DELIVERY OF MEDICINAL CANNABIS

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Abstract

Cannabis can be administered via inhalation, oral, buccal, sublingual, rectal, topical, ophthalmic and systemic route. Taking preferences of patients into consideration is essential in improving the quality of life of patients. The aims of this study were (i) to evaluate delivery systems used for medicinal cannabis and patient preferences for delivery approaches (ii) to review studies focusing on medicinal cannabis dosage forms. Two self-administered questionnaires were developed, one for users and another one for potential users of medicinal cannabis, to evaluate the onset and duration of effect and side effects experienced with medicinal cannabis. Reasons why potential users would consider starting using medicinal cannabis were also assessed. Both questionnaires evaluated the preferred methods of medicinal cannabis administration. The questionnaires were developed in English and Maltese and were validated using the Delphi method. Questionnaires were disseminated at two different clinics and online, following ethics approval. Two systematic reviews were conducted to identify studies published between 2010 and 2020, about medicinal cannabis dosage forms and opinions of medicinal cannabis users about cannabis dosage forms. HyDi, a tool offered by the University of Malta which provides access to different databases, was used for the search. Eighty-seven users (mean 39 years; SD ±1.08 years) and 100 potential users (mean 41 years; SD ±1.20 years) of medicinal cannabis completed the questionnaires. The desired effect is perceived within few seconds when taking Pedanios 22/1 (41%, n=11), Pedanios 20/1 (29%, n=8), Bedrocan 22 (35%, n=13) and CBD oil (21%, n=7) and within 1 to 15 minutes for Pedanios 22/1 (44%, n=12), Pedanios 20/1 (54%, n=15), Bedrocan 22 (49%, n=18), Bediol 6/8 (86%, n=6) and CBD oil (41%, n=13). The effect of medicinal cannabis perceived to remain for 1 to 2 hours (41%, n=32) and 2 to 3 hours (26%, n=20).

The main side effects of medicinal cannabinoids were feeling hungry (56%, n=44), energised (51%, n=40) and sleepy (44%, n=34). Potential users would consider using medicinal cannabis because they heard of others benefitting from the treatment (58%, n=50), they read a lot about it (49%, n=42) and mainstream medication is not enough to treat their condition (28%, n=24). Main reasons for not wanting to start using medicinal cannabis were the fear about health consequences (38%, n=13) and social implications (29%, n=10) and complexity of the process to obtain medicinal cannabis (27%, n=9). Medicinal cannabis users rated cookies or other food items (n=66), tea (n=65) and drinking oil (n=72) and potential users rated water (n=79), vegetarian capsule (n=79) and tea (n=83) as the most preferred method of administering cannabis orally. Users prefer cannabis in the form of cigarettes (n=71) and tincture (n=67) while potential users prefer as patch (n=78), tincture (n=83) and ointment (n=74). The systematic reviews identified 89 articles about medicinal cannabis dosage forms related to pharmacodynamics (n=41), pharmacokinetics (n=32) and types of dosage form used (n=12) and 10 articles assessed opinions of medicinal cannabis users about cannabis dosage forms. Sixty-two studies focused on one administration form, mainly smoked form (n=32), followed by the oral form (n=15) of cannabis. Twenty-five studies compared two forms such as smoked versus oral (n=9) and oral versus oro-mucosal (n=5). Twelve studies involved multiple dosage forms including smoked, vaped, edible, oral, oro-mucosal and topical forms. This study contributes to the knowledge about perception of patient-centred cannabis delivery systems. The availability of different dosage forms preferred by patients, other than cannabis flowers, ensures a patient-centred medicinal cannabis delivery system.

Keywords:

Medicinal cannabis, patient-preferred delivery systems, mode of administration, patient-centred approach

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List of Abbreviations

2-AG	2-arachidonoyl glycerol
7-COOH-CBD	Cannabidiol-7-oic acid
7-OH-CBD	7-hydroxy-cannabidiol
11-OH-THC	11-hydroxy-tetrahydrocannabinol
ADHD	Attention Deficit Hyperactivity Disorder
AEA	Anandamide
AIDS	Acquired Immunodeficiency Syndrome
AMP	Dextroamphetamine
BA	Bioavailability
BCS	Biopharmaceutical Classification System
cAMP	Cyclic adenosine monophosphate
CB_1	Cannabinoid-1
CB_2	Cannabinoid-2
CBC	Cannabichromene
CBD	Cannabidiol
CBE	Cannabielsoin
CBF	Cannabifuran
CBG	Cannabigerol
CBL	Cannabicyclol
CBN	Cannabinol
CBND	Cannabinodiol
CBT	Cannabitriol
CDC	Centers for Disease Control and Prevention
CINV	Chemotherapy-induced nausea and vomiting
CYP	Cytochrome
ECB	Endocannabinoid system
E-cig	Electronic cigarette
EVALI	E-cigarette or vaping associated lung injury
FAAH	Fatty acid amide hydrolase
FREC	Faculty Research Ethics Committee
GABA	Gamma aminobutyric acid
HIV	Human Immunodeficiency Virus
IBS	Irritable bowel syndrome
MAGL	Monoacylglycerol lipase
MDMCU	Methods of Delivery for Medicinal Cannabis Users
MDNMCU	Methods of Delivery for non-users of Medicinal Cannabis
MHE	Multiple hereditary exostoses
OCD	Obsessive compulsive disorder
OF	Oral fluid
PK	Pharmacokinetic
SEDDS	Self-emulsifying drug delivery systems
THC	Tetrahydrocannabinol
THC-COOH	11-carboxy-tetrahydrocannabinol

1. Introduction

1.1 Background

Cannabis products and their modes of administration have increased in the past 5 years.[1] Since 2015, there was an increase in the number of countries which approved cannabis, which may be attributed to an increase in awareness related to the potential of using medicinal cannabis. There is limited information about the cannabis delivery systems, only a few studies explored different cannabis delivery systems which mainly focused on specific populations such as people with chronic diseases like cancer or AIDS (Murphy et al, 2015). Taking preferences of patients into consideration is essential in improving the quality of life of patients (Lowe et al, 2016; Capano et al, 2019). The perception of patients can provide comparable information and gives the possibility to see ideas that are different from the information obtained through the literature, which is important in the dissemination of accurate information (Murphy et al, 2015).

1.2 Historical Use of Cannabis

The use of cannabis for medicinal purposes dates back to thousands of years (Table 1.1). The first use of cannabis is indicated to have taken place in China (Hanuš, 2009) and Romania in 2700 BC (Bridgeman & Abazia, 2017; Landa et al, 2018) and was documented in Assyrians dictionary of botany around 3000-2000 BC (Zias et al, 1993). The medicinal use of cannabis was recorded in Chinese pharmacopoeia, Shen-nung pen ts'ao ching in 400 AD (Hanuš, 2009; Bridgeman & Abazia, 2017). In the 1800s, before aspirin was introduced, cannabis was used as a common analgesic drug in Western

[1] Prohibition Partners. The European Cannabis Report: 3rd edition [Internet]. London: Prohibition partners; 2018 [cited 2019 Dec 6]. Available from URL: https://mgcpharma.com.au/wp-content/uploads/2018/07/The3rdEditionoftheEuropeanCannabisReport.pdf

medicine (Devinsky et al, 2014; Landa et al, 2018). The 19th and 20th centuries were the golden period of cannabis, where many studies were conducted in Europe and the USA (Bifulco & Pisanti, 2017). However, cannabis was then removed from the UK Pharmacopoeia (1932) and the US Pharmacopoeia (1941) due to the complexity in composition and unpredictable shelf-life (Kalant, 2001). After the discovery of the chemical structure of the psychoactive component tetrahydrocannabinol (THC) and the endocannabinoid signalling system, cannabis was brought into scientific attention again and more studies were conducted (Bifulco & Pisanti, 2017).

Table 1. 1 Historical Use of Cannabis

Period	Historical Use	References
2700 BC	China and Romania	Zias et al, Nature 1993; Hanuš, Medical research reviews 2009; Pain, Nature 2015; Bridgeman & Abazia, Pharmacy and therapeutics 2017; Landa et al, Biomedical papers 2018
3000-2000 BC	Assyrians (Dictionary of Assyrian Botany)	Zias et al, Nature 1993; Hanuš, Medical research reviews 2009
2000-1400 BC	India (Atharva Veda)	Hanuš, Medical research reviews 2009
1534 BC	Egyptians (The Ebers Papyrus)	Zias et al, Nature 1993; Hanuš, Medical research reviews 2009
1200 BC	Persia (Zend Avesta)	Zias et al, Nature 1993; Hanuš, Medical research reviews 2009
90 AD	Greece (Materia Medica)	Zias et al, Nature 1993; Hanuš, Medical research reviews 2009
400 AD	Chinese pharmacopoeia (Shen-nung pen ts'ao ching)	Bridgeman & Abazia, Pharmacy and therapeutics 2017

Table 1.1 *(cont.)* Historical Use of Cannabis

Period	Historical Use	References
1800s	Western medicine	Devinsky et al, Epilepsia 2014; Landa et al, Biomedical Papers 2018
19^{th}- 20^{th} Century	Golden period of Cannabis in Europe and the USA	Kalant, Pain research and management 2001
1932	Removed from the UK Pharmacopoeia	Kalant, Pain research and management 2001
1941	Removed from the US Pharmacopoeia	Kalant, Pain research and management 2001; Bifulco & Pisanti, European molecular biology organization reports 2017
1945	A pause of studies (USA)	Bifulco & Pisanti, European molecular biology organization reports 2017
1960	Classified as substance of abuse (USA)	Bifulco & Pisanti, European molecular biology organization reports 2017
1964	Identification of Δ^9-THC chemical structure (Israel)	Bifulco & Pisanti, European molecular biology organization reports 2017
1990	Discovery of endocannabinoid system	Pacher et al, Pharmacological reviews, 2006; Bifulco & Pisanti, European molecular biology organization reports 2017

Legalisation related to medicinal cannabis use changed over the years. The year medicinal cannabis was approved as well as the approved cannabis-based products differ across countries, states and provinces. In this section, legislation history of medicinal cannabis in Europe (Table 1.2)[1], the USA (Table 1.3) and Canada (Table1.4) are presented.

Table 1. 2 Legislation History of Medicinal Cannabis in Europe[1]

Country	Year Introduced	Approved Cannabis-based Products
Austria	2008 (Cultivation)	Sativex Dronabinol
Belgium	2015	Sativex Dronabinol
Croatia	2015	Dronabinol Nabilone Cannabis Flowers Cannabis Teas Cannabis Ointments Cannabis Capsules
Czech Republic	2013	Cannabis Flowers
Denmark	2018	Sativex Marinol
Estonia	2005	Marinol
Finland	2017	Sativex Cannabis Flowers
France	2013	Sativex
Germany	2017	Sativex Cannabidiol Cannabis oil Nabilone Dronabinol Cannabis flower
Greece	2017	Unknown

[1] Prohibition Partners. The European Cannabis Report: 3rd edition [Internet]. London: Prohibition partners; 2018 [cited 2019 Dec 12]. Available from URL: https://mgcpharma.com.au/wp-content/uploads/2018/07/The3rdEditionoftheEuropeanCannabisReport.pdf

Table 1.2 *(cont.)* Legislation History of Medicinal Cannabis in Europe

Country	Year Introduced	Approved Cannabis-based Products
Ireland	2013	Sativex Nabilone
Israel	1994	Cannabis Flowers
Italy	2013	Dronabinol Sativex Cannabis Flowers Cannabis Tea Cannabis Oil Cannabis Capsules
Luxembourg	2017	Sativex Cannabis Flowers Cannabis Oils Cannabis Sprays Cannabis Tinctures
Macedonia	2016	CBD Oil THC Oil
Malta	2018	Sativex Cannabis Flowers
Norway	2016	Unknown
Poland	2017	Sativex Cannabis Flowers
Portugal	Inconsistent 2001	Sativex
Romania	Legal	Cannabis-derived products (tinctures and resins)
Serbia	2014	Cannabis oil under exhaustive circumstances
Slovenia	Illegal, certain cannabinoids are permitted	Sativex Marinol
Spain	2017	Sativex Epidiolex Nabilone Dronabinol THC is prohibited
Sweden	2017	Sativex Bediol
Switzerland	Legal	Sativex
The Netherlands	2003	Cannabis Flowers
The United Kingdom	Illegal except Nabilone and Sativex	Nabilone Sativex
Turkey	2016	Sativex CBD Oil

Table 1. 3 Legislation History of Medicinal Cannabis in the USA[2]

State	Year Introduced	Approved Cannabis-based Products
Alaska	1998	Cannabis plants[2]
Arizona	2010	Epidiolex[3]
Arkansas	2016	Marinol[3]
California	1996	
Colorado	2000	
Connecticut	2012	
Delaware	2011	
Florida	2016	
Hawaii	2000	
Illinois	2013	
Louisiana	2016	
Maine	1999	
Maryland	2014	
Massachusetts	2012	
Michigan	2008	
Minnesota	2014	
Missouri	2018	
Montana	2004	
Nevada	2000	
New Hampshire	2013	
New Jersey	2010	
New Mexico	2007	
New York	2014	
North Dakota	2016	
Ohio	2016	
Oklahoma	2018	
Oregon	1998	
Pennsylvania	2016	
Rhode Island	2006	
Utah	2018	
Vermont	2004	
Washington	1998	
Washington, DC	2010	
West Virginia	2017	

[2] Pros & Cons of Current Issues Reliable Nonpartisan Empowering (Procon.org). Legal medical marijuana states and dc, laws, fees, and possession limits [Internet]. USA: Procon; 2019 [cited 2020 Jan 20]. Available from URL: https://medicalmarijuana.procon.org/legal-medical-marijuana-states-and-dc/

[3] U.S. Food & Drug Administration (FDA). FDA and cannabis: research and drug approval process. [Internet]. USA: FDA; 2020 [cited 2020 Jan 20]. Available from URL: https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process

Table 1. 4 Legislation History of Medicinal Cannabis in Canada[4,5]

Province	Year Introduced	Approved Cannabis-based Products
Alberta British Columbia Manitoba New Brunswick Newfoundland and Labrador Northwest Territories Nova Scotia Nunavut Ontario Prince Edward Island Quebec Saskatchewan Yukon	2001 Medicinal 2018 Recreational	Dried cannabis (30 grams or equivalent)[6] Cannabis oil Cannabis plants Cannabis seeds

[4] Controlled Drugs and Substances Act. Act of 2001, Pub. L. No. SOR/2001-227, Marihuana Medical Access Regulations [cited 2020 Jan 20]. Available from URL: https://laws-lois.justice.gc.ca/eng/regulations/sor-2001-227/page-1.html

[5] Health Canada. Data on cannabis for medical purposes. Canada: Health Canada; 2018 [cited 2020 Jan 20]. Available from URL: https://www.canada.ca/en/health-canada/services/drugs-medication/cannabis/research-data/medical-purpose.html

[6] Health Canada. Department of Justice. Cannabis Legalization and Regulation. Canada: Health Canada; 2018 [cited 2020 Jan 20]. Available from URL: https://www.justice.gc.ca/eng/cj-jp/cannabis/

1.3 Endocannabinoid System

The mechanism of action of cannabis is linked to the endocannabinoid (eCB) system, a complex signalling system which comprises of cannabinoid-1 (CB_1) and cannabinoid-2 (CB_2) G-protein coupled receptors, endogenous cannabinoids (endocannabinoids) and synthesizing and degrading enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) (Nesto & Mackie, 2008; Bouchard et al, 2016; Dabrowski & Skrajda, 2017; Meyer et al, 2018; Sun et al, 2019). Cannabinoid receptors bind to endogenous cannabinoids like anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) to produce a physiological effect (Hanuš, 2009; Meyer et al, 2018).

The eCB system operates both centrally and peripherally (Nesto & Mackie, 2008). CB_1 receptors are principally located in the central nervous system and are also found in various tissues such as hepatocytes, adipocytes, connective tissues and skeletal muscle tissues (Nesto & Mackie, 2008; Bridgeman & Abazia, 2017; Halawa et al, 2018). CB_2 receptors are primarily expressed in the immune system cells, but are also present in the central nervous system (Hanuš, 2009; Dabrowski & Skrajda, 2017). Expression of CB_1 receptor results in synaptic plasticity, cell migration and neuronal growth of cannabinoids, whereas CB_2 receptor expression is linked to mechanisms such as preventing, abating and repairing of the inflicted damage (Dabrowski & Skrajda, 2017).

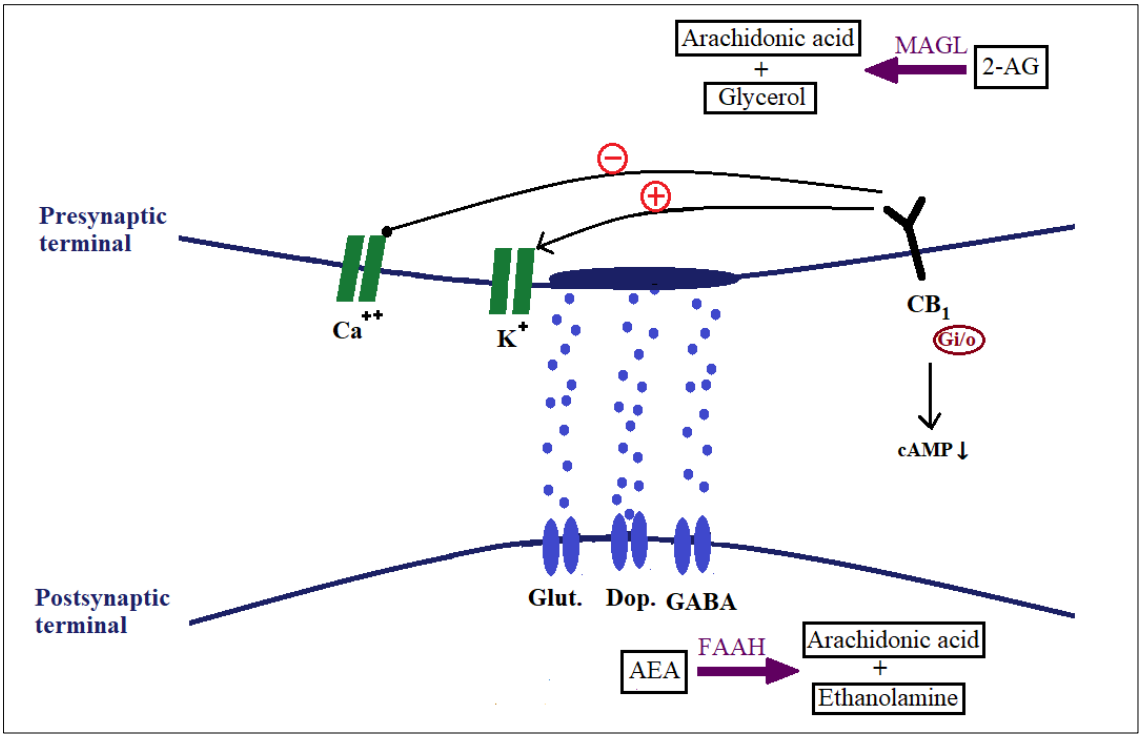

Figure 1. 1 Endocannabinoid System Signalling (This diagram was composed of the descriptions given in these two references: Russo EB, Hohmann AG. Role of cannabinoids in pain management. Deer et al. editors. Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches. American Academy of Pain Medicine; 2013. p. 181-197 and Halawa OI, Furnish TJ, Wallace MS. Chapter 56 - role of cannabinoids in pain management. Essentials of Pain Medicine. 2018;4:509-520.)

ECB signalling in brain is greatly linked to CB_1 receptor which is couple with Gi and Go (Figure 1.1). Cyclic adenosine monophosphate (cAMP) and cAMP-dependent protein kinase activity decreases as a result of G-coupling (Dabrowski & Skrajda, 2017; Meyer et al, 2018). This bring forth A-type potassium channels activation along with voltage-gated calcium channels inhibition, which affect the release of neurotransmitters such as gamma aminobutyric acid (GABA), glutamate and dopamine (Kalant, 2001; van Hell et al, 2012; Di Marzo et al, 2015; Aung-Din, 2016; Halawa et al, 2018; Meyer et al, 2018). The mechanism follows with the enzymatic breakdown of AEA into arachidonic acid and ethanolamine by FAAH and of 2-AG into arachidonic acid and glycerol by MAGL. These enzymes contribute in the natural signalling process of eCB ligands. Inhibition of the

enzymatic activity of FAAH and MAGL may result in prolongation of the eCB ligands activity. ECB signalling can be modulated by targeting these enzymes (Russo & Hohmann, 2013; Meyer et al, 2018).

The eCB system is involved in numerous physiological processes including mood, memory, sensation, pain (Moreira et al, 2009), temperature control, appetite stimulation, inflammation control, bone resorption (Bab & Melamed, 2009; Sun et al, 2019), modulation of nausea as well as immune responses and metabolic disorders (Aung-Din, 2016; Sun et al, 2019). The eCB system maintains eating, learning, protecting from medical conditions, growth and development homeostasis (Devinsky et al, 2014; Bridgeman & Abazia, 2017) and may protect or exacerbate medical disorders (Bridgeman & Abazia, 2017).

Disturbance in the eCB system may lead to pathologic conditions, deficiencies may lead to conditions such as multiple sclerosis (Di Filippo et al, 2008), depression (Parolaro et al, 2010), Parkinson's and Huntington's diseases (Di Marzo et al, 2015), fibromyalgia, irritable bowel syndrome (Russo, 2016), migraine (Sarchielli et al, 2007; Russo, 2016; Bridgeman & Abazia, 2017), schizophrenia (Fakhoury 2017), anorexia and motion sickness (Choukèr et al, 2010; Bridgeman & Abazia, 2017). Overactivation of the eCB system may impact on cardiometabolic risk factors and result in dyslipidaemia, thrombosis, atherosclerosis (Boyd, 2006; Tang, 2006; Mach & Steffens, 2008; Nesto et al, 2008; Van Eenige et al, 2019), hypertension (Polak et al, 2018) and diabetes mellitus morbidities (de Luis et al, 2010; Veilleux et al, 2019).

1.4 Components of Cannabis

Cannabis is a complex dioecious type of plant (Bruni et al, 2018) which belongs to the Cannabaceae family (ElSholy & Slade, 2005; Mansouri & Asrar, 2012; Bridgeman & Abazia, 2017; Landa et al, 2018, Zhou et al, 2018) and consists of three major species; Cannabis Sativa, Cannabis Indica and Cannabis Ruderalis (Dabrowski & Skrajda, 2017; Morales et al, 2017).

Cannabis Sativa L. (hemp) can be classified into two crude products i) marijuana from dried flowers and flowering heads and ii) hashish from upper leaves and flower buds (Kalant, 2001; Hanuš, 2009; Wang et al, 2017). Isolation of these products results in pure cannabinoids and hundreds of non-cannabinoid compounds. There are 483 constituents identified in Cannabis (Brenneisen, 2007), of these 142 are phytocannabinoids (Ujváry & Hanuš, 2016).

There are various cannabinoid originating compounds which are grouped into subclasses (Table 1.5) (Kalant, 2001; Brenneisen, 2007; Mansouri & Asrar, 2012; Chandra et al, 2013; Devinsky et al, 2014; Riemer & Holmes, 2014; Hanuš et al, 2016; Kill et al, 2016; Ujváry & Hanuš, 2016; Dabrowski & Skrajda, 2017; Lewis et al, 2017; Landa et al, 2018). The psychoactive Δ^9-tetrahydrocannabinol (THC) and the non-psychoactive but active cannabidiol (CBD) phytocannabinoids will be the focus in this dissertation. CBD was isolated in 1940 and its structure was elucidated in 1963 (ElSholy & Slade, 2005; Brenneisen, 2007; Ujváry & Hanuš, 2016; Morales et al, 2017). THC was isolated in 1942, the structure was identified in 1964 (Brenneisen, 2007).

Table 1. 5 Chemistry of Cannabis Plant (Adopted from: Brenneisen R. Chemistry and analysis of phytocannabinoids and other cannabis constituents. In: ElSohly MA, editors. Marijuana and the Cannabinoids. Forensic Science and Medicine. Totowa, NJ: Humana Press; 2007. p. 17-49 and Chandra S, Lata H, Khan IA, ElSohly MA. The role of biotechnology in cannabis sativa propagation for the production of phytocannabinoids. In: Chandra S, Lata H, Varma A, editors. Biotechnology for Medicinal Plants; 2013. p. 123-148.)

Cannabinoid origin compounds	Non-cannabinoid origin compounds
Δ^8-THC type (n=2)	Terpenoids (n=140)
Δ^9-THC type (n=17)	Hydrocarbons (n=50)
CBC (Cannabichromene) type (n=8)	Nitrogen-containing compounds (n>70)
CBD (Cannabidiol) type (n=8)	Monosaccharides (n=13), Disaccharides (n=2), Polysaccharides (n=5)
CBE (Cannabielsoin) type (n=5)	Sugar alcohols and Cyclitols (n=12), Amino sugars (n=2)
CBF (Cannabifuran) type	Flavonoids (n=23), Fatty acids (n=33), Phenols (n=33)
CBG (Cannabigerol) type (n=16)	Alcohols (n=7), Aldehydes (n=12), Ketones (n=13)
CBL (Cannabicyclol) type (n=3)	Acids (n=21)
CBN (Cannabinol) type (n=10)	Phytosterols (n=11), Vitamin (n=1)
CBND (Cannabinodiol) type (n=3)	Elements (n=18)
CBT (Cannabitriol) type (n=9)	
Miscellaneous types (n=18)	

There is a potential interaction between the non-cannabinoid originating constituents (ElSholy & Slade, 2005; Brenneisen, 2007; Lewis et al, 2017). Terpenoids and flavonoids have shown to enhance the beneficial effects of cannabis (Mathre, 2002). The THC/CBD ratios differ according to the strain; Cannabis Sativa contains higher THC ratios than Cannabis Indica, this characteristic makes Sativa more stimulatory whereas Indica is more sedative (Devinsky et al, 2014).

1.5 Modes of Cannabis Administration

Cannabinoids can be administered (i) by inhalation including smoking cannabis cigarettes, electronic cigarettes, using vaporisers, nebulisers and aerosols (Grotenhermen, 2003; Newmeyer et al, 2016; Lippmann & Singh, 2017), pipes, water pipes and other metal, glass or ceramic devices (Murphy et al, 2015) (ii) orally including tinctures (Lim & Kirchhof, 2018), tablets, capsules, by adding in food or liquid (Barry et al, 2014; Pizarro-Osilla, 2016; Punyamurthula et al, 2017) and as an oil (McCoy et al, 2018) (iii) buccally example using lozenges (Karschner et al, 2011; Crowley et al, 2018; Mehrpour et al, 2018) (iv) sublingually such as by using oro-mucosal sprays (Wade, 2012; Stott et al, 2013; Landa et al, 2018) (v) rectally as suppositories (Huestis, 2005; Landa et al, 2018) (vi) topically including creams, lotions, ointments, soaps, shampoos, conditioners,[7] balms, oils, salves and transdermal patch (Grotenhermen, 2003; Lim & Kirchhof, 2018) (vii) by topical ophthalmic route for example using eye drops, solid lipid nanoparticles (Grotenhermen, 2003; Punyamurthula et al, 2017) and (viii) systemically via intramuscular (Tramèr et al, 2001) and intravenous injections (Huestis, 2007).

1.6 Pharmacokinetics of Cannabinoids

The pharmacokinetics of cannabinoids is complex and vary in the mode of delivery, individuals' variability (metabolic factors, age) (ElSholy & Slade, 2005; Brenneisen, 2007; Ginsburg, 2015; Lewis et al, 2017; Bruni et al, 2018) and by non-cannabinoid origin components included in the plant such as terpenoids (Russo, 2011; Hazekamp et al, 2013).

[7] Botanic Alternatives CBD. Botanic alternatives cbd and cannabis accessories [Internet]. Chicago: IL;2014 [cited 2019 Dec 14]. Available from URL: https://www.botanicalternatives.com/

1.6.1 Absorption

Cannabinoids are very lipophilic molecules and have very poor water solubility. The physico-chemical characteristics of cannabis is complex (Bruni et al, 2018; MacCallum & Russo, 2018). Absorption is erratic and can be affected by bioavailability, lipophilicity and organ tissue diversity (dermal, gastric and alveolar) (MacCallum & Russo, 2018). The route of administration is among the determinant factors for the rate of drug absorption (Huestis, 2007).

i. Inhalation

Smoking cannabis cigarette has been recognised as a common method of cannabis administration for years (Kalant, 2001; Frederick et al, 2007; Huestis, 2007; Peters et al, 2016; Kostygina et al, 2017; Giovenco et al, 2018). Administration of cannabis by smoking provides rapid absorption of drug within seconds and a prompt delivery from the lungs into the blood stream and the brain (Kalant, 2001; Grotenhermen, 2004a; Huestis, 2005; Huestis, 2007; Murphy et al, 2015; Lucas et al, 2018). The onset of action is attained within seconds which is as rapid as the intravenous injection (Kalant, 2001; Grotenhermen, 2004a). The effect can be perceived within 20-30 minutes and the psychoactive effects last for one up to four hours (Grotenhermen, 2004a; Borodovsky et al, 2016). Concentration of THC is detectable after the first puff, and peak plasma concentration can be measured within 10 minutes of smoking (Grotenhermen, 2003; McGilveray, 2005; Lucas et al, 2018). Bioavailability of THC ranges between 2-56% following smoking (Grotenhermen, 2004a; Huestis, 2005; Lucas et al, 2018), while a bioavailability of 10-35% was observed for regular consumers (Grotenhermen, 2004a). Bioavailability of CBD was recorded to be between 6-31% (Zhornitsky & Potvin, 2012; Lucas et al, 2018). Smoking marijuana may impair lung function as a result of combustion

at 600-900 °C and release of toxic by-products including tar, cyanide, carbon monoxide, polycyclic aromatic hydrocarbons and ammonia (Chapkis & Webb, 2005; MacCallum & Russo, 2018).

Vaporisers and electronic cigarettes (e-cigs) can be used to administer cannabinoids by inhalation (Hazekamp et al, 2006; Giroud et al, 2015; Newmeyer et al, 2016; Lippmann & Singh, 2017; Hemsing & Greaves, 2018; Poklis et al, 2019). Vaporisers are devices that heat the cannabinoids at 160-230 °C by using electricity and release the resin of cannabis as vapour (Malouff et al, 2014; Ginsburg, 2015; Lewis et al, 2017) and thereby producing less harmful by-products (polycyclic aromatic hydrocarbons) compared to smoking (Tashkin, 2015; MacCallum & Russo, 2018; Russell et al, 2018; Spindle et al, 2018). Vaping of cannabinoids (cannavaping) provides similar effects, onset, peak plasma concentration and duration with possibly higher bioavailability to smoking (Grotenhermen, 2004a; Borgelt et al, 2013; Borodovsky et al, 2016; Hindocha et al, 2016; Lanz et al, 2016; Peace et al, 2016; Shiplo et al, 2016; Varlet et al, 2016; Lippmann & Singh, 2017).

Vaping cannabis was considered to be a less harmful alternative method to smoking, however, recent studies found that it is not completely harmless and that vaping can be a potential detriment to health (Budney et al, 2015; Tanne, 2019; Blount et al, 2020; Christiani, 2020). In the study of Spindle et al (2018), it was found that consuming cannabis acutely via vaporization produced significantly higher drug effects, cognitive and psychomotor impairment, and higher THC concentrations in blood than the same doses of cannabis administered via traditional smoking. By November 2019, over 2711 e-cigarette or vaping associated lung injury (EVALI) cases with 60 deaths were reported by Centers for Disease Control and Prevention (CDC) in the USA and the District of

Columbia (Kalininskiy et al, 2019; Tanne, 2019). Ninety-four percent of patients had detectable THC in bronchoalveolar-lavage fluid or vaped THC products and the 83% were THC or CBD vapers (Blount et al, 2020; Christiani, 2020). The symptoms of EVALI include cough, dyspnoea, chest pain, gastrointestinal symptoms (nausea, vomiting, diarrhoea), fever and chills, weight loss, fatigue and pain in the abdominal area (Kalininskiy et al, 2019; Tanne, 2019). The key factor of the EVALI could be vitamin E acetate, which is found in oil formulations of cannabinoids. Vitamin E is not an approved additive for vaping marijuana products and it is harmless when administered onto skin or taken as a vitamin. A possible mechanism assumes that the heated vitamin E acetate oil inhaled as an aerosol may accumulate into the lower airways and triggers the vaping linked illness called lipoid pneumonia (Kalininskiy et al, 2019; Tanne, 2019; Blount et al, 2020; Christiani, 2020). E-cigarette fluids containing THC, CBD or nicotine products when inhaled, have been shown to contain potentially toxic molecules (chemicals, heavy metals, volatile organic compounds) that can lead to the serious respiratory disease 'popcorn lung' and chronic conditions, including cancer (Hashibe et al, 2005; Tanne, 2019; Blount et al, 2020; Christiani, 2020).

The use of cannabis inhaler could be another alternative to smoking as a smoke-free delivery system. Whole-plant cannabis can be inhaled using a thermal-metered dose inhaler. A consistent and therapeutically effective dosage of cannabinoids can be delivered by this route (Eisenberg et al, 2014).

Nebulisers can be counted as substitutes to smoking marijuana. Nebulising is a process where an aqueous liquid is aerosolized by oxygen and inhaled into the lung. They provide rapid onset and easy titratability of the effect (Grinspoon, 2000). Nebulising is the only

inhalation delivery system that does not require heating of the cannabis product, this characteristic makes this system a safe and efficient way of administering cannabinoids.[8]

Absorption of cannabinoids ranges from 10 to 60% when cannabis is inhaled or smoked. Absorption can be influenced by many factors, including the origin of the plant material, contents of the cigarette, inhalation device, depth of inhalation, frequency and duration of puffs, smoking technique and breath-holding duration (Kalant, 2001; Grotenhermen, 2004a; McGilveray, 2005; Huestis, 2007; Lucas et al, 2018; MacCallum & Russo, 2018).

ii. Oral Administration

Absorption is irregular and as low as 2-14% when cannabinoids are administered orally (Grotenhermen, 2003; Heuberger et al, 2015; Lucas et al, 2018; Pelessi et al, 2018). The onset of action is delayed, and is attained within 30-90 minutes, with the maximum effect being achieved within 2 to 3 hours. The effects of cannabinoids lasts for more than 6 hours, which is longer than the inhalation route (Grotenhermen, 2004a; Borodovsky et al, 2016; Bridgeman & Abazia, 2017). Peak plasma concentrations can be generally observed within 1 to 2 hours post administration, however there is the possibility to have more than one peak and late peak plasma concentration after 4 to 6 hours, depending on individual variability (Grotenhermen, 2003; Grotenhermen, 2004a; McGilveray, 2005; Bridgeman & Abazia, 2017; Lucas et al, 2018), the dose of medicine, vehicle used in the formulation and different pharmacokinetic factors (Huestis, 2005).

[8] Cannaneb. Use of cannabis nebulizers vs. smoking and vaporizing. [Internet]. Cannaneb; 2016 [cited 2019 Dec 15]. Available from URL: http://www.cannaneb.com/blog/use-of-cannabis-nebulizers-vs-smoking-and-vaporizing

Dronabinol, the formulation of Δ^9-THC is pharmaceutically available as a capsule and an oral solution. The plasma concentration of the capsule formulation of Dronabinol was found to be more variable to the oral solution formulation (Lile et al, 2013; Parikh et al, 2016; Badowski, 2017).

Bioavailability following oral ingestion of THC is low, ranging between 5-10% (Grotenhermen, 2004a; Huestis, 2005; McGilveray, 2005; Karschner et al, 2011; Abrams, 2016). Oral bioavailability is greatly reduced by the liver through first-pass metabolism before reaching the site of action. THC is broken down into the active 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC) metabolite by the acid in the stomach and it is then metabolised into the inactive 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH) metabolite in the liver (McGilveray, 2005; Zhornitsky & Potvin, 2012; Ujváry & Hanuš, 2016; Newmeyer et al, 2017b; Lucas et al, 2018; Pellesi et al, 2018). The bioavailability of a 20 mg THC cookie was found to be as low as 6% (Grotenhermen, 2004a). CBD is also affected by first-pass metabolism, whereby it breaks down into its metabolites 7-hydroxy-CBD (7-OH-CBD) and CBD-7-oic acid (7-COOH-CBD). Bioavailability of CBD is variable, ranging between 6-31% (Zhornitsky & Potvin, 2012; Ujváry & Hanuš, 2016; Lucas et al, 2018; Pellesi et al, 2018).

The pharmacokinetic factors of cannabinoids after oral ingestion may be influenced by (i) the dosage form and excipients used in the formulation, (ii) food intake, (iii) physiological factors such as motility, (iv) pathophysiological factors such as liver function and (v) use of co-medications like antiemetics including metoclopramide and itopride (Benjamin & Fossler, 2016; Landa et al, 2018).

iii. Buccal Administration

Lozenges can be used for the buccal administration of cannabinoids by placing the dosage form between the gums and cheek (Karschner et al, 2011; Hua, 2019). Buccal administration can be considered as an alternative method to the oral route, providing similar pharmacokinetics. A large portion of cannabinoids is absorbed by the buccal mucosa, while the remaining portion is absorbed by the intestine (Grotenhermen, 2004a; Guy & Robson, 2004).

Lozenges may take up to 25 minutes to completely disperse in the mouth. When cannabis products are administered via the buccal route, the onset of the effect occurs within 5-40 minutes (Karschner et al, 2011; Crowley et al, 2018). The bioavailability of buccal and oral administration is similar (Devinsky et al, 2014). Peak plasma concentration following buccal administration can be observed within 45-120 minutes, the peak concentration of CBD is slower than THC (Guy & Robson, 2004). Absorption through the oral mucosa can be affected by intra-subject variability factors such as food, amount of dose swallowed and exercise (Guy & Robson, 2004).

iv. Sublingual Administration

Sublingual administration provides another route for the administration of cannabis extract by placing or spraying the drug under the tongue. Oro-mucosal sprays are formulated mainly as a mixture of THC and CBD components in alcohol (Scully, 2007; Wade, 2012). Sublingual delivery provides rapid absorption through the mucosa as a result of direct entry of the drug into the vascular system and reduced first pass metabolism (Grotenhermen, 2004a; Karschner et al, 2011; Stott et al, 2013; Landa et al, 2018; Lucas et al, 2018). Crushed sublingual tablets resulted in slower absorption compared to the oral route (Klumpers et al, 2012; Landa et al, 2018). A rapid onset of

action is achieved by the sublingual route, with higher plasma concentrations compared to the oral route. Peak plasma concentration appears within 15 minutes to 1 hour. THC preparations in ethanol and propylene glycol showed psychic effects within 45 minutes and the maximum effect was observed after 180 minutes (Grotenhermen, 2004a; Karschner et al, 2011; Stott et al, 2013; Landa et al, 2018; Lucas et al, 2018). Bioavailability of sublingual route is similar to the oral route but with less variability (Devinsky et al, 2014).

v. Rectal Administration

Few studies have covered cannabinoids in suppository form. Formulation of esters of cannabinoids can be applied rectally using suppositories (Kalant, 2001; McGilveray, 2005). Absorption is fast by rectal administration, whereby the drug is transferred into the systemic circulation instantly, bypassing the first pass metabolism (Kalant, 2001). Peak plasma concentration was observed within 2 to 8 hours (Huestis, 2005; Landa et al, 2018). The bioavailability of rectally administered cannabinoids is 13.5% which is twice as high compared to the oral form, and varies depending on how it is formulated (Brenneisen et al, 1996; Grotenhermen, 2003; Grotenhermen, 2004a; Landa et al, 2018).

vi. Topical Administration

Cannabinoids are highly lipophilic; this characteristic leads to diffusion-related difficulties and accumulation on the skin layer following slow permeation across the membranes. First-pass metabolism is bypassed by transdermal application, yet absorption is very delayed (Grotenhermen, 2004a; Hess et al, 2017). A steady state concentration occurs within 17 hours for THC and in 24 hours for CBD transdermal patch and remains effective for 14 hours for THC and up to 72 hours for CBD (Grotenhermen, 2004a).

Absorption via the transdermal route can be affected by blood flow of the area of application and skin permeability (Lucas et al, 2018).

vii. Ophthalmic Administration

Ophthalmic administration of cannabinoids was used to decrease intraocular pressure. This route leads to a bioavailability of 6-40% and does not present psychotropic effects due to the lack of systemic absorption (Grotenhermen, 2004a). Peak plasma concentration is observed within 1 hour and pursues for several hours (Kalant, 2001; Grotenhermen, 2003; Grotenhermen, 2004a).

viii. Systemic Administration

Another way to administer cannabinoids includes via the intramuscular or intravenous route by injection or infusion (Kalant, 2001; Tramèr et al, 2001). Systemic delivery of cannabis provides an onset of action within seconds and a short duration of action as a result of rapid decline (Grotenhermen, 2004a; Bridgeman, 2017). Plasma concentration of THC administered systemically is similar to smoking and can be measured within 10 minutes. Water solubility of THC is very poor (2.8mg/L), special water-miscible formulations are necessary to enhance systemic absorption of THC (Kalant, 2001; Grotenhermen, 2004a; Bridgeman, 2017).

1.6.2 Distribution

Distribution of cannabinoids is affected by their physicochemical characteristics (Grotenhermen, 2003). The distribution of THC is initiated rapidly following the absorption phase, due to its high lipophilic character which leads to a high volume of distribution (5.7-10L/kg) (McGilveray, 2005, Landa et al 2018). About 95-99% of THC is plasma protein bound (Grotenhermen, 2003). THC binds to fatty tissues and quickly

penetrates into high vascularised tissues including heart, fat tissue, lung, liver and brain then into less vascularised tissues (Grotenhermen, 2003; Lucas et al, 2018). THC can cross the blood-brain barrier and placenta and is excreted into breast milk. The concentration of THC in foetus blood is lower than in maternal plasma and tissues, it is assumed to be one-tenth following oral administration (Grotenhermen, 2003; Huestis, 2005; McGilveray, 2005; Northrup et al, 2017; Baker et al, 2018; Grant et al, 2018). Only about 1% of THC can be found in the brain, this low concentration could be due to the high perfusion rate of the brain causing rapid movement of THC into and out of the brain (Grotenhermen, 2003; Grotenhermen, 2004a; McGilveray, 2005). Distribution of CBD is also affected by its lipophilicity and has a high volume of distribution (32 L/kg). CBD rapidly penetrates the brain, adipose tissue and other organs (Devinsky et al, 2014).

Chronic regular administration of cannabinoids precipitates accumulation in tissues over time and may increase the volume of distribution (Kalant, 2001; Devinsky et al, 2014; Landa et al, 2018). Distribution of cannabinoids can be influenced by body size and composition and by any factor which may disturb the permeability of blood-tissue barriers such as the disease state (Landa et al, 2018; Lucas et al, 2018).

1.6.3 Metabolism

Cannabinoids are mainly metabolised by the liver and a lesser portion by extra-hepatic metabolism in tissues including brain, intestine and lung (Huestis, 2005). Different metabolites prevail, based on the administration route used to deliver cannabinoids (McGilveray, 2005). Hepatic metabolism of THC mainly occurs via cytochrome P450 (CYP 450) isoenzymes CYP2C9, CYP2C19 and CYP3A4. Metabolism of THC is complex, involving oxidation, epoxidation and decarboxylation followed by conjugation. Nearly 100 THC metabolites were found in humans. Hydroxylation of THC leads to the

formation of the 11-hydroxy-THC (11-OH-THC) metabolite and oxidation results in 11-carboxy-THC (THC-COOH), the two major metabolites of THC (Figure 1.2). This is followed by glucuronidation to 11-nor-9-carboxy-THC glucuronide and excretion. Extra-hepatic metabolism of THC takes place in tissues which expresses CYP 450 (Grotenhermen, 2003; Cho et al, 2005; Lucas et al, 2018). CBD is also metabolised hepatically by oxidation and hydroxylation processes via CYP 450 isoenzymes CYP2C19 and CYP3A4, then undergoes further metabolization and excretion (Huestis, 2005; Devinsky, 2014; Lucas et al, 2018; Gonçalves et al, 2019).

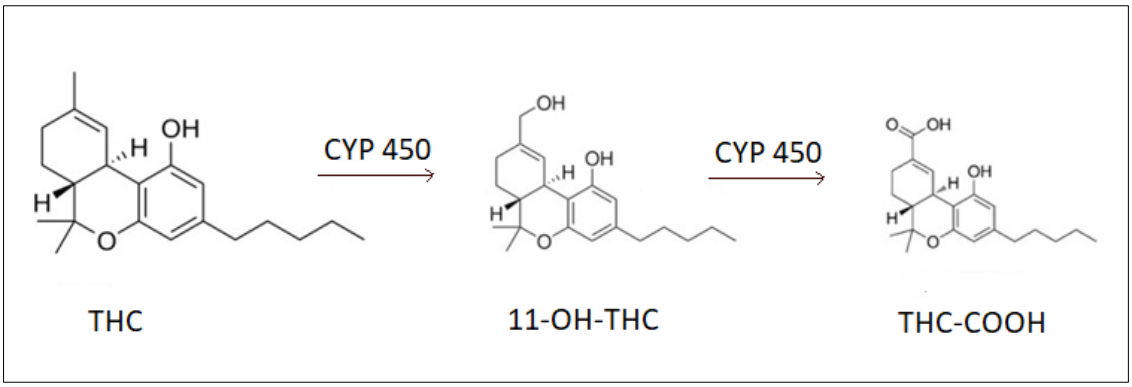

Figure 1. 2 Metabolites of THC (Adopted from: Gonçalves J, Rosado T, Soares S, Simão AY, Caramelo D, Luís Â, et al. Cannabis and its secondary metabolites: their use as therapeutic drugs, toxicological aspects, and analytical determination. Medicines (Basel). 2019;6(1):31.)

1.6.4 Elimination

The metabolites of THC are excreted in the faeces (65%) and urine (20%) when administered orally (McGilveray, 2005). Elimination of 80% to 90% of THC occurs within 5 days. Acidic metabolites which are found in urine as glucuronic acid conjugates improve water solubility. The acid-linked THC-COOH glucuronide conjugate is excreted in urine, while 11-OH-THC metabolite is excreted in the faeces (Huestis, 2005).

Elimination of metabolites after smoked or injected THC takes place within 72 hours from administration, where 13-17% of the administered dose is excreted in urine and 25-30% in the faeces (Kalant, 2001). Biliary excretion is considered as the major route of elimination for orally administered THC and its metabolites (McGilveray, 2005). Ten to fifteen percent of the oral dose is excreted in the urine within 72 hours of administration, while 48-53% is excreted via faeces and less than 5% is excreted unchanged in the faeces (Kalant, 2001; McGilveray, 2005).

The elimination half-life of THC ranges between 25 to 36 hours and that of its metabolites, 11-OH-THC and THC-COOH, ranges between 12 to 36 hours and 25 to 55 hours respectively after oral or intravenous administration (Kalant, 2001; Grotenhermen, 2003). The elimination half-life of CBD is different following intravenous injection (18 to 32 hours), inhalation or smoking (27 to 35 hours) and after repeated daily oral administration (2 to 5 days) (Zhornitsky & Potvin, 2012; Devinsky, 2014; Lucas et al 2018). The slow elimination of THC may be attributed to a delayed THC redistribution from body fat and other tissues into the blood (Grotenhermen, 2003). Low levels of cannabis metabolites can be traced in urine and faeces, for more than five weeks following the administration of a single dose of oral THC (McGilveray, 2015). The elimination half-life of cannabis in heavy users is longer (Lucas et al, 2018).

1.7 Pharmacokinetics, Advantages and Disadvantages of Cannabinoid Delivery Systems

A summary of the pharmacokinetics (PK) and the advantages and disadvantages of each delivery mode of cannabis are presented in Table 1.6. The summary of PK profile includes absorption, bioavailability (BA), onset of the effect, peak effect and duration of the desired effect.

Table 1. 6 Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Smoking	Absorption: 10-60% THC BA: 2-56% CBD BA: 6-31% Onset of effect: within seconds Peak effect: 10 minutes Duration of effect: 1-4 hours	Dose self-titrating possibility Easy to administer Rapid onset of effect, as rapid as intravenous route Efficient delivery Higher bioavailability than oral forms Similar pharmacokinetic profile as intravascular route	Irritation of lungs and mucosa Risk to the respiratory health Release of toxic by-products Short duration of effect Absorption can be affected by inhalation technique Inter-patient variability The accurate dosage may vary depending on the strain and source of the cannabis plant Smell	Kalant, 2001; Grotenhermen, 2003; Grotenhermen, 2004b; Chapkis & Webb, 2005; Huestis, 2005; McGilveray, 2005; Frederick et al, 2007; Huestis, 2007; Zhornitsky & Potvin, 2012; Murphy et al, 2015; Borodovsky et al, 2016; Peters et al, 2016; Shiplo et al, 2016; Ciccone, 2017; Kostygina et al, 2017; Romero-Sandoval et al, 2017; Bruni et al, 2018; Giovenco et al, 2018; Lucas et al, 2018; MacCallum & Russo, 2018

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Vaporisation (use of vaporisers or electronic cigarettes)	Similar PK profile as smoking	Alternative to smoking Minimized impact on respiratory health Less harmful by-products Taste better compared to smoking	Short duration of action Necessity of a device Inter-patient variability E-cigarette or vaping associated lung injury (EVALI) Popcorn lung (e-cig) Absorption may vary as the smoking route	Kalant, 2001; Mathre, 2002; McGilveray, 2005; Huestis, 2007; Borgelt et al, 2013; Borodovsky et al, 2016; Hindocha et al, 2016; Lanz et al, 2016; Peace et al, 2016; Shiplo et al, 2016; Varlet et al, 2016; Lippmann & Singh, 2017; Romero-Sandoval et al, 2017; Lucas et al, 2018; Kalininskiy et al, 2019; Tanne, 2019; Blount et al, 2020; Christiani, 2020
Inhalation (use of inhalers or nebulisers)	Similar PK profile as smoking	Alternative to smoking and vaping Minimized impact on respiratory health Smoke-free, no smell, better taste than smoking Only inhalation method does not heat cannabis (nebuliser)	Short duration of action Necessity of a device Inter-patient variability Absorption may vary as the smoking route	Grinspoon, 2000; Kalant, 2001; Mathre, 2002; Grotenhermen, 2004a; McGilveray, 2005; Huestis, 2007; Eisenberg et al, 2014; Borodovsky et al, 2016; Shiplo et al, 2016; Romero-Sandoval et al, 2017; Lucas et al, 2018; MacCallum & Russo, 2018; Christiani, 2020

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Oral	Absorption: 2-14% THC BA: 5-10% CBD BA: 6-31% Onset of effect: 30-90 minutes Peak effect: 2-3 hours Duration of effect: More than 6 hours	Accurate doses and concentrations Simple route of administration Longer duration of action than inhalation forms	Slow erratic and variable absorption Delayed onset of action Extensive first-pass liver metabolism Unpredictable psychotropic effects	Grotenhermen, 2003; Grotenhermen, 2004a; Huestis, 2005; McGilveray, 2005; Karschner et al, 2011; Zhornitsky & Potvin, 2012; Lile et al, 2013; Heuberger et al, 2015; Abrams, 2016; Benjamin & Fossler, 2016; Borodovsky et al, 2016; Parikh et al, 2016; Badowski, 2017; Bridgeman & Abazia, 2017; Newmeyer et al, 2017b; Romero-Sandoval et al, 2017; Bruni et al, 2018; Landa et al, 2018; Lucas et al, 2018; Pelessi et al, 2018

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Intranasal	Rapid systemic delivery Fast onset of action No first-pass metabolism and irritation	Easy and pleasant mode of administration	May result in nasal irritation Nasal congestion may interfere with delivery of drug Frequent administration may lead to mucosal damage	Parvathi, 2012; Bryson & Sharma, 2017
Edibles	BA of 20 mg THC cookie: 6% Onset of effect: 1- 4 hours (variable) Duration of effect: More than 8 hours	Long period of duration of effects Variety in formulations (added in baked products, candies, and drinks) Taste, no smell Less intense high	Delayed and variable onset and duration of effect Absorption can be affected by recent meal Less accurate dosing titration, easy to overdose, serving size Oily base is necessary to extract cannabis from the plant material	McGilveray, 2005; Zhornitsky & Potvin, 2012; Murphy et al, 2015; Borodovsky et al, 2016; Newmeyer et al, 2017b; Bruni et al, 2018; Giombi et al, 2018; Lucas et al, 2018; Pellesi et al, 2018; Webb, 2018; Grewal & Loh, 2020[9]

[9] Connely D. A quick guide to medical cannabis. The Pharmaceutical Journal. 2018;301(7915) [cited 2020 Jan 5]. Available from URL: https://www.pharmaceutical-journal.com/news-and-analysis/infographics/a-quick-guide-to-medical-cannabis/20205224.article?firstPass=false

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Buccal/ sublingual	Similar PK profile as oral route Onset of effect for buccal: 5-40 minutes Onset of effect for sublingual: 15-45 minutes Duration of sublingual: 6-8 hours	Avoid first pass metabolism Fast onset of action High bioavailability Self-titration possibility of dose Less psychotropic effects compared to smoked cannabis Adverse effects generally resolve	Slower onset of action compared to inhalation PH of the saliva may influence the drug absorption May cause xerostomia, dental carries, white lesions, oral burning sensation	Mathre, 2002; Grotenhermen, 2004a; Guy & Robson, 2004; Scully, 2007; Karschner et al, 2011; Klumpers et al, 2012; Wade, 2012; Stott et al, 2013; Devinsky et al, 2014; Crowley et al, 2018; Landa et al, 2018; Lucas et al, 2018; Hua, 2019[9]
Rectal	Twice as high systemic bioavailability compared to oral form Peak effect: 2-8 hours BA: 13.5% (may vary)	Can be indicated for specific patient population (palliative care, gastro-intestinal symptoms, patients unable to take oral or inhalation formulations, paediatric or elderly)	Less practical and preferred	Brenneisen et al, 1996; Kalant, 2001; Grotenhermen, 2003; Grotenhermen, 2004a; Huestis, 2005; McGilveray, 2005; Landa et al, 2018; MacCallum & Russo, 2018; Mouhamed et al, 2018

[9] Connely D. A quick guide to medical cannabis. The Pharmaceutical Journal. 2018;301(7915) [cited 2020 Jan 5]. Available from URL: https://www.pharmaceutical-journal.com/news-and-analysis/infographics/a-quick-guide-to-medical-cannabis/20205224.article?firstPass=false

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Topical	Slow permeation across skin layers Variable onset Delayed absorption	Reduction in side effects experienced with systemic formulations Ideal for localised dermatologic conditions	Local irritation Useful only treating localised symptoms May accumulate on skin layer	Grotenhermen, 2004a; Bruni et al, 2017; Hess et al, 2017; Lucas et al, 2018; MacCallum & Russo, 2018
Transdermal	Very delayed absorption Onset of effect THC: 17 hours, CBD: 24 hours Duration of effect THC: 14 hours, CBD: up to 72 hours	Avoids the first-pass metabolism Prolonged period of time for drug delivery Minimised adverse effect profile Ideal for localised treatments Convenient for treating conditions including, nausea, vomiting and anorexia	Local irritation possibility Need of carrier Hydrophobic nature limits permeation through aqueous skin layers, penetration enhancers are needed to improve the penetration and increase solubility	Grotenhermen, 2004a; Bruni et al, 2017; Lucas et al, 2018

Table 1.6 *(cont.)* Pharmacokinetics, advantages and disadvantages of cannabinoid delivery systems

Delivery mode	Pharmacokinetics	Advantages	Disadvantages	References
Ophthalmic	6-40% BA Peak effect: 1 hour Duration of effect: several hours	Local effect No psychotropic effects	Need for carrier or prodrug	Kalant, 2001; Grotenhermen, 2003; Grotenhermen, 2004a; Mouhamed et al, 2018
Systemic	Onset of action: within seconds Duration of effect: within 4 hours High BA	Fast onset of action Possibility to administer unconscious patients	Invasive method Least preferred route Only possible with aqueous synthetic cannabinoids	Kalant, 2001; Tramèr et al, 2001; Grotenhermen, 2004a; Bridgeman, 2017

1.8 Pharmacodynamics of Cannabinoids

Cannabis exerts an anti-inflammatory, antiviral and antitumor effect (Whyte et al, 2010; Hernán Pérez de la Ossa et al, 2013; Godsey & Grundmann, 2016; Parmar et al, 2016; Erices et al, 2018; Jin & Lee, 2018). It can be used in hard to treat conditions or rare diseases when the standard therapeutic options have failed to be effective or when risks outweigh the benefits (MacCallum & Russo, 2018; Sagy et al, 2018).

As Bifulco and Pisanti (2015) stated that *"there is no unique list of pathologies that can be treated with cannabis-based drugs, since it is not a cure, but rather a palliative treatment. It is up to physicians to decide under which circumstances cannabis should be prescribed and which patients could benefit from the treatment".* Cannabinoids has been used for the treatment of various health conditions (Table 1.7), including the treatment of dermatological conditions using topical formulations (Table 1.8).

Table 1. 7 Health Conditions Treated with Cannabinoids

Health Condition	References
Acquired Immunodeficiency Syndrome (AIDS) and weight loss in AIDS	Lutge et al, 2013; Bifulco & Pisanti, 2015
Addictions	Panlilio et al, 2013; Fraguas-Sánchez & Torres-Suárez, 2018
Attention deficit hyperactivity disorder (ADHD)	Loflin et al, 2014
Alzheimer's disease	Fraguas-Sánchez & Torres-Suárez, 2018
Amyotrophic lateral sclerosis	Williams et al, 2016
Anorexia	Parikh et al, 2016; Reuter & Martin, 2016; Bruni et al, 2018
Anxiety	Schier et al, 2012; Buckner & Zvolensky, 2014; Fraguas-Sánchez & Torres-Suárez, 2018
Asthma	Caligiuri et al, 2018
Cancer pain	Johnson et al, 2010; Bar-Lev et al, 2018
Chemotherapy-induced nausea and vomiting (CINV)	Tramèr et al, 2001; Machado et al, 2008; Lynch et al, 2014; Smith et al, 2015; Punyamurthula et al, 2016; Agar, 2018; Fraguas-Sánchez & Torres-Suárez, 2018

Table 1.7 *(cont.)* Health Conditions Treated with Cannabinoids

Health Condition	References
Chronic pain	Ogborne et al, 2000; Lynch & Campbell, 2011; Lucas, 2012; Romero-Sandoval et al, 2017; Romero-Sandoval et al, 2018; Sagy et al, 2018; Philpot et al, 2019
Chron's disease	Naftali et al, 2011; Schicho & Storr, 2014; Abuhasira et al, 2018a
Dravet syndrome	Wirrell et al, 2017; McCoy et al, 2018
Epilepsy and seizures	Welty et al, 2014; Tzadok et al, 2016; Treat et al, 2017; McCoy et al, 2018
Fibromyalgia	Skrabek et al, 2008; Staud & Koo, 2008; Fiz et al, 2011; Fitzcharles et al, 2016a
Headache	Pellesi et al, 2018; Corroon et al, 2019
Human Immunodeficiency Virus (HIV)	Lutge et al, 2013
Huntington's disease	Fraguas-Sánchez & Torres-Suárez, 2018
Infection	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Inflammation	Corroon et al, 2019; Lim & Kirchhof, 2019
Inflammatory skin diseases	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Lennox-Gastaut syndrome	Barrack & Chamberlin, 2018
Lou Gehrig's Disease	Williams et al, 2016
Mood disorders	Zuardi et al, 2006; Sexton et al, 2016
Multiple sclerosis	Indorato et al, 2016; Szaflarski & Sirven, 2017; Landa et al, 2018
Muscle spasms	Parmar et al, 2016
Neuropathic pain	Fine & Rosenfeld, 2014; Grant et al, 2015; Lee G, 2018; MacCallum & Russo, 2018
Nonspecific pain	Abuhasira et al, 2018a; Splinter, 2019
Parkinson's disease	Fraguas-Sánchez & Torres-Suárez, 2018
Postoperative pain	Aviram & Samuelly-Leichtag, 2017
Post-traumatic stress disorder	Williams et al, 2016; Fraguas-Sánchez & Torres-Suárez, 2018
Schizophrenia	Leweke et al, 2012; Bruni et al, 2018
Shingles	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Skin cancer	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Sleeping problems	Webb & Webb, 2014; Parmar et al, 2016
Spastic conditions	Landa et al, 2018
Terminal illnesses	Bifulco & Pisanti, 2015; Williams et al, 2016
Tourette syndrome	Fraguas-Sánchez & Torres-Suárez, 2018
Ulcerative colitis	Abuhasira et al, 2018a

Table 1. 8 Dermatologic Conditions Treated with Topical Cannabinoids

Dermatologic condition	References
Acne	Oláh et al, 2014; Ali & Akhtar, 2015; Jin & Lee, 2018
Aging	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Alopecia	Telek et al, 2007; Tóth et al, 2019
Arthritis	Fukuda et al, 2014; Fitzcharles et al, 2016a
Bruising	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Cosmesis	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Dermatitis	Callaway et al, 2005; Nam et al, 2016; Scheau et al, 2020
Dryness	Oláh et al, 2016; Zákány et al, 2018
Eczema	Mounessa et al, 2017; Lim & Kirchhof, 2019
Ehlers-Danlos syndrome	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Glaucoma	Punyamurthula et al, 2017
Hirsutism	Telek et al, 2017; Tóth et al, 2019
Infections	Appendino et al, 2008; Lim & Kirchhof, 2018
Inflammations	Nam et al, 2016; Mounessa et al, 2017; Oláh & Bíró; 2017
Lupus	Nagarkatti et al, 2009
Lyme disease	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Nail-patella syndrome	Dhadwal & Kirchhof, 2018
Neurofibromatosis	Dhadwal & Kirchhof, 2018
Pain	Flores et al, 2012; Lim & Kirchhof, 2019
Pigmentation disorders	Tóth et al, 2019
Pruritus	Ho et al, 2019
Psoriasis	Wilkinson & Williamson, 2007; Mounessa et al, 2017
Scars	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Scleroderma	del Río et al, 2016; Scheau et al, 2020
Sjögren syndrome	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019
Skin cancer	Armstrong et al, 2015
Skin healing	Chelliah et al, 2018
Skin irritation	Ali & Akhtar, 2015
Sun burns	Moore et al, 2013
Warts	Lim & Kirchhof, 2018; Lim & Kirchhof, 2019

Efficacy of cannabis can be associated to its formulation and THC/CBD content (Rubens, 2014). The benefits and risks of cannabinoids are dependent on the product, dose administered, duration of utilisation and the patient population.[10]

Scientific evidence is suggesting the effectiveness of medicinal cannabinoids in the following conditions:[10,11]

1. Spasticity in multiple sclerosis resistant to all standard therapies and interventions (Koppel et al, 2014; Whiting et al, 2015; Freeman et al, 2019)
2. Chemotherapy-induced nausea and vomiting despite the use of standard anti-emetic regimes[3] (Whiting et al, 2015; Freeman et al, 2019)
3. Chronic pain despite standard therapies (Koppel et al, 2014; Whiting et al, 2015; Freeman et al, 2019)
4. Severe treatment-resistant epilepsy that has failed to respond to standard anticonvulsant medications (Freeman et al, 2019)

[3]U.S. Food & Drug Administration (FDA). FDA and cannabis: research and drug approval process. [Internet]. USA: FDA; 2020 [cited 2020 Jan 20]. Available from URL: https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process

[10] Health Products Regulatory Authority. Cannabis for medical use - a scientific review [Internet] Ireland: 2017 [cited 2020 Jan 20]. Available from URL: https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7

[11] Health Canada. Information for health care Professionals [Internet]. Ottawa: Health Canada; 2018 [cited 2020 Jan 20]. Available from URL: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf

Clinical trials for cannabis use in chronic pain, include a variety of conditions such as cancer pain, neuropathic pain and fibromyalgia. Buccal spray formulations containing THC and CBD were observed to have clinically promising effectiveness for the treatment of chronic neuropathic pain or non-cancer pain.[12]

There is currently no evidence supporting the benefit in treating cancer, despite anecdotal reports or animal studies[10] (Fraguas-Sánchez & Torres-Suárez, 2018). The evidence is limited to support the benefit of cannabis in other conditions such as appetite stimulation in AIDS, Parkinson's disease, Alzheimer's disease, depression, dementia, sleep disorders, inflammatory disorders such as Crohn's disease, rheumatoid arthritis, ulcerative colitis, glaucoma, anxiety or post-traumatic stress disorder[11] (Fraguas-Sánchez & Torres-Suárez, 2018).

Common side effects of cannabinoids include dizziness, drowsiness, disorientation, dry mouth, fatigue, somnolence, red eyes, nausea (Borràs et al, 2011; Kraft, 2012; Ware et al, 2015; Birdsall et al, 2016; Joshi & Ashley, 2016; Babalonis et al, 2017), vomiting, relapsing of MS, urinary tract infections, confusion and hallucination (Whiting et al,

[10] Health Products Regulatory Authority. Cannabis for medical use - a scientific review [Internet] Ireland: 2017 [cited 2020 Jan 20]. Available from URL: https://www.hpra.ie/docs/default-source/publications-forms/newsletters/cannabis-for-medical-use---a-scientific-review.pdf?sfvrsn=7

[11] Health Canada. Information for health care Professionals [Internet]. Ottawa: Health Canada; 2018 [cited 2020 Jan 20]. Available from URL: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-medication/cannabis/information-medical-practitioners/information-health-care-professionals-cannabis-cannabinoids-eng.pdf

[12] Canadian Agency for Drugs and Technologies in Health (CADTH). Cannabinoid buccal spray for chronic non-cancer or neuropathic pain: a review of clinical effectiveness, safety, and guidelines. 2016: Final report [Internet]. Ottawa (ON): CADTH; 2016 [cited 2020 Jan 20]. Available from URL: https://www.ncbi.nlm.nih.gov/books/NBK395789/

2015; Bridgeman & Abazia, 2017) and euphoria (Pearce et al, 2014; Ware et al, 2015; Babalonis et al, 2017).

Short-term use of cannabis may impair short-term memory and motor coordination, alter judgment and may lead to anxiety (Gomes et al, 2011; Cox, 2015; Bridgeman & Abazia, 2017) and paranoia (Freeman et al, 2013; Ware et al, 2015) or psychosis at high doses (Fridberg et al, 2011; Wolff & Johnston, 2014; Abrams, 2019; Mensen et al, 2019). THC can induce tachycardia and orthostatic hypotension (Grotenhermen, 2004b; Bridgeman & Abazia, 2017; Fischbach, 2017).

Long-term or heavy use of cannabis in individuals who begin at early age may lead to addiction, altered brain development, cognitive impairment and mood disturbances in persons with a predisposition, poor educational outcomes, impulsive decision making, reduced life satisfaction, stroke and ischemic attack (Crean et al, 2011; Solowij et al, 2012; Bridgeman & Abazia, 2017; Schauer et al, 2017). Long-term use of THC may be associated with cardiovascular conditions including bradycardia and myocardial infarction as well as respiratory event like chronic bronchitis (Grotenhermen, 2004b; Khullar et al, 2014; Bridgeman & Abazia, 2017; Fischbach, 2017; DeFilippis et al, 2020).

Cannabinoid tolerance has shown to affect nociception, hypolocomotion, catalepsy, hypothermia, impairment in learning and memory and neuroendocrine effects (Martin, 2005; McKinney et al, 2008; McMahon, 2011; Singh et al, 2011; Panlilio et al, 2013).

Discontinuation of cannabis may result in withdrawal symptoms, including drug craving, gastrointestinal symptoms, sleep disturbances, irritability, restlessness, nervousness, anxiety and aggression (Haney et al, 1999a; Haney et al, 1999b; Budney et al, 2004; Panlilio et al, 2013; Herrmann et al, 2015).

Co-administration of ketoconazole with cannabis products containing THC and CBD results in an increase in the maximum serum concentration in cannabinoids, by 1.2-fold to 1.8-fold for THC and by 2-fold for CBD (Bridgeman & Abazia, 2017). Co-administration of rifampin may result in reduced THC and CBD levels (Bridgeman & Abazia, 2017).

1.9 Approved Formulations of Medicinal Cannabis

There are various medicinal cannabis formulations approved worldwide. The CBD-based oral solution derived from pure plant, and marketed as Epidiolex® was approved for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients of two years and older. Lennox-Gastaut and Dravet Syndromes are the severe forms of seizure which arise in childhood[13] (Barrack & Chamberlin, 2018; Fraguas-Sánchez & Torres-Suárez, 2018).

The oro-mucosal spray nabiximol, marketed as Sativex® has been approved for use in spasticity due to multiple sclerosis and neuropathic pain, when previous treatments have failed. This liquid formulation contains THC and CBD at a ratio of 1:1 (Karschner et al, 2011; Abuhasira et al, 2018b; Barrack & Chamberlin, 2018; Bruni et al, 2018; Fraguas-Sánchez & Torres-Suárez, 2018; Freeman et al, 2019).

[13] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Medical use of cannabis and cannabinoids [Internet]. Lisbon: EMCDDA; 2018 [cited 2020 Jan 22]. Available from URL: https://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf

Two formulations containing the synthetic Δ^9-THC dronabinol, the oral capsule marketed as Marinol® and the oral solution marketed as Syndros®, have been approved by FDA[3] (Badowski, 2017). The main indications for use are anorexia associated with weight loss in patients with AIDS, CINV and neuropathic pain after previous treatments have failed (Karschner et al, 2011; Lee & Huestis, 2014; Parmar et al, 2016; Abuhasira et al, 2018b; Barrack & Chamberlin, 2018; Fraguas-Sánchez & Torres-Suárez, 2018).

The oral capsules containing the synthetic cannabinoid nabilone, marketed as Cesamet® and Canemes®, are indicated for the treatment of chronic pain, fibromyalgia pain, neuropathic pain and CINV (Badowski, 2017) after the failure or intolerance of previous treatments (Parmar et al, 2016; Tsang & Giudice, 2016; Ciccone, 2017; Abuhasira et al, 2018b; Fraguas-Sánchez & Torres-Suárez, 2018).

Cannabis flowers, marketed as Bedrocan® and Pedanios® have been approved in Europe to treat various conditions including pain, insomnia, stress, multiple sclerosis and depression (Chiurchiù et al, 2018; Fraguas-Sánchez & Torres-Suárez, 2018). The formulations of medicinal cannabis flowers vary depending on the THC and CBD ratio. Bedrocan® is derived from the Sativa species which contains 19% of THC and less than 1% of CBD.[13] Medicinal cannabis flowers can be administered via inhalation or orally such as by adding it to food or taken as tea (Barrack & Chamberlin, 2018; Chiurchiù et al, 2018; Fraguas-Sánchez & Torres-Suárez, 2018).

[3] U.S. Food & Drug Administration (FDA). FDA and cannabis: research and drug approval process. [Internet]. USA: FDA; 2020 [cited 2020 Jan 22]. Available from URL: https://www.fda.gov/news-events/public-health-focus/fda-and-cannabis-research-and-drug-approval-process

[13] European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Medical use of cannabis and cannabinoids [Internet]. Lisbon: EMCDDA; 2018 [cited 2020 Jan 22]. Available from URL: https://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf

Cannabis extracts, marketed as Tilray®, are formulated at different ratios of THC and CBD as an oral solution or capsules. They are indicated for the treatment of various conditions including pain, insomnia, stress, multiple sclerosis and depression (Fraguas-Sánchez & Torres-Suárez, 2018).

1.10 Physico-chemical Properties of Cannabinoids and their formulation

Cannabinoids are highly lipophilic molecules and have very low water solubility. The physico-chemical characteristics of cannabis is complex (Bruni et al, 2018; MacCallum & Russo, 2018).

Poor bioavailability of cannabinoids may result in ineffective therapy, side effects as well as the need for higher doses. Specific formulations are needed to enhance the bioavailability of cannabinoids. CBD is less lipophilic compared to THC (Lucas et al, 2018). Stability is another concern as THC is an amorphous molecule. Liquid formulations can easily undergo degradation due to the effects of temperature, light and auto-oxidation (Bruni et al, 2018). Permeation ability of THC is 10-fold slower than the CBD (Grotenhermen, 2004a; Bruni et al, 2018; Lucas et al, 2018).

According to the FDA biopharmaceutical classification system (BCS) of drugs[14] cannabis (dronabinol) was considered as a class 2 or 4 drug, which have low solubility with an unknown permeability resulting in poor bioavailability (Jain et al, 2012). The physico-chemical profile of cannabis lead to challenges when formulating this drug for

[14] US Food & Drug Administration (FDA). Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms based on a biopharmaceutics classification system guidance for industry [Internet]. New Hampshire: FDA; 2017 [cited 2020 Jan 23]. Available from URL: https://www.fda.gov/media/70963/download

different routes of delivery (Jain et al, 2012; Bruni et al, 2018; MacCallum & Russo, 2018).

Formulation may play a critical role in physicochemical stability and solubility of drugs and to overcome challenges related to the physicochemical characteristics of drugs. Possible strategies to enhance physicochemical properties of poorly soluble substances like cannabinoids, include salt formation via pH adjustment, addition of cosolvents (ethanol, propylene glycol and PEG400), micellization (polysorbate 80, cremophor ELP), nano-micro-emulsification, complexation with cyclodextrins, solid dispersion (fusion or solvent method) and encapsulation in liposomes, nanoparticles and solid lipid nanoparticles (Banga, 2006; Zhang et al, 2006; Jain et al, 2012; Durán-Lobato et al, 2016; Bruni et al, 2018).

Particle size reduction is a known method in enhancing dissolution rates. Nanoparticles (10–100nm) can easily penetrate and allow efficient delivery of drug at the target sites. Biodegradable nanoparticles can enable sustained release of the drug within the target site for an extended period of time (Azad & Rojanasakul, 2006; Kawabata et al, 2011; Jain et al, 2012). Solid dispersion is forming of eutectic mixtures of drugs with water-soluble carriers, this is done by melting of the mixtures to be able to dissolve the carriers which will lead to precipitation of the drug in a finely divided state in water (Jain et al, 2012). The use of cross linking and barrier forming polymers as an excipient, may improve the stability of solid formulations of THC and introducing a lipid matrix may enhance the bioavailability of THC (Punyamurthula et al, 2016). Bioavailability of cannabinoids was found to be higher in oil formulations than in decoction forms. Bioavailability can be improved by formulation of cannabinoids in oil such as sesame oil and glycocholate (Grotenhermen, 2003; Grotenhermen, 2004a; Huestis, 2005; Heuberger et al, 2015; Newmeyer et al, 2016; Pellesi 2018).

Modified release formulations may help achieving effective treatment and protecting patients from side effects. For example, by maintaining a suitable level of THC in the plasma and reducing the concentration of THC psychoactive metabolite in the plasma, the psychiatric side effects of THC could be reduced (Punyamurthula et al, 2016; Siew, 2017).

Cannabinoid prodrugs can be advantageous in providing gastro-resistant formulations and preventing narcotic effects. Self-emulsifying drug delivery systems (SEDDS) are the isotropic mixtures of oils (soybean and sesame oils, oleic acid), surfactants (oleoyl polyoxyl-6 glycerides, medium-chain mono-glycerides and di-glycerides, PEG hydrogenated castor oil, propylene glycol esters), solvents and co-solvents. SEDDS can be used in oral formulations to improve absorption, dissolution, stability and bioavailability of highly lipophilic cannabinoids (Šoltýsová et al, 2016; Bruni et al, 2018).

Oral administration of cannabinoids undergoes first-pass liver metabolism, resulting in poor gastrointestinal permeability. Designing nasal, inhaled-pulmonary, transdermal and oral transmucosal delivery formulations may facilitate drug uptake and bypass the first-pass metabolism. Administration through intra-nasal cavity delivers the drug directly into the systemic circulation. These formulations could be beneficial for patients having nausea, vomiting, oral mucositis and impaired gastrointestinal function (Bruni et al, 2018). Paudel et al (2010) prepared formulations of CBD in PEG400 and PEG/saline/ethanol solvents and used permeation enhancers such as 1% sodium glycocholate or 1% dimethyl-beta-cyclodextrin for intranasal administration and absorption was significantly improved (Bruni et al, 2018). Bryson and Sharma (2017) have represented nasally administered semi-solid and liquid cannabinoid formulations as well as devices which provide precise nasal administration.

The use of Δ^8-isomer for topical formulations, rather than Δ^9-isomer of THC, improves permeability (Touitou et al, 1988). Producing hydrophilic prodrugs, micellar solutions and emulsion formulations using valine, dipeptides or amino acid-dicarboxylic esters provide improved corneal permeability for topical ophthalmic THC preparations (Bruni et al, 2018).

1.11 History of Medicinal Cannabis in Malta

The use of cannabis for medicinal purposes was legalised in Malta in March 2015, when the 'Drug Dependence (Treatment not Imprisonment) Act' was launched and amended in 2018.[15] The Act entitled licenced medical practitioners who are registered in accordance with the Health Care Professions Act, to prescribe medicinal cannabis. Medicinal cannabis preparations must be licensed under the Medicines Act or manufactured under Good Manufacturing Practice. The use of medicinal cannabis can be an option if no alternative is found, despite other protocols. Smoking forms of cannabis are prohibited.

In April 2018, the 'Production of Cannabis for Medicinal or Research Purposes Act' was launched by the Maltese Parliament, which sets guidelines on the production of cannabis for medicinal and research purposes in Malta.[16] Necessary approvals, authorisations, licences and permits need to be obtained as required and under all applicable laws for cultivation, importation, processing and production of cannabinoids for medicinal and research purposes.[15]

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[15] The Drug Dependence (Treatment not Imprisonment) Act of 2015, Malta Medicines Authority [cited 2020 Jan 25]. Available from URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=12289&l=1

[16] The Production of Cannabis for Medicinal and Research Purposes Act of 2018, Malta Medicines Authority [cited 2020 Jan 25]. Available from URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=12821&l=1

Pedanios (22/1, 20/1 ratios of THC/CBD), Bedrocan (22 THC, less than 1 CBD) and Bediol (6/8 ratios of THC/CBD) flowers were approved for medicinal purposes in Malta.[17,18,19] CDB oil is not approved locally. Patients can access their medicinal cannabis preparations from a licenced pharmacy by presentation of a green prescription, control card and approval from the Superintendent of Public Health.[20]

1.12 Aim and Objectives

The aims and objectives of this study were (i) to evaluate delivery systems used for medicinal cannabis and patient preferences for delivery approaches using two self-administered questionnaires, one addressed to medicinal cannabis users and another one for potential users of medicinal cannabis (ii) to review studies focusing on medicinal cannabis dosage forms and opinions of medicinal cannabis users about cannabis dosage forms.

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[17] Ohle M. Aurora cannabis to supply medical cannabis to Malta [Internet]. Pot Stock News; 2018 [cited 2020 Jan 25]. Available from URL: https://potstocknews.com/aurora-supplies-medical-cannabis-malta

[18] Pascual A. Cannabis applications in Malta await guidelines from government. Marijuana Business Daily, 2018 [cited 2020 Jan 25]. Available from URL: https://mjbizdaily.com/cannabis-applications-in-malta-await-guidelines-from-government/

[19] The Pain Clinic. THC [Internet]. Malta: Pain Clinic; 2017 [cited 2020 Jan 25]. Available from URL: http://www.painclinic.com.mt/thc/

[20] Superintendent of Public Health SPH Circular Prescribing and dispensing of medical cannabinoids 2018 [Internet]. Malta: [cited 2020 Jan 25]. Available from URL: https://deputyprimeminister.gov.mt/en/Pharmaceutical-Unit/Documents/Circulars/SPH_Circular_2-2018.pdf

2. Methodology

2.1 Study Design

The study was divided into 2 parts. The first part entailed a prospective cross-sectional study which assessed the perception of users and potential users of medicinal cannabis in Malta. The second part of the study consisted of a systematic review about cannabis dosage forms.

2.2 Part I - Development of the Questionnaires

Two self-administered questionnaires were developed, one for medicinal cannabis users and another one for potential users of medicinal cannabis. The questionnaires aimed to evaluate the perception of patients about existing delivery methods used for medicinal cannabis and their preferred methods of administration. The questionnaires were developed in both English and Maltese languages.

Development of the questionnaires was based on comprehensive literature review to determine pharmacokinetics and pharmacodynamics of cannabis, accessible dosage forms of medicinal cannabis in Malta and existing dosage forms worldwide.

2.2.1 Questionnaire for Medicinal Cannabis Users

The questionnaire developed for medicinal cannabis users entitled 'Methods of Delivery for Medicinal Cannabis Users' (MDMCU – Appendix 1) is divided into 2 sections. The first section collected the demographic data such as age, gender, level of education, nationality and locality. Section two consisted of 13 questions which included 2 multiple choice questions to assess why they use medicinal cannabis (Bifulco & Pisanti, 2015; Parmar et al, 2016; Fraguas-Sánchez & Torres-Suárez, 2018; Landa et al, 2018; Lim & Kirchhof, 2018; MacCallum & Russo, 2018; McCoy et al, 2018) and side effects experienced when using their medication (Kalant, 2001; Pearce et al, 2014). Six questions

aimed at assessing the type of prescribed medicinal cannabis currently utilised[17,18,19] (Fraguas-Sánchez & Torres-Suárez, 2018), the period the patient was prescribed with medicinal cannabis[21], the onset of the desired effect, how long does the effect of their medication last (Kalant, 2001; Grotenhermen, 2003; Grotenhermen, 2004a; Karschner et al, 2011; Heuberger et al, 2015; Shiplo et al, 2016; Bridgeman & Abazia, 2017; Lucas et al, 2018) and to specify if they have tried other forms of medicinal cannabis other than the dosage form they are currently using. One five-point Likert scale question assessed how easy it is to administer medicinal cannabis with their current delivery system. Two open-ended questions evaluated whether participants would switch to another form of medicinal cannabis and reasons why. Two five-point Likert scale questions required participants to rate different dosage forms of medicinal cannabis according to their preference, one question consisted of dosage forms which are administered orally (Scully, 2007; Punyamurthula et al, 2017; Ciolino et al, 2018b; Crowley et al, 2018; Pelessi et al, 2018; Abd-Elsalam et al, 2019), rectally (Lim & Kirchhof, 2018) or systemically (Huestis, 2007), the other question included dosage forms applied topically (Ciolino et al,

[17] Ohle M. Aurora cannabis to supply medical cannabis to Malta [Internet]. Pot Stock News; 2018 [cited 2020 Feb 8]. Available from URL: https://potstocknews.com/aurora-supplies-medical-cannabis-malta

[18] Pascual A. Cannabis applications in Malta await guidelines from government. Marijuana Business Daily, 2018 [cited 2020 Feb 8] Available from URL: https://mjbizdaily.com/cannabis-applications-in-malta-await-guidelines-from-government/

[19] The Pain Clinic. THC [Internet]. Malta: Pain Clinic; 2017 [cited 2020 Feb 8]. Available from URL: http://www.painclinic.com.mt/thc/

[21] Pace M. Malta has officially legalised medical cannabis [Internet]. Maltatoday; 2018 [cited 2020 Feb 8]. Available from URL: https://www.maltatoday.com.mt/news/national/85616/malta_has_officially_legalised_medical_cannabis#.XTMJHegzY2w

2018a; Lim & Kirchhof, 2018) or via inhalation (Grotenhermen, 2003; Hazekamp et al, 2006; Huestis, 2007; Newmeyer et al, 2016; Lippmann & Singh, 2017).

An online version of the MDMCU questionnaire was developed using Google forms. This questionnaire was then translated into Maltese language and 'Metodi t'amministrazzjoni tal-kannabis mediċinali għall-utenti questionnaire' (Appendix 2) was developed. Translation was performed with assistance of Maltese nationals and using Maltese dictionary and 'Google Translate'.

2.2.2 Questionnaire for potential users of Medicinal Cannabis

The questionnaire developed for potential users of medicinal cannabis entitled 'Methods of Delivery for non-users of Medicinal Cannabis' (MDNMCU – Appendix 3) was based on the questionnaire developed for medicinal cannabis users and is divided into 2 sections. A demographic section and a section consisting of 13 questions. Eight questions assessed for which condition they would begin using medicinal cannabis, whether they are currently consuming pain medications and if yes how many, if they have ever tried cannabis and if yes, what form of cannabis they tried[7] and if cannabis assisted them to feel better. One five-point Likert scale evaluated, which pain intensity would require commencing the use of medicinal cannabis. Faces portraying pain were used to help in the understanding and rating of pain (Hicks et al, 2001). Two multiple choice questions aimed at assessing whether if presented with the opportunity to use medicinal cannabis, they would start using it or not and the reasons why.

[7] Botanic Alternatives CBD. Botanic alternatives cbd and cannabis accessories [Internet]. Chicago: IL;2014 [cited 2020 Feb 8]. Available from URL: https://www.botanicalternatives.com/

The remaining two questions required participants to rate numerous dosage forms of medicinal cannabis as per their preference if they were to use medicinal cannabis, this was separated according to method of administration as per in the users questionnaire.

The questionnaire for potential users was translated into Maltese language by using same sources as the medicinal cannabis users questionnaire and the 'Metodi t'amministrazzjoni tal-kannabis Mediċinali Questionnaire' (Appendix 4) was developed.

2.3 Validation of the Questionnaires

Validation of the questionnaires was conducted by a panel composed of six members including three doctors, one academic pharmacist, one statistician and one lay person. Content validation of the questionnaires in two versions (Maltese and English language) was performed using the Delphi Technique (Habibi et al, 2014), which comprised of two rounds. In the first round of the validation process, participants were requested to rate each question on relevance and level of agreement on a five-point Likert scale, where 1 corresponds to not relevant and strongly disagree and 5 corresponds to highly relevant and strongly agree (Habibi et al, 2014). Participants were requested to indicate any recommended changes and remarks following each question. Participants were provided two weeks to submit their feedback.

Suggested changes were accepted if the proposed changes facilitated the understanding of questions by participant or if proposed by a majority. Suggested changes were rejected when requested by the minority of the validation panel. Once the suggested changes were reviewed and incorporated, the questionnaires were re-sent one week apart for the second Delphi round. Accepted changes and the reason for rejections were emphasised when submitting the revised questionnaire to the validation panel. The second version of the questionnaires were approved by all the participants without any further suggestions.

2.4 Approvals

Approvals were sought prior to the dissemination of the questionnaires. Approvals were obtained from the Pain Clinic (Appendix 5) and Primary Health Care (Appendix 6) to carry out the research at these facilities. The study was also approved by the Faculty Research Ethics Committee (FREC) of the University of Malta (Appendix 7).

2.5 Dissemination of the Questionnaires

Questionnaires were disseminated at the Pain Clinic, Primary Health Care and online to patients attending these institutions. The selection criteria for MDMCU questionnaire encompassed patients who were prescribed with medicinal cannabis due to conditions which including chronic pain, chemotherapy-induced nausea and vomiting, spasticity in multiple sclerosis and treatment resistant epilepsy (Koppel et al, 2014; Whiting et al, 2015; Freeman et al, 2019). Patients who were considered as eligible prospective users of medicinal cannabis were selected for MDNMCU questionnaire. Prospective users had medical conditions for which medicinal cannabis is indicated and for which standard therapies had already been prescribed. Patients were identified and invited to take part in the study by the doctor when visiting the clinic. The MDMCU questionnaire was also distributed online to medicinal cannabis users by their doctor, using the Mailchimp account. The questionnaires were anonymous and participation was voluntary with the possibility to opt to leave the study at any point. Participants consented to take part in the study by answering the questionnaire. The questionnaires were disseminated between 25th September 2019 and 8th February 2020.

2.6 Analysis of the Data

The data collected from the questionnaires was statistically analysed using six different tests, namely the Friedman test, Post-hoc test, Mann-Whitney test, Kruskal-Wallis test, Proportion test and the Chi-squared test. The Friedman test was used to compare mean rating scores ranged from 1 to 5, where 1 corresponds to least preferred, and 5 corresponds to most preferred dosage form. The null hypothesis specifies that the mean rating scores are similar. Post-hoc analysis was performed as an extension to the Friedman test for making pairwise comparisons and see the differences in mean rating scores.

The Mann-Whitney test was used to compare the mean preference scores between two independent groups, such as users and potential users of medicinal cannabis. The mean preference scores ranged from 1 to 5, where 1 corresponds to least preferred, and 5 corresponds to most preferred dosage form. The null hypothesis specifies that the mean preference scores varies marginally between the two groups.

The Kruskal-Wallis test was used as an extension to the Mann-Whitney test, because it compares mean preference scores between several (more than two) independent groups such as age, level of education and locality. The null hypothesis specifies that the mean preference scores varies slightly.

Proportion test was used to compare differences between several (more than two) groups such as age and time period. The null hypothesis specifies that the proportions (probabilities) of cases are the same for each group.

The Chi-squared test was utilised to analyse the association between two nominal or categorical variables. The null hypothesis indicates that there is no association between the two variables. For all tests, the null hypothesis is accepted if the p-value was greater

than the 0.050 level of significance, indicating that there is no statistically significant difference. The alternative hypothesis specifies a significant association between the two variables and is accepted if the p-value is below the 0.050 criterion. Statistical analysis was conducted using SPSS software version 26 and RStudio software version 1.3.959.

2.7 Part II – Systematic Reviews

Two systematic reviews were conducted, one about medicinal cannabis dosage forms and another one about preferences of patients on cannabinoid dosage forms, to identify studies conducted regarding medicinal cannabis dosage forms.

2.7.1 General Systematic Review

An extensive literature review was carried out using HyDi, a tool offered by the University of Malta, which provides access to different databases, books, e-books, articles and digital media.

Articles about medicinal cannabis dosage forms were reviewed using the PRISMA flow chart method (Moher et al, 2009). The databases ProQuest Central, Natural Science Collection, PubMed/Medline, DOAJ, Elsevier and EBSCO host Medline were used for the study. Advanced search strategy included the key words: (Subject contains:) ‘medical cannabis’ or ‘cannabis’, ‘medicinal cannabis’, ‘medical marijuana’, ‘marijuana’, ‘cannabinoids’ and (Subject contains:) ‘dosage forms’ or ‘products’, ‘different dosage forms’, ‘formulations’, ‘forms’, ‘delivery systems’, ‘delivery methods’, ‘inhaled’, ‘smoked’, ‘topical’, ‘oral’, ‘injected’.

Literature published from 2010 until 2020 was included in the study. The year 2010 was selected as a starting point because there was an increase in the number of studies published compared to previous years, with a total of 208 articles related to cannabis

being published between 2010 and 2015. The inclusion criteria were based on studies assessing any topic related to medicinal cannabis dosage form(s), since this was a general systematic search to identify the conducted studies about cannabis dosage forms (Table 2.1). Studies evaluating human participants as cannabis users were considered for the effects of cannabis on humans. Cannabis dosage forms compared one-to-one with drug, placebo, tobacco, alcohol were included, since one-to-one comparisons could be relevant to observe effectivity or side effect profile. Studies including multiple substances such as addictive drugs and/or tobacco, alcohol had to include two dosage forms of cannabis as a minimum criterion for inclusion, to be able to identify cannabis-focused studies. The exclusion criteria included studies which do not specify the mode of cannabis administration and compare cannabis as a whole with tobacco, addictive drugs, alcohol, since the systematic search focused on cannabis dosage forms. Animal studies were excluded as the focus was not toxicology. Reviews were excluded to be able to evaluate the primary sources of the information.

Table 2. 1 Inclusion and exclusion criteria for general systematic review

Inclusion criteria	Exclusion criteria
Publication date between 2010-2020	Publication date before 2010
Published in English language & peer-reviewed journals	Published in language other than English
Include human participants as medicinal or recreational cannabis users or any volunteer to take part in the study	Animal studies & reviews
Related to one or more medicinal cannabis dosage form(s)	Studies do not focus any mode of cannabis administration
Compare cannabis dosage form one-to-one with drug, placebo, tobacco or alcohol	Assess whether they use cannabis or not
Compare two dosage forms of cannabis with drugs, placebo, tobacco and alcohol	Studies with focus on cannabis addiction
	Compare cannabis with tobacco, addictive drugs, alcohol, without specification of dosage form
	Studies which could not be accessed

2.7.2 Systematic Review about Preferences on Cannabinoid Dosage Forms

An extensive literature review was carried out using the tool HyDi. Patient surveys about medicinal cannabis dosage form preferences were reviewed using the PRISMA flow chart method (Moher et al, 2009). ProQuest Central, PubMed Central, Springer Standard Collection, Elsevier, EBSCO host Medline and EBSCO host Academic Search Ultimate databases were included in the study.

Advanced search strategy included the key words: (Any field contains:) 'medical cannabis' or 'cannabis', 'medicinal cannabis', 'medical marijuana', 'marijuana', 'cannabinoids' and (Any field contains:) 'dosage forms' or 'products', 'different dosage forms', 'forms', 'delivery systems', 'delivery methods', 'administration methods', 'administration' and (Subject contains:) 'survey' or 'patients survey', 'preference', 'questionnaire', 'opinion'.

Articles published between 2010 and 2020 were considered for the study. The year 2010 was considered, because the increment in the number of studies published between the years 2010-2015 (n=63) was considerably higher compared to previous years. The inclusion criteria were based on surveys assessing opinions of patients on cannabis dosage forms, since the focus in this research was patients' preferences for dosage forms of medicinal cannabis (Table 2.2). The exclusion criteria were studies assessing addiction or substance use as this study did not focus on cannabis addiction. Surveys of individuals other than patients or medicinal cannabis users and studies that do not include preferences on cannabis dosage forms were excluded to identify similar studies, since this study focused on opinions of patients or medicinal cannabis users on cannabis dosage forms.

Table 2. 2 Inclusion and exclusion criteria for systematic review about preferences

Inclusion criteria	Exclusion criteria
Publication date between 2010-2020	Publication date before 2010
Published in English language & peer-reviewed journals	Published in language other than English
Include human participants as patients or medicinal cannabis users	Surveys to individuals other than patients or medicinal cannabis users
Opinions, likes and dislikes related to medicinal cannabis dosage forms	Do not include preferences on cannabis dosage forms
Surveys related to one or more medicinal cannabis dosage forms	Assess addiction, current or past cannabis or substance use
	Studies which could not be accessed

2.8 List of Publications and Abstracts

Two abstracts (Appendix 8) by Bereketoglu C, Sammut Bartolo N, Serracino-Inglott A entitled "Perception of delivery systems used for medicinal cannabis" and "Systematic reviews about medicinal cannabis dosage forms" were accepted for the FIP's 80th World Congress of Pharmacy and Pharmaceutical Sciences to be held virtually in September 4-25, 2020.

3. Results

3.1 Questionnaire Validation

Two questionnaires were developed, one for medicinal cannabis users (MDMCU) and one for potential users (MDNMCU). Both questionnaires were validated using the Delphi Technique.

3.1.1 Validation results for the medicinal cannabis users questionnaire

The suggested changes received for the MDMCU English questionnaire during the first Delphi round are presented in Appendix 9. Suggestions included modifications to make the questionnaire more user friendly, to include the 'Locality' in the demographic section, to list some of the medical conditions as sub-section to other related medical conditions, to modify the time intervals used to evaluate the period participants have been using medicinal cannabis, the time they start feeling the desired effect and duration of the desired effect and to clarify what is the difference between the two questions. These changes were accepted to facilitate the understanding of question and avoid inaccurate responses.

All questions were rated to be relevant by the panel. One out of six participants suggested to change the option for the gender, in the demographics section, from 'other' to 'intersex'. This suggestion was rejected since intersex does not cover all the possible sexes and other participants agreed with the option 'other'. One participant suggested to add more health conditions in question 1, this was rejected since it was suggested by a minority of the panel and the 'other (please specify……)' option was provided in the answers and there could be a variety of reasons to use medicinal cannabis, therefore it was limited with the main medical conditions for which the use of medicinal cannabis is indicated in the literature. One out of six participants suggested to remove some of dosage forms of medicinal cannabis listed in question 12 and 13 and include only the existing

methods rather than all the options listed, it was explained to the participant that only available dosage forms of medicinal cannabis were included in the tables and since this change was suggested by minority, the change was rejected. One out of six participants highlighted that smoking or the use of electronic cigarette is illegal, it was clarified to the participant that this question does not look at the legality, but to assess the preferred method of delivery within all available forms of cannabis, since this was suggested by the minority of the panel, this change was rejected.

The suggestions for the MDMCU English questionnaire was applied to the Maltese version of the questionnaire as the panel requested. Additional recommendations included changes to the wording of questions to facilitate the understanding of the questionnaire. These suggestions were accepted.

3.1.2 Validation results for the potential medicinal cannabis users questionnaire

The suggested changes received for the MDNMCU English questionnaire during the Delphi round are presented in Appendix 10. Suggestions included to add 'Locality' in the demographics section, to provide more choices beside yes and no options, to list possible reasons why participants would opt to use or not medicinal cannabis and to clarify the difference between the two questions that require ranking. The majority of the panel requested to clarify the difference between the questions 12 and 13 that require ranking as well as to change the structure of these two questions from ranking to rating on a 5-point scale according to preference. These changes were accepted.

All questions were rated to be relevant by the panel. Two members from the panel suggested to clarify whether in the question assessing if participants have ever tried cannabis, if the purpose of the question is medicinal or recreational. This question was

rated as highly relevant. One out of six participants suggested to remove the question which assesses why participants would opt not to start using medicinal cannabis if presented with the opportunity. Since this change was suggested by a minority, it was rejected. Another participant suggested to change the structure of the same question from open-ended to a multiple-choice question, with the addition of possible reasons not to start using medicinal cannabis. This suggestion was accepted and the suggested choices were introduced.

Suggestions for the English MDNMCU questionnaire were applied to the Maltese version of the questionnaire together with changes to improve the ease of understanding of the questionnaire.

3.2 The perception of medicinal cannabis users about their treatment

The MDMCU questionnaire was disseminated to medicinal cannabis users at a Health Centre, a Pain Clinic and online. The questionnaire evaluated the perception about medicinal cannabis, duration of action and experienced side effects.

3.2.1 Demographic data of users of medicinal cannabis

A total of 87 participants answered the MDMCU (Table 3.1). The majority of users (70%, n=61) were male. The mean age of medicinal cannabis users was 38.9 years (SD ±1.08 years). Thirty percent (n=24) of the users had a secondary or tertiary (30%, n=24) educational level. The majority for users (85%, n=74) were Maltese nationals, while the other nationalities were English (n=3), German (n=2), Italian (n=2), Romanian (n=1), American (n=1), Norwegian (n=1), Icelandic (n=1), Polish (n=1) and Macedonian (n=1). The majority of the users population were from the Northern area (28%, n=19) followed by the Northern Harbour (26%, n=18) and Southern Harbour (25%, n=17).

Table 3. 1 Demographics of medicinal cannabis users (N=87)

		Medicinal cannabis users
Gender	Female	29.9% (26)
	Male	70.1% (61)
Age	30 years or less	25.0% (21)
	31-40 years	34.5% (29)
	41-50 years	19.0% (16)
	More than 50 years	21.4% (18)
Level of Education	Primary	2.5% (2)
	Secondary	30.0% (24)
	Post-secondary	28.7% (23)
	Tertiary	30.0% (24)
	Post-graduate	8.8% (7)
Nationality	Maltese	85.1% (74)
	Other	14.9% (13)
Locality	Southern Harbour	25.0% (17)
	Northern Harbour	26.5% (18)
	South Eastern	13.2% (9)
	Western	5.9% (4)
	Northern	27.9% (19)
	Gozo	1.5% (1)

3.2.2 Reasons for medicinal cannabis use

The majority of the participants were using medicinal cannabis due to pain (51%, n=41), including fibromyalgia pain (n=7), arthritis pain (n=6), back pain (n=4), chronic pain (n=2), injury induced pain (n=2), pain in leg (n=2) and hip (n=1) and sciatica induced pain (n=1). Anxiety (35%, n=28) was the second most prevalent condition among medicinal cannabis users, this was followed by insomnia (18%, n=15), fibromyalgia (17%, n=14) and arthritis (14%, n=11). Two patients specified having migraine (n=1) and cluster headache (n=1) (Table 3.2).

Table 3. 2 Reasons for using medicinal cannabis (N=81)

Medical Condition	Sample Size
Alopecia	1.2% (1)
Anxiety	**34.6% (28)**
Arthritis	13.6% (11)
Asthma	1.2% (1)
Attention deficit hyperactivity disorder (ADHD)	4.9% (4)
Cancer	2.5% (2)
Chron's disease	1.2% (1)
Chemotherapy-induced nausea and vomiting	1.2% (1)
Concentration problem	1.2% (1)
Depression	8.6% (7)
Endometriosis	1.2% (1)
Fibromyalgia	17.3% (14)
Glaucoma	1.2% (1)
Headache	3.7% (3)
Hyperactivity	1.2% (1)
Insomnia	18.5% (15)
Irritable bowel syndrome (IBS)	4.9% (4)
Loss of appetite	2.5% (2)
Multiple hereditary exostosis	1.2% (1)
Multiple sclerosis	1.2% (1)
Obsessive compulsive disorder (OCD)	1.2% (1)
Pain	**50.6% (41)**
Psoriasis	1.2% (1)
Restless leg syndrome	1.2% (1)
Sciatica	1.2% (1)
Spinal fluid leak	1.2% (1)
Stress	7.4% (6)

Out of the 28 (100%) participants who use medicinal cannabis for anxiety, 11 participants (39%) use medicinal cannabis for treating anxiety on its own while 17 use it for other conditions beside anxiety (Table 3.3). Pain (25%, n=7), fibromyalgia (21%, n=6) and insomnia (21%, n=6) are the most prevalent conditions for the co-use of medicinal cannabis in anxiety. Four (36%) out of the 11 participants who are using medicinal cannabis for the anxiety only, are using Pedanios and/or Bedrocan flowers. Two participants who are using medicinal cannabis to treat cancer-induced pain, are also benefit from the properties of cannabis for chemotherapy-induced nausea and vomiting (CINV) and easing of insomnia respectively. Thirty-five (49%) out of 72 participants have made use of more than one type of medicinal cannabis to manage their condition. For all medical conditions except Chron's disease, endometriosis and multiple hereditary exostosis (MHE) patients made use of Pedanios and/or Bedrocan flowers (Table 3.4).

Table 3. 3 Conditions for which medicinal cannabis is used, beside anxiety (N=17)

Conditions beside anxiety	Sample Size
Alopecia	3.6% (1)
Arthritis	3.6% (1)
Asthma	3.6% (1)
Depression	7.1% (2)
Fibromyalgia	21.4% (6)
Insomnia	21.4% (6)
IBS	3.6% (1)
Loss of appetite	3.6% (1)
OCD	3.6% (1)
Pain	25.0% (7)
Psoriasis	3.6% (1)
Restless leg syndrome	3.6% (1)
Spinal fluid leak	3.6% (1)
Stress	14.3% (4)

Table 3. 4 Medicinal cannabinoids utilised according to medical conditions (N=72)

Medical Condition	Medicinal Cannabis	Frequency in use	Sample Size
Anxiety	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil CBG oil	37.5% (9) 33.3% (8) 54.2% (13) 4.2% (1) 37.5% (9) 4.2% (1)	24
Arthritis	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 CBD oil	33.3% (3) 66.7% (6) 55.6% (5) 88.9% (8)	9
Asthma	Bedrocan 22 CBD oil	100.0% (1) 100.0% (1)	1
ADHD	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil	75.0% (3) 75.0% (3) 75.0% (3) 25.0% (1) 50.0% (2)	4
Cancer	Pedanios 22/1 CBD oil	50.0% (1) 100.0% (2)	2
Chron's disease	Bediol 6/8	100.0% (1)	1
CINV	Pedanios 22/1 CBD oil	100.0% (1) 100.0% (1)	1
Concentration problem	Bedrocan 22	100.0% (1)	1
Depression	Pedanios 22/1 Bedrocan 22 Bediol 6/8 CBD oil	20.0% (1) 80.0% (4) 20.0% (1) 60.0% (3)	5

Table 3. 4 *(cont.)* Medicinal cannabinoids utilised according to medical conditions (N=72)

Medical Condition	Medicinal Cannabis	Frequency in use	Sample Size
Endometriosis	CBD oil	100.0% (1)	1
Fibromyalgia	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil 50/50 oil	13.3% (2) 33.3% (5) 40.0% (6) 26.7% (4) 40.0% (6) 6.7% (1)	15
Headache	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 CBD oil	33.3% (1) 66.7% (2) 66.7% (2) 66.7% (2)	3
Hyperactivity	Pedanios 22/1	100.0% (1)	1
IBS	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil 50/50 oil	50.0% (2) 50.0% (2) 50.0% (1) 25.0% (1) 50.0% (2) 25.0% (1)	4
Insomnia	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil CBG oil	46.2% (6) 15.4% (2) 53.8% (7) 7.7% (1) 23.1% (3) 7.7% (1)	13
Loss of appetite	Pedanios 20/1 Bedrocan 22 CBD oil	100.0% (2) 50.0% (1) 50.0% (1)	2
MHE	CBD oil	100.0% (1)	1

Table 3. 4 *(cont.)* Medicinal cannabinoids utilised according to medical conditions (N=72)

Medical Condition	Medicinal Cannabis	Frequency in use	Sample Size
Multiple sclerosis	Pedanios 20/1 Bedrocan 22 CBD oil	100.0% (1) 100.0% (1) 100.0% (1)	1
OCD	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 CBD oil	100.0% (1) 100.0% (1) 100.0% (1) 100.0% (1)	1
Pain	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 Bediol 6/8 CBD oil	33.3% (12) 47.2% (17) 47.2% (17) 11.1% (4) 66.7% (24)	36
Restless leg syndrome	Pedanios 22/1 Bedrocan 22	100.0% (1) 100.0% (1)	1
Spinal fluid leak	Pedanios 22/1 Pedanios 20/1 CBD oil	100.0% (1) 100.0% (1) 100.0% (1)	1
Stress	Pedanios 22/1 Pedanios 20/1 Bedrocan 22 CBD oil	40.0% (2) 40.0% (2) 80.0% (4) 40.0% (2)	5

3.2.3 Period and type of medicinal cannabis use

Thirty-four percent (n=27) of the participants had been using medicinal cannabis for a period of 1 to 6 months, followed by more than 18 months (19%, n=15) (Figure 3.1).

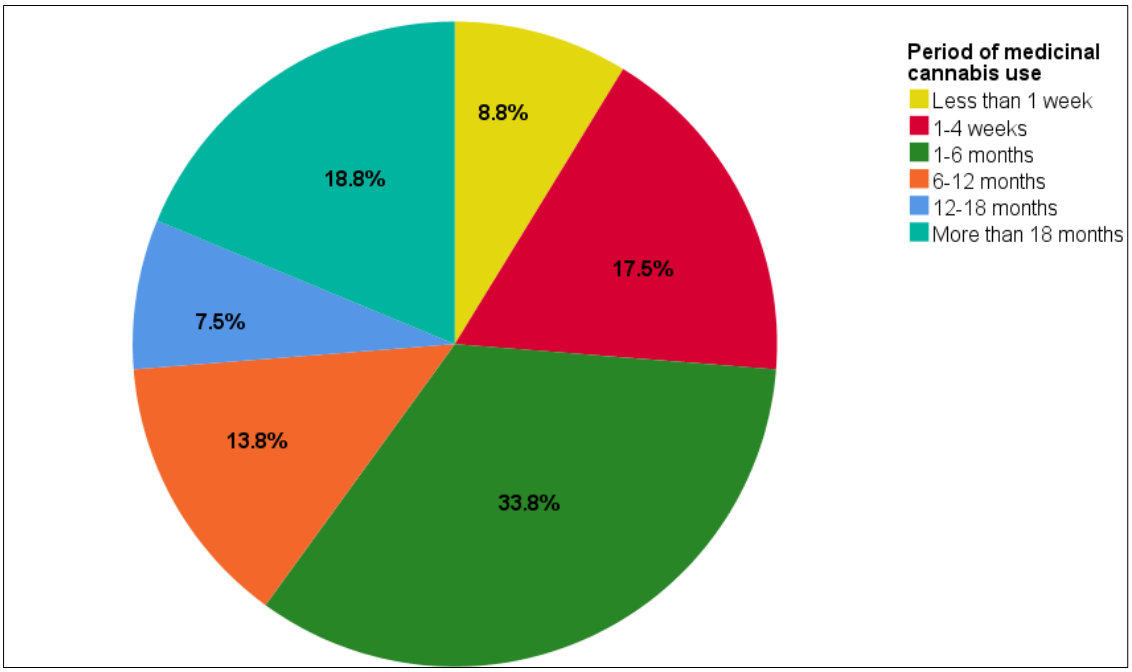


Figure 3. 1 Period of Medicinal Cannabis Use (N=80)

Seventy-four participants (85%) out of 87 answered the question about the type of medicinal cannabis they are currently using. Thirty-five participants made use of more than one type of medicinal cannabis. The majority of the participants (53%, n=39) use Bedrocan flower 22, followed by CBD oil (51%, n=38) (Figure 3.2).

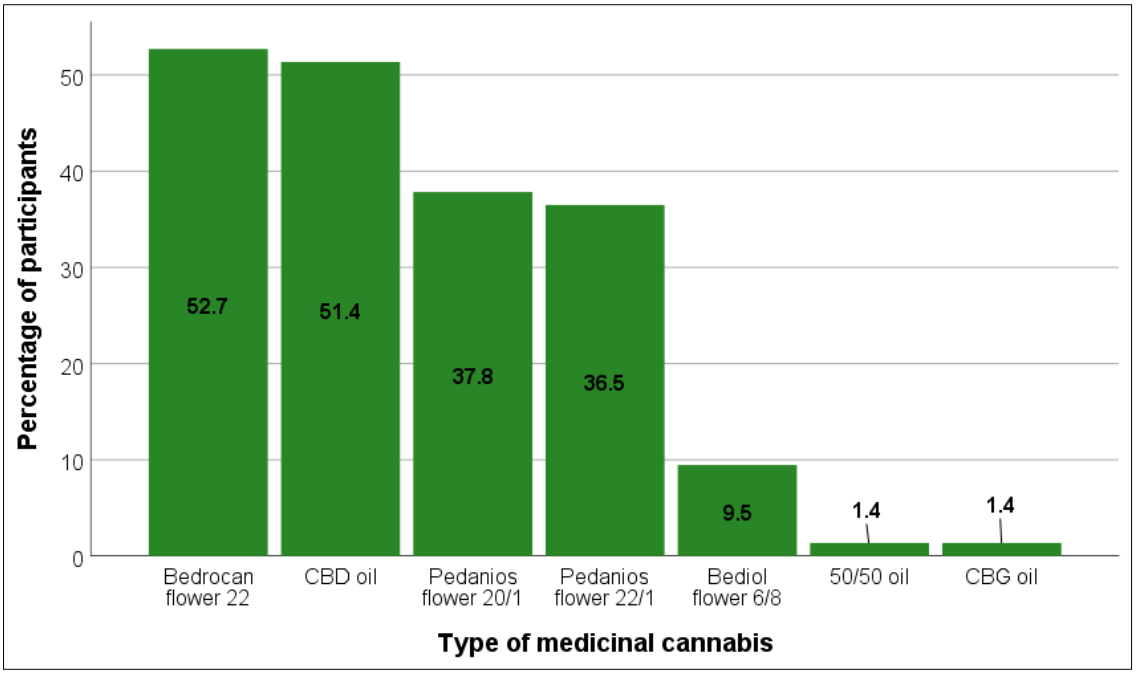


Figure 3. 2 Types of medicinal cannabis utilised (N=74)

Medicinal cannabis users were asked whether they have tried other types of medicinal cannabinoids other than Pedanios flowers, Bedrocan flower and CBD oil respectively. The majority (74%, n=56) of users did not try other types of medicinal cannabinoids. When asked to specify the type of medicinal cannabis they made use of, 3 participants stated that they had used cannabis concentrate and brownie forms of cannabis, followed by cannabis cookie (n=2), CBD vape (n=1), cheese (n=1), oil (n=1) and wax (n=1) forms of cannabis.

3.2.4 Onset of the effect of medicinal cannabis

Fifty-one percent (n=39) of participants achieve the desired effect of their medicinal cannabis within 1 to 15 minutes of taking the medication. This was followed by participants achieving an effect in a few seconds (25%, n=19) and within 15 to 60 minutes (17%, n=13). One participant perceived the onset of action to be between 3 to 5 hours (1%, n=1), one participant was unsure about the onset of the desired effect (1%, n=1).

Another participant highlighted that an effect was not achieved with the oil formulation of medicinal cannabis, but was told that the dose will be increased (1%, n=1).

The desired effect is perceived within few seconds for flowers of Pedanios 22/1 (41%, n=11), Pedanios 20/1 (29%, n=8), Bedrocan 22 (35%, n=13) and CBD oil (21%, n=7) and within 1 to 15 minutes for Pedanios 22/1 (44%, n=12), Pedanios 20/1 (54%, n=15), Bedrocan 22 (49%, n=18), Bediol 6/8 (86%, n=6) flowers and CBD oil (41%, n=13) (Figure 3.3). The p-values for onset of the effect for Pedanios 22/1 (p=0.204), Pedanios 20/1 (p=0.900), Bedrocan 22 (p=0.306), Bediol 6/8 (p=0.393) and CBD oil (p=0.113) were above the 0.050 criterion, indicating that the onset for perceiving medicinal cannabis effect do not differ significantly within each group of medicinal cannabis formulation users. Two participants selected the option 'other' for the type of medicinal cannabis and specified to perceive the desired effect within few seconds after using Cannabigerol (CBG) oil (n=1) and within 1 to 15 minutes after using 50/50 oil (n=1).

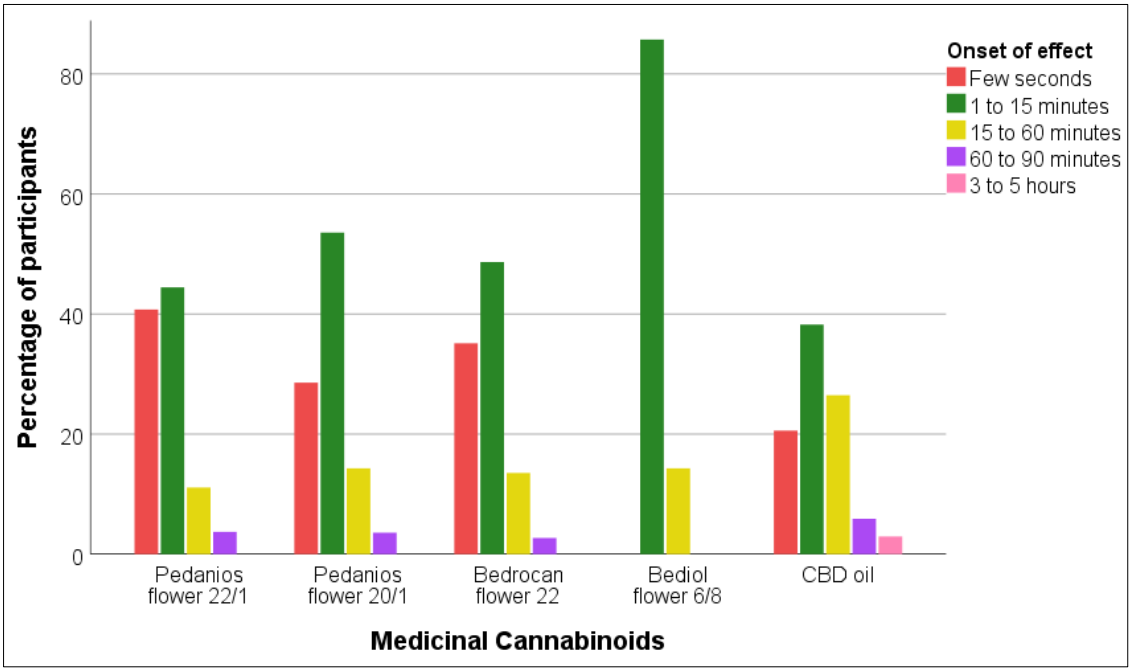


Figure 3. 3 Onset of the effect of medicinal cannabinoids (N=66)

The time period necessary to obtain the desired effect after taking a dose of medicinal cannabis were evaluated across different age groups (Figure 3.4). Participants across all age groups, such as 30 years or less (59%, n=10), 31-40 years (48%, n=12), 41-50 years (57%, n=8) and more than 50 years (45%, n=8), mainly achieved an effect within 1 to 15 minutes. The p-value (p=0.632) is above the 0.050 level of significance, indicating that time needed to reach the desired effect of medicinal cannabis does not differ remarkably across different ages.

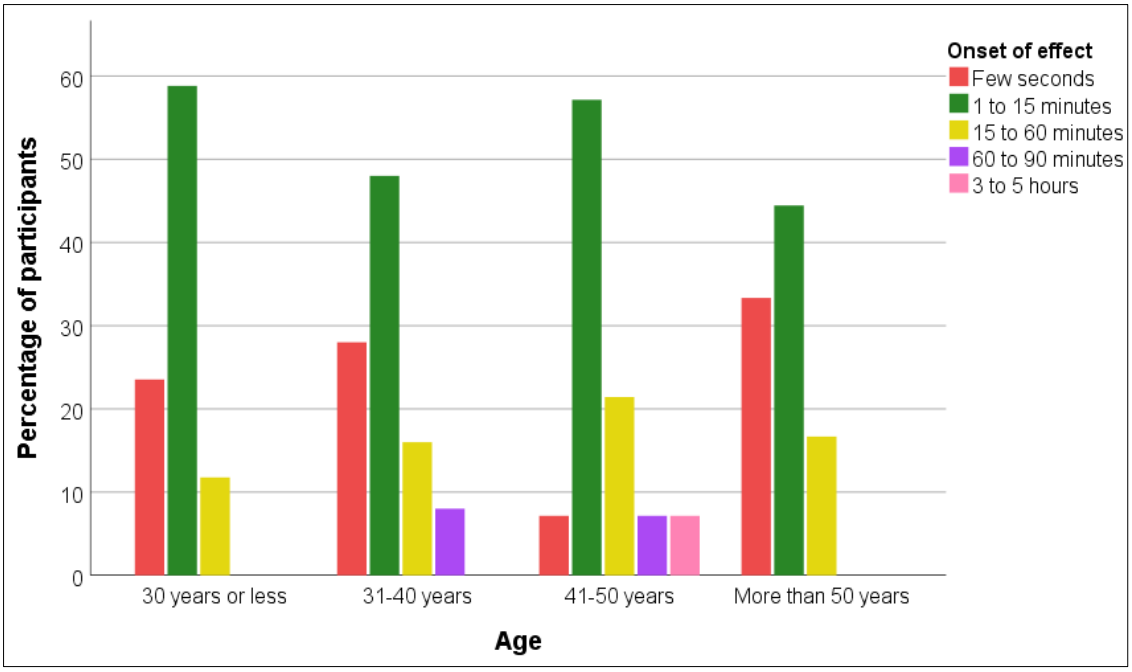


Figure 3. 4 Onset of the effect of medicinal cannabis according to age groups (N=74)

3.2.5 Effective period of medicinal cannabis

When asked about the effective period of medicinal cannabis, some participants selected more than one answer, since they are concurrently using more than one type of medicinal cannabis. Thirteen percent (n=10) of the participants are having a short-term effect with medicinal cannabis, which remains effective for a period of 30 to 45 minutes. However the majority of participants are experiencing the desired effect for 1 to 2 hours (41%, n=32) followed by 2 to 3 hours (26%, n=20) (Figure 3.5).

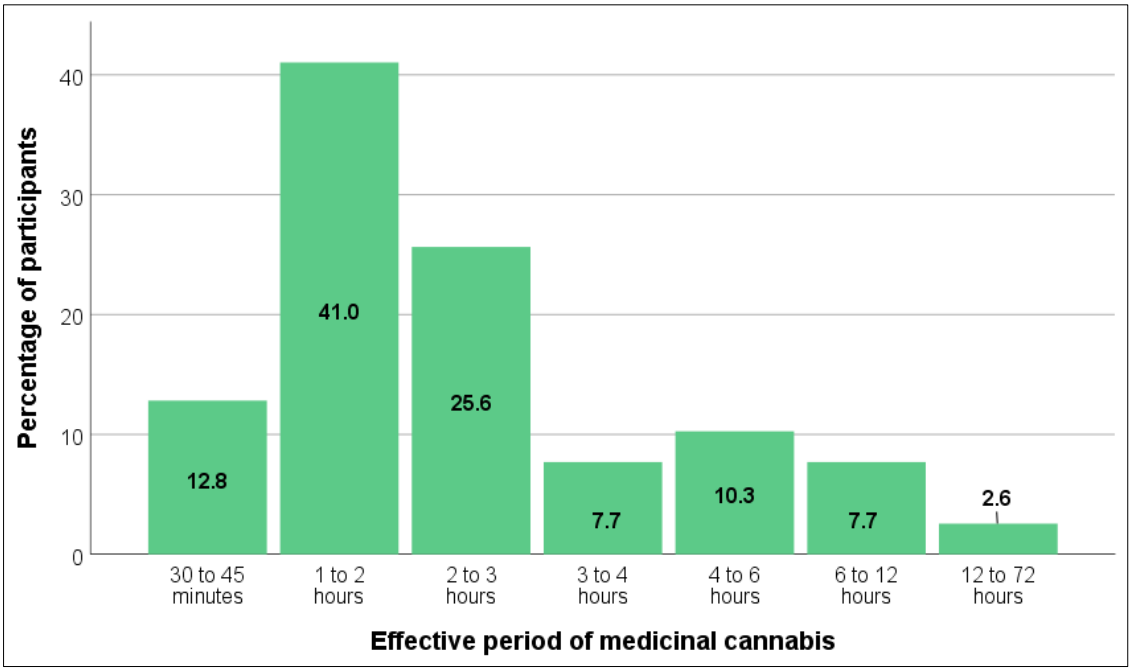


Figure 3. 5 Effective period of medicinal cannabis (N=78)

The effective time period was compared amongst different formulations of medicinal cannabis (Figure 3.6). The majority of the flower formulations such as Pedanios 22/1 (41%, n=11), Pedanios 20/1 (43%, n=12), Bedrocan 22 (51%, n=19) as well as the CBD oil (37%, n=13) remain effective for 1 to 2 hours, followed by 2 to 3 hours by Pedanios 22/1 (30%, n=8), Pedanios 20/1 (29%, n=8), Bedrocan 22 (22%, n=8) flowers and the CBD oil (23%, n=8). Bediol 6/8 users (43%, n=3) reported that the effect of medicinal cannabis lasted for 2 to 3 hours, followed by 3 to 4 hours (29%, n=2) and 6 to 12 hours (29%, n=2). Three percent (n=1) of the participants using Bedrocan flower and 14% (n=1) using Bediol flower experience prolong effect lasting from 12 to 72 hours. Two participants selected the option 'other' and specified that they are using CBG oil (n=1) with a perceived effect lasting for 1 to 2 hours and 50/50 oil (n=1) with the desired effect lasting for 3 to 4 hours.

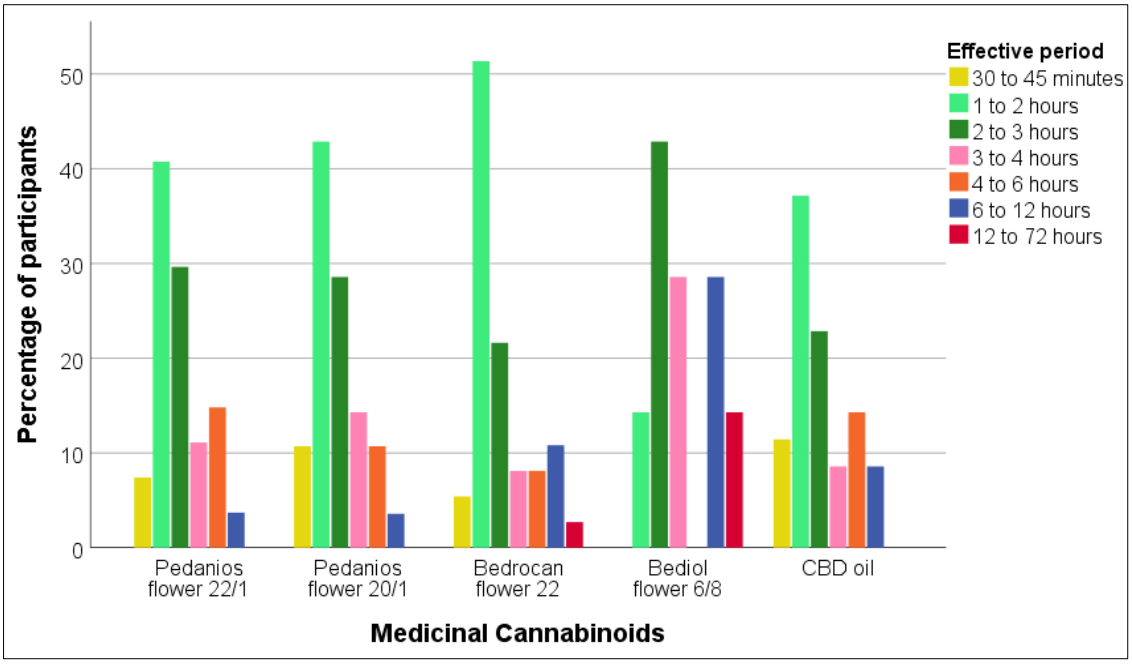


Figure 3. 6 Effective period of different formulations of cannabinoids (N=67)

The participants within the age groups 30 years or less (50%, n=9), 31-40 years (36%, n=9), 41-50 years (36%, n=5) and more than 50 years (50%, n=9) are experiencing the desired effect of their medicinal cannabis for 1 to 2 hours (Figure 3.7). Forty percent (n=10) of the participants within the 31-40 years of age group and other age groups such as 30 years or less (17%, n=3), 41-50 years (14%, n=2) and 50 years and more (22%, n=4) experience an effect for 2 to 3 hours. Twenty-one percent (n=3) of participants aged between 41-50 years experience an effect for 6 to 12 hours. The p-values for effective periods of 30 to 45 minutes (p=0.870), 1 to 2 hours (p=0.529), 2 to 3 hours (p=0.250), 3 to 4 hours (p=0.657), 4 to 6 hours (p=0.964), 6 to 12 hours (p=0.102) and 12 to 72 hours (p=0.386) were above the 0.050 criterion. This indicates that the period which medicinal cannabis remains effective do not differ meaningfully across different age groups.

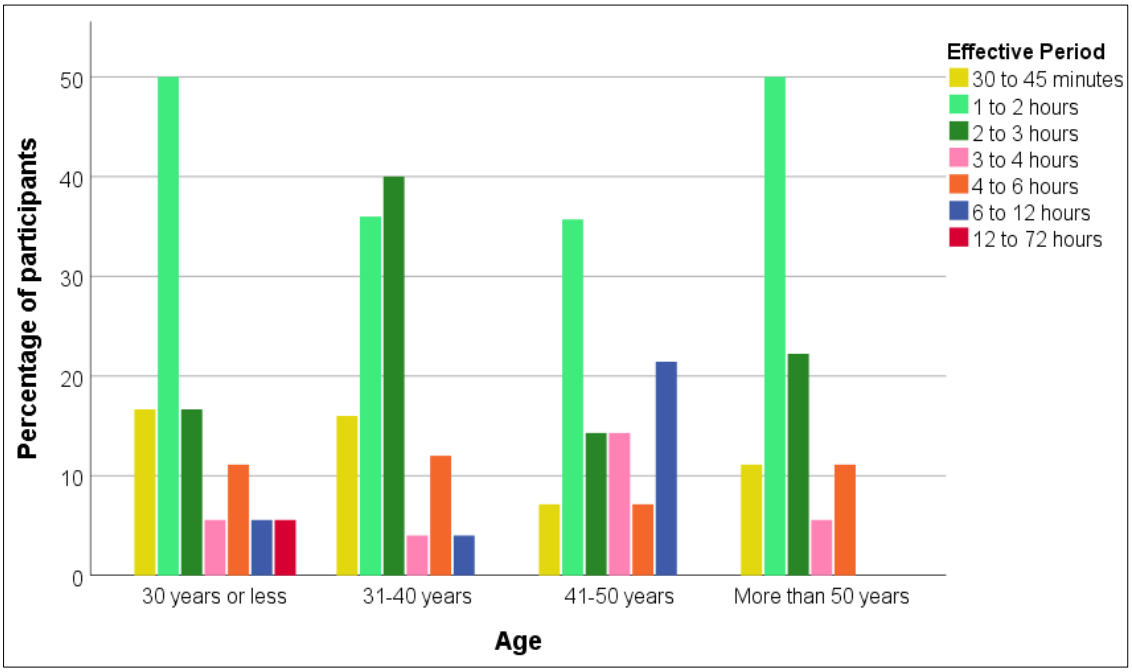


Figure 3. 7 Effective period of medicinal cannabis across age groups (N=75)

3.2.6 Side effects of medicinal cannabinoids

Side effects experienced by medicinal cannabis users are demonstrated in Figure 3.8. More than half of the participants (56%, n=44) feel hungry when they take medicinal cannabis, this is followed by feeling energised (51%, n=40), sleepy (44%, n=34) and feeling high (33%, n=26). Some participants feel dizzy (5%, n=4), calm and peaceful (4%, n=3), nauseated (3%, n=2) and more alert (1%, n=1). One participant specified that the effects are strain dependent, sometimes he would be feeling energised and other times feeling sleepy (1%, n=1).

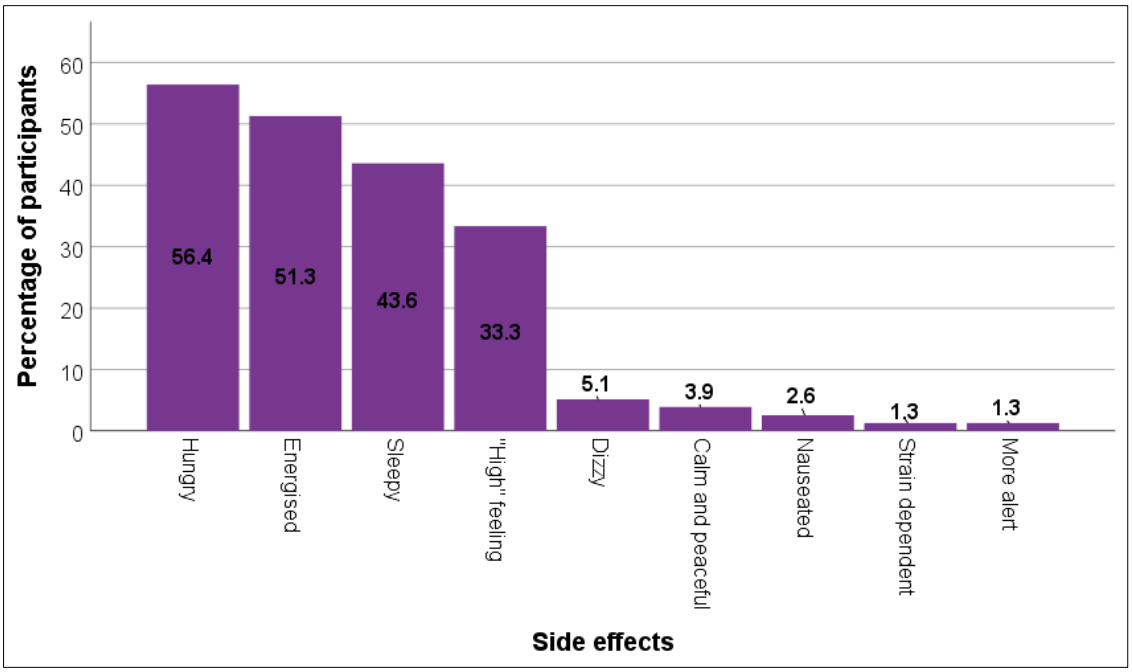


Figure 3. 8 Side effects of medicinal cannabinoids (N=78)

Participants using Pedanios 22/1 (63%, n=17), Pedanios 20/1 (79%, n=22), Bediol 6/8 (86%, n=6) and CBD oil (57%, n=20) are likely to feel more energised (Figure 3.9). Bedrocan 22 flower users are likely to sense more hunger (73%, n=27), followed by feeling energised (59%, n=22), sleepy (46%, n=17) and high (40%, n=15). Users of Pedanios 22/1 (8%, n=2), Pedanios 20/1 (4%, n=1) and Bedrocan 22 (5%, n=2) reported a feeling of calmness and peacefulness. Some CBD oil users feel dizzy (9%, n=3) and more alert (3%, n=1) after taking medicinal cannabis. One participant specified that Pedanios flower makes him feel energised and hungry, and that Bedrocan flower gives him hunger and a 'high' feeling. Two participants selected the option 'other' and reported to feel energised and high when using CBG oil (n=1) and hungry, energised and high when using 50/50 oil (n=1).

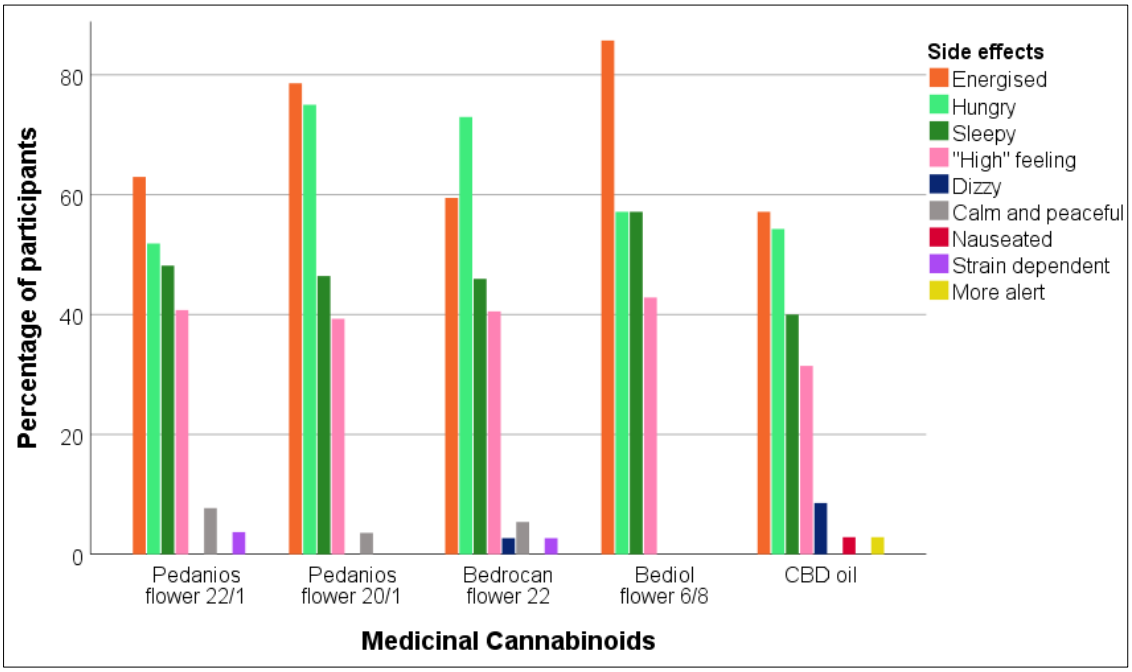


Figure 3. 9 Side effects among different formulations of cannabinoids (N=67)

The side effects experienced by the user population were correlated with the period of medicinal cannabis use (Figure 3.10). Participants who had started using medicinal cannabis for less than a week reported that they felt sleepy (50%, n=3), hungry (50%, n=3), energised (33%, n=2) and high (33%, n=2) post administration of their medicine. These effects were observed to remain, regardless of the length of time they used medicinal cannabis for. Dizziness was reported to be experienced by some participants using medicinal cannabis for a period between 1 to 6 months (4%, n=1), 6 to 12 months (9%, n=1) and more than 18 months (7%, n=1). The p-values for energised (p=0.114), hungry (p=0.666), sleepy (p=0.677), high feeling (p=0.320), dizzy (p=0.809), calm and peaceful (p=0.545), nauseated (p=0.791), strain dependent (p=0.495) and more alert (p=0.850) exceeded the 0.050 level of significance. This shows that side effects experienced with post administration of medicinal cannabis are similar regardless of the time period medicinal cannabis was started.

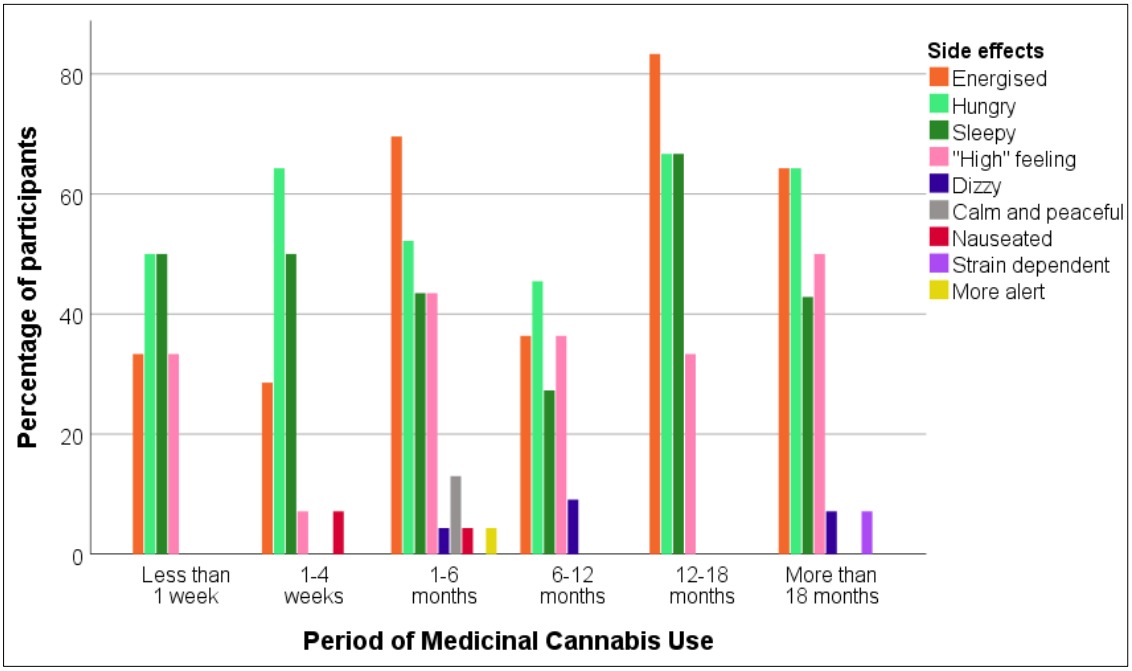


Figure 3. 10 Side effects according to period of medicinal cannabis use (N=74)

Side effects experienced by user population after administering their medicinal cannabis were correlated with different age categories (Figure 3.11). Participants aged between 30 years or less felt sleepy (61%, n=11), followed by hungry (50%, n=9), high (50%, n=9) and energised (44%, n=8) after administering their medicinal cannabis. Groups aged between 31-40 years (62%, n=16) and 41-50 years (69%, n=9) felt hungry, followed by energised (31-40_{years}=46%, 41-50_{years}=54%), sleepy (31-40_{years}=42%, 41-50_{years}=39%) and high (31-40_{years}=31%, 41-50_{years}=15%). Participants aged 50 years or more felt energised (61%, n=11), followed by hungry (44%, n=8), high (33%, n=6) and sleepy (28%, n=5). The p-values for feeling energised (p=0.484), hungry (p=0.750), sleepy (p=0.399), high (p=0.242), dizzy (p=0.237), calm and peaceful (p=0.116), nauseated (p=0.442), strain dependent (p=0.589) and more alert (p=0.589) were above the 0.050 criterion, indicating that side effects with medicinal cannabis use do not differ significantly between the age groups and medicinal cannabis users population mainly feel energised, hungry, sleepy and high regardless of their age.

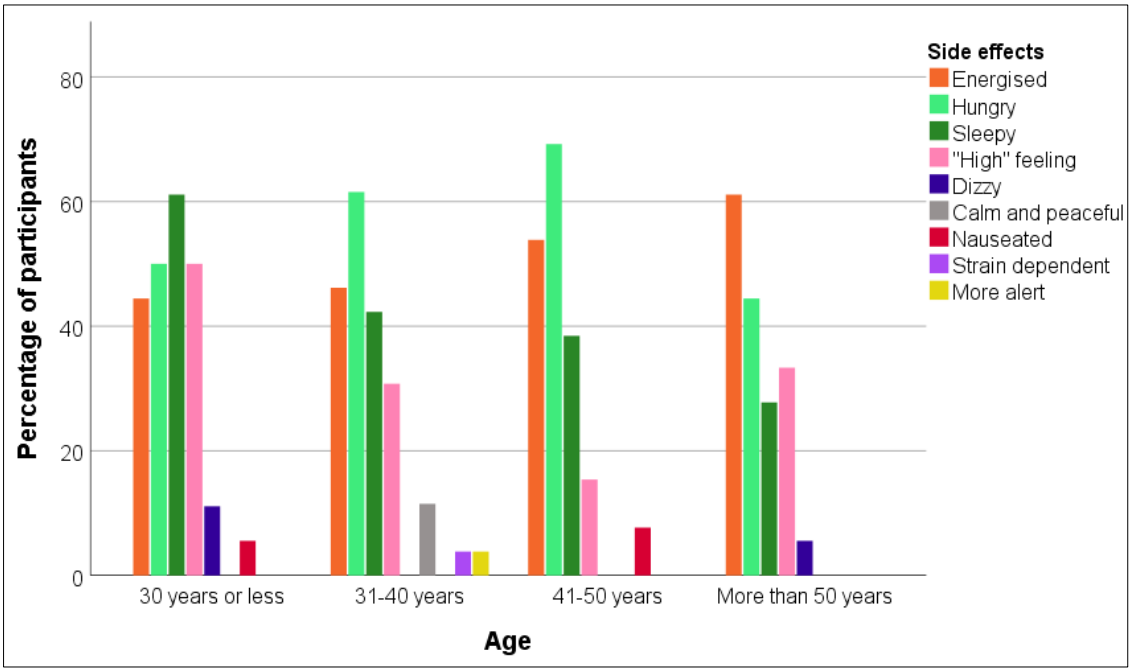


Figure 3. 11 Side effects of medicinal cannabinoids according to age (N=75)

Side effects resulted with the use of medicinal cannabis were correlated with gender (Table 3.5). More than half (56%, n=30) of the male participants and 42% (n=10) of the female participants felt energised. P-values for feeling energised (p=0.374), hungry (p=1), sleepy (p=0.607), high (p=0.794), dizzy (p=0.764), calm and peaceful (p=1), nauseated (p=0.169), strain dependent (p=1) and more alert (p=0.675) were calculated and all exceeded the 0.050 level of significance. This indicates that side effects resulted with the use of medicinal cannabis do not differ significantly between males and females.

Table 3. 5 Side effects of medicinal cannabinoids according to gender (N=78)

		Gender	
		Female (n=24)	**Male (n=54)**
Side effects of medicinal cannabis	Energised	41.7% (10)	55.6% (30)
	Hungry	58.3% (14)	55.6% (30)
	Sleepy	50.0% (12)	40.7% (22)
	"High" feeling	37.5% (9)	31.5% (17)
	Dizzy	8.3% (2)	3.7% (2)
	Calm and peaceful	4.2% (1)	3.7% (2)
	Nauseated	8.3% (2)	0.0% (0)
	Strain dependent	0.0% (0)	1.9% (1)
	More alert	4.2% (1)	(0.0% (0)

3.2.7 The ease of medicinal cannabis administration

Medicinal cannabis users were asked to rate how easy it is to administer their current medicinal cannabis ranging from 1 to 5, where 1 corresponds to very easy and 5 corresponds to very difficult (Figure 3.12). The types of medicinal cannabis stated in the option 'other' included cannabis concentrate (n=3) and brownie (n=3), cannabis cookie (n=2), CBD vape (n=1), 50/50 oil (n=1), cheese (n=1) and wax (n=1) forms of cannabis.

The mean rating scores for the different types of medicinal cannabis range between 1.78 and 2.14, indicating that patients on average find the administration of their medicinal cannabis easy. The error bars overlap and the p-value (p=0.913) exceeds the 0.050 criterion, indicating that the mean rating scores for medicinal cannabis administration do not differ significantly between various types of medicinal cannabis.

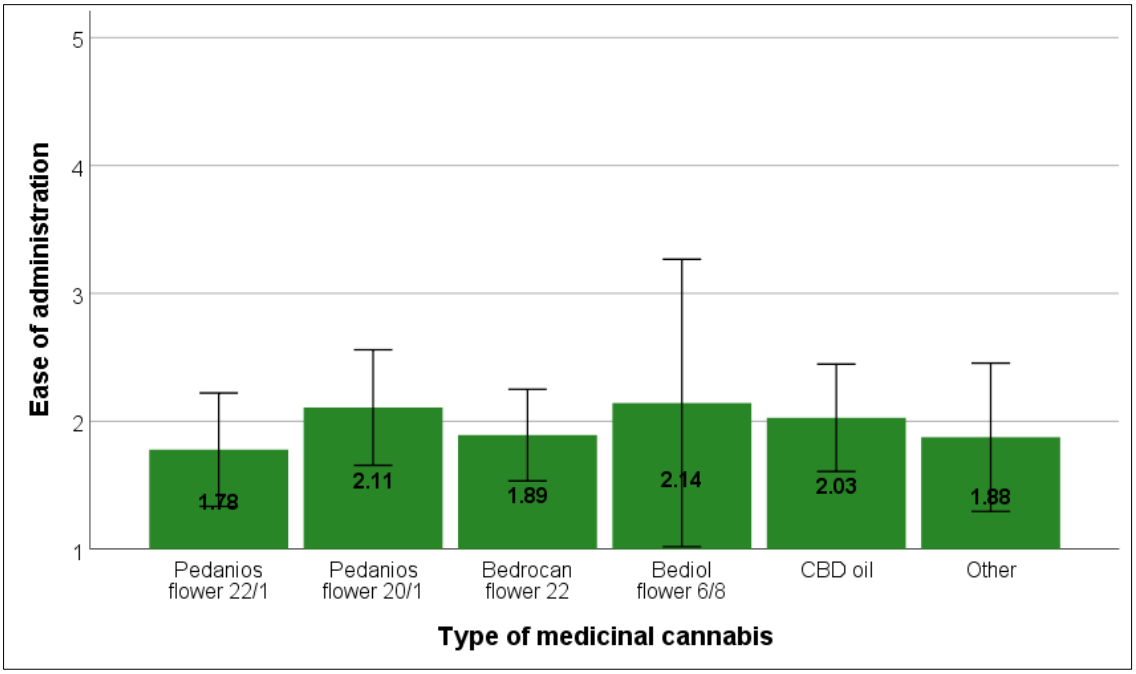


Figure 3. 12 Ease of administering medicinal cannabinoids (N=80)

3.2.8 Switching to another mode of medicinal cannabis administration

Medicinal cannabis users were asked whether they would like to switch to another form of medicinal cannabis. Fifty-five percent (n=41) of the participants do not want to switch to another form, while 45% (n=33) of the participants would like to switch.

The wish to switch to another mode of medicinal cannabis administration or not was compared to the type of medicinal cannabis they are currently using (Table 3.6). The majority of the participants using Pedanios flower 22/1 (52%, n=13), Pedanios flower 20/1 (54%, n=15), Bediol flower 6/8 (57%, n=4) and CBD oil (60%, n=21) respectively, reported to be in favour of switching to another mode of medicinal cannabis administration. P-values for Pedanios 22/1 (p=1), Pedanios 20/1 (p=0.789), Bediol 6/8 (p=1) flowers and CBD oil (p=0.151) exceeded the 0.050 level of significance. Sixty-six percent (n=23) of the Bedrocan 22 flower users do not want to switch their mode of medicinal cannabis administration significantly with a p-value (p=0.016) below the 0.050 criterion.

Table 3. 6 Switching to another mode of administration according to current mode (N=65)

	Would you switch to another mode of cannabis administration?	
	Yes	**No**
Pedanios flower 22/1	52.0% (13)	48.0% (12)
Pedanios flower 20/1	53.6% (15)	46.4% (13)
Bedrocan flower 22	34.3% (12)	65.7% (23)
Bediol flower 6/8	57.1% (4)	42.9% (3)
CBD oil	60.0% (21)	40.0% (14)
CBG oil	0.0% (0)	100.0% (1)
50/50 oil	0.0% (0)	100.0% (1)

When participants were asked why they would like to switch to another form of medicinal cannabis administration, the majority of the respondents (n=11) stated that they wanted to compare their current method of administration to alternatives, followed by due to the experienced health effects (n=8) (Table 3.7). The majority of participants (n=19) do not want to switch to another mode of administration because of the effectiveness of the medication which they are currently taking.

Table 3. 7 Reasons for users to switch or not their medicinal cannabis dosage form

	Category	**Number of respondents**	**Examples of the responses obtained**
Reasons why participants ***want*** to switch to another mode of administration	To compare with other alternatives	11	*"To see what works best"; "I would change the method for some time, then will return back to the first method"*
	Experienced health effects	8	*"Because it is good"*
	To improve taste and smell	4	*"I would like edibles"; "the CBD oil I am currently taking has a very bad taste which makes me feel sick for a good 6 hours"*
	Inconvenience in use	4	*"To make it easier for taking my medication at work"*
Reasons why participants ***do not want*** to switch to another mode of administration	Effectiveness	19	*"It works well for me"*
	Complexity in process	8	*"Availability"; "it is not easy to get legal cannabis"*
	Ease of administration	7	*"It is comfortable and easy to vaporize or make tea"*
	Health concerns	5	*"My health"; "I prefer it in its natural state"*

3.3 The perception of potential medicinal cannabis users

The MDNMCU questionnaire was distributed to potential users of medicinal cannabis. The questionnaire assessed the perception of potential users about medicinal cannabis, including whether they would be willing to make use of this drug.

3.3.1 Demographic data of potential medicinal cannabis users

A total of 100 participants answered the MDNMCU questionnaire (Table 3.8). The majority of potential medicinal cannabis users (56%, n=55) were male. The mean age of potential users was 40.5 years (SD ±1.20 years). Twenty-six percent (n=25) of the potential users had a post-secondary and 25% (n=24) had a tertiary level of education. Ninety-four percent (n=91) of the potential users were Maltese, while the 6% (n=6) were Filipino (n=2), Greek (n=2), Portuguese (n=1) and Spanish (n=1). The majority of the potential users population were from the Southern Harbour (35%, n=32) and South Eastern area (27%, n=24).

Table 3. 8 Demographics of potential medicinal cannabis users (N=100)

		Potential users of medicinal cannabis
Gender	Female	43.8% (43)
	Male	56.1% (55)
Age	30 years or less	30.4% (28)
	31-40 years	29.3% (27)
	41-50 years	10.9% (10)
	More than 50 years	29.3% (27)
Level of Education	Primary	4.1% (4)
	Secondary	23.9% (23)
	Post-secondary	26.0% (25)
	Tertiary	25.0% (24)
	Post-graduate	20.8% (20)
Nationality	Maltese	93.8% (91)
	Other	6.1% (6)
Locality	Southern Harbour	35.5% (32)
	Northern Harbour	15.5% (14)
	South Eastern	26.7% (24)
	Western	13.3% (12)
	Northern	6.6% (6)
	Gozo	2.2% (2)

3.3.2 Current pain medication use

Current use of pain medication was evaluated for potential users of medicinal cannabis. Ninety-three out of 100 respondents answered this question. Seventy-four percent (n=69) of the respondents do not make use of any pain medications. The majority of participants take two pain medications (49%, n=17) to be able to control their pain, followed by one pain medication (40%, n=14) (Figure 3.13).

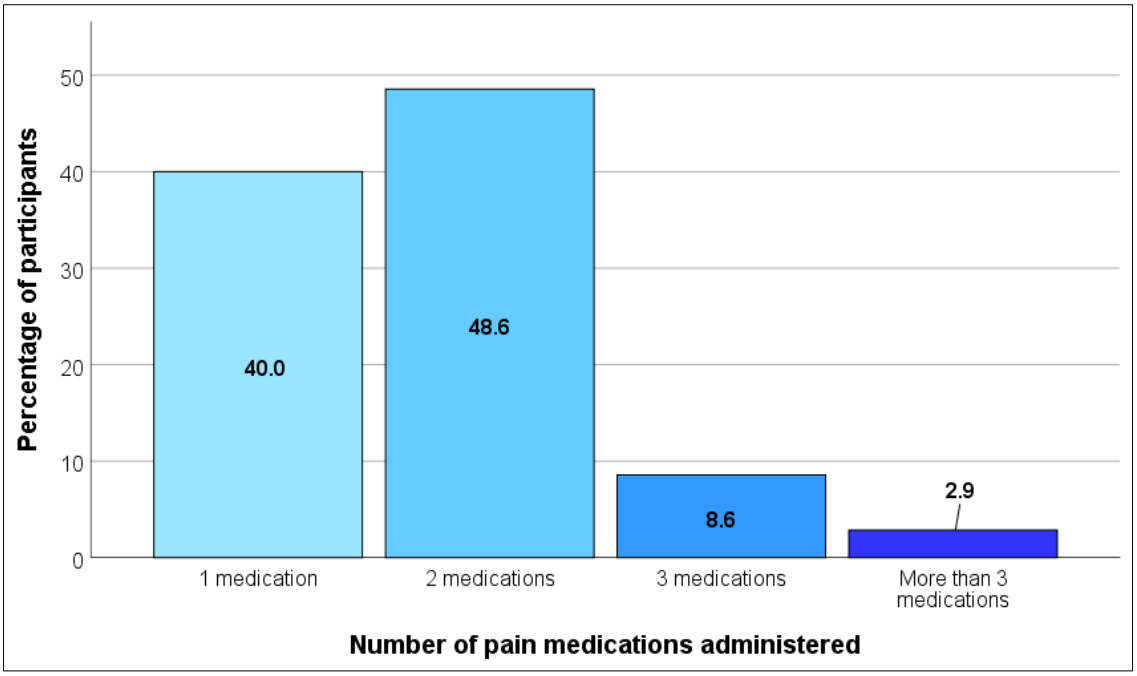


Figure 3. 13 Number of pain medications administered by potential users (N=35)

Participants were asked whether they are benefitting from their pain treatment. Forty-six percent (n=16) of the potential users of medicinal cannabis stated that they are able to control their pain with their current pain medication, 29% (n=10) are unable to control their pain, while 26% (n=9) are unsure.

3.3.3 Conditions for prospective medicinal cannabis use

Potential users of medicinal cannabis were asked for which conditions they would use medicinal cannabis (Table 3.9). The majority of participants would use medicinal cannabis for pain (63%, n=62), followed by cancer (45%, n=44), fibromyalgia (36%, n=35), epilepsy (16%, n=16) and multiple sclerosis (16%, n=16).

Table 3. 9 Conditions for which participants would consider using medicinal cannabis (N=98)

Medical Condition	Sample size
Anxiety	15.3% (15)
Arthritis	15.3% (15)
Asthma	1.0% (1)
ADHD	2.0% (2)
Blood pressure	1.0% (1)
Cancer	**44.9% (44)**
CINV	11.2% (11)
Depression	5.1% (5)
Epilepsy	16.3% (16)
Fibromyalgia	35.7% (35)
General mental wellbeing	1.0% (1)
Glaucoma	1.0% (1)
If my doctor recommends	2.0% (2)
Injury	1.0% (1)
Insomnia	1.0% (1)
IBS	2.0% (2)
Multiple sclerosis	16.3% (16)
Obsessive compulsive disorder	1.0% (1)
Pain	**63.2% (62)**
Parkinson's Disease	1.0% (1)
Stroke	1.0% (1)
Stress	6.1% (6)
Thrombosis induced pain	1.0% (1)
Weight	2.0% (2)

Participants were asked to rate the intensity of pain from 1 to 5, where 1 is mild pain and 5 is severe pain, for which the use of medicinal cannabis is required. Ninety (90%) participants responded this question. The majority of the respondents (32%, n=29) considered severe pain to warrant the use of medicinal cannabis. This was followed by moderate pain (28%, n=25), moderate to severe pain (25%, n=23), mild to moderate pain (9%, n=8) and mild pain (6%, n=5).

3.3.4 Experience of potential users with cannabis

When asked whether they have ever tried cannabis before, 50% (n=50) of the participants stated that they had tried it before. Participants have tried a variety of cannabis dosage forms (Figure 3.14), with the more popular way of consuming cannabis was using cannabis cigarette (84%, n=42) followed by electronic cigarette or vape (26%, n=13).

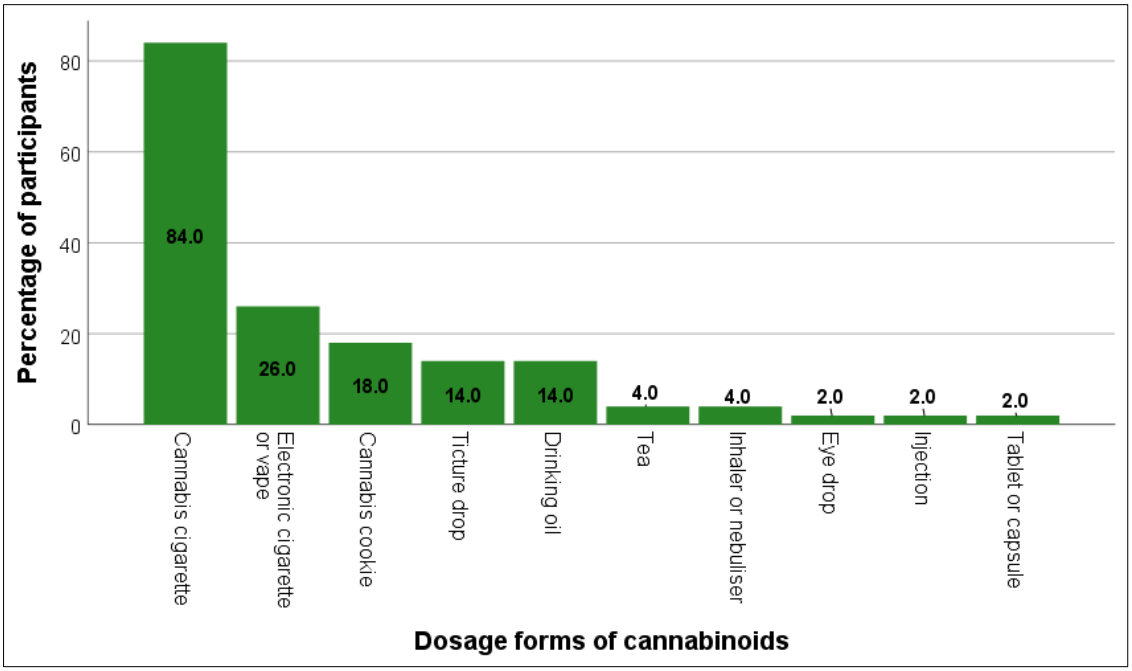


Figure 3. 14 Dosage forms of cannabinoids administered by potential users (N=50)

Eighty-seven percent (n=40) of participants who tried cannabis stated that cannabis helped them feel better.

When the feeling obtained when using cannabis was compared to the type of dosage form used (Table 3.10) it was observed that the majority of the participants who used cannabis as a cigarette (90%, n=36), cannabis cookie (89%, n=8) and tincture drop (83%, n=5) forms had considerably high responses. Participants who used cannabis as an injection (n=1) and eye drop (n=1) did not answer this question.

Table 3. 10 Aid of cannabis dosage forms for potential users (N=45)

		Did cannabis help you feel better?	
		Yes	**No**
Dosage forms administered	Cannabis cigarette	90.0% (36)	10.0% (4)
	Electronic cigarette or vape	100.0% (13)	0.0% (0)
	Inhaler or nebuliser	100.0% (2)	0.0% (0)
	Tablet or capsule	100.0% (1)	0.0% (0)
	Cannabis cookie	88.9% (8)	11.1% (1)
	Drinking oil	100.0% (7)	0.0% (0)
	Tincture drop	83.3% (5)	16.7% (1)
	Tea	100.0% (2)	0.0% (0)

3.3.5 Commencing medicinal cannabis use

Participants were asked whether they would start using medicinal cannabis if presented with the opportunity. Eighty-five percent (n=83) of participants would start using medicinal cannabis if presented with the possibility, while 5% (n=5) stated that they would not and 10% (n=10) were unsure.

The level of agreement of potential users was correlated to the number of pain medications taken. Most of the participants currently taking one (86%, n=12) or two (65%, n=11) pain medications would be willing to begin using medicinal cannabis if presented with the opportunity. All participants currently taking 3 (100%, n=3) or more than 3 (100%, n=1) medications would be willing to start using medicinal cannabis. When correlating the willingness to start using medicinal cannabis with the number of pain medications taken, a p-value of 0.592, which exceeds the 0.050 level of significance was obtained, which indicates that the differences in level of agreement for medicinal cannabis to be started do not differ meaningfully across number of pain medications administered.

The level of agreement of starting to use medicinal cannabis was assessed in relation to success with pain management (Figure 3.15). Eighty percent (n=8) of the participants who stated that their current medication is not successfully controlling the pain, would like to start using medicinal cannabis. This was followed by 78% (n=7) of participants who are unsure about whether their pain is successfully controlled with the current treatment. When the willingness to start using medicinal cannabis was correlated with the pain control with the current pain medication, a p-value of 0.797 was obtained, which indicates that the differences in preferences of starting medicinal cannabis do not differ significantly relative to pain control.

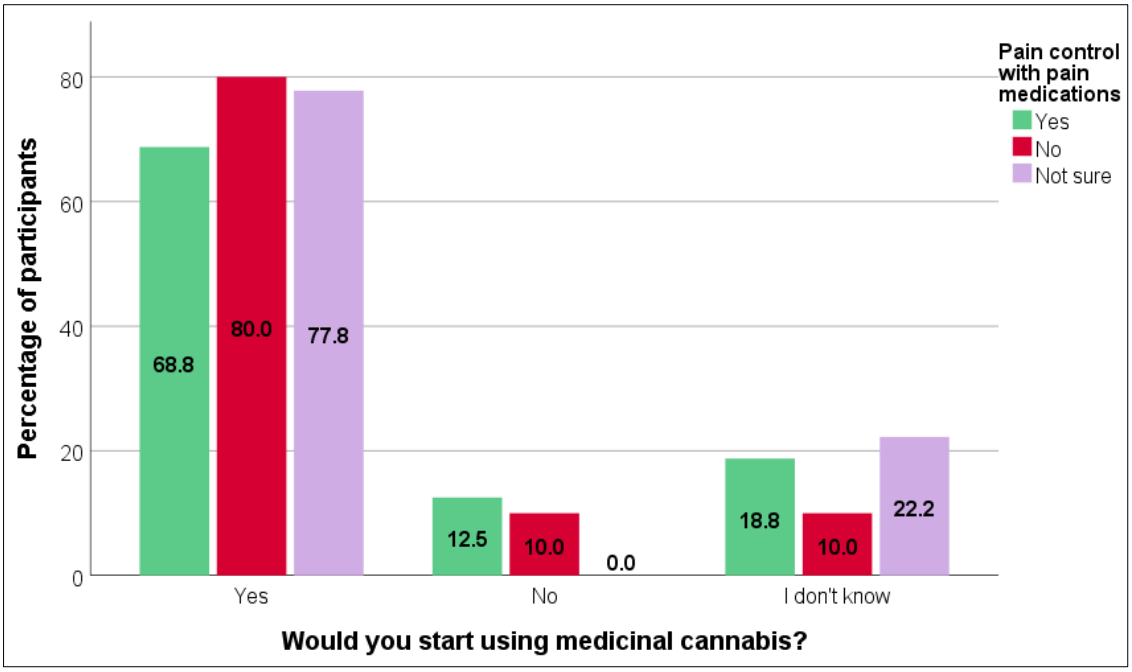


Figure 3. 15 Commencing medicinal cannabis according to pain control (N=35)

The level of agreement for potential users in commencing the use of medicinal cannabis in relation to prior cannabis administration are displayed in Figure 3.16. Ninety-six percent (n=48) of the participants with prior cannabis use would be willing to start using medicinal cannabis. The majority of participants (73%, n=36) who have never tried cannabis would be willing to start medicinal cannabis if provided. Differences in preferences for starting medicinal cannabis were found to be statistically significant in relation to prior cannabis administration with a p-value of 0.007. This indicates that, someone who has never tried cannabis would be more reluctant to start using medicinal cannabis compared to individuals with prior cannabis exposure.

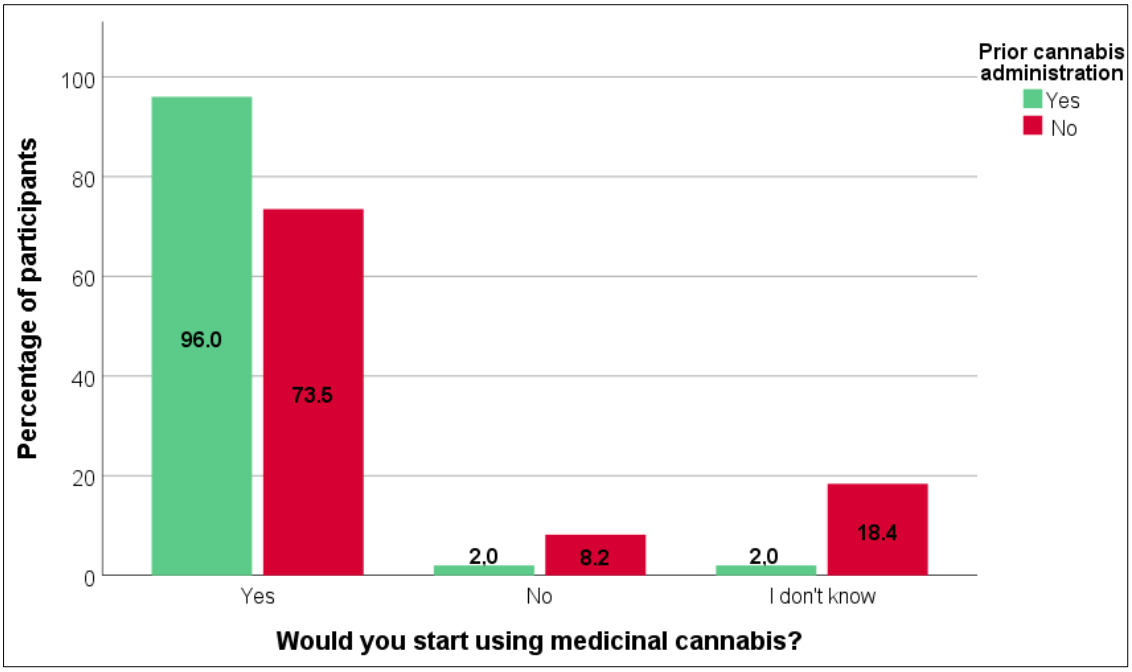


Figure 3. 16 Commencing medicinal cannabis according to prior administration (N=99)

The effect experienced by participants when trying cannabis was correlated with the willingness to start using medicinal cannabis. Nearly all of the participants who tried cannabis and benefitted from it (97%, n=39) would be willing to start using medicinal cannabis if introduced with the opportunity. The majority of respondents (83%, n=5) who did not feel better when taking cannabis would be willing to begin using medicinal cannabis. There is a statistically significant difference in the level of agreement for starting medicinal cannabis use with a p-value of 0.031, which is lower than the 0.050 level of significance. This indicates that, individuals who benefitted from the trial of cannabis would be more willing to start using medicinal cannabis compared to those who did not benefit from the trial and might be more hesitant to start using it.

When respondents were asked why they would be willing to start using medicinal cannabis, 58% (n=50) stated that they heard of others who have benefitted from the treatment and that they have been reading a lot about it (49%, n=42) (Table 3.11). Reasons for not being willing to start using medicinal cannabis included being afraid of long-term health consequences (38%, n=13) and being afraid of the social implications (29%, n=10).

Table 3. 11 Reasons to start using medicinal cannabis or not

		Sample size
Reasons for using medicinal cannabis (N=85)	I have been reading a lot about it	49.4% (42)
	I have heard of others who benefitted	58.1% (50)
	My doctor has already suggested it	14.0% (12)
	Mainstream medication is not enough	27.9% (24)
	I would simply like to try	15.1% (13)
	Neutral	1.2% (1)
	If my doctor recommends it	2.3% (2)
	It is natural and organic	2.3% (2)
	My family helps me a lot	1.2% 1)
	It is regulated	1.2% (1)
	In severe pain only	1.2% (1)
	I have tried it and it worked	1.2% (1)
	It helped in what antidepressants did not	1.2% (1)
Reasons for not using medicinal cannabis (N=34)	I do not believe it has any therapeutic value	8.8% (3)
	I do not believe it will help me but it might help others	14.7% (5)
	I would not know from where to start	20.6% (7)
	I am afraid of side-effects	26.5% (9)
	I am afraid of long-term health consequences	38.2% (13)
	It is difficult to get a doctor to prescribe it	17.6% (6)
	The whole process is too complicated	26.5% (9)
	I am afraid of the social implications	29.4% (10)
	I cannot carry it with me	2.9% (1)
	I would like to use more evaluated medicine before	2.9% (1)

3.4 Preferred methods of administration for medicinal cannabis

Medicinal cannabis users and potential users of medicinal cannabis were asked to rate different types of dosage forms from 1 to 5, according to their level of preference, where 1 is the least preferred and 5 is the most preferred. The dosage forms were divided into 2 sections, one section was related to dosage forms administered orally, rectally and systemically and the other section consisted of dosage forms administered topically or via inhalation.

3.4.1 Oral, rectal and systemic dosage form preferences of medicinal cannabis

Dosage form preferences for orally, rectally and systemically administered medicinal cannabis by users (n=72) and potential users (n=82) of medicinal cannabis are presented in Table 3.12. Medicinal cannabis users rated cookies or other food items (n=66), tea (n=65) and drinking oil (n=72) as the most preferred method of administering cannabis orally, followed by cannabis water (n=64) and vegetarian capsule (n=65). The preferred method of administration by potential users were cannabis water (n=79), followed by vegetarian capsule (n=79) and tea (n=83). The mean rating scores for injection (Mean $Score_{users}$=1.20, Mean $Score_{potential\ users}$=1.61) are the lowest indicating the least preferred method of administration by both groups, followed by suppository (Mean $Score_{users}$=1.36, Mean $Score_{potential\ users}$=1.61). A statistically significant difference in the mean rating scores of round tablet (p=0.004), caplet (p=0.001), capsule (p=0.008) and injection (p=0.022) was observed between the two groups with p-values lower than the 0.050 level of significance, these dosage forms were in favour of potential users of medicinal cannabis group.

Table 3. 12 Oral, rectal and systemic dosage form preferences of medicinal cannabis (N=154)

Form	Group	Sample size	Mean	Std. Dev.	p-value
Round tablet	Users	62	2.44	1.386	**0.004**
	Potential users	80	3.23	1.676	
Caplet	Users	62	2.39	1.383	**0.001**
	Potential users	78	3.29	1.530	
Capsule	Users	61	2.62	1.293	**0.008**
	Potential users	79	3.28	1.484	
Vegetarian capsule	Users	65	3.08	1.303	0.051
	Potential users	79	3.51	1.440	
Buccal tablet	Users	60	2.27	1.219	0.564
	Potential users	75	2.45	1.436	
Sublingual tablet	Users	61	2.43	1.372	0.521
	Potential users	74	2.61	1.479	
Cookies or other food items	Users	66	3.68	1.349	0.178
	Potential users	80	3.26	1.628	
Tea	Users	65	3.58	1.310	0.862
	Potential users	83	3.45	1.571	
Drinking oil	Users	72	3.53	1.353	0.220
	Potential users	82	3.16	1.637	
Suppository	Users	61	1.36	0.984	0.141
	Potential users	76	1.61	1.167	
Injection	Users	64	1.20	0.760	**0.022**
	Potential users	76	1.61	1.212	
Water	Users	64	3.30	1.422	0.168
	Potential users	79	3.57	1.566	

Users who would prefer switching to another mode of medicinal cannabis administration were selected. Preferences for orally, rectally and systemically administered dosage forms of cannabis among selected medicinal cannabis users were evaluated. The mean rating scores of selected dosage forms and their respective standard deviation is presented in Figure 3.17. Participants show interest in taking their medicinal cannabis as cookies or other food items (n=28), these were followed by tea (n=27), water (n=24), drinking oil (n=29) and vegetarian capsule (n=25), capsule (n=25), sublingual tablet (n=25), caplet (n=24), round tablet (n=24), buccal tablet (n=23), suppository (n=24) and injection (n=25) dosage forms. Significant differences in preferences were observed with pairwise comparisons with p-values below the 0.050 criterion, this indicated that medicinal cannabis users who would be willing to switch their dosage form would prefer using cookies or other food items significantly more than buccal tablet (p=0.015), round tablet (p=0.021) and caplet (p=0.036) forms. They prefer vegetarian capsule (p_{inj}=0.003, p_{supp}=0.006), drinking oil (p_{inj}=0.000, p_{supp}=0.000), cookies or other food items (p_{inj}=0.000, p_{supp}=0.000), tea (p_{inj}=0.000, p_{supp}=0.000) and water (p_{inj}=0.000, p_{supp}=0.001) forms significantly more than injection and suppository. They prefer capsule (p_{inj}=0.049) form more than the injection form.

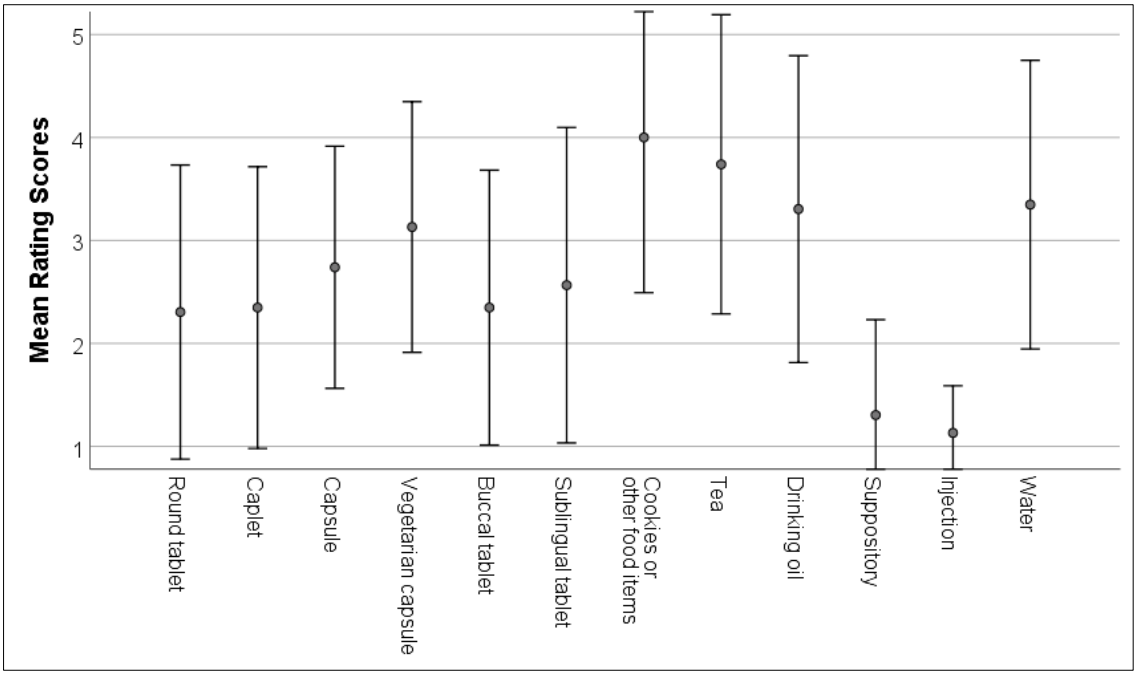


Figure 3. 17 Mean rating scores of selected medicinal cannabis users on oral, rectal and systemic dosage forms (N=29)

Dosage form preferences of users and potential users of medicinal cannabis for orally, rectally and systemically administered medicinal cannabis were evaluated according to the age (Table 3.13). A statistically significant difference was observed for the mean rating scores for round tablets with a p-value of 0.026, which is lower than the 0.050 criterion. Round tablets were not favoured with the 31-40 years age group (Mean Score 1.91) and were preferred by participants above 50 years (Mean score 3.63). A low mean rating score (<2) was observed for suppositories and injections, across all age groups.

For potential users, a statistically significant difference was found for the mean rating scores for capsule (p=0.028) and drinking oil (p=0.008) with p-values lower than the 0.050 criterion. Capsules were not so popular for the less than 30 years age group (Mean Score 2.63) but were popular between 41 years and older groups (Mean score 3.86). Drinking oil was not so popular among the >50 years age group (Mean Score 2.22) but was very popular between ages of 31 and 40 years (Mean Score 3.81).

Table 3. 13 Oral, rectal and systemic dosage form preferences according to age

		Medicinal Cannabis Users (N=69)			Potential Medicinal Cannabis Users (N=75)		
Form	**Age group**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Round tablet	30 years or less	19	2.74	**0.026**	25	2.92	0.475
	31-40 years	22	1.91		22	3.00	
	41-50 years	10	2.50		7	3.57	
	More than 50 years	8	3.63		21	3.57	
Caplet	30 years or less	19	2.47	0.224	23	2.83	0.065
	31-40 years	23	2.04		21	2.95	
	41-50 years	10	2.90		7	3.43	
	More than 50 years	7	3.14		22	3.95	
Capsule	30 years or less	18	2.61	0.223	24	2.63	**0.028**
	31-40 years	23	2.35		21	3.05	
	41-50 years	10	2.90		7	3.86	
	More than 50 years	7	3.43		22	3.86	
Vegetarian capsule	30 years or less	20	3.20	0.067	24	2.92	0.062
	31-40 years	22	2.55		21	3.43	
	41-50 years	11	3.45		8	3.50	
	More than 50 years	9	3.67		23	4.04	
Buccal tablet	30 years or less	19	2.37	0.219	22	2.14	0.576
	31-40 years	22	1.86		20	2.25	
	41-50 years	10	2.30		6	3.00	
	More than 50 years	6	2.83		21	2.62	
Sublingual tablet	30 years or less	19	2.53	0.237	23	2.26	0.139
	31-40 years	22	2.09		20	2.55	
	41-50 years	10	2.20		5	4.00	
	More than 50 years	7	3.29		21	2.62	

Table 3.13 *(cont.)* Oral, rectal and systemic dosage form preferences according to age

		Medicinal Cannabis Users (N=69)			Potential Medicinal Cannabis Users (N=75)		
Form	**Age group**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cookies or other food items	30 years or less	20	3.80	0.732	26	3.65	0.171
	31-40 years	23	3.78		20	3.35	
	41-50 years	10	3.20		7	3.71	
	More than 50 years	10	3.60		20	2.55	
Tea	30 years or less	19	3.47	0.932	25	3.56	0.742
	31-40 years	23	3.78		22	3.73	
	41-50 years	10	3.50		7	2.86	
	More than 50 years	10	3.50		23	3.39	
Drinking oil	30 years or less	21	3.29	0.504	24	3.42	**0.008**
	31-40 years	24	3.50		21	3.81	
	41-50 years	15	3.60		9	3.78	
	More than 50 years	9	4.00		23	2.22	
Suppository	30 years or less	19	1.26	0.888	24	1.29	0.211
	31-40 years	22	1.32		20	1.50	
	41-50 years	10	1.60		6	2.33	
	More than 50 years	7	1.57		21	1.76	
Injection	30 years or less	19	1.05	0.170	24	1.29	0.187
	31-40 years	23	1.04		20	1.35	
	41-50 years	12	1.42		6	2.17	
	More than 50 years	7	1.86		21	2.00	
Water	30 years or less	20	3.15	0.794	24	3.67	0.962
	31-40 years	22	3.18		3.50	3.50	
	41-50 years	11	3.45		3.67	3.67	
	More than 50 years	8	3.63		3.54	3.54	

Preferences of medicinal cannabis users for oral, rectal and systemic dosage forms did not differ significantly between males and females, since the p-values exceeded the 0.050 level of significance (Table 3.14). For potential users, a statistically significant difference was observed for the mean rating scores for suppositories with a p-value of 0.013 which is lower than the 0.050 criterion. Females (Mean Score 1.91) rated suppositories higher than males (Mean Score 1.27).

Table 3. 14 Oral, rectal and systemic dosage form preferences according to gender

		Medicinal Cannabis Users (N=66)			**Potential Medicinal Cannabis Users (N=81)**		
Form	**Gender**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Round tablet	Female	16	2.63	0.056	36	3.42	0.396
	Male	46	2.37		42	3.10	
Caplet	Female	16	2.44	0.534	34	3.59	0.172
	Male	46	2.37		42	3.10	
Capsule	Female	16	2.44	0.906	35	3.63	0.072
	Male	45	2.69		42	3.00	
Vegetarian capsule	Female	16	3.19	0.535	35	3.86	0.055
	Male	49	3.04		43	3.21	
Buccal tablet	Female	16	2.38	0.730	31	2.23	0.321
	Male	44	2.23		42	2.57	
Sublingual tablet	Female	17	2.65	0.834	31	2.42	0.386
	Male	44	2.34		41	2.73	
Cookies or other food items	Female	18	3.72	0.588	33	3.18	0.962
	Male	48	3.67		45	3.29	
Tea	Female	17	3.47	0.719	36	3.39	0.854
	Male	48	3.63		45	3.44	
Drinking oil	Female	22	3.77	0.829	35	2.74	0.061
	Male	50	3.42		45	3.47	
Suppository	Female	16	1.63	0.316	33	1.91	**0.013**
	Male	45	1.27		41	1.27	
Injection	Female	17	1.12	0.506	33	1.79	0.113
	Male	47	1.23		41	1.39	
Water	Female	16	3.00	0.764	35	3.77	0.248
	Male	48	3.40		42	3.38	

Preferences for oral rectal and systemic dosage forms of medicinal cannabis were assessed in relation to level of education (Table 3.15). For medicinal cannabis users, a statistically significant difference was observed for the mean rating scores for caplets with a p-value 0.048 which is lower than the 0.050 level of significance. Caplets were preferred by participants with a tertiary level of education (Mean Score 3.00) when compared with primary level of education (Mean Score 1.00). For potential users, a statistically significant difference was observed for cookies or other food items (p=0.012) and injection (p=0.009) forms with p-values lower than the 0.050 criterion. Cookies or other food items were preferred by participants having post-secondary educational level (Mean Score 3.80) and rated lower by individuals with a primary level of education (Mean Score 1.00). In contrast, injection was preferred by participants having a primary level of education (Mean Score 2.75) compared to individuals with a post-graduate level of education (Mean Score 1.00).

Preferences for oral, rectal and systemic dosage forms of cannabis varied marginally across different localities in the medicinal cannabis users group, since the p-values were above the 0.050 criterion. For potential users of medicinal cannabis, a statistically significant difference was observed for tablets (p=0.032) with a p-value lower than the 0.050 criterion, this indicates that round tablets are preferred by residents from the South Eastern area of Malta (Mean Score 3.96) and not so preferred by Northern Harbour (Mean Score 2.00) and Gozo (Mean Score 1.00) habitants (Table 3.16).

Table 3. 15 Oral, rectal and systemic dosage form preferences according to education level

		Medicinal Cannabis Users (N=66)			Potential Medicinal Cannabis Users (N=79)		
Form	**Education level**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Round tablet	Primary	1	1.00	0.054	4	5.00	0.063
	Secondary	17	2.76		15	2.80	
	Post-secondary	15	1.67		19	2.74	
	Tertiary	19	2.79		21	3.67	
	Post-graduate	6	2.50		17	3.35	
Caplet	Primary	1	1.00	**0.048**	4	4.50	0.366
	Secondary	17	2.53		14	2.86	
	Post-secondary	16	1.87		19	3.21	
	Tertiary	19	3.00		20	3.55	
	Post-graduate	6	2.00		17	3.29	
Capsule	Primary	1	3.00	0.116	4	4.75	0.265
	Secondary	17	2.94		13	2.92	
	Post-secondary	15	2.27		20	3.15	
	Tertiary	19	3.05		20	3.25	
	Post-graduate	6	1.67		18	3.44	
Vegetarian capsule	Primary	1	3.00	0.916	4	4.25	0.480
	Secondary	17	3.24		15	3.87	
	Post-secondary	16	2.81		21	3.43	
	Tertiary	20	3.20		20	3.20	
	Post-graduate	6	3.00		16	3.50	
Buccal tablet	Primary	1	4.00	0.589	4	2.00	0.569
	Secondary	16	2.31		12	2.08	
	Post-secondary	15	2.07		19	2.32	
	Tertiary	19	2.26		21	2.52	
	Post-graduate	6	2.67		15	2.87	
Sublingual tablet	Primary	1	4.00	0.374	4	2.50	0.419
	Secondary	17	2.59		12	2.00	
	Post-secondary	15	2.00		18	2.50	
	Tertiary	19	2.42		20	2.85	
	Post-graduate	6	3.17		16	2.94	

Table 3.15 *(cont.)* Oral, rectal and systemic dosage form preferences according to education level

		Medicinal Cannabis Users (N=66)			Potential Medicinal Cannabis Users (N=79)		
Form	**Education level**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cookies or other food items	Primary	1	5.00	0.707	3	1.00	**0.012**
	Secondary	18	3.56		16	2.44	
	Post-secondary	17	3.59		20	3.80	
	Tertiary	20	3.65		20	3.60	
	Post-graduate	6	4.00		17	3.59	
Tea	Primary	1	5.00	0.410	4	3.00	0.313
	Secondary	18	3.50		15	2.73	
	Post-secondary	16	3.56		22	3.95	
	Tertiary	20	3.40		20	3.55	
	Post-graduate	6	4.33		18	3.56	
Drinking oil	Primary	1	5.00	0.588	4	2.00	0.388
	Secondary	21	3.71		15	3.20	
	Post-secondary	18	3.33		21	3.19	
	Tertiary	21	3.43		20	2.95	
	Post-graduate	6	3.00		18	3.67	
Suppository	Primary	1	1.00	0.478	4	1.00	0.070
	Secondary	17	1.59		12	2.17	
	Post-secondary	15	1.13		19	1.42	
	Tertiary	19	1.32		20	1.90	
	Post-graduate	6	1.67		17	1.06	
Injection	Primary	1	1.00	0.331	4	2.75	**0.009**
	Secondary	17	1.35		12	2.25	
	Post-secondary	16	1.00		19	1.16	
	Tertiary	20	1.35		20	1.85	
	Post-graduate	6	1.00		17	1.00	
Water	Primary	1	5.00	0.629	4	2.75	0.622
	Secondary	17	3.53		13	3.54	
	Post-secondary	16	3.25		20	3.45	
	Tertiary	19	3.16		22	3.95	
	Post-graduate	6	3.67		16	3.44	

Table 3. 16 Oral, rectal and systemic dosage form preferences according to locality

		Medicinal Cannabis Users (N=57)			Potential Medicinal Cannabis Users (N=75)		
Form	**Locality**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Round tablet	Southern Harbour	13	2.77	0.233	27	3.37	**0.032**
	Northern Harbour	14	1.71		9	2.00	
	South Eastern	7	2.86		23	3.96	
	Western	3	2.33		8	3.63	
	Northern	12	2.67		5	2.60	
	Gozo	1	1.00		1	1.00	
Caplet	Southern Harbour	13	2.46	0.212	26	3.27	0.134
	Northern Harbour	14	1.64		9	2.56	
	South Eastern	7	2.86		23	4.00	
	Western	3	2.33		7	3.29	
	Northern	13	2.85		5	3.60	
	Gozo	1	1.00		1	1.00	
Capsule	Southern Harbour	13	2.54	0.853	26	3.19	0.143
	Northern Harbour	14	2.57		9	2.56	
	South Eastern	7	2.71		23	3.91	
	Western	2	3.00		8	3.63	
	Northern	13	2.54		5	3.00	
	Gozo	1	1.00		1	1.00	
Vegetarian capsule	Southern Harbour	15	3.33	0.657	26	3.58	0.402
	Northern Harbour	14	2.86		11	3.36	
	South Eastern	7	3.14		23	3.96	
	Western	3	3.33		6	3.33	
	Northern	13	3.15		5	3.20	
	Gozo	1	1.00		1	1.00	
Buccal tablet	Southern Harbour	13	1.92	0.253	24	2.46	0.866
	Northern Harbour	13	2.23		8	2.00	
	South Eastern	7	2.29		22	2.27	
	Western	3	1.33		7	2.86	
	Northern	12	2.92		5	2.60	
	Gozo	1	1.00		2	3.00	
Sublingual tablet	Southern Harbour	13	2.00	0.191	25	3.00	0.455
	Northern Harbour	14	2.57		8	2.00	
	South Eastern	7	2.29		21	2.38	
	Western	3	1.00		7	2.86	
	Northern	13	2.92		5	2.40	
	Gozo	1	1.00		1	1.00	

Table 3.16 *(cont.)* Oral, rectal and systemic dosage form preferences according to locality

		Medicinal Cannabis Users (N=57)			Potential Medicinal Cannabis Users (N=75)		
Form	**Locality**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cookies or other food items	Southern Harbour	15	3.67	0.493	25	2.76	0.436
	Northern Harbour	14	3.93		9	3.00	
	South Eastern	7	3.14		23	3.74	
	Western	3	4.33		10	3.40	
	Northern	13	3.38		4	3.25	
	Gozo	1	5.00		1	3.00	
Tea	Southern Harbour	14	3.86	0.424	26	3.00	0.144
	Northern Harbour	14	3.64		10	3.30	
	South Eastern	7	3.00		24	3.96	
	Western	3	3.00		9	2.78	
	Northern	13	3.62		5	3.60	
	Gozo	1	5.00		1	5.00	
Drinking oil	Southern Harbour	16	3.75	0.821	26	2.85	0.287
	Northern Harbour	14	3.29		12	3.92	
	South Eastern	7	3.29		23	2.78	
	Western	3	2.67		7	3.14	
	Northern	16	3.56		5	2.60	
	Gozo	1	4.00		1	5.00	
Suppository	Southern Harbour	13	1.31	0.863	25	1.48	0.510
	Northern Harbour	14	1.14		8	1.25	
	South Eastern	7	1.57		22	1.68	
	Western	3	1.67		8	1.25	
	Northern	12	1.67		5	2.20	
	Gozo	1	1.00		1	1.00	
Injection	Southern Harbour	14	1.07	0.973	25	1.68	0.478
	Northern Harbour	14	1.07		8	1.00	
	South Eastern	7	1.57		22	1.68	
	Western	3	1.00		8	1.13	
	Northern	14	1.29		5	2.00	
	Gozo	1	1.00		1	1.00	
Water	Southern Harbour	14	2.86	0.842	26	2.92	0.170
	Northern Harbour	14	3.36		9	3.78	
	South Eastern	7	3.43		22	4.09	
	Western	3	3.33		7	3.86	
	Northern	13	3.62		5	4.20	
	Gozo	1	4.00		1	3.00	

Dosage form preferences of the users group were assessed according to the five most prevalent medical conditions that they are using medicinal cannabis for (Table 3.17). The mean rating scores range from 1 to 5, where 1 corresponds to the least preferred and 5 corresponds to the most preferred administration method. Participants with anxiety (n=20) and pain (n=18) prefer cookies or other food items as dosage forms of medicinal cannabis, while participants with arthritis (n=7) and insomnia (n=14) prefer tea form and those with fibromyalgia (n=11) prefer drinking oil.

Table 3. 17 Mean rating scores for users preferences according to medical condition medicinal cannabis is used for (N=61)

	Anxiety (n=20)	**Arthritis (n=7)**	**Fibromyalgia (n=11)**	**Insomnia (n=14)**	**Pain (n=18)**
Round tablet	2.15	1.28	2.00	2.29	2.00
Caplet	2.05	1.86	2.00	2.36	2.11
Capsule	2.55	2.86	2.45	2.64	2.61
Vegetarian capsule	3.05	3.00	3.09	3.29	3.22
Buccal tablet	2.35	2.00	2.55	2.29	2.67
Sublingual tablet	2.50	2.00	2.91	2.57	2.67
Cookies or other food items	**4.10**	3.44	3.45	4.00	**4.28**
Tea	3.85	**4.33**	3.09	**4.14**	4.06
Drinking oil	3.50	4.00	**3.82**	3.57	3.56
Suppository	1.25	1.14	1.18	1.36	1.28
Injection	1.05	1.00	1.09	1.29	1.11
Water	3.45	2.86	3.00	3.79	3.72

Dosage form preferences of potential users group were evaluated according to the five most prevalent medical conditions for which they would use medicinal cannabis (Table 3.18). Participants suggesting the use of medicinal cannabis for fibromyalgia (n=24), multiple sclerosis (n=12) and pain (n=45) prefer using vegetarian capsules, while those suggesting medicinal cannabis for epilepsy (n=14) and cancer (n=44) prefer cannabis cookies or other food items and cannabis water respectively.

Table 3. 18 Mean rating scores for potential users preferences according to medical condition cannabis would be used (N=78)

	Cancer (n=44)	**Epilepsy (n=14)**	**Fibromyalgia (n=24)**	**MS (n=12)**	**Pain (n=45)**
Round tablet	3.21	3.50	3.29	3.42	3.36
Caplet	3.27	3.36	3.42	3.25	3.47
Capsule	3.52	3.29	3.67	**3.83**	3.42
Vegetarian capsule	3.76	3.50	**4.00**	**3.83**	**3.60**
Buccal tablet	2.36	2.43	2.25	2.42	2.36
Sublingual tablet	2.73	2.71	2.54	2.92	2.53
Cookies or other food items	3.39	**3.64**	3.08	3.75	3.11
Tea	3.39	3.43	3.46	3.33	3.22
Drinking oil	2.73	3.50	3.21	3.25	3.00
Suppository	1.91	1.14	1.67	1.92	1.67
Injection	1.79	1.36	1.46	1.50	1.51
Water	**3.91**	3.29	3.96	3.58	3.47

Dosage form preferences of users were evaluated according to the medicinal cannabis currently being used (Table 3.19). Pedanios 22/1 (n=20), Pedanios 20/1 (n=19) and Bedrocan 22 (n=29) flowers and CBD oil (n=27) users rated cannabis cookies or other food items as the most preferred compared to other dosage forms, while Bediol 6/8 (n=6) users rated sublingual tablets as the most preferred form.

Table 3. 19 Mean rating scores for users preferences according to current medicinal cannabis (N=54)

	Pedanios flower 22/1 (n=20)	**Pedanios flower 20/1 (n=19)**	**Bedrocan flower 22 (n=29)**	**Bediol flower 6/8 (n=6)**	**CBD oil (n=27)**
Round tablet	2.20	2.11	2.28	2.50	2.48
Caplet	2.15	2.21	2.28	2.50	2.48
Capsule	2.60	2.79	2.59	3.00	2.81
Vegetarian capsule	2.95	2.84	2.97	3.17	3.19
Buccal tablet	2.35	2.32	2.34	3.17	2.48
Sublingual tablet	2.55	2.53	2.45	**3.83**	2.44
Cookies or other food items	**3.65**	**3.95**	**3.83**	2.67	**4.00**
Tea	3.45	3.32	3.41	3.17	3.93
Drinking oil	3.30	3.42	3.34	3.33	3.70
Suppository	1.45	1.37	1.45	1.00	1.41
Injection	1.30	1.11	1.21	1.33	1.11
Water	3.30	3.37	3.45	3.67	3.67

Preferences of potential users for oral, rectal and systemic forms were evaluated according to previously administered cannabis dosage form(s). The mean rating scores of the five mainly used dosage forms are exhibited in Table 3.20. Tea was rated with higher scores among users of cannabis cigarette (n=25) and cannabis cookie (n=6), while drinking oil was preferred more than other forms among electronic cigarette or vape (n=6), drinking oil (n=5) and tincture drop (n=5) users. One participant who injected cannabis rated the injection form with the lowest possible score (Mean Score 1.00).

Table 3. 20 Mean rating scores for potential users preferences according to dosage forms administered (N=34)

	Cannabis cigarette (n=25)	**Electronic cigarette or vape (n=6)**	**Cannabis cookie (n=6)**	**Drinking oil (n=5)**	**Tincture drop (n=5)**
Round tablet	2.28	1.50	2.67	2.20	1.80
Caplet	2.36	2.00	2.67	2.00	2.60
Capsule	2.60	2.50	3.00	2.60	3.80
Vegetarian capsule	3.04	3.00	3.17	3.00	4.00
Buccal tablet	2.20	2.33	1.83	2.20	2.60
Sublingual tablet	2.40	2.17	2.00	2.20	2.80
Cookies or other food items	3.76	4.00	4.33	4.00	2.60
Tea	**3.96**	4.50	**4.50**	4.20	4.00
Drinking oil	3.92	**4.67**	4.33	**4.80**	**4.20**
Suppository	1.12	1.00	1.17	1.00	1.80
Injection	1.00	1.17	1.00	1.20	1.80
Water	3.08	3.33	3.67	2.80	**4.20**

3.4.2 Topical and inhalation dosage form preferences of medicinal cannabis

Preferences for topical and inhalation dosage forms of medicinal cannabis by users (n=71) versus potential users (n=89) of medicinal cannabis were evaluated (Table 3.21). The mean rating scores range from 1 to 5, where 1 corresponds to the least preferred and 5 corresponds to the most preferred administration method. Medicinal cannabis users rated cannabis cigarette (n=71), tincture (n=67) and electronic cigarette (n=63) as the most preferred method to administer cannabis topically or via inhalation, followed by applying oil on skin (n=62) and inhaler (n=66) forms. Potential users prefer patches (n=78), tincture (n=83) and balm or ointment (n=74), followed by inhaler (n=79) and cream (n=76). The mean rating scores for eye drop (Mean $Score_{users}$=2.23, Mean $Score_{potential\ users}$=2.07) are the lowest indicating the least preferred method of administration by both groups, this is followed by nebuliser (Mean $Score_{users}$=2.32, Mean $Score_{potential\ users}$=2.37). Differences in mean rating scores were found to be statistically significant in cannabis cigarette (p=0.000) and electronic cigarette (p=0.004) as the p-values are nearly zero, these dosage forms were in favour of medicinal cannabis users group.

Table 3. 21 Topical and inhalation dosage form preferences of medicinal cannabis (N=160)

Form	Group	Sample size	Mean	Std. Dev.	p-value
Cannabis cigarette	Users	71	3.89	1.347	**0.000**
	Potential users	89	2.80	1.785	
Electronic cigarette	Users	63	3.41	1.509	**0.004**
	Potential users	81	2.60	1.671	
Inhaler	Users	66	3.12	1.295	0.766
	Potential users	79	3.03	1.561	
Nebuliser	Users	63	2.32	1.401	0.772
	Potential users	76	2.37	1.365	
Spray	Users	58	2.90	1.320	0.701
	Potential users	80	2.98	1.518	
Tincture	Users	67	3.60	1.207	0.092
	Potential users	83	3.11	1.608	
Cream	Users	62	3.03	1.201	0.904
	Potential users	76	2.99	1.579	
Balm or Ointment	Users	63	3.10	1.214	0.928
	Potential users	74	3.05	1.516	
Shampoo, Conditioner, Body wash	Users	62	2.77	1.311	0.790
	Potential users	75	2.73	1.501	
Apply oil on skin	Users	62	3.15	1.353	0.451
	Potential users	78	2.95	1.537	
Eye drop	Users	60	2.23	1.267	0.321
	Potential users	75	2.07	1.319	
Patch	Users	60	2.87	1.371	0.322
	Potential users	78	3.13	1.631	

Users who would prefer switching to another mode of medicinal cannabis administration were selected. Preferences for topical and inhalation dosage forms of cannabis among selected medicinal cannabis users were evaluated. The mean rating scores of selected dosage forms and their respective standard deviation is presented in Figure 3.18. Participants show interest in administering their medicinal cannabis as cannabis cigarette (n=30), this is followed by tincture (n=29), electronic cigarette (n=26), balm or ointment (n=27), cream (n=27), apply oil on skin (n=25), patch (n=25), inhaler (n=26), spray (n=23), shampoo, conditioner or body wash (n=25), eye drop (n=25) and nebuliser (n=23) dosage forms. Significant differences in preferences were observed with pairwise comparisons with p-values below the 0.050 criterion, this indicated that medicinal cannabis users who would be willing to switch their dosage form would prefer using cannabis cigarette (p=0.002), tincture (p=0.010), electronic cigarette (p=0.041) and balm or ointment (p=0.004) forms significantly more than nebuliser form of cannabis.

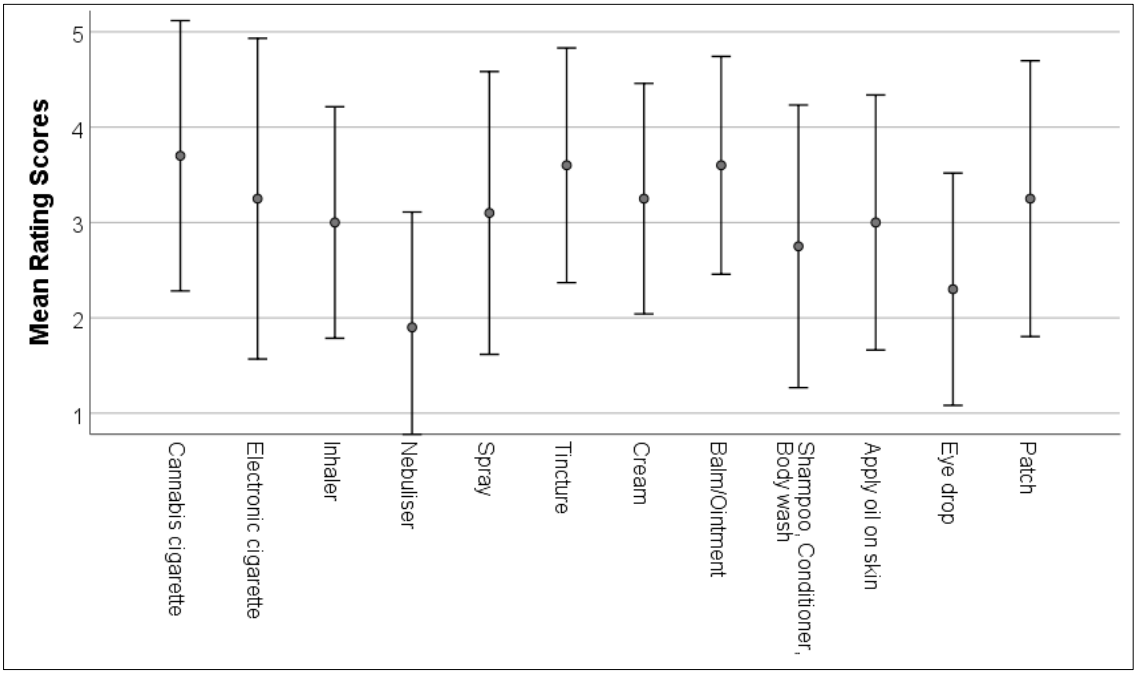


Figure 3. 18 Mean rating scores of selected medicinal cannabis users on topical and inhalation dosage forms (N=30)

Preferences for topical and inhalation dosage forms of medicinal cannabis across different age groups were evaluated for users and potential users of medicinal cannabis (Table 3.22). For medicinal cannabis users, a statistically significant difference was found for spray form with a p-value (p=0.036) below the 0.050 criterion. Participants above 50 years of age (Mean Score 4.33) rated spray higher compared to participants aged between 31 and 40 years (Mean Score 2.57).

For potential users, statistically significant differences were observed for cannabis cigarette (p=0.032) and tincture (p=0.020) with p-values less than the 0.050 level of significance. Participants of 30 years or less (Mean Score 3.46) rated cannabis cigarette higher compared to participants who are >50 years old (Mean Score 2.00). Participants within the 41-50 years (Mean Score 3.88) age group, rated tincture higher compared to the >50 years of age group (Mean Score 2.43).

Table 3. 22 Topical and inhalation dosage form preferences according to age

		Medicinal Cannabis Users (N=68)			Potential Medicinal Cannabis Users (N=81)		
Form	**Age group**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cannabis cigarette	30 years or less	19	4.11	0.175	28	3.46	**0.032**
	31-40 years	23	4.22		24	2.67	
	41-50 years	12	3.25		6	2.50	
	More than 50 years	14	3.64		23	2.00	
Electronic cigarette	30 years or less	19	4.00	0.227	26	2.88	0.131
	31-40 years	23	3.17		22	2.86	
	41-50 years	12	3.00		5	2.20	
	More than 50 years	6	3.33		21	1.90	
Inhaler	30 years or less	17	3.24	0.175	25	2.84	0.423
	31-40 years	24	2.67		21	3.10	
	41-50 years	12	3.42		7	3.86	
	More than 50 years	10	3.60		21	2.76	
Nebuliser	30 years or less	18	2.28	0.813	25	2.08	0.268
	31-40 years	22	2.50		20	2.65	
	41-50 years	11	2.00		6	2.83	
	More than 50 years	9	2.44		20	2.15	
Spray	30 years or less	18	2.72	**0.036**	26	2.65	0.084
	31-40 years	21	2.57		21	3.24	
	41-50 years	10	2.80		6	4.17	
	More than 50 years	6	4.33		22	2.64	
Tincture	30 years or less	19	3.37	0.130	26	3.00	**0.020**
	31-40 years	23	3.52		21	3.81	
	41-50 years	14	3.50		8	3.88	
	More than 50 years	8	4.50		23	2.43	

Table 3.22 *(cont.)* Topical and inhalation dosage form preferences according to age

		Medicinal Cannabis Users (N=68)			Potential Medicinal Cannabis Users (N=81)		
Form	**Age group**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cream	30 years or less	19	3.16	0.138	24	2.83	0.886
	31-40 years	22	2.73		21	3.14	
	41-50 years	10	2.70		6	3.33	
	More than 50 years	8	3.75		20	3.00	
Balm or Ointment	30 years or less	19	3.16	0.274	24	2.79	0.653
	31-40 years	22	2.77		20	3.25	
	41-50 years	10	3.00		6	3.33	
	More than 50 years	9	3.67		19	3.21	
Shampoo, Conditioner, Body wash	30 years or less	19	2.84	0.492	23	2.65	0.872
	31-40 years	22	2.64		21	3.00	
	41-50 years	10	2.40		6	2.83	
	More than 50 years	8	3.38		20	2.70	
Apply oil on skin	30 years or less	20	3.15	0.304	26	2.69	0.692
	31-40 years	21	2.86		21	3.14	
	41-50 years	11	3.09		6	3.00	
	More than 50 years	7	4.00		19	3.16	
Eye drop	30 years or less	18	2.22	0.716	24	2.00	0.538
	31-40 years	22	2.09		20	2.05	
	41-50 years	10	2.20		6	2.67	
	More than 50 years	7	2.86		20	2.05	
Patch	30 years or less	18	2.56	0.226	25	2.52	0.056
	31-40 years	22	2.68		3.14	3.14	
	41-50 years	10	3.00		3.75	3.75	
	More than 50 years	7	3.86		3.74	3.74	

Preferences for topical and inhalation dosage forms of medicinal cannabis were evaluated between males and females (Table 3.23). No statistically significant differences were observed in mean preference scores of users, since the p-values exceeded the 0.050 criterion. For potential users, statistically significant differences were observed for cannabis cigarette (p=0.004) and electronic cigarette (p=0.010) with p-values less than the 0.050 level of significance. Males preferred cannabis cigarette (Mean Score 3.26) and electronic cigarette (Mean Score 2.98) forms more than females.

Table 3. 23 Topical and inhalation dosage form preferences according to gender

		Medicinal Cannabis Users (N=71)			**Potential Medicinal Cannabis Users (N=87)**		
Form	**Gender**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cannabis cigarette	Female	22	3.77	0.559	34	2.03	**0.004**
	Male	49	3.94		53	3.26	
Electronic cigarette	Female	19	3.11	0.279	32	2.00	**0.010**
	Male	44	3.55		47	2.98	
Inhaler	Female	19	3.26	0.615	34	3.15	0.482
	Male	47	3.06		43	2.88	
Nebuliser	Female	19	2.47	0.701	32	2.44	0.511
	Male	44	2.25		42	2.26	
Spray	Female	17	3.00	0.730	35	3.17	0.192
	Male	41	2.85		43	2.74	
Tincture	Female	21	3.71	0.562	35	3.23	0.419
	Male	46	3.54		46	2.96	
Cream	Female	17	3.18	0.738	32	2.91	0.875
	Male	45	2.98		42	2.98	
Balm or Ointment	Female	17	3.24	0.588	30	3.03	0.911
	Male	46	3.04		42	3.00	
Shampoo, Conditioner, Body wash	Female	16	2.50	0.267	31	2.87	0.438
	Male	46	2.87		42	2.60	
Apply oil on skin	Female	17	3.18	0.910	32	3.06	0.405
	Male	45	3.13		44	2.77	
Eye drop	Female	16	2.00	0.414	31	2.00	0.711
	Male	44	2.32		42	2.10	
Patch	Female	16	3.25	0.185	32	3.25	0.523
	Male	44	2.73		44	3.02	

Preferences for topical and inhalation dosage forms of medicinal cannabis in relation to level of education were evaluated (Table 3.24). Differences in mean preference scores within the users group did not differ significantly with the p-values exceeding the 0.050 criterion. For potential users group, statistically significant differences were observed for cannabis cigarette (p=0.002), electronic cigarette (p=0.023) and inhaler (p=0.034) forms with p-values below the 0.050 level of significance. This indicates that, cannabis cigarette (Mean Score 3.58), electronic cigarette (Mean Score 3.45) and inhaler (Mean Score 3.83) are very popular with respondents who had post-secondary level of education and not so popular with respondents who had primary level of education (Mean Scores 1.00).

Preferences for topical and inhalation dosage forms of medicinal cannabis were evaluated according to locality (Appendix 11) for users and potential users of medicinal cannabis. For both users and potential users groups p-values exceeded the 0.050 level of significance, this indicates that mean preference scores do not vary significantly across different regions.

Table 3. 24 Topical and inhalation dosage form preferences according to education level

		Medicinal Cannabis Users (N=66)			Potential Medicinal Cannabis Users (N=85)		
Form	**Education level**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cannabis cigarette	Primary	2	5.00	0.628	3	1.00	**0.002**
	Secondary	18	3.89		20	3.35	
	Post-secondary	20	3.95		24	3.58	
	Tertiary	19	3.74		21	1.81	
	Post-graduate	7	3.86		17	2.47	
Electronic cigarette	Primary	1	5.00	0.326	3	1.00	**0.023**
	Secondary	16	2.88		15	2.33	
	Post-secondary	19	3.58		22	3.45	
	Tertiary	18	3.61		20	2.00	
	Post-graduate	6	3.67		17	2.59	
Inhaler	Primary	2	3.50	0.145	3	1.00	**0.034**
	Secondary	16	3.44		16	2.75	
	Post-secondary	18	2.61		18	3.83	
	Tertiary	19	3.47		20	3.10	
	Post-graduate	6	2.33		18	2.83	
Nebuliser	Primary	2	4.00	0.085	3	1.67	0.558
	Secondary	17	2.47		13	2.62	
	Post-secondary	17	2.00		19	2.74	
	Tertiary	17	2.59		20	2.20	
	Post-graduate	5	1.20		17	2.12	
Spray	Primary	1	3.00	0.174	3	1.67	0.261
	Secondary	16	3.31		15	2.53	
	Post-secondary	16	2.56		20	3.40	
	Tertiary	17	3.18		20	3.15	
	Post-graduate	5	1.80		18	2.94	
Tincture	Primary	1	4.00	0.593	3	2.00	0.313
	Secondary	19	3.79		17	3.71	
	Post-secondary	18	3.56		21	2.86	
	Tertiary	19	3.47		21	3.05	
	Post-graduate	6	2.83		17	3.18	

Table 3.24 *(cont.)* Topical and inhalation dosage form preferences according to education level

		Medicinal Cannabis Users (N=66)			Potential Medicinal Cannabis Users (N=85)		
Form	**Education level**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cream	Primary	1	2.00	0.817	3	2.00	0.567
	Secondary	17	3.18		14	3.07	
	Post-secondary	17	3.00		19	3.16	
	Tertiary	18	2.83		20	2.70	
	Post-graduate	6	3.17		16	3.31	
Balm or Ointment	Primary	1	4.00	0.904	3	1.67	0.372
	Secondary	17	3.18		12	3.00	
	Post-secondary	17	2.94		19	3.37	
	Tertiary	18	3.00		20	2.85	
	Post-graduate	6	3.17		16	3.31	
Shampoo, Conditioner, Body wash	Primary	1	4.00	0.383	3	1.33	0.410
	Secondary	17	3.00		14	2.50	
	Post-secondary	17	2.94		19	3.00	
	Tertiary	17	2.35		19	2.74	
	Post-graduate	6	2.33		16	3.00	
Apply oil on skin	Primary	1	4.00	0.435	3	2.00	0.831
	Secondary	17	3.41		13	3.00	
	Post-secondary	18	3.22		20	3.10	
	Tertiary	16	2.56		21	2.86	
	Post-graduate	6	3.00		17	3.00	
Eye drop	Primary	1	4.00	0.456	3	2.33	0.769
	Secondary	17	2.35		13	2.23	
	Post-secondary	16	1.88		19	2.37	
	Tertiary	17	2.35		20	2.00	
	Post-graduate	6	2.00		16	1.69	
Patch	Primary	1	3.00	0.939	3	3.67	0.695
	Secondary	17	2.88		14	3.07	
	Post-secondary	16	2.69		20	3.00	
	Tertiary	17	3.06		20	3.60	
	Post-graduate	6	2.67		17	2.88	

Preferences of users group for topical and inhalation dosage forms was assessed according to the five most prevalent medical conditions for which they specified that they are using medicinal cannabis for (Table 3.25). The mean rating scores range from 1 to 5, where 1 indicates the least preferred and 5 indicates the most preferred administration method. Participants with anxiety (n=21), arthritis (n=6) and insomnia (n=14) rated cannabis cigarette as the most preferred dosage form, while participants with fibromyalgia (n=11) and pain (n=17) prefer the tincture form.

Table 3. 25 Mean rating scores for users preferences according to medical condition medicinal cannabis is used for (N=67)

	Anxiety (n=21)	**Arthritis (n=6)**	**Fibromyalgia (n=11)**	**Insomnia (n=14)**	**Pain (n=17)**
Cannabis cigarette	**4.14**	**4.33**	3.18	**3.79**	3.76
Electronic cigarette	3.10	2.67	2.36	3.29	3.06
Inhaler	3.14	2.00	3.00	3.21	2.47
Nebuliser	2.24	1.33	2.18	2.21	1.53
Spray	2.95	2.67	3.55	2.71	2.94
Tincture	3.67	4.00	**4.00**	3.71	**3.82**
Cream	3.05	3.17	3.09	3.00	3.41
Balm or Ointment	3.05	3.83	3.27	3.07	3.65
Shampoo, body wash	2.67	3.17	2.45	2.64	3.41
Apply oil on skin	2.57	3.33	3.18	2.57	3.47
Eye drop	2.05	1.83	1.73	2.00	2.06
Patch	2.62	3.00	3.55	2.57	3.18

Dosage form preferences of potential users group were evaluated according to the five most prevalent medical conditions for which they would use medicinal cannabis. Mean rating scores are presented in Table 3.26. Participants suggesting using medicinal cannabis for multiple sclerosis (n=13) rated sprays as the most preferred dosage form, while for epilepsy (n=13) the cream form was preferred. Cannabis patch was the most preferred form among cancer (n=35), fibromyalgia (n=25) and pain (n=46) groups and second most preferred form among epilepsy (Mean Score 2.80) and multiple sclerosis (Mean Score 3.31) groups.

Table 3. 26 Mean rating scores for potential users preferences according to medical condition cannabis would be used (N=88)

	Cancer (n=35)	**Epilepsy (n=13)**	**Fibromyalgia (n=25)**	**MS (n=13)**	**Pain (n=46)**
Cannabis cigarette	2.14	2.62	1.96	2.15	2.11
Electronic cigarette	2.03	2.38	2.00	2.23	2.22
Inhaler	2.80	2.38	2.40	2.69	2.78
Nebuliser	2.26	1.85	2.40	2.15	2.41
Spray	3.34	2.69	2.96	**3.38**	2.96
Tincture	3.03	2.38	3.00	2.31	2.89
Cream	3.11	**2.85**	3.04	2.77	2.87
Balm or Ointment	2.97	2.77	2.88	2.77	2.96
Shampoo, body wash	2.86	2.62	2.68	2.85	2.76
Apply oil on skin	3.14	2.77	2.88	2.77	2.98
Eye drop	2.17	1.62	2.08	1.85	1.91
Patch	**3.37**	2.80	**3.10**	3.31	**3.25**

Users currently making use of Pedanios 22/1 (n=18), Pedanios 20/1 (n=17) and Bedrocan 22 (n=25) flowers rated cannabis cigarette as the most preferred dosage form. Bediol 6/8 flower (n=6) and CBD oil (n=23) users preferred the tincture form more than other forms. Bediol 6/8 flower users prefer electronic cigarettes and tinctures of medicinal cannabis, with both dosage forms obtaining a mean rating score of 3.83. CBD oil users prefer cannabis ointments and tinctures with both dosage forms obtaining a mean score of 3.65 (Table 3.27).

Table 3. 27 Mean rating scores for users preferences according to current medicinal cannabis (N=61)

	Pedanios flower 22/1 (n=18)	**Pedanios flower 20/1 (n=17)**	**Bedrocan flower 22 (n=25)**	**Bediol flower 6/8 (n=6)**	**CBD oil (n=23)**
Cannabis cigarette	**4.22**	**4.00**	**4.04**	3.17	3.52
Electronic cigarette	3.44	3.29	3.32	**3.83**	3.22
Inhaler	2.94	2.82	3.16	2.83	3.13
Nebuliser	2.22	1.88	2.36	1.67	2.04
Spray	2.89	2.88	2.76	3.00	3.30
Tincture	3.56	3.65	3.44	**3.83**	**3.65**
Cream	2.94	3.24	3.00	2.83	3.48
Balm or Ointment	3.11	3.59	3.12	3.00	**3.65**
Shampoo, body wash	2.72	3.06	2.80	2.00	3.26
Apply oil on skin	2.72	3.35	2.96	2.67	3.48
Eye drop	2.56	2.65	2.40	2.00	2.35
Patch	2.83	3.35	2.92	3.50	3.17

Dosage form preferences of potential users were evaluated according to 5 cannabis dosage forms which were previously administered (Table 3.28). Participants who administered cannabis cigarette (n=26) and cannabis cookie (n=6) rated cannabis

cigarette as the most preferred inhalation dosage form, while electronic cigarette or vape group (n=7) preferred electronic cigarettes. Participants who administered drinking oil (n=7) and tincture drop forms (n=5) of cannabis rated cannabis tincture as the most preferred form. Drinking oil group prefer ointments and tinctures with both dosage forms obtaining a mean rating score of 3.83. One participant who administered cannabis eye drops rated eye drops with lowest possible score (Mean Score 1.00).

Table 3. 28 Mean rating scores for potential users preferences according to dosage forms administered (N=48)

	Cannabis cigarette (n=26)	**Electronic cigarette or vape (n=7)**	**Cannabis cookie (n=6)**	**Drinking oil (n=7)**	**Tincture drop (n=5)**
Cannabis cigarette	**4.00**	2.86	**3.50**	3.50	2.60
Electronic cigarette	3.73	**4.00**	3.33	3.17	3.00
Inhaler	2.85	3.29	2.83	3.00	1.60
Nebuliser	1.88	2.57	1.67	2.67	2.40
Spray	2.73	2.86	3.17	2.83	3.20
Tincture	3.31	3.71	3.17	**3.83**	**4.20**
Cream	2.92	2.86	3.33	3.67	2.40
Balm or Ointment	2.88	3.00	3.33	**3.83**	2.20
Shampoo, body wash	2.50	2.29	3.17	3.00	2.20
Oil on Skin	2.73	2.43	3.33	3.17	2.40
Eye drop	2.04	2.29	2.67	2.33	2.00
Patch	2.42	2.71	3.17	2.67	2.20

3.5 Results of the Systematic Literature Reviews

Two systematic reviews were conducted, (i) a general systematic review about medicinal cannabis dosage forms and (ii) a review about the opinions of medicinal cannabis users or patients about dosage forms of medicinal cannabis.

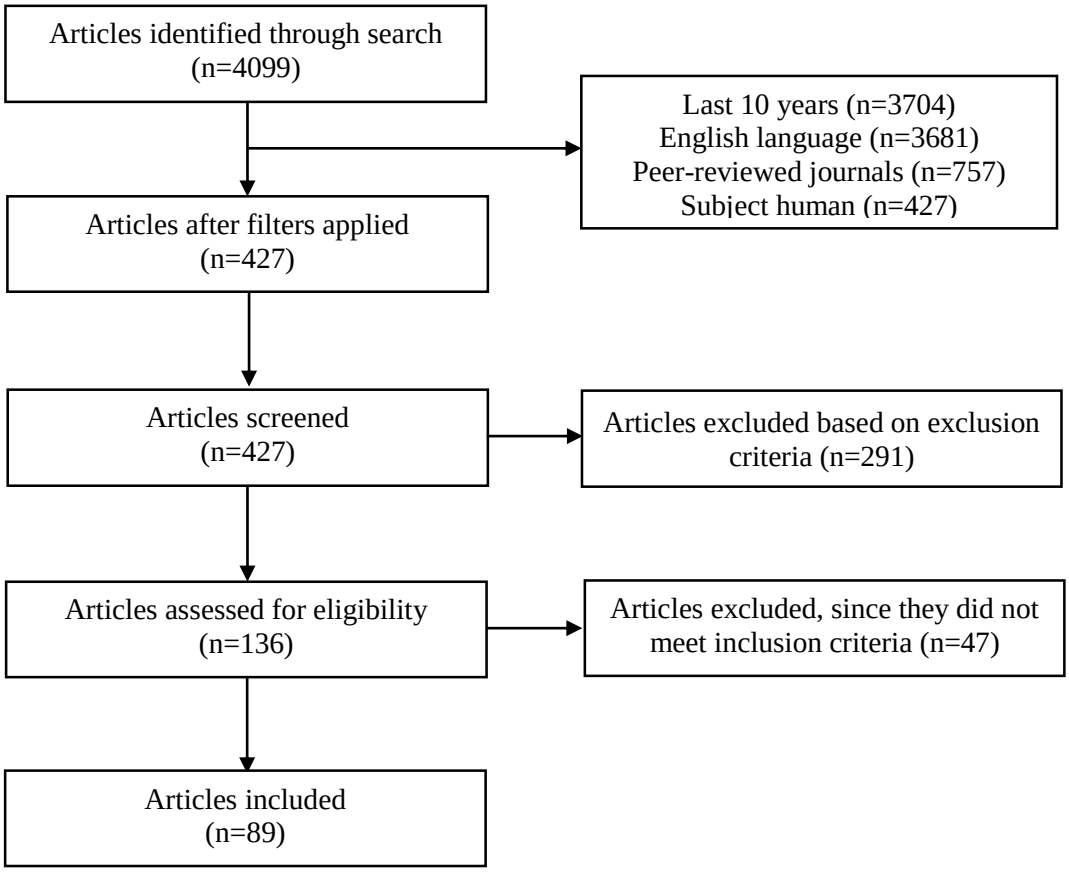
3.5.1 General Systematic Review

A systematic literature review was undertaken to identify studies which focused on cannabis dosage forms. Initially a total of 4099 articles were determined to be related to medicinal cannabis dosage forms. The following filters were applied: Publication date of last 10 years (n=3704), articles in English language (n=3681), peer-reviewed journals (n=757) and subject as human (n=427). A total of 427 articles were shortlisted and 89 of them met the inclusion criteria (Flowchart 3.1).

Eighty-nine studies which assessed medicinal cannabis dosage forms were identified for the study (Appendix 12). The majority of the studies were carried out in the USA (n=55), followed by Germany (n=6), Australia (n=5) and Switzerland (n=5), Canada (n=4) and the United Kingdom (n=4), Italy (n=3), the Netherlands (n=2), China (n=1), New Zealand (n=1), France (n=1), Israel (n=1) and Poland (n=1). Participants were recreational cannabis users (n=66), healthy volunteers (n=20) or medicinal cannabis users (n=3). Few studies (n=8) considered medical conditions, amongst which the focus was a single medical condition such as cancer or chemotherapy-induced nausea and vomiting (n=4), spasticity in multiple sclerosis (n=3) or pyoderma gangrenosum (n=1). The scope of the studies were mainly the pharmacodynamics (n=41) of cannabis including side effects (n=11), withdrawal effects (n=4), tolerance (n=3), abuse potential (n=3) and effect on driving performance (n=2). Thirty-two studies were related to the pharmacokinetic profile of cannabis, with special focus on the quantification or stability of cannabis in oral fluid

(n=17), plasma (n=9) or urine (n=4). Other studies assessed types of dosage form used (n=12) and opinions about medicinal cannabis dosage forms (n=4).

Flowchart 3. 1 Flowchart based on PRISMA method for systematic reviews (Adopted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Medicine. 2009;6(7):e1000097.)



Forty-three studies had a small number of participants, not more than 20, while 28 recruited 20 to 50 participants. Most (n=11) of the countries involved less than 20 participants in their study. Four studies in the USA included over 3000 participants (Table 3.29). Eighteen studies were published in 2017, followed by 13 studies published in 2018 and studies in 2013 (n=11) and 2014 (n=11) (Table 3.30).

Table 3. 29 Participants in the general systematic review (N=89)

Number of Participants	Number of Studies	Country
<20	43	Australia, Canada, China, Germany, Israel, Italy, New Zealand, Switzerland, The Netherlands, UK, USA
20-50	28	Australia, Canada, Germany, Poland, Switzerland, The Netherlands, UK, USA
51-100	5	Australia, France, USA
101-500	5	Canada, Germany, Italy, USA
501-1000	1	USA
1001-3000	3	Switzerland, UK, USA
3001-6000	2	USA
>6000	2	USA

Table 3. 30 Publication year of the studies in the general systematic review (N=89)

Publication Year of the Studies
2010 (n=5) 2011 (n=8) 2012 (n=9) 2013 (n=11) 2014 (n=11) 2015 (n=7) 2016 (n=7) 2017 (n=18) 2018 (n=13)

Fifty-nine studies were related to one type of cannabis delivery system, the majority being about smoked medicinal cannabis (n=30), followed by oral cannabis (n=15). Twenty-four studies compared two types of cannabis delivery, including smoked versus oral (n=9), oral versus oro-mucosal (n=5) and smoked versus vaped (n=4). Six studies involved 3 types of cannabis delivery such as oral, vaped, smoked (n=4) and smoked, vaped, edible (n=2). Studies including 3 types of cannabis delivery were performed in the UK and the USA (Table 3.31).

Table 3. 31 Delivery systems in the general systematic review (N=89)

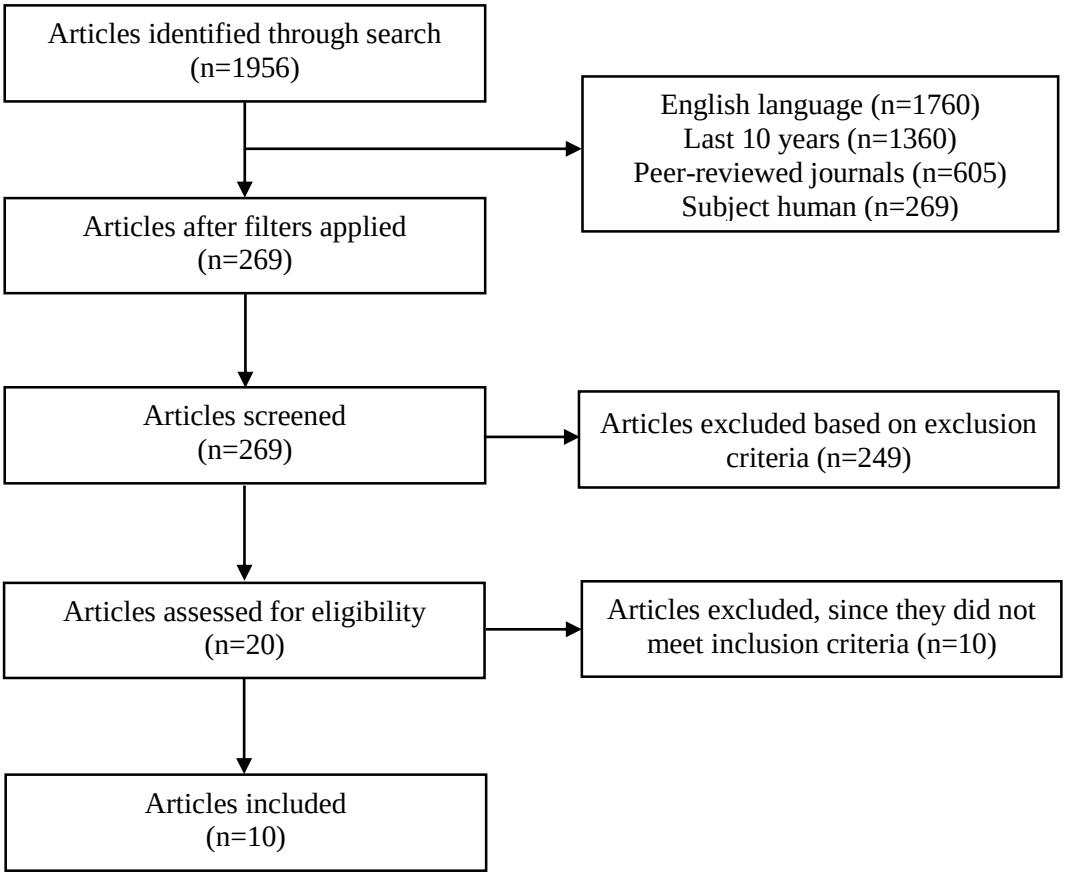
Number of delivery systems	Delivery type	Number of Studies	Country
1	Smoked (n=30) Oral (n=15) Oro-mucosal (n=5) Edible (n=4) Vaporised (n=2) Systemic (n=2) Topical (n=1)	59	Australia, Canada, China, France, Germany, Italy, New Zealand, Poland, Switzerland, The Netherlands, UK, USA
2	Smoked-oral (n=9) Oral-oromucosal (n=5) Smoked-vaped (n=4) Smoked-edible (n=3) Oral-oral (n=2) Oral-systemic (n=1)	24	Canada, Israel, Switzerland, UK, USA
3	Oral-vaped-smoked (n=4) Smoked-vaped-edible (n=2)	6	UK, USA

3.5.2 Systematic Review about Preferences on Cannabinoid Dosage Forms

A systematic review of the literature published over the last 10 years, was undertaken to identify studies based on opinion of patients or medicinal cannabis users about cannabinoid dosage forms. Initially 1956 articles related to opinions about medicinal cannabis dosage forms were identified. The following filters were applied: Articles in English language (n=1760), publication date of last 10 years (n=1360), peer-reviewed

journals (n=605) and subject as human (n=269). A total of 269 articles were reviewed and 10 of them met the inclusion criteria (Flowchart 3.2).

Flowchart 3. 2 Flowchart based on PRISMA method for systematic reviews (Adopted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Medicine. 2009;6(7):e1000097.)



Ten studies assessed opinions of patients or medicinal cannabis users about cannabinoid dosage forms (Appendix 13). Most studies (n=6) were carried out in the USA, followed by studies included countries from multiple regions (n=2) including Canada, Germany, Hungary, Ireland, Spain, Japan and the USA, Germany (n=1) and Australia (n=1). Participants of the studies were generally medicinal cannabis users (n=7) or patients with medical conditions (n=3). Six studies included multiple medical conditions, while 3

focused on single medical conditions such as head and neck cancer (n=1), epilepsy (n=1) and amyotrophic lateral sclerosis (n=1) and one did not specify the condition. Scope in the studies were opinion of patients or medicinal cannabis users on cannabinoid dosage forms (n=9), and likes and dislikes about cannabis dosage forms (n=1).

Four studies were performed in Australia, Germany and the USA and included less than 100 participants, while 3 were performed in the USA and recruited more than 1000 participants. Two studies were performed in multiple countries and involved number of participants over 500 up to 1000 (Table 3.32). Four studies were published in 2018, followed by studies published in 2013 (n=2) and 2016 (n=2) (Table 3.33).

Table 3. 32 Participants in the systematic review about preferences (N=10)

Number of Participants	Number of Studies	Country
<100	4	Australia, Germany, USA
100-500	1	USA
501-1000	2	Multiple Countries including Canada, Germany, Hungary, Ireland, Spain, Japan and USA
>1000	3	USA

Table 3. 33 Publication year of the studies in the systematic review about preferences (N=10)

Publication Year of the Studies
2013 (n=2) 2016 (n=2) 2017 (n=1) 2018 (n=4) 2019 (n=1)

Three studies were related to one type of cannabis delivery such as smoked (n=2) and oro-mucosal (n=1) forms. One study compared smoked and vaped cannabis. Four studies involved 3 to 5 types of cannabis delivery including smoked, vaped and edible (n=2) forms. Two studies involved 6 to 8 types of cannabis delivery systems including smoked, vaped, edible, oral, oro-mucosal and topical (n=1) forms and were performed in Australia (n=1) and 31 countries including the USA and Germany (n=1) (Table 3.34).

Table 3. 34 Delivery systems in the systematic review about preferences (N=10)

Number of delivery systems	Delivery type	Number of Studies	Country
1	Smoked (n=2) Oro-mucosal (n=1)	3	Germany, USA and Multiple Countries including USA, UK, Canada,
2	Smoked-vaped (n=1)	1	USA
3-5	Smoked-vaped-edible (n=2) Smoked-vaped-edible-topical (n=1) Smoked-vaped-edible-oral-oromucosal (n=1)	4	USA
6-8	Smoked-vaped-edible-oral tablets-capsules-oro-mucosal-topical (n=1) Oral tablets-capsules-sublingual drop-sublingual spray-inhaled-enteral feeding liquid-suppository-topical (n=1)	2	Australia and 31 Countries including USA, Germany and France

4. Discussion

There is a variety of delivery systems available for medicinal cannabis worldwide, but there is limited information about the perception of patients about delivery systems. This is an innovative study including 25 different dosage forms of medicinal cannabis while other studies focused on 2 dosage forms of cannabis or did not include more than 8 forms (Hazekamp et al, 2013; Elliott et al, 2016; Lee et al, 2016; Daniulaityte et al, 2017; Bruce et al, 2018; Kerai et al, 2018). This study focused on patient-centred approach which may have an impact on quality of life of patients with chronic comorbidities. Taking a patient-focused approach when formulating medicinal products is essential in improving the quality of life of patients (Fiz et al, 2011; Ware et al, 2015; Lowe et al, 2016; Sexton et al, 2016; Capano et al, 2019).

This study did not only consider opinions of medicinal cannabis users, but also included potential users of medicinal cannabis, thereby the opinions of prospective users of medicinal cannabis were also evaluated. Most of the patients who are prescribed medicinal cannabis attend at the clinics where the study was undertaken.

This study adds to the knowledge about the pharmacokinetic profile of medicinal cannabis including onset for reaching the desired effect, duration of the effect and perceived side effects. Differences in preferences and pharmacokinetic findings could be evaluated by taking patients demographics into consideration.

4.1 Perception and preferences of medicinal cannabis users and potential users

Two self-administered questionnaires were developed, one for medicinal cannabis users and another one for potential users of medicinal cannabis, to identify patient-centred delivery approaches. The questionnaires focused on i) reasons for medicinal cannabis use and prospective use ii) pharmacokinetic profile and ease of administration of medicinal cannabinoids used in Malta iii) contentment of patients with current medicinal cannabis

delivery systems iv) experience of potential users on cannabis dosage forms v) pain intensity to start using medicinal cannabis vi) perception of potential users about starting medicinal cannabis use vii) pain management of potential users of medicinal cannabis and viii) perception of users and potential users about medicinal cannabis and preferred delivery methods used for medicinal cannabis.

The main reason for using medicinal cannabis among the study population was pain, followed by anxiety, insomnia, fibromyalgia and arthritis. Medicinal cannabis was being used to cope for a broad range and co-existing medical conditions. Some of the conditions for which medicinal cannabis is being used for is not approved by the scientific community. These findings are similar to other studies assessing reasons for using medicinal cannabis in Spain (Fiz et al, 2011), the United States of America[22] (Buckner & Zvolensky, 2014; Bonn-Miller et al, 2014; Pearce et al, 2014; Webb & Webb, 2014; Sexton et al, 2016; Reiman et al, 2017), Australia (Luckett et al, 2016; Lintzeris, 2018) and Canada (Shiplo et al, 2016) and a study involving 31 countries including the USA, Germany, France, the Netherlands and Spain (Hazekamp et al, 2013). Potential users would consider using medicinal cannabis for pain and cancer, followed by fibromyalgia, epilepsy and multiple sclerosis. In this study, there were only two participants making use of medicinal cannabis for treating cancer and chemotherapy-induced conditions. The sample included participants with multiple comorbidities and the majority of the

[22] Hello MD. Medical marijuana patient survey results [Internet]. California: Hello MD; 2016 [cited 2020 May 10]. Available from URL: https://s3-us-west-2.amazonaws.com/hellomd-news/HelloMD_Medical_Marijuana_Patient_Survey.pdf

participants were using or would use medicinal cannabis for chronic pain which is among the main indications to use cannabis for medicinal purposes.

Some of the patients were using medicinal cannabis solely to manage anxiety, and among these, some patients were using high tetrahydrocannabinol (THC) containing formulations of cannabis. Medicinal cannabis formulations approved in Malta mainly contain high levels of THC. Cannabidiol (CBD) is may be beneficial for treating anxiety-like conditions, however THC is known to cause anxiety as a side effect (Gomes et al, 2011; Cox, 2015; Whiting et al, 2015; Bridgeman & Abazia, 2017; Reiman et al, 2017; Abrams, 2019; Shannon et al, 2019).

Flower (Pedanios 22/1 & 20/1, Bedrocan 22, Bediol 6/8) and oil (CBD, CBG, 50/50) formulations of medicinal cannabis are used by patients in Malta. Nearly half (49%) of the study population use more than one type of medicinal cannabis to manage co-existing conditions. Pharmacokinetic characteristics such as onset of the desired effect, effective period and side effects experienced when administering medicinal cannabis formulations were assessed. It was found that, overall onset with flower and oil formulations were reached within few seconds to 15 minutes by the majority of participants. Medicinal cannabis was perceived to remain effective for 1 to 2 hours and 2 to 3 hours by the majority of the respondents. There was no difference in onset of effect or effective period across the age groups. Effective period was assessed according to type of medicine. Participants perceive a similar duration of effect with different types of medicinal cannabis.

The main side effects of medicinal cannabis were feeling hungry, energised, sleepy and high. Some participants also experienced feeling dizzy, calm and peaceful, nauseated and more alert after administering their medicinal cannabis. These side effects were also

reported in studies conducted in Spain (Borràs et al, 2011), the USA (Pearce et al, 2014; Sagar et al, 2018) and Australia (Agar, 2018). Participants reported feeling energised and sleepy after taking their medicine, this could be due to the variety in medicinal cannabis strains or the mood and life-style of patients. At times they would feel sleepier maybe due to not getting enough sleep and at times feeling energised while they experience stressful moments at work. Side effects of medicinal cannabis were evaluated in relation to the period they have been using medicinal cannabis, age, gender and the type of medicine. The side effect profile of medicinal cannabis did not differ significantly with the period when medicinal cannabis was started or age of participants. No statistically significant differences were observed in relation to gender. These findings are similar to a study conducted in the USA (Fogel et al, 2017). More Pedanios and Bediol flowers and CBD oil users reported that they feel energised compared to other dosage forms. While Bedrocan flower users feel hungry. Interestingly, users administering different THC and CBD ratios (22/1, 20/1, 22, 6/8) of medicinal cannabis flowers reported to feel high in similar proportions (40%), this is may be due to the co-use of medicinal cannabinoids.

Ease of medicinal cannabis administration was evaluated. Patients on average find the administration of their medicinal cannabis easy. More than half of the participants were not willing to change their current delivery method and correlated with the type of medicinal cannabis they are using. A statistically significant difference was observed for Bedrocan flower users. The majority of Bedrocan users were identified to be in favour of keeping their current mode of cannabis delivery. Reasons for switching to another mode of cannabis delivery were perceived to be the inconvenience in use at work and dislike over CBD oil taste and compare with other alternatives, since there are many alternatives for using medicinal cannabis. Participants believe other modes of cannabis may also help them and perhaps be cheaper in price. These reasons show that although patients are

happy with their current mode of delivery, they would like to try other modes of medicinal cannabis.

Reasons for not switching to another mode of cannabis delivery cited by participants include that their current medicinal cannabis is effective and that they find it easy to administer the current medication since they are used to calculating their doses. Other reasons included complexity in the process of getting legal medicinal cannabis and that cannabis may have an impact on their health therefore they would not be in favour of changing their current mode. These reasons were in accordance with studies conducted in Australia (Malouff & Rooke, 2014; Luckett et al, 2016), Switzerland (Etter, 2015) and were similar to studies evaluating the reasons for other medicinal cannabis dosage form (tincture, edibles, oro-mucosal spray, concentrates) in 31 countries (Hazekamp et al, 2013), the USA (Cavazos-Rehg et al, 2018; Giombi et al, 2018) and Germany (Meyer et al, 2019). The findings were in accordance with studies comparing the reasons for preferences between two cannabis dosage forms such as vaping versus smoking in Canada (Shiplo et al, 2016) and the USA (Lee et al, 2016; Morean et al, 2017).

As highlighted by users, the process of getting legal medicinal cannabis is complex. The procedure required to obtain medicinal cannabis entails an application signed by medical practitioner and patient. Superintendent of Public Health reviews the application and once approve, medical practitioner apply for the control card. The first permit approved by the Superintendent of Public Health provides a limited access (2 weeks to 1 month) for medicinal cannabis.

Patients require a copy of the permit signed by Superintendent of Public Health, a control card and a green prescription for buying medicinal cannabis. After two weeks to one month a second application needs to be submitted to the Superintendent of Public Health

to obtain a permit for a longer period of time. [20] This submission needs to go through the same procedure used for the first application. It is suggested to revise the system, to improve patients' access and not to discourage patients from applying and making use of the drug.

Patients need to pay for the vaporiser as well as the medicinal cannabis out of pocket each time they need to fill the prescription. Patients with chronic conditions for which medicinal cannabis may be required for a long period of time might find it difficult to acquire the medicine in terms of affordability. In Malta, the Mighty Medic® or Volcano® vaporiser (Hazekamp et al, 2006) which needs to be bought once costs €250. A gram of Pedanios, Bedrocan or Bediol flower costs €16 in Malta while a gram of cannabis flower costs €5.80 in the Netherlands and the prices of cannabis flowers may go up to €25 depending on the country.[23] Consumption of medicinal cannabis may vary among patients, some patients use 0.2 grams daily while some patients use 2 grams daily. Medicinal cannabis can be included in the formulary or provide a partial reimbursement scheme for patients with chronic conditions for which medicinal use of cannabis is approved by the scientific community. The availability of the other dosage forms preferred by patients, other than cannabis flowers, and a less complex process ensures to have a patient-centred medicinal cannabis delivery system and an improved medication access.

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[20] Superintendent of Public Health SPH Circular Prescribing and dispensing of medical cannabinoids 2018 [Internet]. Malta: [cited 2020 May 12]. Available from URL: https://deputyprimeminister.gov.mt/en/Pharmaceutical-Unit/Documents/Circulars/SPH_Circular_2-2018.pdf

[23] Bedrocan. A fully standardised product, but with different prices. How come? 2020 [Internet]. The Netherlands [cited 2020 June 8]. Available from URL: https://bedrocan.com/fully-standardised-product-but-with-different-prices/

Half of the potential users have used cannabis and were assessed about their experience and opinions on cannabis dosage forms. The majority of potential users tried cannabis cigarette, and other forms of cannabis used were electronic cigarette or vape, cannabis cookie, tincture drop, drinking oil, tea, inhaler or nebuliser, tablet or capsule, eye drop and injection. Studies in Spain (Fiz et al, 2011), the USA and Canada (Goodman et al, 2020) also assessed cannabis dosage forms administered by potential users, and found that the use of smoked or vaped cannabis, concentrates, tablets, edibles and oils were prevalent among potential users. The majority of the potential users have shown that they benefitted from the trial of cannabis dosage forms. Similarly studies in Canada (Ware et al, 2015) and the USA (Elliott et al, 2016; Cofield et al 2017; Reiman et al, 2017; Sagar et al, 2018) found improvements in patients with cannabis use.

Potential users considered severe pain to warrant the use of medicinal cannabis, this was followed by moderate pain and moderate to severe pain.

Reasons why potential users would start using medicinal cannabis were evaluated. Most of the potential users (85%) would be willing to start using medicinal cannabis if presented with the possibility to do so. This finding was in accordance with a study conducted in Canada where 73% of participants were willing to start using medicinal cannabis (Shiplo et al, 2016). No correlation was observed between the desire to use medicinal cannabis and the number of pain medications being taken or success in pain management with currently administered pain medications. The decision was influenced by prior cannabis administration and benefit, for someone who tried cannabis before would be more willing to start using medicinal cannabis, while one who never tried cannabis would be more worried of starting using it. Similarly, individuals who benefitted from the trial of cannabis would be more willing to start using medicinal cannabis

compared to those who did not benefit from the trial and might be more hesitant to start using it.

Reasons to start using medicinal cannabis included reading a lot about medicinal cannabis and hearing from others who benefitted from cannabis use. Participants also believe that mainstream medications may not be enough to treat their medical condition and some participants would simply like to try medicinal cannabis. The main concern for not starting to use medicinal cannabis was the complexity of the application process, which was also cited by medicinal cannabis users. Patients visiting clinics for palliative care may not have enough time to go through the process to be eligible to be prescribed with medicinal cannabis. The other main concern for not starting medicinal cannabis use was the implications on health, this may be because patients read a lot and are aware of consequences associated with long-term use of cannabis including psychosis, effect on brain development at early age, concentration problems and becoming addicted to other substances (Crean et al, 2011; Solowij et al, 2012; Bridgeman & Abazia, 2017; Schauer et al, 2017; Mensen et al, 2019). The reported reasons are in accordance with a study conducted in Australia (Luckett et al, 2016). Patients could be given more information about medicinal cannabis to help them overcome their fear of using cannabis. Information is already being given to patients through the Pain Clinic whereby workshops about medicinal cannabis. Such lectures given by doctors could be very useful to empower patients and increase their confidence in the treatment with medicinal cannabis and overcome their fear. Shiplo et al (2016) conducted a study in Canada whereby they assessed reasons why potential users do not want to start using vaporisers, and these included affordability and difficulty in using vaporiser. Potential users in Canada never used vaporiser whereas potential users in this study used some forms of cannabis

including vaporisers. Since participants in the Canada study never used a vaporiser, they could have perceived their use as being difficult.

Some participants of the potential users group were observed to use 3 or more types of pain medications and some participants were unable or unsure whether their pain was under control with current pain medications. It is important to evaluate the chronic pain management of patients. Administering multi-medications and not obtaining control may cause more harm than benefit, as all medications have side effects and possible interactions. This study did not assess the type of pain medications administered. Some pain medications like opioids have a substantial impact on respiratory health, medicinal cannabis could be used in conjunction with opioids and thereby may decrease the use of opioids and related potential side effects (McCarberg, 2007; Elliott et al, 2016; Capano et al, 2019). Patients who are currently administering multiple pain medications could be considered for starting the use of medicinal cannabis.

Perception of users and potential users about medicinal cannabis and preferred delivery methods used for medicinal cannabis were evaluated. Preferences about i) oral, rectal systemic dosage forms and ii) topical and inhalation dosage forms of medicinal cannabis were considered separately. To evaluate preferences for dosage forms of medicinal cannabis, the rating scores of users and potential users were compared.

Evaluation of oral, rectal and systemic dosage form preferences of medicinal cannabis identified that, cookies or other food items, tea and drinking oil are preferred by medicinal cannabis users. This finding is in accordance with studies conducted in the USA (Elliott, 2016; Bruce et al, 2018; Boehnke et al, 2019). Potential users of medicinal cannabis prefer using cannabis water, vegetarian capsules and cannabis tea. Tablet, capsule and injection forms were significantly preferred by potential users compared to users. These forms

were also preferred in studies performed in Australia (Luckett et al, 2016; Kerai et al, 2018). Cannabis injection was rated the lowest by both users and potential users group, indicating that injection is the least preferred form. This might be attributed to the invasiveness of this type of administration.

The currently approved delivery system in Malta are cannabis flowers used with vaporisers. The approval of edibles, drinking oil, tea, water and vegetarian capsules would lead to the availability of dosage forms which are more favoured by patients. Edible forms are easier to administer and carry around. Any undesirable taste can be masked and one might be given the option to choose the preferred flavour. However it is challenging to dose edibles when formulating and administering them. Edibles have unpredictable pharmacokinetic profile. An oily base would be necessary in the formulation to extract cannabis from the plant material (Murphy et al, 2015; Borodovsky et al, 2016; Bruni et al, 2018). Patients with chronic conditions may benefit from the long lasting effects of edible cannabis.

Using tea, drinking oil and water forms of cannabis could be beneficial for paediatric and elderly populations as well as for patients with conditions associated with eating difficulties including anorexia, palliative care, post-surgery and dental conditions. Vegetarian capsules could have been preferred by participants due to the trend and popularity in choosing vegetarian or they could be vegetarians. Since the demand for vegetarian formulations is high among patients, the pharmaceutical industry can address this demand by using vegetarian friendly ingredients such as by substituting the gelatine capsule with hydroxypropyl methylcellulose (HPMC) which was found to be as efficient as gelatine (Sherry Ku et al, 2010). This change can be implemented without compromising the stability of the formulation to produce a patient-centred medicinal cannabis formulations. Vegetarian capsules have a longer duration of effects compared

to inhaled forms, however it undergoes first pass metabolism like any other oral formulations (Grotenhermen, 2004a; Borodovsky et al, 2016; Bridgeman & Abazia, 2017). Patient-preferred dosage forms like capsules, edibles, oils and waters could be convenient to administer in public and would not require preparation.

The preferences of medicinal cannabis users who are willing to switch their mode of cannabis delivery is comparable to the users population who do not want to change their current delivery system. Preferences for oral, rectal and systemic dosage forms varied significantly for round tablets among users of medicinal cannabis. Users above 50 years of age tend to prefer using round tablets more than participants aged between 31-40 years. Capsules are the preferred form for potential users who are 41 years and older, while not so popular for less than 30 years of age. Drinking oil was preferred by potential users aged between 31 and 40 years and was less favoured by participants above 50 years. Among medicinal cannabis users, females prefer edible forms more than males. This observation is in accordance with a study conducted in the USA (Boehnke et al, 2019), however in this study gender preferences did not differ significantly. Female participants within the potential users of medicinal cannabis rated suppositories higher than males. For medicinal cannabis users, caplets were preferred by participants having a tertiary level of education when compared with participants with primary level of education. For potential users cookies or other food items were preferred by participants having post-secondary educational level more than primary level and injection was preferred by primary level more than post-graduate level of education. Preferences of medicinal cannabis users did not vary across different localities, however for potential users round tablet was preferred by residents from South Eastern area and not so preferred by Northern Harbour and Gozo habitants. To the author's best knowledge, there is only one study which included demographics in relation to cannabis dosage form preferences

(Boehnke et al, 2019). When participants were grouped according to demographic characteristics, differences in preferences were observed for some dosage forms like round tablet, capsule, drinking oil, suppository, caplet, edibles and injection. This was important in seeing how ideas and preferences differ among several groups and showed that the appearance of the tablet (round tablet, caplet) could be important when formulating medicinal cannabis. Formulating a tablet whether it is round or elongated is not a challenging procedure, the main concern could rather be the stability of the tablet. Cannabis may require special formulations due to its highly lipophilic nature and complex physico-chemical characteristics (Bruni et al, 2018; MacCallum & Russo, 2018). Ester formulation of medicinal cannabis can be used when formulating suppositories (Kalant, 2001; McGilveray, 2005) and water-miscible formulations can be used when formulating injection to improve absorption (Kalant, 2001; Grotenhermen, 2004a; Bridgeman, 2017). First pass metabolism can be bypassed by using rectal and systemic routes (Kalant, 2001). Cannabis suppository and injection could be indicated for specific patient populations such as cancer, paediatric and elderly as well as patients with oral and dental problems.

Preferences were assessed in relation to the five most prevalent medical conditions for which users are using medicinal cannabis for. Participants with anxiety and pain rated cookies or other food items as the most preferred, while participants with arthritis and insomnia preferred tea and those with fibromyalgia preferred drinking oil. Medical conditions for which potential users specified they would be using medicinal cannabis were correlated with preferences. Participants selecting fibromyalgia, multiple sclerosis and pain rated vegetarian capsule as the most preferred, while epilepsy and cancer groups prefer cannabis cookies or other food items and cannabis water respectively. The studies in Australia evaluated patients and identified cannabis tablets and capsules to be preferred among cancer (Luckett et al, 2016) and multiple sclerosis patients (Kerai et al, 2018),

another study in the USA assessing preferences also found edible forms of cannabis to be preferred among chronic pain patients (Boehnke et al, 2019). Cannabis water provides easy administration and its use could be favourable in chemotherapy-induced nausea and vomiting and palliative care. Dosage forms with long-lasting effect profile (tablet/capsule/edibles) could be advantageous for the use in chronic conditions like chronic pain, multiple sclerosis, epilepsy, fibromyalgia and cancer.

Oral, rectal, systemic dosage form preferences of users in relation to medicinal cannabis being used and potential users of medicinal cannabis in relation to prior cannabis dosage form(s) administered were evaluated. Medicinal cannabis users making use of Pedanios and Bedrocan flowers and CBD oil rated edibles as the most preferred dosage form, while Bediol users prefer sublingual tablet form. Potential users have tried more cannabis dosage forms compared to medicinal cannabis users which currently use cannabis flowers and/or oils, this was also the case in the USA (Boehnke et al, 2019). Participants who administered cannabis cigarette and edibles rated cannabis tea as the most preferred, while electronic cigarette or vape, drinking oil and tincture groups preferred cannabis drinking oil. Participant who injected cannabis rated the injection form with lowest score possible, indicating that cannabis injection is not a pleasant dosage from to administer. Using the sublingual route could be favourable for conditions that require quicker onset of medicinal cannabis effects due to its faster onset of action compare to the oral route. The sublingual route also present the advantage of a longer duration of action compared to the inhalation route (Grotenhermen, 2004a; Karschner et al, 2011; Stott et al, 2013; Landa et al, 2018; Lucas et al, 2018).

Topical and inhalation dosage form preferences for medicinal cannabis was also conducted. Medicinal cannabis users prefer cannabis cigarette, tincture and electronic cigarette, while potential users prefer patches followed by tincture and ointment. Preferences for cannabis cigarette and electronic cigarette forms were significant between the two groups. Other studies performed in 31 countries (Hazekamp et al, 2013), Canada (Shiplo et al, 2016) and the USA (Borodovsky et al, 2016; Elliott et al, 2016; Bruce et al, 2018; Boehnke et al, 2019) also identified the preferred mode of delivery as smoking and/or tincture. Patients prefer smoked forms of cannabis dosage forms perhaps because it is a known method of cannabis administration. The decision could have been influenced by smoking status, however this study did not assess whether participants were cigarette smokers or not. Smokers could have preferred cannabis cigarettes and electronic cigarettes more than other forms. Smoking cannabis has a fast onset of action (Murphy et al, 2015; Lucas et al, 2018), however considering the impact of smokable forms of cannabis on respiratory health (Chapkis & Webb, 2005; MacCallum & Russo, 2018), which should be the primary focus, it would not be ideal to support the availability and supply of smokable forms of medicinal cannabis. Smoking has other disadvantages including the short duration of action and smell, it could be difficult to dose and the dose may differ each time (Murphy et al, 2015; Borodovsky et al, 2016; Shiplo et al, 2016; Ciccone, 2017; Romero-Sandoval et al, 2017; Bruni et al, 2018; McCallum & Russo, 2018).

Participants possibly preferred tincture because of the taste. Tinctures also have other advantages such as an easy administration and no distinct smell like the smoked forms of cannabis. Tinctures can also be added in food or to liquids. However, tinctures can lead

to issues related to evaporation, they should be stored well in tightly closed containers, protected from light and humidity and at cool temperatures.[24]

Cannabis balms and ointments could have been preferred by participants due to their smell and ease of application. Ointments have several advantages such as not having systemic psychotropic effects, cannabis ointments can be applied topically on the affected area and could provide benefit in using them in conditions like localised pain and other skin conditions. Disadvantage of ointment is being applicable only for the treatment of limited areas (Bruni et al, 2017; MacCallum & Russo, 2018).

The preferences of medicinal cannabis users who would be willing to switch their mode of cannabis delivery did not vary from the study population preferences. A statistically significant difference was observed for the spray form. Users over 50 years of age tend to prefer using spray more than participants aged between 31-40 years. For potential users group cannabis cigarettes were preferred by participants of 30 years or less, while not so preferred by those older than 50 years. The tincture form of cannabis was preferred by participants aged between 41 and 50 years and not so preferred by those older than 50 years. No statistically significant differences were observed between genders in relation to preference among medicinal cannabis users. A study in the USA also evaluated preferences of medicinal cannabis users and found a significant difference between males and females, where males preferred smoked and vaped forms and females preferred tincture and topical forms of cannabis (Boehnke et al, 2019). This difference was also observed in this study, however it was not statistically significant.

[24] Green Rush Packaging. Tips for Cannabis Tincture Packaging 2019 [Internet]. California [cited 2020 June 12]. Available from URL: https://greenrushpackaging.com/tips-for-cannabis-tincture-packaging/

Spray form could be preferred due to an easy application. Beside an easy application cannabis spray can be advantageous for providing higher bioavailability than the oral form and avoiding the first pass metabolism. Disadvantages of sprays include side effects such as dental carries, white lesions and oral burning sensation (Mathre, 2002; Guy & Robson, 2004; Versteeg et al, 2008; Crowley et al, 2018; Hua, 2019). It is important for cannabis spray users to do routine self-check and contact their medical or dental practitioner about their oral health.

In the potential users of medicinal cannabis group, males showed more interest than females in cannabis cigarette and electronic cigarette forms. Preferences among users did not differ meaningfully in relation to level of education. For potential users, cannabis cigarette, electronic cigarette and inhaler forms were preferred by respondents who had post-secondary level of education more than those with primary level of education. Preferences among both users and potential users of medicinal cannabis groups did not differ significantly in relation to locality.

The preferred topical and inhaled dosage form were correlated with the five most prevalent medical conditions for which users are making use of medicinal cannabis. Participants who have anxiety, arthritis and insomnia rated cannabis cigarettes as the most preferred, while those with fibromyalgia and pain preferred tinctures. Medical conditions for which potential users would use medicinal cannabis were correlated with the preferred dosage form. Participants selecting epilepsy preferred applying cream, while those selecting multiple sclerosis preferred using spray form. Cannabis patch was rated as the most preferred dosage form by participants selecting cancer, fibromyalgia and pain and the second most preferred form by epilepsy and multiple sclerosis groups. The study performed in 31 countries did not find clear differences between conditions and preference in method of intake (Hazekamp et al, 2013). Chronic pain patients using

cannabis preferred smoked and vaped cannabis in the USA (Boehnke et al, 2019), this could be due to differences in study populations. The USA study included recreational and medicinal cannabis users as one group and medicinal cannabis users only as another group. In this study the focus was the medicinal use of cannabis and participants with pain or suggesting the use of medicinal cannabis for pain, were considered separately as medicinal cannabis users or potential users. Patch form seems very popular among potential users, this is may be due to an easy application. Using cannabis patch could be advantageous for chronic conditions like cancer, chronic pain, fibromyalgia, epilepsy and multiple sclerosis because it offers a long duration of action sometimes lasting up to 72 hours, however has a delayed onset of effect (Grotenhermen, 2004a). It is essential to educate patients about how to apply and remove patches and point out not to use damaged patches. Formulating transdermal patch could be challenging, penetration enhancers could be needed in the formulation to improve the penetration of medicinal cannabis throughout the skin layers (Grotenhermen, 2004a; Bruni et al, 2017; Lucas et al, 2018).

Spray form was popular among multiple sclerosis group, considering the approved nabiximol, oro-mucosal spray may provide improvements for spasticity in multiple sclerosis conditions (Novotna et al, 2011; Koppel et al, 2014; Whiting et al, 2015; Rice & Cameron, 2018; Freeman et al, 2019).

Topical and inhalation dosage form preferences of users in relation to medicinal cannabis currently being used and potential users in relation to prior cannabis dosage form(s) administered was assessed. Medicinal cannabis users making use of Pedanios and Bedrocan flowers rated cannabis cigarette as the most preferred dosage form, while Bediol flower and CBD oil users preferred tincture form of medicinal cannabis. Bediol users also preferred electronic cigarette form and CBD oil users also preferred ointment form. Potential users who administered cannabis cigarette and edibles rated cannabis

cigarette as the most preferred dosage form, while participants with electronic cigarette or vape experience preferred electronic cigarettes and participants with drinking oil and tincture experience preferred tinctures. Drinking oil group also preferred ointments as much as the tinctures. Eye drop group rated cannabis eye drop with the lowest score possible, this indicates that cannabis eye drop is not a pleasant dosage form to administer. The results demonstrate the influence of patients' experience in dosage form preferences. It is worthy to give the possibility for every medicinal cannabis user to experience a variety of formulations, make self-comparisons and decide which form works the best for their condition. Giving a possibility to make clinical judgement is important to identify advantages and disadvantages between different formulations and determine which formulation is more patient-centred in terms of administration. Sometimes the decision taken by patients may not be the best for treating their condition, such as the importance of using eye drops in glaucoma. Cannabis eye drop was the least preferred dosage form among the two study populations. Patients may discuss their preference with their medical practitioner and choose an option which is convenient and effective for their condition.

4.2 Published literature about medicinal cannabis dosage forms and patient's opinion

A general systematic review of the literature identified 89 studies which focused on cannabis dosage forms in the last 10 years. Studies were mainly performed in the USA. Participants in the studies were recreational cannabis users, healthy volunteers or medicinal cannabis users. There were only a few studies which considered medical conditions, among which the focus was about single medical conditions. Forty-three studies included less than 20 participants and 28 studies included between 20 and 50 participants. The majority of the identified studies included single dosage form of cannabis and focused on smoked form, followed by oral form of cannabis. These findings are in accordance to the review in Canada (Russell et al, 2018). The scope in the studies

were mainly the pharmacodynamics and pharmacokinetic profile of cannabis, few studies focused on opinions about cannabis dosage forms. The findings demonstrate the lack of studies with high number of participants and with multiple dosage forms. This could be due to the selection criteria used to recruit the participants which were mainly volunteers such as recreational cannabis users who are currently consuming cannabis or volunteers without medical conditions. Evaluation of pharmacokinetics and pharmacodynamics are essential in understanding the dosage forms better, however most of the articles focused on smoked and oral forms of cannabis. Considering the variety of administration routes available to administer cannabis, there is a need for the evaluation of dosage forms other than smoked and oral forms.

A systematic review of the literature identified 10 studies which are based on opinion of patients or medicinal cannabis users about cannabinoid dosage forms, in the last 10 years. Studies were mainly performed in the USA. Participants of the studies were generally medicinal cannabis users since this was the inclusion criteria. Six studies included multiple medical conditions, while three focused on a single medical condition. Four studies included less than 100 participants. Studies included one medicinal cannabis dosage form or compared 2 forms. Studies which involved multiple forms did not include more than 8 dosage forms and overall included smoked, vaped, inhaled, oral, sublingual, edible and rectal forms of medicinal cannabis. Scope in the studies were opinion of patients or medicinal cannabis users on cannabinoid dosage forms, likes and dislikes about cannabis dosage forms.

The systematic reviews identified that studies on patient preferences and studies with multiple dosage forms of cannabis are lacking. Other systematic reviews in the last 10 years mainly focused on the efficacy (Andreae et al, 2015; Amato et al, 2017; Aviram & Samuelly-Leichtag, 2017; Blake et al, 2017; Häuser et al, 2017; Lim et al, 2017; Halladay

et al, 2018; Mücke et al, 2018; Elliott et al, 2019; Hoch et al, 2019) and/or safety (Gloss & Vickrey, 2014; Koppel et al, 2014; Deshpande et al, 2015; Fitzcharles et al, 2016b; Kansagara et al, 2017; Allan et al, 2018; Kafil et al, 2018; French et al, 2019; Ghasemiesfe et al, 2019; Kleckner et al, 2019; van der Steur et al, 2020) of cannabis generally on a specific medical condition. Of these only four reviews included the type of dosage form(s) of cannabis being discussed (Häuser et al, 2017; Halladay et al, 2018; Kafil et al, 2018; French et al, 2019). There were some systematic reviews focusing on the prevalence of cannabis use (Chapman et al, 2017; Papazisis et al, 2018; Sarvet et al, 2018; Fataar et al, 2019; Kleckner et al, 2019). Both systematic reviews conducted in this study were cannabis dosage form-focused, while many other reviews found in literature did not take into consideration the dosage form of cannabis.

4.3 Limitations of the Study and Recommendations for future research

The current database of medicinal cannabis users does not contain the email address of all the patients who are taking medicinal cannabis, therefore, the whole sample of medicinal cannabis users could not be reached. The preferences and outcomes of using cannabis dosage forms could be tested on a larger sample in the future to improve the representation of the studied population.

The study was limited to a single country where only flower formulations of cannabis are approved and patients did not use many forms of cannabis. However this was seen in other studies assessing opinion of patients on cannabis dosage forms (Elliott et al, 2016; Lee et al, 2016; Daniulaityte et al, 2017; Bruce et al, 2018; Cavazos-Rehg et al, 2018; Kerai et al, 2018; Sagar et al, 2018; Meyer et al, 2019). Future studies comparing the opinions of medicinal cannabis users in different countries and using different dosage forms can be conducted.

Another limitation is that only studies which were accessible as full text through HyDi were selected for the systematic reviews. Studies which required a fee to be accessed were omitted from the study. This could have led to the rejection of articles which would have contributed to the systematic review.

Smoking status of the participants could be assessed in further studies to be able to see if smoked forms of cannabis are mostly preferred by cigarette smokers.

The physico-chemical characteristics of cannabis make it difficult to formulate this medicine for different routes of delivery. More studies are needed to overcome the complexity of cannabis and enhance its poor solubility. Possible strategies like particle size reduction, addition of water-soluble carriers or emulsifying agents, complexation with cyclodextrins and additions of penetration enhancers for topically applied formulations can be suggested for improving the physico-chemical characteristics of medicinal cannabis.

4.4 Conclusion

Taking a patient-centred approach when formulating medicinal products is essential in improving the quality of life of patients. This study contributes to the knowledge about perception of patients and patient-centred cannabis delivery systems, by evaluating the opinion of users and potential future users of medicinal cannabis about the preferred methods of administration. In Malta, cannabis flowers are currently approved for use with vaporisers or administered orally as tea. Although patients are happy with their current mode, they would like to try other modes of medicinal cannabis. The availability of other dosage forms would lead to access of dosage forms which are preferred by patients. Patient-preferred oral delivery systems are cookies or food items, tea and drinking oil for medicinal cannabis users, while water, vegetarian capsule and tea forms are preferred by

potential users of medicinal cannabis. Patient-preferred topical and inhalation delivery systems are cannabis cigarette, tincture, electronic cigarette by users and patches, tinctures and ointments by potential users. Each dosage form has its advantages and disadvantages. Considering the impact of smokable forms of cannabis in respiratory health, it would not be ideal to support the availability and support of cannabis cigarette and electronic cigarette for patients. Dosage forms preferred by patients can be convenient to administer in public places, while still achieving a long duration of effect. Using tea, drinking oil, water, tincture and patch forms of cannabis could be beneficial for paediatric and elderly populations as well as for conditions with eating difficulties including anorexia and palliative care, post-surgery and dental conditions. Medicinal cannabis can be included in the formulary or provide a partial reimbursement scheme for patients with chronic conditions for which medicinal use of cannabis is approved by the scientific community. The availability of the different dosage forms preferred by patients, other than cannabis flowers and a less complex process, ensures a patient-centred medicinal cannabis delivery system and an improved medication access.

References

Abd-Elsalam WH, Alsherbiny MA, Kung JY, Pate DW, Löbenberg R. LC-MS/MS quantitation of phytocannabinoids and their metabolites in biological matrices. Talanta. 2019;204:846-867.

Abrams DI, Couey P, Shade SB, Kelly ME, Benowitz NL. Cannabinoid–opioid interaction in chronic pain. Clinical Pharmacology and Therapeutics. 2011;90(6):844-851.

Abrams DI. Should oncologists recommend cannabis? Current Treatment Options in Oncology. 2019;20(7):59.

Abrams DI. Using medical cannabis in an oncology practice. Oncology. 2016;30(5):397-404.

Abuhasira R, Schleider LB, Mechoulam R, Novack V. Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly. European Journal of Internal Medicine. 2018a;49:44-50.

Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products–regulations in Europe and North America. European Journal of Internal Medicine. 2018b;49:2-6.

Agar M. Medicinal cannabinoids in palliative care. British Journal of Clinical Pharmacology. 2018;84(11):2491-2494.

Ahmed AI, van den Elsen GA, Colbers A, van der Marck MA, Burger DM, Feuth TB, et al. Safety and pharmacokinetics of oral delta-9-tetrahydrocannabinol in healthy older subjects: a randomized controlled trial. European Neuropsychopharmacology. 2014;24(9):1475-1482.

Ali A, Akhtar N. The safety and efficacy of 3% cannabis seeds extract cream for reduction of human cheek skin sebum and erythema content. Pakistan Journal of Pharmaceutical Sciences. 2015;28(4):1389-1395.

Allan GM, Finley CR, Ton J, Perry D, Ramji J, Crawford K, et al. Systematic review of systematic reviews for medical cannabinoids: pain, nausea and vomiting, spasticity, and harms. Canadian Family Physician Medecin de Famille Canadien. 2018;64(2):e78-e94.

Amato L, Minozzi S, Mitrova Z, Parmelli E, Saulle R, Cruciani F, et al. Systematic review of safeness and therapeutic efficacy of cannabis in patients with multiple sclerosis, neuropathic pain, and in oncological patients treated with chemotherapy. Epidemiologia e Prevenzione. 2017;41(5-6):279-293.

Andreae MH, Carter GM, Shaparin N, Suslov K, Ellis RJ, Ware MA, et al. Inhaled cannabis for chronic neuropathic pain: a meta-analysis of individual patient data. The Journal of Pain: Official Journal of the American Pain Society. 2015;16(12):1221-1232.

Anizan S, Bergamaschi MM, Barnes AJ, Milman G, Desrosiers N, Lee D, et al. Impact of oral fluid collection device on cannabinoid stability following smoked cannabis. Drug Testing and Analysis. 2015;7(2):114-120.

Anizan S, Milman G, Desrosiers N, Barnes AJ, Gorelick DA, Huestis MA. Oral fluid cannabinoid concentrations following controlled smoked cannabis in chronic frequent and occasional smokers. Analytical and Bioanalytical Chemistry. 2013;405(26):8451-8461.

Antognoli E, Koopman Gonzalez S, Trapl E, Cavallo D, Lim R, Lavanty B, et al. The social context of adolescent co-use of cigarillos and marijuana blunts. Substance Use & Misuse. 2018;53(4):654-661.

Appendino G, Gibbons S, Giana A, Pagani A, Grassi G, Stavri M, et al. Antibacterial cannabinoids from cannabis sativa: a structure-activity study. Journal of Natural Products. 2008;71(8):1427-1430.

Armstrong JL, Hill DS, McKee CS, Hernandez-Tiedra S, Lorente M, Lopez-Valero I, et al. Exploiting cannabinoid-induced cytotoxic autophagy to drive melanoma cell death. The Journal of Investigative Dermatology. 2015;135(6):1629-1637.

Astruc-Diaz F. Cannabinoids delivery systems based on supramolecular inclusion complexes and polymeric nanocapsules for treatment of neuropathic pain [dissertation]. Lyon (France): Department of human health and pathology, Université Claude Bernard; 2012.

Aung-Din R. Therapeutic focus - direct effects (tm) cannabinoid therapy: medical cannabis without psychoactive & systemic effects. Drug Development & Delivery. 2016;16(5):58-63.

Aviram J, Samuelly-Leichtag G. Efficacy of cannabis-based medicines for pain management: a systematic review and meta-Analysis of randomized controlled trials. Pain Physician. 2017;20(6):E755-E796.

Azad N, Rojanasakul Y. Nanobiotechnology in drug delivery. American Journal of Advanced Drug Delivery. 2006;4(2):79-88.

Bab I, Zimmer A, Melamed E. Cannabinoids and the skeleton: from marijuana to reversal of bone loss. Annals of Medicine. 2009;41(8):560-567.

Babalonis S, Haney M, Malcolm RJ, Lofwall MR, Votaw VR, Sparenborg S, et al. Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers. Drug and Alcohol Dependence. 2017;172:9-13.

Badowski ME. A review of oral cannabinoids and medical marijuana for the treatment of chemotherapy-induced nausea and vomiting: a focus on pharmacokinetic variability and pharmacodynamics. Cancer Chemotherapy and Pharmacology. 2017;80(3):441-449.

Baggio S, Deline S, Studer J, Mohler-Kuo M, Daeppen JB, Gmel G. Routes of administration of cannabis used for nonmedical purposes and associations with patterns of drug use. Journal of Adolescent Health. 2014;54(2):235-240.

Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem RR, Hale TW. Transfer of inhaled cannabis into human breast milk. Obstetrics and Gynecology. 2018;131(5):783-788.

Ballard ME, Gallo DA, de Wit H. Psychoactive drugs and false memory: comparison of dextroamphetamine and delta-9-tetrahydrocannabinol on false recognition. Psychopharmacology. 2012;219(1):15-24.

Banga AK. New technologies to allow transdermal delivery of therapeutic proteins and small water-soluble drugs. American Journal of Advanced Drug Delivery. 2006;4(4):221-230.

Bar-Lev Schleider L, Mechoulam R, Lederman V, Hilou M, Lencovsky O, Betzalel O, et al. Prospective analysis of safety and efficacy of medical cannabis in large unselected population of patients with cancer. European Journal of Internal Medicine. 2018;49:37-43.

Barrack J, Chamberlin KW. Epidiolex: approved for two pediatric epilepsy syndromes. Drug Topics. 2018;162(9):27.

Barry RA, Hiilamo H, Glantz SA. Waiting for the opportune moment: the tobacco industry and marijuana legalization. The Milbank Quarterly. 2014;92(2):207-242.

Bedi G, Cooper ZD, Haney M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. Addiction Biology. 2013;18(5):872-881.

Benjamin DM, Fossler MJ. Edible cannabis products: it is time for FDA oversight. The Journal of Clinical Pharmacology. 2016;56(9):1045-1047.

Bhattacharyya S, Crippa JA, Allen P, Martin-Santos R, Borgwardt S, Fusar-Poli P, et al. Induction of psychosis by Δ9-tetrahydrocannabinol reflects modulation of prefrontal and striatal function during attentional salience processing. Archives of General Psychiatry. 2012;69(1):27-36.

Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, et al. Opposite Effects of D-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology. 2010;35:764-774.

Bifulco M, Pisanti S. Medicinal use of cannabis in Europe. European Molecular Biology Organization Reports. 2015;16(2):130-132.

Birdsall SM, Birdsall TC, & Tims LA. The use of medical marijuana in cancer. Current Oncology Reports. 2016;18(7):1-9.

Blake A, Wan BA, Malek L, DeAngelis C, Diaz P, Lao N, et al. A selective review of medical cannabis in cancer pain management. Annals of Palliative Medicine. 2017;6(Suppl 2):S215-S222.

Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, et al. Vitamin e acetate in bronchoalveolar-lavage fluid associated with evali. The New England Journal of Medicine. 2020;382(8):697-705.

Blundell M, Dargan P, Wood D. A cloud on the horizon-a survey into the use of electronic vaping devices for recreational drug and new psychoactive substance (nps) administration. QJM: An International Journal of Medicine. 2018;111(1):9-14.

Boehnke KF, Scott JR, Litinas E, Sisley S, Clauw DJ, Goesling J, et al. Cannabis use preferences and decision-making among a cross-sectional cohort of medical cannabis patients with chronic pain. The Journal of Pain: Official Journal of the American Pain Society. 2019;20(11):1362-1372.

Bonn-Miller MO, Boden MT, Bucossi MM, Babson KA. Self-reported cannabis use characteristics, patterns and helpfulness among medical cannabis users. The American Journal of Drug and Alcohol Abuse. 2014;40(1):23-30.

Borgelt LM, Franson KL, Nussbaum AM, Wang GS. The Pharmacologic and clinical effects of medical cannabis. Pharmacotherapy. 2013;33(2):195-209.

Borodovsky JT, Crosier BS, Lee DC, Sargent JD, Budney AJ. Smoking, vaping, eating: is legalization impacting the way people use cannabis? The International Journal on Drug Policy. 2016;36:141-147.

Borràs R, Modamio P, Lastra CF, Marino EL. Medicinal Use of Cannabis in Spain. Alternative Therapies. 2011;17(5):52-54.

Bosker WM, Kuypers KP, Theunissen EL, Surinx A, Blankespoor RJ, Skopp G, et al. Medicinal Δ(9)-tetrahydrocannabinol (dronabinol) impairs on-the-road driving performance of occasional and heavy cannabis users but is not detected in standard field sobriety tests. Addiction. 2012;107(10):1837-1844.

Bouchard JF, Casanova C, Cécyre B, Redmond WJ. Expression and function of the endocannabinoid system in the retina and the visual brain. Neural Plasticity. 2016;2016:1-14.

Boyd ST. The Endocannabinoid system. Pharmacotherapy. 2006;26(12 Pt 2):218S-221S.

Brenneisen R. Chemistry and analysis of phytocannabinoids and other cannabis constituents. In: ElSohly MA, editors. Marijuana and the Cannabinoids. Forensic Science and Medicine. Totowa, NJ: Humana Press; 2007. p. 17-49.

Brenneisen R, Egli A, Elsohly MA, Henn V, Spiess Y. The effect of orally and rectally administered delta 9-tetrahydrocannabinol on spasticity: a pilot study with 2 patients. International Journal of Clinical Pharmacology and Therapeutics. 1996;34(10):446-452.

Brenneisen R, Meyer P, Chtioui H, Saugy M, Kamber M. Plasma and urine profiles of Delta9-tetrahydrocannabinol and its metabolites 11-hydroxy-delta9-tetrahydrocannabinol and 11-nor-9-carboxy-delta9-tetrahydrocannabinol after cannabis smoking by male volunteers to estimate recent consumption by athletes. Analytical and Bioanalytical Chemistry. 2010;396(7):2493-2502.

Bridgeman MB, Abazia DT. Medicinal Cannabis: history, pharmacology, and implications for the acute care setting. Pharmacy and Therapeutics. 2017;42(3):180-188.

Bruce D, Brady JP, Foster E, Shattell M. Preferences for medical marijuana over prescription medications among persons living with chronic conditions: alternative, complementary, and tapering uses. The Journal of Alternative and Complementary Medicine. 2018;24(2):146-153.

Bruni N, Della Pepa C, Oliaro-Bosso S, Pessione E, Gastaldi D, Dosio F. Cannabinoid Delivery Systems for Pain and Inflammation Treatment. Molecules. 2018;23(10):1-25.

Bryson N, Sharma AC, inventors. Nasal cannabidiol compositions. World Intellectual Property Organization. United States patent WO 2017208072 A2. 2017.

Buckner JD, Zvolensky MJ. Cannabis and related impairment: the unique roles of cannabis use to cope with social anxiety and social avoidance. The American Journal on Addictions. 2014;23(6):598-603.

Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. American Journal of Psychiatry. 2004;161:1967-1977.

Budney AJ, Sargent JD, Lee DC. Vaping cannabis (marijuana): parallel concerns to e-cigs? Addiction. 2015;110(11):1699-1704.

Caligiuri FJ, Ulrich EE, Welter KJ. Pharmacy student knowledge, confidence and attitudes toward medical cannabis and curricular coverage. American Journal of Pharmaceutical Education. 2018;82(5):6296.

Callaway J, Schwab U, Harvima I, Halonen P, Mykkänen O, Hyvönen P, et al. Efficacy of dietary hempseed oil in patients with atopic dermatitis. The Journal of Dermatological Treatment. 2005;16(2):87-94.

Capano A, Weaver R, Burkman E. Evaluation of the effects of cbd hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study. Postgraduate Medicine. 2019;133(1):56-61.

Cassidy RN, Meisel MK, DiGuiseppi G, Balestrieri S, Barnett NP. Initiation of vaporizing cannabis: Individual and social network predictors in a longitudinal study of young adults. Drug and Alcohol Dependence. 2018;188:334-340.

Cavazos-Rehg PA, Krauss MJ, Sowles SJ, Floyd GM, Cahn ES, Chaitan VL et al. Leveraging user perspectives for insight into cannabis concentrates. The American Journal of Drug and Alcohol Abuse. 2018;44(6):628-641.

Chandra S, Lata H, Khan IA, ElSohly MA. The role of biotechnology in cannabis sativa propagation for the production of phytocannabinoids. In: Chandra S, Lata H, Varma A, editors. Biotechnology for Medicinal Plants; 2013. p. 123-148.

Chapkis W, Webb RJ. Mother's milk and the muffin man: grassroots innovations in medical marijuana delivery systems. Journal of Ethnicity in Substance Abuse. 2005;4(3-4):183-204.

Chapman C, Slade T, Swift W, Keyes K, Tonks Z, Teesson M. Evidence for Sex convergence in prevalence of cannabis use: a systematic review and meta-regression. Journal of Studies on Alcohol and Drugs. 2017;78(3):344-352.

Chelliah MP, Zinn Z, Khuu P, Teng JMC. Self-initiated use of topical cannabidiol oil for epidermolysis bullosa. Pediatric Dermatology. 2018;35(4):e224–e227.

Chiurchiù V, van der Stelt M, Centonze D, Maccarrone M. The endocannabinoid system and its therapeutic exploitation in multiple sclerosis: clues for other neuroinflammatory diseases. Progress in Neurobiology. 2018;160:82-100.

Cho CM, Hirsch R, Johnstone S. General and oral health implications of cannabis use. Australian Dental Journal. 2005;50(2):70-74.

Choukèr A, Kaufmann I, Kreth S, Hauer D, Feuerecker M, Thieme D, et al. Motion sickness, stress and the endocannabinoid system. Plos One. 2010;5(5):e10752.

Christiani DC. Vaping-induced acute lung injury. The New England Journal of Medicine. 2020;382(10):960-962.

Ciccone CD. Medical marijuana: just the beginning of a long, strange trip? Physical Therapy. 2017;97(2):239-248.

Ciolino LA, Ranieri TL, Taylor AM. Commercial cannabis consumer products part 1: GC-MS qualitative analysis of cannabis cannabinoids. Forensic Science International. 2018a;289:429-437.

Ciolino LA, Ranieri TL, Taylor AM. Commercial cannabis consumer products part 2: hplc-dad quantitative analysis of cannabis cannabinoids. Forensic Science International. 2018b;289:438-447.

Cofield SS, Salter A, Tyry T, Crowe C, Cutter GR, Fox RJ, et al. Perspectives on marijuana use and effectiveness: a survey of narcoms participants. Neurology® Clinical Practice. 2017;7(4):333-343.

Cohn A, Johnson A, Ehlke S, Villanti AC. Characterizing substance use and mental health profiles of cigar, blunt, and non-blunt marijuana users from the National Survey of Drug Use and Health. Drug and Alcohol Dependence. 2016;160:105-111.

Cooper ZD, Comer SD, Haney M. Comparison of the analgesic effects of dronabinol and smoked marijuana in daily marijuana smokers. Neuropsychopharmacology. 2013;38(10):1984-1992.

Corroon J, Sexton M, Bradley R. Indications and administration practices amongst medical cannabis healthcare providers: a cross-sectional survey. BMC Family Practice. 2019;20(1):174.

Cox B. Can the research community respond adequately to the health risks of vaping? Addiction. 2015;110(11):1708-1709.

Crean RD, Crane NA, Mason BJ. An evidence based review of acute and long-term effects of cannabis use on executive cognitive functions. Journal of Addiction Medicine. 2011;5(1):1-8.

Crowley K, de Vries ST, Moreno-Sanz G. Self-reported effectiveness and safety of trokie lozenges: a standardized formulation for the buccal delivery of cannabis extracts. Frontiers in Neuroscience. 2018;12(564):1-5.

Dabrowski G, Skrajda M. Cannabinoids from cannabis sp.: mechanism of their activity and potential health benefits in human body. Journal of Education, Health and Sport. 2017;7(8):936-945.

Daniulaityte R, Lamy FR, Barratt M, Nahhas RW, Martins SS, Boyer EW et al. Characterizing marijuana concentrate users: A web-based survey. Drug and Alcohol Dependence. 2017;178:399-407.

de Luis DA, Sagrado MG, Aller R, Izaola O, Conde R, Romero E. C358A missense polymorphism of the endocannabinoid degrading enzyme fatty acid amide hydrolase (faah) and insulin resistance in patients with diabetes mellitus type 2. Diabetes Research and Clinical Practice. 2010;88(1):76-80.

DeFilippis EM, Navkaranbir SB, Singh A, Malloy R, Givertz MM, Blankstein R, et al. Marijuana use in patients with cardiovascular disease: jacc review topic of the week. Journal of the American College of Cardiology. 2020;75(3):320-332.

del Río C, Navarrete C, Collado JA, Bellido ML, Gómez-Cañas M, Pazos MR, et al. The cannabinoid quinol vce-004.8 alleviates bleomycin-induced scleroderma and exerts potent antifibrotic effects through peroxisome proliferator-activated receptor-γ and cb2 pathways. Scientific Reports. 2016;6:21703.

Deshpande A, Mailis-Gagnon A, Zoheiry N, Lakha SF. Efficacy and adverse effects of medical marijuana for chronic noncancer pain: systematic review of randomized controlled trials. Canadian Family Physician Medecin de Famille Canadien. 2015;61(8):e372-e381.

Desrosiers NA, Himes SK, Scheidweiler KB, Concheiro-Guisan M, Gorelick DA, Huestis MA. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. Clinical Chemistry. 2014;60(4):631-643.

Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia. 2014;55(6):791-802.

Dhadwal G, Kirchhof MG. The risks and benefits of cannabis in the dermatology clinic. Journal of Cutaneous Medicine and Surgery. 2018;22(2):194-199.

Di Filippo M, Pini LA, Pelliccioli GP, Calabresi P, Sarchielli P. Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis. Journal of Neurology, Neurosurgery, and Psychiatry. 2008;79(11):1224-1229.

Di Marzo V, Stella N, Zimmer A. Endocannabinoid signalling and the deteriorating brain. Nature Reviews Neuroscience. 2015;16(1):30-42.

Durán-Lobato M, Martín-Banderas L, Lopes R, Gonçalves LM, Fernández-Arévalo M, Almeida AJ. Lipid nanoparticles as an emerging platform for cannabinoid delivery: physicochemical optimization and biocompatibility. Drug Development and Industrial Pharmacy. 2016;42(2):190-198.

Eggers ME, Lee YO, Jackson K, Wiley JL, Porter L, Nonnemaker JM. Youth use of electronic vapor products and blunts for administering cannabis. Addictive Behaviors. 2017;70:79-82.

Eisenberg E, Ogintz M, Almog S. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. Journal of Pain and Palliative Care Pharmacology. 2014;28(3):216-225.

Elliott DA, Nabavizadeh N, Romer JL, Chen Y, Holland JM. Medical marijuana use in head and neck squamous cell carcinoma patients treated with radiotherapy. Support Care Cancer. 2016;24(8):3517-3524.

Elliott J, DeJean D, Clifford T, Coyle D, Potter BK, Skidmore B, et al. Cannabis-based products for pediatric epilepsy: a systematic review. Epilepsia. 2019;60(1):6-19.

ElSholy MA, Slade D. Chemical constituents of marijuana: the complex mixture of natural cannabinoids. Life Sciences. 2005;78(5):539-548.

Erices JI, Torres Á, Niechi I, Bernales I, Quezada C. Current natural therapies in the treatment against glioblastoma. Phytotherapy Research. 2018;32(11):2191-2201.

Etter JF. Electronic cigarettes and cannabis: an exploratory study. European Addiction Research. 2015;21(3):124-130.

Fabritius M, Chtioui H, Battistella G, Annoni JM, Dao K, Favrat B, et al. Comparison of cannabinoid concentrations in oral fluid and whole blood between occasional and regular cannabis smokers prior to and after smoking a cannabis joint. Analytical and Bioanalytical Chemistry. 2013;405(30):9791-9803.

Fabritius M, Favrat B, Chtioui H, Battistella G, Annoni JM, Appenzeller M, et al. THCCOOH concentrations in whole blood: are they useful in discriminating occasional from heavy smokers? Drug Testing and Analysis. 2014;6(1-2):155-163.

Fakhoury M. Role of the endocannabinoid system in the pathophysiology of schizophrenia. Molecular Neurobiology. 2017;54(1):768-778.

Fataar F, Hammond D. The prevalence of vaping and smoking as modes of delivery for nicotine and cannabis among youth in Canada, England and the United States. International Journal of Environmental Research and Public Health. 2019;16(21):4111.

Fine PG, Rosenfeld MJ. Cannabinoids for neuropathic pain. Current Pain and Headache Reports. 2014;18(10):451:1-9.

Fischbach P. The role of illicit drug use in sudden death in the young. Cardiology in the Young. 2017;27(S1):S75–S79.

Fitzcharles MA, Baerwald C, Ablin J, Häuser W. Efficacy, tolerability and safety of cannabinoids in chronic pain associated with rheumatic diseases (fibromyalgia syndrome, back pain, osteoarthritis, rheumatoid arthritis): a systematic review of randomized controlled trials. Schmerz. 2016a;30(1):47-61.

Fitzcharles MA, Ste-Marie PA, Häuser W, Clauw DJ, Jamal S, Karsh J, et al. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. Arthritis Care & Research. 2016b;68(5):681-688.

Fiz J, Durán M, Capellà D, Carbonell J, Farré M. Cannabis use in patients with fibromyalgia: effect on symptoms relief and health-related quality of life. Plos One. 2011;6(4):e18440.

Flores MP, Castro AP, Nascimento JS. Topical analgesics. Revista Brasileira Anestesiologia. 2012;62(2):244-252.

Fogel JS, Kelly TH, Westgate PM, Lile JA. Sex differences in the subjective effects of oral Δ^9-thc in cannabis users. Pharmacology, Biochemistry and Behavior. 2017;152:44-51.

Fraguas-Sánchez AI, Torres-Suárez AI. Medical use of cannabinoids. Drugs. 2018;78(16):1665-1703.

Frederick BD, Lindsey KP, Nickerson LD, Ryan ET, Lukas SE. An mr-compatible device for delivering smoked marijuana during functional imaging. Pharmacology Biochemistry & Behavior. 2007;87(1):81-89.

Freeman D, Morrison PD, Murray RM, Evans N, Lister R, Dunn G. Persecutory ideation and a history of cannabis use. Schizophrenia Research. 2013;148(1-3):122-125.

Freeman TP, Hindocha C, Green SF, Bloomfield MAP. Medicinal use of cannabis based products and cannabinoids. British Medical Journal. 2019;365:l1141.

French CE, Coope CM, McGuinness LA, Beck CR, Newitt S, Ahyow L, et al. Cannabis use and the risk of tuberculosis: a systematic review. BioMed Central Public Health. 2019;19(1):1006.

Fridberg DJ, Vollmer JM, O'Donnell BF, Skosnik PD. Cannabis users differ from non-users on measures of personality and schizotypy. Psychiatry Research. 2011;186(1):46-52.

Friese B, Slater MD, Annechino R, Battle RS. Teen use of marijuana edibles: a focus group study of an emerging issue. The Journal of Primary Prevention. 2016;37(3):303-309.

Friese B, Slater MD, Battle RS. Use of marijuana edibles by adolescents in California. The Journal of Primary Prevention. 2017;38(3):279-294.

Fukuda S, Kohsaka H, Takayasu A, Yokoyama W, Miyabe C, Miyabe Y, et al. Cannabinoid receptor 2 as a potential therapeutic target in rheumatoid arthritis. BioMed Central. 2014;15(275):1-10.

Ghasemiesfe M, Barrow B, Leonard S, Keyhani S, Korenstein D. Association between marijuana use and risk of cancer: a systematic review and meta-analysis. Journal of the American Medical Association Network Open. 2019;2(11):e1916318.

Ginsburg BC. Toward a comprehensive model of Δ9-tetrahydrocannabinol pharmacokinetics using a population pharmacokinetics approach. Clinical Pharmacokinetics. 2015;54(2):129-131.

Giombi KC, Kosa KM, Rains C, Cates SC. Consumers' perceptions of edible marijuana products for recreational use: likes, dislikes, and reasons for use. Substance Use & Misuse. 2018;53(4):541-547.

Giovenco DP, Miller Lo EJ, Lewis MJ, Delnevo CD. "They're pretty much made for blunts": product features that facilitate marijuana use among young adult cigarillo users in the United States. Nicotine & Tobacco Research. 2017;19(11):1359-1364.

Giovenco DP, Spillane TE, Mauro CM, Martins SS. Cigarillo sales in legalized marijuana markets in the U.S. Drug and Alcohol Dependence. 2018;185:347-350.

Giroud C, de Cesare M, Berthet A, Varlet V, Concha-Lozano N, Favrat B. E-cigarettes: a review of new trends in cannabis use. International Journal of Environmental Research and Public Health. 2015;21;12(8):9988-10008.

Gloss D, Vickrey B. Cannabinoids for epilepsy. The Cochrane Database of Systematic Reviews. 2014;2014(3):CD009270.

Godsey J, Grundmann O. Review of various herbal supplements as complementary treatments for oral cancer. Journal of Dietary Supplements. 2016;13(5):538-550.

Gomes FV, Resstel LB, Guimarães FS. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology. 2011;213(2-3):465-473.

Gonçalves J, Rosado T, Soares S, Simão AY, Caramelo D, Luís Â, et al. Cannabis and its secondary metabolites: their use as therapeutic drugs, toxicological aspects, and analytical determination. Medicines (Basel). 2019;6(1):31.

Goodman S, Wadsworth E, Leos-Toro C, Hammond D, International Cannabis Policy Study team. Prevalence and forms of cannabis use in legal vs. illegal recreational cannabis markets. The International Journal on Drug Policy. 2020;76:102658.

Gorelick DA, Goodwin RS, Schwilke E, Schroeder JR, Schwope DM, Kelly DL, et al. Around-the-clock oral thc effects on sleep in male chronic daily cannabis smokers. The American Journal on Addictions. 2013;22(5):510-514.

Gorelick DA, Goodwin RS, Schwilke E, Schwope DM, Darwin WD, Kelly DL, et al. Antagonist-elicited cannabis withdrawal in humans. Journal of Clinical Psychopharmacology. 2011;31(5):603-612.

Grant I, Schatma ME, Whiting P, Wolff R. Medical use of cannabinoids. Journal of the American Medical Association. 2015;314(16):1750-1751.

Grant KS, Petroff R, Isoherranen N, Stella N, Burbacher TM. Cannabis use during pregnancy: pharmacokinetics and effects on child development. Pharmacology & Therapeutics. 2018;182:133-151.

Grassin-Delyle S, Naline E, Buenestado A, Faisy C, Alvarez JC, Salvator H, et al. Cannabinoids inhibit cholinergic contraction in human airways through prejunctional cb1 receptors. British Journal of Pharmacology. 2014;171(11):2767-2777.

Gray TR, Eiden RD, Leonard KE, Connors GJ, Shisler S, Huestis MA. Identifying prenatal cannabis exposure and effects of concurrent tobacco exposure on neonatal growth. Clinical Chemistry. 2010;56(9):1442-1450.

Grewal JK, Loh LC. Health considerations of the legalization of cannabis edibles. Canadian Medical Association Journal. 2020;192(1):E1-E2.

Grinspoon L. Whither medical marijuana? Contemporary Drug Problems. 2000; 27(1):3-15.

Grotenhermen F. Cannabinoids for therapeutic use. Designing systems to increase efficacy and reliability. American Journal of Drug Delivery. 2004a;2(4):229-240.

Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical Pharmacokinetics. 2003;42(4):327-360.

Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinology Letters. 2004b;25(1-2):14-23.

Guy GW, Robson PJ. A phase i, open label, four-way crossover study to compare the pharmacokinetic profiles of a single dose of 20 mg of a cannabis-based medicine extract (cbme) administered on 3 different areas of the buccal mucosa and to investigate the pharmacokinetics of cbme per oral in healthy male and female volunteers. Journal of Cannabis Therapeutics. 2004;93(5):1176-1184.

Habibi A, Sarafrazi A, Izadyar S. Delphi technique theoretical framework in qualitative research. The International Journal of Engineering and Science. 2014;3(14):08-13.

Halawa OI, Furnish TJ, Wallace MS. Chapter 56 - role of cannabinoids in pain management. Essentials of Pain Medicine. 2018;4:509-520.

Halladay J, Petker T, Fein A, Munn C, MacKillop J. Brief interventions for cannabis use in emerging adults: protocol for a systematic review, meta-analysis, and evidence map. Systematic Reviews. 2018;7(1):106.

Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin R. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. Neuropsychopharmacology. 2013;38(8):1557-1565.

Haney M, Malcolm RJ, Babalonis S, Nuzzo PA, Cooper ZD, Bedi G, et al. Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. Neuropsychopharmacology. 2016;41(8):1974-82.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral thc administration to humans. Psychopharmacology. 1999a;141(4):385-394.

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology. 1999b;141(4):395-404.

Hanuš LO. Pharmacological and therapeutic secrets of plant and brain (endo)cannabinoids. Medicinal Research Reviews. 2009;29(2):213-271.

Hanuš LO, Meyer SM, Muñoz E, Taglialatela-Scafati O, Appendino G. Phytocannabinoids: a unified critical inventory. Royal Society of Chemistry. Natural Product Reports. 2016;33(12):1357-1392.

Hartman RL, Brown TL, Milavetz G, Spurgin A, Gorelick DA, Gaffney G, et al. Controlled cannabis vaporizer administration: blood and plasma cannabinoids with and without alcohol. Clinical Chemistry. 2015;61(6):850-869.

Hashibe M, Straif K, Tashkin DP, Morgenstern H, Greenland S, Zhang ZF. Epidemiologic review of marijuana use and cancer risk. Alcohol. 2005;35(3):265-275.

Hayley AC, Downey LA, Hansen G, Dowell A, Savins D, Buchta R, et al. Detection of delta-9-tetrahydrocannabinol (thc) in oral fluid, blood and urine following oral consumption of low-content thc hemp oil. Forensic Science International. 2018;284:101-106.

Hazekamp A, Ruhaak R, Zuurman L, Van Gerven J, Verpoorte R. Evaluation of a vaporizing device (volcano) for the pulmonary administration of tetrahydrocannabinol. Journal of Pharmaceutical Sciences. 2006;95(6):1308-1317.

Hazekamp A, Ware MA, Müller-Vahl KR, Abrams D, Grotenhermen F. The medicinal use of cannabis and cannabinoids-an international cross-sectional survey on administration forms. Journal of Psychoactive Drugs. 2013:45(3):199-210.

Häuser W, Fitzcharles MA, Radbruch L, Petzke F. Cannabinoids in pain management and palliative medicine. Deutsches Arzteblatt International. 2017;114(38):627-634.

Hemsing N, Greaves L. New challenges: developing gendered and equitable responses to involuntary exposures to electronic nicotine delivery systems (ends) and cannabis vaping. International Journal of Environmental Research and Public Health. 2018;15(10):E2097.

Hernán Pérez de la Ossa D, Lorente M, Gil-Alegre ME, Torres S, García-Taboada E, Aberturas Mdel R. Local delivery of cannabinoid-loaded microparticles inhibits tumor growth in a murine xenograft model of glioblastoma multiforme. Plos One. 2013;8(1):e54795.

Herrmann ES, Weerts E, Vandrey R. Gender differences in cannabis withdrawal symptoms among treatment-seeking cannabis users. Drug and Alcohol Dependence. 2015;156:e95.

Hess C, Krämer M, Madea B. Topical application of thc containing products is not able to cause positive cannabinoid finding in blood or urine. Forensic Science International. 2017;272:68-71.

Heuberger JA, Guan Z, Oyetayo OO, Klumpers L, Morrison PD, Beumer TL, et al. Population pharmacokinetic model of thc integrates oral, intravenous, and pulmonary dosing and characterizes short- and long-term pharmacokinetics. Clinical Pharmacokinetics. 2015;54(2):209-219.

Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough B. The faces pain scale-revised: toward a common metric in pediatric pain measurement. Pain. 2001;93(2):173-183.

Hindocha C, Freeman TP, Winstock AR, Lynskey MT. Vaping cannabis (marijuana) has the potential to reduce tobacco smoking in cannabis users. Addiction. 2016;111(2):375.

Hindocha C, Lawn W, Freeman TP, Curran HV. Individual and combined effects of cannabis and tobacco on drug reward processing in non-dependent users. Psychopharmacology. 2017;234(21):3153-3163.

Ho C, Martinusen D, Lo C. A Review of Cannabis in Chronic Kidney Disease Symptom Management. Canadian Journal of Kidney Health and Disease. 2019;6:1-14.

Hoch E, Niemann D, von Keller R, Schneider M, Friemel CM, Preuss UW, et al. How effective and safe is medical cannabis as a treatment of mental disorders? A systematic review. European Archives of Psychiatry and Clinical Neuroscience. 2019;269(1):87-105.

Hua S. Advances in nanoparticulate drug delivery approaches for sublingual and buccal administration. Frontiers in Pharmacology. 2019;10(1328):1-9.

Huestis MA. Human cannabinoid pharmacokinetics. Chemistry & Biodiversity. 2007;4(8):1770-1804.

Huestis MA. Pharmacokinetics and metabolism of the plant cannabinoids, Δ^9-tetrahydrocannabinol, cannabidiol and cannabinol. Springer-Verlan. 2005;168:657-690.

Indorato F, Liberto A, Ledda C, Romano G, Barbera N. The therapeutic use of cannabinoids: forensic aspects. Forensic Science International. 2016;265:200-203.

Jain S, Sandhu P, Gurjar M, Malvi R. Solubility enhancement by solvent deposition technique: an overview. Asian Journal of Pharmaceutical and Clinical Research. 2012;5(4):15-19.

Jin S, Lee MY. The ameliorative effect of hemp seed hexane extracts on the propionibacterium acnes-induced inflammation and lipogenesis in sebocytes. Plos One. 2018;13(8):e0202933.

Johnson JR, Burnell-Nugent M, Lossignol D, Ganae-Motan ED, Potts R, Fallon MT. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of thc:cbd extract and thc extract in patients with intractable cancer-related pain. Journal of Pain and Symptom Management. 2010;39(2):167-179.

Joshi S, Ashley M. Cannabis: a joint problem for patients and the dental profession. British Dental Journal. 2016;220(11):597-601.

Kafil TS, Nguyen TM, MacDonald JK, Chande N. Cannabis for the treatment of ulcerative colitis. The Cochrane Database of Systematic Reviews. 2018;11(11):CD012954.

Kalant H. Medicinal use of cannabis: history and current status. Pain Research and Management. 2001;6(2):80-91.

Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, et al. E-cigarette, or vaping, product use associated lung injury (evali): case series and diagnostic approach. The Lancet Respiratory Medicine. 2019;7(12):1017-1026.

Kansagara D, O'Neil M, Nugent S, Freeman M, Low A, Kondo K, et al. Benefits and harms of cannabis in chronic pain or post-traumatic stress disorder: a systematic review. Department of Veterans Affairs (US). 2017.

Karschner EL, Barnes AJ, Lowe RH, Scheidweiler KB, Huestis MA. Validation of a two-dimensional gas chromatography mass spectrometry method for the simultaneous quantification of cannabidiol, delta(9)-tetrahydrocannabinol (thc), 11-hydroxy-thc, and 11-nor-9-carboxy-thc in plasma. Analytical and Bioanalytical Chemistry. 2010;397(2):603-611.

Karschner EL, Darwin WD, Goodwin RS, Wright S, Huestis MA. Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration. Clinical Chemistry. 2011;57(1):66-75.

Kawabata Y, Wada K, Nakatanib M, Yamada S, Onoue S. Formulation design for poorly water-soluble drugs based on biopharmaceutics classification system: basic approaches and practical applications. International Journal of Pharmaceutics. 2011;420(1):1-10.

Kerai A, Sim TF, Emmerton L. Medical cannabis: a needs analysis for people with epilepsy. Complementary Therapies in Clinical Practice. 2018;33:43-48.

Khullar V, Jain A, Sattari M. Emergence of new classes of recreational drugs-synthetic cannabinoids and cathinones. Journal of General Internal Medicine. 2014;29(8):1200-1204.

Kill JB, Oliveira IF, Tose LV, Costa HB, Kuster RM, Machado LF, et al. Chemical characterization of synthetic cannabinoids by electrospray ionization ft-icr mass spectrometry. Forensic Science International. 2016;266:474-487.

Kleckner AS, Kleckner IR, Kamen CS, Tejani MA, Janelsins MC, Morrow GR, et al. Opportunities for cannabis in supportive care in cancer. Therapeutic Advances in Medical Oncology. 2019;11:1758835919866362.

Klumpers LE, Beumer TL, van Hasselt JG, Lipplaa A, Karger LB, Kleinloog HD, et al. Novel Δ^9-tetrahydrocannabinol formulation Namisol® has beneficial pharmacokinetics and promising pharmacodynamic effects. British Journal of Clinical Pharmacology. 2012;74(1):42-53.

Kneisel S, Auwärter V. Analysis of 30 synthetic cannabinoids in serum by liquid chromatography-electrospray ionization tandem mass spectrometry after liquid-liquid extraction. Journal of Mass Spectrometry. 2012;47(7):825-835.

Koopman Gonzalez SJ, Cofie LE, Trapl ES. "I just use it for weed": the modification of little cigars and cigarillos by young adult African American male users. Journal of Ethnicity in Substance Abuse. 2017;16(1):66-79.

Koppel BS, Brust JC, Fife T, Bronstein J, Youssof S, Gronseth G, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders. American Academy of Neurology. 2014;82(17):1556-1563.

Kostygina G, Huang J, Emery S. TrendBlendz: how splitarillos use marijuana flavours to promote cigarillo use. Tobacco Control. 2017;26(2):235-236.

Kraft B. Is there any clinically relevant cannabinoid-induced analgesia? Pharmacology. 2012;89(5-6):237-246.

Lam RPK, Tang MHY, Leung SC, Chong YK, Tsui MSH, Mak TWL. Supraventricular tachycardia and acute confusion following ingestion of e-cigarette fluid containing ab-fubinaca and adb-fubinaca: a case report with quantitative analysis of serum drug concentrations. Clinical Toxicology. 2017;55(7):662-667.

Landa L, Jurica J, Sliva J, Pechackova M, Demlova R. Medical cannabis in the treatment of cancer pain and spastic conditions and options of drug delivery in clinical practice. Biomedical Papers of the Medical Faculty of University Palacky, Olomouc, Czech Republic. 2018;162(1):18-25.

Lanz C, Mattsson J, Soydaner U, Brenneisen R. Medicinal cannabis: in vitro validation of vaporizers for the smoke-free inhalation of cannabis. Public Library of Science One. 2016;11(1):1-18.

Lee D, Huestis MA. Current knowledge on cannabinoids in oral fluid. Drug Testing and Analysis. 2014;6(1-2):88-111.

Lee D, Milman G, Barnes AJ, Goodwin RS, Hirvonen J, Huestis MA. Oral fluid cannabinoids in chronic, daily Cannabis smokers during sustained, monitored abstinence. Clinical Chemistry. 2011;57(8):1127-1136.

Lee D, Milman G, Schwope DM, Barnes AJ, Gorelick DA, Huestis MA. Cannabinoid stability in authentic oral fluid after controlled cannabis smoking. Clinical Chemistry. 2012;58(7):1101-1109.

Lee D, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, et al. Cannabis withdrawal in chronic, frequent cannabis smokers during sustained abstinence within a closed residential environment. The American Journal on Addictions. 2014,23(3):234-242.

Lee D, Vandrey R, Mendu DR, Anizan S, Milman G, Murray JA, et al. Oral fluid cannabinoids in chronic cannabis smokers during oral Δ9-tetrahydrocannabinol therapy and smoked cannabis challenge. Clinical Chemistry. 2013a;59(12):1770-1779.

Lee D, Vandrey R, Mendu DR, Murray JA, Barnes AJ, Huestis MA. Oral fluid cannabinoids in chronic frequent cannabis smokers during ad libitum cannabis smoking. Drug Testing and Analysis. 2015;7(6):494-501.

Lee D, Vandrey R, Milman G, Bergamaschi M, Mendu DR, Murray JA, et al. Oral fluid/plasma cannabinoid ratios following controlled oral thc and smoked cannabis administration. Analytical and Bioanalytical Chemistry. 2013b;405(23):7269-7279.

Lee DC, Crosier BS, Borodovsky JT, Sargent JD, Budney AJ. Online survey characterizing vaporizer use among cannabis users. Drug and Alcohol Dependence. 2016;159:227-233.

Lee G, Grovey B, Furnish T, Wallace M. Medical cannabis for neuropathic pain. Current Pain and Headache Reports. 2018;22(1):8.(1-12).

Lenné MG, Dietze PM, Triggs TJ, Walmsley S, Murphy B, Redman JR. The effects of cannabis and alcohol on simulated arterial driving: Influences of driving experience and task demand. Accident Analysis and Prevention. 2010;42(3):859-866.

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, et al. Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia. Translational psychiatry. 2012;2(3):e94.

Lewis MM, Yang Y, Wasilewski E, Clarke HA, Kotra LP. Chemical profiling of medical cannabis extracts. American Chemical Society Omega. 2017;2(9):6091-6103.

Lile JA, Kelly TH, Charnigo RJ, Stinchcomb AL, Hays LR. Pharmacokinetic and pharmacodynamic profile of supratherapeutic oral doses of Δ9-thc in cannabis users. The Journal of Clinical Pharmacology. 2013;53(7):680-690.

Lile JA, Kelly TH, Hays LR. Separate and combined effects of the cannabinoid agonists nabilone and Δ⁹-thc in humans discriminating Δ⁹-thc. Drug and Alcohol Dependence. 2011;116(1-3):86-92.

Lim K, See YM, Lee J. A systematic review of the effectiveness of medical cannabis for psychiatric, movement and neurodegenerative disorders. Clinical Psychopharmacology and Neuroscience: The Official Scientific Journal of the Korean College of Neuropsychopharmacology. 2017;15(4):301-312.

Lim M, Kirchhof MG. Dermatology-related uses of medical cannabis promoted by dispensaries in Canada, Europe, and the United States. Journal of Cutaneous Medicine and Surgery. 2018;23:1-7.

Lim M, Kirchhof MG. Dermatology-related uses of medical cannabis promoted by dispensaries in Canada, Europe, and the United States. Journal of Cutaneous Medicine and Surgery. 2019;23(2):178-184.

Lintzeris N, Driels J, Elias N, Arnold JC, McGregor IS, Allsop DJ. Medicinal cannabis in Australia, 2016: the cannabis as medicine survey (cams-16). The Medical journal of Australia. 2018;209(5):211-216.

Lippmann S, Singh D. Vaping marijuana? The Journal of Family Practice. 2017;66(11):654-655.

Loflin M, Earleywine M, De Leo J, Hobkirk A. Subtypes of attention deficit-hyperactivity disorder (adhd) and cannabis use. Substance use & misuse. 2014;49(4):427-434.

Loflin MJE, Earleywine M, Farmer S, Slavin M, Luba R, Bonn-Miller M. Placebo effects of edible cannabis: reported intoxication effects at a 30-minute delay. Journal of Psychoactive Drugs. 2017;49(5):393-397.

Lowe ML, Blaser DA, Cone L, Arcona S, Ko J, Sasane R, et al. Increasing patient involvement in drug development. Value in Health. 2016;19(6):869-878.

Lucas CJ, Galettis P, Schneider J. The pharmacokinetics and the pharmacodynamics of cannabinoids. British Journal of Clinical Pharmacology. 2018;84(11):2477-2482.

Lucas P. Cannabis as an adjunct to or substitute for opiates in the treatment of chronic pain. Journal of Psychoactive Drugs. 2012;44(2):125-133.

Luckett T, Phillips J, Lintzeris N, Allsop D, Lee J, Solowij N, et al. Clinical trials of medicinal cannabis for appetite-related symptoms from advanced cancer: a survey of preferences, attitudes and beliefs among patients willing to consider participation. Internal Medicine Journal. 2016;46(11):1269-1275.

Lutge EE, Gray A, Siegfried N. The medical use of cannabis for reducing morbidity and mortality in patients with hiv/aids. Cochrane Database of Systematic Reviews. 2013;(4):1-45.

Lynch ME, Campbell F. Cannabinoids for treatment of chronic non-cancer pain; a systematic review of randomized trials. British Journal of Clinical Pharmacology. 2011;72(5):735-744.

Lynch ME, Cesar-Rittenberg P, Hohmann AG. A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain. Journal of Pain and Symptom Management. 2014;47(1):166-173.

MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine. 2018;49:12-19.

Mach F, Steffens S. The role of the endocannabinoid system in atherosclerosis. Journal of Neuroendocrinology. 2008;20(Suppl1):53-57.

Machado Rocha FC, Stéfano SC, De Cássia Haiek R, Rosa Oliveira LM, Da Silveira DX. Therapeutic use of cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. European Journal of Cancer Care. 2008;17(5):431-443.

Maida V, Corban J. Topical medical cannabis: a new treatment for wound pain-three cases of pyoderma gangrenosum. Journal of Pain and Symptom Management. 2017;54(5):732-736.

Malouff JM, Rooke SE, Copeland J. Experiences of marijuana-vaporizer users. Substance Abuse. 2014;35(2):127-128.

Maniscalco GT, Aponte R, Bruzzese D, Guarcello G, Manzo V, Napolitano M, et al. Thc/cbd oromucosal spray in patients with multiple sclerosis overactive bladder: a pilot prospective study. Neurological Sciences. 2018;39(1):97-102.

Mansouri H, Asrar Z. Effects of abscisic acid on content and biosynthesis of terpenoids in Cannabis sativa at vegetative stage. Biologia Plantarum. 2012;56(1):153-156.

Martin BR. Role of lipids and lipid signaling in the development of cannabinoid tolerance. Life Sciences. 2005;77(14):1543-1558.

Mathre ML. Cannabis series-the whole story part 5: research and development of cannabis preparations and delivery systems. Drugs and Alcohol Today. 2002;2(4):4-8.

McCarberg BH. Cannabinoids: their role in pain and palliation. Journal of Pain & Palliative Care Pharmacotherapy. 2007;21(3):19-28.

McCoy B, Wang L, Zak M, Al-Mehmadi S, Kabir N, Alhadid K, et al. A prospective open-label trial of a cbd/thc cannabis oil in dravet syndrome. Annals of Clinical and Translational Neurology. 2018;5(9):1077-1088.

McDonald EA, Popova L, Ling PM. Traversing the triangulum: the intersection of tobacco, legalised marijuana and electronic vaporisers in Denver, Colorado. Tobacco Control. 2016;25(1):i96-i102.

McGilveray LJ. Pharmacokinetics of cannabinoids. Pain Research and Management. 2005;10(SupplA):15A-22A.

McKinney DL, Cassidy MP, Collier LM, Martin BR, Wiley JL, Selley DE, et al. Dose-related differences in the regional pattern of cannabinoid receptor adaptation and in vivo tolerance development to delta9-tetrahydrocannabinol. The Journal of Pharmacology and Experimental Therapeutics. 2008;324(2):664-673.

McMahon LR. Chronic delta-tetrahydrocannabinol treatment in rhesus monkeys: differential tolerance and cross-tolerance among cannabinoids. British Journal of Pharmacology. 2011;162(5):1060-1073.

Mehrpour O, Lamarine RJ, Nakhaee S. Majoon birjandi (mb): a rationale for the medical use of a traditional and uniquely processed Iranian folk medicine containing cannabis. Medical Hypotheses. 2018;119:102-103.

Mensen VT, Vreeker A, Nordgren J, Atkinson A, de la Torre R, Farré M. Psychopathological symptoms associated with synthetic cannabinoid use: a comparison with natural cannabis. Psychopharmacology. 2019;236(9):2677-2685.

Mersiades AJ, Tognela A, Haber PS, Stockler M, Lintzeris N, Simes J, et al. Oral cannabinoid-rich thc/cbd cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (cannabiscinv). British Medical Journal Open. 2018;2018;8(9):e020745.

Metrik J, Kahler CW, Reynolds B, McGeary JE, Monti PM, Haney M, et al. Balanced placebo design with marijuana: pharmacological and expectancy effects on impulsivity and risk taking. Psychopharmacology. 2012;223(4):489-499.

Meyer HC, Lee FS, Gee DG. The role of the endocannabinoid system and genetic variation in adolescent brain development. Neuropsychopharmacology. 2018;43(1):21-33.

Meyer T, Funke A, Münch C, Kettemann D, Maier A, Walter B et al. Real world experience of patients with amyotrophic lateral sclerosis (als) in the treatment of spasticity using tetrahydrocannabinol:cannabidiol (thc:cbd). BioMed Central Neurology. 2019;19(1):222.

Milman G, Barnes AJ, Schwope DM, Schwilke EW, Goodwin RS, Kelly DL, et al. Cannabinoids and metabolites in expectorated oral fluid after 8 days of controlled around-the-clock oral thc administration. Analytical and Bioanalytical Chemistry. 2011;401(2):599-607.

Milman G, Bergamaschi MM, Lee D, Mendu DR, Barnes AJ, Vandrey R, et al. Plasma cannabinoid concentrations during dronabinol pharmacotherapy for cannabis dependence. Therapeutic Drug Monitoring. 2014;36(2):218-224.

Milman G, Schwope DM, Gorelick DA, Huestis MA. Cannabinoids and metabolites in expectorated oral fluid following controlled smoked cannabis. Clinica Chimica Acta. 2012;413(7-8):765-770.

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Plos Medicine. 2009;6(7):e1000097.

Molnar A, Fu S, Lewis J, Allsop DJ, Copeland J. The detection of thc, cbd and cbn in the oral fluid of Sativex® patients using two on-site screening tests and lc–ms/ms. Forensic Science International. 2014;238:113-119.

Molnar A, Lewis J, Doble P, Hansen G, Prolov T, Fu S. A rapid and sensitive method for the identification of delta-9-tetrahydrocannabinol in oral fluid by liquid chromatography-tandem mass spectrometry. Forensic Science International. 2012;215(1-3):92-96.

Moore C, Cevikbas F, Pasolli HA, Chen Y, Kong W, Kempkes C, et al. UVB radiation generates sunburn pain and affects skin by activating epidermal TRPV4 ion channels and triggering endothelin-1 signaling. Proceedings of the National Academy of Sciences of the United States of America. 2013;17;110(38):15502.

Morales P, Reggio PH, Jagerovic N. An Overview on medicinal chemistry of synthetic and natural derivatives of cannabidiol. Frontiers in Pharmacology. 2017;8(422):1-18.

Morean ME, Kong G, Camenga DR, Cavallo DA, Krishnan-Sarin S. High school students' use of electronic cigarettes to vaporize cannabis. Pediatrics. 2015;136(4):611-616.

Morean ME, Lipshie N, Josephson M, Foster D. Predictors of adult e-cigarette users vaporizing cannabis using e-cigarettes and vape-pens. Substance Use and Misuse. 2017;52(8):974-981.

Moreira FA, Grieb M, Lutz B. Central side-effects of therapies based on cb1 cannabinoid receptor agonists and antagonists: focus on anxiety and depression. Best Practice & Research Clinical Endocrinology & Metabolism. 2009;23(1):133-144.

Mouhamed Y, Vishnyakov A, Qorri B, Sambi M, Frank SS, Nowierski K, et al. Therapeutic potential of medicinal marijuana: an educational primer for health care professionals. Drug, Health Care and Patient Safety. 2018;10:45-66.

Mounessa JS, Siegel JA, Dunnick CA, Dellavalle RP. The role of cannabinoids in dermatology. Journal of the American Academy of Dermatology. 2017;77(1):188-190.

Murphy F, Sales P, Murphy S, Averill S, Lau N, Sato SO. Baby boomers and cannabis delivery systems. Journal of Drug Issues. 2015;45(3):293-313.

Mücke M, Phillips T, Radbruch L, Petzke F, Häuser W. Cannabis-based medicines for chronic neuropathic pain in adults. The Cochrane Database of Systematic Reviews. 2018;3(3):CD012182.

Naftali T, Lev LB, Yablecovitch D, Half E, Konikoff FM. Treatment of crohn's disease with cannabis: an observational study. The Israel Medical Association journal: IMAJ. 2011;13(8):455-458.

Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. Future Medicinal Chemistry. 2009;1(7):1333-1349.

Nam G, Jeong SK, Park BM, Lee SH, Kim HJ, Hong SP, et al. Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. Annals of Dermatology. 2016;28(1):22-29.

Nesto RW, Mackie K. Endocannabinoid system and its implications for obesity and cardiometabolic risk. European Heart Journal Supplements. 2008;10(Suppl B):B34-B41.

Newmeyer MN, Desrosiers NA, Lee D, Mendu DR, Barnes AJ, Gorelick DA, et al. Cannabinoid disposition in oral fluid after controlled cannabis smoking in frequent and occasional smokers. Drug Testing and Analysis. 2014;6(10):1002-1010.

Newmeyer MN, Swortwood MJ, Abulseoud OA, Huestis MA. Subjective and physiological effects, and expired carbon monoxide concentrations in frequent and occasional cannabis smokers following smoked, vaporized, and oral cannabis administration. Drug and Alcohol Dependence. 2017a;175:67-76.

Newmeyer MN, Swortwood MJ, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabis edibles: blood and oral fluid cannabinoid pharmacokinetics and evaluation of oral fluid screening devices for predicting Δ9-tetrahydrocannabinol in blood and oral fluid following cannabis brownie administration. Clinical Chemistry. 2017b;63(3):647-662.

Newmeyer MN, Swortwood MJ, Barnes AJ, Abulseoud OA, Scheidweiler KB, Huestis MA. Free and glucuronide whole blood cannabinoids' pharmacokinetics after controlled smoked, vaporized, and oral cannabis administration in frequent and occasional cannabis users: identification of recent cannabis intake. Clinical Chemistry. 2016;62(12):1579-1592.

Newmeyer MN, Swortwood MJ, Taylor ME, Abulseoud OA, Woodward TH, Huestis MA. Evaluation of divided attention psychophysical task performance and effects on pupil sizes following smoked, vaporized and oral cannabis administration. Journal of Applied Toxicology. 2017c;37(8):922-932.

Northrup TF, Klawans MR, Villarreal YR, Abramovici A, Suter MA, Mastrobattista JM, et al. Family physicians' perceived prevalence, safety, and screening for cigarettes, marijuana, and electronic-nicotine delivery systems (ends) use during pregnancy. Journal of the American Board of Family Medicine. 2017;30(6):743-757.

Novotna A, Mares J, Ratcliffe S, Novakova I, Vachova M, Zapletalova O, et al. A randomized, double-blind, placebo-controlled, parallel-group, enriched-design study of nabiximols* (Sativex(®)), as add-on therapy, in subjects with refractory spasticity caused by multiple sclerosis. European Journal of Neurology. 2011;18(9):1122-1131.

Ogborne AC, Smart RG, Adlaf EM. Self-reported medical use of marijuana: a survey of the general population. Canadian Medical Association Journal. 2000:162(12):1685-1686.

Oláh A, Bíró T. Targeting cutaneous cannabinoid signaling in inflammation - a "high"-way to heal? EBioMedicine. 2017;16:3-5.

Oláh A, Markovics A, Szabó-Papp J, Szabó PT, Stott C, Zouboulis CC, et al. Differential effectiveness of selected non-psychotropic phytocannabinoids on human sebocyte functions implicates their introduction in dry/seborrhoeic skin and acne treatment. Experimental Dermatology. 2016;25(9):701-707.

Oláh A, Tóth BI, Borbíró I, Sugawara K, Szöllõsi AG, Czifra G, et al. Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes. The Journal of Clinical Investigation. 2014;124(9):3713-3724.

Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacological Reviews. 2006;58(3):389-462.

Pacula RL, Kilmer B, Wagenaar AC, Chaloupka FJ, Caulkins JP. Developing public health regulations for marijuana: lessons from alcohol and tobacco. American Journal of Public Health. 2014;104(6):1021-1028.

Pain S. A potted history. Nature. 2015;525(7570):S10-S11.

Panlilio LV, Justinova Z, Goldberg SR. Inhibition of faah and activation of ppar: new approaches to the treatment of cognitive dysfunction and drug addiction. Pharmacology and Therapeutics. 2013;138(1):84-102.

Papazisis G, Siafis S, Tsakiridis I, Koulas I, Dagklis T, Kouvelas D. Prevalence of cannabis use among medical students: a systematic review and meta-analysis. Substance Abuse: Research and Treatment. 2018;12:1178221818805977.

Parikh N, Kramer WG, Khurana V, Smith CC, Vetticaden S. Bioavailability study of dronabinol oral solution versus dronabinol capsules in healthy volunteers. Clinical Pharmacology: Advances and Applications. 2016;8:155-162.

Parmar JR, Forrest BD, Freeman RA. Medical marijuana patient counseling points for healthcare professionals based on trends in the medical uses, efficacy, and adverse effects of cannabis-based pharmaceutical drugs. Research in Social and Administrative Pharmacy. 2016;12(4):638-654.

Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Experimental Neurology. 2010;224(1):3-14.

Parvathi M. Intranasal drug delivery to brain: an overview. International Journal of Research in Pharmacy and Chemistry. 2012;2(3):889-895.

Paudel KS, Hammell DC Agu RU, Valiveti S, Stinchcomb AL. Cannabidiol bioavailability after nasal and transdermal application: effect of permeation enhancers. Drug Development and Industrial Pharmacy. 2010;36(9):1088-1097.

Peace MR, Butler KE, Wolf CE, Poklis JL and Poklis A. Evaluation of two commercially available cannabidiol formulations for use in electronic cigarettes. Frontiers in Pharmacology. 2016;7(279):1-6.

Pearce DD, Mitsouras K, Irizarry KJ. Discriminating the effects of cannabis sativa and cannabis indica: a web survey of medical cannabis users. The Journal of Alternative and Complementary Medicine. 2014;20(10):787-791.

Pellesi L, Licata M, Verri P, Vandelli D, Palazzoli F, Marchesi F, et al. Pharmacokinetics and tolerability of oral cannabis preparations in patients with medication overuse headache (moh)-a pilot study. European Journal of Clinical Pharmacology. 2018;74(11):1427-1436.

Peters EN, Schauer GL, Rosenberry ZR, Pickworth WB. Does marijuana "blunt" smoking contribute to nicotine exposure?: Preliminary product testing of nicotine content in wrappers of cigars commonly used for blunt smoking. Drug and Alcohol Dependence. 2016;168:119-122.

Philpot LM, Ebbert JO, Hurt RT. A survey of the attitudes, beliefs and knowledge about medical cannabis among primary care providers. BMC Family Practice. 2019;20(1):17.

Pisanti S, Bifulco M. Medicinal use of cannabis in Europe. European Molecular Biology Organization Reports. 2015;16(2):130-132.

Pizarro-Osilla C. "Medibles": dangerous treats. Journal of Emergency Nurses. 2016;42(4):361-362.

Poklis JL, Mulder HA, Peace MR. The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids. Forensic Science International. 2019;294:e25-e27.

Polak A, Harasim-Symbor E, Malinowska B, Kasacka I, Lewandowska A, Chabowski A. The endocannabinoid system affects myocardial glucose metabolism in the doca-salt model of hypertension. Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology. 2018;46(2):727-739.

Punyamurthula NS, Adelli GR, Gul W, Repka MA, ElSohly MA, and Majumdar S. Ocular disposition of Δ^8-tetrahydrocannabinol from various topical ophthalmic formulations. American Association of Pharmaceutical Scientists. 2017;18(6):1936-1945.

Punyamurthula NS, Hingorani T, Adelli G, Gul W, ElSohly MA, Repka MA, et al. Controlled release tablet formulation containing natural Δ(9)-tetrahydrocannabinol. Drug Development and Industrial Pharmacy. 2016;42(7):1158-1164.

Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis and Cannabinoid Research. 2017;2(1):160-166.

Reuter SE, Martin JH. Pharmacokinetics of cannabis in cancer cachexia-anorexia syndrome. Clinical Pharmacokinetics. 2016;55(7):807-812.

Rice J, Cameron M. Cannabinoids for treatment of ms symptoms: state of the evidence. Current Neurology and Neuroscience Reports. 2018;18(8):50.

Riemer L, Holmes R. Under the influence: informing oral health care providers about substance abuse. The Journal of Evidence-Based Dental Practice. 2014;14S:(e1)127-135.

Romero-Sandoval EA, Fincham JE, Kolano AL, Sharpe BN, Alvarado-Vázquez PA. Cannabis for chronic pain: challenges and considerations. Pharmacotherapy. 2018;38(6):651-662.

Romero-Sandoval EA, Kolano AL, Alvarado-Vázquez PA. Cannabis and cannabinoids for chronic pain. Current Rheumatology Reports. 2017;19(11):67.

Rubens M. Political and medical views on medical marijuana and its future. Social Work in Public Health. 2014;29(2):121-131.

Ruchlemer R, Amit-Kohn M, Raveh D, Hanuš L. Inhaled medicinal cannabis and the immunocompromised patient. Supportive Care in Cancer. 2015;23(3):819-822.

Russell C, Rueda S, Room R, Tyndall M, Fischer B. Routes of administration for cannabis use - basic prevalence and related health outcomes: a scoping review and synthesis. The International Journal on Drug Policy. 2018;52:87-96.

Russo EB. Clinical endocannabinoid deficiency reconsidered: current research supports the theory in migraine, fibromyalgia, irritable bowel, and other treatment-resistant syndromes. Cannabis and Cannabinoid Research. 2016;1(1):154-165.

Russo EB, Hohmann AG. Role of cannabinoids in pain management. Deer et al. editors. Comprehensive Treatment of Chronic Pain by Medical, Interventional, and Integrative Approaches. American Academy of Pain Medicine; 2013. p. 181-197.

Russo EB. Taming thc: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology. 2011;163(7):1344-1364.

Sagar KA, Lambros AM, Dahlgren MK, Smith RT, Gruber SA. Made from concentrate? A national web survey assessing dab use in the United States. Drug and Alcohol Dependence. 2018;190:133-142.

Sagy I, Peleg-Sagy T, Barski L, Zeller L, Jotkowitz A. Ethical issues in medical cannabis use. European Journal of Internal Medicine. 2018;49:20–22.

Sarchielli P, Pini LA, Coppola F, Rossi C, Baldi A, Mancini ML, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology. 2007;32(6):1384-1390.

Sarvet AL, Wall MM, Fink DS, Greene E, Le A, Boustead AE, et al. Medical marijuana laws and adolescent marijuana use in the United States: a systematic review and meta-analysis. Addiction. 2018;113(6):1003-1016.

Sastre-Garriga J, Vila C, Clissold S, Montalban X. Thc and cbd oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis. Expert Review of Neurotherapeutics. 2011;11(5):627-637.

Schauer GL, Rosenberry ZR, Peters EN. Marijuana and tobacco co-administration in blunts, spliffs, and mulled cigarettes: a systematic literature review. Addictive Behaviors. 2017;64:200-211.

Scheau C, Badarau IA, Mihai LG, Scheau AE, Costache DO, Constantin C, et al. Cannabinoids in the pathophysiology of skin inflammation. Molecules. 2020;25(3):652.

Scheidweiler KB, Andersson M, Swortwood MJ, Sempio C, Huestis MA. Long-term stability of cannabinoids in oral fluid after controlled cannabis administration. Drug Testing and Analysis. 2017;9(1):143-147.

Scheidweiler KB, Schwope DM, Karschner EL, Desrosiers NA, Gorelick DA, Huestis MA. In vitro stability of free and glucuronidated cannabinoids in blood and plasma following controlled smoked cannabis. Clinical Chemistry. 2013;59(7):1108-1117.

Schep LJ, Slaughter RJ, Hudson S, Place R, Watts M. Delayed seizure-like activity following analytically confirmed use of previously unreported synthetic cannabinoid analogues. Human and Experimental Toxicology. 2015;34(5):557-560.

Schicho R, Storr M. Cannabis finds its way into treatment of crohn's disease. Pharmacology. 2014;93(1-2):1-3.

Schier AR, Ribeiro NP, Silva AC, Hallak JE, Crippa JA, Nardi AE, et al. Cannabidiol, a cannabis sativa constituent, as an anxiolytic drug. Revista Brasileira de Psiquiatria. 2012;34(1):S104-S110.

Schlienz NJ, Cone EJ, Herrmann ES, Lembeck NA, Mitchell JM, Bigelow GE, et al. Pharmacokinetic characterization of 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol in urine following acute oral cannabis ingestion in healthy adults. Journal of Analytical Toxicology. 2018a;42(4):232-247.

Schlienz NJ, Lee DC, Stitzer ML, Vandrey R. The effect of high-dose dronabinol (oral thc) maintenance on cannabis self-administration. Drug and Alcohol Dependence. 2018b;187:254-260.

Schoedel KA, Chen N, Hilliard A, White L, Stott C, Russo E, et al. A randomized, double-blind, placebo-controlled, crossover study to evaluate the subjective abuse potential and cognitive effects of nabiximols oromucosal spray in subjects with a history of recreational cannabis use. Human Psychopharmacology. 2011;26(3):224-236.

Schwope DM, Karschner EL, Gorelick DA, Huestis MA. Identification of recent cannabis use: whole-blood and plasma free and glucuronidated cannabinoid pharmacokinetics following controlled smoked cannabis administration. Clinical Chemistry. 2011;57(10):1406-1414.

Scully C. Cannabis; adverse effects from an oromucosal spray. British Dental Journal. 2007;203(E12):1-4.

Sewell RA, Schnakenberg A, Elander J, Radhakrishnan R, Williams A, Skosnik PD, et al. Acute effects of thc on time perception in frequent and infrequent cannabis users. Psychopharmacology. 2013;226(2):401-413.

Sexton M, Cuttler C, Finnell JS, Mischley LK. A cross-sectional survey of medical cannabis users: patterns of use and perceived efficacy. Cannabis and Cannabinoid Research. 2016;1(1):131-138.

Shannon S, Lewis N, Lee H, Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. The Permenante Journal. 2019;23:18-041.

Sherry Ku M, Li W, Dulin W, Donahue F, Cade D, Benameur H, et al. Performance qualification of a new hypromellose capsule: part I. Comparative evaluation of physical, mechanical and processability quality attributes of vcaps plus, quali-v and gelatin capsules. International Journal of Pharmaceutics. 2010;386(1-2):30-41.

Shiplo S, Asbridge M, Leatherdale ST, Hammond D. Medical cannabis use in Canada: vapourization and modes of delivery. Harm Reduction Journal. 2016;13(30):1-10.

Siew A. Designing optimized formulations. Pharmaceutical Technology. 2017;41(4):16-21.

Singh H, Schulze DR, McMahon LR. Tolerance and cross-tolerance to cannabinoids in mice: schedule-controlled responding and hypothermia. Psychopharmacology. 2011;215(4):665-675.

Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the treatment of pain in fibromyalgia. The Journal of Pain. 2008;9(2):164-173.

Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Database of Systematic Reviews. 2015;12(11):CD009464.

Solowij N, Jones KA, Rozman ME, Davis SM, Ciarrochi J, Heaven PC, et al. Reflection impulsivity in adolescent cannabis users: a comparison with alcohol-using and non-substance-using adolescents. Psychopharmacology. 2012;219(2):575-586.

Šoltýsová I, Toropilová D, de Vringer T. Lipid based formulations of biopharmaceutics classification system (bcs) class II drugs: strategy, formulations, methods and saturation. Folia Veterinaria. 2016;60(4):63-69.

Spindle TR, Cone EJ, Schlienz NJ, Mitchell JM, Bigelow GE, Flegel R, et al. Acute effects of smoked and vaporized cannabis in healthy adults who infrequently use cannabis a crossover trial. The Journal of the American Medical Association Network Open. 2018;1(7):e184841.

Splinter W. Novel approaches for treating pain in children. Current Oncology Reports. 2019;21(2):11.

Squintani G, Donato F, Turri M, Deotto L, Teatini F, Moretto G, et al. Cortical and spinal excitability in patients with multiple sclerosis and spasticity after oromucosal cannabinoid spray. Journal of the Neurological Sciences. 2016;370:263-268.

Staud R, Koo EB. Are cannabinoids a new treatment option for pain in patients with fibromyalgia? Nature Clinical Practice Rheumatology. 2008;4(7):348-349.

Stott CG, White L, Wright S, Wilbraham D, Guy GW. A phase I study to assess the single and multiple dose pharmacokinetics of thc/cbd oromucosal spray. European Journal of Clinical Pharmacology. 2013;69(5):1135-1147.

Sun J, Zhou YQ, Chen SP, Wang XM, Xu BY, Li DY, et al. The endocannabinoid system: novel targets for treating cancer induced bone pain. Biomedicine and Pharmacotherapy 120. 2019;22:1-18.

Swortwood MJ, Newmeyer MN, Andersson M, Abulseoud OA, Scheidweiler KB, Huestis MA. Cannabinoid disposition in oral fluid after controlled smoked, vaporized, and oral cannabis administration. Drug Testing and Analysis. 2017;9(6):905-915.

Szaflarski M, Sirven JI. Social factors in marijuana use for medical and recreational purposes. Epilepsy & Behavior. 2017;70(Pt B):280-287.

Tang CH, Ten Z, Wang XS, Yang XQ. Physicochemical and functional properties of hemp (cannabis sativa l.) protein isolate. Journal of Agricultural and Food Chemistry. 2006;54:8945-8950.

Tanne JH. Don’t vape, CDC says, as US lung disease epidemic grows. British Medical Journal. 2019;366(l5479):1-2.

Tashkin DP. How beneficial is vaping cannabis to respiratory health compared to smoking? Addiction. 2015;110(11):1706-1707.

Telek A, Bíró T, Bodó E, Tóth BI, Borbíró I, Kunos G, et al. Inhibition of human hair follicle growth by endo- and exocannabinoids. Federation of American Societies for Experimental Biology Journal. 2007;21(13):3534-3541.

Theunissen EL, Kauert GF, Toennes SW, Moeller MR, Sambeth A, Blanchard MM, et al. Neurophysiological functioning of occasional and heavy cannabis users during thc intoxication. Psychopharmacology. 2012;220(2):341-350.

Toennes SW, Geraths A, Pogoda W, Paulke A, Wunder C, Theunissen EL, et al. Excretion of metabolites of the synthetic cannabinoid jwh-018 in urine after controlled inhalation. Journal of Pharmaceutical and Biomedical Analysis. 2018a;150:162-168.

Toennes SW, Geraths A, Pogoda W, Paulke A, Wunder C, Theunissen EL, et al. Pharmacokinetic properties of the synthetic cannabinoid JWH-018 in oral fluid after inhalation. Drug Testing and Analysis. 2018b;10(4):644-650.

Tóth KF, Ádám D, Bíró T, Oláh A. Cannabinoid signaling in the skin: therapeutic potential of the "c(ut)annabinoid" system. Molecules. 2019;24(5):918.

Touitou E, Fabin B, Dany S, Almog S. Transdermal delivery of tetrahydrocannabinol. International Journal of Pharmaceutics. 1988;43(1-2):9-15.

Tramèr MR, Carroll D, Campbell FA, Reynolds DJM, Moore RA, McQuay HJ. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. British Medical Journal. 2001;323(7303):16-21.

Treat L, Chapman KE, Colborn KL, Knupp KG. Duration of use of oral cannabis extract in a cohort of pediatric epilepsy patients. Epilepsia. 2017;58(1):123-127.

Trojano M. Thc:cbd observational study data: evolution of resistant ms spasticity and associated symptoms. European Neurology. 2016;75(1):4-8.

Tsang CC, Giudice MG. Nabilone for the management of pain. Pharmacotherapy. 2016;36(3):273-286.

Tzadok M, Uliel-Siboni S, Linder I, Kramer U, Epstein O, Menascu S, et al. Cbd-enriched medical cannabis for intractable pediatric epilepsy: the current Israeli experience. Seizure. 2016;35:41-44.

Ujváry I, Hanuš L. Human metabolites of cannabidiol: a review on their formation, biological activity, and relevance in therapy. Cannabis and Cannabinoid Research. 2016;1(1):90-101.

van der Steur SJ, Batalla A, Bossong MG. Factors moderating the association between cannabis use and psychosis risk: a systematic review. Brain Sciences. 2020;10(2):97.

Van Eenige R, Tambyrajah LL, Wang Y, Rensen PCN, Kooijman S. Inhibition of the endocannabinoid system alleviates dyslipidemia and attenuates atherosclerosis development. Atherosclerosis. 2019;287:e72-e73.

van Hell HH, Jager G, Bossong MG, Brouwer A, Jansma JM, Zuurman L, et al. Involvement of the endocannabinoid system in reward processing in the human brain. Psychopharmacology. 2012;219(4):981-990.

Vandrey R, Herrmann ES, Mitchell JM, Bigelow GE, Flegel R, LoDico C, et al. Pharmacokinetic profile of oral cannabis in humans: blood and oral fluid disposition and relation to pharmacodynamic outcomes. Journal of Analytical Toxicology. 2017;41(2):83-99.

Varlet V, Concha-Lozano N, Berthet A, Plateel G, Favrat B, De Cesare M, et al. Drug vaping applied to cannabis: is “cannavaping” a therapeutic alternative to marijuana? Scientific Reports. 2016;6(25599):1-13.

Veilleux A, Di Marzo V, Silvestri C. The expanded endocannabinoid system/endocannabinoidome as a potential target for treating diabetes mellitus. Current Diabetes Reports. 2019;19(11):117.

Versteeg PA, Slot DE, van der Velden U, van der Weijden GA. Effect of cannabis usage on the oral environment: a review. International Journal of Dental Hygiene. 2008;6(4):315-320.

Wade D. Evaluation of the safety and tolerability profile of sativex®: is it reassuring enough? Expert Review of Neurotherapeutics. 2012;12(4 Suppl.):9-14.

Walter C, Oertel BG, Felden L, Nöth U, Vermehren J, Deichmann R, et al. Effects of oral Δ^9-tetrahydrocannabinol on the cerebral processing of olfactory input in healthy non-addicted subjects. European Journal of Clinical Pharmacology. 2017;73(12):1579-1587.

Walter C, Oertel BG, Ludyga D, Ultsch A, Hummel T, Lötsch J. Effects of 20 mg oral Δ(9)-tetrahydrocannabinol on the olfactory function of healthy volunteers. British Journal of Clinical Pharmacology. 2014;78(5):961-969.

Wang M, Wang YH, Avula B, Radwan MM, Wanas AS, Mehmedic Z, et al. Quantitative determination of cannabinoids in cannabis and cannabis products using ultra-high-performance supercritical fluid chromatography and diode array/mass spectrometric detection. Journal of Forensic Sciences. 2017;62(3):602-611.

Ware MA. Clearing the smoke around medical marijuana. Clinical Pharmacology and Therapeutics. 2011;90(6):844-851.

Ware MA, Martel MO, Jovey R, Lynch ME, Singer J. A prospective observational study of problematic oral cannabinoid use. Psychopharmacology. 2018;235(2):409-417.

Ware MA, Wang T, Shapiro S, Collet JP, COMPASS study team. Cannabis for the management of pain: assessment of safety study (compass). The Journal of Pain: Official Journal of the American Pain Society. 2015;16(12):1233-1242.

Webb CW, Webb SM. Therapeutic benefits of cannabis: a patient survey. Hawai'i Journal of Medicine & Public Health. 2014;73(4):109-111.

Webb D. Where cannabis is legal, edibles may offer a tasty alternative. Environmental Nutrition. 2018;41(9):3.

Welty TE, Luebke A, Gidal BE. Cannabidiol: promise and pitfalls. Epilepsy Currents. 2014;14(5):250-252.

Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, et al. Cannabinoids for medical use: a systematic review and meta-analysis. The Journal of the American Medical Association. 2015;313(24):2456-2473.

Whyte DA, Al-Hammadi S, Balhaj G, Brown OM, Penefsky HS, Souid AK. Cannabinoids inhibit cellular respiration of human oral cancer cells. Pharmacology. 2010;85(6):328-335.

Wilkinson JD, Williamson EM. Cannabinoids inhibit human keratinocyte proliferation through a non-cb1/cb2 mechanism and have a potential therapeutic value in the treatment of psoriasis. Journal of Dermatological Science. 2007;45(2):87-92.

Williams AR, Olfson M, Kim JH, Martins SS, Kleber HD. Older, less regulated medical marijuana programs have much greater enrollment rates than newer 'medicalized' programs. Health Affairs. 2016;35(3):480-488.

Winstock AR, Barrattc MJ. Synthetic cannabis: A comparison of patterns of use and effect profile with natural cannabis in a large global sample. Drug and Alcohol Dependence. 2013;131(1-2):106-111.

Wirrell EC, Laux L, Donner E, Jette N, Knupp K, Meskis MA, et al. Optimizing the Diagnosis and management of dravet syndrome: recommendations from a North American consensus panel. Pediatric Neurology. 2017;68:18-34.

Wolff K, Johnston A. Cannabis use: a perspective in relation to the proposed UK drug-driving legislation. Drug Testing and Analysis. 2014;6(1-2):143-154.

Zając M, Świątek R. The effect of hemp seed and linseed addition on the quality of liver pâtés. Acta Scientiarum Polonorum Technologia Alimentaria. 2018;17(2):169-176.

Zákány N, Oláh A, Markovics A, Takács E, Aranyász A, Nicolussi S, et al. Endocannabinoid tone regulates human sebocyte biology. The Journal of Investigative Dermatology. 2018;138(8):1699-1706.

Zhang J, Purdon CH, Smith EW. Solid lipid nanoparticles for topical drug delivery. American Journal of Advanced Drug Delivery. 2006;4(4):215-220.

Zhornitsky S, Potvin S. Cannabidiol in humans-the quest for therapeutic targets. Pharmaceuticals. 2012;5:529-552.

Zhou Y, Wang S, Lou H, Fan P. Chemical constituents of hemp (cannabis sativa l.) seed with potential antineuroinflammatory activity. Phytochemistry Letters. 2018;23:57-65.

Zias J, Stark H, Sellgman J, Levy R, Werker E, Breuer A, et al. Early medical use of cannabis. Nature. 1993;363(6426):215.

Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a cannabis sativa constituent, as an antipsychotic drug. Brazilian Journal of Medical and Biological Research. 2006;39(4):421-429.

Appendix 1 – Methods of Delivery for Medicinal Cannabis Users Questionnaire

Dear participant,

I am a student enrolled for the Doctorate in Pharmacy Degree and currently I am conducting a study entitled "Delivery of Medicinal Cannabis" under the supervision of Dr. Nicolette Sammut Bartolo.

Part of my study entails the distribution of a questionnaire to medicinal cannabis users to evaluate the preferred methods of cannabis administration and challenges encountered.

I would like to kindly invite you to participate in my study by filling in the questionnaire. Your participation will contribute to my study and the knowledge about medicinal cannabis.

This questionnaire is completely anonymous. No personal information which may divulge your identity will be requested. Participation is voluntary and one can opt to leave the study at any point. By answering the questionnaire you are consenting to take part in this study.

If you require any further information please do not hesitate to contact me on:

Email: ceren.bereketoglu.17@um.edu.mt

Phone: +356 993 10911

Regards,

Ceren Bereketoglu

Doctorate in Pharmacy student

Methods of Delivery for Medicinal Cannabis Users

Age:	
Gender:	☐Female ☐Male ☐Other
Level of Education:	☐Primary ☐Secondary ☐Post-secondary ☐Tertiary ☐Post-tertiary
Nationality:	☐Maltese ☐Other (Please specify: .....)
Locality:	

1. **For which condition are you using medicinal cannabis?** ***(You may choose more than 1 option).***

   ☐ Cancer
      ☐ Nausea and vomiting
      ☐ Pain
      ☐ Other (Please specify: .....)
   ☐ Multiple sclerosis
   ☐ Fibromyalgia
   ☐ Arthritis
      ☐ Pain
      ☐ Other (Please specify: .....)
   ☐ Epilepsy
   ☐ Other (Please specify: .....)

2. **How long have you been using prescribed medicinal cannabis?**

   ☐ Less than 1 week
   ☐ 1 to 4 weeks
   ☐ 1 to 6 months
   ☐ 6 to 12 months
   ☐ 12 to 18 months
   ☐ More than 18 months

3. **Which type of medicinal cannabis are you using?**

   ☐ Pedanios flower 22/1
   ☐ Pedanios flower 20/1
   ☐ Bedrocan flower 22
   ☐ CBD oil
   ☐ Other (Please specify: .....)

4. **Did you try other types of medicinal cannabis other than that specified in question 3?**

   ☐ Yes (Please specify: .....)
   ☐ No

5. **Once you take the medicinal cannabis, how long does it take you to start feeling the desired effect?**

☐ Few seconds
☐ From One up to 15 minutes
☐ From 15 up to 60 minutes
☐ From 60 up to 90 minutes
☐ From 1.5 up to 3 hours
☐ From 3 up to 5 hours
☐ More than 5 hours
☐ Other (Please specify: ……..)

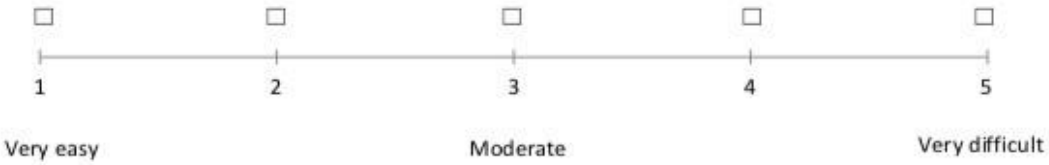
6. **How long does the desired effect of the medicinal cannabis last?**

☐ 30 to 45 minutes
☐ 1 to 2 hours
☐ 2 to 3 hours
☐ 3 to 4 hours
☐ 4 to 6 hours
☐ 6 to 12 hours
☐ 12 to 72 hours

7. **When you take medicinal cannabis, do you feel any of these effects?** ***(You may choose more than 1 option).***

☐ Sleepy
☐ Hungry
☐ Energised
☐ Nauseated
☐ Dizzy
☐ "High'' feeling
☐ Other (Please specify: ……)

8. **Kindly rate the ease of taking a dose of your current medicinal cannabis** ***(where 1 is very easy and 5 is very difficult).***



9. **If you had the option to switch to another mode of administration of cannabis would you do it?**

☐ Yes *(Please go to question 10)*
☐ No *(Please go to question 11)*

10. **Why?**

……

11. **What keeps you from doing so?**

……

12. **Please rate the following dosage forms which are administered orally, rectally or systemically from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred)*.**

Dosage Forms	Image	Preference				
		1 least preferred	2	3 neutral	4	5 most preferred
Round tablet						
Caplet (elongated tablet)						
Capsule						
Vegetarian capsule						
Buccal tablet (placed between the gum and the cheek)						
Sublingual tablet (placed under the tongue)						
Cookies or Other food items						
Tea						
Drinking oil						
Suppository						
Injection						
Water						

13. **Please rate the following dosage forms which are administered topically or via inhalation from 1 to 5 according to your preference** ***(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).***

Dosage Forms	Image	Preference				
		1 least preferred	2	3 neutral	4	5 most preferred
Cannabis cigarrette						
Electronic cigarette						
Inhaler						
Nebuliser (with oxygen tube)						
Spray						
Tincture (drops under the tongue)						
Cream						
Balm/Ointment (dense cream)						
Shampoo, Conditioner, Body wash						
Apply oil on skin						
Eye drop						
Patch						

Appendix 2 – Metodi t'amministrazzjoni tal-kannabis mediċinali għall-utenti Questionnaire

Għażiż/a parteċipant/a,

Jiena studenta irreġistrata għad-Dottorat fil-Farmaċija u bħalissa qed nagħmel studju intitolat "Delivery of Medicinal Cannabis" taħt is-supervižjoni ta' Dr. Nicolette Sammut Bartolo.

Parti mill-istudju tiegħi jinvolvi t-tqassim ta' kwestjonarju lil persuni li jużaw l-kannabis mediċinali, biex nevalwa l-metodi t' amministrazzjoni ppreferuti għal-kannabis u l-isfidi li jiltaqaw magħhom min jużahom.

Nixtieq nistiednek sabiex tipparteċipa f'dan l-istidju billi timla dan il-kwestjonarju. Il-parteċipazzjoni tiegħek tikkontribwixxi għall-istudju tiegħi u għall-għarfien dwar il-kannabis mediċinali.

Dan il-kwestjonarju huwa kompletament anonimu. Ma tintalab l-ebda informazzjoni personali li tista tikxef l-identità tiegħek. Il-parteċipazzjoni tiegħek hija fuq bażi volontarja u wieħed jista' jagħżel li jħalli l-istudju fi kwalunkwe punt. Billi twieġeb il-kwestjonarju qed taqbel li tieħu sehem f'dan l-istudju.

Jekk teħtieġ aktar informazzjoni jekk jogħġbok ikkuntattjani fuq:

Posta elettronika: ceren.bereketoglu.17@um.edu.mt

Mowbajl: +356 993 10911

Tislijiet,

Ceren Bereketoglu

Studenta tad-Dottorat fil-Farmaċija

Metodi t'amministrazzjoni tal-kannabis mediċinali għall-utenti

Età:	
Sess:	☐Mara ☐Raġel ☐Oħrajn
Livel ta' Edukazzjoni:	☐Primarja ☐Sekondarja ☐Post-sekondarja ☐Terzjarja ☐Post-terzjarja
Nazzjonalita:	☐Maltija ☐Oħrajn (Jekk jogħġbok speċifika' : .....)
Lokalità:	

1. **Ghall liema kundizzjoni tuza il kannabis mediċinali?** ***(Tista' tagħżel iktar minn għażla waħda).***

   ☐ Kanċer
      ☐ Dardir jew remettar
      ☐ Uġigħ
      ☐ Oħrajn (Jekk jogħġbok speċifika' : .....)
   ☐ Skleroži multipla
   ☐ Fibromialġia
   ☐ Artrite
      ☐ Uġigħ
      ☐ Oħrajn (Jekk jogħġbok speċifika' : .....)
   ☐ Epilessija
   ☐ Oħrajn (Jekk jogħġbok speċifika': .....)

2. **Kemm ilek tuża l-kannabis mediċinali preskritta min tabib/a?**

   ☐ Inqas minn ġimgħa
   ☐ 1 sa 4 gimgħat
   ☐ 1 sa 6 xhur
   ☐ 6 sa 12 il-xhar
   ☐ 12 sa 18 il-xhar
   ☐ Iktar minn 18 il-xhar

3. **Liema tip ta' kannabis mediċinali qed tuża?**

   ☐ Pedanios flower 22/1
   ☐ Pedanios flower 20/1
   ☐ Bedrocan flower 22
   ☐ CBD oil
   ☐ Oħrajn (Jekk jogħġbok speċifika': .....)

4. **Ippruvajt tipi oħra ta' kannabis mediċinali għajr dawk msemmija fil-mistoqsija numru 3?**

   ☐ Iva (Jekk jogħġbok speċifika': .....)
   ☐ Le

5. **Meta tieħu l-kannabis mediċinali kemmiddum biex tibda tħoss l-effett mixtieq?**

☐ Ftit sekondi
☐ Minn 1 sa 15 il-minuta
☐ Minn 15 sa 60 minuta
☐ Minn 60 sa 90 minuta
☐ Minn 1.5 sa 3 siegħat
☐ Minn 3 sa 5 sieghat
☐ Iktar minn 5 sieghat
☐ Oħrajn (Jekk jogħġbok speċifika': .....)

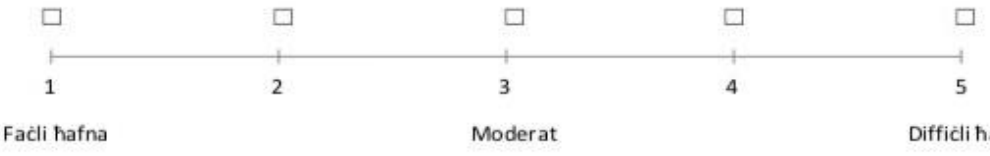
6. **Kemm idum l-effett mixtieq tal-kannabis mediċinali?**

☐ 30 sa 45 minuta
☐ 1 sa 2 siegħat
☐ 2 sa 3 siegħat
☐ 3 sa 4 siegħat
☐ 4 sa 6 siegħat
☐ 6 sa 12 il-siegħa
☐ 12 sa 72 siegħa

7. **Meta tieħu l-kannabis medicinali tħoss xi wieħed/wħud minn dawn l-effetti?** ***(Tista' tagħżel iktar minn għażla waħda).***

☐ Bi nas
☐ Bil-Ġuħ
☐ Bl-energija
☐ Dardir jew remettar
☐ Sturdut
☐ Thossok "high"
☐ Oħrajn (Jekk jogħġbok speċifika': .....)

8. **Immarka min 1 sa 5 kemm issibha faċli li tieħu doża tal-mediċina tiegħek tal-kannabis** ***(fejn 1 huwa faċli ħafna u 5 huwa diffiċli ħafna).***



9. **Kieku kellek l-għażla li taqleb għal metodu ieħor t'amministrazjoni ta' kannabis tagħmel hekk?**

☐ Iva (*mur għall mistoqsija 10)*
☐ Le (*mur għall mistoqsija 11)*

10. **Għaliex?**

.....

11. **X'qed iżommok milli tagħmel hekk?**

.....

12. **Jekk jogħġbok immarka l-formoli tad-dożaġġ mil-lista li ġejja ta' prodotti li jiġu amministrati b'mod orali, rettali jew sistemiku skond il-preferenza tiegħek min 1 sa 5** ***(Fejn 1 huwa l-inqas preferut, 3 huwa newtrali u 5 huwa l-aktar preferut).***

Forma tad-doża	Stampa	Preferenza				
		1 l-inqas preferut	2	3 newtrali	4	5 l-aktar preferut
Pillola tonda						
Kaplet (pillola tawwalija)						
Kapsula						
Kapsula vegetarjana						
Pillola li titqiegħed bejn il-wardiet ta' wiccek u l-ħanek						
Pillola ta' taħt l-ilsien						
Gallettina jew ikel iehor						
Te'						
Żejt li jinxtorob						
Suppożitorju						
Injezzjoni						
Ilma						

13. **Jekk jogħġbok immarka l-formola tad-dożaġġ mil-lista li *ġejja ta' prodotti li jiġu amministrati b'mod topiku jew b'inalazzjoni skond il-preferenza tiegħek* min 1 sa 5 *(Fejn 1 huwa l-inqas preferut, 3 huwa newtral u 5 huwa l-aktar preferut).***

Forma tad-doża	Stampa	Preferenza				
		1 l-inqas preferut	2	3 newtrali	4	5 l-aktar preferut
Sigarett tal-kannabis						
Sigarett elettroniku						
Inalatur						
"Nebuliser" (jintuża mal-maskla tal-ossiġnu)						
Sprej						
Taqtir (qtar taħt l-ilsien)						
Krema						
Balzmu/ingwent (krema densa)						
Xhampoo, "Conditioner", Sapun likwidu						
Żejt li tapplikah fuq il-ġilda						
Taqtir tal-għajnejn						
"Patch"						

Appendix 3 – Methods of Delivery for non-users of Medicinal Cannabis Questionnaire

Dear participant,

I am a student enrolled for the Doctorate in Pharmacy Degree and currently I am conducting a study entitled "Delivery of Medicinal Cannabis" under the supervision of Dr. Nicolette Sammut Bartolo.

Part of my study entails the distribution of a questionnaire to evaluate the preferred methods of cannabis administration for non-users of medicinal cannabis.

I would like to kindly invite you to participate in my study by filling in the questionnaire. Your participation will contribute to my study and the knowledge about medicinal cannabis.

This questionnaire is completely anonymous. No personal information which may divulge your identity will be requested. Participation is voluntary and one can opt to leave the study at any point. By answering the questionnaire you are consenting to take part in this study.

If you require any further information please do not hesitate to contact me on:

Email: ceren.bereketoglu.17@um.edu.mt

Phone: +356 993 10911

Regards,

Ceren Bereketoglu

Doctorate in Pharmacy student

Methods of Delivery for non-users of Medicinal Cannabis

Age:	
Gender:	☐Female ☐Male ☐Other
Level of Education:	☐Primary ☐Secondary ☐Post-secondary ☐Tertiary ☐Post-tertiary
Nationality:	☐Maltese ☐Other (Please specify: .....)
Locality:	

1. **For which condition would you use medicinal cannabis?**

   ☐ Pain
   ☐ Nausea and vomiting
   ☐ Cancer
   ☐ Multiple sclerosis
   ☐ Fibromyalgia
   ☐ Arthritis
   ☐ Epilepsy
   ☐ Other (Please specify: .....)

2. **Are you currently taking any pain medications?**

   ☐ Yes *(go to question 3 & 4)*
   ☐ No *(go to question 5)*

3. **How many types of medications are you taking to control your pain?**

   ☐ 1
   ☐ 2
   ☐ 3
   ☐ More than 3

4. **Are the pain medications which you are currently taking successfully controlling your pain?**

   ☐ Yes
   ☐ No
   ☐ Not sure

5. **Have you ever tried cannabis?**

   ☐ Yes *(go to question 6 & 7)*
   ☐ No *(go to question 8)*

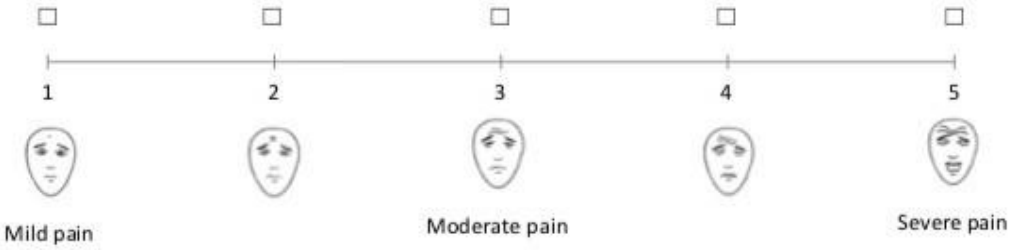
6. **Did cannabis help you feel better?**

   ☐ Yes
   ☐ No

7. **What form of cannabis have you tried?**

☐ Cannabis cigarette
☐ Electronic cigarette or vape
☐ Inhaler or nebuliser
☐ Tablet or capsule
☐ Cannabis cookie
☐ Drinking oil
☐ Tincture drop
☐ Tea
☐ Injection
☐ Cream
☐ Transdermal patch
☐ Eye drop
☐ Suppository

8. **Kindly rate the intensity of pain which you think may require for medicinal cannabis to be started (*Where 1 is mild pain and 5 is severe pain).*[1]**



9. **If you had the opportunity to start using medicinal cannabis, would you do it?**

☐ Yes *(go to question 10)*
☐ No *(go to question 11)*
☐ I don't know *(go to question 11)*

10. **Why? *(You may choose more than 1 option).***

☐ I have been reading a lot about it
☐ I have heard of others who benefitted
☐ My doctor has already suggested it
☐ Mainstream medication is not enough
☐ I would simply like to try
☐ Other (Please Specify: ……)

11. **Why not? *(You may choose more than 1 option).***

☐ I do not believe it has any therapeutic value
☐ I do not believe it will help me but it might help others
☐ I would not know from where to start
☐ I am afraid of side-effects
☐ I am afraid of long-term health consequences
☐ It is difficult to get a doctor to prescribe it
☐ The whole process is too complicated
☐ I am afraid of the social implications
☐ Other (Please Specify: ……)

[1] **The pictures was taken from Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough, B. The Faces Pain Scale – Revised: Toward a common metric in paediatric pain measurement. Pain. 2001;93(2):173-183.**

12. **If you were to use medicinal cannabis, how would you prefer to take it? Please rate the following dosage forms which are administered orally, rectally or systemically from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).***

Dosage Forms	Image	Preference				
		1 least preferred	2	3 neutral	4	5 most preferred
Round tablet						
Caplet (elongated tablet)						
Capsule						
Vegetarian capsule						
Buccal tablet (placed between the gum and the cheek)						
Sublingual tablet (placed under the tongue)						
Cookies or other food items						
Tea						
Drinking oil						
Suppository						
Injection						
Water						

13. **If you were to use medicinal cannabis, how would you prefer to take it? Please rate the following dosage forms which are administered topically or via inhalation from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).***

Dosage Forms	Image	Preference				
		1 least preferred	2	3 neutral	4	5 most preferred
Cannabis cigarette						
Electronic cigarette						
Inhaler						
Nebuliser (with oxygen tube)						
Spray						
Tincture (drops under the tongue)						
Cream						
Balm/Ointment (dense cream)						
Shampoo, Conditioner, Body wash						
Apply oil on skin						
Eye drop						
Patch						

Appendix 4 – Metodi t'amministrazzjoni tal-kannabis Mediċinali Questionnaire

Għażiż/a parteċipant/a,

Jiena studenta irreġistrata għad-Dottorat fil-Farmaċija u bħalissa qed nagħmel studju intitolat "Delivery of Medicinal Cannabis" taħt is-superviżjoni ta' Dr. Nicolette Sammut Bartolo.

Parti mill-istudju tiegħi jinvolvi t-tqassim ta' kwestjonarju lil persuni li jużaw l-kannabis mediċinali, biex nevalwa l-metodi t' amministrazzjoni ppreferuti għal-kannabis.

Nixtieq nistiednek sabiex tipparteċipa f'dan l-istidju billi timla dan il-kwestjonarju. Il-parteċipazzjoni tiegħek tikkontribwixxi għall-istudju tiegħi u għall-għarfien dwar il-kannabis mediċinali.

Dan il-kwestjonarju huwa kompletament anonimu. Ma tintalab l-ebda informazzjoni personali li tista tikxef l-identità tiegħek. Il-parteċipazzjoni tiegħek hija fuq bażi volontarja u wieħed jista' jagħżel li jħalli l-istudju fi kwalunkwe punt. Billi twieġeb il-kwestjonarju qed taqbel li tieħu sehem f'dan l-istudju.

Jekk teħtieġ aktar informazzjoni jekk jogħġbok ikkuntattjani fuq:

Posta elettronika: ceren.bereketoglu.17@um.edu.mt

Mowbajl: +356 993 10911

Tislijiet,

Ceren Bereketoglu

Studenta tad-Dottorat fil-Farmaċija

Metodi t'amministrazzjoni tal-kannabis Mediċinali

Età:	
Sess:	☐Mara ☐Raġel ☐Oħrajn
Livel ta' Edukazzjoni:	☐Primarja ☐Sekondarja ☐Post-sekondarja ☐Terzjarja ☐Post-terzjarja
Nazzjonalita:	☐Maltija ☐Oħrajn (Jekk jogħġbok speċifika' : .....)
Lokalità:	

1. **Ghal liema kundizzjoni tista tuza il kannabis mediċinali?**

   ☐ Uġigħ
   ☐ Dardir u tirremeti
   ☐ Kanċer
   ☐ Skleroži multipla
   ☐ Fibromialġia
   ☐ Artrite
   ☐ Epilessija
   ☐ Oħrajn (Jekk jogħġbok speċifika':.....)

2. **Qed tiehu xi tip ta mediċina għall-uġigħ?**

   ☐ Iva *(mur għall mistoqsija 3 u 4)*
   ☐ Le *(mur għall mistoqsija 5)*

3. **Kemm-il tip ta' mediċina qed tiehu biex tikkontrolla l-ugieh?**

   ☐ 1
   ☐ 2
   ☐ 3
   ☐ Aktar minn 3

4. **Il-mediċini li qed tieħu bħalissa għall-uġigħ qeghdin jikkontrolawlek l-uġigħ?**

   ☐ Iva
   ☐ Le
   ☐ Mhux ċert/a

5. **Ġieli ppruvajt tieħu kannabis?**

   ☐ Iva *(mur għall mistoqsija 6 & 7)*
   ☐ Le *(mur għall mistoqsija 8)*

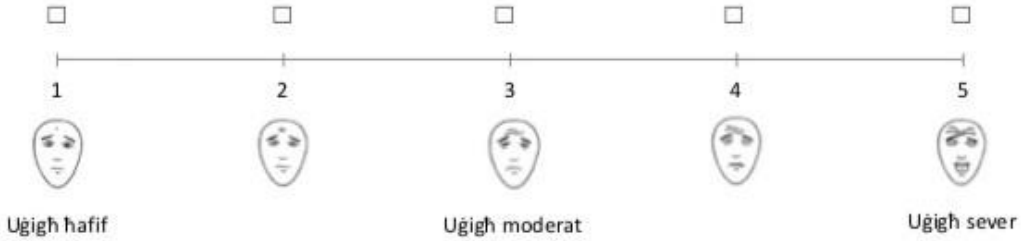
6. **Ħassejtek mort tajjeb bil-kannabis?**

   ☐ Iva
   ☐ Le

7. **F'liema forma kienet il-kannabis li ġieli ħadt?**

☐ Sigarett tal-kannabis
☐ Sigarett elettroniku jew vape
☐ Inalatur jew nebuliser
☐ Pillola jew kapsula
☐ Cannabis cookie
☐ Tixrob iz-zejt
☐ Taqtir
☐ Te'
☐ Injezzjoni
☐ Krema
☐ "Patch"
☐ Qtar għall-għajnejn
☐ Suppożitorju

8. **Jekk jogħġbok ikklassifika l-intensita' ta' uġigħ li taħseb li jista' jwassal għall-bżonn li jinbeda l-kannabis mediċinali *(Fejn 1 huwa uġigħ ħafif u 5 huwa uġigħ sever).*[1]**



9. **Kieku kellek l-opportunità li tibda tuża l-kannabis mediċinali, tagħmel hekk?**

☐ Iva *(mur għall mistoqsija 10)*
☐ Le *(mur għall mistoqsija 11)*
☐ Ma nafx *(mur għall mistoqsija 11)*

10. **Għaliex? *(Tista' tagħżel iktar minn għażla waħda).***

☐ Qrajt ħafna fuq is-suġġett
☐ Smajt b-oħrajn l-ibenefikaw
☐ It-tabib ġa tani parir biex nuża
☐ Mediċina tas-soltu mhix biżżejjed
☐ Nixtieq nippruvha
☐ Oħrajn (Jekk jogħġbok speċifika' : .....)

11. **Għaliex le? *(Tista' tagħżel iktar minn għażla waħda).***

☐ Ma nemminx li għandha effett terapewtiku
☐ Ma nemminx li tista tgħajni mma tista tgħajn lil ħadtieħor
☐ Ma nkunx naf minn fejn se nibda
☐ Nibża minn xi effetti ħżiena
☐ Nibża minn konsegwenzi fuq saħti fit-tul
☐ Diffiċli biex issib tabib jagħmillek riċetta
☐ Il-proċess kumplikat wisq
☐ Nibża li niġi ġġudikat
☐ Oħrajn (Jekk jogħġbok speċifika' : .....)

[1] L-istampi ġew meħuda minn Hicks CL, von Baeyer CL, Spafford PA, van Korlaar I, Goodenough, B. The Faces Pain Scale – Revised: Toward a common metric in paediatric pain measurement. Pain. 2001;93(2):173-183.

12. **Jekk ikollok tuża kannabis mediċinali, kif tippreferi toħodha? Jekk jogħġbok immarka l-forma preferuta tiegħek mil-lista li ġejja ta' prodotti li jiġu amministrati b'mod orali, rettali jew sistemiku skond il-preferenza tiegħek min 1 sa 5** ***(fejn 1 huwa l-inqas preferut, 3 huwa newtrali u 5 huwa l-aktar preferut).***

Forma tad-doża	**Stampa**	**Preferenza**				
		1 l-inqas preferut	**2**	**3 newtrali**	**4**	**5 l-aktar preferut**
Pillola tonda						
Kaplet (pillola tawwalija)						
Kapsula						
Kapsula vegetarjana						
Pillola li titqiegħed bejn il-wardiet ta' wiċċek u l-ħanek						
Pillola ta' taħt l-ilsien						
Gallettina jew ikel ieħor						
Te'						
Żejt li jinxtorob						
Suppożitorju						
Injezzjoni						
Ilma						

13. **Jekk ikollok tuża kannabis mediċinali, kif tippreferi tieħdu? Jekk jogħġbok immarka l-forma preferuta tiegħek mil-lista li ġejja ta' prodotti li jiġu amministrati b'mod topiku jew b'inalazzjoni skond il-preferenza tiegħek min 1 sa 5 *(fejn 1 huwa l-inqas preferut, 3 huwa newtrali u 5 huwa l-aktar preferut).***

Forma tad-doża	Stampa	Preferenza				
		1 l-inqas preferut	2	3 newtrali	4	5 l-aktar preferut
Sigarett tal-kannabis						
Sigarett elettroniku						
Inalatur						
"Nebuliser" (jintuża mal-maskla tal-ossiġnu)						
Sprej						
Taqtir (qtar taħt l-ilsien)						
Krema						
Balzmu/ingwent (krema densa)						
Xhampoo, "Conditioner", Sapun likwidu						
Żejt li tapplikah fuq il-ġilda						
Taqtir tal-għajnejn						
"Patch"						

Appendix 5 – Approval from the Pain Clinic

the painclinic
21, Triq Tal-Borg, Paola
21666903 | painclinic.com.mt

To whom it may concern:

I, the undersigned, hereby confirm that I am providing consent to Ceren Bereketoglu to carry out a study on the use of medical cannabis at my clinic located at 21, Triq Tal-Borg, Paola.

A questionnaire will be distributed to patients and they will be asked to fill it in at the clinic.

The questionnaires will be kept at the clinic until the researcher collects them.

Dr Andrew Agius
MD MSc PGC Reg. no. 2724
the painclinic
21 Triq Tal-Borg Paola PLA1250
7985 4595 | painclinic.com.mt

21/5/19

Appendix 6 – Approval from the Primary Health Care

Vella Mario A at Health-... 20.05.2019

To: Ceren Cc: West Details

VH

Dear Ceren Bereketoglu,

I am pleased to inform you that permission to conduct the study **has been granted** on the grounds that the survey/questionnaire would remain completely anonymous throughout and the participants' consent is sought beforehand. Participation should be voluntary and one should be left free to leave the study at any point if so desired.

This e-mail may be used as a formal permission for your survey from Primary HealthCare.

GDPR Motto - Collect personal data only if strictly necessary and what you cannot adequately protect, DO NOT COLLECT !

Sincerely,

Dr Mario Vella
DPO
Primary HealthCare, 7, Harper Lane Floriana FRN 1940

t +356 21239993 e mario.a.vella@gov.mt
https://health.gov.mt | www.publicservice.gov.mt
Valletta 2018 - European Capital of Culture www.valletta2018.org

MINISTRY FOR HEALTH

Appendix 7 – Ethics Approval

L-Università ta' Malta

Faculty of
Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: **FRECMDS_1819_91**

Thursday 29th August 2019

Ms Ceren Bereketoglu
29, Kanun Area,
Triq il-Fidiel,
Hamrun. HMR1352.

Dear Ms Ceren Bereketoglu,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Delivery of Medicinal Cannabis

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

L-Università ta' Malta

Faculty of
Medicine & Surgery
University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

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Ref No: **FRECMDS_1819_091**

Monday 25th November 2019

Ms Ceren Bereketoglu
29, Kanun Area,
Triq il-Fidiel,
Hamrun. HMR 1352.

Dear Ms Ceren Bereketoglu,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Delivery of Medicinal Cannabis

The Faculty Research Ethics Committee granted ethical approval for the above mentioned protocol after providing amendments done on 16.10.2019 and 23.11.2019 and which study was already ethically approved on 29.08.2019.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

Appendix 8 – Publications and Abstracts

SIG on Drug Delivery and Manufacturing
FIPSUB-1763 /

Perception of delivery systems used for Medicinal Cannabis

Ceren Bereketoglu[1], Nicolette Sammut Bartolo[1], Anthony Serracino-Inglott*[1]
[1]Department of Pharmacy, University of Malta, Msida, Malta

My preferred method of presentation is: Poster Presentation
Please fill in the presenting author's organization: University of Malta

Background: Cannabis for medicinal use is available in various dosage forms. The opinion of patients about medicinal cannabis dosage forms has not been evaluated.
Purpose: To evaluate the preferred delivery methods for medicinal cannabis through a patient-focused analysis.
Methods: Two self-administered questionnaires were developed to evaluate opinions of users and potential users of medicinal cannabis with regards cannabis dosage forms. The questionnaires were validated using the Delphi method and disseminated at two clinics in Malta following ethics approval. Participants were asked to rate methods of administration using a 5-point Likert scale (where 1 is least preferred and 5 is most preferred).
Results: The 87 (61 male) users and 101 (55 male) non-users of medicinal cannabis completed the questionnaires. Medicinal cannabis users rated edibles (n=66), tea (n=65), drinking oil (n=72) dosage forms and non-users rated liquid (n=79), vegetarian capsule (n=79) and capsule (n=79) as the most preferred methods of cannabis administration orally. Users prefer cannabis in the form of: cigarettes (n=71) and tincture (n=67) while non-users prefer spray (n=80), patch (n=78), and nebuliser (n=76).
Conclusion: Both users and non-users of cannabis for medicinal purposes, indicated different preferences for medicinal cannabis dosage forms. Availability of patient-preferred dosage forms is desirable to meets patients' needs. The great variety of dosage forms requested by potential patients is a challenge to the evolving manufacturing industry for medicinal cannabis.

Pharmaceutical practice:
Health and medicines information
FIPSUB-1765 /

Systematic Reviews about Medicinal Cannabis dosage forms

Ceren Bereketoglu[1], Nicolette Sammut Bartolo[1], Anthony Serracino-Inglott*[1]
[1]Department of Pharmacy, University of Malta, Msida, Malta

My preferred method of presentation is: Poster Presentation
Please fill in the presenting author's organization: University of Malta

Background: Studies about cannabis dosage forms, with the inclusion of perspectives of users, lead to understanding of medicinal cannabis better.
Purpose: To review studies focusing on medicinal cannabis dosage forms.
Methods: A comprehensive systematic review was conducted between February and March 2020, to identify studies published in the last 10 years about medicinal cannabis dosage forms and opinions of medicinal cannabis users about cannabis dosage forms. HyDi, a tool offered by the University of Malta with access to different databases, was used for the search.
Results: Eighty-nine articles were related to medicinal cannabis dosage forms and 10 articles were based on opinions. Majority of the studies (n=97) were performed in a single country, more than half (n=61) in the US. Participants were cannabis recretational users (n=66), healthy volunteers (n=20) or medicinal cannabis users (n=13). Studies included one administration form (n=62) of cannabis mainly the smoked form (n=31), followed by the oral form (n=12). Some studies compared two forms (n=23) such as smoked versus vaped or oral, edible, oral versus oro-mucosal. Studies with multiple dosage forms (n=14) involved variety of forms including smoked, vaped, inhaled, oral, sublingual, edible, rectal and systemic forms. Scope in the studies were pharmacodynamics (n=41), pharmacokinetics (n=32), use patterns and opinions on medicinal cannabis dosage forms (n=26).
Conclusion: Various studies were conducted about medicinal cannabis dosage forms. There is still need for more studies related to patient perception.

Appendix 9 – Validation Results for the MDMCU Questionnaire

Table 3. 35 Suggested changes in the validation process for MDMCU English questionnaire

Question Number	Question Before Validation	Suggested Change
Demographics		Locality……..
1	☐ Pain ☐ Nausea and vomiting ☐ Cancer ☐ Arthritis	☐ Cancer ☐ Nausea and vomiting ☐ Pain ☐ Other (Please Specify:…..) ☐ Arthritis ☐ Pain ☐ Other (Please Specify:….)
2	medicinal cannabis ☐ More than 2 weeks ☐ Less than 6 months ☐ More than 6 months ☐ A year	prescribed medicinal cannabis ☐ 1 to 4 weeks ☐ 1 to 6 months ☐ 6 to 12 months ☐ More than 12 months ☐ Other (Please specify: ……..)
4	Did you try other types of cannabis?	Did you try other types of cannabis other than that specified in question 3?
5	☐ 15 minutes ☐ 30 to 60 minutes ☐ 90 minutes ☐ 2 to 3 hours ☐ 4 to 5 hours	☐ From 1 up to 15 minutes ☐ From 15 up to 60 minutes ☐ From 60 up to 90 minutes ☐ From 1.5 up to 3 hours ☐ From 3 up to 5 hours
6	☐ 1 hour ☐ 6 hours ☐ Up to 12 hours ☐ 72 hours	☐ 1 to 2 hours ☐ 4 to 6 hours ☐ 6 to 12 hours ☐ 12 to 72 hours
7	☐ Vomiting	☐ Nauseated or Nausea and vomiting
11	Why not?	What keeps you from doing so?
12	Please rank your preferred dosage form from the following list *(where 1 is the most preferred and 12 is the least preferred).*	Please rate your preferred dosage form which are administered orally, rectally or systemically from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).*
13	Please rank your preferred dosage form from the following list *(where 1 is the most preferred and 12 is the least preferred).*	Please rate your preferred dosage form which are administered topically or via inhalation from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).*

Appendix 10 – Validation Results for the MDNMCU Questionnaire

Table 3. 36 Suggested changes in the validation process for MDNMCU English questionnaire

Question Number	Question Before Validation	Suggested Change
Demographics		Locality……..
4	☐ Yes ☐ No	☐ Yes ☐ No ☐ Not sure
7	☐ Electronic cigarette	☐ Electronic cigarette or vape
9	☐ Yes *(go to question 10)* ☐ No *(go to question 11)*	☐ Yes *(go to question 10)* ☐ No *(go to question 11)* ☐ I don't know *(go to question 11)*
10	Why? ……	Why? *(You may choose more than 1 option).* ☐ I have been reading a lot about it ☐ I have heard of others who benefitted ☐ My doctor has already suggested it ☐ Mainstream medication is not enough ☐ I would simply like to try ☐ Other (Please Specify: ……)
11	Why not? ……	Why not? *(You may choose more than 1 option).* ☐ I do not believe it has any therapeutic value ☐ I do not believe it will help me but it might help others ☐ I would not know from where to start ☐ I am afraid of side-effects ☐ I am afraid of long-term health consequences ☐ It is difficult to get a doctor to prescribe it ☐ The whole process is too complicated ☐ I am afraid of the social implications ☐ Other (Please Specify: ……)

Table 3.36 *(cont.)* Suggested changes in the validation process for MDNMCU English questionnaire

Question Number	Question Before Validation	Suggested Change
12	Please rank your preferred dosage form from the following list *(where 1 is the most preferred and 12 is the least preferred).*	Please rate the following dosage forms which are administered orally, rectally or systemically from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).*
13	Please rank your preferred dosage form from the following list *(where 1 is the most preferred and 12 is the least preferred).*	Please rate the following dosage forms which are administered topically or via inhalation from 1 to 5 according to your preference *(where 1 is the least preferred, 3 is neutral and 5 is the most preferred).*

Appendix 11 – Topical and inhalation dosage form preferences of medicinal cannabis

Table 3. 37 Topical and inhalation dosage form preferences according to locality

		Medicinal Cannabis Users (N=58)			Potential Medicinal Cannabis Users (N=80)		
Form	**Locality**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cannabis cigarette	Southern Harbour	15	3.87	0.103	28	2.50	0.255
	Northern Harbour	16	4.44		11	3.91	
	South Eastern	6	2.83		22	2.23	
	Western	4	3.50		11	3.00	
	Northern	16	4.31		6	2.67	
	Gozo	1	3.00		2	3.00	
Electronic cigarette	Southern Harbour	14	3.07	0.104	25	2.00	0.271
	Northern Harbour	15	3.53		9	2.89	
	South Eastern	6	3.50		22	2.45	
	Western	3	3.33		10	2.60	
	Northern	14	4.43		5	3.40	
	Gozo	1	1.00		1	5.00	
Inhaler	Southern Harbour	14	3.21	0.227	26	2.62	0.211
	Northern Harbour	16	3.19		11	2.55	
	South Eastern	6	2.83		21	3.57	
	Western	4	4.50		8	3.00	
	Northern	13	3.08		4	3.50	
	Gozo	1	1.00		1	5.00	
Nebuliser	Southern Harbour	13	2.15	0.406	25	2.12	0.333
	Northern Harbour	16	2.31		8	1.75	
	South Eastern	6	2.50		21	2.57	
	Western	4	3.75		8	2.50	
	Northern	11	2.27		5	3.00	
	Gozo	1	1.00		1	1.00	
Spray	Southern Harbour	13	2.46	0.321	26	2.54	0.088
	Northern Harbour	14	3.07		9	2.22	
	South Eastern	6	3.50		22	3.55	
	Western	2	2.50		8	3.38	
	Northern	12	2.83		5	3.40	
	Gozo	1	1.00		1	1.00	
Tincture	Southern Harbour	17	3.65	0.709	27	2.81	0.803
	Northern Harbour	14	3.21		11	3.18	
	South Eastern	5	3.40		22	3.18	
	Western	3	3.00		7	3.00	
	Northern	15	3.53		5	3.20	
	Gozo	1	5.00		1	5.00	

Table 3.37 *(cont.)* Topical and inhalation dosage form preferences according to locality

		Medicinal Cannabis Users (N=58)			Potential Medicinal Cannabis Users (N=80)		
Form	**Locality**	**Sample**	**Mean**	**p-value**	**Sample**	**Mean**	**p-value**
Cream	Southern Harbour	15	3.00	0.538	26	2.92	0.808
	Northern Harbour	14	3.00		8	3.00	
	South Eastern	6	2.83		21	3.14	
	Western	3	2.33		7	2.71	
	Northern	12	3.17		5	2.60	
	Gozo	1	1.00		1	1.00	
Balm or Ointment	Southern Harbour	15	2.87	0.442	24	3.17	0.749
	Northern Harbour	14	3.21		8	2.88	
	South Eastern	6	2.83		21	3.05	
	Western	3	2.33		7	2.57	
	Northern	12	3.08		5	3.00	
	Gozo	1	1.00		1	1.00	
Shampoo, Conditioner, Body wash	Southern Harbour	13	2.69	0.773	26	2.65	0.689
	Northern Harbour	14	2.57		8	2.50	
	South Eastern	6	3.00		21	3.00	
	Western	3	3.00		6	2.33	
	Northern	13	2.92		5	3.00	
	Gozo	1	1.00		1	1.00	
Apply oil on skin	Southern Harbour	15	3.07	0.629	25	2.96	0.722
	Northern Harbour	14	2.79		8	2.75	
	South Eastern	5	3.20		21	3.19	
	Western	3	3.67		9	2.56	
	Northern	13	3.23		5	3.00	
	Gozo	1	1.00		1	1.00	
Eye drop	Southern Harbour	13	1.62	0.415	25	2.28	0.082
	Northern Harbour	14	2.14		8	1.13	
	South Eastern	6	2.67		21	2.14	
	Western	3	2.33		7	1.43	
	Northern	12	2.42		5	3.00	
	Gozo	1	1.00		1	1.00	
Patch	Southern Harbour	13	2.54	0.612	26	3.54	0.069
	Northern Harbour	14	2.43		10	1.90	
	South Eastern	6	3.17		20	3.45	
	Western	3	2.33		8	2.63	
	Northern	12	2.83		5	3.60	
	Gozo	1	1.00		1	1.00	

Appendix 12 – Results of the General Systematic Review

Table 3. 38 General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Australia	33 drivers	N/A	Smoked marijuana, alcohol	The effect of three doses of cannabis and alcohol alone and co-administered, on driving performance	High levels of cannabis induced greater impairment, while alcohol had few effects and no synergistic effects were observed.	Lenné et al, 2010
UK	15 men with cannabis exposure	Healthy	Oral D-9-THC, CBD and intravascular D-9-THC, CBD	Neurophysiological effects on brain when Cannabidiol (CBD) and Tetrahydrocannabinol (THC) are co-administered	CBD pre-treatment precluded the acute psychotic symptoms caused by D-9-THC. CBD and D-9-THC can have opposing effects on regional brain, explaining variances in symptomatic and behavioural effects.	Bhattacharyya et al, 2010
Switzerland	12 male volunteers	Healthy	Smoked THC cigarette	Profile of Δ^9-THC and its metabolites (THC-OH, THC-COOH) in plasma and urine after cannabis smoking	In addition to THC-COOH, THC and THC-OH should be utilised for the urine analysis.	Brenneisen et al, 2010

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	86 pregnant women (38 cannabis users and 48 non-users)	Pregnant cannabis consumers	Smoked cannabis cigarette and tobacco	Prenatal exposure of cannabis and tobacco smoking, oral fluid (OF) sample collection	Prenatal exposure to cannabis was linked with reduction in foetal growth. Meconium testing can detect prenatal cannabis exposure which occurs in the third trimester of gestation.	Gray et al, 2010
USA	10 subjects with cannabis smoking history	N/A	Oral THC and oro-mucosal Sativex spray	Quantification in concentrations of CBD, Δ9-THC and its metabolites in plasma by two-dimensional gas chromatography mass spectrometry (2D-GCMS)	This 2D-GCMS assay presents a new way of quantifying CBD, THC and the metabolites.	Karschner et al, 2010
USA	28 male chronic, daily cannabis smokers	N/A	Smoked cannabis	Quantification of cannabinoid concentrations for chronic, daily cannabis smokers	THC, THCCOOH, CBD and CBN (Cannabinol) concentration quantification in oral fluid is suggested.	Lee et al, 2011

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	10 male daily cannabis smokers	N/A	Oral THC, oral CB_1 (cannabinoid-1) receptor antagonist	Assessing cannabis withdrawal effects in relation to antagonist administration	Pre-determined criteria for antagonist-triggered cannabis withdrawal were not observed at doses of 20 or 40 mg of rimonabant.	Gorelick et al, 2011
USA	6 cannabis users	Free from psychiatric disorders	Oral THC, Nabilone and D9-THC	Cannabis users survey to differentiate between oral THC versus placebo (Nabilone and D9-THC administered alone and in combination)	Cannabis combined Nabilone may be safe and well tolerated.	Lile et al, 2011
Canada	23 recreational cannabis users	Healthy	Spray vs. capsule	To evaluate the abuse potential of nabiximols at three doses, with placebo and dronabinol at two doses	Both dronabinol and nabiximols had meaningful abuse potential at high doses. Nabiximols showed slightly less abuse potential than dronabinol.	Schoedel et al, 2011

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	10 participants	Healthy	Smoked cannabis	Pharmacokinetics of whole-blood and plasma cannabinoid following controlled smoked cannabis administration	Human whole-blood cannabinoid profile after smoking cannabis can help in whole blood and plasma cannabinoid evaluation by identifying recent cannabis ingestion.	Schwope et al, 2011
USA	10 cannabis smokers	Healthy	Oral THC	Cannabinoids and cannabinoid metabolites detection in oral fluid	Quantification of THCCOOH may advance the detection and elucidation for OF tests	Milman et al, 2011
USA	9 cannabis smokers	N/A	Oral and oro-mucosal cannabis	Pharmacokinetics of controlled orally D-9-THC and oro-mucosally administered cannabis extract	CBD modulation of THC's effects is not due to a pharmacokinetic interaction.	Karschner et al, 2011
USA	24 vaporized cannabis exposed subjects	Chronic non-cancer pain	Vaporized cannabis	Further research on vaporized cannabis effect on opioid plasma levels in chronic non-cancer pain	*"Vaporized cannabis does not meaningfully affect opioid plasma levels and may augment the efficacy in patients with chronic noncancer pain."* This comment is hard to fault.	Abrams et al, 2011; Ware, 2011

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
The Netherlands	12 occasional, 12 heavy cannabis users	Healthy	Oral cannabis (Dronabinol)	Effects on driving performance	Dose-dependent Dronabinol impairs driving performance but to a smaller degree in heavy users may be due to tolerance.	Bosker et al, 2012
Germany	12 occasional and 12 heavy cannabis users	Healthy	Smoked cannabis in combination with tobacco	Tolerance evaluation of occasional and heavy users of cannabis following acute administration of Δ9-THC	Heavy users of cannabis develop tolerance to several behavioural effects of cannabis.	Theunissen et al, 2012
UK	15 occasional cannabis users (men)	Healthy	Gelatine capsules	The acute effects of A9-THC and CBD on brain function	Δ9-THC and CBD modulate striatal differentially, and hippocampal and prefrontal function during attentional salience processing.	Bhattacharyya et al, 2012
Australia	A chronic cannabis smoker	Healthy	Smoked cannabis	Development of a method for detecting delta-9-THC in oral fluid which is applicable to small volumes and low concentrations	A sensitive and rapid method for detecting THC was developed and validated. The method is applicable for forensic purposes.	Molnar et al, 2012

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	10 adult cannabis users	Healthy	Smoked cannabis	Cannabinoids in OF after controlled smoked cannabis	THCCOOH in OF indicates no passive contamination, CBD and CBN indicate recently smoked cannabis.	Milman et al, 2012
USA	136 adult regular marijuana users	Free from psychotic disorders	Smoked marijuana	Pharmacological effects and expecting to receive cannabis	Effects of cannabis on impulsive disinhibition express direct pharmacologic effects for participants which did not compensate.	Metrik et al, 2012
USA	10 cannabis smokers	Free from clinically significant illness	Smoked cannabis	Variance of cannabinoid oral fluid stability following controlled cannabis smoking.	Using devices with an elution or stabilization buffer, storing the sample at 4 °C and analysing within 4 weeks may greatly contribute the result accuracy in OF collection.	Lee et al, 2012
Germany	227 samples with synthetic cannabinoids in serum	N/A	Spice products and herbal mixtures	Analysing synthetic cannabinoids in serum using liquid-liquid extraction and mass spectrometer	The method involves 24 synthetic cannabinoids, which were previously identified in herbal mixtures.	Kneisel & Auwärter, 2012

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	50 volunteers	Healthy	Capsules	Dextroamphetamine (AMP) and Δ9-THC effects on false memory using the Deese/Roediger-McDermott illusion	AMP increased memory of studied words while THC reduced. False memory was not influenced significantly by neither drug compared to placebo.	Ballard et al, 2012
USA	10 participants	N/A	Smoked cannabis	Stability of cannabinoids in blood and plasma	For accurate quantitative results, blood and plasma cannabinoid samples could be stored at -20 °C and for no more than 3 and 6 months.	Scheidweiler et al, 2013
USA	11 cannabis smokers	N/A	Smoked vs. oral cannabis	OF cannabinoid testing	Oral dosing of THC considerably influenced THCCOOH in OF, but minimally affected THC OF concentrations.	Lee et al, 2013a

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	30 participants	Healthy	Capsule vs. smoked cannabis	Comparing the magnitude and duration of effects of smoked cannabis and dronabinol	Cannabis and dronabinol reduced pain. Dronabinol produced longer-lasting effects in pain sensitivity and lower ratings for abuse-related effects.	Cooper et al, 2013
USA	13 male chronic daily cannabis smokers	Free from clinically significant medical disease	Oral THC	Variations in sleep characteristics over time and associations with plasma cannabinoid concentrations	Somnolence from oral THC may dissipate when used chronically at a high-dose.	Gorelick et al, 2013
USA	14 regular marijuana smokers	Healthy	Two formulations of oral cannabis	Cognitive and cardiovascular dose-effect profile of oral forms of cannabis in smokers of marijuana.	Nabilone improves the mood with lawful cardiovascular alterations than dronabinol. Nabilone was well tolerated and had better bioavailability.	Bedi et al, 2013

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	44 subjects	Free from psychiatric disorders	Injected THC (intravascular)	Effects of frequently consumed cannabis on time perception	Chronic cannabis use and dose had no influence on time perception. Infrequent users observed to show temporal overestimation.	Sewell et al, 2013
USA	11 cannabis smokers	Healthy	Smoked cannabis and capsule	Nabilone administration on cannabis withdrawal symptoms and marijuana relapse relative to placebo.	Nabilone decreased cannabis relapse and reversed withdrawal-related irritability, sleep disturbance and food consumption.	Haney et al, 2013
USA	11 chronic cannabis smokers	Free from medical conditions	Oral vs. smoked cannabis	Assessing OF and plasma cannabinoid ratios	The association between OF and plasma concentrations is important for making conclusions about clinical outcomes.	Lee et al, 2013b
USA	24 cannabis smokers	Free from clinically significant illness	Smoked cannabis	Differences in OF cannabinoid concentrations before and after smoking THC	Detection of THCCOOH varied for chronic regular cannabis smokers (more than 30 hours) and for occasional smokers (0–24 hours).	Anizan et al, 2013

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Switzerland	22 occasional, 14 heavy cannabis smokers	Healthy	Smoked cannabis	Sociodemographic comparison of occasional and heavy cannabis smokers	Confusion was sensed by the regular smokers was much lower compared with the occasional smokers and the feeling of intoxication remained unchanged.	Fabritius et al, 2013
USA	7 cannabis users	Free from psychiatric conditions	Oral cannabis	Pharmacokinetic and pharmacodynamic findings of oral Δ9 – THC at supratherapeutic doses	Large doses of oral D9-THC can be administered to people with cannabis use history, the pharmacokinetic variability of oral D9-THC dose adjustment based on individual is necessary for avoiding side effects, maximizing therapeutic effect.	Lile et al, 2013
The Netherlands	12 older subjects	Healthy	Oral tablet	The safety and pharmacokinetics of Namisol® (THC)	THC was observed to be safe and well tolerated by healthy and older individuals.	Ahmed et al, 2014

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	11 occasional and 14 regular smokers	Healthy	Smoked cannabis	Quantification of blood and plasma cannabinoids in regular and occasional cannabis smokers	Smoking history of cannabis plays an important role in detection. The existence of CBD, CBN or THC-glucuronide indicates recent use.	Desrosiers et al, 2014
Switzerland	25 occasional and 23 heavy smokers	N/A	Smoked cannabis	Differences between the occasional and regular smokers	A free THCCOOH concentration less than 3 μg/L suggests an occasional use (≤ 1 joint/week) which no medical assessment would be required.	Fabritius et al, 2014
USA	10 occasional and 14 frequent smokers	Free from clinically significant illness	Smoked cannabis	Cannabinoid disposition in oral fluid after controlled cannabis smoking	The Oral-Eze® collection device was effective for monitoring the oral fluid cannabinoids in occasional and frequent smokers.	Newmeyer et al, 2014
Germany	15 subjects	Healthy	Oral THC	Oral Δ9-THC (20 mg) impact on the olfactory function	THC-based medicines may be linked to noticeable decline in olfactory acuity.	Walter et al, 2014

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Canada	16 patients	Chemotherapy-induced neuropathic pain (CINV)	Oro-mucosal spray	Pain intensity and outcome measure	Five respondents stated a two-point or more decrease in their pain. Nabiximols can be useful as an adjunctive for treating CINV.	Lynch et al, 2014
USA	11 daily cannabis smokers	Healthy	Oral vs. smoked cannabis	Pharmacokinetics profile in chronically smoked cannabis and oral THC	Oral THC dosing aid in suppression in withdrawal symptoms, after smoking THC concentrations were noticeable for short period to identify cannabis relapse.	Milman et al, 2014
Switzerland	1763 cannabis users	Non-medical conditions	Joint with or without tobacco, water pipe, mixed with food	Method of administration, problematic cannabis and illicit drug use	Diversity in administration routes can be linked to heavy use of drugs (water pipe). Users of cannabis without tobacco were the exception.	Baggio et al, 2014
Australia	10 users with withdrawal symptoms	Stable medical or psychiatric conditions	Oro-mucosal spray	The roadside screening tests for patients taking Sativex®	Sativex® users may have positive results for THC drug testing within 2-3h of use.	Molnar et al, 2014

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
France	88 patients	Patients with lung cancer undergoing surgical operation	Smoked marijuana	Natural and synthetic cannabinoids impact on cholinergic bronchial contraction	Prejunctional CB_1 receptors activation mediates decrease the electrical field stimulation-evoked cholinergic contraction in human bronchus, this could explain the acute bronchodilation caused by cannabis smoking.	Grassin-Delyle et al, 2014
USA	29 male cannabis smokers	Healthy	Smoked cannabis	Withdrawal effects of cannabis in chronic frequent smokers	More intense abstinence symptoms were observed in the initial phase. Sleep disturbance persisted for a long period; therefore, hypnotics may be helpful for the treatment of cannabis dependence.	Lee et al, 2014
USA	32 adult cannabis smokers	Healthy	Vaporizer	Blood and plasma concentrations before and after ingestion	Higher blood THC values were observed when co-administered with alcohol, possibly there is a greater impairment in performance as a result of combination.	Hartman et al, 2015

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	3847 high school students	N/A	Electronic cigarette (e-cigarette), electronic vaporizer (e-vaporizer)	Survey evaluating e-cigarette and e-vaporizer use	Vaporizing cannabis with e-cigarettes was the common method. Students were utilising e-cigarettes to vaporize THC infused products such as hash oil and wax. Portable e-vaporizers were utilised to vape dried leaves of cannabis.	Morean et al, 2015
Israel	19 years old male patient	Cancer	Smoked and vaporized cannabis	Identifying the safest method for immunocompromised patients to consume medicinal cannabis	Systematic sterilization of medicinal cannabis can be essential in eliminating the risk of cannabis induced fatal opportunistic infections among immunosuppressed patient population.	Ruchlemer et al, 2015
USA	16 cannabis smokers	Healthy	Smoked cannabis	Cannabis stability in oral fluid	For oral fluid concentration accuracy, analysis within 4 weeks at 4 °C storage or within 24 weeks at -20 °C depending on the device used for collection.	Anizan et al, 2015

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	11 chronic cannabis smokers	Free from psychiatric disease	Smoked cannabis	Oral fluid cannabinoid pharmacokinetics	Oral fluid was greatly affected by the time of last smoke and composition of cannabis, frequency and increased administration, possibly showing occurrence of cannabis tolerance.	Lee et al, 2015
New Zealand	One recreational synthetic cannabis user	No previous seizure history	Smoked cannabis	Symptoms of smoking synthetic cannabinoids	This was a case about a patient treated twice in 12 hours for seizures caused by synthetic cannabis intoxication.	Schep et al, 2015
Switzerland	61 cannabis smokers and vapers	N/A	E-cigarette, e-vaporizer, vaporizer, smoked cannabis	Evaluating benefits and drawbacks of vaping cannabis compared to smoking	Vaping helped half of the participants to reduce total cannabis consumption, had no impact for 37% and increased the consumption for 6%. Vaping was perceived as healthier and less odorous. Disadvantages were dry mouth and fewer positive cannabis effects.	Etter, 2015

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	39 high school teens	N/A	Edibles	Assessing cannabis edibles use, reasons to use and awareness of consequences by teens	Both users and non-users were aware of the consequences of using edibles. Female non-users were more worried than other groups.	Friese et al, 2016
USA	31 participants	Healthy	Oral CBD, smoked cannabis	Effect of oral cannabidiol on smoked cannabis	Orally administered CBD does not decrease the physiological or positive subjective effects of smoked marijuana.	Haney et al, 2016
Italy	322 patients	Spasticity in multiple sclerosis (MS)	Oro-mucosal spray	Outcomes associated with cannabis-based oro-mucosal spray	During 3 months' observation, treatment discontinuations were limited and patients had significant improvements and less adverse events at mean daily doses that were 30% lower than what is utilised in the randomized controlled trial in Germany.	Trojano, 2016

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Italy	19 patients	Treatment-resistant spasticity in MS	Oro-mucosal spray	Assessing the effect of Sativex® before and 4 weeks after the treatment	Sativex® showed clinical benefit on spastic hypertonia and by modulating both cortical and spinal circuits, it may influence the spinal excitability.	Squintani et al, 2016
USA	54 occasional, 72 frequent cann abis smokers	Healthy	Smoked, vaporized, oral cannabis	Pharmacokinetics of different dosage forms of cannabis	Vaporization and smoking provide similar cannabinoid delivery. Presence of CBG (Cannabigerol) and CBN indicate recent use via inhalation and absence does not exclude it.	Newmeyer et al, 2016
USA	32 young adults	N/A	Smoked cannabis, e-cigarette, cigars, water pipe, vaporizer, edible	Beliefs and practices about tobacco, marijuana and vaporiser use	Smoking marijuana was common. Marijuana vaporisers were used at work or when driving. Young adults considered second-hand cannabis smoke as benign and second-hand tobacco smoke as dangerous.	McDonald et al, 2016

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	54,309 participants	N/A	Smoked cannabis as blunt, non-blunt, cigar, dual cigar-blunt	Assessing prevalence and correlations of substance use	Blunt-only and cigar-blunt users appeared as the most severe risk groups.	Cohn et al, 2016
Germany	15 volunteers	Healthy	Capsule	Assessment of the central processing of THC on olfactory function	Cannabinoids causing negative effects on the human sense of smell contributed in the literature that THC-based medicines can be among drugs impairing olfactory function.	Walter et al, 2017
USA	40 cigar or cigarillo users	N/A	Smoked cannabis	Marijuana use and perceptions about marijuana products	Cigarillo use is popular among young adults, mainly as blunts. Product features like brand, flavour, packaging and price effect the cigarillo choices.	Giovenco et al, 2017
USA	9 frequent and 7 occasional cannabis smokers	Free from medical conditions	Edible cannabis (cookie, brownie)	Oral fluid and pharmacokinetics of cannabinoids	THC concentrations in blood were higher in frequent than occasional smokers, concentrations in OF were similar.	Newmeyer et al, 2017

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Canada	3 patients	Pyoderma gangrenosum	Topical cannabis oil	Pyoderma gangrenosum cases treated with topical medical cannabis in organic sunflower oil	Topical medical cannabis improved pain with reduced opioid utilization in all three patients suffering from wounds of overall classes.	Maida & Corban, 2017
USA	11 regular and 9 occasional smokers	Healthy	Oral, smoked and vaped cannabis	Evaluation of subjective and physiological effects in regular and occasional cannabis consumer following placebo, smoked, vaped and orally taken cannabis	All users had increase subjective effects with smoked and vaped cannabis, only occasional smokers showed tolerance for oral cannabis when used frequently. Vaped cannabis is more attractive than smoked or oral forms, effects appear quicker and doses can be titrated.	Newmeyer et al, 2017a
USA	12,320 students	N/A	E-vaporizer, smoked cannabis	Evaluating electronic vaporizer and cannabis joint use prevalence	Electronic vaporizers may provide a new route of cannabis administration that appeals to groups more than using cannabis joints.	Eggers et al, 2017

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	522 cannabis vapers	N/A	E-cigarette, vape-pen, cannabis joint	Preferences on types of vapes and motivations for vaping cannabis versus smoking	Reasons to vape cannabis included: better taste, healthier, easier to hide, not strong smell, more convenient and produces better high than smoking cannabis.	Morean et al, 2017
USA	5390 marijuana users	Healthy	Edibles, smoked cannabis	How edible cannabis users vary in cannabis use and perceived risks from non-edible cannabis consumers	Edible users reported using cannabis more frequently compare to other marijuana users. Edible users were less likely to believe for edible use to be very risky.	Friese et al, 2017
USA	20 participants	N/A	Edible cannabis (lollipops)	Edible cannabis intoxication placebo effect	Study demonstrates that placebo effect can be induced with edibles when consumers are told that they are receiving cannabis.	Loflin et al, 2017

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	11 regular, 9 occasional cannabis smokers	Healthy	Smoked, vaped and edible cannabis	Psychophysical evaluations (balance, walk and turn, one leg stand and turn tasks) eye exam (pupil size effects)	Meaningful impairment was seen following oral administration. Pupil sizes were larger than the placebo at 3.5 hours for all participants. Oral administration worsened the performance on the psychophysical tasks.	Newmeyer et al, 2017c
USA	7 frequent and 8 occasional cannabis smokers	Healthy	Smoked cannabis	Long-term stability of cannabis in OF	Oral fluid specimens should be kept at 4 °C and not more than 2 months for accurate quantitative results.	Scheidweiler et al, 2017
USA	31 frequent marijuana smokers	Healthy	Oral cannabis alone and co-administered with smoked cannabis	Abuse potential of oral CBD versus oral placebo and smoked cannabis	CBD did not show any signals of abuse at doses 200, 400 and 800 mg. These results may aid in informing U.S. regulatory decisions concerning schedule of CBD on the Controlled Substances Act.	Babalonis et al, 2017

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	30 cannabis users	Healthy	Oral cannabis	Gender variances in endocannabinoid function and response to cannabis	Females had greater subjective responses to 5mg oral Δ^9-THC than males. Males were more perceptive to the subjective effects at 15mg dose of Δ^9-THC.	Fogel et al, 2017
USA	18 participants	Healthy	Oral cannabis	Pharmacokinetics of oral cannabinoids in humans	Cognitive effects were found to be dose dependent. Method used for cannabis administration is important regarding the toxicology.	Vandrey et al, 2017
UK	24 non-dependent cannabis and tobacco smokers	Free from respiratory, psychiatric or physical disorders	Smoked cannabis	The effect of smoked cannabis alone and combined with tobacco on cannabis smokers	Cannabis decreased like of cannabis-linked stimuli and cannabis demand, tobacco did not alter the beneficial effects of cannabis.	Hindocha et al, 2017
USA	11 regular and 9 occasional cannabis smokers	Healthy	Oral, smoked, vaporized cannabis	Evaluating oral fluid of cannabis at three different administration routes	Similar maximum time between routes were observed. More THC metabolites were seen with oral route relative to inhaled routes in occasional cannabis smokers.	Swortwood et al, 2017

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	17 cigar and cigarillo users	N/A	Smoked cannabis	Survey about co-administered cannabis and tobacco use, opinions about marijuana and its risks, and reasons for smoking	Some participants were aware about the health consequences of cigarillo blunt use and had reasons for continuation in use. The reason for modifying non tipped cigarillos was the thinking that tobacco has low quality.	Koopman Gonzalez et al, 2017
China	1 man	Healthy	E-cigarette	Case report about the toxicity of accidently ingested synthetic cannabinoids contained in e-cigarette liquid	AB-FUBINACA and ADB-FUBINACA are the two synthetic orally bioavailable cannabinoids with rapid onset of toxicity after ingestion. This case resulted supraventricular tachycardia post-exposure.	Lam et al, 2017
USA	13 daily cannabis users	Free from psychiatric and cardiac disorders	Smoked and oral cannabis	Influence of high-dose dronabinol on self-administration of cannabis among daily consumers	Chronic dronabinol dosing may decrease self-administration of cannabis in daily consumers and abate withdrawal effects.	Schlienz et al, 2018b

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Germany	6 participants	N/A	Smoked cannabis	Pharmacokinetics of synthetic inhaled cannabinoid JWH-018 in urine	Hydroxy metabolites of cannabis were found in concentrations less than 1ng/ml and 10 hours later following inhalation, this may aid in evaluating time of use.	Toennes et al, 2018a
USA	30 cigarillo smokers	N/A	Smoked cannabis	Interview about preferences, beliefs and experiences with smoked products	All participants smoke cigarillos. As preferences, cigarillos perceived to prolong the high of marijuana which promotes the co-use and considered substitute for unavailable marijuana.	Antognoli et al, 2018
Poland	50 consumers	N/A	Edible (as added in food)	Three meat products were produced: one with hemp seed, one with hemp seed and linseed and one control. The products were tested by consumers on the fatty acid profile, texture and colour	The hardness, chewiness and adhesiveness increased with oil seeds. The quality of added oil seed was comparable to the traditional ones. The products with hemp and linseed can be considered as a good source of fatty acids.	Zając & Świątek, 2018

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Canada	265 patients prescribed with oral cannabinoids	Pain, sleep disturbances, spasticity, anxiety and nausea	Oro-mucosal spray, capsule	The occurrence of problematic use of prescribed cannabis (PPCBU) and factors associated, in patients with cannabinoid therapy	The PPCBU should be routinely evaluated and monitored during the therapy, especially for patients having psychiatric or substance use history.	Ware et al, 2018
Australia	80 patients	Chemotherapy-induced nausea and vomiting (CINV) despite traditional antiemetics	Capsule	Evaluating complete response to CINV and influence on quality of life and health system	This will be randomised cross-over, placebo-controlled pilot study and a subsequent phase III trial will include more patients.	Mersiades et al, 2018
USA	62 edible marijuana consumers	N/A	Edibles vs. smoked cannabis	Preferences of edibles over smoking marijuana, likes and dislikes about edible products	Majority preferred edibles. Reasons for likes include convenience, discreetness, longer-lasting and less intense euphoria, relaxation more than smoking. Dislikes included late effects and variable high and inconsistent marijuana dispersion.	Giombi et al, 2018

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	18 adults	Healthy	Edible (cannabis brownie)	Pharmacokinetics of 11-nor-9-carboxy-Δ^9-THC in urine	Consuming cannabis brownies (10 and 25 mg) provided THCCOOH concentrations different in magnitude and time course compared to previous reports on smoking route at similar doses.	Schlienz et al, 2018a
UK	2501 participants	N/A	Cannabis joint, vaporizer, e-cigarette, oral, electronic nicotine devices	The commonness of electronic vaping devices use for recreational purposes	The majority of respondents consume cannabis via smoking route. The most common lifetime recreational drug was cannabis vaped with e-cigarettes.	Blundell et al, 2018
USA	1313 college students	N/A	Vaporized cannabis	Prevalence of vaping cannabis	Students with the highest risk of initiating vaped cannabis were those with other cannabis and ENDS use history.	Cassidy et al, 2018

Table 3. 38 *(cont.)* General Systematic Review about Medicinal Cannabis Dosage Forms (N=89)

Country	Number of Participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Germany	6 regular cannabis users	Healthy	Smoked cannabis	Pharmacokinetic profile of JWH-018 in oral fluid	Maximum concentration of synthetic cannabinoid JWH-018 in oral fluid was appeared within minutes following inhalation, metabolites were not detected. A considerable amount was eliminated in the following hour.	Toennes et al, 2018b
Australia	35 adults	Free from medical and psychiatric conditions	THC oil	Evaluation of delta-9-THC in blood, oral fluid and urine after oral administration	THC was not detected in blood, oral fluid or urine at any time-point after ingestion regardless of the dose.	Hayley et al, 2018
Italy	15 patients	MS with moderate to severe spasticity	Oro-mucosal spray	Assessment of complete neurological evaluation, including spasticity	Oro-mucosal formulation of cannabis was more effective in easing the overactive bladder in MS patients indicating influence on over activity.	Maniscalco et al, 2018

Appendix 13 – Results of the Systematic Review about Preferences on Cannabinoid Dosage forms

Table 3. 39 Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA, UK, Canada, Australia, New Zealand, Finland, Hungary, Japan, Ireland, Mexico, Poland, South Africa	975 medicinal cannabis users	Loss of appetite, sedation and other conditions	Smoked cannabinoids	Preferences of medicinal cannabis users about synthetic cannabinoids (SC) versus natural cannabinoids (NC)	Natural cannabinoids are favoured over synthetic ones by 93% of consumers. The latter has fewer desirable effects.	Winstock & Barrattc, 2013
31 countries including USA (40 states), Germany, France, Canada, The Netherlands, Spain	953 medicinal cannabis users	Back pain, depression, injury or accident-induced pain, sleeping problems, multiple sclerosis, other	Smoking vs. vaping vs. tea vs. food/tincture vs. oral vs. THC vaporizer vs. oro-mucosal	Preferences of medicinal cannabis users about administration methods	Most preferred method of administering medicinal cannabis was smoking, followed by oro-mucosal, vaporizing, oral as Dronabinol, food/tincture, tea, oral as Nabilone and THC vaporizer (Dronabinol)	Hazekamp et al, 2013

Table 3. 39 *(cont.)* Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	2910 patients	N/A	Smoking vs. vaping	Cannabis use characteristics according to method of administration, types of vaporizer devices used and preferences on smoking vs. vaping	The most popular method was the vaping pen, followed by tabletop, portable device and e-cigarette. Cannabis consumers who prefer vaping rated it as more positive experience relative to smoking.	Lee et al, 2016
USA	15 patients	Head and neck cancer	Smoking vs. eating vs. vaporizing vs. other	Preferred methods of administering marijuana products	Patients noted preferred methods of use as smoking followed by eating, vaporizing and other (making own concentrated oil)	Elliott et al, 2016

Table 3. 39 *(cont.)* Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	1082 patients	Aid in sleeping problems, pain, appetite, control of nausea, quit using other substances, problems, get experiment	Dabs/oil rig (special type of water pipe) vs. vape pen vs. pipe vs. marijuana joint vs. marijuana blunt vs. gravity bong vs. nectar collector vs. hookah	Preferred methods of consuming marijuana concentrates	Dabs rig was the most common method of consuming concentrates, followed by vape pens, pipe, marijuana joint, marijuana blunt, gravity bong, hookah, nectar and collector.	Daniulaityte et al, 2017
Western Australia	33 medicinal cannabis users and 38 health professionals	Epilepsy	Oral tablets vs. capsules vs. sublingual drop or spray vs. oral liquid vs. inhaler vs. enteral feeding liquid vs. suppository	Preferred cannabinoid delivery methods	Cannabis tablets or capsules were the most preferred method followed by sublingual drop or spray or oral liquid these were more popular among epilepsy, suppository was the least preferred dosage form.	Kerai et al, 2018

Table 3. 39 *(cont.)* Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA (43 states)	234 recreational and medicinal cannabis users	Pain/inflammation, anxiety and insomnia	Buds or flower vs. joints or blunts vs. edibles vs. other drugs and alcohol	Dislikes about marijuana concentrates	Dislikes about concentrates are: Expensive, potency, flavour, increasing tolerance, difficulty in accessing and side effects (cough, headache, nausea), not as natural compared to other forms, chemical, could create negative consequences or long-term effects on health, stronger high feeling, not much known, illegal.	Cavazos-Rehg et al, 2018

Table 3. 39 *(cont.)* Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
USA	33 medicinal cannabis users	Rheumatoid arthritis, spinal cord injury, Crohn's disease, hepatitis C, cancer, stress disorder, fibromyalgia, chronic regional pain syndrome, epilepsy, HIV, multiple sclerosis, Parkinson's disease	Smoking vs. vaporization vs. edibles vs. topical oil	Preferred methods of cannabis ingestion	Preferred medicinal cannabis ingestion method is smoking cannabis flower (60%) followed by vaporization (20%), edibles (16.7%) and topical oil (3%)	Bruce et al, 2018
USA	3744 flower users, 869 dab users	Sleeping problems, social anxiety	Concentrates use as joint/blunt/spliff, bowl/pipe/one-hitter, bong/water pipe/bubbler, dabbing, vaporizer/vape, edibles	Preferences of dab users versus conventional flower users	Dab users do not choose dabs over flower products regarding beneficial effects such as relief of symptoms, but choose dabs for experimentation and curiosity.	Sagar et al, 2018

Table 3. 39 *(cont.)* Systematic Review about Preferences on Cannabinoid Dosage Forms (N=10)

Country	Number of participants	Health conditions	Dosage form(s)	Scope of the study	Main outcome	Reference
Germany	32 medicinal cannabis users	Amyotrophic lateral sclerosis or related spasticity	THC:CBD oro-mucosal spray	Treatment satisfaction questionnaire for medication use	The 38% of the participants were extremely satisfied with their oro-mucosal spray, one third were very satisfied, 18% were satisfied, 6% were somewhat satisfied and the 9% were unsatisfied.	Meyer et al, 2019