannabis or cannabinoids for chronic pain (Schlag et al., 2021). As an example of such real world evidence, a recent prospective study on 1.045 chronic pain patients in Israel receiving medical cannabis show that among those that were available for follow up 12 months later (n=551) there were a modest, but significant reduction (20%) in pain intensity (Aviram et al., 2021). However, there are several limitations of this study, most notable the missing data from almost half of the initial study population, limiting the external validity of the findings. Also, it is debatable whether this modest reduction in pain intensity is clinically significant (Aviram et al., 2021).

Taken together, there still is insufficient evidence to conclude on the efficacy of cannabis for most of the conditions for which it is currently used in practice by medicinal users. In light of the several accounts of positive experiences from the use of CaM both in Denmark and internationally, it is critical that we explore the potential utility of cannabis further. The MCPP offered a unique opportunity for the creation of such knowledge, as whole-plant cannabis was prescribed to patients through the program, however as I will now demonstrate, the barriers to cannabis research were still relevant.

4.2.5. Evidence generated from the MCPP

The two large randomized controlled trials that were set in motion with the initiation of the MCPP based their study on one or two cannabinoids, either CBD and THC (Hendricks et al., 2019) or CBD alone (Vela et al., 2021). Thus, these studies did not contribute to the research on whole-plant cannabis, but on cannabinoids. A third RCT did use whole-plant cannabis in the exploration of cannabis for neuropathic pain, but this study was impeded by supply issues (Gustavsen et al., 2021), which further illustrates the barriers to conducting whole-plant cannabis research related to access to cannabis (see section 1.3.2. *Barriers to whole-plant cannabis research*). Also, beyond the three RCTs that were set up, the MCPP offered a great opportunity for generating patient-reported outcomes for whole-plant cannabis, but the MCPP was designed by the Danish Medicines Agency in a way that only ensured systematic documentation of adverse events and not experienced effects. This means that for the 10.071

prescriptions for whole-plant medical cannabis distributed among the 2.550 patients, there has not been collected systematic knowledge on experienced effects. Moreover, in 33% of the instances where whole-plant cannabis has been prescribed in the MCPP, there is no indication for which condition it was prescribed (Danish Ministry of Health, 2020). However, some register-based research was conducted in the context of the MCPP, comparing Danish patients receiving either cannabinoids or whole-plant cannabis to control cases on various outcomes (Hjorthøj et al., 2022; Kudahl et al., 2021), discussed in the section above 4.2.4 *Efficacy of cannabis or cannabinoids*). In sum, despite the opportunities for knowledge production on whole-plant cannabis, so far, the MCPP in Denmark has contributed little to the already limited body of knowledge on the efficacy of whole-plant cannabis. The current state of affairs underscores the value of generating real-world evidence (RWE), and the current PhD project has contributed to this by exploring the experiences of medicinal users in practice, of which the vast majority used whole-plant cannabis. Considering the current situation regarding studies on whole-plant cannabis in Denmark, more RWE should be gathered in Denmark by systematically documenting the experiences of whole-plant cannabis users in the MCPP, to supplement RCTs and bridge the current evidence gaps (Nutt et al., 2020; Schlag et al., 2021).

4.2.6. Does cannabis function as a substitute for opioids?

The Study 2 of the Ph.D. project showed that a small majority of respondents had used CaM with the purpose of replacing a prescribed drug and that these substitution users overwhelmingly indicated that they substituted pain medication. This finding is in congruence with a recent survey of 44.119 cannabis users from the U.S and Canada, showing that substitution of cannabis for opioids or prescription pain medication is commonly reported (84% and 78%) among those who report using cannabis for pain (Wadsworth et al., 2022). In Study 2, most respondents also reported a reduction in, or cessation from, prescription drugs used as a consequence of their use of CaM as a substitute, a finding that also has been reported among medical cannabis users in the U.S. (Boehnke et al., 2019; Piper et al., 2017). These findings may reflect a broader narrative among users of CaM, characterized by skepticism of “big pharma” and a dichotomized perception on substances, where something produced by nature is viewed as more benign than something produced by pharma (Dahl et al., 2011; Pedersen et al., 2013; Satterlund et al., 2015). For instance, in a study of 100 Norwegian medicinal cannabis users, Pedersen et al. found that for many participants, prescription medicine was synonymous with ‘chemicals’ and contrasted with the organic and ‘green’ values of the traditional cannabis culture. Thus, the findings should be viewed in the potential context of such negative perceptions. However, in the light of these user-reported outcomes and the negative public health outcomes associated with the increase in opioid use, particularly in the

U.S (Kolodny et al., 2015; Kuczyńska et al., 2018), it is still relevant to consider whether cannabis do in fact function as a substitute for opioids.

Since the initiation of my Ph.D. project, more research has emerged on the topic, adding to the literature discussed in Study 2. For one, more ecological studies have emerged, showing an association between the legalization of either medical cannabis (Liang et al., 2018; Lopez et al., 2021; Shah et al., 2019) or recreational cannabis (Kropp Lopez et al., 2020; McMichael et al., 2020) in the U.S and a reduction in opioid prescriptions. For instance, when analysing a data set of over 1.5 billion individual opioid prescriptions in the U.S. between 2011 and 2018, McMichael et al. found that recreational and medical cannabis access laws reduced the number of morphine milligram equivalents prescribed each year by 11.8 and 4.2 per cent, respectively (McMichael et al., 2020). Further, negative associations have also been found between the prevalence of medical and recreational cannabis stores (dispensaries) and opioid-related mortality rates (Chan et al., 2020; Hsu et al., 2021). However, other researchers have not found an association between medical cannabis laws and a reduction in opioid use disorder or a reduction in non-medical use of prescription opioids (Segura et al., 2019), indicating that medical cannabis laws may not be a tool for combatting these opioid-related outcomes. In fact, a prospective cohort study from 2016 to 2019 in New York found that among 211 adults with substance use disorders, the odds of opioid use appeared to be approximately doubled on the days when cannabis was used (Gorfinkel et al., 2021).

Moreover, a recent longitudinal study has found that cannabis use is a risk factor for increased opioid use (Olfson et al., 2018). Secondly, findings from ecological studies on an association between access to cannabis and decrease in opioid prescriptions do not demonstrate causality. Thus, it cannot be ruled out that, a potential explanation for the observed association could be that in many U.S. states, the implementation of medical cannabis laws coincides with other initiatives designed to reduce opioid overprescribing (Tormohlen et al., 2021). Yet another argument against the relevance of use of cannabis as a substitute for opioids is that there currently is limited high quality evidence for the use of cannabis in pain management (De Aquino et al., 2021; Humphreys et al., 2019), see also section 4.2.4. *Efficacy of cannabis or cannabinoids.*

Despite the arguments listed above concerning the limitations of ecological findings and the lack of high-quality research on the use of cannabis in pain management, there may still be plausible indications of cannabis being a relevant substitute for opioids. Cannabinoids have been shown to modulate pain processing pathways and may, beyond their direct analgesic effects, work synergistically to enhance opioid analgesia (Nielsen et al., 2017; Woodhams et al., 2015). Some researchers have explored the potential opioid-sparing effects of cannabis or cannabinoids at the individual level, either through RCTs or observational studies, and the

results of this body of research are summarized in a recent systematic review and meta-analysis, which concludes that the opioid-sparing effects of medical cannabis remain uncertain due to very low certainty evidence (Noori et al., 2021). The review included four RCTs exploring Sativex (a combination of THC and CBD) as an add-on therapy given to 1,176 cancer patients with poorly controlled chronic pain and found that adding Sativex was not associated with a reduction in opioid use (Noori et al., 2021). However, as the authors point out, this is very poor quality evidence, since the studies were not designed to explore substitution use and all the patients in the four studies were instructed not to alter their dose of opioids (Noori et al., 2021). Of the eight observational studies reviewed, the authors found very low certainty evidence suggesting that adding medical cannabis allows patients with chronic non-cancer pain to reduce their use of opioids (Noori et al., 2021). After this review, other relevant studies have emerged, one in support of cannabis as a substitute for opioids and another against it. A prospective observational study of 1,045 Israeli patients with chronic pain who initiated use of medical cannabis found that, among the 551 who completed the 12-months follow-up, there were 42% reduction in opioids use (Aviram et al., 2021). Yet another prospective observational study of 1,145 Canadian medical cannabis patients found that 28% of the patients reported opioid use at baseline, while only 11% reported opioid use after six months (Lucas et al., 2021). Also, the same study found that the daily opioid use reported by the prescribing physician went from 152 mg morphine milligram equivalent (MME) at baseline to 32.2 mg MME at 6 months, resulting in a 78% reduction in mean opioid dosage. However, a register-based study on 2,741 Danish pain patients redeeming at least one prescription for either cannabis-based medicines or whole-plant cannabis via the MCPP, shows that compared with propensity score-matched controls, these patients did not reduce their use of opioids (Hjorthøj et al., 2022). In fact, users of pure THC used more opioids during follow-up than controls. These recent studies have both strengths and limitations. For instance, the study by Lucas et al. had a long duration (6 months) and explores use of whole-plant cannabis, however they rely on a convenience sample of medical cannabis users and rely on some self-report, which introduce the same biases as the Ph.D. project, with selection bias and self-report bias. Moreover, the study is funded by Tilray, a for-profit cannabis production company, which holds the risk of industry sponsorship bias (Burnham et al., 2019; Holman et al., 2018). The study by Hjorthøj et al used register data, and thus it is not subject to the same biases as self-reported data. Also, the study used matched controls, so they were able to account for natural fluctuations in use of medication. However, in this study, the treatment period for some of the patients included is shorter (only one prescription redeemed), and the intervention in this population was a mix of both cannabis-based medicines, Sativex and whole-plant cannabis, making it more difficult to infer the study findings to medical use of whole-plant cannabis.

In sum, with respect to the potential substitution effect of cannabis on opioids, there seems to be the same overall picture (and challenge) as with the question of the efficacy of cannabis, namely that while real-world evidence indicates that cannabis may function as a substitute for prescription drugs, in particular opioids, there is currently limited high-quality evidence to support using cannabis as a substitute for opioids.

4.2.7. Paths to becoming a medicinal cannabis user

Study 3 explored the paths that users take when becoming a medicinal cannabis user. In this study, I found great heterogeneity in demographics, motives for use, and patterns of use, depending on the level of previous recreational experience (RE) with cannabis and on whether medicinal use had developed on a gradual transition from recreational use.

A small majority of participants (53,9%) had RE, which is a higher rate than in the general population, where data on the prevalence of RE has shown that 44.8% of Danes between 16-44 years of age had used cannabis at least once in their life (Danish Health Authorities, 2020). Moreover, 26,5% of the participants in this study had regular RE, which is substantially higher than in the general population, where estimates of “high-risk” use (<20 days/month) are 0.9% of Danes aged between 16-64 years (Danish Health Authorities, 2019). A higher prevalence of previous RE compared to the general population is a consistent finding among users of CaM. For example, observational studies from the U.S. (Boehnke et al., 2019; Pacula et al., 2016; Reinarman et al., 2011) and Canada (Walsh et al., 2013) have all found that a majority of users of medical cannabis had previous RE with cannabis.

There are several ways of interpreting this higher prevalence of RE among users of CaM. For one, those who already have experience with cannabis use may be less reluctant to experiment with medicinal use compared to never users. Also, those who try cannabis recreationally are likely to be more willing to experiment with the use of CaM, compared to those who do not try cannabis recreationally. Moreover, the higher rate of RE among users of CaM can be understood as the medicalization of current use; as discussed in Study 3, re-negotiating a current recreational and/or problematic cannabis use as a medicinal cannabis use could be viewed as a discursive tool to escape criminalization and instead trade “badness for sickness”. Indeed, a context where medical cannabis use is legal and recreational cannabis use is not will likely encourage current users of cannabis to medicalize use to avoid criminalization and stigmatization (Lankenau et al., 2018; Satterlund et al., 2015). However, several qualitative studies have found that some cannabis users appear to express a sincere

perception of their cannabis use as use that has transitioned from being recreational to currently being wholly or at least partly medicinal (Cohen, 2015; Dahl et al., 2011; Lankenau et al., 2018; Pedersen, 2015). In all, the different study findings indicate some of the dilemmas in the field of medical cannabis use, which to some degree can be said to mirror dilemmas in medicine with respect to pleasure and non-medical use of prescribed drugs (Bundy et al., 2017; Keane, 2008; Pawson et al., 2017).

Findings from Study 3 also show that medicinal cannabis users with a high degree of RE are characterized by being younger, more likely male, and more likely to use smoked cannabis products that are conventionally high in THC compared to medicinal users without RE. Also, findings from Study 3 show that having RE is associated with using CaM to treat mental health conditions, particularly when medicinal use has happened on a gradual transition from recreational use. These findings are echoed in previous qualitative studies on the process of becoming a medicinal cannabis user (Cohen, 2015; Dahl et al., 2011).

Findings also show that when establishing the use of CaM, users with no RE rely more on social networks of information, such as online descriptions of use or guidance from other users of CaM, while users with RE rely more on self-experimentation. Aside from the relevance of exploring cannabis as a drug through RCTs that explore the efficacy (or lack of efficacy) in the treatment of mental health conditions, these findings point to the relevance of exploring how cannabis use is constructed. For one, these findings indicate the role that cannabis-positive sub-cultures may play with regards to initiation (and continued use) of CaM. Secondly, the findings underline the relevance of how cannabis use is constructed in an interplay between the drug itself and the *set and settings*, that is, the mindset of the user and the context that inspired and shaped the use of medicinal cannabis. Indeed, it could be argued that substantially different drug effects are produced depending on context of use. The findings suggest that having “medicine in mind” when initiating cannabis use may play a major role in shaping the patterns and practices of use and thus lead to a more medicalized approach to the use of CaM. Conversely, when cannabis use is initiated in a recreational context, the findings suggest that patterns and practices of use are more likely to produce (intended) intoxicating effects. It is very likely that such user practices appear to ‘spill over’, even when cannabis use is reinterpreted as medicinal. In this context, it is worth discussing whether initiation of cannabis use in a recreational context may in fact, make potential underlying therapeutic explanations for cannabis use less visible. This may particularly be the case for users with undiagnosed mental health conditions, where the pleasure and positive effects associated with cannabis in part may be due to the fact that cannabis intoxication may alleviate uncomfortable mental states in the short term. Indeed, the blurred boundaries between pleasurable and medicinal effects have been articulated by users of CaM (Newhart et al., 2018; Ryan et al., 2017). Also,

there are indications that some users prefer the interpretation of recreational use over the stigma that comes with having a mental disorder (Newhart et al., 2018).

The findings on links between a high degree of RE with cannabis and a tendency to treat mental health conditions with cannabis are extremely relevant for research and clinical practice that address dual diagnosis or co-morbidity consisting of both problematic substance use and one or more mental health conditions (Benjaminsen et al., 2020; Johansen, 2018; Thomsen et al., 2018). Indeed, the uncomfortable state of the onset of a mental health condition may lead to increased cannabis use as self-medication (Suh et al., 2008; Thomsen et al., 2018), or cannabis use may alter neuronal regulation increasing the risk of developing mental health conditions (Jenkins et al., 2021). Further, other pre-existing factors may contribute to the development of both problematic cannabis use and mental health conditions (Demontis et al., 2019; Pasman et al., 2018).

Although the relationship between problematic cannabis use and mental health conditions is a complex issue (National Academies of Sciences Engineering and Medicine, 2017), it is noteworthy that the medicalization of cannabis has attracted a group of previous recreational users who are interested in medicalizing their use. Thus, while the medicalization of cannabis for a large part, has been driven forward by activists and patient groups arguing for legal access to medical cannabis for patients with severe somatic conditions, such as cancer and MS (Nunberg et al., 2011; Taylor, 2010), it also appears to have attracted people who are interested in, or who currently are, using cannabis for managing chronic pain, sleep problems, and mental health conditions. Despite the experienced effect, choosing such a path is not without risk, as cannabis use has been associated with the worsening of some mental health conditions (National Academies of Sciences Engineering and Medicine, 2017). However, the magnitude of that risk is arguably dependent on the context of the use of CaM, and it could be relevant to discuss to what extent users could benefit from entering a professional treatment context, where other enabling resources are available to help them manage their condition and where issues such as dosage, cannabinoid composition, coping strategies and motivation for use can be discussed and guided. As part of this discussion, it could also be relevant to discuss to what extent more research in this area is warranted, as it may potentially contribute to the development of novel approaches in the treatment of both mental health conditions (Cohen et al., 2020; Sarris et al., 2020; Scherma et al., 2020) and cannabis use disorder (Freeman et al., 2020b; Thomsen et al., 2021).

4.3. Conclusion of the thesis

My hope is that this thesis contributes to a better understanding of a seemingly growing trend in Denmark with regard to using cannabis as medicine. Besides contributing with more knowledge on who embarks on this trend and why they do it, I also hope that this thesis will contribute by informing policymakers, clinical practitioners, and the general public on the complexity related to the development of medicinal cannabis use. Findings from the thesis indicate that a large majority of users of cannabis as medicine (CaM) remain outside the safe and legal framework created by the Medical Cannabis Pilot Program (MCP). The question is what we do about this and how we make sure that they get the help they need for their conditions and improve their quality of life.

Importantly, findings from this thesis also indicate the emergence of a novel subtype of cannabis use that is distinct from the conventional practices of recreational cannabis use. The prevalent use of cannabis oils and low potency CBD oils, in particular, indicates that many of the users have an interest in effects of cannabis beyond the high conventionally associated with recreational cannabis use. Moreover, findings from this thesis also indicate that users of CaM outside the MCP use cannabis for managing a variety of conditions, of which the most prevalent are chronic pain, sleep disturbances, stress, arthritis, anxiety, and depression, all conditions for which there is currently insufficient or no high-quality evidence of efficacy. Despite this lack of evidence, most users report experiencing positive effects from use, however, these findings cannot be interpreted as evidence of efficacy of cannabis due to limitations related to the study (See 5.2 *Limitations*).

The thesis also explores the use of CaM in the context of existing pharmacological treatments available, and findings from the thesis indicate that substitution of prescription drugs is a frequent motive for the use of CaM, as a majority of the respondents report having used cannabis in order to replace a prescribed drug, predominantly pain medication. Also, findings show that the users experience cannabis to be an effective substitute for prescription drugs, as most report cessation or substantial reduction as a consequence of the use of CaM. However, it is not possible to know whether these findings do, in fact, reflect a substitution effect of cannabis on prescription drugs due to limitations related to the study (See 5.2 *Limitations*), and at present, there is limited high-quality evidence on the use of cannabis as a substitute for opioids.

Lastly, findings from the thesis also show that some of the heterogeneity among users of CaM, in terms of demographics, motives for use, and patterns of use, is associated with the level of previous recreational experience (RE). Compared to medicinal users without RE, findings show that users with recreational experience were more likely male, more likely to use smoked

cannabis products that are conventionally high in THC, and more likely to treat mental health conditions - and even more so if medicinal use had evolved on a gradual transition from recreational use.

Taken together, the findings in this thesis indicate that the concept of medical cannabis has attracted different sub-groups of users in Denmark; cannabis novices with a medicalized approach to the use of CaM and previous recreational cannabis users who are interested in medicalizing their current use of cannabis.

I find that two main points arise from the findings in my thesis.

On the one hand, it points to the relevance of exploring cannabis as a drug in high-quality RCTs, to further explore potential efficacy of cannabis in order to improve our understanding of the use of CaM that is occurring. However, as such research is still challenged by the multiple barriers to whole-plant cannabis research, which I also discussed in Chapter 1, it also points to the relevance of monitoring the current medical and medicinal use among users in the MMCP and outside through the collection of real-world data. On the other hand, it also shows that it is highly relevant to consider and examine how cannabis is being constructed as medicine. The mindset of the users and the settings where their use is initiated appear to have great implications for the initiation and continuation of cannabis use, particularly for the patterns of use of CaM. Consequently, more qualitative research is needed on the paths of the individual CaM user, including the cannabis positive-subcultures and the broader societal context that appear to play a major part in shaping the use of CaM.

Chapter 5. Strengths and Limitations

An important part of research is to be aware of the strengths and limitations of the conducted studies and how they affect the weight of the study findings and stated evidence. Thus, in this chapter, I highlight the strengths and limitations of the thesis.

5.1. Strengths

The Ph.D. project explores a phenomenon in society that is of great public health interest and of broader societal interest, both nationally and internationally. There are several strengths in this Ph.D. project. For one, the method of using an anonymous web-based survey presents a superior method for exploring a sensitive topic in a hidden population, making it the best available method for exploring the use of CaM in Denmark, where a large proportion of use occurs outside the safe and legal parameters of the MCPP. Another strength of the project is that the used survey instrument explores multiple elements and aspects of the use of CaM, and that the design of the survey was based on the existing literature, expert knowledge on medicinal cannabis use, and available online testimonials, which was revised through pilot interviews and input from laypeople, experts on medicinal cannabis use, and other drug researchers. Another strength of the project is the extensive and active recruitment process of respondents, based on experiences from previous survey studies that have successfully recruited cannabis users for participation. This recruitment method resulted in a large sample size with a wide distribution of age and geography. Also, it allowed for extensive overview of the studied phenomenon in a large sample, including an exploration of subsets of users with regards to experiences with cannabis as a substitute for prescribed drugs as well as users with recreational experience with cannabis use. Lastly, a strength of the project is the aim of including well-known perspectives on cannabis, both as a drug and as a construct, that is, the aim of including both the bio-chemical effects of cannabis, the mindset of the user of CaM, and the contexts that shape this use.

5.2. Limitations

5.2.1. Limitations of the Ph.D. project

It is also important to mention the limitations of the Ph.D. project. As the sample is a self-selected convenience sample, it limits the ability to generalize the study findings to the whole

population of interest. Consequently, this project does not explore the use of cannabis as medicine among all Danes, but among those Danes who had knowledge about the project and were willing and able to answer the survey. Consequently, the project may be missing aspects of the studied phenomena in subsets of the Danish population. Also, as a result of using a self-selected convenience sample, the sample in this project may weigh towards users with positive experiences with the use of CaM, as users who have found cannabis ineffective or experienced adverse events may have disengaged from the topic and therefore have been less likely to be aware of the project or to feel inclined to answer the survey. That this may be the case is indicated in the analysis of break-offs, where respondents who broke off before answering the whole survey reported a significantly lower experienced effect of use of CaM compared to respondents who answered the entire survey. Thus, this finding demonstrates that the respondents who experience the greatest effects may be likely to be more motivated to answer a somewhat lengthy survey about their use of CaM. Moreover, self-reported data generated through an online survey may be prone to self-reporting biases, such as recall bias or social desirability bias (Krumpal, 2013); that is, respondents may report answers that they perceive to be socially acceptable in order to gain social approval, preserve a positive self-image, or because they perceive themselves to be stakeholders in the outcomes of potential survey findings. Further, as IP addresses were not available to me, it is impossible to rule out repeated participation.

Moreover, I cannot rule out that the recruitment material may have oversampled current users, as some of the recruitment material indicated currency in use of CaM. Also, the recruitment strategy used in this project may have resulted in an oversampling of users with positive experiences with the use of CaM by recruiting from venues that arguably are likely to be over-represented by people with favourable views on cannabis in general or on the use of CaM in particular; it is likely that the utilization of Facebook support groups may have led to oversampling of users with positive perceptions on CaM, as these groups may cultivate positive perceptions on CaM.

Lastly, while my Ph.D. project draws inspiration from qualitative studies and utilizes a constructivist processed based approach to the quantitative data in one of the studies, it does not involve an exhaustive inquiry into the complexities of the lives of medicinal cannabis users. As a consequence, several aspects of the research questions on why users use CaM remain unaddressed. More qualitative studies are warranted to explore the complexities related to medicinal cannabis use, including the process of becoming a medicinal cannabis user, issues related to access to cannabis and experienced stigma, the motives of substitution use, and the blurred boundaries between medicinal and recreational/problematic cannabis use.

5.2.2. Specific survey limitations

While it is impossible to cover all aspects of the studied phenomenon with a survey instrument, some aspects could have been useful to add or relevant to alter in a further exploration of use of CaM when using a survey. For one, the survey lacked a question on where the respondents had become aware of the survey, as this would have allowed for more knowledge on which recruitment strategies were most effective. Also, the survey could have benefitted from a question on the age of first use of cannabis, as early onset of use has shown to be an important factor in developing problematic cannabis use. Moreover, the categories for the item exploring classes of prescription drugs substituted could have benefitted from the inclusion of categories such as anxiety medication and sleep medication, as the fact that these classes of drugs were lacking as categories may have led to them being underreported. However, the respondents were able to note the type of medication they used.

Further, the survey lacks a sentence at the beginning explaining to respondents that they could withdraw their consent for participation at any time until the survey was completed. Such a sentence was excluded from the introductory text after the pilot interviews revealed that the text was too long and people did not read it. However, according to the Helsinki Declaration, respondents must be informed of their right to withdraw their consent to participate (World Medical Association, 2013). Also, the survey lacked an explicit declaration that participants should be 18 years of age or older, which meant that 3 of the respondents had to be removed from the samples used in the three studies. Also, the survey originally included open-ended questions about the positive and negative aspects of being a medicinal cannabis user (see appendix 1); however, these questions were discarded following advice from a senior researcher. These questions could potentially have generated qualitative material that would have been valuable to the project, particularly in the context of the adjusted scope of the Ph.D.

Further, the item exploring a gradual transition from recreational use to use of CaM could have been formulated differently and rephrased so that the response option about the initiation of medicinal use “from one day to the next” was changed to “I have had a period of cessation between recreational and medicinal cannabis use.” This change could have made the question more precise and potentially easier to understand for the respondents. Lastly, a future avenue for exploration in a survey is the experienced challenges related to driving, as this is likely a dilemma for many medicinal users because of the risk of criminalization while driving with THC in the blood.

Chapter 6. Reflections on findings

The finding from the thesis points to several potential public health problems that are important to discuss. In chapter 6 of the thesis, I outline the potential public health problems related to the use of unregulated cannabis used with a medical motive and reflect on potential harm reduction strategies and strategies to mitigate the use of unregulated CaM.

6.1. Addressing the trend of medicinal cannabis use

In this section, I discuss the relevance of addressing the challenges related to medicinal cannabis use in Denmark, i.e., the use that occurs outside the safe and legal framework created by the Medical Cannabis Pilot Program (MCPP). Also, I suggest strategies to reduce the harms of this type of use and strategies to decrease the use of medicinal cannabis in Denmark.

This thesis shows that substantial use of cannabis with a medical motive currently is occurring outside of the safe and legal framework created by the MCPP. Therefore many users who use cannabis for somatic and mental health conditions seemingly rely on an unregulated market for supply. While the MCPP has allowed approximately 2.550 patients access to safe and legal cannabis products, the interest in the use of CaM appears to be much more widespread in the Danish population. As a result, the 'black market' appears to have been quick to accommodate this demand, which is mirrored in an apparent rise in the availability of cannabis oils in this market. Findings from this thesis also indicate that medicinal users treat a great variety of conditions with cannabis, experience a substantial relief of symptoms related to these conditions, and to a large extent, experience limited side effects. In a critical interpretation of the findings, the use of CaM could be seen as a fad among a subgroup of Danes, who are inspired by post-factual discourse, brought on by a concert of media attention, celebrity validation and cannabis activism, displaying cannabis as a panacea despite limited high-quality evidence. In a generous interpretation of the findings, the use of CaM could be seen as an indication that some Danes are currently experiencing a lack of adequate relief from conventional treatment and therapies targeting somatic and mental health conditions, to the extent that they solicit an illegal market, where some of them find a solution to their distress. Regardless of which interpretation one maybe inclined to lean towards, the trend in the use of CaM that the findings indicate is important to address.

In light of the relatively easy access to illegal cannabis products in Denmark and the implicit societal acceptance of medicinal use signalled with the initiation of the MCPP, it is unlikely that this trend in the use of medicinal cannabis in Denmark will diminish on its own accord or

as a consequence of discouragement of use from health officials. Therefore, it is important to consider the potential public health problems related to the use of medicinal cannabis and discuss relevant strategies that may mitigate such problems. Article 20 of the Helsinki Declaration states that *medical research with a vulnerable group is only justified if the researcher is responsive to the health needs or priorities of this group* (World Medical Association, 2013, p. 2192). As medicinal cannabis users arguably form a vulnerable group due to risks of criminalisation and stigmatization, based on the findings in this thesis, I have chosen to focus on the potential public health problems related to their use and suggest potential relevant strategies that may mitigate these problems. Below, I outline three potential public health problems related to the current medicinal cannabis use in Denmark as I see them.

6.2. Potential public health problems

From my point of view, the extensive medicinal use of cannabis from the illegal market presents at least three significant potential public health problems: 1) use is unguided by a medical professional, 2) the cannabis products that are used are unregulated, and 3) the cannabis use may have negative health impacts.

The first potential public health problem is related to the fact that medicinal cannabis use is unguided by a medical professional, both for dosing strategies and the pharmacokinetic considerations related to absorption of the consumed cannabis product. The general approach to cannabis initiation is “start low, go slow, and stay low” (MacCallum et al., 2018, p. 13). A lack of medical guidance in this process may increase the risk of acute and chronic overdosing. Further, without the guidance of a medical professional, less consideration may be given to the contraindications of medical cannabis use, such as pregnancy, history of psychosis, and cardiac conditions (MacCallum et al., 2021b). Moreover, when cannabis is consumed without medical supervision, there is no professional monitoring of potential drug interactions between cannabis and other prescription drugs prescribed for the patient. Several studies indicate that cannabinoids affect drug-metabolizing enzymes (Brown, 2020; Qian et al., 2019), and medicinal cannabis use unguided by a medical professional may alter the disposition of concomitantly consumed prescription drugs, potentially reducing effects or enhancing adverse effects of such drugs. Further, it is well-known that far from all patients respond adequately to treatment based only on medication, and lack of professional monitoring may risk ruling out access to relevant therapeutic interventions that support improved somatic and mental health, for example, by increasing awareness of the condition(s)

and by strengthening coping skills and problem-solving (Klainin-Yobas et al., 2016; Lukens et al., 2006; Motlova et al., 2017).

The second potential public health problem is the unregulated cannabis product consumed, as there are several product quality issues related to unregulated use. First and foremost, the cannabinoid composition of illegal cannabis products is often unknown to the user, and the marked increase in THC content in the last decades (Freeman et al., 2020a; Rømer Thomsen et al., 2019) may have exposed some users to higher levels of THC, as findings from naturalistic studies indicate that users do not fully adjust their use to differences in THC concentration (Freeman et al., 2014; van der Pol et al., 2014). Also, in the instances where the main cannabinoids (THC/CBD) are declared on the product, such labelling has been found to have inaccuracies, both in Denmark (Eriksen et al., 2020), elsewhere in Europe (Hazekamp, 2018; International Cannabis and Cannabinoids Institute, 2018), and the US (Bonn-Miller et al., 2017). In some cases, the THC content is higher than labelled, which leaves the users unknowingly in violation of the Euphoric Substances Act, which prohibits the consumption of cannabis with more than 0.2% THC (Danish Medicines Agency, 2018).

Moreover, illegal cannabis products have been found to contain natural contaminants related to production, such as fungi, bacteria, heavy metals, pesticides, or other chemicals (Lenton et al., 2018; MacCallum et al., 2021a; National Academies of Sciences Engineering and Medicine, 2017). The direct human toxicology of these production-related contaminants is underexplored but includes infection, carcinogenicity, reproductive, and developmental impact (Dryburgh et al., 2018). In addition, illegal cannabis products have been found to contain artificial contaminants related to marketing, such as lead or glass beads, which have been added to increase the weight of the product, or in the form of other substances added to increase the psychoactive effect of the product (National Academies of Sciences Engineering and Medicine, 2017). Indeed, both natural and artificial contaminants pose a potential health risk for users of cannabis from the unregulated market, and such contaminants could be particularly problematic in clinical populations, where the immune system is often already compromised (MacCallum et al., 2021a).

The third potential public health problem is related to the biochemical effects of the cannabis plant, i.e., the potential adverse effects of the cannabinoids in the consumed product. A review of systematic reviews of cannabis use-related health harms has found that cannabis use is associated with harm to mental health (psychosis, bipolar disorder, depression, anxiety, and cannabis dependence), somatic conditions (respiratory, cardiovascular, gastrointestinal, nervous system, cognitive functions, and some cancers), and injuries (motor vehicle collisions,

violence, and suicidal behaviour) (Campeny et al., 2020). While these associations can contribute to our understanding of the potentially harmful effects of cannabinoids, it is worth noting that this body of evidence is comprised of observational studies, limiting the ability to infer causality between cannabis use and adverse outcomes. Also, it is important to note that these potential adverse effects of cannabis use are related to the cannabinoid composition of the cannabis product consumed (as discussed in section 2.4.3. *Cannabis composition matters*), the mode of intake (Russell et al., 2018), and the co-administration of tobacco with cannabis (Gurillo et al., 2015; Hindocha et al., 2016). Notwithstanding, there are potential adverse effects of the bio-medical effects of cannabinoids, which add to the overall potential public health problems related to medicinal cannabis use.

6.3. Reducing harms related to medicinal cannabis use

In the following section, I discuss two harm reduction strategies that could address the public health problems related to medicinal cannabis use in Denmark: improving and expanding the MCPP and legalizing and regulating the sale of cannabis products with low THC content.

6.3.1. Improve and expand the MCPP

A central defining characteristic of harm reduction is focusing on reducing harm as the primary goal rather than attempting to reduce drug use (Lenton et al., 1998). Thus, in this case, a harm reduction approach means taking measures that could reduce the adverse effects related to the medicinal cannabis use that is already occurring. The current MCPP could be viewed as such an approach, as the intent is to create a *safe framework for the use of medical cannabis within the healthcare system (...) providing a legal alternative for some of the patients who self-medicate with illegal products*" (Ministry of Health, 2016, p. 1). Expanding the MCPP to include more patient groups could reduce the harms related to the use of unregulated cannabis products without guidance from a medical professional. However, as several patient organizations have pointed out (Danish Ministry of Health, 2020), there are current challenging issues with the MCPP, such as medical doctors reluctant to prescribe cannabis and expensive cannabis products - both factors that may create significant barriers for qualified treatment with medical cannabis in Denmark. Such issues need to be addressed for an expansion of the MCPP to have harm-reducing effects of mitigating potential public health problems related to medicinal cannabis use. A potential solution to addressing the reluctance of medical doctors to prescribe medical cannabis to patients could be to re-structure the MCPP, so that the medical doctors are not required to prescribe cannabis to the individual patient but merely to

acknowledge that they are eligible for access to medical cannabis following the MCPP guidelines, which then serves as a permit to buy medical cannabis legally. Such a framework resembles some states' legal, medical cannabis in the U.S, where cannabis is obtained via a medical doctor's recommendation and not a prescription.

6.3.2. Legalize and regulate low THC cannabis products

Beyond expanding and improving on the current MCPP, another strategy that could reduce potential harms related to medicinal cannabis use is to legalize and regulate the market for cannabis products with high CBD and low THC content, as this has the potential to create safer material conditions for the medicinal users of such products. Moreover, the legalization of low THC products could also impact consumption patterns among users of other subtypes of cannabis, as it may have done in the case of the unintended legalization in Italy. In Italy, the increased availability of low THC products has been significantly associated with a decrease in confiscations of illegal cannabis and drug-related arrests (Carrieri et al., 2019), suggesting a substitution effect of low THC products on other illegal cannabis products. Conversely, it could be argued that the legalization of cannabis products with high CBD and low THC content could negatively affect public health, as it may expose new user groups that would have otherwise remained cannabis novices. This is a relevant argument, as findings from this Ph.D. project found greater use of CBD oils among cannabis novices, thus indicating that these products may appear more attractive and accessible to novices. Still, it could also be argued that this has already happened in Denmark to some extent, as possession and use of cannabis products with less than 0,2% THC became legal in 2018. However, the sale of such products remains a grey area, as they are estimated to be illegal to sell in most cases under the Danish Medicines Act (Danish Medicines Agency, 2018). Thus, the current policy in Denmark seems to have created a situation where the use of CaM is legal while the products used are not, leaving legal users to navigate an illegal, unregulated market. Hence, it is worth discussing to what extent these conditions could be improved by legalizing and regulating the market for low THC cannabis products.

6.4. Strategies to reduce medicinal cannabis use

Beyond harm reduction strategies that could mitigate the potential harms related to medicinal cannabis use, it is also relevant to consider how to reduce medicinal cannabis use or reduce the influx of new users to this trend. In the following, I discuss strategies that could be employed to reduce the use of medicinal cannabis use in Denmark by addressing treatment barriers and challenges, the current business model of social media, the current consumerist tendencies in health care, and the dominant bio-medical perspective on health and illness.

6.4.1. Address barriers and challenges in the formal treatment

One strategy that could potentially decrease the use of medicinal cannabis in Denmark could be to address potential barriers and challenges in the formal treatment of the conditions for which people currently use medicinal cannabis. In particular, the prevalent use of medicinal cannabis in the treatment of pain conditions, and the finding that medicinal users who treat chronic pain are more likely to use cannabis as a substitute for prescription drugs, could be indicative of broader issues in the current management of non-malignant chronic pain in Denmark. Such issues have been addressed in an analysis made in 2017 by the Danish Psychological Association (DPA) in collaboration with other societies and patient organizations (Danish Psychological Association, 2017). The analysis was made in the context of a request to make non-malignant chronic pain the topic of a national network tasked with exploring the possibilities for improving treatment for various areas in the health care system. The analysis concludes that the quality of care for Danish patients with chronic pain does not reflect current best practice, pointing to low levels of knowledge about pain treatment in the primary sector, a one-sided focus on pharmacological interventions such as opioids, long waiting periods before a suitable treatment is offered, as well as large geographical variations in treatment quality. Improving on the issues raised in the analysis may be an important part of a bigger strategy that aims to reduce the use of medicinal cannabis in the Danish population, as insufficiencies in the existing treatment system may be a factor leading some Danes to seek the illegal market for medicinal cannabis to manage their pain condition. As the recommendation made by the DPA in 2017 to create a national network focused on improving the treatment of non-malignant chronic pain patients was not accepted (Bell, 2021), it appears that the prevalent use of illegal cannabis products to treat various pain conditions offers yet another reason why such a national network is still needed.

Moreover, the increasing use of the “weaker” opioid Tramadol in Denmark (Danish Health Authority, 2016), the media attention to Tramadol use in 2017, and the subsequent decision

to take regulatory action to decrease use (Sørensen et al., 2021), may have been an independent factor in increasing use of medicinal cannabis in Denmark. In September 2017, following media scrutiny of increased Tramadol use, the Danish Medicines Agency made reporting on adverse events for Tramadol use mandatory for doctors (Danish Medicines Agency, 2017b). From January 2018, Tramadol was put under more strict regulatory restrictions in the same category as morphine and oxycodone (Danish Medicines Agency, 2017a). The media attention on this topic and the regulatory action that was taken appear to have substantially impacted the number of Tramadol users, which fell from 30 out of 1.000 individuals in late 2016 to 18 out of 1.000 individuals in January 2020 (Sørensen et al., 2021). Of note, The data in this thesis were collected in the last half of 2018 and found that of the 1.246 respondents who reported the type of pain medication they substituted with cannabis, Tramadol was the most common pain medication reported (27,2% of all pain medication substituted). While this finding may reflect the fact that Denmark had a high rate of Tramadol use at the time of the data collection, it may also reflect the media scrutiny of Tramadol or reduced access to Tramadol, leading users to seek other therapies and ending up consulting an illegal market for medicinal cannabis. Indeed, drug use and abuse exist in a complex, interconnected space, and reducing the access to legal opioids when a large consumer base has already been established leaves a vacuum that can be filled by the illegal market (Pacula et al., 2018).

Interestingly, the increased use of Tramadol in Denmark happened largely due to another vacuum in the available pharmacological treatments for chronic pain patients, namely as a consequence of the reduction in the use of nonsteroidal anti-inflammatory drugs (NSAIDs) following the discovery of serious long term side-effect from use of these types of drugs in 2013 (Danish Health Authority, 2016; Sørensen et al., 2021). Recently, it appears that, beyond the potential spill over into the illegal cannabis market, the vacuum left by Tramadol has been followed by an increased use of oxycodone (MEDSTAT.DK, 2021; Sørensen et al., 2021, see also Appendix 2). Thus, from NSAIDs to Tramadol to Oxycodone (and perhaps also to medicinal cannabis), it appears that there may be a cycle of vacuums in the pharmacological treatment of non-malignant pain patients in Denmark. This observation further underscores the relevance of creating the national network suggested by the DPA that explores the possibilities for improving treatment for this patient group.

6.4.2. Regulate the attention economy

Another strategy to reduce the emergence of new medicinal cannabis users could be to consider the proliferation of “cannabis positive” subcultures online, and the incentives of social media sites to promote such content to its users. In the last decades, the internet has created fundamental shifts in the diffusion of health-related knowledge and the availability of practical experiences with illicit drug use. Thus, in the last 10-15 years, there has been a marked increase in the utilization of social media for health communication, where people within a specific patient group interact, share tailored health information, offer peer support, and debate health care policies (Hale et al., 2014; Moorhead et al., 2013; Partridge et al., 2018). Parallel to this development, there has been a formation of supportive drug-related communities online, where users share experiences and advice on drug use (Miller et al., 2010; Walsh, 2011), often with a harm reduction perspective that is defined on the drug users’ terms (Boothroyd et al., 2016; Rönkä et al., 2017; Soussan et al., 2014). Such support groups also appear to have emerged for medicinal cannabis use, as described in section 1.1.3. *The medicinal cannabis use*, with a plethora of large private support groups on Facebook, where experienced users guide newcomers in using medicinal cannabis. The findings in this thesis indicate that social media indeed is a source of inspiration for initiating medicinal cannabis use, particularly among novices, suggesting that these “cannabis positive” subcultures may encourage novices to experiment with medicinal cannabis use.

While Danish medicinal cannabis users may have found their way into these groups independently or had them suggested by friends or family, the groups may also have been suggested by Facebook, as the platform uses personalized algorithms to predict content that will increase user engagement on the platform. As an example of how these algorithms work, Tristan Harris, the co-founder of the Center for Humane Technology, points to an experience of his co-worker, who was a new mom and who joined a “make your own baby food”-group on Facebook, where Facebook subsequently began recommending that she joined anti-vaccine groups (Kantrowitz, 2020). Following leaks of internal documents from Facebook and interviews with former employers, Facebook has recently come under scrutiny for turning a blind eye to its active role in promoting polarizing content to gain user attention and increase time spent on the platform (Danner, 2021; Horwitz et al., 2020). To prevent the inspiration of new medicinal cannabis users, it may be prudent to further explore social media's role in promoting content with illegal drug use. However, it should be noted that the complete removal of medicinal cannabis support groups on Facebook may be counterproductive to public health, as such groups may also function as harm reduction, because they offer prospective users guidance from a “hive-mind” in the absence of formal medical advice. Still, it could be argued

that such groups should not be pushed on initially disinterested people via personalized algorithms by social media companies for profit.

6.4.3. Address consumerist and individualist trends in health care

Lastly, a third strategy to reduce the use of medicinal cannabis in the Danish population could be to address the broader current societal trends in Denmark, related to the commodification of health care and the emphasis on individual responsibility in health-related matters. Sociologist Peter Conrad studies on medicalization (the process of expanding the medical vocabulary to novel areas of the human condition that have previously been understood as a form of deviance (i.e., addiction) or normal life event (i.e., menopause), suggests that we are witnessing a shift in the engines driving medicalization processes (Conrad, 2005). According to Conrad, while doctors still function as gatekeepers for medical treatment, their authority is increasingly challenged by consumer and market interests, creating a fundamental shift in the power to define what can be regarded as medicine. This analysis seems relevant in the context of the re-medicalization of cannabis, where a consumer challenge to the medical authority is definitely at play, and a new market interest seems to be taking shape (Reklaitis, 2019; Richter et al., 2014). Consumerist tendencies in health care are arguably pronounced in Denmark, with a restructuring of the health care sector in the last decades, following neoliberal ideals, introducing private competition to public sector monopoly and enabling free choice in health care services (Kristensen et al., 2016; Larsen et al., 2015; Ranerup, 2010; Rostgaard, 2011). Thus, it can be argued that the current development within the healthcare sector plays a part in promoting the idea that healthcare services can be viewed as commodities in a market, which in turn then makes the patient a consumer. In addition to the consumerist tendencies in health care, it has been argued that we are witnessing the rise of new modes of subjectivity, where individuals are increasingly expected to take responsibility for their health and disease, as well as their individual genetic risk (Rose, 2009). Perceptions of personal responsibility in health management may be particularly relevant in a Danish context, where the public health program has been found to be more liberalistic compared to other Scandinavian countries, emphasizing behaviour and individual choice as causes of ill health (Vallgård, 2011).

Thus, when health care is increasingly understood to be a commodity and health outcomes are increasingly framed in behavioural terms, with self-responsibility in health (and disease), it may also inspire “Do-It-Yourself” health trends, such as the use of medicinal cannabis. Indeed, authority can encourage individual autonomy and self-governance in health-related issues; however, as this thesis demonstrates, it cannot dictate all its modes of practice.

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Appendix

Appendix 1 – Discarded open-ended questions on the positive and negative aspects of medicinal cannabis use.

The image shows a document editor interface with two pages. The left page, labeled 'Side 11', contains two questions. The first question, numbered 27, asks about positive consequences of medicinal cannabis use. The second question, numbered 28, asks about negative consequences. Both questions include a text input field and a rich text editor toolbar. The right page, labeled '[s_64]', shows a zoomed-in view of the question text from the second question on page 11. The text reads: 'Fortæl os hvilke negative konsekvenser dit medicinske cannabisforbrug har for dig i dagligdagen. Er der aktiviteter som bliver sværere at deltage i pga dit medicinske cannabisforbrug?'. The toolbar above the text includes options for font type, size, bold, italic, underline, link, image, table, and HTML export.

Side 11

Fortæl os hvilke positive konsekvenser dit medicinske cannabisforbrug har for dig i dagligdagen. Er der aktiviteter som bliver lettere at deltage i pga dit medicinske cannabisforbrug?

27 Fortæl os hvilke positive konsekvenser

Fortæl os hvilke negative konsekvenser dit medicinske cannabisforbrug har for dig i dagligdagen. Er der aktiviteter som bliver sværere at deltage i pga dit medicinske cannabisforbrug?

28 Fortæl os hvilke negative konsekvenser

Side 12

[s_64]

Skrifttype Skr... A B I U [E] HTML

Fortæl os hvilke negative konsekvenser dit medicinske cannabisforbrug har for dig i dagligdagen. Er der aktiviteter som bliver sværere at deltage i pga dit medicinske cannabisforbrug?

Appendix 2 – Development in number of patients prescribed Oxycodone from 2015 (53.565 patients) to 2020 (90.660 patients).

MEDSTAT.DK

ATC kode: **Alle lægemidler, N02AA05**
 Sægevariabel: **Antal personer**
 Aldersgrupper: **Alle**
 Køn: **Køn, samlet**
 Sektor: **Primærsektor**
 Region: **Hele landet**

Personhenførbart salg	2015	2016	2017	2018	2019	2020
Alle lægemidler	4.097.525	4.125.870	4.122.325	4.108.875	4.129.265	4.064.665
N02AA05 (Oxycodon)	53.565	62.865	69.470	79.645	88.885	90.660

ATC kode	2015	2016	2017	2018	2019	2020
Alle lægemidler	82%	81%	80%	79%	80%	80%
N02AA05 (Oxycodon)	99%	99%	99%	99%	>99%	>99%

Signaturforklaring
 0 eller 0,0 Værdien er så lille, at den ikke kan vises efter afrunding, eller hvor antal personer er 1-4 og data derfor er diskretioneret.
 For antal personer er tallene for Køn, samlet og Alle aldre, afrundet til nærmeste 5
 - Intet salg eller ingen data.

Luk

AARHUS BSS CENTER FOR RUSMIDDELFORSKNING
PSYKOLOGISK INSTITUT
AARHUS UNIVERSITET

AACSB ACCREDITED AMBA ACCREDITED EQUIS ACCREDITED

Bruger du cannabis som medicin?

Del dine erfaringer med os anonymt og hjælp os med at skabe et vidensgrundlag, som kan kvalificere debatten om cannabis som medicin.

En landsdækkende undersøgelse skal gøre os klogere på danskernes brug af cannabis som medicin. Undersøgelsen er en del af et ph.d.-projekt på Center for Rusmiddelforskning, Aarhus BSS, Aarhus Universitet.

Formålet er at skabe et overblik over, hvilke typer af cannabis, der anvendes, hvilke lidelser cannabis anvendes til, samt hvilke effekter og bivirkninger folk oplever.

Kontakt slk.crf@psy.au.dk for mere information.

FIND SPØRGESKEMAET ONLINE: crf.au.dk/cannabis

Appendix 4 - The online survey designed to explore use of cannabis as medicine.

Introductory text:

As a participant in this survey, you are anonymous and your answer is stored in accordance with the Personal Data Act

The questionnaire takes approximately 15 minutes to fill out and your replies will only be used for the research project

The questionnaire is a part of a PhD project at the Center for Alcohol and Drug Research, exploring the use of cannabis as medicine among Danes

We want to know what types of cannabis people use as medicine, why they use cannabis as medicine and what effects they are experiencing.

In addition, we ask some practical questions, for example about what inspired the use of cannabis as a medicine, about where you get your cannabis from, and about how many people know about your use of cannabis as medicine

If you have any questions, please contact Sinikka Lehmann Kvamme by email slk.crf@psy.au.dk or by phone: 87165778.
Thank you in advance

.....

Sections of the survey in colour codes:

MOTIVES FOR USE

SUBSTITUTION EFFECT

PATTERNS OF USE

BECOMING A MEDICINAL CANNABIS USER

ACCESS /STIGMA

ATTITUDES AND DEMOGRAPHICS.

Follow-up questions, that were only available to a subset of respondents, are denoted with both a number and a letter (i.e. 1A, 1B)

Meta text: First we would like to know the following:

MOTIVES

1 - Do you use cannabis as medicine?

- (1) Yes
- (2) No
- (3) I have used, but I stopped using.
- (4) I am answering on behalf of someone who cannot answer the survey themselves.

Activation:

"No" turns of the survey with this text: *Thank you for your interest bot this questionnaire is only for those who are current or former users of cannabis as medicine.*

"Stopped using" activates 1A

"Answering on behalf" activates 1B

(1A) – Why have you stopped using cannabis as medicine. (You can choose more than one answer and please answer the rest of the questionnaire with your previous experiences with using cannabis as medicine)?

- (1) It did not work
- (2) I could not afford it
- (3) I did not like getting high
- (4) I did not like that cannabis is illegal
- (5) I did not like the side effects
- (6) I had trouble obtaining cannabis
- (7) I got well and therefore no longer needed cannabis as medicine
- (8) My relatives wanted me to quit
- (9) Other reasons, state which _____
- (10) Do not know
- (11) Do not wish to answer

(1B) – Who do you answer on behalf of? (Please answer the rest of the questionnaire with that person's information)?

- (1) Someone under 18
- (2) An elderly person
- (3) A terminal patient
- (5) Someone too sick to answer the questionnaire
- (4) Other state who _____
- (6) Do not know

2 - Do you have a prescription for cannabis?

- (1) No
- (6) Yes
- (3) Yes and I use other cannabis beside the cannabis I get on prescription
- (4) Do not know
- (5) Do not wish to answer

3 - Have you asked your doctor for a prescription for cannabis?

- (1) Yes
- (2) No
- (4) Do not know
- (5) Do not wish to answer

Meta text: Here comes some questions about what you use cannabis for and about the effect of cannabis that you have experienced

You can use cannabis as medicine for many different conditions. Here is a list of conditions in alphabetical order.

4 – Choose one or more conditions for which you are using cannabis as medicine (you can choose more than one and add your condition if it is missing)?

- (1) Acne
- (2) ADHD/ADD
- (3) Dependence (alcohol)
- (4) Dependence (hard drugs)
- (5) Dependence (prescription drugs)
- (6) AIDS/HIV
- (7) Alzheimer's
- (8) Anxiety
- (9) Anorexia
- (10) Asthma
- (11) Autism
- (12) Bipolar disorder
- (13) Crohn's disease
- (14) Depression

- (15) Herniated disc
- (16) Dystonia
- (17) Eczema
- (18) Epilepsy
- (19) Endometriosis
- (20) Fibromyalgia
- (21) Arthritis (rheumatoid)
- (22) Arthritis (Osteoarthritis)
- (23) Arthritis (Psoriatic)
- (24) Cataracts
- (25) Hepatitis
- (26) Brain damage
- (27) COPD
- (28) Cancer (including side effects from chemo therapy)
- (29) Chronic fatigue syndrome
- (30) Chronic nerve inflammation
- (31) Chronic pain
- (32) Migraine
- (33) Menstrual pain
- (34) Multiple sclerosis
- (35) Neurodermatitis
- (36) Irritable bowel syndrome
- (37) Lupus (SLE)
- (38) OCD
- (39) End-of-life (palliative care)
- (40) Parkinson's
- (41) Peripheral neuropathy
- (42) Psoriasis
- (43) PTSD
- (44) Spinal cord injury
- (45) Pain following operation
- (46) Pain following an accident
- (47) Schizophrenia
- (48) Sleep disturbances/sleeplessness
- (49) Stress
- (50) Tinnitus
- (51) Trigeminal neuralgia
- (52) Tourette's/Tics
- (53) My condition is not on the list (write condition here)_____

(Please note that the entire list of conditions only appear in the question above – after that the respondent only relates to the conditions that they have already chosen)

5 - What is the purpose of your use of cannabis as medicine (you can choose more than one option)? –

- 1. to dampen side effects of other treatment,**
- 2: to dampen symptoms of the disorder,**
- 3: to cure the disorder.**
- 4: don't know.**
- 5: do not wish to answer**

6 - In your experience how has your use of cannabis as medicine affected the symptoms of the condition/conditions you are treating?

- 4: very large improvement.**
- 3: large improvement.**
- 2: moderate improvement.**
- 1: Small improvement.**
- 0 no change.**
- 1 small aggravation.**
- 2: moderate aggravation.**
- 3: Large aggravation.**
- 4: very large aggravation.**

7 - Which of the condition you are treating with cannabis have you been diagnosed with?

- 1: diagnosed.**
- 2: not diagnosed.**
- 3: don't know.**

8 - Which symptoms do you find that cannabis alleviates?

- (1) Thoughts of worry
- (13) Hyperactivity

- (7) Nausea
- (5) Inner turmoil
- (6) Irritability
- (3) Loss of appetite
- (8) Nightmares
- (22) Muscle tension
- (15) Depressive mood.
- (19) Vomiting
- (14) Pain
- (10) Spasticity
- (24) Stress
- (9) Sleep disturbances
- (18) Rumination.
- (11) Tics
- (16) Other, state which_____
- (23) I have not experienced any effect of cannabis on any symptoms.
- (20) Do not know
- (21) Do not wish to answer

Activation:

If you click "Sleep problems or sleeplessness" you get 8A

If you click "Pain" you get 8B

(8A) How many hours do you sleep at night when you are not using cannabis?

- (13) Click here and write a number _____
- (5) Do not know
- (3) Do not wish to answer

(8A) How many hours do you sleep at night when you are using cannabis??

- (1) Click here and write a number _____
- (4) I do not sleep longer when I use cannabis as medicine, but the quality of sleep is improved
- (2) Do not know
- (3) Do not wish to answer

Meta text: We would like to know more about your experiences with use of cannabis for pain

Therefore, we now inquire into your pain level with and without the use of cannabis

(8B) When you are experiencing pain, how would you evaluate that pain without the use of cannabis as medicine?

Please indicate the level of pain on a scale from 0 to 10, where 0 is not pain and 10 is the worst pain imaginable?

- (1) 0
- (2) 1
- (3) 2
- (4) 3
- (5) 4
- (6) 5
- (7) 6
- (8) 7
- (9) 8
- (10) 9
- (11) 10

(8B) When you are experiencing pain, how would you evaluate that pain with the use of cannabis as medicine?

Please indicate the level of pain on a scale from 0 to 10, where 0 is not pain and 10 is the worst pain imaginable?

- (1) 0
- (2) 1
- (3) 2
- (4) 3
- (5) 4
- (6) 5
- (7) 6
- (8) 7
- (9) 8
- (10) 9
- (11) 10

9 - Which side-effects do you experience from the use of cannabis as medicine? – (you can chose more than one)

- (21) I have not experienced any side-effects related to my use of cannabis as medicine.
- (6) Anxiety
- (20) Getting “high”
- (19) Thoughts of worry
- (15) Diarrhea
- (9) Memory impairment.
- (14) Passing psychosis.
- (18) Constipation.
- (1) Increased tiredness.
- (23) Heartburn
- (25) Palpitations/elevated pulse
- (16) Headache
- (3) Irritability
- (10) Dry mouth.
- (11) Muscle fatigue
- (5) Red eyes
- (22) Sweating
- (24) Dizziness.
- (17) Dry skin
- (2) Other, state which_____
- (12) Do not know
- (13) Do not wish to answer

10. How do these statements apply to your situation (Indicate how much you agree/disagree with the statement)?

Strongly agree Agree Somewhat agree Neutral Somewhat disagree Disagree Strongly disagree Do not know Do not wish to answer

1. The use of cannabis as medicine makes it easier for me handle practical chores

(1) (2) (3) (4) (5) (6) (7) (8) (9)

2. The fact that cannabis is illegal is a restraint on my daily life.

(1) (2) (3) (4) (5) (6) (7) (8) (9)

3. The use of cannabis as medicine makes it easier for me to handle my job, education or job-related activities.

(1) (2) (3) (4) (5) (6) (7) (8) (9)

4. I am often worried about being penalized for my use of cannabis as medicine.

(1) (2) (3) (4) (5) (6) (7) (8) (9)

5. The use of cannabis as medicine makes it easier for me to participate in social event

(1) (2) (3) (4) (5) (6) (7) (8) (9)

6. I often find it necessary to hide my use of cannabis as medicine.

(1) (2) (3) (4) (5) (6) (7) (8) (9)

SUBSTITUTION EFFECT

11 - Do you have prior or current experiences with the use of prescription drugs in the treatment of your condition?

- (1) Yes
- (2) No
- (4) Do not know
- (3) Do not wish to answer

"Yes" activates to 11A and 11B and 11C

(11A) Overall, how would you compare the effect of cannabis on your condition compared to prescription drugs that you have tried?

- (1) Cannabis is much more effective than other medication
- (2) Cannabis is slightly more effective than other medication
- (3) Cannabis is just as effective as other medication
- (4) Other medication is slightly more effective than cannabis
- (5) Other medication is much more effective than cannabis
- (6) Do not know
- (7) Do not wish to answer

(11B) Overall, how would you compare the side-effects of cannabis compared to other medication that you have tried?

- (1) The side effects of cannabis are much worse
- (3) The side effects of cannabis are slightly worse
- (2) The side effects for cannabis are equal to the side effects of other medication
- (4) The side effects of other medication are slightly worse
- (5) The side effects of other medication are much worse
- (6) Do not know
- (7) Do not wish to answer

(11C) Have you ever used cannabis as medicine with the purpose of replacing a prescribed drug?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

Activation:

Yes on 11C activates 11D and 11E

(11D) Which type of prescription drug have you replaced with cannabis?

- (1) Anti-depressive medication (indicate which brand) _____
- (8) Anti-psychotic medication (indicate which brand) _____
- (3) Anti-epileptic medication (indicate which brand) _____
- (2) Pain medication (indicate which brand) _____
- (4) Arthritis medication (indicate which brand) _____
- (5) Other, indicate which _____
- (6) Do not know
- (7) Do not wish to answer

(11E) How has your use of cannabis as medicine affected your use of other medication

- (5) I have stopped using other medication
- (1) My use of other medication has been reduced substantially
- (2) My use of other medication has been reduced slightly
- (9) My use of other medication is unchanged
- (3) My use of other medication has increased slightly
- (4) My use of other medication has increased substantially
- (7) Do not know
- (8) Do not wish to answer

PATTERNS OF USE

Meta text: Here comes some questions about what types of cannabis you use and how you use it.

12 - Which type of cannabis do you use? (You can chose more categories)

- (1) THC Olie (angiv styrke i %, hvis du kender den) _____
- (2) CBD Olie (angiv styrke i %, hvis du kender den) _____
- (3) Hash
- (4) Pot
- (5) Skunk
- (11) Sativex (THC og CBD ekstrakter af Cannabis sativa L)
- (13) Dronabinol (Marinol - syntetisk THC)
- (16) Cesament (Nabilone - syntetisk THC)

- (14) Bediol "CannGros"
- (15) Bedrocan "CannGros"
- (6) Other, state what _____
- (9) Do not know
- (10) So not wish to answer

(The chosen product in item 12 was/were the only suggestion(s) shown in item 14)

13 - How often do you use cannabis as medicine?

- (2) 6-7 days a week
- (3) 3-5 days a week
- (4) 1-2 days a week
- (5) A few times a month
- (6) Very rarely
- (7) Do not know
- (8) Do not wish to answer

14 – How much cannabis do you use on average a day as medicine?

- (1) Number of THC drops pr day _____
- (3) Number of CBD drops pr day: _____
- (4) Grams of hash pr day: _____
- (5) Grams of pot pr day: _____
- (2) Grams of skunk pr day _____
- (15) Number of puffs Sativex pr day _____
- (17) Number of capsules of Marinol pr day _____
- (22) Number of capsules of Nabilone pr dag _____
- (23) Grams of Bediol "CannGros" pr day _____
- (24) Grams of Bedrocan "CannGros" pr day _____
- (6) Other (state quantity) _____
- (7) I only use THC occasionally when needed
- (10) I only use CBD occasionally when needed
- (11) I only use hash occasionally when needed
- (12) I only use pot occasionally when needed
- (13) I only use skunk occasionally when needed
- (16) I only use Sativex occasionally when needed
- (18) I only use Marinol occasionally when needed

- (19) I only use Nabilone occasionally when needed
- (20) I only use Bediol "CannGros" occasionally when needed
- (21) I only use Bedrocan "CannGros" occasionally when needed
- (14) I only use "Other" occasionally when needed
- (8) Do not know
- (9) Do not wish to answer

15 – What is your most frequent form of intake of cannabis as medicine?

- (1) Smoked with tobacco
- (3) Smoked without tobacco
- (2) Vaporized
- (4) Oil
- (5) The
- (6) Rectal
- (9) "Edibles" (cannabis in food)
- (12) Capsules
- (7) Topical (cream)
- (8) Other, state what _____
- (10) Do not know
- (11) Do not wish to answer

Meta text: That was the first part of the questionnaire. Thank you for helping us uncover the use of cannabis as a medicine.

The next part contains questions exploring the paths to becoming a user of cannabis as medicine

BECOMING A MEDICINAL CANNABIS USER

16 - How did you reach your current dose of cannabis? (You can choose more than one option)

- (1) Self-experimentation
- (2) I read others descriptions on the internet.
- (3) I was guided by a doctor.
- (4) I have been advised by someone with the same condition as med who use cannabis as medicine.
- (8) I have been advised by a user of cannabis as medicine.

- (9) I have been advised by cannabis seller.
- (10) I have been advised by someone who also guides others on the use of cannabis as medicine.
- (5) Other, state what _____
- (6) Do not know
- (7) Do not wish to answer

18 - How did you discover that cannabis could be used as medicine? (You can choose more than one answer)

- (2) It was suggested to me by someone with the same condition as me.
- (3) A friend/family member suggested it to me
- (4) I read about medical cannabis in the media.
- (5) I read about other people's use of cannabis as medicine on social media.
- (10) I saw a documentary about medical cannabis
- (1) It was suggested to me by a doctor
- (6) I became aware of a medical affect through a recreational (i.e. non-medical) use of cannabis.
- (7) Other, state what _____
- (8) Do not know
- (9) Do not wish to answer

18 - Which statement fits your situation best?

- (1) I started using cannabis as medicine from one day to the next.
- (2) My use of cannabis as medicine has been a sliding scale from recreational (i.e. non-medical) use.
- (3) Do not know
- (4) Do not wish to answer

Activation:

“From one day to the next” activates 18A

(18A) How long did it take from the time you started using cannabis as a medicine until you experienced an effect on your disorder?

- (1) I experienced effect immediately
- (4) 1 day
- (2) 2-3 days
- (3) 3-5 days
- (5) A week
- (7) Two weeks
- (9) A month
- (10) Two months
- (11) Other state what _____
- (12) Do not know
- (13) Do not wish to answer

20 – How much experience did you have with recreational (i.e. non-medical) cannabis use before you began using cannabis as medicine?

- (1) No experience – (i had never used it before)
- (2) Lesser degree of experience – (i had tried it less than five times in my life)
- (3) Some degree of experience – (i had used it occasionally, below 10 times in a year)
- (4) High degree of experience – (I have used it periodically, several times a month.)
- (5) Very high degree of experience – (I have used it almost daily for several years)
- (6) Do not know
- (7) Do not wish to answer

21 - How long have you used cannabis as medicine?

- (1) Less than six months
- (9) 6 months – 1 year
- (2) 1-2 years
- (3) 2-5 years
- (4) 6-10 years
- (5) 11-20 years

- (6) More than 20 years
- (7) Do not know
- (8) Do not wish to answer

Meta text: It's moving forward - we're almost halfway there!

Now we inquire into your access to cannabis as a medicine.

ACCESS/STIGMA

22 – Where do you get your cannabis as medicine from (you can choose more than one answer)?

- (1) I buy it online
- (2) I have a prescription
- (10) I buy it in a store
- (11) I buy it at Christiania
- (4) I buy it from a dealer
- (5) I buy/get it from a friend
- (12) I buy/get it from a person who guides other people on medicinal cannabis use.
- (6) I grow it myself
- (8) Other, state what _____
- (3) Do not know
- (7) Do not wish to answer

"I grow it myself" activates 22A

(22A) Do you supply others who use cannabis as medicine?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

23 – Have you experienced not being able to procure the type of cannabis that you prefer to use as medicine?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

24 - Have you experienced not being able to procure any type of cannabis for medicinal use?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

25 – Have you experienced significant changes in the effect of the cannabis you used when you purchased a new amount of cannabis?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

"Yes" activates 25A

(25A) – What was different about the new amount of cannabis?

- (2) The effect was different
- (1) The side-effects was different
- (3) Both effect and side-effects were different
- (4) Do not know
- (5) Do not wish to answer

26 – How much money do you spend on average on cannabis for medicinal use pr. month?

- (2) Less than 500
- (5) 500-1000
- (6) 1000-1500
- (7) 1500-2000
- (8) 2000-2500
- (9) More than 2500
- (4) Do not know
- (3) Do not wish to answer

27 – Have you experienced sanctions in connection to your use of cannabis as medicine?

- (1) No
- (8) Yes, I have been given a warning by police
- (2) Yes, I have been fined
- (4) Yes, I have had my cannabis confiscated
- (9) No, i have a legal prescription for cannabis
- (5) Other, state what _____
- (6) Do not know
- (7) Do not wish to answer

28 – Have you advised others in the use of cannabis as medicine?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

Meta text: We have reached the last part of the questionnaire!

Here we ask questions about who knows about your use of cannabis as medicine and their reactions to your use.

29 – How many people know about your use of cannabis as medicine?

- (10) No one
- (2) 1 person
- (3) 2 to 5 people
- (4) 6 to 10 people
- (5) 11 to 20 people
- (6) 21 to 30 people
- (11) More than 30 people
- (8) Do not know
- (9) Do not wish to answer

"No one" skips to question 33

30 – Overall, how have the people that know about your use of cannabis as medicine reacted to it?

- (1) Very positive
- (5) Positive
- (2) Neutral
- (3) Negative
- (6) Very negative
- (8) Nobody knows about my use of cannabis as medicine
- (7) Do not know
- (4) Do not wish to answer

31 – Have you experienced disagreements/conflicts with anyone in connection with your use of cannabis as medicine?

- (1) No at all
- (5) To a lesser degree
- (6) To some degree
- (7) A high degree
- (8) A very high degree
- (3) Do not know
- (4) Do not wish to answer

"No at all" skips to 32

(31A) Who have you experienced disagreements/conflicts with in relation to your use of cannabis as medicine (you can choose more than one answer)?

- (1) Spouse/partner
- (2) Friends
- (3) Other family
- (4) Children
- (5) Collages
- (9) Acquaintances
- (8) Other, state who _____
- (6) Do not know
- (7) Do not wish to answer

32 – Have you told anyone in the health care system about your use of cannabis as medicine?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

“Yes” activates 32A 32B

(32A) Who have you told?

- (1) Private GP
- (2) Specialist
- (4) Nurse
- (5) Case manager
- (6) Psychologist
- (7) Psychiatrist
- (10) Other, state who _____
- (8) Do not know
- (9) Do not wish to answer

(32B) Overall, how did they react?

- (1) Very positive
- (6) Positive
- (2) Neutral
- (7) Negative
- (3) Very negative
- (4) Do not know
- (5) Do not wish to answer

33 – Have you ever considered not using cannabis as medicine?

- (1) Yes
- (2) No
- (5) I have stopped

- (3) Do not know
- (4) Do not wish to answer

"Yes" activates 33A

(33A) Why have you considered not using cannabis as medicine (you can choose more than one answer)?

- (1) It does not work
- (2) I cannot afford it
- (10) I do not like getting high
- (3) I do not like that it is illegal
- (4) I do not like the side effects
- (5) I have trouble procuring cannabis
- (7) I wish I did not need it.
- (11) My relatives want me to quit
- (6) Other, state what_____
- (8) Do not know
- (9) Do not wish to answer

Meta text: Now we are almost done. But we would like to inquire into your views on medical cannabis.

ATTITUDES AND DEMOGRAPHICS.

34. How much to you agree with the following statement?

	Strongly agree	Agree	Somewhat agree	Neutral	Somewhat disagree	Disagree	Strongly disagree	Do not know	Do not wish to answer
Cannabis should be fully legalized	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
Cannabis as medicine can be valuable for people with physical conditions.	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
There is a risk of developing addiction when using cannabis as medicine	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
The medical cannabis pilot program in Denmark should be continued and expanded	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
Cannabis as medicine can be valuable for people with physical conditions	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
Danish doctors do not know enough about medical cannabis	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
Cannabis as medicine, when prescribed by a doctor, can be harmful to mental health	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>
There is too little research into medical cannabis	(1) <input type="checkbox"/>	(2) <input type="checkbox"/>	(10) <input type="checkbox"/>	(3) <input type="checkbox"/>	(11) <input type="checkbox"/>	(9) <input type="checkbox"/>	(7) <input type="checkbox"/>	(5) <input type="checkbox"/>	(6) <input type="checkbox"/>

Meta text: This is the last part of the questionnaire – you are almost done!

35. Who old are you?

36. What gender are you?

- (1) Man
- (2) Woman
- (5) Other
- (4) Do not wish to answer

37. What region do you live in?

- (1) Northern Jutland
- (2) Central Jutland
- (3) Southern Jutland
- (4) Capital
- (5) Zealand
- (6) Do not wish to answer

38. How many people live in your city?

- (1) Under 3.000
- (2) Over 3.000
- (5) Do not know
- (4) Do not wish to answer

39. How long is the drive from where you live to the nearest big city (Big cities are København, Aarhus Odense, Aalborg, Esbjerg, Randers, Kolding, Horsens, Vejle, Roskilde, Herning og Helsingør)

- (1) Less than a half hour drive
- (2) More than a half hour drive
- (3) Do not know
- (4) Do not wish to answer

40. What is your current occupational status?

- (21) Working full time
- (22) Working part time
- (3) Student full time
- (11) Student part time
- (10) Self-employed

- (6) On sick-leave
- (18) Unemployed
- (16) Flex job
- (14) Work ability enhancement program
- (17) Job testing
- (4) Job with wage subsidies
- (13) Maternity leave
- (25) Early retirement
- (12) Pension
- (8) Disability pension
- (19) Stay-at-home
- (15) Vocational rehabilitation
- (9) Other, state what _____
- (23) Do not know
- (24) Do not wish to answer

Work full time or part time activates 40A

(40A) Do you think that you risk getting fired if your boss finds out that you are using cannabis as medicine?

- (1) Yes
- (2) No
- (3) Do not know
- (4) Do not wish to answer

41. Who do you live with (you can choose more than one answer)?

- (1) I live alone
- (3) My kid/kids
- (10) My parents
- (11) My grand parents
- (4) My spouse/partner
- (6) Other family members
- (7) Friends
- (12) Roommates
- (9) Other, stat who _____
- (13) Do not wish to answer

42. What is your most recent degree?

- (8) 9th grade
- (9) 9th grade- 11th grade
- (10) High school
- (2) Vocational secondary education
- (11) Short-cycle higher education
- (3) Medium-cycle higher education
- (6) Long-cycle higher education
- (12) None
- (13) Other, state which _____
- (14) Do not know
- (7) Do not wish to answer

43. What is your primary source of income?

- (4) Income maintenance
- (6) Provided for by relatives
- (10) Integration benefits
- (3) Unemployment benefits
- (1) Salary
- (2) Pension
- (5) SU
- (7) Other, state what _____
- (8) Do not know
- (9) Do not wish to answer

44. Do you have a final comment or feedback on the project?

We are also investigating the use of cannabis as a medicine through interviews. Here we focus on the process of becoming a user of cannabis as medicine and the potential challenges are associated with using cannabis as medicine. Therefore, we are looking for people who are interested in sharing their experiences with use of cannabis as medicine in greater detail. If you would like to participate in such an

interview, please provide your name and telephone number or email address below and we will contact you

Meta text: This is the last page. When you click "Finish", your answer will be sent. Click "Finish" to submit your answer. Thank you very much for your participation

Summary in English

This dissertation is centered on exploring the who, what, and why related to the use of cannabis as medicine in Denmark. The motivation for exploring the topic is that there have been several indications of a large use of illegal cannabis with a medical motive in Denmark in recent years, and that a medical cannabis pilot program (MCP) has been introduced by a majority of parliament, with the aim of creating a safe and legal framework for the treatment of selected patient groups with medical cannabis. However, while the MCP has set the parameters for formal legal use of medical cannabis in Denmark, we lack knowledge about the parameters set by Danish users of unregulated cannabis as medicine in practice.

Data collection was made through use of an anonymous online questionnaire made available for a convenience sample in Denmark, which is a superior method for exploring sensitive topics in so-called "hidden populations". The term hidden population refers to the fact that the target population are "hidden", because they are engaged in something that is either illegal or stigmatized or both. As the sample is self-selected, this method does not provide a representative sample of the overall population of interest, the dissertation does not technically examine "use of cannabis as medicine in Denmark", but rather the Danish users who knew about of the study and were interested in participating in it.

Study 1 is a mapping of the use of cannabis as medicine in Denmark, and findings from this study show that users of cannabis as medicine constitute a heterogeneous group with a great variety in patterns of use and motives for use. There were an overweight of women among the users and an average age of 49 years, indicating that cannabis users with a medical motive for use in Denmark differ significantly from the recreational users, who are typically younger and more often men. Moreover, CBD (Cannabidiol) oils were most commonly used, which are products with a low level of THC (Tetrahydrocannabinol), the component in cannabis that causes the euphoric effects associated with "being high". This finding indicates that many users of cannabis as medicine are interested in aspects beyond the high conventionally associated with cannabis use. Patterns of use were related to gender and age, where women and older users are more likely to use CBD oil exclusively. Also, the most common disorders that the users treat with cannabis are chronic pain, sleep problems, stress, arthritis, anxiety, and depression, which differs significantly from the conditions that give access to medical cannabis use through the MCP (treatment-resistant patients with multiple sclerosis, spinal cord injury, chronic pain (with a neuralgic component) or side-effects from chemotherapy).

Finally, the study findings show that a majority of users report experiencing symptom relief when using cannabis as a medicine, with limited or no side effects.

Study 2 examines substitution of prescription drugs as a motive for the use of cannabis as medicine and a small majority of the users reported having used cannabis with the purpose of replacing a prescribed drug. Pain medication was the type of medication that is most often substituted with cannabis, followed by antidepressants, and arthritis medication. CBD oil is the most common used type of cannabis as a substitute for prescription drugs among all users, with the exception of those users who substitute antipsychotic drugs, where hash, pot, or skunk are the most prevalent subtypes used. A large majority of substitution users reported that they had either stopped using prescription drugs, or had reduced their use significantly as a consequence of their use of cannabis as medicine. Furthermore, most substitution users reported that they found cannabis to be more effective and cause fewer side effects compared to other prescription drugs. The study indicates that substitution of prescription drugs may be a motive for the use of cannabis as medicine in Denmark, particularly opioids.

Study 3 makes use of Howard Becker's social constructivist perspective on becoming a cannabis user, to explore the paths to becoming a medicinal cannabis user, in a context where formal medical guidance is absent. The focus of the study is on what inspires medicinal cannabis use, as well as what sources of information users draw on when shaping their consumption patterns of medicinal cannabis. Also, the study explores the relevance of having previous recreational experience when becoming a medicinal cannabis user. Lastly, it is explored to what extent the users have overcome various forms of social control that Becker identified as barriers to becoming a daily cannabis user. The findings from this study show that the heterogeneity that exists in the sample of users - both in relation to demographics, consumption patterns, and motives for use - is related to the degree of previous recreational experience. Also, the heterogeneity in the sample is related to whether the use of cannabis as medicine has developed as a gradual transition from recreational use, suggesting the significance of having medicine in mind before the onset of cannabis use.

The dissertation concludes that there are indications of a large unregulated use of cannabis as medicine in Denmark, which takes place outside the safe and legal framework that the MCPP intended to create. Findings from this thesis also indicate the emergence of a novel subtype of cannabis use that is distinct from the conventional practices of recreational cannabis use. The prevalent use of cannabis oils and low potency CBD oils, in particular, indicates that many of the users have an interest in effects of cannabis beyond the high conventionally associated with recreational cannabis use. Moreover, findings from this thesis

indicate that users of CaM outside the MCPP use cannabis for managing a variety of conditions and for most of these conditions there is currently insufficient or no high-quality evidence on efficacy of cannabis. Likewise, there is currently no high-quality research available exploring whether cannabis can function as a substitute for pain medication, despite the fact that it is the type of medication that users most often substitute with cannabis. Overall, findings from the thesis indicate that the concept of medical cannabis may have attracted different sub-groups of users in Denmark; cannabis novices with a more medicalized approach to the use of CaM and previous recreational cannabis users who are interested in medicalizing their current use of cannabis.

In light of the relatively easy access to illegal cannabis products in Denmark, it is unlikely that this trend in the use of medicinal cannabis will diminish. Therefore, it is relevant to consider the potential public health problems related to this use, such as the lack of medical guidance, lack of quality control of unregulated cannabis products and potential negative health effects of cannabis use. The dissertation reflects on possible harm-reducing and prevention strategies that could be taken to mitigate the challenges related to use of unregulated cannabis as medicine.

Summary in Danish

Denne afhandling undersøger hvem, hvad og hvorfor relateret til brug af cannabis som medicin i Danmark. Motivationen for at undersøge emnet er, at der de seneste 5-10 år har været flere indikationer på, at der er opstået et stort brug af illegal cannabis med et medicinsk motiv i Danmark, samt at der fra politisk side er blevet indført en medicinsk cannabisordning med det formål at skabe en legal og sikker rammer for behandling af udvalgte patientgrupper med helplante cannabis. I denne forsøgsordning er der blevet sat nogle formelle rammer for brug af medicinsk cannabis, men vi mangler viden om hvilke rammer brugerne sætter for brug af cannabis som medicin i praksis.

Data blev indsamlet igennem et anonymt online-spørgeskema, som er blevet gjort tilgængeligt for et bekvemmelighedssample, da dette er vurderet som en kvalificeret metode til at undersøge sensitive emner i det, som kan beskrives som en "skjult population". Begrebet "skjult population" henviser til, at de personer, undersøgelsen retter sig mod er "skjult", fordi de er beskæftiget med noget, som enten er ulovligt eller stigmatiseret eller begge dele. Metoden giver ikke et repræsentativt udsnit af populationen, hvorfor afhandlingen teknisk set ikke undersøger "danskernes brug af cannabis som medicin", men derimod de danske brugere, som har haft kendskab til undersøgelsen og har været interesseret i at deltage i den.

Studie 1 er en kortlægning af brug af cannabis som medicin i Danmark, som finder at brugere af cannabis som medicin er en heterogen gruppe med et væld af forbrugsmønstre og motiver for brug. Dog ses nogle tendenser i data, blandt andet, at der er en overvægt af kvinder blandt brugerne og at gennemsnitsalderen blandt brugerne er 49 år, hvilket indikerer, at cannabisbrugere med et medicinsk motiv for brug i Danmark adskiller sig væsentligt fra de rekreative brugere, som typisk er lidt yngre og oftere er mænd. Der var en overvægt af brugere af CBD (Cannabidiol)-olier, som er produkter der typisk har et lavt niveau af THC (Tetrahydrocannabinol), som er den komponent i cannabis, som forårsager de euforiserende effekter som man forbinder med det "at være skæv". Dette fund indikerer, at mange brugere af cannabis som medicin er interesseret i andet end de euforiserende effekter af cannabis. Forbrugsmønstrene er relateret til køn og alder, således at kvinder og ældre er mere tilbøjelige til udelukkende at bruge CBD-olie. De mest hyppige lidelser, som brugerne angiver at de behandler med cannabis, er kroniske smerter, søvnproblemer, stress, gig, angst og depression, hvilket adskiller sig væsentligt fra de lidelser, som giver adgang til medicinsk cannabis brug igennem forsøgsordningen (behandlingsresistente patienter med multipel

sklerose, rygmarvsskade, kroniske smerter (med en neuralgisk komponent) eller bivirkninger fra kemoterapi). De fleste brugere rapporterer at de oplever symptomlindring ved brug af cannabis som medicin samt begrænsede eller ingen bivirkninger.

Studie 2 undersøger erstatning af receptpligtig medicin, som motiv for brug af cannabis som medicin. Et lille flertal af brugerne i undersøgelsen angiver at de har brugt cannabis med det formål at erstatte anden receptpligtig medicin. Smertemedicin udgør den type medicin, som brugerne hyppigst forsøger at erstatte med cannabis, efterfulgt af antidepressiv medicin og gigtmicin. CBD-olie er den mest hyppigt brugte type af cannabis som erstatning for receptpligtig medicin blandt alle brugere, med undtagelse af de brugere, som erstatter antipsykotisk medicin, hvor hash, pot eller skunk er mest udbredt. Et stort flertal af dem som angiver at de har brugt cannabis som erstatning for receptpligtig medicin, rapporterer at de enten er holdt op med at bruge receptpligtig medicin, eller har reduceret brug betydeligt som en konsekvens af deres brug af cannabis som medicin. Endvidere rapporterer de fleste brugere, at de oplever at cannabis er mere effektiv og medfører færre bivirkninger sammenlignet med anden receptpligtig medicin. Fundene fra studiet indikerer således at erstatning af receptpligtig medicin også er et motiv for brug af cannabis som medicin i Danmark.

Studie 3 anvender Howard Beckers socialkonstruktivistiske perspektiv på hvordan man bliver en cannabis bruger, til at undersøge veje til at blive bruger af cannabis som medicin uden formel vejledning fra en læge. Undersøgelsen fokuserer på, hvad der inspirerer til medicinsk cannabisbrug, samt hvilke informationskilder brugerne trækker på, når de former deres forbrugsmønstre. Derudover undersøger studiet, hvilken betydning tidligere rekreativ erfaring spiller i denne sammenhæng. Slutteligt undersøger studiet, i hvilken udstrækning brugerne har overvundet forskellige former for social kontrol, som Becker identificerede som barrierer for at blive en daglig bruger af cannabis. Fund fra studiet viser at den heterogenitet, som der er i blandt brugerne - både i relation til demografi, forbrugsmønstre og motiver for brug - er relateret til graden af tidligere rekreativ erfaring. Yderligere er heterogeniteten i samlet relateret til brug af cannabis som medicin har udviklet sig som en gradvis overgang fra rekreativt brug, hvilket understreger betydningen af at have medicin i tankerne fra cannabisbrugets begyndelse.

Afhandlingen konkluderer, at der er tegn på et stort ureguleret brug af cannabis som medicin i Danmark, som foregår uden for de legale og sikre rammer, som forsøgsordningen havde til hensigt at skabe. Desuden indikerer fund fra afhandlingen at der er opstået en subtype af cannabisbrug, der adskiller sig fra konventionelle praksiser relateret til rekreativt

cannabisbrug. Det udbredte brug af cannabisolier med lavt THC indhold indikerer, at mange af brugerne har en interesse i effekter af cannabis ud over det at blive "skæv", en effekt som konventionelt er associeret med et rekreativt cannabisbrug. Resultaterne fra afhandlingen indikerer også, at brugere som ikke er inkluderet i forsøgsordningen, bruger cannabis til at håndtere en række forskellige lidelser, hvor der i øjeblikket er utilstrækkelig eller ingen forskning af høj kvalitet der indikerer terapeutiske effekter af cannabis. Ligeledes findes der heller ikke forskning af høj kvalitet som indikerer at cannabis kan fungere som erstatning for smertemedicin, til trods for at det er den type medicin som brugerne oftest indikerer at de erstatter med cannabis. Derudover indikerer fund fra afhandlingen, at medikaliseringen af cannabis kan have tiltrukket forskellige subgrupper; cannabis novicer, som har en mere medikaliseret tilgang til brugen og samt mennesker med et tidligere rekreativt cannabis brug, som var interesseret i at medikalisere deres nuværende brug af cannabis.

I betragtning af at der er relativt let adgang til illegale cannabisprodukter i Danmark, er det usandsynligt, at den udbredte tendens til brug af cannabis som medicin vil aftage. Det er derfor relevant at overveje de potentielle folkesundhedsproblemer relateret til det uregulerede brug, som knytter sig til manglede lægefaglig vejledning, samt den manglende kvalitetskontrol med uregulerede cannabisprodukter og de potentielle negative sundhedseffekter af cannabisbrug. Afhandlingen reflekterer over mulige skadesreducerende og præventive strategier til at håndtere brug af ureguleret cannabis som medicin.

Chapter 7. The papers

7.1 Paper nr 1: Beyond the high. Mapping the patterns of use and motives for use of cannabis as medicine

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SCHOOL OF BUSINESS AND SOCIAL SCIENCES
AARHUS UNIVERSITY

Declaration of co-authorship*

Full name of the PhD student: Sinikka Lehmann Kvamme

This declaration concerns the following article/manuscript:

Title:	Beyond the high. Mapping the patterns of use and motives for use of cannabis as medicine
Authors:	Sinikka L. Kvamme, Michael M. Pedersen, Sagi Alagem-Iversen, Birgitte Thylstrup

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If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No Yes If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

- A. Has essentially done all the work
- B. Major contribution
- C. Equal contribution
- D. Minor contribution
- E. Not relevant

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	A
2. Planning of the experiments/methodology design and development	A
3. Involvement in the experimental work/clinical studies/data collection	A
4. Interpretation of the results	B
5. Writing of the first draft of the manuscript	A
6. Finalization of the manuscript and submission	B

Signatures of the co-authors

Date	Name	Signature
15-12-2021	Michael M Pedersen	
16-12-2021	Sagi Alagem-Iversen	
17-12-2021	BIRGITTE THYLSTRUP	

In case of further co-authors please attach appendix

Date: 17-12-2021

Signature of the PhD student:

*As per policy the co-author statement will be published with the dissertation.

Beyond the high: Mapping patterns of use and motives for use of cannabis as medicine

Sinikka L. Kvamme 

Aarhus University, Aarhus C, Denmark

Michael M. Pedersen

Aarhus University, Aarhus C, Denmark

Sagi Alagem-Iversen

Consultant, Aarhus N, Denmark

Birgitte Thylstrup

Aarhus University, Copenhagen S, Denmark

Abstract

Background: In Denmark the boundaries between cannabis as an illicit drug and licit medicine have shifted rapidly in recent years, affecting also policy. However, the vast majority of Danes, who use cannabis as medicine (CaM) continue to rely on the unregulated market for supply. This study explores patterns of use and motives for use of CaM in Denmark. **Methods:** An anonymous online survey was made available to a convenience sample of users of CaM from July 14, 2018 to November 1, 2018. Participants were recruited through patient organisations, social and public media, and the illegal open cannabis market. **Results:** Of the final sample ($n = 3,021$), a majority were women (62.6%) and the mean age was 49 years. Most had no prescription for CaM (90.9%), a majority had no or limited previous experience with recreational cannabis use (63.9%), and had used CaM for two years or less (65.0%). The most common form of intake was oil (56.8%) followed by smoke (24.0%). CBD oil (65.0%) was used more than hash, pot or skunk (36.2%). Most frequent conditions treated were chronic pain (32.0%), sleep disturbances (27.5%), stress (23.7%),

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Corresponding author:

Sinikka L. Kvamme, Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Building 1322, 217, Bartholins allé 10, 8000 Aarhus C, Denmark.

Email: slk.crf@psy.au.dk



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osteoarthritis (22.7%), anxiety (19.6%), and depression (19.6%). Overall, users experienced CaM to be effective in managing somatic and mental health conditions and reported relatively few side-effects. CBD oil only users were more likely to be women, older, have limited recreational experience and have initiated use recently. **Conclusions:** A new user group has emerged in Denmark that, for the most part, use illegally sourced CaM to treat a broad range of somatic and mental health conditions, often with experienced effect and relatively low level of side-effects. The prevalent use of low-potency CBD oil indicates an interest in effects beyond the high normally associated with cannabis use. More clinical research into the effects and side-effects of CaM is needed to draw the boundaries of the medical utility of cannabis.

Keywords

cannabis, CBD, medical cannabis, medicinal cannabis, motives for use, user patterns

The first documented use of cannabis as medicine (CaM) dates back almost 5,000 years (Touw, 1981) and at the turn of the 19th century, cannabis was an integral part of medicine in Europe and the United States, where commercial preparations of cannabis tinctures, pills, and extracts were used mainly as analgesic, anti-inflammatory, and anti-spastic drugs (Pisanti & Bifulco, 2017). As recreational cannabis use increased in the latter half of the 20th century, cannabis was prohibited, and the plant's medical use was all but forgotten (Zuardi, 2006). In the new millennium, the boundaries between cannabis as an illicit "drug" and licit "medicine" have shifted once again, and it has been argued that we are witnessing a re-medicalisation of cannabis (O'Brien, 2013; Pedersen & Sandberg, 2013; Taylor, 2008), which for a large part is driven by three forces: (1) The discovery of the endogenous cannabinoid system (eCS) in the 1980s; (2) The pharmaceutical industry and its interest in the eCS, which led to the development and licensing of cannabis-based medicines; (3) The user demand for safe access to medical cannabis (Taylor, 2008). In recent years, the user demand for medical cannabis has intensified (Hurley, 2018; Pacula & Sevigny, 2014) and cannabis policy has undergone rapid changes in various jurisdictions around the world, with more than 30 states in the US (National

Conference of State Legislatures, 2020) and several European countries (Abuhasira et al., 2018) adopting medical cannabis laws.

In Denmark, the user demand has been a substantial factor in the public health debate, and in shaping the current cannabis policy. For years, patient organisations have advocated for access to *medical cannabis* (i.e., legal, prescribed cannabis) (Færch, 2014), which have been supported by Danish celebrities and politicians, who have been vocal about their *medicinal cannabis* use (i.e., no prescription, illicitly sourced cannabis) for their somatic and mental health conditions (Elabdi & Ehrbahn, 2017; Jørgensen, 2017). That the public debate on CaM has received widespread attention in recent years is underlined by a content analysis of Danish newspapers that found that articles on CaM increased from approximately 2% in 2012 to 16% in 2016 (Houborg & Enghoff, 2018), and a national survey in 2017 that found that 80% of Danes supported a legalisation of medical cannabis (Blackman, 2017).

In November 2016, a large majority of the Danish parliament agreed to initiate a four-year medical cannabis pilot programme (MCP) from January 2018. The purpose of the MCP was to establish a "safe framework for the use of medical cannabis within the healthcare system (. . .) providing a legal alternative for some of the patients who are already self-medicating

with cannabis” (Ministry of Health, 2016, p. 2). As instructed by the political parties, The Danish Medicines Agency recommended four patient groups, where there existed *some documentation that medical cannabis may have an effect* (Lægemedelstyrelsen, 2019a, our translation) to be included in the MCPP: treatment-resistant patients with multiple sclerosis, spinal cord injury, chronic pain (with a neuralgic component) or side-effects from chemotherapy (Lægemedelstyrelsen, 2019a). Thus, the MCPP marked a paradigm shift in Denmark, as it gave selected patient groups access to the cannabis flower as medicine, and from January 2018 to July 2019, 2,133 patients have been included in the trial (Danish Health Data Authority, 2019b). However, several factors indicate that the vast majority of cannabis consumption with a medical purpose still occurs outside the safe and legal framework that the MCPP intended to create. A national poll estimated already in 2016 that at least 50,000 Danes use CaM, and there has been a considerable growth in web-shops selling low-potency cannabis oil (Damløv, 2016). Moreover, there are several Danish social media support groups offering guidance in medicinal use of cannabis oil. Furthermore, cannabis oil has for some time been a standard commodity at the largest open illegal cannabis market, Christiania, in the capital of Denmark (Færch, 2013), and the Danish police and customs have reported an increase in confiscations of cannabis oil (Sørensen & Skaaning, 2017). Users of cannabis oil are in a legal grey area, as sale and possession of a cannabis product with less than 0.2% *tetrahydrocannabinol* (THC) became legal in 2018, unless the cannabis product is regarded as a drug by the Danish Medicines Agency (Lægemedelstyrelsen, 2018). The Danish Medicines Agency estimates that most cannabis oil sold online, containing less than 0.2% THC, are in fact drugs, and therefore illegal to sell (but not illegal to possess) (Lægemedelstyrelsen, 2019b).

In order to evaluate the public health effects of the current use of CaM and to qualify future

cannabis policy, two areas are important to investigate: patterns of use and motives for use. Patterns of use are important, due to the complexity of the cannabis plant and the various forms of intake, resulting in diverse effects of using CaM. To date, 120 cannabinoids and 445 non-cannabinoids have been identified (Bonn-Miller et al., 2018), of which the primary focus have been the cannabinoids *tetrahydrocannabinol* (THC) and *cannabidiol* (CBD). A growing body of evidence suggest that THC and CBD display opposing neural, cognitive, and behavioural effects (Colizzi & Bhattacharyya, 2017; Rømer Thomsen et al., 2017), and that CBD may have a superior safety profile (Bergamaschi et al., 2011; Iffland & Grotenhermen, 2017) and limited abuse potential (Schoedel et al., 2018) compared to THC. Nonetheless, pre-clinical and clinical studies have found therapeutic effects of THC (National Academies of Sciences Engineering and Medicine, 2017) and THC may be more effective when combined with CBD (Boggs et al., 2018; Russo, 2011) and other components of the cannabis plant (McPartland & Russo, 2014). Moreover, the effects of cannabis use depend on mode of intake (Newmeyer et al., 2017); while inhalation has a rapid onset, onset is delayed when ingesting (30–60 minutes), which may increase the risk of overdosing (Grotenhermen, 2001), but hold fewer health risks compared to smoking cannabis (Russell et al., 2018).

An equally important area to investigate is motives for use, as it is relevant to know which conditions and symptoms drive some users to disregard advice from the medical authorities in Denmark and consult an illegal market for medicine. Users of CaM risk stigmatisation (Satterlund et al., 2015), criminalisation (in cases where the cannabis used contains more than 0.2% THC), and hazards of interacting with an illegal market, so it is important to know what motivates them to take these risks. Motives for both medicinal and medical cannabis use have been explored on a larger scale in the United Kingdom (Ware et al., 2005), Australia (Lintzeris et al., 2018), Norway (Pedersen

& Sandberg, 2013), Canada (Lucas et al., 2019; Walsh et al., 2013), and cross-nationally (Corroon & Phillips, 2018; Hazekamp et al., 2013; Sexton et al., 2016). A recent literature review found that pain was the most common motive for use of CaM, and that users of CaM frequently report symptom relief of pain conditions, sleep disturbances and anxiety symptoms (Park & Wu, 2017).

The current body of scientific literature on the health effects of cannabis and cannabinoids has set the parameters for the legal use of medicinal cannabis in Denmark, but we lack knowledge about the parameters set by both the medical and medicinal users in practice. This is important, as user perspectives are instrumental in elucidating perspectives on cannabis use unseen by society at large (Dahl, 2004; Hakkarainen et al., 2015). To our knowledge, the use of CaM in Denmark has, until now, only been explored in selected samples, i.e., small-scale cannabis cultivators (Dahl & Frank, 2011; Hakkarainen et al., 2015) and specific patient groups (Gustavsen et al., 2019).

It is of particular public health interest to study the use of low-potency CBD oil with a medical motive. In recent years, there has been a dramatic increase in the availability of CBD-based cannabis products globally, while regulatory control is lacking (Hazekamp, 2018; Manthey, 2019). However, to our knowledge, there are no systematic studies on users of CBD products in Europe. The trend in use of low-potency CBD oil is important to study, because it seeks to exclude the main component, THC, that causes the psychotropic effects of cannabis (Colizzi & Bhattacharyya, 2017; McPartland & Russo, 2014). The availability of these relatively novel cannabis products that seek to exclude effects conventionally associated with cannabis use (the “high”), is likely to attract novice users who would have otherwise refrained from using cannabis products (Manthey, 2019).

The aim of this study was to characterise the users of CaM in Denmark, and to map patterns and motives related to the use of CaM.

An additional aim was to explore user characteristics of those who use low-potency CBD oil only.

Methods

Design

The present study is part of a larger study on the use of CaM in Denmark. A novel survey was developed inspired by previous surveys on medicinal and medical cannabis use (Grotenhermen & Schnelle, 2003; Hazekamp et al., 2013; Reiman et al., 2017; Reinerman et al., 2011; Sexton et al., 2016; Ware et al., 2005; Webb & Webb, 2014), and was tested and revised following nine pilot interviews with users of CaM as well as input from researchers and selected others with insight into the use of CaM in Denmark. The questionnaire consisted of 42 structured questions and 21 possible follow-up questions, answered in a Yes/No format, multiple-choice response, and rating scales. All questions included the possibility to answer “Do not know” or “Do not wish to answer”, except for questions on conditions treated and evaluation of effect of use. Questions used for the current study involved six key domains: sociodemographics, motivation for use, duration and frequency of use, method of administration, evaluation of experienced effect, and adverse effects. The questionnaire took approximately 15 minutes to complete, and was available in Danish only. Data were collected through Survey-Xact. IP addresses of the respondents were not saved, or available to the researchers, as the respondents’ fear of loss of anonymity was considered a greater issue than the possibility of repeated participation (Barratt et al., 2017).

Sampling and recruitment

The survey was made available online to a self-selected convenience sample of users of CaM from July 14, 2018 to November 1, 2018. Inclusion criteria were age 18 years or older and

being a current or former user of CaM (it was possible to answer on behalf of someone else – next of kin). Participants were recruited online and via flyers and posters containing survey information, a survey link and QR code. Recruitment material was disseminated on Facebook groups for medicinal and recreational cannabis use, through patient organisations, in selected doctors' offices and hospitals, at the illegal open drug market, Christiania, at the first Cannabis Expo in Denmark held in Copenhagen, and via headshops selling cannabis-related items. Additionally, the survey was made available to users of Smokeboddy (an app where users monitor potential police presence on the illegal open drug market in Christiania) and the survey was reported on by the national media, The Danish Broadcasting Corporation. Previous studies have found Facebook to be a valuable recruitment tool in hard-to-reach populations (Weiner et al., 2017), and this study made great use of the platform, since many Facebook administrators agreed to share information on the survey with group members, increasing the reach and trustworthiness of the survey among potential respondents. In order to engage prospective participants (Miller & Sonderlund, 2010), the primary researcher was available on the platform to answer questions related to the study throughout the recruitment period.

Measures

Patterns of use. Respondents were presented with a list of cannabis products, and could choose more than one. Respondents were presented with a list of forms of most frequent intake, and could choose only one. All users were asked to indicate their daily dose of cannabis, either as drops of oil or grams of plant matter. Users of CBD oil and THC oil were asked to indicate the strength of the oil as a percentage. Further, we asked users to indicate the level of “recreational (non-medicinal)” use of cannabis before their use of CaM.

Motives for use. Respondents were presented with a list of 52 somatic and mental health conditions, and asked to indicate conditions for which they used CaM. The 52 conditions were categorised as either somatic conditions ($n = 37$) or psychiatric conditions ($n = 13$) (see Appendix 1) based on ICD-10 classifications, except for “sleep disturbances” and “stress”, which were kept as independent categories as they are relatively large and difficult to classify. For every chosen condition, respondents were asked to indicate the purpose of their use by choosing one or more of three listed purposes (“symptom relief”, “cure”, and “managing side-effects of other treatment”). Respondents were asked if they had used CaM with the purpose of replacing a prescribed drug. The experienced effect of using CaM was evaluated on the symptoms of each of the chosen conditions on a nine-point Likert scale ($-4 =$ very large aggravation and $+4 =$ very large improvement). Respondents were asked which side-effects they had experienced when using CaM, and were presented with a list of 18 potential side-effects. Further, respondents were presented with a list of 17 potential symptoms, and asked to indicate on which symptoms they had experienced an effect of CaM. Respondents who indicated that CaM had an effect on relief from pain rated their experienced pain with and without the use of CaM on a pain visual analogue scale, ranging from (0 = no pain to 10 = worst pain imaginable) (VAS; Jensen et al., 2003). Respondents who indicated that CaM had an effect on relief from sleep disturbances were asked to report the increase in number of hours slept. To evaluate the overall effect of using CaM on daily life, respondents were asked to evaluate three statements on a five-point Likert scale (0 = Strongly disagree to 5 = Strongly agree).

Data analysis

Statistical analyses were conducted using Stata SE/15. Means with standard deviations and simple proportions were used to describe

respondent characteristics, patterns of use and motives for use. The overall experienced effect of CaM was calculated by dividing the total experienced effect by the total number of conditions reported. Shapiro-Wilks tests were used to assess normality before choosing a test for comparison of means. As none of the variables were normally distributed, the Wilcoxon signed-rank test was used to assess the difference between means related to experienced effect of CaM on sleep and pain. We coded a dummy variable on CBD oil only use, distinguishing between those who exclusively used CBD oil and those who used other forms of cannabis, with CBD oil only coded as 1. This variable was used as the dependent variable in the logistic regression analysis. Odds ratios (ORs) were used to estimate the strength of association.

Ethics

All data collected were anonymous. Participants could withdraw from the survey at any time before completion without any data being included in the results. Participants who agreed to be contacted at a later stage for participation in a qualitative interview were asked to list their contact information. Data were stored on secure servers, and procedures for data handling and storage were approved by the Danish Data Protection Agency. Since the data used for this study were collected and stored for monitoring, no ethics evaluation was needed under Danish law.

Results

Sample characteristics

A total of 4,570 respondents opened the survey, and 3,140 answered all questions. Of these, 119 respondents were excluded: 59 were under the age of 18 years, seven respondents had inconsistencies in answers, and 53 were identified as duplicates, leaving a total number of respondents of 3,021 (see Table 1).

More than half of the sample were women (62.6%), and the age range was 18–99 years (Mean (*M*) 49, standard deviation (*SD*) 13.8), with most respondents aged between 45 and 64 years (51.2%). Current employment status was mixed, and the most prevalent categories were full-time employment (25.4%), disability pension (21.6%), reduced employment (18.1%), and retirement (14.2%). More than a quarter of respondents had a medium-cycle higher education (28.3%), followed by vocational secondary education (17.9%). All five regions in Denmark were represented relative to the total sample size.

Patterns of use

The most common type of cannabis used was CBD oil (65%), followed by “hash, pot or skunk” (36.2%) and THC oil (25.3%) (see Table 2). About one third of the sample (37.8%) reported using CBD oil only, and more than half of the sample (56.8%) reported oil as their most frequent form of intake, followed by “smoked (with tobacco)” (20.0%). The total proportion of the sample who reported inhalation as the most frequent form of intake (either smoke or vapour) was 27.4%. The majority (75.4%) used cannabis 6–7 days a week. A majority of the sample (64.8%) had used CaM for 2 years or less, 18.1% had used CaM for 2–5 years and 16.5% for more than 5 years. Almost half (48.1%) had no previous recreational (non-medicinal) experience before initiating use of CaM, and 15.8% had limited experience with recreational cannabis use (less than five times). Most of the respondents (90.9%), did not have a prescription, whereas 8.4% did. Of those with a prescription for CaM, 37.8% supplemented their use with cannabis from the illegal market. Of those without a prescription, 72.2% had not asked their doctor for a prescription for CaM (see Table 2). The majority (87.5%) were current users of CaM, 3.8% answered on behalf of a family member (not able to answer due to illness or old age) and 8.7% were previous users of CaM.

Table 1. Sample characteristics.

	N = 3,021
	n (%)
Gender	
Male	1,097 (36.3)
Female	1,891 (62.6)
Other	6 (0.2)
Missing	27 (0.9)
Age (years)	
Mean	49 (SD 13.8)
18–24	138 (4.6)
25–34	356 (11.8)
35–44	583 (19.3)
45–54	831 (27.6)
55–64	710 (23.6)
65–74	328 (10.9)
> 75	68 (2.3)
Missing	7 (0.2)
Current employment	
Full-time employment	767 (25.4)
Part-time employment	114 (3.8)
Student	132 (4.4)
Unemployed	52 (1.7)
Retired (pension and early retirement)	430 (14.2)
Stay-at-home	25 (0.8)
Disability pension (due to reduced working capacity)	651 (21.6)
Sick leave	94 (3.1)
Reduced employment (due to reduced working capacity)	548 (18.1)
Other	163 (5.4)
Missing	45 (1.5)
Education	
None	45 (1.5)
9th grade	346 (11.5)
9th–11th	150 (5)
High school	295 (9.8)
Vocational secondary education	541 (17.9)
Short-cycle higher education	349 (11.6)
Medium-cycle higher education	855 (28.3)
Long-cycle higher education	251 (8.3)
Other	112 (3.7)
Missing	77 (2.6)
Region	
Capital	713 (23.6)
Central Jutland	652 (21.6)
Zealand	593 (19.6)

(continued)

Table 1. (continued)

	N = 3,021
Southern Denmark	572 (18.9)
Northern Jutland	367 (12.2)
Missing	124 (4.1)

Of the THC oil users, 49.3% indicated the percentage compared to 77.3% of the CBD oil users. The mean for THC oil was 37.5% THC (*SD* 30) and 13.8% (*SD* 14.4) for CBD oil. The mean daily dose indicated by THC users was 6.5 (*SD* 8.4) drops/day and 8.3 (*SD* 9) drops/day for CBD oil users. Users of plant material (hash, pot, skunk) reported means ranging from 1.3–1.4 grams per day; hash (*M* 1.3, *SD* 1.3), pot (*M* 1.4, *SD* 2.6) and skunk (*M* 1.4, *SD* 1.7) (see Table 2).

Motives for use

The most frequent conditions treated with CaM were chronic pain (32.0%), sleep disturbances (27.5%), and stress (23.7%) (see Figure 1).¹ Arthritis was also listed as a frequent condition, as 22.7% treated osteoarthritis, 8.1% treated rheumatoid arthritis and 3.3% treated psoriatic arthritis. Mental health conditions, such as anxiety (19.6%), depression (19.6%), ADHD/ADD (9.8%) and PTSD (9.4%) were also frequent motives for use of CaM. Pain-related conditions such as fibromyalgia (11.5%), herniated disc (11.1%) and migraine (9.8%) were also frequently reported, and CaM was also used in the treatment of pain related to an accident (11.6%) and in the treatment of post-operative pain (6.4%). Further, 7.1% indicated the use of CaM in relation to cancer or cancer-related treatment (e.g., chemotherapy).

A large majority indicated treating a somatic condition with CaM (79.3%) and more than a third used CaM in the treatment of a mental health condition (36.7%) (see Table 3). The most prevalent purpose for use of CaM was

Table 2. Patterns of use.

	(<i>N</i> = 3,021)
Types of cannabis	<i>n</i> (%)
THC oil	765 (25.3)
CBD oil	1,965 (65.0)
Hash, pot, skunk	1,092 (36.2)
Cannabis-based therapy (prescription: Sativex, Marinol, Nabilone)	173 (6.0)
Whole-plant trial (prescription Bedrocen, Bediol)	56 (1.8)
Other	232 (7.7)
Missing	32 (1.1)
CBD oil only users	1,141 (37.8)
Most frequent form of intake	
Smoked (with tobacco)	603 (20.0)
Smoked (no tobacco)	120 (4.0)
Vaporised	103 (3.4)
Oil	1,717 (56.8)
Rectal	15 (0.5)
Tea	41 (1.4)
“Edibles” (cannabis in food)	47 (1.6)
Topical (cream)	50 (1.7)
Capsules	129 (4.3)
Other	175 (6.3)
Missing	21 (0.7)
Frequency of use	
6–7 days a week	2,277 (75.4)
3–5 days a week	386 (12.8)
1–2 days a week	170 (5.6)
A few times a month	96 (3.2)
Very rarely	54 (1.8)
Missing	38 (1.3)
Duration of use	
< 6 months	578 (19.1)
6 months–1 year	628 (20.8)
1–2 years	752 (24.9)
2–5 years	547 (18.1)
6–10 years	227 (7.5)
11–20 years	130 (4.3)
< 20 years	141 (4.7)
Missing	18 (0.6)
Previous recreational experience	
None (never tried before medicinal use)	1,452 (48.1)
Little (lifetime use < 5 times)	477 (15.8)

(continued)

Table 2. (continued)

	(<i>N</i> = 3,021)
Some (occasionally < 10 times/ year)	319 (10.6)
High degree (periodically several times/month)	355 (11.8)
Very high degree (almost daily for several years)	352 (11.7)
Missing	66 (2.2)
Status of use	
Current user	2,642 (87.5)
Previous user	264 (8.7)
Answering on behalf of someone else	115 (3.8)
Prescription user	
No	2,745 (90.9)
Yes	158 (5.2)
Yes, and I supplement with unregulated cannabis	96 (3.2)
Missing	22 (0.7)
Asked doctor for prescription for medical cannabis (<i>n</i> = 2,745)	
Yes	748 (27.3)
No	1,982 (72.2)
Missing	15 (0.5)
Mean percent of oil	–
THC oil (<i>n</i> = 377)	37.5% (<i>SD</i> 30.0)
CBD oil (<i>n</i> = 1,518)	13.8% (<i>SD</i> 14.4)
Mean daily dose	
THC oil (<i>n</i> = 518)	6.5 drops (<i>SD</i> 8.4)
CBD oil (<i>n</i> = 1,528)	8.3 drops (<i>SD</i> 9.0)
Hash (<i>n</i> = 409)	1.3 g (<i>SD</i> 1.3)
Pot (<i>n</i> = 189)	1.4 g (<i>SD</i> 2.6)
Skunk (<i>n</i> = 248)	1.4 g (<i>SD</i> 1.7)

Note. THC = Tetrahydrocannabinol; CBD = Cannabidiol.

“symptom relief” (81.2%), followed by “cure” (22.7%), and “managing side-effects of other treatment” (6.1%). A majority (52.8%) had used CaM with the purpose of replacing a prescribed drug. In total, the respondents reported using CaM for 9,653 conditions, with a mean of just above three conditions per respondent (*M* 3.2, *SD* 2.49) (see Table 3). The reported mean effect of using CaM for each condition is indicated in Figure 1. The reported mean effect across all 9,653 conditions was 2.82 (*SD* 0.96), resulting in an overall effect of just below

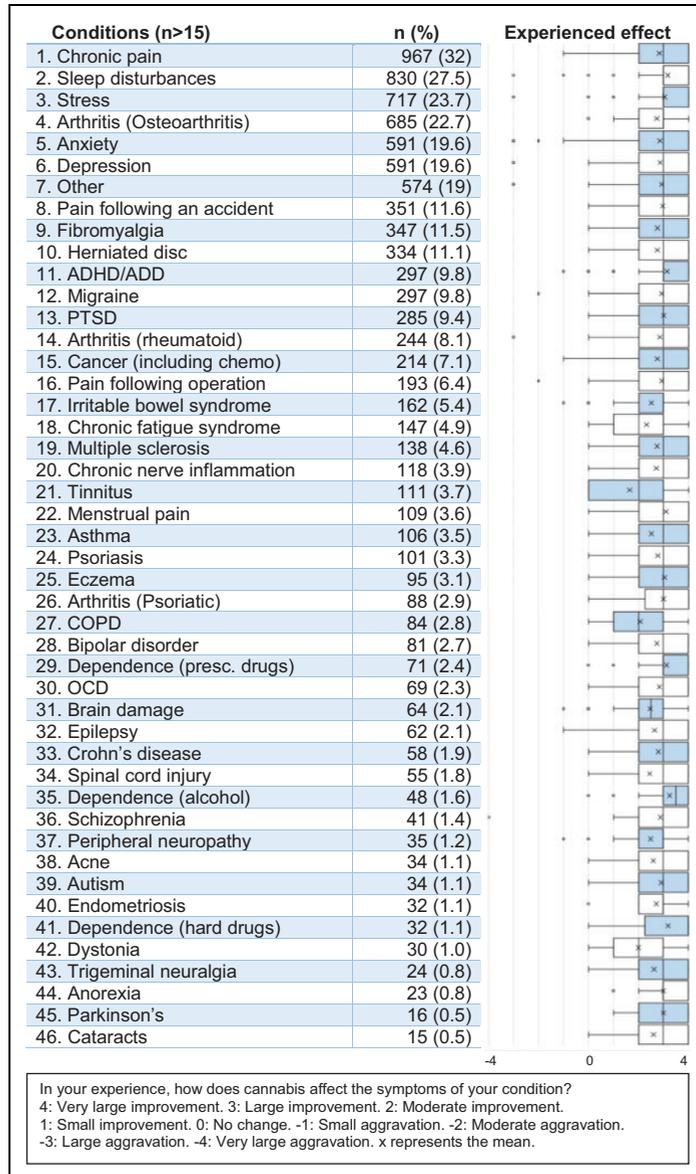


Figure 1. Motives for use: Conditions treated with CaM and experienced effect.

“Large improvement (3)” (see Figure 1). Seven respondents (0.23%) reported an overall negative effect on symptoms, and 67 (2.2%) reported an overall null effect on symptoms. The highest mean effect was reported on alcohol dependence ($M 3.25, SD 0.96$), dependence on hard drugs ($M 3.19, SD 1.12$) and sleep

disturbances ($M 3.16, SD 1.03$) (see Figure 1). The lowest mean effects were reported for tinnitus ($M 1.64, SD 1.34$), dystonia ($M 2.0, SD 1.20$) and chronic obstructive pulmonary disease (COPD) ($M 2.07, SD 1.10$), meaning the lowest mean effect was above “Small improvement (1)”.

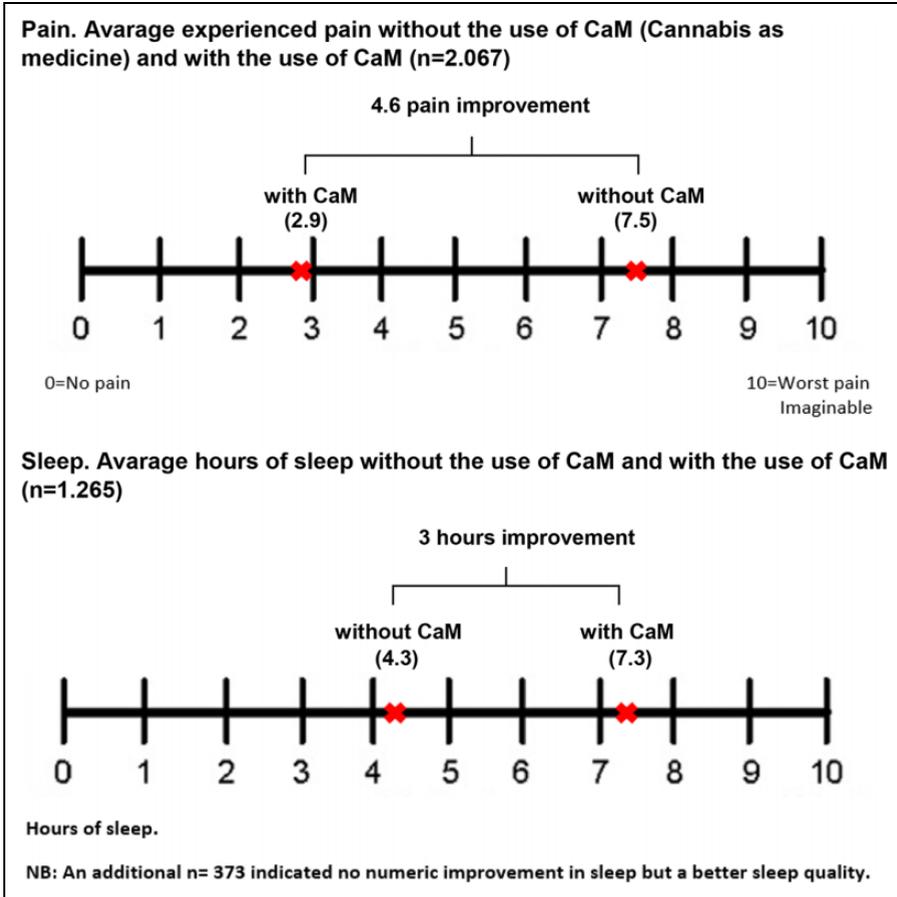


Figure 2. Motives for use: Pain and sleep.

Almost all respondents (95.1%) chose at least one symptom on which they had experienced an effect of CaM, with a mean of 5.23 (*SD* 3.78) symptoms chosen. In all, 3.3% indicated no effect on any symptoms (see Table 3). Pain (68.4%) was the most common symptom, followed by sleep disturbances (59.7%), and inner turmoil (50.7%). A majority (52.3%) indicated no side-effects of CaM, and 45.8% chose at least one side-effect, with a mean of 1.09 (*SD* 1.60) side-effects chosen. The most common side-effect was “dryness of mouth” (22.2%), followed by “being high” (16.2%).

Among respondents reporting “pain” as a symptom relieved by use of CaM (68.4%), the average VAS pain score was 7.5 (*SD* 1.78)

without the use of CaM, and 2.9 (*SD* 1.76) with the use of CaM. The average improvement of 4.6 in the VAS pain score (see Figure 2) was significant ($p < .001$). Among respondents reporting “sleep disturbances” as a symptom relieved by use of CaM (59.7%), 70.1% indicated a mean of 4.3 (*SD* 1.71) hours of sleep without the use of CaM, and a mean of 7.3 (*SD* 1.23) hours of sleep with the use of CaM. The average improvement was 3 hours, and the difference was significant ($p < .001$) (see Figure 2). An additional 20.7% reported no improvement in hours slept, but an improvement in sleep quality.

A total of 87.5% agreed/strongly agreed that their use of CaM made it easier to handle

Table 3. Motives for use: Purpose, symptoms, side-effects and means.

N = 3,021	
Purpose for use for all conditions (n = 9,653)	n (%)
To relieve symptoms of the condition	7,839 (81.2)
To cure the condition	2,188 (22.7)
To manage side-effects of other treatment	588 (6.1)
Missing	100 (1.0)
Conditions treated with CaM	
Somatic condition	2,394 (79.3)
Mental health condition	1,109 (36.7)
Sleep disturbances	830 (27.5)
Stress	717 (23.7)
Used CaM with the purpose of replacing a prescribed drug	
Yes	1,596 (52.8)
No	1,348 (44.6)
Missing	77 (2.5)
Symptoms	
Pain	2,067 (68.4)
Sleep disturbances	1,804 (59.7)
Inner turmoil	1,531 (50.7)
Muscle tension	1,373 (45.5)
Stress	1,204 (39.9)
Racing thoughts	1,106 (36.6)
Thoughts of worry	1,050 (34.8)
Depressed mood	964 (31.9)
Irritability	894 (29.6)
Lack of appetite	801 (26.5)
Nausea	704 (23.3)
Hyperactivity	427 (14.1)
Other	423 (14.0)
Nightmares	363 (12.0)
Vomiting	252 (8.3)
Essential tremor	237 (7.9)
Spasticity	217 (7.2)
Tics	146 (4.8)
No effect on any symptoms	101 (3.3)
Missing	48 (1.6)
Side-effects	n (%)
No side-effects of cannabis	1,581 (52.3)
Dryness of mouth	671 (22.2)
Being high	488 (16.2)
Red eyes	388 (12.8)
Other	281 (9.3)
Increased tiredness	263 (8.7)
Memory impairment	254 (8.4)

(continued)

Table 3. (continued)

N = 3,021	
Diarrhoea	124 (4.1)
Palpitations/elevated pulse	117 (3.9)
Sweating	116 (3.8)
Dizziness	102 (3.4)
Headache	90 (3.0)
Heartburn	83 (2.8)
Anxiety	49 (1.6)
Thoughts of worry	45 (1.5)
Constipation	42 (1.4)
Muscle fatigue	38 (1.3)
Dry skin	34 (1.1)
Irritability	32 (1.1)
Passing psychosis	19 (0.6)
Missing	58 (1.9)
Means	Mean (SD)
Conditions treated	3.20 (2.49)
Experienced effect across conditions	2.82 (0.96)
Symptoms	5.23 (3.78)
Side-effects	1.09 (1.60)

Note. CaM = cannabis as medicine.

practical chores in their daily life, 71.3%, agreed/strongly agreed that CaM made it easier to handle job, education or job-related activities, and 71.6% agreed/strongly agreed that CaM made it easier for them to participate in social events (see Figure 3).

Compared to other CaM users, CBD oil only users were 3.36 times more likely to be women (CI: 1.95–4.01, $p < 0.001$) and there was a trend of an association between increased age and increased odds of using CBD oil only (see Table 4). There were few significant differences between CBD oil only users and other CaM users with respect to current employment and level of education. Using CBD oil only was negatively associated with duration of use and level of previous experience with recreational use (see Table 4).

Discussion

To our knowledge, this is the first study mapping the use of CaM in Denmark. The findings

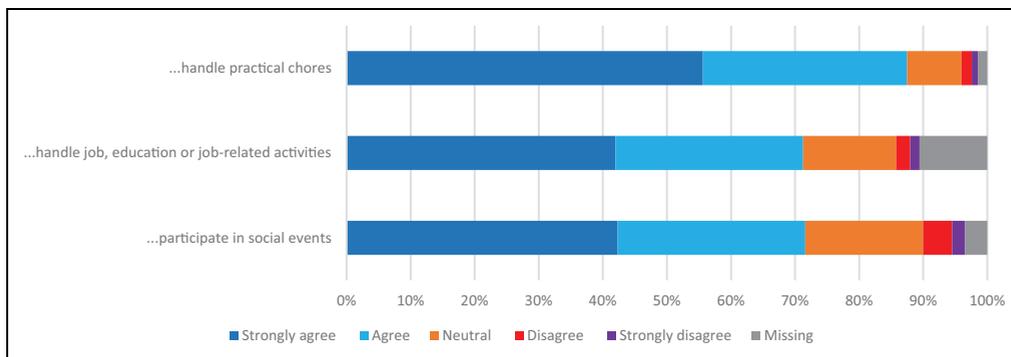


Figure 3. Effect of CaM on daily life: How do these statements apply to your situation: “CaM makes it easier for me to...”.

indicate that use of CaM may be a growing trend among Danes, and that the majority of the current users of CaM in Denmark remain outside the “safe framework” established by the MCPP. The study shows that users of CaM are far from homogenous when it comes to demographics, patterns of use and motives for use, and that the unregulated use of CaM is associated with treatment of somatic and mental health conditions not included in the MCPP.

Most of the users of CaM in our study were women and a majority were 45 year or older. Nearly half of the users had a medium-cycle higher or a vocational secondary education, and employment status was diverse and nearly evenly distributed between full-time employment, disability pension, reduced employment, and retirement. Most of the users of CaM had initiated use within the last two years and a majority had little to no previous experience with recreational cannabis use. Furthermore, few had a prescription for CaM and more than one third of those with a prescription supplemented their use with cannabis from the unregulated market. Oil was the most frequent form of intake and CBD oil was the most frequent form of cannabis used. CaM was used for a variety of somatic and mental health conditions, of which the most prevalent were chronic pain, sleep disturbances, stress, osteoarthritis, anxiety and depression. Most users experienced

substantial symptom relief from using CaM, limited or no side-effects and a positive impact on daily life function. CBD oil only users were more likely to be women, older, have initiated use recently and have no recreational experience.

The study resembles previous studies in terms of recruitment strategies and findings on motives for use, but differs from some studies in terms of demographics and patterns of use. Two studies (Lintzeris et al., 2018; Sexton et al., 2016) reported a majority of male users, a mean age in the late 30s, and more than 80% reporting inhalation as the most common form of intake. The difference in samples and study findings is likely to reflect the rapid change in the use of CaM, due to the increasing popularity of medicinal use of CBD oil (see also Haze-kamp, 2018; Manthey, 2019). Of note, a recent survey on the use of CBD products in the US found that the majority of medicinal CBD users were women, and that nearly half were over 55 years of age (Corroon & Phillips, 2018). These findings match the findings from our study, where the odds of using CBD oil only were higher among women and increased with age.

Patterns of use

The average daily dose among users of “hash, pot or skunk” in our study is almost double the average dose used by medical cannabis patients

Table 4. Odds ratios (ORs) and 95% confidence intervals (Cis) of using CBD oil only ($n = 1,141$).

	Total sample $N = 3,021$	CBD oil only users ($n = 1,141$)	OR of CBD oil only use
	n (%)	n (%)	OR (95% CI)
Gender			
Male	1,097 (36.3)	220 (19.3)	1.00 (reference)
Female	1,891 (62.6)	909 (79.6)	3.36*** (1.95–4.01)
Age (years)			
18–24	138 (4.6)	23 (2.0)	1.00 (reference)
25–34	356 (11.8)	67 (5.9)	1.14 (0.66–1.99)
35–44	583 (19.3)	181 (15.9)	2.07** (1.24–3.46)
45–54	831 (27.6)	343 (30.1)	2.88*** (1.75–4.74)
55–64	710 (23.6)	319 (28.0)	3.28*** (1.99–5.43)
65–74	328 (10.9)	169 (14.8)	4.55*** (2.68–7.72)
> 75	68 (2.3)	38 (3.3)	5.35*** (2.67–10.72)
Current employment^{a,b}			
Disability pension (due to reduced working capacity)	651 (21.6)	220 (19.3)	0.53*** (0.41–0.67)
Other	163 (5.4)	38 (3.3)	0.42*** (0.27–0.64)
Education^{a,b}			
Short-cycle higher education	349 (11.6)	167 (14.6)	2.37* (1.03–5.48)
Duration of use^a			
< 6 months	578 (19.1)	352 (31.0)	1.00 (reference)
6 months–1 year	628 (20.8)	338 (29.7)	0.75* (0.59–0.95)
1–2 years	752 (24.9)	335 (29.5)	0.52*** (0.42–0.66)
2–5 years	547 (18.1)	101 (8.9)	0.16*** (0.12–0.22)
6–10 years	227 (7.5)	8 (0.7)	0.04*** (0.02–0.08)
11–20 years	130 (4.3)	1 (0.1)	0.01*** (0.00–0.06)
< 20 years	141 (4.7)	2 (0.2)	0.01*** (0.00–0.05)
Previous recreational experience^a			
None (never tried before medicinal use)	1,452 (48.1)	839 (73.5)	1.00 (reference)
Little (lifetime use < 5 times)	477 (15.8)	191 (16.7)	0.55*** (0.45–0.69)
Some (occasionally < 10 times/year)	319 (10.6)	44 (3.9)	0.15*** (0.11–0.21)
High degree (periodically several times/month)	355 (11.8)	24 (2.1)	0.08*** (0.05–0.12)
Very high degree (almost daily for several years)	352 (11.7)	23 (2.0)	0.08*** (0.05–0.12)

^aControlled for age and gender. ^bOnly significant results reported.

* $p < 0.5$. ** = $p < .01$. *** = $p < .001$.

in the Netherlands (de Hoop et al., 2018). This discrepancy may be related to differences in setting related to use, as Dutch medical cannabis patients have access to medical guidance, while the Danish CaM users self-medicate. The preference for CBD oil found in our study indicates that the majority of the medicinal cannabis users in Denmark are interested in effects beyond the “high”, as CBD does not induce the

euphoric effects most often associated with cannabis use (Colizzi & Bhattacharyya, 2017; McPartland & Russo, 2014). It is worth noting that the preference for low-potency CBD oil among the Danish medicinal cannabis users found in this study differs significantly from a recent development on the illegal cannabis market in Denmark. In analyses of hashish seized by police in Denmark we found a three-fold

increase in THC concentration from 2000 (mean: 8.3%) to 2017 (mean: 25.3%) (Rømer Thomsen et al., 2019) while CBD levels remained stable (mean around 6%); a development that is also found elsewhere in Europe (Freeman et al., 2019). From a public health perspective, it could be considered positive that most medicinal users in our study prefer CBD oil and bypass smoked plant material like hashish, as CBD oil may be less harmful, both in terms of cannabinoid composition (Bergamaschi et al., 2011; Englund et al., 2017) and mode of intake (Russell et al., 2018). Conversely, it has been suggested that the popularity of CBD products may have adverse net public health outcomes, as it may expose a subgroup of the population that otherwise would have remained cannabis novices (Manthey, 2019). This may indeed be the case in our study, where CBD oil only users were more likely to have been cannabis novices before onset of CaM use. However, the risks associated with use of CBD products may not be related to the effects of CBD, but to the composition and quality of the available CBD products (Hazekamp, 2018). A recent examination of CBD oils available in Denmark by the Department of Forensic Medicine in Odense, revealed that 38% of CBD oils tested contained between 0.2% and 1.2% THC, despite being advertised as below 0.2% THC (Eriksen & Christoffersen, 2020) and similar labelling inaccuracies of CBD products have also been found in the US (Bonn-Miller et al., 2017) and Europe (Hazekamp, 2018; International Cannabis and Cannabinoids Institute, 2018). This is problematic as it increases the risk of exposure to undesired euphoric effects among users and could potentially leave the users unknowingly in violation of the Euphoric Substances Act, which prohibits the consumption of cannabis with more than 0.2% THC (Lægemedelstyrelsen, 2018). The challenges related to product quality do not only concern CBD oils, but all types of cannabis use, as the products may contain hazardous contaminants related to production (fungi, bacteria, heavy metals, growth enhancers or pesticides) or

marketing (lead or glass beads to increase weight or psychoactive substances to increase effect) (Lenton et al., 2018; National Academies of Sciences Engineering and Medicine, 2017). The risks associated with product quality and marketing are relevant in the public health assessment of the unregulated use of CaM, as they may be particularly problematic in clinical populations (Ruchlemer et al., 2015).

Motives for use

The heterogeneity among the CaM users in the current study is reflected in the great variety in motives for use, as they involved a broad range of somatic and mental health conditions, of which chronic pain, sleep disturbances, stress, osteoarthritis, anxiety, and depression were most prevalent; a finding which resembles other studies (Corroon & Phillips, 2018; Lintzeris et al., 2018; Lucas et al., 2019; Park & Wu, 2017; Reinerman et al., 2011; Sexton et al., 2016; Walsh et al., 2013; Ware et al., 2005). The fact that sleep disturbances and stress were among the most prevalent conditions treated with CaM, may indicate a tendency to manage these conditions without formal medical advice and assistance, or that these conditions are more likely to be underdiagnosed, as they are often co-morbidities of other somatic or mental health conditions (Cranford et al., 2017; Melkevik et al., 2018). The reported effects of CaM on pain and sleep found in this study were substantial, and while it can be argued that pain is a subjective experience (Koyama et al., 2005), the improvement in number of hours slept provides a more tangible and objective result. An improvement in sleep may mediate an improvement in somatic and mental health conditions. A plethora of studies have found that sleep disturbances are associated with an array of disease risk (Laposky et al., 2016) and mental health disorders (Sutton, 2014), such as anxiety and depression (Alvaro et al., 2013). Indeed, there is an intimate and bidirectional relationship between sleep and emotion (Kahn et al., 2013), and a

positive change in sleep patterns improves positive affect and overall wellbeing (Ong et al., 2017). However, research on cannabinoids and sleep is in its infancy, and more research is needed regarding the long-term effects on sleep patterns (Babson et al., 2017).

The use of CaM in treatment of mental health conditions has raised concerns due to the limited scientific support for such use, for example regarding anxiety and depression (Black et al., 2019; Turna et al., 2017) and a substantial body of evidence has linked the use of cannabis with a worsening of some mental health issues and increased incidence of certain psychiatric conditions (National Academies of Sciences Engineering and Medicine, 2017). However, the current evidence is primarily based on observational and epidemiological studies on non-medical use of cannabis and may not be generalisable to the clinical implications of medical cannabis use in treatment of mental health disorders (Walsh et al., 2017). Importantly, research shows that the clinical implications of medical cannabis use are related to patterns of use, due to the opposing effects of THC and CBD (Boggs et al., 2018; Englund et al., 2017; Rømer Thomsen et al., 2017), and that CBD may hold potential for the treatment of mental health conditions (Khan et al., 2020). Consequently, more research is needed into the safety and effects of subtypes of cannabis.

Medicinal use of CaM and the MCPP

The current re-medicalisation of cannabis has prompted Danish politicians to push the boundaries between cannabis as an illicit drug and as a licit medicine, with the initiation of the MCPP. However, substantial discrepancies between the MCPP and the unregulated use of CaM in Denmark remain. For one, it is striking that the only consistently available product in the MCPP has been the cannabis flower, with suggested intake as a tea or in a vaporiser (Danish Health Data Authority, 2019a; Lægemedelstyrelsen, 2019d), whereas findings from our study and trends in the medical cannabis programme in

the Netherlands (de Hoop et al., 2018) suggest that cannabis oil may in fact be the most preferred form of CaM. It is also striking that the most prevalent conditions reported in our study (chronic pain, sleep disturbances, stress, arthritis, anxiety, and depression) differ from the recommended conditions in the MCPP, except for chronic pain. It could be argued that the need for safe and legal access to medical cannabis is relevant for other patient groups than the patients who are currently included in the MCPP. Conversely, it could be argued that even the current inclusion of chronic pain patients in the MCPP presents a considerable problem, as the current evidence does not allow a full recommendation of using CaM in treatment of chronic pain (Hoffman, 2018; Stockings et al., 2018).

Aside from the limitations of the MCPP in terms of available products and eligible conditions that can be treated, other factors may also contribute to the high rate of medicinal use found in our study, including: limitations on access to the MCPP, fear of stigma, and cost of medical cannabis. For one, access to the MCPP may have been limited, as some Danish GPs may be unwilling to prescribe medical cannabis to their patients. The Danish College of General Practitioners have critiqued the MCPP and advised their members against prescribing medical cannabis to patients, due to the lack of high-quality documentation (Bro, 2018) and several doctors' offices have issued official statements to their patients declaring that they do not prescribe medical cannabis (Hjort, 2018). Moreover, fear of stigma has been shown to have a profound impact on treatment-seeking behaviour of potential medical cannabis patients (Satterlund et al., 2015) and fear of stigma may also represent a barrier to the MCPP, as findings from our survey showed that a large majority (72.2%) had not asked their GP for a prescription for medical cannabis. Lastly, we cannot rule out that the high prevalence of users of CaM outside the MCPP is a consequence of the cost of the legal cannabis products that, despite government

reimbursements, remain many times higher than that of illegally sourced products (Videbæk & Bergmann, 2019). Unfortunately, we cannot compare the experienced effect among users of whole-plant cannabis in the MCPP to the experienced effect reported in our study, as only adverse events of medical cannabis use have been reported by medical doctors (Dahlin, 2017; Lægemedelstyrelsen, 2019c), of which there have been relatively few (Lægemedelstyrelsen, 2020).

Our study indicates that the pressure on politicians to formulate medical cannabis policy remains largely unresolved. Firstly, the majority of users of CaM remain outside the MCPP and therefore they continue to rely on an unregulated illegal market. Secondly, as use of CaM appears to be a growing trend among Danes and as many users find CaM effective in managing their conditions, the demand for safe access to medical cannabis is likely to increase. More clinical research on the effects and side-effects of whole-plant cannabis is needed, as this would allow for a more qualified drawing of boundaries of the medical utility of cannabis.

Strengths and limitations

The strengths of the study include the sample size, the wide distribution on age, geography, and the depth of exploration of patterns and motives for use. The method of using anonymous internet-based surveys holds an advantage in studying sensitive topics in so-called “hidden populations” (Barratt, Potter, et al., 2015), where it is impossible to establish who constitutes the population, and where strong privacy issues are at stake, due to illegal behaviour and risk of stigmatisation (Heckathorn, 1997).

However, some limitations must be noted. Firstly, we wish to state that this is not a study on the efficacy of CaM, as this should be assessed through double-blind placebo-controlled trials (D’Souza & Ranganathan, 2015). Furthermore, the self-selected convenience sample is limited by selection bias, and

may not be representative of the population of users of CaM in Denmark (Barratt, Ferris, & Lenton, 2015). The sample may weigh towards successful users of CaM, as those who have found cannabis either ineffective or experienced adverse effects may have disengaged from the topic. Moreover, the sample may weight towards users with internet access, a familiarity with online surveys, and the cognitive abilities to answer such surveys, and represent a part of the population that is more actively engaged in the topic of CaM on social media.

We should also note that the data in this study may be subject to self-reporting biases such as recall bias or social desirability bias (Althubaiti, 2016). Although all questions were framed with respect to their sensitivity in wording, in order to reduce social desirability bias (Näher & Krumpal, 2012), respondents may still exaggerate effects of cannabis or underreport adverse effects, as they may perceive themselves to be stakeholders in the outcomes of potential survey findings. Although duplicates were excluded from the analyses, we cannot rule out multiple responses from the same person. Also, although the reported use of dose would have been more precise in mg/k, we made a trade-off between precision and presumed knowledge of the respondents. Likewise, the response categories concerning use of THC oil and CBD oil may cover a wide variety of products. In the interest of mapping this new area in Denmark, we included previous users and answers on behalf of someone next of kin, which may have decreased the validity of the findings. Despite these limitations, the study provides a valuable insight in into the unregulated use of CaM in Denmark.

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ORCID iD

Sinikka L. Kvamme  <https://orcid.org/0000-0002-8376-2013>

Note

1. Conditions with $n < 15$ indications [AIDS, Alzheimer's, hepatitis, neurodermatitis, Lupus (SLE), end-of-life (palliative care) Tourette's] were excluded from the figures.

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- disc, dystonia, eczema, epilepsy, endometriosis, fibromyalgia, osteoarthritis, rheumatoid arthritis, psoriatic arthritis, cataracts, hepatitis, brain damage, COPD, cancer, CFS (chronic fatigue), chronic nerve inflammation, chronic pain, migraine, menstrual pain, multiple sclerosis, neurodermatitis, IBS, lupus (SLE), end-of-life (palliative care), Parkinson's, peripheral neuropathy, psoriasis, spinal cord injury, pain following operation, pain following an accident, tinnitus, trigeminal neuralgia

Psychiatric conditions (13): ADHD, anxiety, dependence (alcohol), dependence (hard drugs), dependence (prescription drugs), anorexia, autism, bipolar disorder, depression, OCD, PTSD, schizophrenia, Tourette's/tics

Potential comorbidities (2): sleep disturbances, stress

Appendix I

Somatic conditions (37): acne, AIDS, Alzheimer's, asthma, Chron's disorder, herniated

7.2. Paper nr 2: Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample

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Declaration of co-authorship

Full name of the PhD student: Sinikka Lehmann Kvamme

This declaration concerns the following article/manuscript:

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If accepted or submitted, state journal:

Has the article/manuscript previously been used in other PhD or doctoral dissertations?

No Yes If yes, give details:

The PhD student has contributed to the elements of this article/manuscript as follows:

- A. Has essentially done all the work
- B. Major contribution
- C. Equal contribution
- D. Minor contribution
- E. Not relevant

Element	Extent (A-E)
1. Formulation/identification of the scientific problem	A
2. Planning of the experiments/methodology design and development	A
3. Involvement in the experimental work/clinical studies/data collection	A
4. Interpretation of the results	B
5. Writing of the first draft of the manuscript	A
6. Finalization of the manuscript and submission	B

Signatures of the co-authors

Date	Name	Signature
15-12-2021	Michael M. Pedersen	
15.12.2021	Kristine Rømer Thomsen	
17.12.2021	BIRGITTE THYLSTRUP	

Date: 17/12-2021

In case of further co-authors please attach appendix

Signature of the PhD student:

*As per policy the co-author statement will be published with the dissertation.

RESEARCH

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Exploring the use of cannabis as a substitute for prescription drugs in a convenience sample

Sinikka L. Kvamme^{1*} , Michael M. Pedersen¹, Kristine Rømer Thomsen¹ and Birgitte Thylstrup²

Abstract

Background: The use of cannabis as medicine (CaM) both prescribed and non-prescribed has increased markedly in the last decade, mirrored in a global shift in cannabis policy towards a more permissive stance. There is some evidence that cannabis functions as a substitute for prescription drugs, particularly opioids; however, more knowledge is needed on the motives of substitution users, their patterns of use, and perceived effects of substitution use.

Aims: To explore who substitutes prescription drugs with cannabis, the type of prescription drugs substituted and the type of cannabis used, and the impact that substitution with cannabis has on prescription drug use as well as the motives for substitution in terms of experienced effects and side effects.

Methods: A self-selected convenience sample was recruited through social media, public media, and patient organizations to take part in an anonymous online survey. Inclusion criteria were 18 years or older and use of cannabis (prescribed or non-prescribed) with a medical purpose.

Results: The final sample included 2.841 respondents of which the majority (91%) used non-prescribed cannabis, and more than half (54.6%) had used CaM with the purpose of replacing a prescribed drug. Compared to non-substitution users, substitution users were more likely to be women and to use CaM in the treatment of chronic pain and other somatic conditions. Pain medication (67.2%), antidepressants (24.5%), and arthritis medication (20.7%) were the most common types of drugs replaced with CaM. Among substitution users, 38.1% reported termination of prescription drug use, and 45.9% a substantial decrease in prescription drug use. The most frequent type of cannabis used as a substitute was CBD-oil (65.2%), followed by 'hash, pot or skunk' (36.6%). More than half (65.8%) found CaM much more effective compared to prescription drugs, and 85.5% that the side effects associated with prescription drug use were much worse compared to use of CaM.

Conclusion: CaM is frequently used as a substitute for prescription drugs, particularly opioids. More research is needed on the long-term consequences of use of CaM, including the impact from low and high THC cannabis products on specific somatic and mental health conditions.

Keywords: Substitution, Medical cannabis, Opioid use, Prescription drugs, Cannabidiol

Background

In recent years, there has been a global shift in perspectives on the utility of cannabis. While cannabis has predominantly been associated with recreational and/or problematic use, the plant or its components, *cannabinoids*, are increasingly regarded as a viable treatment option for medical conditions, such as chronic pain,

*Correspondence: slk.crf@psy.au.dk

¹ Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Building 1322, Bartholins Allé 10, 8000 Aarhus C, Denmark
Full list of author information is available at the end of the article



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spasticity, nausea, and epilepsy [1], and as a potential treatment of other conditions [2–4].

The medicalization of cannabis is in large part driven by the discovery of the endocannabinoid system in the late eighties, pharmaceutical interests in cannabinoids, and a growth in user demand for access to *medical cannabis* (cannabis prescribed by a doctor) [5, 6]. This development is mirrored in the rapidly shifting policy on the adoption of medical cannabis laws in more than 30 states in the USA [7], Australia [8], Canada [9] and several European countries [10], including Denmark [11]. However, the introduction of medical cannabis into medicine is controversial and highly debated. While critics caution use of medical cannabis due to the limited high-quality evidence [12, 13], proponents argue that medical cannabis constitutes an important harm reduction strategy and may function as a qualified substitute for prescription drugs, particularly opioids [14, 15] in the context of the opioid-epidemic in the USA [16] and Canada [17].

In drug research, the term “substitution” is conventionally associated with the use of opioid antagonists, such as methadone, in the treatment of opioid addiction [18, 19]. The concept of substitution has its origins in behavioral economics and involves the assessment of the interaction of multiple concurrent commodities [20]. According to this concept, a substance is regarded as a *substitute* if it acts as a replacement, or leads to reduced use of another substance (e.g., treating heroin addiction with buprenorphine) [21]. Conversely, two substances may be *complimentary* when the increased consumption of one substance enhances the consumption of the other (e.g., tobacco smoking is often linked to excessive use of alcohol) [22]. Lastly, if there is no interaction on consumption patterns between substances, they are *independent* (e.g., it has been found that a change in price of alcohol has no impact on consumption of ecstasy [23]).

Substitution of cannabis for prescription drugs

Emerging research indicates that the increased use of CaM (cannabis as medicine) has had a substitution effect on prescription drug use. In several cross-sectional surveys conducted in the USA and Canada users of CaM report substituting cannabis for prescription drugs, of which opioid, anti-depressive, and anxiolytic drugs are the most prevalent [24–29]. In fact, substitution of prescription drugs is the most common motive among users of medical cannabis, surpassing substitution rates for alcohol and illicit drugs [24, 25, 30, 31]. Moreover, state medical cannabis laws in the USA have been associated with a sizeable reduction in prescription drugs [32], particularly opioid prescriptions [33–35], and with fewer prescription opioid-related hospitalizations, lower rates of opioid overdoses, and decreases in opioid-related

healthcare costs [36]. A potential substitution effect of CaM on prescription drug use in a European context is much less explored, and findings from the USA in particular, may not be applicable, due to the considerable variations in health care systems [37, 38] and laws on prescription drugs and cannabis. However, a recent Italian study found that an unintended legalization of cannabis products with less than 0.6% Δ -9-*tetrahydrocannabinol* (THC; main psychoactive component of cannabis) between December 2016 and May 2019 [39] was associated with a considerable decrease in pharmacy sales of anxiolytics, sedatives and anti-psychotics, and a moderate decrease in the sale of opioids, anti-depressants, anti-epileptics, and migraine medication [40].

When evaluating the harm reduction potential of substituting prescription drugs with CaM, it is relevant to consider the subtype of cannabis used as a substitute. Emerging research shows that potential harms related to consumption of cannabis depend on the composition of active components (cannabinoids) in the cannabis used, as cannabis products with high levels of THC are more harmful in terms of negative impact on cognitive function, anxiety- and psychotic symptoms, and addiction, compared to low THC-products [41–45]. Moreover, other studies indicate that *Cannabidiol* (CBD; main non-psychoactive component of cannabis) has anxiolytic and antipsychotic effects [43–45], and therapeutic effects on addiction, including opioid, stimulant, and cannabis addiction [46, 47]. Further, some evidence suggests that CBD may protect against some of the harmful effects of THC [44, 48]. Taken together, these findings highlight the relevance of the subtype of CaM used in an evaluation of potential harm reduction related to the substitution effect of CaM.

Medical cannabis as the “lesser of two evils?”

In light of recent research findings on the substitution effect of CaM on opioid use, CaM has been suggested as a valuable intervention strategy in combatting the ongoing opioid epidemic in the USA and Canada [14–17, 49]. The most frequent rationales behind this suggestion are the substantial evidence that cannabis is effective in treating chronic pain in adults [1], the prevalent use of medical cannabis in pain management [50], and the fact that, unlike opioids, cannabis has no reported deaths due to overdose [51], as acute effects of cannabis do not depress respiratory function [52, 53]. The non-psychoactive component of cannabis, CBD, has been of particular interest as a target for opioid use disorder [16, 54], as CBD has a discrete modulatory effect on the endocannabinoid system compared to the direct action of THC, giving CBD a broader therapeutic range [16]. Also, there may be an opioid-sparing effect of cannabis,

as pre-clinical studies show that co-administration of cannabinoids with opioids enables a reduction in opioid dose without loss of analgesic efficacy [55]. On the basis of growing indications that cannabis may be a viable tool in targeting the adverse effects of opioid use, some US states have recently modified their medical cannabis laws, allowing patients to substitute their prescribed opioids with medical cannabis [56]. What is interesting about this development is that the medical value of cannabis appears to be based not only on what cannabis *is*, in terms of the available evidence on its efficacy, but also on what cannabis *is not*, when compared to opioids [14, 15, 17]. This perception has also been described in a qualitative study of physicians in Israel, where cannabis was presented as a justified treatment option and as a “the lesser of two evils” by emphasizing problems in standard medications [57]. However, opponents of this position argue that the current evidence for the use of medical cannabis is weak, that more clinical trials are needed [58, 59], and that other efficacious medications for the treatment of problematic opioid use are under prescribed [60]. Furthermore, some evidence suggests medical cannabis may not function as a long-term substitute for opioids [61], and cannabis use is associated with increased risk of problematic opioid use [62, 63]. Still, despite the recommendations to wait for more valid evidence on the long-term effects of substituting prescription drugs with CaM, several studies indicate that many of the current users of CaM are using cannabis as a substitute for prescription drugs, particularly opioids, and report fewer side effects and better symptom management as their motive for substitution [28, 64].

Cannabis as a substitute for prescription drugs in a Danish context

In Denmark, a four year Medical Cannabis Pilot Program (MCP) was initiated in 2018 with the aim of providing a safe and legal framework for prescribed whole plant cannabis to patients with multiple sclerosis, spinal cord injury, chronic pain, or chemotherapy-related nausea, and vomiting [65]. Medical cannabis is not formally categorized in the MCP as a potential substitute for any prescribed drug, and the Danish Medicines Agency recommends that only patients who have failed to respond to conventionally approved drugs are prescribed medical cannabis [65]. Thus, in Denmark, medical cannabis is not officially regarded as a tool to combat misuse of prescription drugs, but instead as a last resort. Despite the changes in policy, there are indications of a large use of *medicinal* (non-prescribed) cannabis occurring outside the legal framework of the MCP [11]. In the first survey in Denmark on the use of CaM, we recently found that the vast majority of respondents (90.9%) reported

use of CaM without a doctor’s prescription [11]. Moreover, we found that most users of CaM reported limited recreational experience (63.9%) and a preference for low potency CBD-oil (65%) [11]. Of note, there are several other indications that cannabis oil has become more prevalent in Denmark in recent years, including a growth in web-shops selling low-potency cannabis oil [66], an increase in selling of cannabis oil at the illegal open drug scene Christiania [67], and an increase in police confiscations of cannabis oil [68]. All use of cannabis outside the MCP is illegal, both sale and possession, except from cannabis products containing less than 0.2% THC. Such products are illegal to sell if they are considered to be medicine by the Danish Medicines Agency, but they are not illegal to possess [69].

The MCP has set the legal parameters for the utility of CaM in Denmark, but we lack knowledge on the parameters users of CaM set in practice; do they substitute prescription drugs with CaM, and do they perceive CaM to be the lesser of two evils in terms of experienced effects and side effects? Examining the use of CaM as a substitute for prescription opioids is of particular public health interest, in the context of the increased use of prescription opioids in the Danish health care system, which has undergone recent media scrutiny in Denmark [70]. As a response, the Danish Medicines Agency started an investigation, which showed that use of the “weaker opioid” Tramadol was driving a substantial part of the rise in opioid use in Denmark [70].

Taken together, we lack knowledge about whether the emerging trend of using CaM in Denmark is related to a motive of replacing prescription drugs. Previous qualitative research found that using cannabis as a substitute for prescription drugs was a motive among Danish growers of cannabis for medicinal purposes, particularly opioids [71]. However, more knowledge is needed on user perspectives on the utility of cannabis as a substitute for prescription drugs, because user perspectives can unveil aspects of illegal drug use unseen by society at large [72]. Also, there is a need for exploring the type of cannabis used as a substitute, as the potential negative health effects of cannabis use varies according to the subtype of cannabis used [73]. Finally, the vast majority of studies have been conducted in the USA and Canada, and we lack studies examining potential use of CaM as substitution for prescription drug use in a European context.

Methods

Aims

The aim of the present study was to examine to what extent CaM is used as a substitute for prescription drugs in a convenience sample of Danish users of CaM, and to characterize the substitution users. Furthermore,

the study aimed to examine what type of prescription drugs are substituted with CaM, what types of cannabis are used as substitution, and the perceived impact on prescription drug use. Finally, we aimed to compare perceived effects and side effects of CaM compared to prescription drugs used.

Study design

The study was based on data from the first survey on use of CaM conducted in Denmark (for more details, see [11]). A novel survey was developed, inspired by previous studies on users of CaM [27, 74–79]. The full survey consisted of 44 structured questions and 19 possible follow-up questions answered in a Yes/No format, multiple-choice response, or rating scales. The survey took about 15 min to complete, and was available in Danish only. Data were collected through SurveyXact. IP addresses of the respondents were not saved or available to the researchers, as the respondent's anonymity was considered a greater issue than the possibility of repeated participation [80]. We have previously reported on the motives for use and patterns of use from 3,021 respondents from this survey [11].

Sampling and recruitment

The survey was made available online to a self-selected convenience sample of users of CaM from July 14th 2018 to November 1st 2018. Inclusion criteria were being 18 years or older and being a user of CaM, either prescribed by a doctor or non-prescribed with a self-perceived medical purpose. Users of CaM who had stopped using cannabis were included in the sample and characterized as former users of CaM. Participants were recruited via online material, flyers, and posters with information about the survey, and a survey link and QR code directing to the survey. The material was disseminated on social media, through patient organizations, in doctors' offices and hospitals, at the illegal open drug market in Denmark (Christiania), the first Cannabis Expo in Denmark, and via headshops selling cannabis-related items. Furthermore, the survey was made available through Smokeboddy (an app where users monitor potential police presence at Christiania) and was covered by the national media (The Danish Broadcasting Corporation).

Measures

The full survey included several key domains; sociodemographics, motivation for use, patterns of use, and evaluation of perceived efficacy and adverse effects. In the

present study, the following domains were used for the data analyses (see description of the remaining measures in [11]).

Current and former users of CaM

Respondents were asked an introductory question: *Do you use CaM?*, and could answer either Yes/No or "I have used CaM, but I stopped". Respondents who answered "Yes" were defined as current users, while those who indicated having past experience with the use of CaM were defined as former users, and those that answered "No" were not included in the study sample.

Users who used CaM as a substitute for prescribed drugs

Respondents were asked if they had experience with using prescription drugs to treat somatic or mental health condition(s). Those who responded positive were asked a follow-up question on whether they had ever used CaM with the purpose of replacing a prescribed drug. Those who answered affirmatively were categorized as "substitution users", while all other respondents were categorized as "non-substitution users."

Type of drug substituted

Respondents were asked which prescription drugs they had replaced with cannabis and were provided with six response categories: Pain-medication, Anti-depressants, Anti-psychotic, Anti-epileptic, Arthritis-medication, and an "Other" category, and could choose more than one category. Each category was followed with an open-ended question, where respondents were encouraged to write the brand of the prescribed drug.

Impact of CaM on prescription drug use

Respondents were asked to evaluate how their use of CaM affected their use of prescription drugs on a 6-point scale from 'use of prescription drugs has increased substantially' (1) to 'use of prescription drugs has decreased substantially' (5), including an option to indicate cessation of prescription drug use; 'I have stopped using prescription drugs' (6).

Effects and side effects

Respondents were asked to evaluate the experienced effects and side effects of CaM compared to the substituted prescription drugs on a 5-point Likert scale from 'CaM is much more effective than prescription drugs' (1) to 'prescription drugs are much more effective than CaM' (5).

Data analysis

Data analysis was conducted using Stata SE/15 [81] and Nvivo 12 [82]. Figures were produced in Excel 2016 and Word 2016. Descriptive statistics were used to describe sample characteristics, conditions treated, and patterns of use. A histogram was used to assess normality in the variable for a number of conditions. As the variables were not normally distributed, the Mann–Whitney U test [83] was used to assess differences in means between substitution users and non-substitution users. We coded a dummy variable, distinguishing between substitution users and non-substitution users, with substitution users coded as 1 (both former and current users of CaM were include). This variable was used as the dependent variable in the logistic regression analysis. Odds ratios (ORs) from multiple logistic regression, controlled for age, gender, and current employment, were used to estimate the strength of association between substituted prescription drug and type of cannabis used. The distribution of the qualitative responses for brands of prescription drugs was quantified in Nvivo 12.

Data management

The 52 conditions that the CaM respondents could choose from, when reporting conditions treated with CaM, were categorized as either somatic conditions ($n=36$) or psychiatric conditions ($n=13$), except for “chronic pain”, “sleep disturbances”, and “stress”, which were kept as independent categories (See “Appendix 2”). In order to explore CBD-oil use only, we coded a dummy variable for use of CBD-oil only (1) and use of other cannabis products (0). Of the 4,570 respondents who opened the survey, 3,140 answered all questions. Of these, 234 were excluded: 59 were under the age of 18, 115 answered on behalf of someone next of kin, seven had inconsistencies in answers, and 53 were identified as duplicates. Respondents with missing responses to the question on substitution as a motive for use of CaM ($n=65$) were also excluded, leaving a final sample of 2,841.

The specific brand of prescription drugs entered in the open-ended questions was grouped together under their shared active ingredient. Non-specific entries (e.g., “strong pain killers” or “migraine medication”) were discarded. All entries for drugs that are also available over the counter (e.g., Ibuprofen or Panodil) were assumed to be obtained via prescription, given the nature of the survey questions. A different approach was taken in the “Other” category, where all entries were coded into new categories. Specific entries such as “melatonin” and “imovane” were coded as “sleep medication” together with non-specific entries, such as “sleeping pills”. The most prevalent new categories ($n > 20$) are reported.

Ethics

Respondents consented to participate and could drop out of the survey at any time before completion. Respondents were not compensated for participating. The data used for this study were collected and stored for monitoring on secure servers, and procedures for data handling and storage were approved by the Danish Data Protection Agency. No ethics evaluation was needed under Danish law.

Results

The majority of respondents were female (63.2%), and aged 45 years or older (64.1%) (see Table 1). The most prevalent level of education was “medium cycle higher-education” (28.7%) and “vocational secondary education” (18%). Employment status was mixed with 25.9% in full-time employment, 21.8% on disability pension, and 18.4% in reduced employment. All five regions of Denmark were represented in the study.

The most prevalent type of CaM was CBD-oil (65.1%), followed by “hash, pot or skunk” (36.4%), and THC-oil (24.5%), and oil was the most frequent form of intake (56.4%) (see Table 2). Most users had limited recreational experience (63.5%), and the vast majority were current users (91.1%), with no prescription for medical cannabis (91%). A majority of respondents used CaM in the treatment of a somatic condition (73.3%), followed by psychiatric conditions (37.1%), chronic pain (32.8%), sleep disturbances (27.9%), and stress (24.1%) (See Table 2). The most prevalent somatic condition treated with CaM was osteoarthritis (23.2%), and almost equally prevalent among the psychiatric conditions were anxiety (19.6%) and depression (19.5%).

CaM used as a substitute for prescription drugs, and substitution user characteristics

The majority (70.1%) indicated that they had experience using prescription drugs in treatment of their condition(s), of which 77.7% ($n=1,546$) had used CaM with the explicit purpose of replacing a prescribed drug. Thus, substitution users made up more than half of the total sample (54.6%).

The odds of using CaM as a substitute for prescription drugs were 1.25 times greater among women (95% confidence interval (CI): 1.05–1.47, $p < 0.05$), 2.21 times higher among users on disability pension (95% CI: 1.75–2.80, $p < 0.001$), and 1.76 times higher among users in reduced employment (95% CI 1.39–2.22, $p < 0.001$), compared to non-substitution users. Users with access to medical cannabis via prescription were 1.68 times more likely to be substitution users (95% CI 1.26–2.24, $p < 0.001$), while level of recreational experience was not significantly associated with substitution use (see Table 2). There were

Table 1 Demographics

	Total sample (n = 2.841) N (%)	Substitution users (n = 1.546) N (%)	Odds of substituting OR (95% CI)
Gender			
Male	1.020 (35.9)	511 (33.1)	1.00 (reference)
Female	1.769 (63.2)	1.024 (66.2)	1.25* (1.05–1.47)
Other	6 (0.2)	3 (0.2)	1.24 (0.20–7.95)
Missing	19 (0.7)	8 (0.5)	
Age			
18–24	126 (4.4)	57 (3.7)	1.00 (reference)
25–34	338 (11.9)	178 (11.5)	1.16 (0.76–1.79)
35–44	555 (19.6)	313 (20.3)	1.20 (0.78–1.84)
45–54	795 (28)	472 (30.5)	1.20 (0.78–1.85)
55–64	681 (24)	365 (23.6)	0.86 (0.55–1.34)
65–74	296 (10.4)	140 (9.1)	0.77 (0.43–1.39)
> 75	47 (1.7)	21 (1.4)	0.71 (0.32–1.57)
Missing	3 (0.1)		
Current employment			
Full-time employment	737 (25.9)	340 (22)	1.00 (reference)
Part-time employment	112 (3.9)	61 (4)	1.40 (0.93–2.10)
Student	128 (4.5)	63 (4.1)	1.25 (0.82–1.90)
Unemployed	50 (1.8)	31 (2)	1.93* (1.06–3.53)
Retired (pension and early retirement)	377 (13.3)	180 (11.6)	1.44 (0.95–2.18)
Stay-at-home	23 (0.8)	10 (0.7)	0.94 (0.40–2.19)
Disability pension	620 (21.8)	401 (25.9)	2.21*** (1.75–2.80)
On sick leave	87 (3.1)	43 (2.8)	1.11 (0.71–1.74)
Reduced employment (due to reduced working capacity)	524 (18.4)	323 (20.9)	1.76*** (1.39–2.22)
Other	147 (5.2)	74 (4.8)	1.21 (0.84–3.54)
Missing	36 (1.3)	20 (1.3)	
Education			
None	35 (1.2)	17 (1.1)	1.00 (reference)
9th grade	322 (11.3)	165 (10.7)	1.15 (0.56–2.35)
9 th –11 th (HG, EFG, EGU)	142 (5)	80 (5.2)	1.34 (0.62–2.86)
High school (STX, HHX, HF)	285 (10)	136 (8.8)	1.05 (0.51–2.17)
Vocational secondary education	512 (18)	307 (19.9)	1.68 (0.83–3.40)
Short-cycle higher education	332 (11.7)	181 (11.7)	1.26 (0.61–2.58)
Medium-cycle higher education	814 (28.7)	460 (29.8)	1.48 (0.74–2.98)
Long-cycle higher education	237 (8.3)	119 (7.7)	1.30 (0.62–2.70)
Other	103 (3.6)	53 (3.4)	1.21 (0.55–2.65)
Missing	59 (2.1)	28 (1.8)	
Region			
Capital	670 (23.6)	344 (22.3)	1.00 (reference)
Central Jutland	623 (21.9)	329 (21.3)	0.96 (0.77–1.21)
Zealand	558 (19.6)	318 (20.6)	1.14 (0.90–1.44)
Southern Denmark	537 (18.9)	309 (20)	1.19 (0.94–1.51)
Northern Jutland	340 (12)	191 (12.4)	1.16 (0.88–1.51)
Missing	113 (4)	55 (3.6)	

OR odds ratio; CI confidence interval

* $p < 0.05$; *** $p < 0.001$

Table 2 Patterns of use and illness/es treated

	Total sample (n = 2.841) N (%)	Substitution users (n = 1.546) N (%)	Odds of substituting OR (95% CI)
Types of cannabis			
THC-oil	697 (24.5)	415 (26.8)	1.28* (1.07–1.53)
CBD-oil	1.850 (65.1)	1.008 (65.2)	0.96 (0.81–1.13)
Hash, pot or skunk	1.035 (36.4)	566 (36.6)	1.16 (0.97–1.38)
Cannabis based (Marinol, Sativex)	172 (6.1)	105 (6.8)	1.22 (0.89–1.69)
Whole plant trial (Bedrocan, Bediol)	54 (1.9)	34 (2.2)	1.42 (0.81–2.51)
Other	221 (7.8)	124 (8)	1.03 (0.78–1.37)
Respondents only using CBD oil	1.086 (38.2)	560 (36.2)	0.79* (0.67–0.93)
Frequency of use			
6–7 days a week	2.141 (75.4)	1.197 (77.4)	1.00 (reference)
3–5 days a week	366 (12.9)	187 (12.1)	0.86 (0.69–1.08)
1–2 days a week	162 (5.7)	76 (4.9)	0.78 (0.56–1.08)
A few times a month	92 (3.2)	45 (2.9)	0.83 (0.54–1.27)
Very rarely	50 (1.8)	24 (1.6)	0.74 (0.42–1.31)
Missing	30 (1.1)	17 (1.1)	
Most frequent form of intake			
Smoked	686 (24.2)	355 (23)	0.94 (0.76–1.13)
Vaporized	102 (3.6)	54 (3.5)	1.03 (0.69–1.56)
Oil	1.601 (56.4)	861 (55.7)	0.87 (0.74–1.02)
Edibles, suppositories, tea, topical	142 (5)	87 (5.6)	1.37 (0.96–1.95)
Capsules	119 (4.2)	71 (4.6)	1.23 (0.84–1.79)
Other	172 (6.1)	107 (6.9)	1.35 (0.97–1.86)
Missing	19 (0.6)	11 (0.7)	
Level of recreational experience			
Novice (lifetime use < 5 times)	1.803 (63.5)	991 (64.1)	1.00 (reference)
Experienced (lifetime use > 5 times)	981 (34.5)	531 (34.4)	1.08 (0.90–1.28)
Missing	57 (2)	24 (1.6)	
Prescription for medical cannabis			
No	2.586 (91)	1.381 (89.3)	1.00 (reference)
Yes	238 (8.4)	162 (10.5)	1.68*** (1.26–2.24)
Missing	17 (0.6)	3 (0.2)	
User status			
Current user of CaM	2.588 (91.1)	1.414 (91.5)	1.00 (reference)
Former user of CaM	253 (8.9)	132 (8.5)	0.94 (0.72–1.23)
Illnesses treated with CaM			
Somatic condition	2.083 (73.3)	1.196 (77.4)	1.44*** (1.21–1.71)
Psychiatric condition	1.055 (37.1)	593 (38.4)	1.15 (0.98–1.35)
Chronic pain	932 (32.8)	642 (41.5)	2.30*** (1.94–2.72)
Sleep disturbances	793 (27.9)	443 (28.7)	1.09 (0.92–1.29)
Stress	684 (24.1)	351 (22.7)	0.91 (0.76–2.94)
Mean number of conditions treated with CaM	3.2 (SD 2.5)	3.6 (SD 2.6)***	$z = -9.01, r = -0.17$

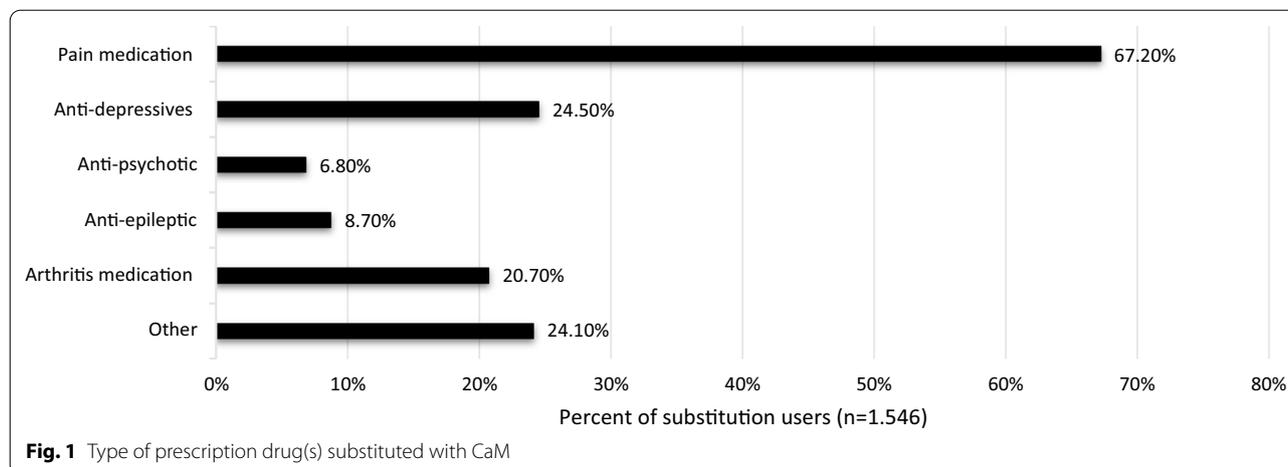
For overview of Somatic and Psychiatric conditions see “Appendix 2”

OR odds ratio; CI confidence interval

* $p < 0.05$; *** $p < 0.001$

no significant associations between using cannabis as substitution and age, education, and region (see Table 1).

Substitution users reported a higher mean of conditions treated with CaM (M 3.6, SD 2.5) compared to other users of CaM (M 3.2, SD 2.5). Substitution users



were 1.44 times more likely to use CaM to treat a somatic condition (95% CI 1.21–1.71, $p < 0.001$), and 2.30 times more likely to use CaM to treat chronic pain (95% CI 1.94–2.72, $p < 0.001$) compared to non-substitution users (see Table 2). There were no associations between a substitution motive and the use of CaM to treat “sleep disturbances”, “stress”, or “psychiatric conditions”.

Prescription drugs substituted and impact of using CaM as a substitute

Pain medication (67.2%) was the most common type of prescription drug substituted, followed by anti-depressants (24.5%), “other” (24.1%), and arthritis medication (20.7%) (see Fig. 1). Specific brands or classes of prescription drugs were listed 1,887 times, of which 1,246 (66%) were pain medication with Tramadol (27.2%) and Morphine (15.5%) as the most common (see Table 3). In the “Other” category, 432 drugs were listed, and the most prevalent medications were “sleep medication” (16%), “ADHD medication” (13.7%), and “anxiety medication” (8.1%).

Among the 1,546 respondents who reported using CaM as a substitute for prescription drugs, the vast majority had stopped using prescription drugs (38.1%) or reduced their use substantially (45.9%). Very few reported a substantial/slight increase in prescription drug use (0.1%) as a consequence of their use of CaM (see Fig. 2).

Type of cannabis used as a substitute

CBD-only users made up one third of all substitution users (36.2%). Substitution users were 1.28 times more likely to use THC-oil (95% CI 1.07–1.53, $p < 0.05$) compared to non-substitution users, and less likely to be CBD-only users (OR: 0.79 (95% CI 0.67–0.93, $p < 0.05$). There were no other significant differences in patterns

of use between substitution users and non-substitution users (see Table 2).

Type of cannabis used varied depending on the types of prescription drugs substituted (see Fig. 3). CBD-oil was the most prevalent type of cannabis used among those who substituted arthritis medication (74.4%), pain medication (66.6%), anti-epileptics (66.4%), and anti-depressants (60.7%), but not among those who substituted anti-psychotics (42%), where “hash, pot or skunk” were the most common types used (80%). The odds of using “hash, pot or skunk” were 1.45 times higher among users who substituted anti-depressants (95% CI 1.08–1.95, $p < 0.05$), and 3.37 times higher among users who substituted anti-psychotics (95% CI 1.87–6.08, $p < 0.001$). Users who substituted pain medication were 1.72 times more likely to use THC-oil (95% CI 1.30–2.27, $p < 0.001$), and users who substituted arthritis medication were 1.46 times more likely to use CBD-oil (95% CI 1.08–1.98, $p < 0.05$).

Experienced effects and side effects

More than half (65.8%) indicated that CaM was a ‘much more effective’ treatment of their condition(s) compared to prescription drugs. A minority indicated that prescription drugs were ‘slightly more effective’ (2.2%) or ‘much more effective’ (1.2%) compared to CaM (see Fig. 4).

When comparing side effects between prescription drugs and CaM, the majority (85.5%) indicated that the side effects of prescription drugs were ‘much worse’ than the side effects of CaM, and a minority reported that the side effects of CaM were ‘slightly worse’ (1%) or ‘much worse’ (0.4%) than the side effects of prescription drugs (see Fig. 5).

Table 3 Five most prevalent classes of prescription drugs substituted with CaM (brands in parentheses)

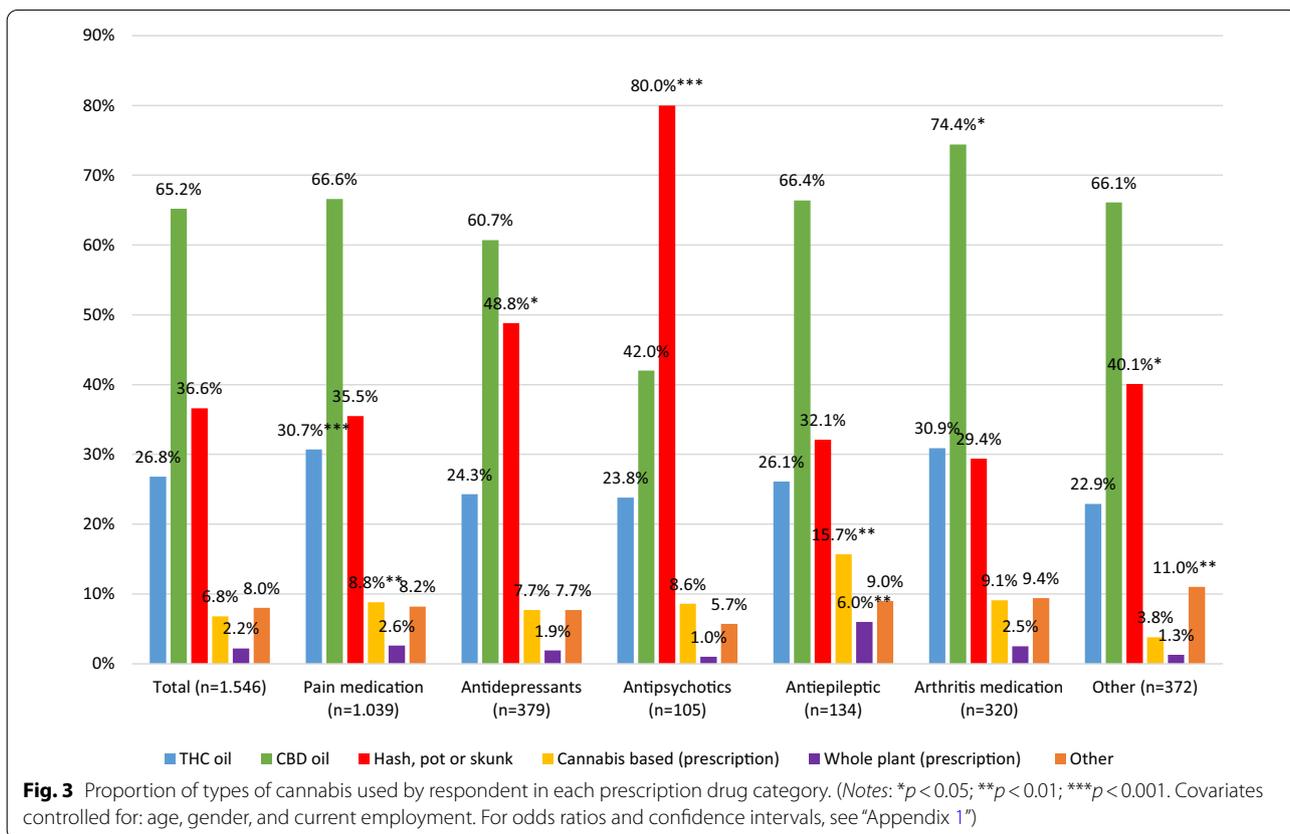
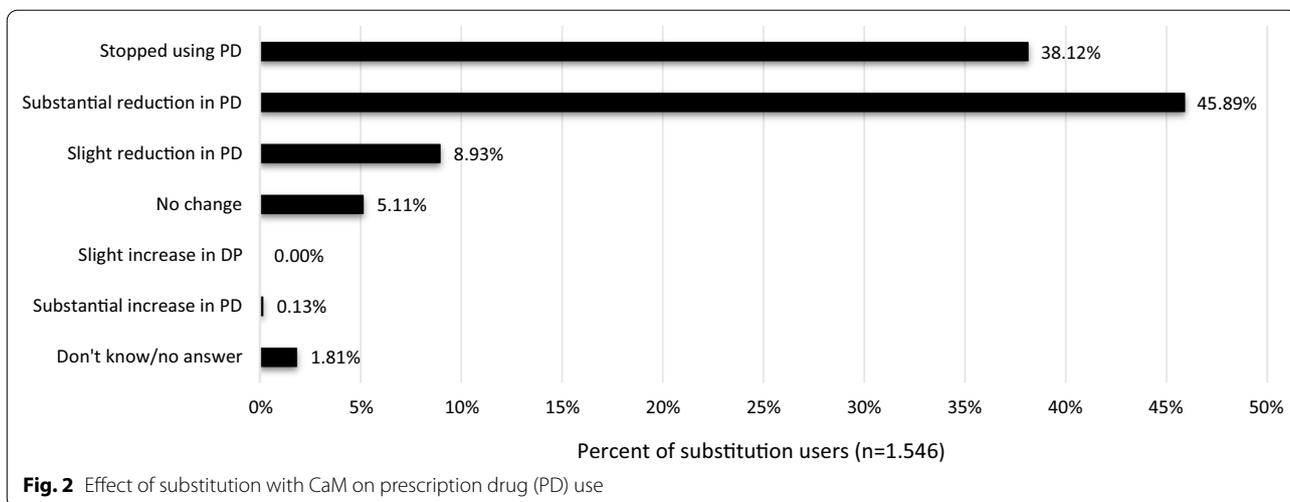
	n (%)
Pain medication (n = 1246)	1.246
Tramadol (Dolol, Gemadol, Nobligan, Mandolgin, Tadol, Tradolan)	339 (27.2)
Morphin (Contalgin, Depolan, Doltard, Malfin)	193 (15.5)
Paracetamol (Kodipar, Fortamol, Doleron, Pamol, Panodil, Pinex)	175 (14.2)
Ibuprofen (Ipren, Ibumetin, Brufen)	151 (12.3)
Oxycodon (Oxiconti, Oxynorm)	67 (5.4)
Antidepressants (n = 209)	209
Sertralin (Sertralin, Zoloft)	35 (16.8)
Citalopram (Citalopram, Cipramil)	29 (13.9)
Venlafaxin (Venlafaxin, Efexor)	24 (11.5)
Duloxetine (Duloxetine, Cymbalta)	21 (10)
Amitriptylin (Amitriptylin, Saroten)	12 (5.7)
Anti-psychotic (n = 82)	82
Quetiapin (Quetiapin, Seroquel)	32 (39.1)
Chlorprothixen (Truxal)	14 (17.1)
Aripiprazol (Abilify)	5 (6.1)
Mathylphenidat (Ritalin, Concerta)	5 (6.1)
Olanzapin (Olanzapin, Zyprexa)	4 (4.9)
Anit-epileptic (n = 114)	114
Gabapentin (Gabapentin)	44 (38.9)
Pregabalin (Lyrica)	37 (32.7)
Lamotrigin (Lamotrigine)	5 (4.4)
Valproat (Deprakine)	4 (3.5)
Clonazepam (Rivotril)	3 (2.7)
Arthritis medication (n = 236)	236
Ibuprofen (Ipren, Ibumetin, Brufen)	123 (52.1)
Diclofenac (Arthrotec, Diclon, Diclofenac, Voltaren)	16 (6.9)
Methotrexat (Metex, Meteozone)	16 (6.9)
Paracetamol (Pamol, Panodil)	9 (3.9)
Naproxen (Naproxen)	7 (3)
Drugs listed in "Other" divided into categories: (n = 432)	432
Sleep medication (Circadin, Melatonin, Halcion, Imozop, Nitrezepam, Zonoc, Stilnoct, Zolpidem, Propavan, Zopiclone)	69 (16)
ADHD medication (Ritalin, Stratea, Elvanse, Concerta, Medikinet, Motiron Methylphenidate)	59 (13.7)
Anxiety medication (Alprazolam, Alprox, Diazepam, Oxapax, Oxazepam, Lorazepam, Stesolid, Hydroxyzine, Atarax)	35 (8.1)
Pain medication (Panodil, Morphin, Tramadol, Dolol, Ibuprofen)	35 (8.1)
Muscle relaxants (Baklofen, Sirdalud, Klorozoxazon, tizanidin)	25 (5.8)
Migraine medication (Sumatriptan, Dixarit, Migea, Triptaner, Imigran, Zomig, Relpax)	25 (5.8)
Topical medication (Dermovat, Locoid, Daivobet, Calcipotriol, Elocon, Zovir, Xamiol)	20 (4.6)
Blood pressure medication (Amlodipine, Ancozan, Aprovel, Candesartan, Doxasozin, Verapamil)	18 (4.2)
Prednisolone (Adrenal cortex hormone)	17 (3.9)

Discussion

To our knowledge, the present study is the largest study to date on self-reported use of CaM as substitution for prescription drugs in a European sample. Further, the study is the first to explore the type of cannabis used as a substitute across different types of prescription drugs, providing valuable insights into user perspectives on

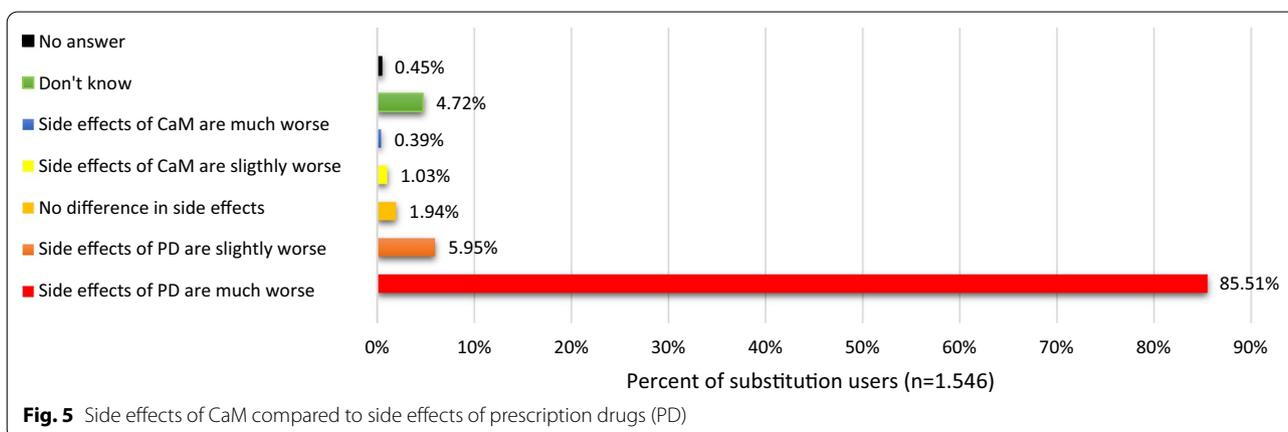
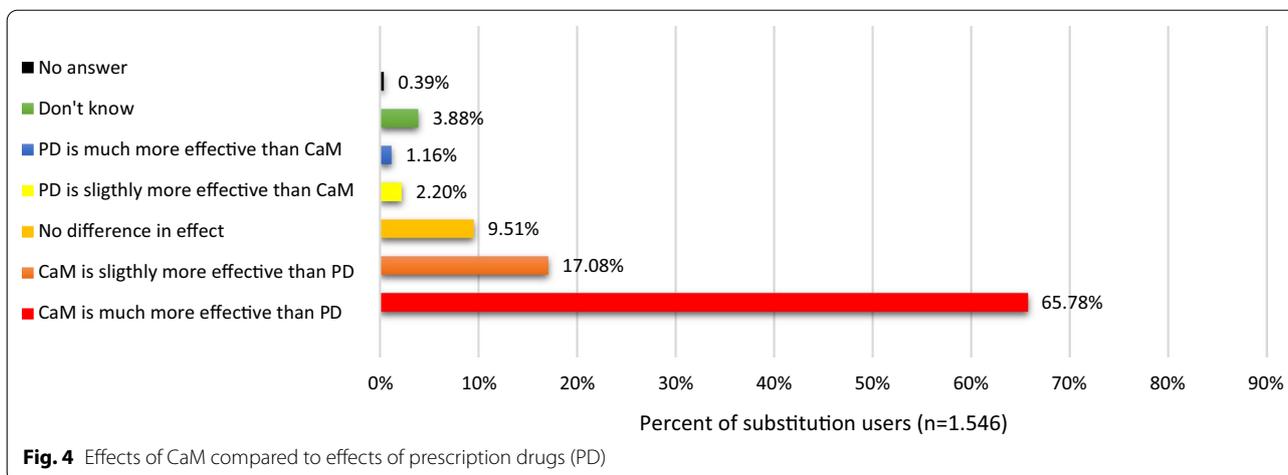
CaM as a substitute for prescription drugs in treating somatic and mental health conditions.

Our findings show that substitution of prescription drugs is a leading motive among users of CaM in a Danish convenience sample, and that this practice is more common among women, people with reduced working capacity due to illness, and people



with chronic pain and other somatic conditions. We found that pain medication by far was the most common type of prescription drug substituted, followed by anti-depressants and arthritis medication, and that Tramadol was the most common class of pain medication that was substituted with CaM. Furthermore, the self-reported substitution effect was considerable, as

the vast majority of substitution users reported either a substantial decrease in, or cessation of, prescription drug use as a consequence of their use of CaM. Across prescription drug categories, we found that CBD-oil was the most common form of cannabis used as substitution, except for people who substituted anti-psychotic medicines, where the use of 'hash, pot or skunk'



was the most prevalent. A majority of the substitution users reported that CaM was much more effective in treating their conditions compared to the prescription drugs that they had used, and a large majority reported that the side effects from their use of prescription drugs were much worse compared to the side effects when using CaM.

Prevalence of substitution and characteristics of substitution users

Studies from Canada and the USA indicate that use of CaM as a substitute for prescription drugs is prevalent among users with legal access to cannabis [24, 26–28, 30, 64, 84, 85]. Our study adds to this literature by showing that substitution of prescription drugs is also a prevalent motive among users of CaM in a European sample, where the majority of substitution use takes place outside a legal medical setting. While a recent international cross-sectional survey found that substitution of prescription drugs was not significantly related to having legal access to medical cannabis [29], we found that users with legal

access to CaM were significantly more likely to be substitution users compared to users without legal access. This difference may be partly explained by the fact that in Denmark, legal medical cannabis is only recommended for specific conditions when other treatment options have proven inadequate [65]. Our finding that users with limited recreational experience with cannabis are just as likely to use cannabis as a substitute for prescription drugs as experienced recreational cannabis users is in line with previous research on substitution as a motive among prescription CaM users [26]. Overall, the present study adds to the growing body of research indicating that use of cannabis as a substitute for prescription drugs is a prevalent phenomenon.

Our finding that women are more likely than men to substitute prescription drugs with CaM resembles previous studies [24, 28, 29] and indicates that there may be a more general pattern of gender differences related to the use of CaM. Of note, a cross-sectional survey of cannabis users from the USA found that female users report significantly lower frequency and quantity of cannabis use and

significantly higher rate of medicinal use for anxiety, irritable bowel syndrome, nausea, anorexia, and migraines compared to men [86]. Further, a qualitative study on legal medical cannabis use, also from the USA, found that gender may influence patterns and practices of use, as the narrative of female users included more collaboration with health care providers compared to the narrative of male users [87]. While other studies have found that older CaM users are more likely to be substitution users [29], our study showed that a substitution motive of CaM was not significantly related to age. The fact that substitution users in our study were more likely to be on disability pension or in reduced employment may indicate that these people encounter treatment barriers in the healthcare system that ‘push’ them towards alternative types of treatment. One such barrier could be the cost of treatment, as the current instability in the prescription drug market with large fluctuations in price [88, 89] may further an economic substitution motive among some low-income patients. However, the use of unregulated cannabis may still be more expensive for most compared to the price of prescription drugs, as government reimbursement of medicine costs in Denmark are substantial [90]. Furthermore, we found that CaM users who treat chronic pain were more likely to be substitution users, which may indicate insufficient treatment options for this patient group, as those suffering from non-malignant chronic pain are potentially undertreated [91, 92].

Type of prescription drug(s) substituted and the impact of substitution

Our finding that pain medications, particularly opioids, were the most common prescription drugs substituted with CaM, followed by anti-depressives and arthritis medication, corresponds with our findings on chronic pain, arthritis, and depression as the most frequent motives for use of CaM. These findings reflect findings from other survey studies; in a large international cross-sectional survey on cannabis users, Corroon et al. [29] found that opioids (13.6%), anxiolytics (12.7%), and antidepressants (12.7%) were the most common classes of prescription drugs substituted with cannabis, and a Canadian cross-sectional survey of medical cannabis patients found that opioid medications accounted for 35.3% of all prescription drug substitutions, followed by antidepressants (21.5%) [24].

The fact that Tramadol was the most common type of prescription drug substituted in our study may in part be explained by the prevalent use of Tramadol in treatment of non-malignant pain in Denmark [70]. However, it may also be related to the decision by the Danish Medicines Agency to surveil prescription patterns of Tramadol among physicians in September 2017, following a rise

in Tramadol use [70] and growing concern among clinicians’ regarding the abuse potential of Tramadol [93]. It is likely that this decision reduced access to prescribed Tramadol for some patients, who subsequently turned to CaM in order to treat their pain condition. In fact, the number of Tramadol users in Denmark decreased for the first time since 2008 in 2017 [94], and continued to decrease from 2017 to 2018 (23% reduction in Tramadol users) [95]. Indeed, problematizing and reducing opioid prescriptions leaves a vacuum that may motivate some patients to seek other therapies such as CaM [96]. Interestingly, the increased use of Tramadol in Denmark earlier occurred as a consequence of another vacuum in the management of non-malignant pain caused by the problematization of nonsteroidal anti-inflammatory drugs (NSAIDs) and the discovery of serious long-term side effects of these drugs [70]. Thus, there seems to be a “cycle of vacuums” in the treatment of non-malignant pain, underscoring the need to rethink the management of non-malignant pain in the Danish health care system [92], as this patient group is potentially undertreated [91].

Our findings on the cessation of and substantial decrease in prescription drug use show a considerable reported substitution effect related to the use of CaM, which is echoed in other studies on the reported substitution effect of CaM among patients with access to medical cannabis. In a survey of dispensary members in New England, the majority reported a decreased use of opioids (76.7%), anxiety medication (71.8%), migraine medication (66.7%) and sleep medication (65.2%) [26]. Similarly, in a survey of American medical cannabis users with chronic pain, the majority of users reported complete cessation of opioids (72%) benzodiazepines (68%), NSAIDs (44%), gabapentanoids (74%), disease-modifying antirheumatic drugs (80%), Serotonin–Norepinephrine Reuptake Inhibitors (78%), and Selective Serotonin Reuptake Inhibitors (80%) [28]. The link to a decrease in opioid use has also been shown over time in a small cohort study in New Mexico, comparing 37 chronic pain patients enrolled in a medical cannabis program to 29 non-enrolled chronic pain patients over the course of 21 months [35]. Findings from this study showed clinically and statistically significant associations between medical cannabis enrollment and opioid prescription cessation and reduction, as well as improved quality of life. Thus, findings from our study add to the growing body of research indicating that from a user perspective, CaM has a substantial substitution effect for a variety of prescription drugs, most notably opioids.

Type of cannabis used as a substitute for prescription drugs

The findings that, in our sample, CBD-oil is the most prevalent type of cannabis used as a substitute for prescription drugs, and that one third of the substitution users used CBD-oil only, are in accordance with findings from a recent survey of 1.483 medicinal CBD users in the USA where CBD was used as a specific therapy for medical conditions, particularly pain and inflammatory disorders, as well as anxiety, depression, and sleep disorders [97]. In the same study, the majority (65.3%) reported that CBD treated their condition(s) moderately or very well without the use of conventional medicine, and 30.4% reported that CBD was effective in combination with conventional medicine. Our findings are also in accordance with a recent Italian study, where the unintended legalization of CBD-based cannabis products with less than 0.6% THC was associated with a significant decrease in the sale of prescription drugs, particularly of anxiolytics, sedatives, and anti-psychotics [40]. This is of particular public health interests, as CBD has been shown to have a better safety profile in terms of side effects and abuse potential, relative to THC [42, 98, 99]. In line with this, a recent review and meta-analysis of clinical trials found that CBD was well tolerated and had few serious side effects across medical conditions [100]. The safety profile of CBD-based cannabis products may also be superior in terms of toxicology and abuse potential compared to some of the prescription medication that is substituted, such as opioids and benzodiazepines [49, 52, 53].

From a public health perspective, the problematic aspects of medicinal use of low THC/high CBD cannabis products are also, and maybe more, related to the fact that these products are unregulated and used without medical supervision [101]. Indeed, use of unregulated cannabis products increases the risk of consuming hazardous contaminants, such as fungi, bacteria, pesticides or heavy metals [1, 102] or consuming a product with undesired psychoactive effects. Interestingly, a recent examination of CBD-oils available in Denmark by Department of Forensic Medicine in Odense, revealed that 38% of CBD-oils tested contained between 0.2% THC and 1.2% THC, despite being advertised as below 0.2% THC¹ [103]. Thus, users of CBD-oil may unknowingly use products that are illegal to consume.

Our finding that users of CaM, who substituted anti-depressants or anti-psychotics, are significantly more inclined to use “hash, pot or skunk” compared to other substitution users is of particular interest to public

health, as the THC content in skunk is high, and the THC content in cannabis resin (hash) and herbal cannabis has increased markedly in the last decades in Europe [104] and the USA [105, 106]. In Denmark, we found a threefold increase in THC concentration in seized hash from 2000 (mean: 8.3%) to 2017 (mean: 25.3%), while CBD levels remained stable (mean around 6%) [107]. This trend is concerning, as increasing evidence suggests that exposure to high-THC and low-CBD cannabis products is associated with higher risk of cannabis-related harms, such as cannabis dependence [108–110], psychosis [111, 112], and cognitive impairment [99, 113], compared to low-THC and high-CBD products. The magnitude of the problem is further underlined by findings from naturalistic studies on users of smoked cannabis products, which indicate that users do not fully adjust their use to differences in THC concentration, suggesting that users of more potent products are exposed to higher levels of THC [114, 115]. Thus, it is possible that use of high THC cannabis products as a substitute for prescription drugs may exacerbate the condition that is the target of the treatment, particularly in relation to treatment of psychotic disorders.

In sum, there is considerable complexity related to the use of cannabis as a substitute for prescription drugs, as an evaluation of whether cannabis is in fact “the lesser of two evils” depends on various factors, such as the cannabinoid composition in the type of cannabis used, the dosage, and the type of prescription drug that is substituted. Recently, another “lesser of two evils”-dynamic is emerging from cannabinoid research, as it is increasingly plausible that low-THC cannabis products are less harmful compared to high-THC cannabis products, and that increased availability of low-THC cannabis products may hold a potential for harm reduction among users of high-THC cannabis products [42]. In line with this reasoning, the unintended legalization of low THC-cannabis products in Italy, was not only associated with a significant decrease in prescription drug use, but also with a decrease in confiscations of illegal cannabis and drug-related arrests [116], indicating a substitution effect of introducing low THC-cannabis products on the consumption of conventional illegal cannabis products.

Experienced effects and side effects

Findings from our sample show that most substitution users find CaM more effective in managing their condition(s) compared to prescription drugs, and that an overwhelming majority found CaM to have a better side effect profile compared to the prescription drugs that they had been prescribed for their condition(s). This is in line with recent findings from Canada and the USA. In a cross-sectional survey, Canadian medical cannabis users listed,

¹ cannabis with less than 0.2% THC is legal to possess.

'relative safety of cannabis to prescription drug,' 'fewer adverse side effects' and 'better symptom management' as their top three reasons for using CaM as a substitute for prescription drugs [24]. In a survey of medical cannabis patients in California who used cannabis as a substitute/in conjunction with opioid-based pain medication, 80% found that cannabis was more effective than opioids for pain, and 92% that the side effects of cannabis were more tolerable than opioids [27]. Moreover, in a survey of American medical cannabis users with chronic pain, respondents listed 'fewer side effects' and 'better symptom management' as their top reasons for using medical cannabis as a substitute for prescription drugs [28]. Lastly, a qualitative study on cannabis users in San Francisco showed similar perceptions among substitution users who found cannabis to be a safer and more effective alternative compared to prescription drugs [31]. It is interesting that substitution users in our and several other studies rate the side effect profile of CaM higher than its effects, when comparing cannabis to prescription drugs. This suggests that substitution users may have the same "lesser of two evils"-perspective on the medical utility of cannabis that was documented among some physicians in Israel [57], where cannabis becomes medicine not only on the basis of what it *is* in terms of effects, but on what it *is not* in terms of side effects when compared to prescription drugs. Considering the growth in use of CaM, it is likely that this perspective will result in an increasing number of people seeking information and advice about the effectiveness of CaM and use CaM as a substitute for prescription drugs, even in the absence of rigorous clinical trials and despite lack of legal access to medical cannabis. Future research is needed to assess effects and side effects of long-term use of CaM from longitudinal studies. Furthermore, placebo-controlled clinical efficacy trials are needed to explore the effects of cannabis beyond placebo, and current barriers to whole plant cannabis research need to be addressed [1].

Limitations

Our study has several limitations. First, this self-selected convenience sample is limited by selection bias, as it likely weighs towards successful users of CaM, users with internet access, a familiarity with online surveys, users engaged with the topic on social media, and with the resources necessary to answer such surveys. Therefore, the survey may not be representative of the population of CaM users or substitution users [117]. Second, the data used in the study may be subject to self-reporting biases, such as recall bias, confirmation bias, placebo effects or

social desirability bias [118]. For example, users are likely to have optimistic expectations regarding the efficacy of CaM [119] and may exaggerate positive effects of CaM or under-report adverse effects. Also, recall bias may be more salient for the small group of respondents who were not current users. Third, although duplicates were excluded from the analyses, we cannot rule out multiple responses from the same person, as IP-addresses were not accessible to researchers. Fourth, the cross-sectional study design lacks a temporal dimension, and we do not know if the reported cessation or reduction in prescription drug use is sustained over time. Fifth, findings on prescription drugs substituted may be skewed by the fact that "sleep medication," "ADHD medication" and "anxiety medication" were not presented to respondents as independent categories. Sixth, the experienced effects and side effects of CaM and prescription drugs could potentially be affected by pharmacokinetic interactions between cannabis products and prescription drugs when taken simultaneously [120, 121]. Also, the reported effects and side effects were a mapping of substitution users experiences with various types of prescription drugs and different subtypes of cannabis, which likely vary in terms of effect and side effect profile.

Conclusions

The use of CaM as a substitute for prescription drugs is a leading motive among Danish users of CaM in our sample. Pain medication was the most prevalent prescription drug substituted with CaM, followed by antidepressants and arthritis medication. Tramadol was the most common pain medication substituted with CaM, which may be related to a change in prescription practices for Tramadol in Denmark. Across prescription drug categories, CBD-oil was the most prevalent type of cannabis used as substitution, except for anti-psychotics, where "hash, pot or skunk" were the most common types used, which is concerning due to the high levels of THC, particularly in hash and skunk. Substitution users reported substantial decrease or cessation of prescription drug use, and a greater effect and far better side effect profile of CaM compared to prescription drugs. Thus, from the perspective of substitution users, CaM may be viewed as the lesser of two evils compared to prescription drugs. More research is needed on the long-term consequences of use of CaM, including the impact from low and high THC cannabis products on specific somatic and mental health conditions.

Appendix 1: Odds of substituting the five classes of drugs related to recreational experience and type of cannabis used, controlled for age, gender and employment

	Pain medication (n = 1.039)	Anti-depressive (n = 379)	Anti-psychotic (n = 105)	Anti-epileptic (n = 134)	Arthritis (n = 320)	Other (n = 372)
Type of cannabis used						
THC-oil	1.72*** (1.30–2.27)	0.91 (0.68–1.22)	0.83 (0.49–1.41)	0.90 (0.59–1.37)	1.19 (0.89–1.57)	0.92 (0.69–1.24)
CBD-oil	1.08 (0.84–1.40)	1.04 (0.79–1.37)	0.75 (0.47–1.20)	1.03 (0.69–1.55)	1.46* (1.08–1.98)	1.11 (0.84–1.48)
Hash, pot or skunk	1.23 (0.92–1.64)	1.45* (1.08–1.95)	3.37*** (1.87–6.08)	0.67 (0.42–1.06)	0.90 (0.66–1.25)	1.43* (1.06–1.95)
Cannabis based medicines	2.68** (1.48–4.88)	1.18 (0.72–1.94)	0.88 (0.37–2.09)	2.59** (1.49–4.51)	1.21 (0.76–1.95)	0.58 (0.31–1.08)
Whole plant	1.65 (0.68–4.01)	0.79 (0.32–1.92)	0.32 (0.04–2.58)	3.28** (1.39–7.73)	1.02 (0.44–2.37)	0.59 (0.22–1.62)
Other	1.17 (0.76–1.81)	1.06 (0.67–1.69)	0.68 (0.27–1.71)	1.11 (0.58–2.12)	1.29 (0.82–2.03)	1.80** (1.17–2.76)

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Appendix 2: All five categories

Somatic condition (36): Acne, Aids, Alzheimer's, Asthma, Chrons disorder, Herniated disc, Dystonia, Eczema, Epilepsy, Endometriosis, Fibromyalgia, Osteoarthritis, Rheumatoid arthritis, Psoriatic arthritis, Cataracts, Hepatitis, Brain damage, COPD, Cancer, FE(chronic fatigue), Chronic nerve inflammation, migraine, Menstrual pain, Multiple sclerosis, Neurodermatitis, IBS, Lupus (SLE), Palliation, Parkinson's, peripheral neuropathy, Psoriasis, Spinal cord injury, pain following operation, pain following an accident, tinnitus, trigeminal neuralgia.

Psychiatric condition (13): ADHD, Anxiety, dependence (alcohol), dependence (hard drugs), dependence (prescription drugs), Anorexia, Autism, Bipolar disorder, Depression, OCD, PTSD, Schizophrenia, Tourettes/tics.

Potential comorbidities (3); Chronic pain, Sleep disturbances, Stress.

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Authors' contributions

SLK designed the study and wrote the first draft of the manuscript. SLK and MMP conducted the formal analysis. SLK, BT, KRT, and MMP interpreted data and wrote the manuscript. All authors have contributed significantly to the study and have read and approved the final manuscript. CRediT (Contributor Roles Taxonomy): SLK contributed to conceptualization, methodology, data curation, formal analysis, investigation, project administration, visualization, writing—original draft, and writing—review and editing; MMP contributed to methodology, data curation, formal analysis and writing - review and editing; KRT contributed with supervision and writing—review and editing; BT contributed to conceptualization, methodology, supervision, and writing—review and editing.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available as it is part of an ongoing PhD project.

Ethics approval and consent to participate

Respondents consented to participate and could drop out of the survey at any time before completion. Respondents were not compensated for participating. The data used for this study were collected and stored for monitoring on secure servers, and procedures for data handling and storage were approved by the Danish Data Protection Agency. No ethics evaluation was needed under Danish law.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Building 1322, Bartholins Allé 10, 8000 Aarhus C, Denmark. ²Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Artillerivej 90, 2. Floor, 2300 Copenhagen S, Denmark.

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7.3. Paper nr 3: With medicine in mind? Exploring the relevance of having recreational experience when becoming a medicinal cannabis user.

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With Medicine in Mind? Exploring the Relevance of Having Recreational Experience When Becoming a Medicinal Cannabis User

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journals.sagepub.com/home/cdxSinikka L. Kvamme¹ 

Abstract

Background: Beyond the legal use of medical cannabis in Denmark for selected patient groups, a large unregulated use of *medicinal* (non-prescribed) cannabis occurs. However, little is known about the paths to becoming a medicinal cannabis user and the role that previous recreational experience plays in this process. **Aim:** Inspired by Becker's social learning approach to becoming a cannabis user, this study explores sources of inspiration for medicinal cannabis use, the social control factors related to use, and the relevance of recreational experience (RE) with cannabis. **Methods:** An anonymous survey was made available online to a convenience sample of 2,281 adults (≥ 18 years) who self-medicate with non-prescribed cannabis. Logistic regression analysis compared users with no RE (46.1%) to users with occasional RE (27.4%) and regular RE (26.5%) in terms of user characteristics, initiation of medicinal use, and experiences with social control factors. **Results:** Compared to users with RE, users with no RE were significantly more likely to be women, older, more frequent users, and to treat somatic conditions and use low potency CBD-oil. Users with no RE were more likely to rely on social networks for information on medicinal cannabis, use online sources for supply, and find supply stable. Moreover, users with no RE were less likely to keep use secret and find use problematic. Also, when medicinal use develops on a gradual transition from recreational use it is associated with increased odds of treating mental health conditions and with use of smoking as form of intake. **Conclusion:** The heterogeneity among medicinal cannabis users in Denmark, in terms of demographics, motives for use, and patterns of use, is related to the level of previous recreational experience and to whether medicinal use developed on a gradual transition from recreational use.

¹ Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Denmark

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Corresponding Author:

Sinikka L. Kvamme, Center for Alcohol and Drug Research, Aarhus BSS, Aarhus University, Building 1322, 217, Bartholins allé 10, 8000 Aarhus C, Denmark.

Email: slk.crf@psy.au.dk

Keywords

medicinal cannabis, medical cannabis, marijuana, cannabidiol, Howard Becker, medicalization

Background

All drugs are inherently ambiguous phenomena, as they can act both as “benevolent cures” and “dangerous toxins” (Keane, 2008). Thus, just as mundane prescription drugs can be transformed into euphoric substances used for pleasure through specific situational contexts and user practices (Bundy & Quintero, 2017), cannabis can be transformed from a euphoric substance into a mundane medicine (Newhart & Dolphin, 2018). In the last decades we have seen a renewed interest in the medical utility of cannabis (Pisanti & Bifulco, 2017; Taylor, 2009), in part due to growing evidence that cannabinoids, the active components of cannabis, are effective in the treatment of chronic pain, spasticity, nausea, and epilepsy (National Academies of Sciences Engineering and Medicine, 2017) and also may be relevant for the treatment of other somatic (Cascio et al., 2017; Toczek & Malinowska, 2018) and mental health conditions (Scherma et al., 2020). Currently, more than 30 states in the U.S. (National Conference of State Legislatures, 2020), Canada (Fischer et al., 2015), and several European countries (Abuhasira et al., 2018) are allowing medical use of whole plant cannabis despite criticisms of this use (D’Souza & Ranganathan, 2015; Hill, 2015). In Denmark, a Medical Cannabis Pilot Program (MCP) was initiated by a political majority in 2018, where patients with treatment resistant multiple sclerosis, spinal cord injury, chronic pain, or chemotherapy-related nausea and vomiting, have been given access to whole plant cannabis via a general practitioner (Ministry of Health, 2016). However, parallel with the growing use of medical cannabis (legal cannabis prescribed by a doctor), use of medicinal cannabis (non-prescribed cannabis used with a medical motive) has emerged. This trend of “Do-It-Yourself”-medicine has been documented in the U.S. (Sexton et al., 2016), the U.K. (Ware et al., 2005), Australia (Lintzeris et al., 2018), Norway (Pedersen & Sandberg, 2013), and Denmark (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021). These studies show that medicinal users tend to find cannabis effective in managing their symptoms and show a great diversity in the conditions treated with medicinal cannabis, often exceeding the official recommendations for legal medical cannabis use. Studies also suggest that medicinal cannabis users form a heterogeneous group (Hakkarainen et al., 2019; Pedersen & Sandberg, 2013) that share traits with both recreational users and licensed medical users, in terms of demographics and patterns of use (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021; Pacula et al., 2016; Sznitman, 2017), suggesting potential blurred boundaries between medicinal cannabis use and recreational and/or problematic cannabis use. By exploring the paths that users take when becoming a medicinal cannabis user, this article seeks to further outline the diversity related to medicinal cannabis use.

Analytical Framework: Becker and Becoming

The popular medicalization of cannabis that takes place outside medical jurisdictions calls for further research and while most of the current research study the “drug” i.e. the bio-medical effects of cannabis, research that explores the “set” and “setting” (Hartogsohn, 2017; Zinberg, 1984) is scarce. Applying a theoretical approach that explores the current development of medicinal cannabis use in its psychological, social, and cultural context is important, as it can further our understanding of how cannabis has become medicine for users who do not receive formal medical guidance. One of the most well-known sociological perspectives on factors related to initiation of illegal drug use was developed in the groundbreaking work of Howard Becker, who more than 50 years ago explored the use of cannabis for pleasure, at a time when cannabis use was fairly rare, illegal, and heavily penalized (Becker, 1953, 1963). Becker’s prime achievement was to explain incidences of cannabis use as the

result of sequences of social experiences, in which the individual acquires a meaning of the behavior, rather than as a result of individual predisposition. In the article *Becoming a Marijuana User* (1953), Becker argued that a person would only be able to use cannabis for pleasure by learning to use cannabis in a dose that produced the desired effects and by learning to recognize and enjoy these effects. According to Becker, this learning process was highly dependent on interaction with members of a “drug-positive” subculture, as this subculture enabled positive interpretations of drug-induced states in the interactions with, and observation of, experienced cannabis users (Becker, 1967). Thus, the Beatles were in tune with Becker’s perspective, where “getting high” quite literally required “a little help from my friends.” Furthermore, Becker argued that in order to advance from being a novice cannabis user to being an occasional or regular cannabis user, it was necessary to overcome “powerful forces of social control that made the act seem inexpedient, immoral, or both” (Becker, 1963, p. 58). Becker listed three forms of social control that regular users had to overcome; gaining and sustaining access to the illegal drug (supply), keeping non-cannabis users from discovering the use (secrecy), and renegotiating conventional perceptions on cannabis use (morality) (Becker, 1963). Overcoming social control aspects related to morality referred to rejecting conventional societal notions of the addictive potential of cannabis and the loss of control stereotypically associated with cannabis use, i.e. that “the user becomes a slave to the drug, that he voluntarily surrenders himself to a habit from which there is no escape” (Becker, 1963, p. 73). According to Becker, “the person who takes such a stereotype seriously is presented with an obstacle to drug use. He will not begin, maintain, or increase his use of marijuana unless he can neutralize his sensitivity to the stereotype by accepting an alternative view of the practice” (Becker, 1963, p. 73). Later research has generally been consistent with Becker’s social-process-based theory on initiation and maintenance of cannabis use (Hallstone, 2002; Hathaway, 1997; Hirsch et al., 1990; Järvinen & Ravn, 2014). However, some have also questioned the strict necessity of socializing with other recreational users, as the growing normalization of cannabis (see also: Duff et al., 2012; Järvinen & Demant, 2011) has made the individual user less dependent on cannabis-positive subcultures (Hathaway, 1997) and the increased potency of cannabis may have made it easier to experience an immediate effect without guidance from experienced users (Hallstone, 2002). Another significant change that may have an impact on the development of cannabis use is the growth in online drug communities that enable drug users to meet and share knowledge across distances (Meacham et al., 2018; Rosino & Linders, 2015; Walsh, 2011).

Path(s) to Becoming a Medicinal Cannabis User

While the process of becoming a medicinal cannabis user is less explored, some qualitative studies have applied Becker’s framework to explore the process of becoming a legal medical cannabis user in the U.S. and Canada. This research shows that the driving forces for seeking a prescription for medical cannabis are the patient’s own initiative and personal research, along with recommendations from friends and family, while doctors play a minor role (Athey et al., 2017; Lankenau et al., 2018; Newhart & Dolphin, 2018). In addition to drawing on their social networks for information on medical and medicinal cannabis, the vast majority of users in these studies had previous recreational experience (RE), and many had discovered therapeutic effects of cannabis in a recreational setting. Similarly, quantitative research shows that most legal medical cannabis users have used cannabis recreationally before initiation of medical cannabis use (Pacula et al., 2016; Reinerman et al., 2011). More nuance is added to the matter of RE in qualitative studies of Danish medicinal cannabis users (Dahl & Frank, 2011) and Canadian medical cannabis users (Cohen, 2015), finding that for some, a medicalized approach to use develops on a sliding scale (Dahl & Frank, 2011) or a seamless transition (Cohen, 2015) from recreational use, while others have had a period of cessation from recreational use before initiating medicinal/medical use. Both studies observed that users with a period of cessation were more

likely to use cannabis for pain relief, while most users with a gradual transition from recreational use treated mental health conditions. Likewise, studies on both medical (O'Connell & Bou-Matar, 2007) and medicinal (Pedersen, 2015) cannabis users describe a gradual transition from recreational use, where recreational or problematic cannabis use over time is interpreted as medicinal, often in relation to mental health issues, such as ADHD, anxiety and depression. Meanwhile, a novel path to medicinal use seems to have emerged, as the popularity of medicinal cannabis in Denmark has attracted a relatively large number of users with no previous RE (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021). The emergence of medicinal users with no previous RE makes this type of medicinal cannabis use particularly interesting to explore and compare to that of medicinal users with RE.

Becker's social learning approach to becoming a cannabis user can help us to better understand the process of becoming a medicinal cannabis user and the role that having RE plays in that process. Following the logic of Becker, having RE with cannabis represents a path to medicinal use that differs in important ways from the path that cannabis novices take when learning to use medicinal cannabis. For instance, when medical cannabis users have RE, the essential features of learning involved in becoming a medical user are not centred around learning to use cannabis, as this is already known, but on targeting and relieving specific symptoms (Athey et al., 2017). Also, users with RE have engaged in practices where cannabis has been constructed as an object of pleasure, an embodied experience of use that is absent among medicinal users with no RE, thus rendering the points of entry to medicinal cannabis use markedly different. Furthermore, the intention to treat an illness or its symptoms for users with RE can develop on a gradual transition from recreational use, sometimes immediately after, sometimes years after first consumption of cannabis (Cohen, 2015; O'Connell & Bou-Matar, 2007; Pedersen, 2015). Conversely, having no RE presents a notably different path when initiating medicinal cannabis use, as the intention to use cannabis as a therapeutic tool predates a debut as a cannabis user. Thus, compared to medicinal users with RE, users with no RE are more likely to have "medicine in mind," and may therefore have a more medicalized approach to cannabis use from the onset of their medicinal cannabis user career. Consequently, it is likely that there are profound differences in patterns of use and motives for use, depending on how far the user has already advanced in the career of recreational cannabis use.

The degree of previous RE is also likely to be reflected in the way the users manage the social control aspects of their medicinal cannabis use. To my knowledge, the social control aspects of medicinal cannabis use are unexplored. In Denmark, there is large public support for legal medical cannabis use (Blackman, 2017) and social control aspects related to medicinal cannabis use may be fairly relaxed, as this is the case with recreational cannabis use (Järvinen & Ravn, 2014). Nonetheless, research shows that there is substantial stigma related to the use of medical cannabis (Satterlund et al., 2015) which may be related to the illness treated with cannabis (Lewis & Sznitman, 2017). Therefore, medicinal users may still have to manage social control aspects related to secrecy and morality. Also, users have to manage supply of an illegal product, as all cannabis products outside the legal medical program are illegal to sell and possess.¹

The emergence of medicinal users who are novices to the effects of cannabis prior to onset of medicinal use in Denmark (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021) presents a unique opportunity to explore the different paths to becoming and sustaining a medicinal cannabis use depending on previous RE. The purpose of the current study was to; (1) describe medicinal cannabis users in terms of demographics, motives for use and patterns of use depending on different levels of previous RE; (2) explore the sources of inspiration for medicinal cannabis use depending on level of previous RE; and (3) explore the social control factors related to sustaining a medicinal cannabis use depending on level of previous RE.

Method

Design

The study was part of a larger survey study on the use of cannabis as medicine in Denmark (see Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021). The survey was inspired by previous surveys on medicinal and medical cannabis use (Grotenhermen & Schnelle, 2003; Hazekamp et al., 2013; Reiman et al., 2017; Reinerman et al., 2011; Sexton et al., 2016; Ware et al., 2005; Webb & Webb, 2014) and by qualitative research on medical and medicinal use (Athey et al., 2017; Dahl & Frank, 2011; Lankenau et al., 2018; Pedersen & Sandberg, 2013). The survey was tested and revised following nine pilot interviews with users of medicinal cannabis. Data was collected through the software tool for generation of online surveys, Survey XACT (Ramboll, 2021). IP addresses of the respondents were not saved or available to the researchers, as the respondents' fear of loss of anonymity was considered a greater issue than the possibility of repeated participation. Participants could withdraw at any time before completion of the survey. All data were stored on secure servers, and procedures for data handling and storage was approved by the Danish Data Protection Agency. For a more detailed description see Kvamme, Pedersen, Alagem-Iversen, and Thylstrup (2021).

Sampling and Recruitment

The survey was made available to a self-selected convenience sample of users of medicinal cannabis from July 14, 2018 to November 1, 2018. Participants were recruited online and via flyers and posters containing survey information, a survey link and QR code. Recruitment material was disseminated via social and public media, patient organizations, selected doctors' offices and hospitals and at the illegal open drug market Christiania.

We have previously reported on the motives and patterns of use of cannabis as medicine (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021) and on the use of cannabis as a substitute for prescription drugs (Kvamme, Pedersen, Thomsen, & Thylstrup, 2021). Of the 4,570 respondents who opened the survey, 3,140 answered all questions. Excluded were <18 ($n = 59$), duplicates ($n = 53$), inconsistent answers ($n = 7$), medical users ($n = 245$), former users ($n = 264$), and those answering on behalf of someone ($n = 115$). Furthermore, 116 were excluded as they were missing or gave inconsistent answers with regard to their level of previous RE, leaving a final study population of $n = 2,281$.

Measures

Patterns of use and motives for use: Respondents were presented with questions related to demographics, patterns of use and motives. For a description of items related to patterns and motives see Kvamme, Pedersen, Alagem-Iversen, and Thylstrup (2021) and Appendix.

Previous recreational experience: When exploring the degree of previous recreational experience, users were asked "how much experience did you have with recreational (non-medicinal) use of cannabis before you started using cannabis as medicine?" and presented with five options. 1: No experience (never tried it before), 2: Lesser degree of experience (less than five times in my life), 3: Some degree of experience (no more than 10 times in a year), 4: High degree of experience (several times a month), 5: Very high degree of experience (almost daily for several years).

Inspiration for use: Respondents were asked how they discovered that cannabis could be used as medicine, and were provided with a list of 7 suggested sources of inspiration and an "other" category, and respondent could choose more than one source of inspiration.

When exploring whether the medicinal cannabis use had developed as a gradual transition from recreational use, users were presented with two statements, and asked to choose the statement that best described their use of medicinal cannabis. Statement 1: "I started using cannabis as medicine from one

day to the next.” Statement 2: “My use of cannabis as medicine has been a gradual transition from recreational (non-medical) use.” Respondents were asked how they reached their current dose and provided with a list of 6 suggested sources of inspiration for current dose and an “other” category, and respondents could choose more than one source of inspiration.

Social control factors: Respondents were asked to list their supply source of medicinal cannabis, and were provided with a list of seven suggested sources of supply and an “other” category and respondents could choose more than one source of supply. Respondents were asked if they had ever experienced not being able to procure the type of cannabis they preferred to use as medicine and could answer either yes/no/don’t know/no answer. When exploring secrecy related to medicinal cannabis use, respondents were presented with the statement “I often find it necessary to hide my use of medicinal cannabis” and could answer on a 5 point Likert scale from Strongly agree (5) to Strongly disagree (1) or choose don’t know/no answer. Respondents were asked if they had ever disclosed their use of medicinal cannabis to any health care providers and could answer either yes/no/don’t know/no answer. When exploring morality related to medicinal cannabis use, respondents were presented with the statement “The use of medicinal cannabis can lead to addiction” and could answer on a 5 point Likert scale from Strongly agree (5) to Strongly disagree (1), or choose don’t know/no answer. Thus, this item explores to what extent cannabis users have neutralized their sensitivity to the typical notion that cannabis use can lead to addiction and make an exemption from this notion when cannabis is used with a medicinal motive. Further, respondents were asked if they had ever considered stopping use of medicinal cannabis and could answer either yes/no/don’t know/no answer. While there are likely many reasons for considering terminating medicinal cannabis use (remission, pregnancy, costs, social pressure, etc.), this item also has potential to capture ambivalence towards use.

Data Analysis

Data analysis was conducted using Stata SE/15 (Hamilton, 2012). Descriptive statistics including simple proportions, means and standard deviations were used to describe demographics, motives for use, patterns of use and items related to initiation of medicinal use, as well as supply, secrecy, and morality. A variable was coded based on the item exploring degree of previous RE, distinguishing between users with no RE (no experience), users with occasional RE (lesser degree of experience and some degree of experience), and users with regular RE (high degree of experience and very high degree of experience), thus adjusting the variable to fit Becker’s terminology. Binary and ordinal logistic regression was used to assess differences between medicinal users with no RE, users with occasional RE, and users with regular RE, with users with no RE as the reference (except for the variable related to transitioning from recreational use where the value among users with no RE was 0). Age and gender were used as control variables. A logistic regression model was made to assess the users with a gradual transition from recreational use on key variables. A histogram was used to assess normality in the variables number of conditions and age. As the variables were not normally distributed, the Mann-Whitney U test was used to assess differences in means between users with no RE, users with occasional RE and users with regular RE.

Results

Characteristics of Medicinal Cannabis Users by Previous Recreational Experience

Demographics. A total of 2,281 medicinal cannabis users were included in the final sample. A majority of users were female (61.3%), range 18–89 years (M 48.6, SD 13.4) (see Table 1). Most medicinal users (46.1%) were novices with no RE prior to initiation of medicinal cannabis use, 27.4% had occasional RE and 26.5% had regular RE (see Table 1). Age and gender was significantly related

Table 1. Characteristics of Medicinal Cannabis Users by Previous Recreational Experience.

User Characteristics	Total 2,281 <i>n</i> (%)	Level of Previous Recreational Experience		
		None 1,052 <i>n</i> (%)	Occasional 624 <i>n</i> (%)	Regular 605 <i>n</i> (%)
Demographics				
Female	1,399 (61.3)	832 (79.1)	382 (61.2)***	185 (30.6)***
Mean age (18–89)	48.6 (SD 13.4)	53.9 (SD 11.5)	46.2 (SD 12.7)***	41.8 (SD 13.3)***
Higher education ^a	1,088 (47.7)	553 (52.6)	337 (54)***	198 (32)
Full-time occupation	713 (31.3)	271 (25.8)	195 (31.3)	247 (40.8)
Motives for medicinal cannabis use				
Conditions treated with medicinal cannabis				
Somatic condition	1,662 (72.9)	846 (80.4)	430 (68.9)**	386 (63.8)**
Mental health condition	907 (39.8)	246 (23.4)	285 (45.7)***	376 (62.2)***
Chronic pain	691 (30.3)	331 (31.5)	184 (29.5)	176 (29.1)
Sleep disturbances	679 (29.8)	224 (21.3)	194 (31.1)**	261 (43.1)***
Stress	608 (26.7)	155 (14.7)	181 (29)***	272 (45)***
Five most frequent conditions				
Arthritis	687 (30.1)	374 (35.6)	177 (28.4)	136 (22.5)
Anxiety	490 (21.5)	143 (13.6)	157 (25.2)**	190 (31.4)***
Depression	486 (21.3)	127 (12.1)	145 (23.2)***	214 (35.4)***
ADHD/ADD	255 (11.3)	38 (3.6)	68 (10.9)**	149 (24.6)***
Herniated disc	241 (10.6)	115 (10.9)	68 (10.9)	58 (9.6)
Mean number of conditions treated with cannabis	3.3 (SD 2.5)	2.8 (SD 2.2)	3.4 (SD 2.4)***	4 (SD 2.8)***
Patterns of medicinal cannabis use				
Types of cannabis				
THC-oil	541 (23.7)	242 (23)	164 (26.3)	135 (22.3)
CBD-oil	1,507 (66.1)	919 (87.4)	366 (58.7)***	222 (36.7)***
Hash, pot, or skunk	884 (38.8)	82 (7.8)	268 (43)***	534 (88.3)***
Other	175 (7.7)	76 (7.2)	55 (8.8)	44 (7.3)
Missing	18 (0.8)	13 (1.2)	5 (0.8)	0 (0)
CBD only	903 (39.6)	664 (63.1)	197 (31.6)***	42 (6.9)***
Most frequent form of intake				
Smoked	595 (26.1)	37 (3.5)	186 (29.8)***	372 (61.5)***
Vaporized	77 (3.4)	11 (1.1)	24 (3.9)**	42 (6.9)**
Oil	1,267 (55.6)	829 (78.8)	316 (50.6)***	122 (20.2)***
Edibles, suppositories, tea, and topical	109 (4.8)	52 (4.9)	32 (5.1)	25 (4.1)
Capsules	89 (3.9)	60 (5.7)	24 (3.9)	5 (0.8)**
Other	137 (6)	61 (5.8)	40 (6.4)	36 (6)
Missing	7 (0.3)	2 (0.2)	2 (0.3)	3 (0.5)
Daily user (7–6 days a week)	1,744 (76.5)	875 (83.2)	428 (68.6)***	441 (72.9)***

Note. Controlled for age and gender.

^aPostsecondary education or higher.

* $p < .05$. ** $p < .01$. *** $p < .001$.

to level of previous RE, as odds of being male rose with level of RE and mean age decreased. When controlled for age and gender, participants with occasional RE were significantly more likely to have a higher education ($p < .001$).

Motives for medicinal cannabis use. A majority (72.9%) used cannabis to treat a somatic condition (see Table 1). Treatment of somatic conditions was significantly more frequent among users with no RE (80.4%) compared to users with occasional RE (68.9%), and regular RE (63.8%) ($p < .01$). Treating a mental health condition was significantly more frequent among users with regular RE (62.2%) compared to users with occasional RE (45.7%), and users without RE (23.4%) ($p < .001$). Treating sleep disturbances and stress increased significantly with level of RE ($p < .001$). The five most frequent conditions were arthritis (30.1%), anxiety (21.5%), depression (21.3%), ADHD (11.3%) and herniated disc (10.6%) and treating anxiety, depression and ADHD increased significantly with increase in RE.

Patterns of medicinal cannabis use. A majority were daily users of medicinal cannabis (76.5%) and users with no RE were significantly more likely to be daily users (83.2%) compared to those with occasional RE (68.6%) and regular RE (72.9%) ($p < .001$) (see Table 1). CBD-oil was the most frequent type of medicinal cannabis used among users with no RE (87.4%) and users with occasional RE (58.7%), while “hash, pot or skunk” was the most frequent type of cannabis among users with regular RE (88.3%). The most frequent form of intake was significantly related to level of previous RE; oil was more frequent among users with no RE (78.8%) compared to users with occasional RE (50.6%), and users with regular RE (20.2%) ($p < .001$), while smoking was the most frequent form of intake among users with regular RE (61.5%). Users with no RE were more likely to be CBD-oil only users (63.1%) compared to users with occasional RE (31.6%) and users with regular RE (6.9%) and this difference was statistically significant ($p < .001$).

Initiation of Medicinal Cannabis Use

Discovery of medicinal cannabis use. Medicinal cannabis use was most frequently discovered through public media (42%), social media (40.1%), or suggested by a friend or family member (30%) or by someone with the same condition (14.6%) (see Table 2). Almost a quarter (24.8%) discovered medicinal use when using cannabis recreationally, while only 2.9% indicated that use was suggested to them by a doctor. Users with regular RE were significantly less likely to discover medicinal use through media (23.6%), social media (22.6%), through friends/family (14.6%) or someone with the same condition (8.4%) ($p < .001$). Users with regular RE (67.6%) and users with occasional RE (20.5%) were significantly more likely to discover medicinal use in a recreational setting ($p < .001$). The only source of inspiration that did not differ significantly between the groups was watching a documentary on medical cannabis.

Gradual transition from recreational use. A majority (72.4%) started their medicinal cannabis use from one day to the next, while 23.8% had a gradual transition from recreational use. A gradual transition from recreational use was less frequent among those with occasional RE (19.9%), compared to those with regular RE (69.3%) and this difference was significant ($p < .001$). Having a gradual transition from recreational use was associated with increased odds of treating a mental health condition (OR: 1.90 (CI 95%: 1.44–2.50) ($p < .001$)) and using smoking as most frequent form of intake (OR: 26.19 (CI 95%: 18.23–37.63) ($p < .001$)) (see Table 3).

Reaching the current dose. In the process of reaching their current dose, most medicinal users relied on self-experimentation (76.3%), reading descriptions from others online (26.6%) and drawing on advice from other medicinal users (24.6%). Users with regular RE (91.7%) and users with occasional RE (78.9%) were significantly more likely to indicate self-experimentation compared to users with no RE (65.9%) ($p < .001$). When reaching the current dose, users with regular RE were less influenced by online descriptions (16.7%), advice from medicinal users (15%) from someone who gives advice to others (8.6%) and from sellers of medicinal cannabis (6.8%) ($p < .001$).

Table 2. Initiation of Medicinal Cannabis Use by Previous Recreational Experience.

	Total 2,281 n (%)	Level of Previous Recreational Experience		
		None 1,052 (46.1) n (%)	Occasional 624 (27.4) n (%)	Regular 605 (26.5) n (%)
Initiation of Medicinal Cannabis Use				
Source(s) for the discovery of medicinal cannabis use				
Read about medical cannabis in the media	959 (42)	530 (50.4)	286 (45.8)	143 (23.6)***
Read about other peoples medicinal use on social media	914 (40.1)	519 (49.3)	258 (41.4)*	137 (22.6)***
Suggested to me by a friend/family member	685 (30)	391 (37.2)	206 (33)	88 (14.6)***
Noticed medical effect when using cannabis Recreationally	565 (24.8)	28 (2.7)	128 (20.5)***	409 (67.6)***
Suggested to me by someone with the same condition as me	334 (14.6)	174 (16.5)	109 (17.5)	51 (8.4)***
Documentary on medical cannabis	318 (13.9)	148 (14.1)	103 (16.5)	67 (11.1)
Suggested to me by a doctor	66 (2.9)	26 (2.5)	31 (5)*	9 (1.5)
Other	168 (7.4)	63 (6)	49 (7.9)	56 (9.3)
Don't know/no answer	31 (1.4)	4 (0.4)	7 (1.1)	20 (3.3)
What statement best describes your situation?				
Initiated medicinal cannabis from one day to the next	1,652 (72.4)	1,033 (98.2)	469 (75.2)	150 (24.8)***
Medicinal cannabis was a gradual transition from recreational use	543 (23.8)	0 (0)	124 (19.9)	419 (69.3)
Don't know/No answer	86 (3.8)	19 (1.8)	31 (5)	36 (6)
Source(s) of inspiration for current dose				
Self-experimentation	1,740 (76.3)	693 (65.9)	492 (78.9)***	555 (91.7)***
Read descriptions from others online	607 (26.6)	325 (30.9)	181 (29)	101 (16.7)***
Advice from a medicinal user	560 (24.6)	301 (28.6)	167 (27.3)	89 (15)***
Advice from a person who guides others in use of medicinal cannabis	352 (15.4)	204 (19.4)	96 (15.4)	52 (8.6)***
Advice from a seller of medicinal cannabis	292 (12.8)	179 (17)	72 (11.5)*	41 (6.8)***
Guidance by a doctor	29 (1.3)	10 (1)	13 (2.1)	6 (1)
Other	75 (3.3)	26 (2.5)	18 (2.9)	31 (5.1)**
Don't know/no answer	11 (0.5)	2 (0.2)	3 (0.5)	6 (1)

Note. Controlled for age and gender.

* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 3. Odds Ratios (ORs) and 95% CIs for Demographics, Using Smoke as Most Frequent Form of Intake and Treating a Mental Health Condition Among Medicinal Users With a Gradual Transition From Recreational Use.

User Characteristics	Gradual Transition From Recreational Use
Gender (male)	1.60 (1.21–2.11)***
Age	0.98 (0.97–0.99)***
Higher education	0.96 (0.72–1.26)
Full-time employment	1.39 (1.04–1.86)*
Treating a mental health condition	1.90 (1.44–2.50)***
Using smoke as most frequent form of intake	26.19 (18.23–37.63)***
R^2	.42

* $p < .05$. *** $p < .001$.

Social Control Factors Related to Medicinal Cannabis

Supply. The most frequent sources for medicinal cannabis was ordering online (47.4%), from a friend (22.8%), or growing it oneself (18.2%) (Table 4). Buying cannabis online decreased significantly with increase in RE ($p < .001$), likewise did acquiring cannabis from a person who guides other people in medicinal cannabis use ($p < .01$). Acquiring cannabis from a friend, from a dealer, from Christiania or growing cannabis oneself increased significantly with an increased degree of RE ($p < .001$). One third of medicinal cannabis users (33.3%) had experienced not being able to procure their preferred type of medicinal cannabis, which increased significantly with increased degree of RE ($p < .001$). Most medicinal users spent less than 500 DKK/month on medicinal cannabis (49.1%), and users with regular RE reported spending significantly more money compared to other users ($p < .001$).

Secrecy. Almost half of users often found it necessary to hide their medicinal cannabis use; 25.8% strongly agreed and 21.4% agreed that secrecy was often necessary. Often finding it necessary to hide use was significantly related to degree of RE ($p < .001$) and among users with regular RE 40.5% strongly agreed and 24.8% agreed that secrecy was often necessary. Most users (57.3%) had disclosed use to a health care provider and this was not significantly related to degree of previous RE.

Morality. Most medicinal users disagreed (24%) or strongly disagreed (32%) that use of medicinal cannabis can lead to addiction. Believing that medicinal cannabis can lead to addiction was positively associated with having RE ($p < 0.05$). A small minority (13.9%) had considered stopping use of medicinal cannabis and having considered stopping was significantly more frequent among users with occasional RE (17.3%) and regular RE (20.2%) ($p < .01$).

Discussion

The present study is the first to explore the role of recreational experience in a large sample of medicinal cannabis users. Further, to my knowledge, the study represents the largest study to date on the initiation of medicinal cannabis use and the social control factors related to use. The study found that the heterogeneity among the medicinal cannabis users in terms of demographics, patterns of use, and motives for use was related to previous recreational experience with cannabis. In fact, when medicinal users were split in groups according to level of previous recreational experience, two significant trends emerged, that can be linked to two very distinct paths to medicinal cannabis use: the novices who are more likely to have medicine in mind from the onset of medicinal use; and users with extensive recreational experience who, for the most part, have a gradual transition from recreational to medicinal use.

The first trend involves users with no previous recreational experience, who are older and more likely to be women, and who initiate medicinal cannabis use predominantly for the treatment of somatic conditions. Most of these users are daily users of medicinal cannabis who use CBD-oil products that are typically low in tetrahydrocannabinol (THC) and therefore less likely to produce the euphoric effects normally associated with the “high” (Colizzi & Bhattacharyya, 2017). When initiating medicinal cannabis use, these users draw on social networks, such as the media and social media, as well as suggestions from friends, family, and other medicinal users. They mostly rely on the illegal online market for supply and their supply is relatively stable, and they are less likely to find it necessary to hide their use. They are also least likely to find use morally problematic, as few agreed that medicinal cannabis use could lead to addiction and few had considered discontinuing use.

The second trend involves medicinal users with regular recreational experience, who are younger, more likely male, and who treat mental health conditions with the same frequency as somatic conditions. A majority of these users have made a gradual transition from recreational use to a medicinal cannabis use, they are less likely to be daily users, more likely to use smoking as form of intake, and to

Table 4. Social Control Factors—Supply, Secrecy, and Morality.

Social Control Factors	Level of Previous Recreational Experience			
	Total 2,281	None 1,052 (46.1)	Occasional 624 (27.4)	Regular 605 (26.5)
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Supply				
Source(s) of medicinal cannabis				
I buy it online	1,081 (47.4)	713 (67.8)	254 (40.7)***	114 (18.8)***
From a friend	519 (22.8)	139 (13.2)	174 (27.9)***	206 (34.1)***
I grow it myself	416 (18.2)	72 (6.8)	133 (21.3)***	211 (34.9)***
From a pusher	367 (16.1)	39 (3.7)	99 (15.9)***	229 (37.9)***
From a person who guides other people in medicinal cannabis use	279 (12.2)	162 (15.4)	78 (12.5)	39 (6.5)**
At Christiania	275 (12.1)	41 (3.9)	79 (12.7)***	155 (25.6)***
From a store	71 (3.1)	41 (3.9)	15 (2.4)	15 (2.5)
Other	58 (2.5)	16 (1.5)	22 (3.5)	20 (3.3)
Don't know/no answer	100 (4.3)	40 (3.8)	23 (3.7)	37 (6.1)
Money spend on medicinal cannabis pr. month				***
<500 DKK. (<67 €)	1,119 (49.1)	591 (56.2)	318 (51)	210 (34.7)
500–1.000 kr. (67 €–134 €)	631 (27.7)	305 (29)	173 (27.7)	153 (25.3)
>1.000 kr. (>134 €)	451 (19.8)	123 (11.7)	119 (19.1)	209 (34.6)
Don't know/no answer	80 (3.5)	33 (3.1)	14 (2.2)	33 (5.5)
Experienced not being able to procure preferred type of medicinal cannabis				
Yes	760 (33.3)	202 (19.2)	239 (38.3)***	319 (52.7)***
No	1,480 (64.9)	835 (79.4)	369 (59.1)	276 (45.6)
Don't know/No answer	41 (1.8)	15 (1.5)	16 (2.6)	10 (1.7)
Secrecy				
I often find it necessary to hide my use of medicinal cannabis				
Strongly agree	589 (25.8)	178 (16.9)	166 (26.6)	245 (40.5)
Agree	488 (21.4)	189 (18)	149 (23.9)	150 (24.8)
Neutral	355 (15.6)	179 (17)	104 (16.7)	72 (11.9)
Disagree	460 (20.2)	266 (25.3)	116 (18.6)	78 (12.9)
Strongly disagree	359 (15.7)	218 (20.7)	83 (13.3)	58 (9.6)
Don't know/no answer	30 (1.3)	22 (2.1)	6 (1)	2 (0.3)
Disclosed medicinal cannabis use to any health care providers				
Yes	1,352 (59.3)	603 (57.3)	380 (60.9)	369 (61)
No	871 (38.2)	417 (39.6)	230 (36.9)	224 (37)
Don't know/no answer	58 (2.5)	32 (3)	14 (2.2)	12 (2)
Morality				
The use of medicinal cannabis can lead to addiction				
Strongly agree	97 (4.3)	26 (2.5)	37 (5.9)	34 (5.6)
Agree	260 (11.4)	50 (4.8)	88 (14.1)	122 (20.2)
Neutral	485 (21.3)	199 (18.9)	136 (21.8)	150 (24.8)
Disagree	548 (24)	262 (24.9)	149 (23.9)	137 (22.6)
Strongly disagree	729 (32)	410 (39)	172 (27.6)	147 (24.3)
Don't know/no answer	162 (7.1)	105 (10)	42 (6.7)	15 (2.5)
Considered stopping use of medicinal cannabis				
Yes	318 (13.9)	88 (8.4)	108 (17.3)**	122 (20.2)**
No	1,884 (82.6)	924 (87.8)	495 (79.3)	465 (76.9)
Don't know/no answer	79 (3.5)	40 (3.8)	21 (3.4)	18 (3)

Note. Controlled for age and gender.

* $p < .05$. ** $p < .01$. *** $p < .001$.

use cannabis products such as “hash, pot or skunk,” products that are higher in THC (Freeman et al., 2020; Rømer Thomsen et al., 2019) compared to CBD-oils available (Eriksen & Christoffersen, 2020). In the initiation process of medicinal use, these users draw less on social networks, predominantly discovered medical effects of cannabis through their recreational use, and relied more on self-experimentation when reaching their current dose. Also, these users rely more on offline cannabis markets for supply, such as “pushers,” friends, home growing, and Christiania, they spend more money per month on medicinal cannabis, and they experience more instability in supply. Most of these users often find it necessary to hide use, and are more inclined to believe that medicinal cannabis use can lead to addiction, and to have considered stopping use.

These two trends underscore the relevance of Becker’s emphasis on drug positive subcultures as crucial in shaping drug use, and suggest the existence of multiple “cannabis positive” subcultures that shape different forms of medicinal cannabis use. Users with occasional recreational experience fall somewhere in between these two trends, but may be more similar to the novices than to users with regular recreational experience, particularly in relation to initiation of medicinal use, where few have a gradual transition from recreational use and draw on social networks of information at almost the same rate as novices.

Novices With Medicine in Mind Seek “Cannabis Without Cannabis”

The study findings suggests that when a person with no recreational experience initiates medicinal cannabis use, their patterns of use differ substantially from the conventional patterns of recreational use. They frequently use routes of administration other than smoking and use products that aim to exclude the “high” normally associated with cannabis use. To a large extent, these users resemble legal medical cannabis users, who tend to use cannabis more frequently than recreational users (Hakkarainen et al., 2019; Lankenau et al., 2017; Pacula et al., 2016; Sznitman, 2017) and have patterns of use that are consistent with routine treatment of medical problems (Woodruff & Shillington, 2016), i.e. using small controlled doses to avoid intoxication and maximize role functioning (Newhart & Dolphin, 2018).

This trend in medicinal use suggests that, while cannabis use up till now for the most part has been synonymous with smoked plant material ingested with the purpose of producing a high (Russell et al., 2018), there has been a diversification of cannabis in recent years with the introduction of novel cannabis products, formulations, and methods of administration (Spindle et al., 2019). The medicalization of cannabis has likely played a role in this reshaping of cannabis use, as medical cannabis users are more likely to use alternative methods of administration of cannabis, such as vaping or ingesting cannabis, compared to recreational cannabis users (Borodovsky et al., 2016; Lankenau et al., 2017). Further, in recent years, CBD-dominant cannabis products have become popular worldwide (Carrieri et al., 2020; Hazekamp, 2018; Manthey, 2019), both as a specific therapy for medical conditions and for general health and wellbeing (Corroon & Phillips, 2018). The popularity of CBD-products can be understood in the context of its broad therapeutic potential (Hurd, 2017; Khan et al., 2020; Russo, 2017), and the fact that CBD is non-intoxicating and has a superior safety profile compared to THC (Bergamaschi et al., 2011; Iffland & Grotenhermen, 2017). The emergence of CBD-dominant cannabis products is particularly interesting, as it seems to offer users the opportunity to use “cannabis without cannabis,” to experiment with the new potential panacea that cannabis is advertised as online (Cavazos-Rehg et al., 2018; Lewis & Sznitman, 2019), while dispensing with the common features of traditional recreational use of smoking and euphoria. The emergence of a large market for cannabis oil in Denmark is likely driven by the medicalization of cannabis that has taken place in recent years, with increased media coverage of medical cannabis and the initiation of the Medical Cannabis Pilot Program (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021). It is likely that this coverage inspires users with no previous experience with recreational cannabis use, who discover medical cannabis in news- and social media and other social networks, and realize that these products are easily available online. The prominence of social media as a source of inspiration for initiating

medicinal cannabis use, particularly among novices, is interesting in the context of the business model of large social media platforms, where attracting and keeping users' attention is central, as attention is the commodity in surveillance capitalism (Deibert, 2019). Therefore, platforms such as Facebook use algorithms to target its users with content that will keep them engaged, a design that skews toward dissemination of content that generates strong emotions (Bakir & McStay, 2018). Illicit drug use with a medicinal motive is likely a great topic for capturing attention and this business model may have furthered the creation of the drug-positive subculture that Becker identified as crucial for becoming a drug user. In Denmark, large groups have emerged on Facebook, offering guidance in the use of medicinal cannabis (Bechgaard, 2014; Cannabis Recovery, 2021; CBD oile, 2021) and they may have inspired novices remote from a recreational setting.

Medicinal Cannabis on a Gradual Transition From Recreational Use

The study findings indicate that medicinal users with recreational experience tend to bring their previous experiences with cannabis in play when shaping their medicinal cannabis use, as they are more likely to remain users of smoked plant material traditionally associated with recreational use (Russell et al., 2018). Users with recreational experience have already acquired "recreational learning" (Cohen, 2015), in form of the skills identified by Becker that are needed to effectively use cannabis (recognizing effects, perceiving them as favorable, and associating them with cannabis). The study findings indicate that having a gradual transition from recreational use increased the odds of "spillover" from recreational learning and treating a mental health condition, which has also been found in previous qualitative research findings, where users with a gradual transition from recreational use were more prone to treat mental health conditions such as depression, anxiety, or ADHD with cannabis (Cohen, 2015; Dahl & Frank, 2011). Thus, a self-medication hypothesis for underlying mental health problems may in large part explain the predominance of mental health conditions treated among users with previous recreational experience. This explanation indicates the blurred boundaries between recreational and medicinal cannabis use experienced by users (Newhart & Dolphin, 2018; Ryan & Sharts-Hopko, 2017), that may be further blurred in cases where the individual user lacks knowledge of, or has received limited psychoeducation on, an underlying mental health condition.

Self-medicalization among cannabis users with recreational experience could be viewed as an attempt to trade badness for sickness, preferring to be declared sick and deserving of help, rather than being viewed as deviant and deserving of criminalization, not unlike the way medicalization has transformed many forms of deviance, including addiction, into treatable conditions (Conrad & Schneider, 2010). Thus, a self-medicalization of cannabis use could be a form of governmentality (Foucault, 1979), where the individual feels pressured to internalize and profess pathology in order to escape criminalization of a behavior that is deemed deviant. Such a user interpretation of personal cannabis use may be a consequence of the narratives that are available and acceptable to the user at the time of interpretation. When quantifying the reports of more than 4,000 cannabis users seeking recommendations for medical cannabis in California, O'Connell identified a consistent pattern of undiagnosed ADHD and childhood trauma among otherwise healthy young men who had initiated cannabis use during adolescence (O'Connell & Bou-Matar, 2007). In this context, O'Connell noted that while he personally believed that their cannabis use had been self-treatment of a mental health condition, the users preferred the interpretation of pleasure over the stigma that came with having a mental disorder (Newhart & Dolphin, 2018), suggesting that in some situations, "badness" is preferred over "sickness." However, qualitative studies indicate that in adulthood, the ADHD diagnosis can become an attractive discursive tool for explaining both problematic childhood behavior and daily cannabis use (Berger & Johansen, 2016; Pedersen, 2015).

From a sociological perspective, the increased use of diagnoses in society both by specialists and laypeople could be viewed as problematic, as it risks drowning out other relevant languages of

suffering (Brinkmann & Petersen, 2016; Rapley et al., 2011; Rose, 2018) and medicalize (and thusly individualize) problems that could also be understood as social, moral or political (Brinkmann, 2014). In this sociological critique, the medical narrative is criticized for being too dominant, but in the case of cannabis, this critique may only be half-true. In fact, in strict biomedical terms, the medical utility of cannabis is still underexplored, particularly in the context of mental health conditions, where the literature is in its infancy, albeit showing a potential therapeutic effect of cannabinoids for conditions such as PTSD and ADHD (Sarris et al., 2020; Scherma et al., 2020). A century of prohibition of cannabis has impeded the medical exploration of the plant's utility (Mikuriya, 1969) and multiple barriers to conducting cannabis research remain (National Academies of Sciences Engineering and Medicine, 2017; Piomelli et al., 2019). However, while much is still unknown, we know enough to make cannabis consumption safer (Englund et al., 2017), as cannabis products high in THC are associated with higher risk of cannabis-related harms compared to low-THC products (Colizzi & Bhattacharyya, 2017; Englund et al., 2017; Freeman et al., 2018). The study findings that a substantial proportion of medicinal users with recreational experience also use CBD-oil, suggests that the process of reinterpreting previous recreational use as medicinal may inspire a change in patterns of use. Indeed, it has been found that gaining access to a medical cannabis program also has an impact on consumption practices (Lankenau et al., 2018) and providing legal access to low-THC cannabis products, could potentially provide safer material conditions for medicinal users and access to other enabling resources within the healthcare system.

Differences in Social Control of Medicinal Cannabis Users

The study findings indicate that novices are the least strained by social control aspects related to medicinal cannabis use, as their supply is more stable, they feel less need to keep use secret, they are the least likely to believe that medicinal use can lead to addiction, and also least likely to consider stopping compared to users with recreational experience. There are several possible reasons for these findings. Firstly, according to Becker, developing a perception that cannabis use can be controlled is a central feature in overcoming social control factors related to use (Becker, 1963) and novices may have an easier task of interpreting and also presenting their use as controlled, as their use is more medicalized with frequent use of products that seeks to exclude intoxication. Secondly, the differences in social control factors may be related to the differences in conditions treated, as novices in the study were less likely to treat mental health conditions compared to users with recreational experience. A randomized experiment found that participants who viewed narratives in which the protagonist treated a stigmatized condition with medical cannabis expressed more negative attitudes toward medical cannabis (Lewis & Sznitman, 2017). Indeed, mental health conditions are more stigmatized than somatic conditions (Rusch & Corrigan, 2013; Vendsborg et al., 2011) and the association between heavy cannabis use and poorer mental health outcomes (National Academies of Sciences Engineering and Medicine, 2017) may further a problematic view on medicinal users who treat mental health conditions. Opinions on use also vary depending on the seriousness of the condition, as public opinion tends to be strongly supportive of medical cannabis use for serious life-threatening conditions such as cancer (Newhart & Dolphin, 2018). Thirdly, the fact that novices appear to be less strained by social control factors may be related to social inequalities in medicalization, as the help and sympathy that medicalization evokes is not equally distributed in society. A striking example of such inequalities comes from the US, where drug addiction appears to be easier medicalized among white middle- and upper-class citizens than poor inner-city black citizens (Anderson et al., 2015; Kerrison, 2015). In this perspective, there is not a "war on drugs," but a war on some people who use some drugs. Furthermore, the majority of women among users with no recreational experience in the study may explain the differences in social control, as women are often found more deserving of help than men (Connell, 2013; Kullberg, 2005). Also, it is curious that a political space for a medical cannabis program opened

up after people with substantial resources such as celebrities and politicians were vocal about their personal use of medicinal cannabis in the media (Kvamme, Pedersen, Alagem-Iversen, & Thylstrup, 2021), pointing to the notion that a medical explanation for drug use among “nice people” is often more easily accepted (Bell & Salmon, 2009).

Strengths and Limitations

The study has several strengths, including its large diverse sample size, which was the result of utilizing multiple recruitment strategies. The use of an anonymous web-based survey is an advantageous tool for studying topics that are sensitive and/or illegal in so-called hidden populations (Barratt et al., 2015), and online self-reported use is generally reliable and valid (Ramo et al., 2012). Also, the study represents a detailed exploration of the heterogeneity of the emerging use of medicinal cannabis in Denmark providing greater insight on a contested topic.

However, some important limitations must be noted. The study sample is a self-selected convenience sample and it may not be representative of the overall population of medicinal cannabis users. The sample likely weighs towards successful users of medicinal cannabis, users who are engaged with the topic on social media, and those with the resources necessary to answer online surveys. Also, the data from the study may be subject to self-reporting biases, such as recall bias, confirmation bias, or social desirability bias (Althubaiti, 2016). Moreover, it is not possible to rule out multiple responses from the same person, as IP addresses were not available to researcher. Furthermore, the cross-sectional study design lacks a temporal dimension and is not able to explore medicinal use over time. An exploration of co-occurring recreational use and age of onset of first cannabis use are relevant factors that should have been explored. Also, it should be noted that while the current study draws a clear distinction between medicinal and recreational cannabis use, these categories are seldom discrete in real life, where the difference between therapeutic and pleasant effects are not easily distinguished (Newhart & Dolphin, 2018; Ryan & Sharts-Hopko, 2017). Therefore, as the survey does not explore motives for initiation of recreational cannabis use among users with previous recreational experience, the findings from the present study can only hypothesize on potential self-medication motives related to the previous recreational use. Lastly, the exploration of social control factors in the current study is not an exhaustive inquiry into the complexity that Becker displayed in his qualitative material.

Appendix

Somatic condition (36): Acne, Aids, Alzheimer’s, Asthma, Chrons disorder, Herniated disc, Dystonia, Eczema, Epilepsy, Endometriosis, Fibromyalgia, Osteoarthritis, Rheumatoid arthritis, Psoriatic arthritis, Cataracts, Hepatitis, Brain damage, COPD, Cancer, FE(chronic fatigue), Chronic nerve inflammation, migraine, Menstrual pain, Multiple sclerosis, Neurodermatitis, IBS, Lupus (SLE), Palliation, Parkinson’s, peripheral neuropathy, Psoriasis, Spinal cord injury, pain following operation, pain following an accident, tinnitus, trigeminal neuralgia.

Psychiatric condition (13): ADHD, Anxiety, dependence (alcohol), dependence (hard drugs), dependence (prescription drugs), Anorexia, Autism, Bipolar disorder, Depression, OCD, PTSD, Schizophrenia, Tourettes/tics.

Potential comorbidities (3): Chronic pain, Sleep disturbances, Stress.

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ORCID iD

Sinikka L. Kvamme  <https://orcid.org/0000-0002-8376-2013>

Note

1. Except from cannabis products containing less than 0.2% THC such products are illegal to sell if they are considered to be medicine by the Danish Medicines Agency, but they are not illegal to possess (Danish Medicines Agency, 2018).

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Author Biography

Sinikka L. Kvamme is a drug researcher at the Center for Alcohol and Drug Research in Aarhus, Denmark. She has a background in political science and psychology. This paper is part of her PhD project exploring the use of cannabis as medicine in Denmark.