CANNABIS FOR MEDICINAL USE IN RARE DISEASES

A thesis submitted
in partial fulfilment of the requirements
of the Degree of Doctorate in Pharmacy

JEKATERINA PAROVINCAKA

Department of Pharmacy
University of Malta
2022

Acknowledgments

I would like to express my sincere gratitude to my supervisor Dr Janis Vella-Szijj and co-supervisor Prof. Anthony Serracino- Inglott. I would like to thank Prof. Lilian Azzopardi, the head of the Department of Pharmacy and all the staff at the Department of Pharmacy. I express my gratitude to my family and friends for their continuous support.

Abstract

Rare diseases (RDs) are severe and usually chronically debilitating and RD patients often lack effective and accessible treatment options. Medicinal Cannabis (MC) is used for symptoms such as pain, spasticity, nausea and vomiting, seizures and anxiety which may be experienced by RD patients. The aim of the study was to identify RDs for which MC can be used and issues related to its use in patients with RDs. The methodology was in two parts: (1) systematic literature review using search engines: PubMed and MEDLINE. Open access peer review journal articles, published between January 2010 – October 2021 were included; (2) development, validation and dissemination of two questionnaires: for RD patients and for healthcare professionals (HCPs) in Malta.

The literature revealed 36 papers that described the use of MC as a possible therapeutic option in 22 different RDs, mainly epileptic conditions (n=7) and neurodegenerative diseases (n=6). Respondents of the questionnaire for HCPs (n=101) were pharmacists (n=40), general practitioners (n=17) and occupational therapists (n=13), with more than 11 years of practice (n=46). HCPs encountered two to four RD patients a year on average. Symptoms experienced by RD patients were pain (n=51), mainly chronic neuropathic pain (n=31), anxiety (n=34) and muscle spasticity (n=33). Fifty-nine HCPs agreed to reply to MC related questions. Twenty-six of 59 HCPs have used MC in their practice. Fifty two out of 59 HCPs consider it to be effective for pain relief, 38 for anxiety and 38 for muscle spasticity. Thirty six out of 59 HCPs agreed on the use of MC in their practice. Regarding the side-effects of MC, confusion (n=30) and addiction (n=29) were reported to be of the most concern.

Study included thirty-eight patients with RDs, mostly 41-50 years old (n=11) and reported pain (n=24), anxiety (n=22) and muscle spasticity (n=10) as commonly experienced symptoms associated with RD. Seven reported experiencing side-effects associated with

the currently used medications. Two respondents had been prescribed MC by a HCP, though 20 would consider MC use to relieve symptoms of their disease. Confusion, possibly associated with MC usage, was reported as the side-effect causing most concern (n=8). Eighteen patients were not concerned with MC side-effects.

Literature supports the use of MC for management of RDs. MC can be effective to relief pain, anxiety and muscle spasticity possibly experienced by RD patients. HCPs and RD patients consider that MC can be used in management of RD symptoms. In lack of efficacious treatment options for RD patients, MC can be an alternative therapy for symptom relief.

Key words: medicinal cannabis, rare diseases, CBD, THC, orphan diseases

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

Δ(8)-THC	Δ^8-Transtetrahydrocannabinol
Δ(9)-THC	Δ^9-Tetrahydrocannabinol, THC
2-AG	2-Arachidonoyl Glycerol
5-HT	Serotonin
5-HT1A	Serotonin 1A Receptor
AAN	American Academy Of Neurology
AEA	Arachidonoylethanolamine (Anandamide)
AEs	Adverse Events
ASMs	Antiseizure Medications
CIPO	Chronic Intestinal Pseudo-Obstruction
CBC	Cannabichromene
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBE	Cannabielsoin
CBG	Cannabigerol
CBL	Cannabicyclol
CBMs	Cannabinoid-Based Medicines
CBN	Cannabinol
CBND	Cannabinodiol
CBT	Cannabitriol
CECD	Clinical Endocannabinoid Deficiency
CNS	Central Nervous System
CRPS	Complex Regional Pain Syndrome
DRG	Dorsal Root Ganglia
DS	Dravet Syndrome
EB	Epidermolysis Bullosa
EBR	Evidence Based Research
ECS	Endogenous Cannabinoid System
EDS	Ehlers-Danlos Syndrome

EMA	European Medicines Agency
EU	European Union
EURORDIS	European Organisation For Rare Diseases
FDA	Food And Drug Administration
FIRES	Febrile Infection-Related Epilepsy Syndrome
GABA	γ-aminobutyric acid
GI	Gastrointestinal
GPCR	G-Protein Coupled Receptors
HD	Huntington's Disease
HIV	Human Immunodeficiency Virus
HRQoL	Health-Related Quality Of Life
LD	Lafora disease
LGS	Lennox-Gastaut Syndrome
LR	Literature Review
MS	Multiple Sclerosis
NF1	Neurofibromatosis Type 1
NMDA	N-methyl-D-aspartate
NP	Neuropathic Pain
NRS	Numerical Rating Scale
OD	Orphan Drug
ODD	Orphan Drug Designation
OOPD	Office of Orphan Products Development
PN	Parenteral Nutrition
PNS	Peripheral Nervous System
PTSD	Post-Traumatic Stress Disorder
PWS	Prader-Willi Syndrome
QOL	Quality Of Life
RD	Rare Disease
RTT	Rett Syndrome
SAD	Social Anxiety Disorder

SCA-3	Spinocerebellar ataxia type-3
SSc	Systemic Sclerosis
TOC	Thoracic Outlet Syndromes
TRPV1	Transient Receptor Potential Vanilloid Type 1
TSC	Tuberous Sclerosis Complex
USA	The United States of America
USP	United States Pharmacopoeia
WBS	Williams–Beuren syndrome
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 Rare diseases

Around 263–446 million patients, or 3.5–5.9% of the worldwide population, are affected by a rare disease (RD) (Shourick et al, 2021). In Malta, 25 - 30,000 persons live with a rare disease[1]. Diagnosis of rare diseases varies between countries. A disease is classified as "rare" under the European Union Regulation if it affected fewer than one person in 2000 patients[2]. Food and Drug Administration (FDA) defines it as a disease encountered in less than 200,000 patients. However, there is no available data on the true prevalence of RDs globally, defined as "the number of persons affected by a condition at a specified instant in time in a given population" (Field and Boat, 2010). According to the literature review study initiated by The European Organisation for Rare Diseases (EURORDIS), the most common RDs with an estimated prevalence of 50 in 100 000 are Brugada syndrome, erythropoietic protoporphyria, Guillain-Barre syndrome, and familial melanoma. Forty in 100 000 individuals are affected by some autism spectrum disorder (e.g., Timothy syndrome, Rett syndrome, Tuberous sclerosis complex), Tetralogy of Fallot or scleroderma. Thirty in 100 000 individuals are diagnosed with focal dystonia, Marfan syndrome, non-Hodgkin, or malignant lymphoma. Rare cancers represent 7.2% of overall cancers[3]. In addition, there are patients with undiagnosed RDs – conditions that cannot be diagnosed because the cause is not identified, no diagnostic test is available, or the disease has not been yet characterized[4].

---

[1] EURORDIS. About Rare Diseases. [Cited 2022 Jan 22]. Can be accessed from URL: https://www.eurordis.org/about-rare-diseases

[2] Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Official Journal L 018, 22/01/2000 P. 0001 – 0005. [Cited 2022 Jan 29]. Can be accessed from URL: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32000R0141

[3] EURORDIS, Orphanet, European Commission (2004117). RARE DISEASES IN NUMBERS. Preliminary report 2005. [Cited 2022 Jan 15]. Can be accessed from URL: https://ec.europa.eu/health/archive/ph_threats/non_com/docs/rdnumbers.pdf

[4] The National Organization for Rare Disorders (NORD). Undiagnosed rare disease patients. [Cited 2022 Apr 22]. Can be accessed from URL: https://rarediseases.org/for-patients-and-families/information-resources/patient-and-caregiver-resource-center/undiagnosed-rare-disease-patients/

1.1.1 Presentation of rare diseases

Most RDs (70 % of the cases) are genetic in origin, and the symptoms may be observed at birth or childhood, leading to neurodevelopmental delays such as osteogenesis imperfecta, Neurofibromatosis, and Rett syndrome (Wakap et al, 2020). Other RDs, such as Amyotrophic Lateral Sclerosis (ALS), Charcot-Marie-Tooth disease, Kaposi's sarcoma, or Crohn's disease, develop during adulthood. Most patients with RDs, including neurological conditions, rare cancers, and autoimmune diseases, present chronic and debilitating symptoms that persist during their lifetime[5].

Many RDs are associated with pain. Conditions such as adult-onset palindromic rheumatism, Complex regional pain syndrome (CRPS), Still's a disease (systemic-onset juvenile idiopathic arthritis), Thoracic outlet syndromes (TOC), neurofibromatosis type 1, Ehlers-Danlos syndrome (EDS), primary biliary cholangitis and sickle cell anaemia are associated with chronic pain[6]. Patients may experience pain of different aetiology, localization, and intensity. Pain restricts patients' physical activity, daily functioning abilities, routine tasks, and sleep. Consequently, patients can experience anger, frustration, and depression, which can provoke an enhanced sensation of pain and poorer therapeutic outcomes (Katz, 2002). Chronic pain's adverse impact is multidimensional on patients' health-related quality of life (HRQoL) (Hadi et al, 2019).

RDs such as complex regional pain syndrome, Multiple sclerosis (MS), Gaucher disease, trigeminal neuralgia, or central pain syndrome are associated with chronic neuropathic

[5] Orphanet. About rare disease. [Cited 2022 Jan 30]. Can be accessed from URL: https://www.orpha.net/consor/cgi-bin/Education_AboutRareDiseases.php?lng=EN

[6] U.S. Department of Health & Human Services. Orphan drug designation database [Cited 2022 Jan 30]. Can be accessed from URL: https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases

pain (NP), which highly impact 'patients' daily functioning (Rahn and Hohmann, 2009). Patients with NP are experiencing constant burning or itching sensation, shooting lancinating sensations, a restrictive feeling of pain, paraesthesia, or irritation, even from a light touch or no contact. Neuropathic pain is often unmanageable with the use of conventional pharmacological treatment, which has a significant benefit for only a few patients and often has negative side effects that often outweigh the positive health outcomes. Opioids can be the second option of therapy for neuropathic pain but have multiple complications, including low tolerance and addiction. Considering the opioid crisis, there is a requirement for alternative treatment for chronic neuropathic pain (Mücke et al, 2018). Patients with poorly managed neuropathic pain have significantly poorer health status and elevated anxiety and depression (Rahn and Hohmann, 2009; Hossain, et al, 2012).

Many RDs are associated with epileptic seizures, such as CDKL5 Deficiency, Dravet Syndrome, Lennox-Gastaut Syndrome, Lafora Disease, and Doose syndrome (Myoclonic-astatic epilepsy). Frequent and severe childhood epilepsies are linked to neurodevelopmental delays, mental health issues, and impaired quality of life (QoL). In a report by the Centers for Disease Control and Prevention, 90% of adults with active epilepsy were taking medication, yet 56% reported uncontrolled seizures in the past year (Tian et al, 2018). Despite a significant number of antiseizure medications (ASMs) available, at least 30% of patients with epilepsy are unresponsive to treatment remaining refractory to common pharmacological treatments (Fattorusso et al, 2021). In addition, the number of seizure-free days significantly impacts the QoL of patients (Auvin et al, 2021). People with epilepsy may consequently develop physical health problems due to seizures, such as fractures from injuries. Seizures are also linked to higher rates of

psychological complications, such as anxiety and depression[7]. In treatment-resistant epilepsies, caregivers frequently seek alternative remedies (Porter and Jacobson, 2013). Patients affected by RDs are also more socially, psychologically, and economically vulnerable (Heuyer, 2017). Patients with chronic conditions are more likely to advance a mental health disorder, due to a disease or diseases, hormonal changes, increased hospitalization, or excessive worry. Patients with chronic symptoms such as pain may experience symptoms of depression - feeling sad, anxious, loss of interest, and sleep disturbances[8] (Ma et al, 2021).

1.1.2 Issues related to treatment for rare disease patients

As reported by European Commission, an estimated 95% of RD patients do not have an approved therapy available for their disease[9]. Treatment of patients with RDs presents additional challenges comparing to the ones presenting more common diseases. Lack of knowledge about the RD and medical expertise leads to patients being undiagnosed or misdiagnosed. Rarity of disease significantly complicates specific medicines' clinical development – a small group of patients in the study recruitment stage, stringent ethical considerations for inclusion of vulnerable patients, and lack of pre-existing knowledge on the rare condition. The development of orphan medications is not always viable for the pharmaceutical industry because of the limited number of patients, which means a small market, lack of funding, and higher production costs (Field, 2010; Stoller, 2018). To improve the treatment outcomes of RD patients, initiatives have been created to

[7] WHO. Epilepsy. Key facts 2019. Last updated 9 February 2022. [Cited 2022 Jan 29]. Can be accessed from URL: https://www.who.int/news-room/fact-sheets/detail/epilepsy

[8] U.S Department of Health and Human Services. National Institutes of Health. Chronic Illness and Mental Health Recognizing and Treating Depression. (Publication No. 21 MH 8015). Last revised 2021. [Cited 2022 Feb 12]. Can be accessed from URL: https://www.nimh.nih.gov/health/publications/chronic-illness-mental-health/21-mh-8015-chronicillness-mentalhealth_151898.pdf

[9] European Commission. Expanding research into rare diseases. [Cited 2022 Jan 22]. Can be accessed from URL: https://ec.europa.eu/research-and-innovation/en/horizon-magazine/expanding-research-rare-diseases

support orphan medicines research and help bring treatments for RD patients to the market. In the USA, since 1983, the Office of Orphan Products Development (OOPD) program has provided incentives for drug companies, aiding them in bringing more than four hundred drugs and biological products to the market (Tiwari, 2015). In Europe, an Orphan Drug designation was developed to increase accessibility and availability of orphan drugs on the market and to help increase profitability[10]. Despite these initiatives, the burden of RDs continues to rise together with associated economic burden. $997 billion was overall economic burden caused by RDs in the USA in 2019, comprising $449 billion in direct medical expenditures, $437 billion in indirect medical costs, $73 billion in non-medical costs, and $38 billion in uninsured healthcare costs. Hospital inpatient treatment and prescription medicine are the leading drivers of extra medical expenditures related with RD, while labour market productivity losses due to absenteeism and early retirement are the leading indirect costs (Yang et al, 2022).

As discussed above, patients affected by RDs are often experiencing pain. Pain management often presents a challenge, as pain sensation varies in type and intensity in different patients. Chronic pain is one of the most common types of chronic disease with incurring costs projected at around €200 billion in Europe, whereas in the USA it is around $560 and $635 billion (Hadi et al, 2019).

RD patients face multiple issues in receiving the required support. Nevertheless, by improving access to proper treatment and medical care can improve patients' quality of life and extend their life expectancy.

[10] European Medicine Agency (EMA). Orphan designation: Overview. [Cited 2022 Jan 31]. Can be accessed from URL: https://www.ema.europa.eu/en/human-regulatory/overview/orphan-designation-overview#rare-diseases-at-a-glance-section

1.1.3 Rare disease patients in Malta

The National Alliance for Rare Diseases in Malta supports the RD patients and their caregivers, unites researchers, medical professionals, and other organizations, and constantly raises awareness on RDs. Data on certain RDs is collected in The National Register through different sources (e.g., Congenital Anomalies Register, the Cancer Registry) and is coded using the Orphanet Classification of Rare Diseases. The National Register allows tracing rare conditions and diseases in Malta, aiming to ensure earlier diagnosis and enhance the patient's QoL by improving access to care[11].

1.2 Cannabis plant

Cannabis belongs to the family Cannabaceae, which consists of three species - *Cannabissativa, Cannabis ruderalis,* and *Cannabis indica*. Cannabis plant carries a versatile amount of compounds – more than 500 compounds, among which are around 120 different phytocannabinoids, classified into 11 types: (–)-delta-9-trans-tetrahydrocannabinol (Δ(9)-THC, with its precursor Δ(9)-THCA), cannabichromene (CBC), cannabinol (CBN), cannabigerol (CBG), cannabicyclol (CBL); cannabidiol (CBD), with its precursor CBDA), cannabidiol (CBND), (–)-delta-8-trans tetrahydrocannabinol (Δ8-THC), cannabielsoin (CBE), cannabitriol (CBT), and miscellaneous-type cannabinoids (listed by a number of compounds in each chemical class) (Pertwee, 2014). Δ(9)-THC, as the principal component in Cannabis, is primarily responsible for most of the psychotropic and physiological effects. Other cannabinoids, including CBD, CBG, and CBN, have negligible to zero psychotropic properties (Koturbash and MacKay, 2020). CBD shows evidence of neuroprotective effects in

[11] Government of Malta. Rare Diseases. 2021. [Cited 2022 Feb 12]. Can be accessed from URL: http://www.orpha.net/consor/cgibin/Education_AboutRareDiseases.php?lng=EN

preclinical studies has been proven to counteract some of the negative anxiogenic effects of Δ(9)-THC, as well as its psychotomimetic effects (Santiago et al, 2019).

CBD was first isolated in 1963, and then Δ(9)-THC isolated in 1964. The percentage of compounds in the cannabis plant varies depending on the strain, soil, climate, and cultivation process, which accounts for medicinal benefits and side effects variability of MC. The cannabis plant also contains many terpenoids, which have potential physiological effects and give its specific aroma and flavour (Atakan, 2012; Baron, 2015). The pharmacological effect of the cannabis plant used as a whole may have greater effects than individual parts used – the so called "entourage concept". This effect is described based on the potential synergy of different plant constituents, including terpenoids. Terpenoids also exert pharmacological effects, such as anxiolytic effects of limonene, induction of gastrointestinal motility by pinene, anticonvulsant, sedative, and anxiolytic effects of linalool sedation, analgesia, and muscle relaxant effects produced by myrcene (Santiago et al, 2019; Ferber et al, 2020).

1.3 The endocannabinoid system

The endogenous cannabinoid system (ECS) consists of the endocannabinoid signalling molecules: anandamide (AEA) or arachidonoylethanolamine and 2-arachidonoyl glycerol (2-AG) - lipid molecules that are produced from the metabolism of fatty acids; G-protein coupled receptors (GPCR) - CB1 and CB2, and the metabolic enzymes that control the endocannabinoid synthesis and degradation (Haugh et al, 2016; Mastinu et al, 2018).

CB1 and CB2 are presynaptic receptors that indicates the distinctive distribution in the body. CB1 receptors are found in the Central Nervous System (CNS), whereas CB2 receptors are found in the Peripheral Nervous System (PNS). The CB1 receptors are

substantially distributed in brain areas with mostly dense expression in the cerebral cortex, caudate, cerebral cortex, putamen, thalamus, globus pallidus, amygdala, substantia nigra, hippocampus, basal ganglia, and cerebellum. Also non-neuronal cells, such as hepatocytes, musculoskeletal and connective tissues, adipocytes and the gonads, express CB1 (Atakan, 2012; Bridgeman and Abazia, 2017). CB1 effect on gamma-aminobutyric acid (GABA), glutamatergic, noradrenalin, dopaminergic, acetylcholine and serotoninergic neurotransmitter systems, explains its effects related to pain perception, motor movements, cognition and memory. CB1 receptors are relatively low in brainstem sites, which are critical for regulating respiration and heart rate, which elucidates the low lethality after marijuana intoxication[12].

The CB2 receptors are primarily expressed by immune cells, explaining cannabinoid effects on reducing inflammation (Atakan, 2012; Turcotte et al. 2016). During inflammation process or after nerve injury, microglial cell activation stimulates CB2 receptor up-regulation escalating CB2 mRNA levels about 100-fold, suggesting that it plays an important role in immune system function (Maresz et al, 2005). CB2 receptors are also found in the spleen, tonsils, and thymus gland and are recently discovered in neuronal tissue - the brainstem, hippocampus, and cerebellum. The CB2 receptor is a more promising therapeutic target in the drug development in particular for the treatment of inflammatory conditions (Atakan, 2012; Turcotte et al, 2016; An et al, 2020).

[12] World Health Organization (WHO). Critical Review of Delta-9-tetrahydrocannabinol. 2018. [Cited 2022 Feb 15]. Can be accessed from URL: https://www.who.int/medicines/access/controlled-substances/THCv1.pdf

Cannabinoids in the cannabis plant activate the human endocannabinoid system by binding to the CB1 and CB2 receptors with variable affinities. Δ(9)-THC is the partial agonist of CB1 and CB2 receptors, but can also modulate other systems by indirect effects on γ-aminobutyric acid (GABA), serotonin (5HT), N-methyl-D-aspartate (NMDA), and opiate receptors. CBD interacts with various enzymes, ion channels, and receptors other than CB1 or CB2 receptors. CBD inhibits cyclooxygenase and lipoxygenase, which explains potent analgesic and anti-inflammatory effects (Baron, 2015).

Other potential cannabinoid-like receptors could explain some non-CB1R/CB2R mediated physiological effects of the cannabinoids. For example, GPR3, GPR6, GPR12, and GPR55 (orphan G protein-coupled receptors) display a very close phylogenetic link with the cannabinoid receptors (CB_1 and $CB_{2)}$ (Bura et al, 2017), are involved in the formation of synaptic contacts as well as in neuronal differentiation and growth. Orphan G protein-coupled receptors may have potential involvement in different neurological processes and be studied for conditions such as Parkinson's disease, Alzheimer's disease, or neuropathic pain (Patzke et al, 2021). Another essential cannabinoid activity site is the transient receptor potential vanilloid type 1 receptor (TRPV1) which has a vital part in the digestive, respiratory and cardiac systems' normal and pathological states. CBD was seen as a full agonist of TRPV1 affecting thermal nociception and reducing inflammatory hyperalgesia (Costa et al, 2004, Du et al, 2019).

The ECS system has a homeostatic role, providing a protective function in some medical conditions. The concept of clinical endocannabinoid deficiency (CECD) was proposed based on the relationship between endocannabinoid function and the pathophysiology of certain conditions such as fibromyalgia, migraine, and irritable bowel syndrome. The theory was first proposed in 2001 based on the genetic overlap, ECS mediated

symptomatology patterns, and exogenous cannabinoid therapy which often provides symptomatic benefit. ECS signalling deficiencies could also be considered in the pathogenesis of Parkinson's disease, chronic motion sickness, depression, schizophrenia, multiple sclerosis (MS), and Huntington's disease (Smith and Wagner, 2014; Russo, 2016).

1.4 Medicinal Cannabis

Cannabis-derived preparations have been used as traditional medicine in different cultures for centuries, and evidence suggested its usage more than five thousand years ago (Crocq, 2022). Cannabis was extensively utilized for medicinal purposes in the USA during the 19th and early 20th centuries, and it was labelled in the *United States Pharmacopoeia* (USP) in 1850 (Bridgeman and Abazia, 2017). In 1942 Cannabis was removed from the USP, prohibited under federal law with legal penalties for possessing it. The inclusion of Cannabis in the Controlled Substances Act of 1970 and its criminalization contributed to limitations on research on Cannabis.

There has been a resurgence of interest in the therapeutic properties of cannabis in the 1960s with the identification of the leading cannabis components Δ(9)-THC and CBD and the discovery of the endocannabinoid system (ECS). MC legislation was passed in the USA first in California in 1996, and patients with a variety of medical conditions could use Cannabis as a treatment. Certain states allow the use of MC in any disease state when the drug provides positive health effects for the individual. MC was used in 2016 in the states of Colorado and Oregon under the law for general health conditions such as pain, epilepsy, cancer, spasticity linked to multiple sclerosis, nausea, PSTD, cachexia, HIV/AIDS, glaucoma, or multiple other degenerative neurological problems (National

Academies of Sciences, Engineering, and Medicine, 2017; Chiu et al, 2021). The American Institute of Medicine in 1999, conducted a scientific literature analysis in consultation with scientists to examine the cannabis plant's and its constituent cannabinoids' possible risks and health benefits. The review highlighted the risks of Cannabis but, more importantly, the benefits of medical Cannabis. Research work highlighted that it helped with nausea and vomiting, seizures, glaucoma, weight loss, joint pain, movement disorders, and anxiety. It was also considered 'probably 'effective' for some symptoms of Multiple Sclerosis (MS) (spasticity, intense central pain, and urinary dysfunction) (Watson et al, 2000). Nevertheless, Cannabis use still remains illegal under federal law but may be used in territories which passed medical marijuana laws - 36 states and the District of Columbia (Donnelly et al, 2022).

1.5 Indications for Medicinal Cannabis

The effect on CB1 and CB2 receptors, both in the peripheral tissues and in the CNS, predicts the clinical effectiveness of cannabinoids in many health conditions. Pharmacological applications of MC are identified as and are not limited to: chemotherapy-induced vomiting and nausea; epileptic seizures; glaucoma; appetite alterations; inflammation associated with autoimmune diseases; spasticity in MS; tremor and dystonic movement disorders; chronic pain, including cancer-related pain and noncancer pain, rheumatoid arthritis, fibromyalgia, chronic neuropathic or phantom limb pain, chronic abdominal pain from Crohn's disease, headache and facial pain (chronic headaches, pseudotumor cerebri, cluster headache, migraine, MS-associated trigeminal neuralgia); tumours (breast, lung, colon cancer, glioma, melanoma, leukaemia); Huntington's disease; levodopa-induced dyskinesia; Tourette's syndrome; Fulminant hepatic encephalopathy; Parkinson's disease; COVID-19; as well as mental health

diseases such as depression, anxiety, autism, mood disorders (Baron, 2015; Stasiłowicz et al, 2021, Turner et al, 2021).

1.5.1 Medicinal Cannabis in pain

Oral cannabinoids, alone and in combination, have shown efficacy in central (Svendsen et al, 2004; Rog et al, 2005) and peripheral (Nurmikko et al, 2007) neuropathic pain, as well as widespread muscle and joint pain, e.g rheumatoid arthritis (Blake et al, 2006). Cannabinoids are also reported to be efficiently used in fibromyalgia management (Skrabek et al, 2008). Cannabinoid-mediated analgesic effects occur through various mechanisms involving neural pathways and neuroinflammatory signalling (Starowicz and Finn, 2017). Cannabinoid receptors are found in areas of the brain that affiliated with pain processing (transmission and pain signals modulation): rostral ventromedial medulla (an essential structure in descending pain modulation), the dorsal horn of the spinal cord, periaqueductal gray, amygdala, dorsal root ganglia (DRG), and the rostral ventromedial medulla (Manzanares et al, 2006).

One of the most accepted well-known pain relief strategies was introduced in 1986 by WHO (World Health Organization) and is a three-step anaesthetic ladder. It is presently used for managing all kinds of pain (noncancer and cancer pain, acute and chronic pain caused due to musculoskeletal diseases, neuropathic pain disorders, and degenerative disorders. The second and third steps for moderate to severe persistent pain respectively include opioids (Anekar and Cascella, 2022). Patients who do not achieve adequate pain relief and experience dose-limiting opioid side effects, require adjuvant analgesics. Cannabinoids may be part of the approach to achieving better pain control (Carlson, 2016; van den Beuken-van Everdingen et al, 2017).

Neuropathic pain

Patients with neuropathic pain often experience constant burning or itching sensation, shooting lancinating sensations, a restrictive feeling of discomfort, paraesthesia, or irritation, even from a light touch or no contact (Lynch and Watson, 2011), and these often provoke elevated anxiety, and depression. The pathology of neuropathic pain is complex, making it challenging to treat it effectively by clinicians (Hossain et al, 2020), symptoms are often refractory to conventional pharmacological treatments (Rahn & Hohmann, 2009). Current pharmacological options provide substantial benefits for only a few patients, often with adverse reactions that outweigh the beneficial health effects (Mücke et al, 2018), which consequently pose a major socioeconomic and clinical challenge (Seltzman et al, 2016). The American Academy of Neurology (AAN) has released a Summary of Systematic Reviews for Clinicians demonstrating that oral cannabis extract is beneficial in reducing patient-reported spasticity scores as well as central discomfort or painful spasms in MS patients (Bridgeman and Abazia, 2017). The analgesic efficacy of smoked cannabis for neuropathic pain was investigated in a double-blind, placebo-controlled, crossover research, where thirty-eight patients with peripheral and central chronic neuropathic pain were enrolled. For five days, patients received smoked cannabis 9.4% THC, which resulted in significant pain reduction in active drug group comparing to the 0% THC group (Wilsey et al, 2008). In another review of the scientific evidence for Nabiximols, a THC:CBD oromucosal spray for the management of chronic pain, Überall (2020) found that analgesic efficacy was apparent in placebo controlled clinical trials of chronic neuropathic pain, particularly MS-associated neuropathic pain, with some patients maintaining long-term (up to 2 years) benefit.

In placebo-controlled studies oral cannabinoids are reported to suppress hyperalgesia and allodynia in neuropathic pain states. A study of a sublingual spray containing (9)-THC alone or in combination with CBD found that the active medication reduced pain by 41% compared to 22% with placebo, additionally reducing sleep disturbances (Rog et al, 2005). A study by Rahn and Hofman in 2019 reported that CB2 agonists have therapeutic benefits in curbing neuropathic pain but will not produce tolerance or resistance when administered alone or in addition to other treatments. Specifically, the combinations of cannabinoids and opioids show promising results as adjunctive analgesics in pain management (Rahn and Hohmann, 2009).

Chronic noncancer pain

Cannabinoids have been reported to be efficacious against chronic pain refractory to conventional analgesics (Ware and Beaulieu, 2005). Cannabinoid analgesics have been studied in numerous randomized clinical trials and have usually been well tolerated with low adverse event profiles (Russo, 2008). The recent study by Johal et al. included thirty-six trials with 4006 participants, looking into four trials of smoked Cannabis, eighteen trials of oral cannabinoids, and fourteen trials of oromucosal cannabis sprays. Cannabinoids showed a considerable reduction in pain on a 0-10 pain visual analogue scale compared to placebo ($p < 0.00001$). The results were stratified by type of pain, type of cannabinoids used, and route of administration. The most pain reduction was achieved with oral cannabinoids (smoked and oromucosal formulations). The authors estimated sufficient evidence to encourage cannabinoid use in chronic, noncancer pain therapy (Johal et al. 2020). Cannabis used in chronic pain can also improve sleep quality and physical functioning of patients (Wang et al, 2021).

1.5.2 Medicinal Cannabis in oncology

Cancer causes pain in variety of pathways, including inflammation and nerve injury as a result of developing malignancies invading sensitive tissues. The pain related to cancer is typically chronic and severe, and treatment resistant (Mack, 2000). Cannabis and cannabinoid-based medicines (CBMs) are emerging as promising therapeutics in palliative oncology to relieve pain and other associated symptoms of advanced cancer, such as pain, nausea, reduced appetite, and sleep disorders, that negatively impact patients QoL (Turgeman and Bar-Sela, 2017). Johnson et al. compared the effectiveness of the Sativex (combination of Δ(9)-THC with CBD) oromucosal spray versus Δ(9)-THC or placebo in 177 patients who were suffering from cancer-related pain but were not fully responding to strong opioids. Sativex group patients had at least 30% reduction in their pain severity score compared to placebo and Δ(9)-THC groups. Δ(9)-THC alone. There was no substantial difference between the treatment and the placebo, but Δ(9)-THC/CBD combination group showed statistically significant change on pain Numerical Rating Scale (NRS) score in comparison to placebo (-1.37 vs. -0.69 respectively) (Johnson et al, 2010). In another large cohort study by Meng et al. in 2020, cancer patients who used Cannabis for more than six months reported reduced pain, improved QoL and reduced use of opioids (Meng et al, 2020).

1.5.3 Medicinal Cannabis for muscle spasticity

A suggested mechanism of cannabinoids effect on spasticity has emerged from a study in which the ECS was found to be highly activated during CNS inflammation in MS patients and to protect neurons from inflammatory damage by activating a negative feedback loop in microglial cells via CB1/2-mediated epigenetic regulation of mitogen-activated protein kinase phosphatase 1 expression (Eljaschewitsch et al., 2006).

Randomized clinical trials have shown that the combination of tetrahydrocannabinol (THC) and cannabidiol (CBD) is an effective and well-tolerated option for treating resistant MS spasticity (Wade et al., 2004; C Collin et al., 2007; Novotna et al., 2011). A 6-week, randomized, double-blind study by C. Collin et al. (2007) on 189 patients with stable MS and poor response to anti-spasticity medications estimated the change from baseline on an 11-point spasticity NRS between Sativex® and placebo groups. The difference of 0.52 points was in favour of the active treatment group ($p = 0.048$). In the active treatment group 40% of patients showed a 30% reduction in NRS spasticity as compared to 21.9% on placebo ($p = 0.014$). On a global impression of change scale, more subjects treated with Sativex® rated their condition as improved (57%) compared to placebo (48%). The mean number of sprays used was 9.4 (C. Collin et al., 2007).

In another Phase 3 study by (Zajicek et al., 2012), 279 patients with stable MS were randomized to receive cannabis extract (2.5 mg THC, 1.25 mg CBD, and < 5% other cannabinoids) or placebo. Spasticity was evaluated on an 11-point category rating scale (CRS) after 12 weeks of treatment compared with the baseline. The spasticity relief in the end of the trial was almost twice as high with cannabis extract than with placebo (29.4% vs 15.7%; $p=0.004$). Patients also reported significant relief from body pain and improvement in sleep disturbance ($p<0.0025$) compared to placebo. Effective pain relief achieved by cannabis extract, was especially significant in patients with a high baseline pain score (Zajicek et al., 2012).

A Phase 3 study by Novotna et al. (2011) confirmed THC:CBD in 1:1 ratio (Sativex®) efficacy in long-term symptomatic treatment of spasticity. Following this run-in period, 241 participants were randomized in the 12-week double-blind, placebo-controlled phase. On the primary endpoint, the treatment difference between the two groups in mean spasticity was 0.84 points ($p = 0.0002$). Secondary endpoints showed significant

superiority of Sativex® to placebo for spasm frequency (P = 0.005), sleep disruption (p < 0.0001), Barthel Activities of Daily Living (p = 0.0067), Physician Global Impression of Change (p = 0.005), Subject Global Impression of Change (p = 0.023) and Carer Global impression of Change in Function (p = 0.005) (Novotna et al., 2011).

A beneficial effect on spasticity due to MS is also reported for inhaled cannabis administration. In a randomized, crossover, placebo-controlled study by Corey-Bloom et al, where 37 participants received smoked cannabis once a day for 3 days. Treatment with smoked cannabis reduced patient scores on the modified Ashworth scale by 2.74 points, compared to placebo (p<0.0001) (Corey-Bloom et al, 2012).

Use of Cannabis based medicines showed promising effects in treatment resistant spasticity in paediatric palliative care in an open, uncontrolled, retrospective study by Kuhlen et al. Paediatric indications of MC are discussed below.

1.5.4 Medicinal Cannabis for seizures

The epileptic seizures treatment with Cannabis was recognized from ancient Greek and Arabic books. CBD and Δ(9)-THC prevented seizures in animal models (Devinsky et al, 2014). In 2013, the first Phase 1 trial with a comprehensive efficacy and tolerability program for Epidiolex (CBD) was conducted. The proved CBD efficacy for the treatment of drug-resistant epilepsy let to the first approval of cannabis-derived drug substance by FDA in 2018 and EMA in 2019. CBD is approved for the treatment of epilepsies of two rare forms: Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients two years and older. Also, purified CBD is the first medicine to be approved for seizures in patients with Dravet syndrome (Nabbout and Thiele, 2020).

1.5.5 Medicinal Cannabis for nausea and/or vomiting

Cannabis has long been recognized as efficient therapy for nausea and vomiting. Clinical trials proved that cannabinoids were an effective treatment for nausea and vomiting caused by chemotherapy (Washabau, 2012). Cannabinoids may be beneficial in treating more complicated nausea symptoms in patients receiving chemotherapy, where conventional pharmacological treatments are ineffective. In the review by Abazia et al, where 23 randomized controlled trials were included, patients who received cannabis-based treatment reported less nausea and vomiting compared to the placebo group. The efficacy results were similar to conventional antiemetics, although more patients dropped out because of cannabis-based products side effects, such as sedation, "feeling high," dizziness, and dysphoria (Bridgeman and Abazia, 2017).

1.5.6 Medicinal Cannabis in mood and anxiety disorders

Cannabis constituents, predominantly CBD have shown efficacy in treatment of neuropsychiatric disorders (Blessing et al, 2015; Newton and Newton, 2020). MC is thought to modulate neurotransmitters (GABA, acetylcholine, dopamine, opiate peptides), which play a vital role in behavioural and emotional regulation. CB1 receptors are primarily consolidated in the brain affecting an individual's mental health. CB1 receptor regulates chronic stress and prevents fear in patients. CBD is hypothesized to control fear and anxiety by interacting with the serotonin 1A receptor (5-HT1A). The TRPV-1 receptor and the CB1 receptor are vital in managing the respective emotions (Lowe et al, 2021). There is evidence for CBD in reducing anxiety and anxiety relates symptoms: post-traumatic stress disorder, generalized anxiety disorder, social anxiety disorder, obsessive-compulsive disorder, panic disorder (Blessing et al, 2015). In the study by Sarris et al, a single 600 mg dose of CBD reduced anxiety, improved speech

performance, and cognitive impairment in therapy-naïve patients with Social Anxiety Disorder (SAD). In addition, CBD increases the brain-derived neurotrophic factor (BDNF) which can also be link to neurogenesis promotion (Sarris et al, 2020). The systematic review and meta-analysis by Black et al. in 2019, which included 82 studies, report that cannabinoids improve symptoms of depressive and anxiety disorders, Tourette syndrome, post-traumatic stress disorder, attention-deficit hyperactivity disorder or psychosis), though the GRADE for evidence was very low (Black et al, 2019). There is controversial data on whether Δ(9)-THC alone should be added to standard pharmacotherapy in patients with psychiatric disorders, considering its possible side effects - anxiety and psychotic symptoms (Stanciu et al, 2021). Cannabinoids are researched as novel alternative therapeutic agents to traditional anti-depressants and anxiolytics medication (Mandolini et al, 2018; Sartori and Singewald, 2019).

1.5.7 Cannabis-based products in paediatrics

Cannabidiol is approved for the indications of severe forms of epilepsy, Lennox-Gastaut and Dravet syndrome (Singer et al, 2020). Cannabinoids are used in children with behavioural conditions. In a study by Aran and Cayam-Rand, children with autism spectrum disorder and severe behavioural symptoms had substantial decrease in irritability and anxiety with the use of CBD-rich MC in therapy. In addition, patients reported no treatment-related severe adverse events (Aran and Cayam-Rand, 2020). Dronabinol drops in doses up to 3.62 mg/day were effective in 6 years old patient with early infant autism. Patient presented substantial improvement in symptoms such as hyperactivity, stereotypical movements, irritability, and speaking abilities (Campbell et al, 2017). Other common paediatric indications for Δ(9)-THC therapy are spasticity, pain, decrease in weight, vomiting or nausea, and dystonia. CBD is used for seizures and sleep

difficulties. CBD's long-term effects on the developing brain are still unknown (Rieder and Canadian Paediatric Society, 2016; Kachru et al, 2021). The potential benefits and risks of using cannabis products in children have not yet been rigorously studied to recommend for other than approved indications (Singer et al, 2020).

1.5.8 Medicinal Cannabis for topical use

In addition to epidermal keratinocytes and melanocytes CB1 and CB2 receptors can be found in cutaneous nerve fibres, hair follicles and endocrine sweat glands (Baswan et al, 2020). Dermatological CBD formulations are found to have antimicrobial and anti-inflammatory activity and may be efficacious for some skin conditions. The combination of Δ(9)-THC and CBD works by reducing pain and pruritus (Schräder et al, 2021). In vitro and in vivo studies highlight that cannabinoids regulate keratinocyte differentiation, skin development, and epidermal cell differentiation (Vanti et al, 2021).

1.6 Recommendations on the use of Medicinal Cannabis

Recommendations on MC use require future research on the physiological impacts of plant-derived and synthetic cannabinoids and endocannabinoids. Different cannabinoids can have varying physiological effects. Cannabinoid use in patients should preferably be short-term (less than six months). Isolated cannabinoids rather than plant mixtures may be used in future clinical development programs to avoid the delivery of harmful substances in smoked marijuana, targeting developing new delivery systems of non-smoked cannabinoids with rapid onset of action. MC use in patients with debilitating symptoms can be recommended in case if approved drugs have failed to give symptom alleviation. MC should be administered under medical supervision to evaluate the

treatment efficacy and supervision strategy in a patient specified indication (Mack, 2000; Busse et al, 2021).

1.7 Cannabis-derived products

"Sativex" oromucosal spray (“Nabiximols”) is the extract of the cannabis plant which contains 2.7 mg Δ(9)-THC and 2.5 mg CBD. In 2010, it was first approved in Europe as a prescription-only medicine in the United Kingdom for treating spasticity due to MS. It was also licenced in Spain and Portugal in the same year. "Epiodylex" (CBD 100 mg/ml oral solution)[13] received both FDA and EMA approval for its use in childhood epilepsy, specifically the Lennox-Gastaut Syndrome and Dravet Syndrome, and as adjunctive therapy of seizures linked to tuberous sclerosis complex (TSC)[14], now studied for glioblastoma multiforme in clinical trials (Wang et al, 2017).

The two oral agents, a synthetic form of Δ(9)-THC – dronabinol (“Marinol”) and nabilone (“Cesamet”), were approved in the USA to treat nausea and vomiting associated with chemotherapy, when other treatment has not been successful. Dronabinol also used to induce appetite and weight gain in patients with human immunodeficiency virus (HIV) infection (O'Donnell et al, 2021).

In Europe, 14 RDs are granted Orphan Drug Designation (ODD) and considered as indications for cannabis-derived treatment or prevention: Glioma, Systemic Sclerosis, Cystic Fibrosis, Dermatomyositis, Dravet syndrome, Perinatal Asphyxia, Graft-versus-

[13] Community Register of orphan medicinal products. European Commission. [Cited 2022 Jan 18]. Can be accessed from URL: https://ec.europa.eu/health/documents/communityregister/html/reg_od_act.htm?sort=a

[14] GW Pharma Ltd. Sativex Oromucosal Spray SmPC. 2020 [Cited 2022 Jan 18]. Can be accessed form URL: https://www.medicines.org.uk/emc/product/602/smpc

host disease, Graft-versus-host disease, Lennox-Gastaut syndrome, Tuberous sclerosis, Rett syndrome, West syndrome, Fragile X syndrome, Complex regional pain syndrome[13]. By now, only one cannabis-derived preparation (CBD, " Epidyolex") has centralized marketing authorization in EU for the indication mentioned above[13].

1.8 Medicinal Cannabis in Malta

Since 2018, the Production of Cannabis for Medicinal and Research Purposes Act[15] has been regulating production of Cannabis for medical and research objectives in Malta. This followed the Drug Dependence Act[16] amendment, which entitles a licensed medical practitioner to prescribe medicinal preparations of the plant cannabis and synthetic cannabinoid products which are registered under the Medicines Act or manufactured under Good Manufacturing Practice (GMP) if it is considered that there is no feasible alternative to such prescription. Patients in Malta can access approved medical cannabis preparations with a medical practitioner's prescription, a control card, and approval from the Superintendent of Public Health dispensed by a pharmacist from a licensed pharmacy. MC strains which are available in Malta are presented in Table 1.1.

[15] Parliament of Malta. The Production of Cannabis for Medicinal and Research Purposes Act, Act No. X of 2018. [Cited 2021 Dec 15]. Can be accessed from URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=12821&l=1

[16] Parliament of Malta. The Drug Dependence (Treatment not Imprisonment) Act No. V of 2018. [Cited 2021 December 15]. Can be accessed from URL: http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=12289&l=1

Table 1.1 Medicinal Cannabis products available in Malta

Brand name	Cannabinoid concentration	Cannabis strain	Packaging
Bedrocan®	Δ(9)-THC 22% CBD <1.0%	Sativa Flos	Child-resistant packages of 15 grams
Bediol®	Δ(9)-THC 6.3% CBD 8%	Sativa Granulate	Tubs of 5 grams
Carbasi Verde	21.7% Δ(9)-THC CBD <1.0%	Indica Flos	Child resistant packages of 15 grams
Cannabis 1A 18/1	18% Δ(9)-THC and <1% CBD	Sativa & indica flos	Tubs of 10 grams
Pedanios 20/1	20% Δ(9)-THC and <1% CBD	Indica Flos	Tubs of 10 grams
Pedanios 22/1	22% Δ(9)-THC and <1% CBD	Indica Flos	Tubs of 10 grams

CBD is available as a food supplement or cosmetic in Malta and can be bought at various outlets such as food stores, vape stores, health shops. CBD products are available as a herbal substance (dry flowers), oil drops, transdermal patches, capsules, inhalers, crystals, chewing gums, chocolates etc. CBD topical products such as creams, oils, body butter etc.

CBG in Malta is available as dried hemp flowers (Buffalo Soldier strain) containing 15% CBG. These flowers have <0.3% Δ(9)-THC. CBG can be vaporized, smoked, or use as herbal tea preparation, boiled for 10 minutes. It is available in combination with cannabinol (CBN) as drops for sublingual administration. CBG is also available as 25 or 48.5% Kief (with Δ(9)-THC 0%) - cannabis crystals, the pure collection of loose cannabis trichomes.

1.9 Medicinal Cannabis formulations

Inhalation via smoking and vaporization, as well as consumption of edible items, are the three most prevalent methods for administering Cannabis. The administration method can affect MC effects' onset, efficacy, and intensity. Smoking is the most viable route for administration, as vaporization has similar effects as smoking while minimizing the exposure to the combustion byproducts and carcinogens while reducing negative respiratory reactions (Bridgeman and Abazia, 2017; Stella et al, 2021).

1.10 Medicinal Cannabis pharmacokinetics and safety

The pharmacokinetics of MC differs based on its administration route. Inhalation maximizes the plasma concentration in a few minutes. Following oral consumption, effects occur within thirty to ninety minutes, after two to three hours, the impact is at its peak. The overall effects last four to twelve hours, based on the administered dose. Clinical studies have shown intra-subjects variability at a high degree based on the pharmacokinetic parameters (Grotenhermen, 2003).

Δ(9)-THC is highly lipophilic, spreading rapidly from highly perfused tissues to fat cells. Plasma concentration of Δ(9)-THC after smoking was similar to intravenous injection, but after oral doses plasma concentration was irregular and comparatively lower, signifying slow and erratic absorption (Bridgeman and Abazia, 2017; Millar et al, 2018).

1.11 Medicinal Cannabis interactions

MC does not potentiate any severe drug-drug interactions, but depending on the MC formulation, some interactions can occur which affect the bioavailability, treatment efficacy or exacerbate adverse events. Hepatic cytochrome 450 (CYP450) isoenzymes play a primary role in the metabolism of exogenous cannabinoids. CYP2C9 and CYP3A4

are responsible for metabolism of Δ(9)-THC and CBN, whereas CBD is metabolized by 2C19 and 3A4. Concomitant administration with ketoconazole can increase the maximum serum concentration for both Δ(9)-THC and CBD by 1.2-fold to 1.8-fold respectively. Rifampin coadministration can reduce plasma levels of CBD and Δ(9)-THC. CBD inhibit CYP2C and CYP3A, enzymes which metabolize AEDs, such as clobazam and valproate. It is possible that carbamazepine and phenytoin may reduce the levels of CBD (Devinsky et al, 2014)

Patients receiving Cannabis are highly likely to receive concomitant medications. When MC is combined with other drugs that have similar physiological effects, (e.g., sedatives, antihistamines, stimulants, tricyclic antidepressants, sympathomimetics), pharmacodynamic interactions are possible. Smoking cannabis, like smoking tobacco, has the ability to boost theophylline metabolism (Bridgeman and Abazia, 2017).

1.12 Medicinal Cannabis toxicity and adverse effects

The most often adverse reactions of Δ(9)-THC and CBD are vertigo and fatigue of mild to moderate severity, which occur during the initial administration, and usually self-resolving[14]. Short-term use of Cannabis may potentiate impairments in short-term memory and motor coordination, however, severe adverse events are very unlikely, as it cannot be fatally overdosed (Busse et al, 2021). Signs and symptoms of acute intoxication based on CB1 agonism type reactions are dizziness, paranoia, hallucinations, bradycardia, or tachycardia with hypotension (Karila et al, 2014).

Inhaled doses of 2 to 3 mg THC and swallowed dosages of 5 to 20 mg THC impair short-term memory, focus, and executive functioning in adolescents and adults. At THC doses greater than 7.5 mg/m^2, more severe side effects such as postural hypotension, anxiety,

delirium, nausea and possibly myoclonic jerks. Higher potency/concentrated cannabis products have also been linked to acute psychosis (Turner, 2021).

When compared to other prescribed medications, the toxicity of Δ(9)-THC is very low. In rats, the median lethal dose (LD50) is 800 mg/kg when given orally, in monkeys 9000 mg/kg and in humans is estimated to be around 30 mg/kg (Hartung et al, 2014). In a 70 kg human, the lethal dose would be around 4 grams of Δ(9)-THC, which is impossible to intake via oral consumption, smoking, or vaping [17]. Animal studies suggest that cannabis may have the cardiovascular risk comparable to that of smoking cigarettes (Karch, 2006). To avoid serious side effects, patients with existing cardiac or cardiovascular conditions should use MC with caution (Simon et al, 2022).

1.13 Aims of the study

The aims of the study were (i) to identify the Rare Diseases for which Medicinal Cannabis can be used and (ii) to identify issues related to the use of Medicinal Cannabis in patients with Rare Diseases.

[17] World Health Organisation (WHO). Expert Committee on Drug Dependence: fortieth report: Dronabinole. World Health Organization; 2018.

CHAPTER 2

METHOD

2.1 Literature review of Medicinal Cannabis use in Rare Diseases

The systematic review approach was used to gather and analyse relevant literature. The systematic review process is evidence-based research (EBR) where good-quality decisions are based on critical thinking and the rigorous, transparent, and careful use of the best available evidence from multiple sources (Christenson et al, 2011). Systematic Literature review is a helpful tool to interpret and discuss the possible outcomes of a research topic in an all-inclusive manner. The literature review was carried out to find out the current evidence of the use of MC in RDs.

PubMed Central and MEDLINE were used to conduct the systematic literature review. Peer review journal articles between January 2010 – October 2021 were included.

The search strategy included a combination of terms and synonyms which define RDs and Medicinal Cannabis or its significant constituents – THC or CBD. Search excluded terms that used the abbreviation CBD for terms other than cannabidiol.

Search terms used in search engines: ((diseases, rare) OR (disease, rare) OR (orphan disease)) AND (cannab* or medical marijuana OR THC OR CBD OR tetrahydrocannabinol OR cannabidiol) NOT "Corticobasal degeneration" NOT "congenital bleeding disorders" NOT "common bile duct" NOT "Cortico-Basal Ganglia Degeneration". All articles which describe the association between any RD and MC were included.

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) tool was used (Boutron, 2021). Records were screened to remove duplicate articles and identify eligible articles. The type of study and study intervention, type of rare disease,

form of MC used, type of subjects, and efficacy endpoints were identified and compared, and information was presented in tables.

Table 2.1 Literature review inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Articles published between 1st January 2010 and 30th October 2021	Articles that describe medical conditions which are not rare
Articles that describe the use of MC in a rare disease	Articles that describe solely side effects (s) of cannabis use or its toxicity
Articles are English	Articles not published in English

2.2 Development, validation, and dissemination of questionnaires for rare disease patients and healthcare professionals

Self-administered questionnaires for RD patients and HCPs were developed. Self-administered questionnaires help eliminate interviewer bias and establish anonymity (Bowling, 2014). In the questionnaires, a combination of quantitative and qualitative approaches was used.

2.2.1 Development of questionnaires

Two questionnaires were developed for: (1) RD patients and (2) HCPs (Appendix 1 and Appendix 2). The questionnaire for patients contained 36 questions. The questionnaire for HCPs contained 31 questions. Time to fill-in each questionnaire was approximately 10-15 minutes. Both questionnaires were divided into 5 sections: demographic information, clinical presentation of the RD, treatment of RD patients, issues related to treatment and the use of MC. Questionnaires comprised close-ended questions (multiple choice, check-box, rating scale), and open-ended questions (comment-boxes). Description of sections and questions included in the questionnaires for HCPs and

patients are presented in Table 2.2. Questionnaires were developed to be distributed in paper format and online. The online questionnaires were developed and distributed via the platform "SurveyMonkey" ("Momentive").

Table 2.2: Description of questions included in the questionnaires for health care professionals (HCP)

Section of a questionnaire	Description of the questions for health care professionals	Description of the questions for RD patients
Demographic information	Gender, age group, profession, area of practice, and years of professional experience.	Gender, age group, country of residence, smoking status, and name of RD.
Clinical presentation of the RD	Symptoms experienced by RD patients; rating of intensity and duration of symptoms experienced by the patients (pain, seizures, nausea and/or vomiting, and stress-related symptoms.	Symptoms experienced with relation to RD; Rating of intensity and duration of symptoms experienced (pain, seizures, nausea and/or vomiting, and stress-related symptoms).
Treatment of RD patients	Treatment options currently used in practice to relieve symptoms experienced by RD patients (pain, muscle spasticity, anxiety, and nausea).	Current treatment for RD, including symptomatic treatment, food supplements, alternative treatment options.
Issus related to treatment	Issues related to existing treatment options for RD patients, evaluation of access to therapy.	Issues related to existing treatment (access to therapy, price of therapy, side-effects, possible non-efficacy / presence of symptoms irrespective of existing therapy, reasons for not-compliance to treatment).
Use of Medicinal Cannabis in treatment	Experience on the use of MC, perception on the MC use in practice, level of confidence to prescribe MC, and concerns related to MC use.	Experience on the use of MC, symptoms for which they would use MC, preferred MC administration form and concerns associated with MC use.

Patients' pain severity assessment was performed using the Numerical Rating Scale (NRS, between 0 and 10), where 0 represents "no pain at all" whereas 10 represents "the worst pain ever possible". NRS is a feasible and compliant pain-assessment tool that strongly associated with other scales (Haefeli and Elfering, 2006).

Nausea severity assessment was performed using a nausea scale (0-5 rating), adopted from Halpin et al. 2010, where zero represents "no nausea" whereas the upper limit represents "frequent vomiting". The scale is concise and easy to use, as well as more effective s compared with the 0-to-10 scale (Halpin et al, 2010).

Seizure severity assessment was performed using a seizure frequency scale with the score ranging from 0 to 12, where – o represents "seizure free, no AEDs" and 12 – "status epilepticus" (Vinton et al, 2007).

5-point scale was used to determine a level of anxiety of RD patients, where 1 represents normal or no anxiety and 5 very severe anxiety, adopted from Likert scale and Beck Anxiety Inventory (Davey et al, 2007). The adopted 5-point Likert scale was used to reflect HCPs' confidence level to use MC in RD patients, with the confidence intervals from 1 to 5, where 1 represents not confident at all and 5 – completely confident.

The adopted 5-point Likert scale was used to reflect the level of concern of HCPs on the possible side-effects of the use of MC in RD patients, from no concern at all to very serious concern; how easy is it to access medications for RD patients, from very easy to almost impossible; and consider the use of MC for RD patients from strongly agree to strongly disagree.

2.2.2 Validation of questionnaires

Validation was performed using the validation tool (Appendix 3) to demonstrate adequate reliability and validity of the questionnaire. The questionnaires were validated by three

pharmacists working in the community, two academic personnel (lecturer, senior lecturer), a pharmacist at the directorate for pharmaceutical affairs, a psychiatric nurse, an occupational therapist, and a family doctor.

For both questionnaires, some formatting and organizing editions were made.

Amendments after the validation of questionnaires for HCPs were:

- The medical doctor answer option was complemented with specialization in general practice, paediatrics, internal medicine, dermatology, pathology, physical medicine and rehabilitation, psychiatry, and neurology.
- "Area of practice" of HCPs was included.
- Trade names of the medicines were removed
- In question "Drug accessibility issues," "due to complex import/permission requirements" answer option was added

Amendments after the validation, questionnaires for RD patients were:

- Question on patients' ethnicity was removed
- Terms that maybe not be well understood by patients were simplified (such as non-pharmacological treatment, oromucosal spray, oral solution)

The list of most prevalent RDs in alphabetical order was attached to the questionnaire for HCPs, based on the 2021 Prevalence and incidence of rare diseases report[18]. Validators established that questionnaires address the research aims and that the content and layout are suitable.

[18] Orphanet. Prevalence and incidence of rare diseases: Bibliographic data. Orphanet Report Series, Nr 1; 2021. Sponsored by the Health Programme of the European Union.[Cited 13 Jan, 2022]. Can be accessed from URL:https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabetical_list.pdf

2.2.3 Ethics approval

The Faculty Research Ethics Committee (FREC) Approval was granted prior to the commencement of the study (Appendix 4).

2.2.4 Participant recruitment

Table 2.3 describes the participants' inclusion and exclusion criteria.

Table 2.3 Inclusion and exclusion criteria for questionnaire participants

Inclusion criteria	Exclusion criteria
Being an HCP* and having a practice in Malta or being an adult RD patient with diagnosed RD	Participants who were under the age of 18 years
Being at least 18 years of age. If a respondent was below 18 years old, the questionnaire was filled by his/her parent or caregivers	Participants who were not HCPs or were not diagnosed with any RD
Being able to read and write in English	Participants who were not able to read and write in English

*Medical doctors (general practitioners or specialty doctors), nurses, pharmacists, midwives, physiotherapists, allied healthcare professionals (occupational therapists, physiotherapists, speech therapists, herbalists, homeopaths);[19]

2.2.5 Dissemination of questionnaires to healthcare professionals

Questionnaires were distributed among healthcare associations, health centres, private medical clinics, pharmacies, and individual healthcare professionals. The dissemination of questionnaires to healthcare professionals in Malta in paper form and online via the survey platform "SurveyMonkey." The link to the online questionnaire was shared via email and social media platforms (Facebook and LinkedIn).

The Data protection approval to distribute online questionnaire among HCPs in Mater Dei Hospital (MDH) was obtained prior the start of distribution (Appendix 5).

2.2.6 Dissemination of questionnaires to patients with RDs

The dissemination of questionnaires to patients with RD was performed through a contact person at one of the following organizations. The contact person at

- National Alliance for Rare Diseases Support in Malta
- The Pain Clinic in Malta
- Malta Association of Occupational Therapists

The contact person distributed the information about the study. The information was distributed physically in paper form and online. The online version of the questionnaires was available on the survey platform "SurveyMonkey" via an electronic link.

[19] World Health Organisation (WHO). Classification of health workforce statistics. Health management personnel. From International Standard Classification of Occupations (ISCO) (ILO 2008). [Cited 4 Jan, 2022]. Can be accessed from URL: http://www.ilo.org/public/english/bureau/stat/isco/isco0

The questionnaires were filled in anonymously. Therefore, no personal data (respondent name, surname, ID, contact details, or another unique personal characteristic) was included during the study.

Anonymized data obtained from the questionnaires were collected, organized, and stored only by the main researcher. Data stored on the researcher's personal computer (all documents in PDF, Word, or Excel format) was protected using a password known only to the main researcher. Any material in hard-copy form was stored securely.

2.3 Data analysis

Quantitative data from the questionnaires was extracted in tables and graphs using "Survey Monkey" and "Microsoft Excel" platforms. Descriptive statistics were used to summarize the characteristics of the data, such as the frequency and average for categorical and nominal variables. Statistical analysis of quantitative data was performed using The IPM Statistical Package for Social Sciences (SPSS), Edition Standard v24. Chi-square was performed for the distribution of categorical variables in the datasets, with statistical significance level $p < 0.05$.

CHAPTER 3

RESULTS

3.1 Literature review on Medicinal Cannabis use in rare diseases

Following the literature search, 239 records were identified, and 36 were included in the Literature Review (LR). During the screening process, publications which discuss rare genetic mutations or rare conditions in patients with non-rare diseases or rare complications of any disease were excluded, as well as those which discuss RDs heritability RDs diagnostic methods and do not discuss RDs treatment. Publications discussing rare cannabinoid receptors as potential drug targets but not have any current clinical implications were excluded. Publications on side-effects/toxicity of cannabinoids used recreationally in patients with RDs were excluded. Figure 3.1 shows the phases of a conducted systematic review.

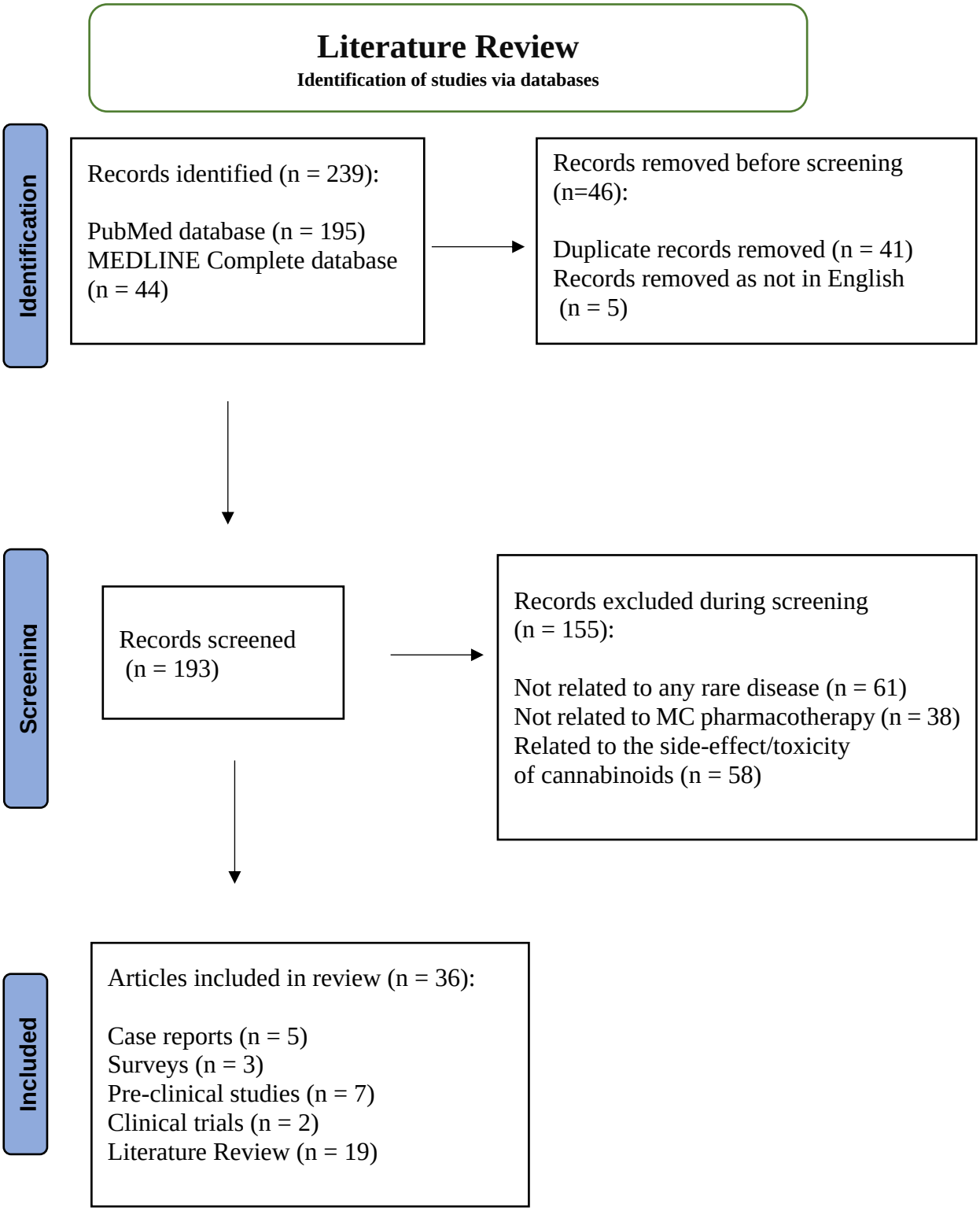

Figure 3.1 PRISMA flow diagram for literature review on Medicinal Cannabis use in Rare Diseases

Of the 36 articles included in the LR the most common type of studies was review studies (n = 19), followed by pre-clinical studies (n = 7). A tabulated summary of all the publications included in the LR on MC use in RDs, by type of study design, is presented in the Appendix 6.

Most of the publications included in the literature review were published in 2021 (n=13) and 2020 (n=11). Table 3.1 shows the number of publications included in the review per year.

Table 3.1: Publications included in the review per year (N=36)

Year of publication	No of publications
2008	1
2015	1
2013	2
2016	3
2018	3
2019	2
2020	11
2021	13

MC was used in 22 different RDs, mainly: epileptic conditions (n=7), neurodegenerative diseases (n=6) or skin disorders (n=4). A full list of RDs is presented in Appendix 7.

The disease onset of RDs was early childhood in most cases (Table 3.2).

Table 3.2: Time of onset of Rare Diseases (RDs)

Disease onset	Nr of RDs
Early childhood (WBS, NF1, CIPO, RTT, PWS, Dravet Syndrome, Lennox-Gastaut Syndrome, Doose syndrome, EB, West syndrome, cystic fibrosis)	11
Early childhood to early adulthood (FIRES)	1
Late childhood to early adulthood (LD, TSC, MS)	3
Mid adulthood (SSc, SCA-3)	2
Childhood or adulthood (DM, SLE, paediatric Alzheimer's, Parkinson's, HD)	5

Twenty of these 22 RDs have currently no available treatment and the treatment is symptomatic.

Seventeen individual studies and 19 review studies, which discuss the use of MC in RDs were included. RDs and indications for which MC was used in individual studies is presented in Appendix 8 and review studies presented in Appendix 9.

The most used cannabinoids in the studies were CBD (n=16), and cannabinoid-based medicines (CBMs) (n=7) (Table 3.5). Studies discuss the use of MC in RDs either as the main therapeutic agent (e.g. in EB, PWS, SSc) or as an add-on therapy (conditions associated with refractory epilepsy).

Table 3.3: Cannabinoids used, and symptoms addressed (in publications included in the literature review)

Cannabinoids used	Number of articles	Symptoms addressed
• CBD • Oral CBD extract 99% ("Epidiolex") • CBD enriched extract	16	Seizures (n=13) Neurological and neuropsychiatric complications in TSC (n=1) Epileptic seizures and cognitive impairment (n=1) Infantile spasms (n=1)
Cannabinoid-based medicines (CBMs)	7	Impact on SCA-3 disease progression (n=1) Pharmaco-resistant seizures (N=2) Neurodegenerative processes (n=1) Difficult to treat pain, spasticity (n=2) Spasticity and central pain (n=1)
Other synthetic agents (e.g. CB1R antagonists, Ajulemic acid, Synthetic CBD derivative quinol)	4	Obesity (n=2) Suppression of tissue scarring, cessation of chronic inflammation and fibrosis (n=1) Antifibrotic effects, wound healing (n=1)
THC: CBD in 1:1 ratio (Sativex-Spray©)	2	Motor symptoms, dystonia (n=1) Neuropathic pain and dysesthesia (n=1)
CBDA (cannabidiolic acid)	1	Chronic pain, thermal hyperalgesia, motor symptoms and anxiety-like symptoms and cognitive deficits (n=1)
Non-psychoactive doses of Medicinal Cannabis	1	Immunosuppression and impact on immune response (n=1)
Synthetic THC (dronabinol)	1	GI complaints (n=1)

The case reports included in the review presented patient cases or patients' cohorts, where RD patients were receiving commercially available forms of MC, such as "Epidiolex" (CBD extract), "Sativex" (THC: CBD in 1:1) or Dronabinol capsules. Five included case reports were on five different RDs but all showed successful improvement in different patients presented symptoms, including chronic sensory and motor symptoms, abdominal pain, drug-resistant seizures. Three survey research publications were included in the current LR, on four different RDs (treatment of Epidermolysis Bullosa (EB), Dravet syndrome, Lennox-Gastaut syndrome and Doose syndrome) and two different indications (skin disorder and seizures). Seven pre-clinical studies were included in the review, of which six were performed on mouse/murine model and one on zebra fish model. Two clinical trials were included in the review were performed on drug-resistant seizures indication, where one was randomised and placebo-controlled, whereas the other was an open-label and not randomised. Studies investigated the efficacy and safety of purified CBD ("Epidyolex" 100 mg/ml) in paediatric and adult patients who were not responsive to ASM treatment. The duration of intervention was 12 months vs 16 weeks and the MC dose varied. The results were closely similar – around half of patients had a reduced seizure frequency.

Most review publications were performed on the use of MC in RDs, which are associated with refractory seizures (n=12), and pain/spasticity. The most common side effects of MC use reported in the included publications were fatigue (Porter et al, 2013; Press et al, 2015; Zemrani et al, 2021) and somnolence (Iannone et al, 2021; Thiele et al, 2021).

Short descriptions of the all the studies included in of the LR are presented in the Appendix 10.

3.2 Questionnaires for healthcare professionals

Hundred and one HCPs responded to the questionnaire. Table 3.4 shows the demographic data of the HCPs who participated in the research.

HCPs participants were mostly female (n=59); most of the respondents were 30-38 years old (n=44) and with more than ten years of practice (n=46). Majority of HCPs were pharmacists (n=40), general practitioners (n=17) and occupational therapists (n=13).

Table 3.4: Demographic information of HCPs (N=101)

Age group (years)	**20-29 (n=7); 30-38 (n=44); 39-47 (n=22); 48-56 (n=16);** **57+ (n=12);**
Gender	Female (n=59); Male (n=42);
Years of practice	0-2 (n=13); 3-5 (n=20); 6-10 (n=22); 11-15 (n=14); > 15 (n=32);
Profession	Pharmacists (n=40); general practitioners (n=17); occupational therapists (n=13); medical specialists (n=11); speech therapist (n=4); physiotherapist (n=4), nurse (n=4), other (n=8)*;
Area of practice	Hospital (n=25); private medical clinic (n=22); community pharmacy (n=29); regulatory (n=8); nursing home (n=5); public health centre (n=5); academia (n=1); other (n=6)**;

* Emergency medicine specialists, physician assistants, midwives, traditional medicine specialist, psychologists

** Private companies, governing institutions

HCPs usually (n=48) encountered 2-4 RD patients a year in their practice. HCP reported that the most common RDs encountered in their practice were Multiple Sclerosis (MS) (n=6), Fibromyalgia (n=4), Amyotrophic Lateral Sclerosis (ALS) (n=3), Fabry disease (n=4), Fragile X syndrome (n=2), Autosomal systemic lupus erythematosus (n=2), Huntington's disease (n=2), Charcot Marie tooth (n=2), and others - Cystic Fibrosis, myasthenia gravis, Familial Mediterranean Fever, Wernicke's Korsakoff, rare types of cancers as oesophageal cancer, thyroid cancer, osteogenic sarcoma, prolactinoma, ocular melanoma, etc.

Questions regarding the symptoms of RD were answered by 70 HCPs. Pain (n=51) was the most frequently encountered symptom experienced by RD patients. This was followed by anxiety (n=34), muscle spasticity (n=33) and sleep disorder (n=20). Moreover, 7 patients had no symptoms (Table 3.5).

Table 3.5: Frequency of RD symptoms encountered by HCP

Symptoms	**No of HCP**
Pain	51
Anxiety	34
Muscle spasticity	33
Sleep disorder	20
Seizures	17
Psychiatric disorder / behavioural changes	17
Respiratory disorder	14
Skin disorder	14
Other	9
Nausea and/or vomiting	8
Appetite alterations	8
Visual disturbance	8
None	7

Persistent chronic neuropathic pain (>3 months) was reported as the most common type of pain (n=31), followed by sporadic pain (n=18) and acute lasting pain (n= 14).

Patients who presented with seizures, he had 1-3 disabling seizures per year in most cases (n=6), followed by 1-3 disabling seizures per month (n=4). HCPs reported that, RD patients presented increased emotional and/or physical stress in most cases (n=22). Most of HCPs (n=11) reported nausea and/or vomiting, experienced by their patients to be light or mild (n=5).

Questions regarding treatment for RD symptoms were answered by 64 HCPs. Table 3.6 shows the most used pharmacotherapy for pain, anxiety, nausea and vomiting, muscle spasms or seizure management in RD patients.

Table 3.6: Commonly used medicines for RDs

Indication	Pharmacotherapeutic group	No of HCPs
Pain management medications	Analgesics and antipyretics, acetaminophen	37
	Tricyclic antidepressants, e.g. amitriptyline	26
Anxiety management medications	Benzodiazepines, e.g diazepam	69
	Tricyclic antidepressants, e.g. amitriptyline	39
Vomiting and nausea management medications	Propulsives, metoclopramide	21
	Propulsives, domperidone	18
Anti-epileptics	Fatty acid derivatives, sodium valproate	23
	Other antiepileptics, levetiracetam	15
Spasmolytics	Muscle relaxant, other centrally acting agent baclofen	35
	Antiepileptics, gabapentin	24

HCPs' review on alternative therapy options for symptom relief include acupuncture (n=21), massage (n=12), and no use of alternative therapy in most cases (n=30).

The most common issues associated with RD patient treatment in HCPs opinion were diagnosis of the RD (n=43), drug accessibility issues due to financial burden caused by the cost of the medicines (n=27) and no appropriate medicine for certain RD (n=26). One reported finding no issues. Issues mentioned in the open-ended section of this question were: (1) doctors and consultants' lack of experience in RD patient management and (2) insufficient pharmacist education about RDs.

Table 3.7: Issues associated with RD patient management (N=64)

Issues	No of HCPs
Diagnosis of the medical condition	43
Drug accessibility issues due to the financial burden caused by the cost of the medicines	27
No appropriate medication for RD	26
Side-effects associated with the use of current medicines	23
Drug accessibility issues due to complex import permission requirements	20
Insufficient symptom relief with the currently available therapeutic options	18
Drug accessibility issues due to drug shortages	15
Contraindication to medicines	10
No issues reported	1

Treatment for RD patients is somewhat hard in most cases (n=36), some respondents report it to be very hard (n=14) or easy (n=11).

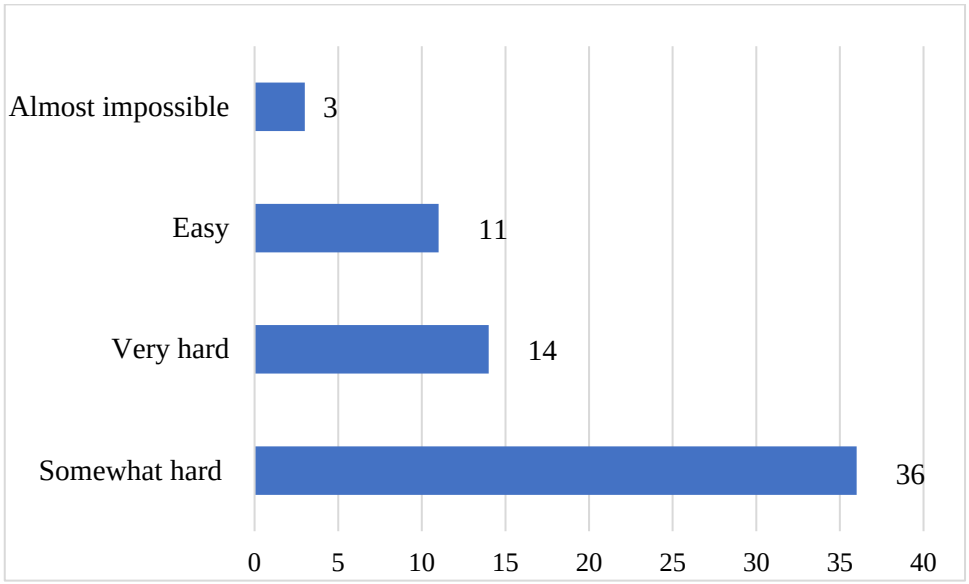

Figure 3.2: HCPs' views on the access to treatment for RD patients (N=64)

Questions regarding MC use were answered by 59 HCPs. Figure 3.3 shows that the majority (n=33) of respondents had no experience on the usage of MC in practice.

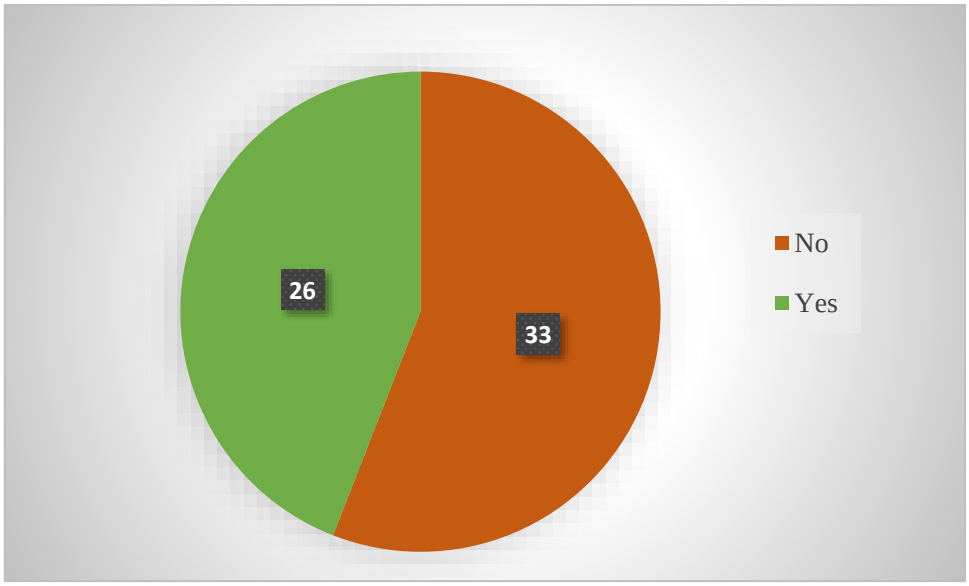

Figure 3.3: HCPs' experience on the use of MC in practice (N=59)

There is no statistically significant difference in experience with MC use across HCPs of different specialties ($X^2(7) = 13,997$, $p=0.051$). HCPs who responded having experience

with MC the most were pharmacists (n=15) and general practitioners (n=6). 65% (n=15) of pharmacists and 50 % (n=6) of general practitioners who participated in the research had experience in the use of MC.

Table 3.8: HCPs' experience on the use of MC by profession (N=59)

	Medical doctor, general practitioner	Medical specialist	Nurse	Pharmacist	Physiotherapist	Occupational therapist	Other HCPs	Total
Yes	6	3	2	15	0	0	0	26
No	6	5	2	8	3	4	5	33

$X^2(7) = 13,997$, p=0.051

Most (n=36) of the participants (N=59) agreed or strongly agree with using MC in their practice for RD patients; two disagreed and the remaining 18 neither agreed nor disagreed. The p-value of the Chi-Square test (0.164) exceeds the 0.05 level of significance, indicating no significant difference by professions on using MC in their practice for RD patients.

There is no statistically significant difference in considering usage of MC for RD patients, across HCPs with different years of professional practice. However, HCPs with 3-5 years of practice agreed / strongly agreed (n=9 of 10) and not one disagreed on MC use, whereas HCPs with 15 and more years of practice had a neutral position (n=11 of 21).

There is no statistically significant difference in consent to use MC for RD patients, across HCPs of different age groups (X2(12) = 19.333, p=0.081). However, HCPs in younger (25-34 and 35-44) age groups agreed to use MC for RD patients, more than disagree or be neutral. Whereas HCPs in the 45-54 age group most often had a neutral position. Two

HCPs who were general practitioners disagree on the using of MC in practice. None of the participants strongly disagreed on the use of MC.

Pain was the most selected symptom for which HCPs would use MC (n=52) in their practice, followed by muscle spasticity (n=38), anxiety (n=38), and sleep disorder (n=32).

Table 3.9: HCPs' consideration of the effectiveness of MC for the treatment of RD by symptoms (N=59)

Indications	No of HCPs
Pain (including neuropathic pain)	52
Muscle spasticity	38
Anxiety	38
Sleep disorder	32
Seizures	21
Nausea and/or vomiting	19
Appetite alterations	15
Anorexia	15
Skin disorders	8
Respiratory disorders	3
Visual disturbances	3

HCPs were concerned about possible side-effects associated with MC use, most commonly about confusion (n=30), addiction to MC (n=29), drowsiness (n=23), reduced level of memory or concentration (n=20), and experience of mid hallucinations (n=20). The majority of HCPs were undecided (n=20) about their level of concern related to the side effects of MC.

Table 3.10: Side-effects that HCPs perceive MC causes (N=59)

MC side-effects	No of HCPs
Confusion	30
Addiction to MC	29
Drowsiness	23
Reduced level of memory or concentration	20
Experience of mild hallucinations	20
Feeling tired or lethargic	16
Anxiety or paranoia	16
Change in appetite	12
Mood swings	11

As shown in figure 3.4, the majority of HCPs were barely confident in the use of MC (n=21 of N=59). Fourteen were not confident, 13 were somewhat confident and 8 were fairly confident (four on the scale from one to five).

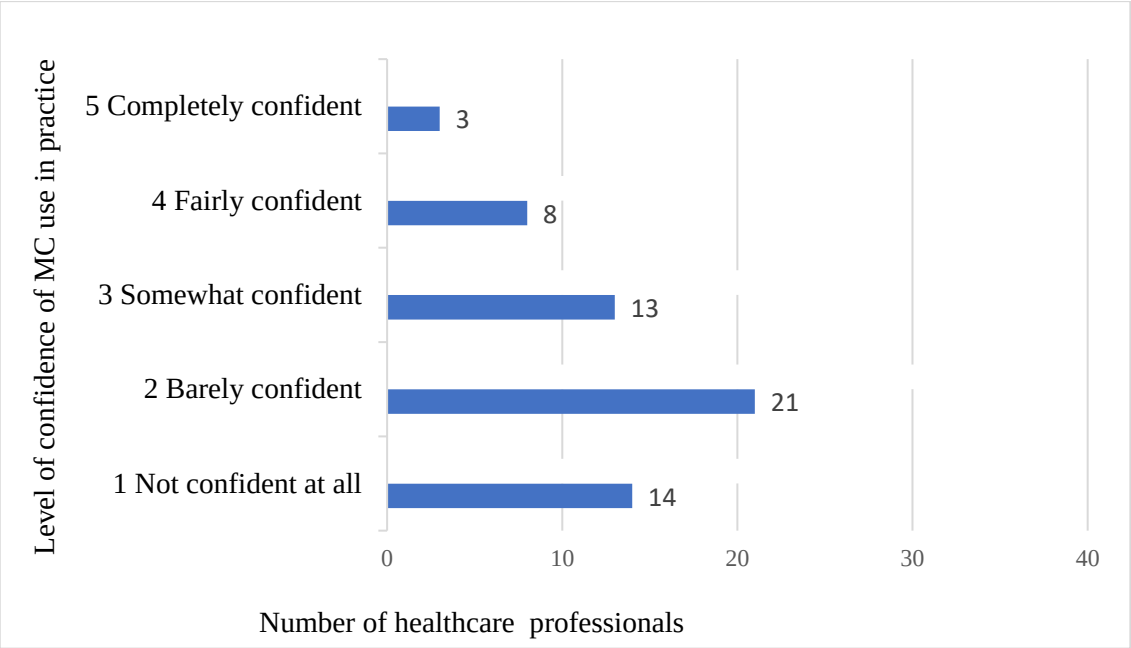

Figure 3.4: HCPs' confidence with the use of MC (N=59)

The p-value of the Chi Square test (p=0.0407) indicates the statistically significant correlation between HCPs' confidence in the use of MC in RD patients and years of professional practice. HCPs with longer years of practice had less confidence in the use of MC in practice (Table 3.11).

Table 3.12: HCPs' confidence in the use of MC in RD patients and years of professional practice (N=59)

		Years of practice					Total
		0-2 years	3-5 years	6-10 years	11-15 years	More than 15 years	
1 Not confident at all	No of HCP	1	4	3	2	4	14
2 Barely confident		1	2	6	3	9	21
3 Somewhat confident		0	2	4	0	7	13
4 Fairly confident		2	2	1	2	1	8
5 Completely confident		1	0	0	1	1	3

$X^2(16) = 16.678$, p=0.0407

In the open-ended "comments" question of the questionnaire, HCPs expressed concern about the lack of knowledge on the safe use of MC and lack of previous experience with its use in RDs.

Another issue of concern stated by HCPs is the burden of formal procedures which are necessary to follow prior to initiating MC treatment.

HCPs' comments generally support the MC use in RDs. Some HCPs commented not being concerned about possible side-effects of MC when it is used safely and effectively, like any other medicinal product.

3.3 Questionnaires for RD patients

Thirty-eight RD patients answered the questionnaire. The research participants mainly were female (N=21) RD patients of different age groups, the majority we adult patients (n=29).

The most common RD experienced were Kabuki Syndrome (n=3) and Fabry Disease (n=2).

Table 3.13: Demographic information of respondents to questionnaire for RD patients (N=38)

Age	**18 years old or less (n=9); 19-40 years old (n=10); 41-50 (n=11); 51 and more (8);**
Gender	Female (n=21); Male (n=17);

Thirty-six RD patients answered questions regarding the encountered symptoms of RD. Pain (n=24) and anxiety (n=22) were RD patients' (N=36) most frequently experienced symptoms. Other less frequent symptoms were muscle spasticity (N=10), and sleep disorder (n=9).

RD patients stated other symptoms related to their disease in the open-ended part of the question: heat and cold intolerance and hearing problems, arrhythmia, fatigue, vertigo, numbness, and tingling in hands and feet.

Table 3.14: Frequency of symptoms experienced by RD patients (N=36)

Symptoms	No of RD patients
Pain	24
Anxiety	22
Muscle spasticity	10
Sleep disorder	9
Nausea and/or vomiting	8
Skin disorders	7
Appetite Alterations	6
Seizures	4
Respiratory disorders	3
Inflammation	3
Visual disturbances	2
Psychiatric disorder/behavioral changes	1

If a patient was in pain (N=24), most commonly, it was a pain in joints (n=5), headache (n=5), full-body pain (n=4), muscle pain (n=4), neuropathic pain (n=3) or pain localised in a single extremity (n=3). Twenty-four patients reported experiencing pain, ranking "6" = distressing, on the pain intensity scale of 1-10 (n=7).

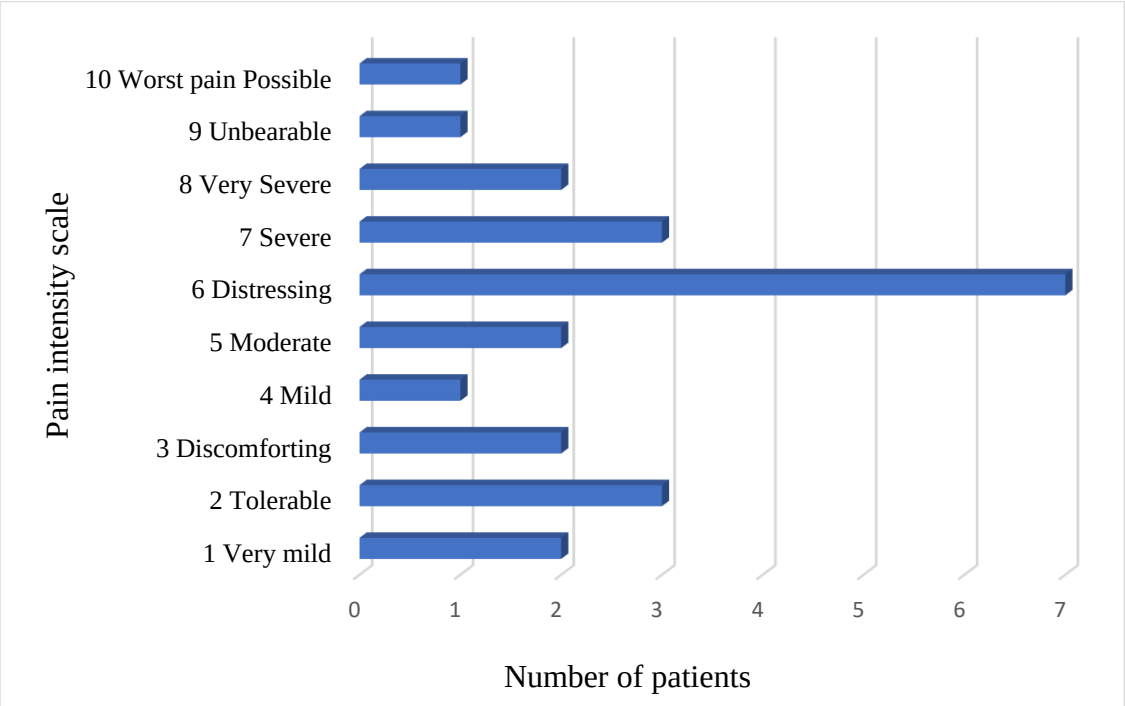

Figure 3.5: Pain intensity perception by RD patients (N=24)

Persistent chronic neuropathic pain (>3 months) was reported as the most common type of pain (n=8) reported by RD patients (N=24), followed by sporadic pain, breakthrough pain, pain caused by activity and acute pain (n=4) each.

Table 3.15: Duration of the pain episode in RD patients (N=24)

Duration of the pain episode	No of RD patients
Persistent chronic pain (more than 3 months)	8
Acute pain (1 - 7 days)	4
Pain caused by activity	4
Breakthrough pain (unpredictable attack)	4
Sporadic (intermittent / episodic pain)	4

Eight RD patients reported experiencing nausea and/or vomiting and most often found it "1" = light symptoms on a scale of 1-5 (n=4). None of the respondents experienced severe nausea or vomiting.

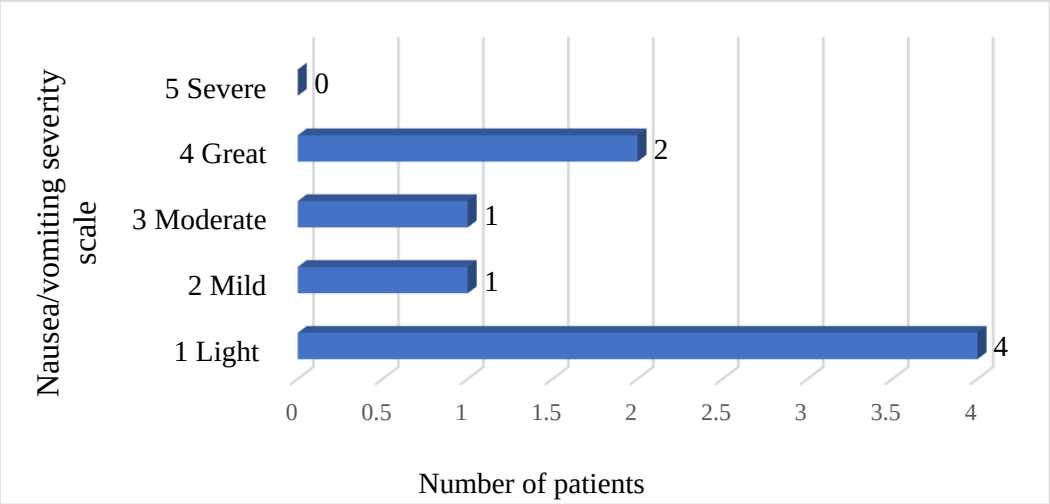

Figure 3.6: Severity of nausea and/or vomiting symptom reported by RD patients (N=8)

Twenty-two RD patients reported experiencing anxiety. As shown in figure 3.7, on a scale from 1 to 5, where "1" normal or no anxiety and 5 – severe anxiety, patients reported "3" = moderate (increased emotional and/or physical stress and feeling worried every day in most cases, n=14).

RD patients also reported experiencing stress-related effects such as difficulties in concentration and memory (n=12), anxious mood, gastro-intestinal symptoms (n=12), weakness and/or dizziness (n=10), insomnia (n=8).

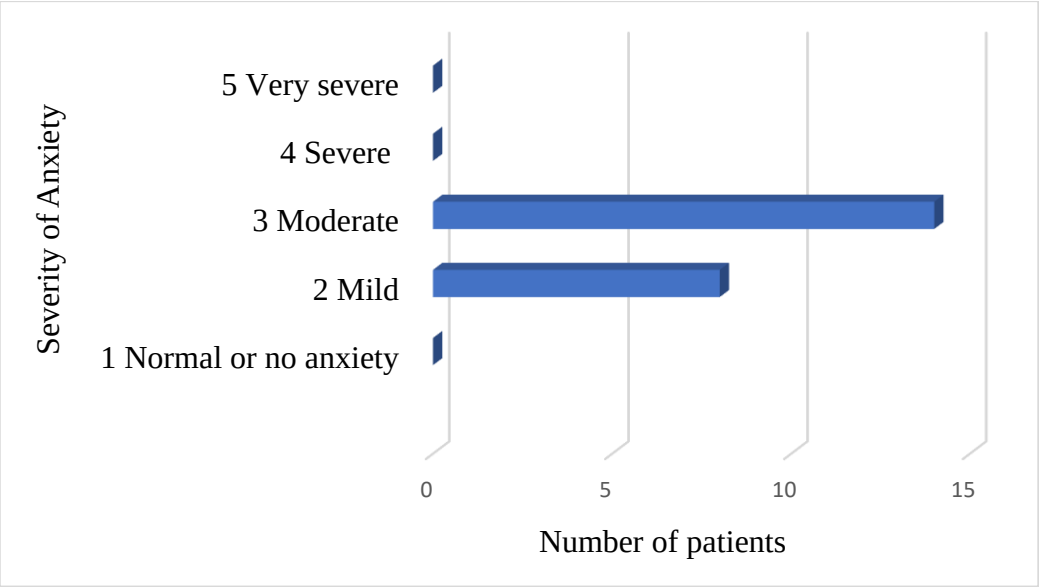

Figure 3.7: Severity of anxiety reported by RD patients (N=22)

Questions regarding the treatment were answered by 36 RD patients.

Twenty-two of RD patients who reported taking medicines for their disease, most often named steroids or hormones. In addition, 10 patients reported taking additional medicines to relieve pain symptom. Most of RD patients (n=25 of N=36) are not taking any food supplements or herbal preparations, and 11 patients report taking vitamin complex, vitamin D, CBD preparations, and Omega fatty acids additionally.

The majority of RD patients (n=17 of N=36) are not undergoing any other therapy, 10 were undergoing physiotherapy, 5 - speech therapy and 5 - occupational therapy.

Alternative therapy options	No of RD patients
None	17
Physiotherapy	10
Speech therapy	5
Occupational therapy	5
Acupuncture	4
Other*	4
Psychotherapy	2

* Aromatherapy, music and hydrotherapy, surgery, patches and supplements, strength training

Table 3.16: Alternative therapy options used by patients with RDs (N=36)

Twenty-nine patients with RDs answered questions regarding the issues with the treatment.

RD patients (N=29) found it easy to access their medicines in 11 cases, and easy most of the times in 9 cases. The medicines' price was not considered a burden by most patients (n=21). Seven of 29 RD patients reported experiencing side-effects associated with the use of current medicines (Figure 3.8). Examples of the side-effects experienced – fatigue (n=2), vertigo and vomiting (n=1), constipation (n=1), body aches and insomnia (n=1). RD patients responded experiencing symptoms: pain (n=16), anxiety (n=7), muscle spasticity (n=5), sleep disorder (n=4), nausea and/or vomiting (n=4) irrespective of the use of current treatment.

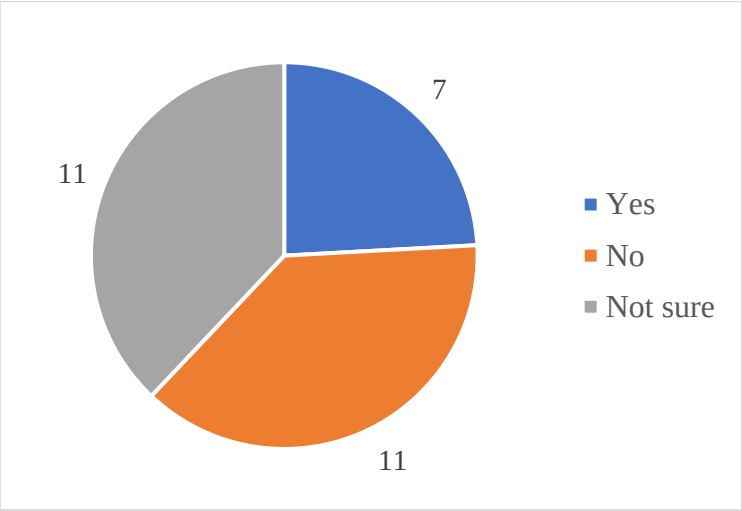

Figure 3.9: RD patients experiencing side-effects associated with the use of current treatment (N=29)

Thirty five patients with RDs answered questions regarding the use of MC. As shown in figure 3.9, most RD patients (n=29 of N=35) do not have experience with the use of MC.

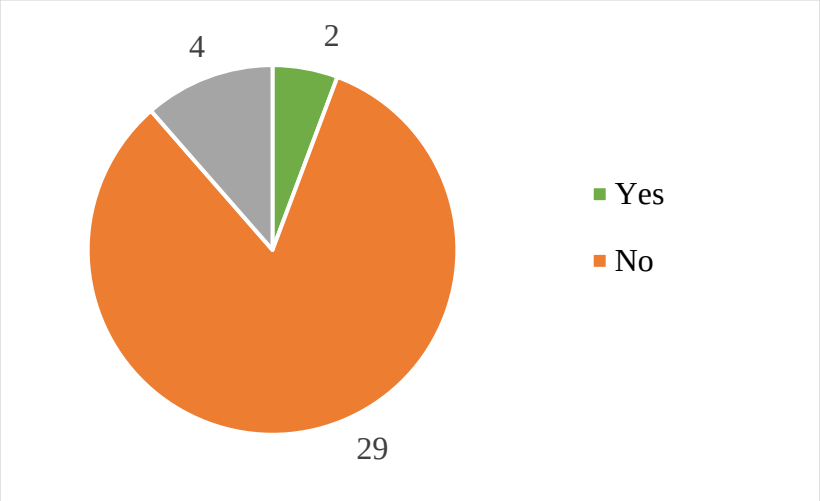

Figure 3.10: RD patients' experience with the use of MC (N=35)

As shown in figure 3.10, the majority, 20 of 35 RD patients consider using MC to treat their condition or relieve the symptoms of the disease.

Patients were asked a multiple-response question on the preferred method of administration of MC. The most preferred were for peroral administration - oral capsules

(n=19), oral spray (n=17), and oil drops (n=15), followed by smoked/vaporised (n=14) and topical administration (n=7).

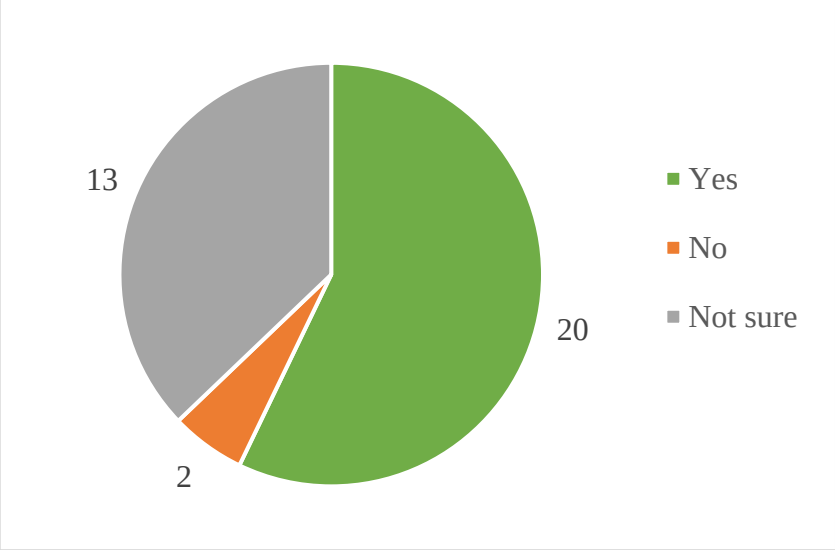

Figure 3.11: RD patients' perception on the use of MC as treatment (N=35)

Thirty-three RD patients answered the multiple-answer question about concerns they have in relation to the MC use. Most RD patients were not concerned about MC related side-effects (n=18 of N=33). Side-effects of most concern with relation to MC use were reported to be confusion (n=8), the experience of mild hallucinations (n=7), reduced level of memory or concentration (n=7), and possible addiction (n=7, Table 3.17). The reported concerns by RD patients besides the MC-related side-effects were the cost of the MC (n=5) and social stigma (n=5). Five of 33 RD patients were concerned about the lack of the previous experience in MC use. None of the RD patients responded that lack of effectiveness of MC is of their concern as well as none of RD patients consider it to be difficult to obtain MC for the regular use.

Table 3.18: Concern of RD patients about MC-related side-effects (N=33)

Side-effects of MC	No of RD patients
No concern on MC side effects	18
Confusion	8
Reduced level of memory or concentration	7
Experience of mild hallucinations	7
Addiction	7
Feeling tired or lethargic	3
Drowsiness	2
Mood swings	2
Change in appetite	1
Anxiety or paranoia	1

As shown in Table 3.17, most patients with RD (n=20 of N=35) consider using MC in treatment. Patients in older age categories were more prone to MC use. Patients of 40 years and older majorly agreed on its use. Patients in the age group 19-40 – disagreed or were unsure of cannabis use.

Table 3.19: Consideration of the use of MC to treat the condition or relieve the symptoms of the disease according to RD patients age group (N=35)

	Age group				
	18 year or less	**19-40 years**	**41-50 years**	**51 years or more**	**Total**
Yes	4	4	6	6	**20**
No	0	1	0	1	**2**
Not sure	3	5	4	1	**13**
Total	**7**	**10**	**10**	**8**	**35**

$X^2(6) = 4.749$, $p = .0576$

In the open-ended "comments" question of the questionnaire, patients expressed consent to use MC in their treatment in case it provides benefits for their health or relieve symptoms of their disease. Some patients expressed their positive experience with the MC use and one patient related the lack of awareness as a concern.

The results of this study shed light on current evidence on the use of MC in RDs and possibly associated issues related to MC therapy.

CHAPTER 4

DISCUSSION

4.1 Current evidence on the use of Medicinal Cannabis in Rare Diseases

This study highlights the global burden of RDs and issues to RD patients' treatment, majorly compounded by the lack of existing treatment options. According to global data on treatment accessibility for RD patients, only 5% have at least one treatment for their disease[20]. Medicines accessibility plays a crucial role in the treatment of patients with RDs as the absence of specific medicines can lead to increased preventable morbidity and mortality (Zamora et al, 2019). The LR demonstrated that research about the use of MC as a therapeutic option in RDs is emerging, with the number of publications included in the study was more than double that of previous years.

Studies included in the LR had different study designs (literature reviews, pre-clinical studies, case report studies, clinical trials), and therefore answered different research questions. Each study design has its advantages and disadvantages and each study research method provided different type of evidence. Qualitative research studies (case studies, surveys) provided in-depth knowledge on experiences or perceptions on MC use. In contrast, quantitative research (pre-clinical, clinical trials) addressed a research question by collecting, structuring and analysing qualitative data to establish the effectiveness of the proposed treatment. Different research methodologies correlate with variability in the aims of the study, the availability of resources, research expertise, potential patient numbers and time to conduct the study (Slade et al, 2018).

[20] Willmer G. The Building blocks to make rare disease treatments more common. Horizon [Internet]. 2022, Feb. [Cited 2022 May 15]. Can be accessed from URL: https://ec.europa.eu/research-and-innovation/en/horizon-magazine/building-blocks-make-rare-disease-treatments-more-common

Case reports included in reviews described an individual RD case or a patient group with a certain RD and discussed the use of MC as a treatment option. All five case reports showed the efficacy of commercially available MC products ("Sativex", "Epidiolex", "Marinol") in reducing the severity of symptoms (such as dystonia, neuropathic pain, seizures) (Table 3.3). Some case reports (FIRES, WBS, CIPO, NF1) also reported an improvement of QOL in patients, including improved mobility, mood and quality of sleep (Appendix 10). Positive impact on patients' QOL can improve their personal and social parts of life and improve their health outcomes (Flanagan et al, 2017). The major limitations of the case reports are the absence of the control group, risk of information misinterpretation, and non-systematized causality assessment. Case report studies cannot be generalized for the population but have a major advantage in providing an in-depth understanding of the patients' disease anamnesis and the outcomes of MC use in specific RDs (Ranganathan and Aggarwal, 2018).

In RDs research, medical surveys or questionnaires is a beneficial tool that allows access to larger cohort of patients, which is particularly important in this patient population. Some ultra-rare diseases can be prevalent in one in half a million, or below that.[19] Medical surveys require less time and resources to conduct and gather a larger amount of information. Surveys included in the research were distributed either online, or in a health centre. Yet, the number of respondents included in the studies was less than 100 patients, making it less significant statistically. The disadvantage of this type of research is less accurate data, as the outcomes are based on subjective opinion. Survey questions are answered by patients or their caregivers, which also may result in inaccuracies in response data due to recall bias. Another limitation of this type of study is the absence of information on precise MC formulation and dosing regimen. The surveys included in the

research questioned the use of MC in RD patients in a general context, and the dosing regimen and level of compliance to treatment was commonly unknown. To complete a successful survey study, questionnaires should be well-designed, validated, and comprise structured questions so that it is easy to use by respondents if they are willing to answer (Heale and Twycross, 2017).

Pre-clinical studies were commonly identified in the literature search. This type of studies provides essential information on the safety and efficacy of a drug before the next stage of clinical trials, performed on humans. Different animal models were used (including fish) though mice were most frequently used (6 out of 7 included studies). Since its genetic profile is 98% similar to humans, mice can be genetically manipulated to mimic a human disease, including RDs (Jones et al, 2013). Pre-clinical studies can provide extensive information on pharmacodynamics, pharmacokinetics and toxicity of certain drug formulation used in RD patients' population. Pre-clinical studies are cost-effective and more time-efficient than clinical trials. Animal model studies should be performed only after exhaustive information is derived from in-vitro models and fit-for-purpose model is ensured (Shegokar, 2020).

A small number of clinical trials in RD patients' population was observed. Only two clinical studies were included in the current review. The performance of clinical trials on RD patients possesses many limitations, including the ethical considerations and small number of possibly enrolled patients with a particular RD diagnosis (Lim, 2019). Clinical trials were performed on the same indication of treatment-resistant epilepsy but using different methods. One study was an open-label prospective trial, whereas the second one was a double-blind, placebo-controlled randomized clinical trial. The presented results

from both clinical trials showed similarly beneficial improvement in symptoms – around half of patients had a reduction in seizure frequency. The cross-clinical study comparison should be very careful, as each study may comprise different baseline characteristics of patients, duration of the intervention, and dose of CBM (Vandamme, 2014).

More than half of the included studies were review studies, which mainly discussed the use of commercially available product ("Sativex", CBD) use in indication of treatment-resistant seizures, which is the only currently approved indication for CBD. CBD was the only CBM included in the research and the oral formulation was used because the target population included paediatric patients. Conduction of studies involving the use of non-psychoactive substances, such as CBD, is less burdensome to perform because of less stringent regulations and ethical considerations. Qualitative review studies are focused on the larger target population, follow a stronger conceptual framework and use a systematic approach, which brings the higher-level of evidence to existing knowledge on MC use in RDs (Snyder, 2019).

Overall, there is a limited number of articles in the literature which discuss MC for RDs. Nevertheless, the current research showed that MC is used in certain RDs.

4.2 Healthcare professionals' and Rare Disease patients' considerations and concerns on the use of Medicinal Cannabis

The results of the two questionnaires for HCPs and RD patients showed similarities. Both questionnaires showed common symptoms experienced by RD patients, which are pain, mostly chronic neuropathic pain, muscle spasticity and anxiety. These results correlate with a similar study by Mueller et al, where symptoms of the patient cohort were presented; the most common were - general weakness and fatigue, pain, and muscle spasticity. Type of pain also correlate in both studies and is usually headache, pain in joints, full body pain and muscle pain (Mueller et al, 2016). Although patients with RDs can experience specific symptoms that differ to a great extent in each individual patient, there are often similar physical and psychological symptoms of RDs.

HCPs and patients share the positive opinion on the possible use of MC for the symptomatic treatment of the disease, for pain, anxiety and muscle spasticity.

The concerns with regards to the side-effects of MC were common in HCPs and RD patients' groups. These side-effects – confusion, reduced memory or concentration and possible mild hallucinations, are associated with the use of MC but are not very common. The perception of HCPs and RD patients on MC use were similar to a major extent, but require further research, when MC is more extensively used in medical practice.

4.2.1 Healthcare professionals' perspective on the use of MC

HCPs who participated in the research were of different specialities, mostly community pharmacists and GPs. HCPs of these specialities usually approach a broader number of patients with multiple diverse diagnoses. Respondents in this study were encountering 2-4 RD patients a year on average, and often with unique diagnostic presentations.

The results of the questionnaires to HCPs confirmed that there were multiple issues to RD patients' treatment. The most common issue reported in this study was the difficulty of establishing a correct medical condition diagnosis, which correlates with literature data. In the European Commission published article, it was reported that: 'On average it takes five years for a patient to get a diagnosis' and in many cases diagnosis remains unestablished [21]. The study highlights the concern of HCPs on the absence of appropriate medication for RD patients' treatment. Despite the remarkable progress which was made in research and medicines development for certain RDs, the number of unique drugs granted ODDs by both the FDA and the European Medicines Agency (EMA) declined over the last years, with a slight increase in 2020 [22]. Another considerable issue to RD patient treatment is limited drug accessibility. Medicines granted ODD may still be not accessible to patients due to multiple reasons, for example, the Clinical and Economic assessment of direct cost savings performed by regulatory bodies, where conventional treatments usually result in greater savings then orphan medications. On average, only between 30 and 60% of orphan medicines are reimbursed in EU countries, which is another limiting factor for the drug access (Field, 2010; Jagadeesan and Wirtz, 2021). HCPs were concerned about the side effects of currently used medicines for RD patients, noting that pain and anxiety management medications, are known to be associated with side-effects.

[21] D'Alession. The long journey to a rare disease diagnosis. Horizon. [Cited 2022 May 19]. Can be accessed from URL: https://ec.europa.eu/research-and-innovation/en/horizon-magazine/long-journey-rare-disease-diagnosis

[22] Global Data Healthcare. Orphan drugs face uphill battle in 2020. [Cited 2022 May 22]. Can be accessed from URL: https://www.pharmaceutical-technology.com/comment/orphan-drugs-2020/

Less than half of the respondents had used MC in practice. Nevertheless, the majority (36 of 59) agreed or strongly agreed they were considering MC in their practice for RD patients, independent of their area of professional experience and duration of professional practice. The main symptoms where this would apply were – pain, muscle spasticity, anxiety, and sleep disorder. The study results are closely similar to results of a survey conducted among HCPs in the USA, where MC was legalized in 29 states at that time. The study by Martins-Welch et al, showed that HCPs strongly supported the use of MC, and most commonly in patients with chronic conditions – cancer (83%), chronic pain (68%), spinal cord injury with spasticity (50%), MS (46%), epilepsy (42%), neuropathy (42%) and Parkinson's disease (41%). In that study most HCPs (77%) believed that MC had the potential to reduce overall opioid use. This was found to be statistically more common among HCPs of younger age (Martins-Welch et al, 2017). Another study by Weisman and Rodriguez in 2021 conducted a systematic review on HCPs' and medical students' perceptions of MC. The study authors evaluated 21 studies (including 8016 participants) and made a conclusion that in the last decades, with the raising interest in MC therapeutic properties, the support of MC use in practice had significantly increased (Weisman and Rodriguez, 2021).

Results of the current study showed that HCPs has a low level of confidence about the use of MC in their practice and reported several associated concerns. HCPs were concerned about MC related side-effects, such as confusion, addiction and drowsiness. In the open-ended part of the questionnaire, HCPs expressed concerns about the lack of knowledge on the safe use of MC and absence of previous experience with its use in RDs. It was reported that physicians are generally unaware of the therapeutic effects of MC, including both positive and negative effects (Philpot et al, 2019). Similar to the current

study results, Weisman and Rodriguez reported that respondents express a strong desire for additional information about MC (Weisman and Rodriguez, 2021).

The research shows that HCPs are facing issues with initiating the MC treatment, given the associated complex bureaucratic procedures. The legal framework must ensure safe use of medicines, but also be clear and concise in order to bypass any complexities that prevent HCPs from prescribing the MC to patients who require it.

The results of this study show that HCP' confidence with the use of MC in RD patients correlates with the years of professional practice. HCPs with longer years of professional practice were less confident in the use of MC ($p<0.05$). HCPs confidence with the use of MC did not correlate with age group, gender or area of expertise. A systematic literature review performed in 2021 by Ronne et al, which included 21 articles from five different countries, found that physicians experienced in prescribing MC were more confident of its advantages and less concerned about adverse consequences than physicians with no experience in MC use (Ronne et al, 2021).

The current study found that HCPs were unwilling to reply to questions regarding MC use, as did the Ronne et al, study, where one-half of HCPs were not willing to answer MC-related questions. However, the majority of HCPs were willing to learn more about MC (Ronne et al, 2021). This might foresee that HCPs will potentially have more interest and involvement in the future studies on MC when the awareness of the use of MC increases.

HCPs should be educated on MC clinical applications, safe use and potential side effects. HCPs serve as a source of trustful information for patients, which plays a crucial role in removing social stigma and facilitating patient access to MC. In the examples of other

countries where MC has been available for decades, such as New Zealand, the national programs and public campaigns have been developed to guide HCPs and patients about MC prescribing, funding and regulations. Educational programs about MC should be developed locally, that would comprise evidence-based information about MC - information on cannabis products available on the market, indications and safety considerations. Additionally, an online application and medical prescription system can improve accessibility to treatment. Healthcare professionals should be aware of the dangers that low-quality data poses and navigate parents or caregivers about the safe use of MC in therapy (Philpot et al, 2019).

4.2.2 Rare disease patients' perspective on the use of MC

Research showed that there were only 3 RDs that were common among the participants. The majority of included RD patient cases were unique, yet experienced certain common symptoms, such as anxiety, pain, and muscle spasticity. It is known that one symptom can be a cause of another, for example patients with chronic pain (including muscle tension, body soreness) are commonly experiencing anxiety disorders [23], as noradrenaline and serotonin involved in the pathophysiology of depression also coincide with the anatomical 'descending inhibition of pain perception' (Singer et al, 2020). The pain intensity experienced by RD patients was - 6 (distressing) on a scale from 1 to 10. Also, the severity of anxiety reported by RD patients was significant - three on a scale of one to five. RD patients reported encountering stress and anxiety as often as pain (62.5%), whereas HCPs considered this symptom was encountered by RD patients less frequently (48.6%).

[23] Anxiety & Depression Association of America (ADAA). Chronic pain. [Cited 2022 Apr 23]. Can be accessed from URL: https://adaa.org/understanding-anxiety/related-illnesses/other-related-conditions/chronic-pain

The importance of anxiety management in RD patients should not be underestimated. It is known that chronic stress and anxiety can lead to the development of many other stress-related symptoms (Woo, 2010). RD patients reported experiencing stress-related symptoms, such as difficulties in concentration and memory, anxious mood, gastro-intestinal symptoms, weakness and/or dizziness, and insomnia. Anxiety in RD patients may be caused by various underlying reasons including chronic symptoms and limited social support, which can lead to reduced QoL.

Although the patients reported to have RDs, which are usually of childhood-onset, the majority of RD patients who participated in the research were adults. Adult RD patients probably experience chronic RD symptoms throughout their lifetime.

The results of the study indicate that RD patients are facing issues with regards their RD treatment, including side-effects associated with the use of prescribed medicines (such as fatigue, vertigo, vomiting and constipation) whilst experiencing symptoms such as pain, stress and anxiety, muscle spasticity, and sleep disorder, irrespective of the use of established therapy.

RD patients who participated in the study consented to the use of MC to relieve the symptoms of their disease. The symptoms for which patients choose to use MC were similar to the results of systematic review and meta-analysis by Kosiba et al in 2019, and included pain, anxiety, and depressive mood (Kosiba et al, 2019). One hundred and fifty-seven patients participated in a survey study by Rosenthal et al. in 2021 which reported similar results. The most common conditions for which MC was used were pain, muscle spasms, anxiety, depression, and insomnia. Many of these symptoms were also reported

to be almost completely relieved in patients who received MC. Additionally, the majority of the patients reported a reduction in or full cessation of their use of other medications or narcotic drugs (Rosenthal and Pipitone, 2021). A study by Zeng at al in 2020 reported that lowering the use of prescription medications was a main driver factor behind the use of MC in most patients, and concerns of addiction, losing control, or mood alteration were disincentives (Zeng, 2021).

The results obtained from the questionnaires of the present study, show that RD patients have little concern about the cost of MC treatment. The cost of orphan medicines is usually notably higher per treatment course, compared to conventional medicines. Orphan medications have a median cost per patient that is 5.5 times higher than non-orphan drugs. Developing a drug intended to treat a RD is often considered as non-profitable for pharmaceutical companies (Villa et al, 2022). In 2017, the median annual cost for an orphan drug was approximately $46,800 in the USA (Ellis, 2019).

Few RD patients were concerned about the social stigma related to MC. The negative stigma associated with MC use which exists also due to a lack of knowledge about MC, creates a barrier to care should be addressed by implementing effective educational programs. The role of HCPs (mostly GPs and pharmacists) is of a great importance, in terms of educating patients about MC use. A pretest-posttest study by Clobes in 2022 evaluated the impact of educational lectures about MC on eradicating historical and contemporary stigma. The study authors came to a conclusion that it was an successful intervention for reducing the stigma associated with MC (Clobes, 2022).

Only few RD patients had experience of MC treatment. Nevertheless, the majority of RD patients considered the use of MC to treat their condition or relieve the symptoms of the disease. RD patients stated that MC was never recommended to them by an HCP.

Most RD patients had no concerns about MC related side effects. This was similar results shown in a study by Zeng et al in 2021, where it was concluded that many patients valued the effectiveness of MC for symptom management even when expecting experiencing adverse events such as reduction in concentration, impaired memory or fatigue (Zeng et al, 2021)**.**

There was no statistically significant difference in patients concerns on MC use between different age groups, gender, or presented symptoms in this study. More rigorous research which involve bigger patient cohort is required to establish statistically significant correlations.

4.3 Study limitations

The literature review was limited by inclusion criteria for the publications - year of publication and the language of publication (English). Search keywords used were general ("diseases, rare" OR "disease, rare") and no names of specific RDs were used, which could limit the number of publications included in the review.

Studies included in the LR were not accessed for research bias. Some articles were not descriptive enough, for example review studies did not provide complete information on the dose of administration or provided limited information on therapy side-effects.

The tool used in the second part of the study, the questionnaires to HCPs and RD patients, had limitations. The information was restricted to questions asked to HCP or RD patients. HCPs and RD patients were not always willing to participate due to lack of time, lack of motivation, insufficient knowledge on the topic. Some questionnaires were not fully completed. A number of items in the questionnaires which were distributed online, remained unanswered (respondents were able to skip the question, or stop their participation). This resulted in a difference in the number of responses in each section of the questionnaire. The majority of respondents were pharmacists. Community pharmacy practice does not allow same evaluation of patients' symptoms as clinical practice. The scales of the symptoms presented in RD patients were not all accessible in the literature and were adapted from other tools (e.g. Likert scale), to perform symptom evaluation.

4.4 Recommendations for future research

Future studies should focus on establishing a clinical rationale for MC use in RD patients, including substantial patient cohorts and a longer duration of follow-up. Cannabis based medicines with different cannabinoid profiles should be clinically investigated, establishing safe and efficacious MC use for different indications.

To better understand HCPs' and patients' perceptions on MC, the research must be performed among respondents with experience in MC usage.

It is essential to assess clinical guidelines for specific RD to determine the rationale of MC use as an alternative treatment option and propose adequate recommendations.

It is important to access policies and regulations associated with the MC to improve its access to patients with rare conditions.

It is recommended to conduct pharmacoeconomic evaluations of MC use in RDs, including possible reimbursement opportunities through government medical assistance programs.

A proactive approach to removing social stigma as a barrier to care is recommended. It is suggested to evaluate the impact of various educational programs, designed to raise the level of knowledge on safe and efficacious MC use.

4.5 Conclusions

The study is first that discusses the use of Medicinal Cannabis in the population of patients with Rare Diseases. Rare Disease patients face multiple challenges to their therapy, ranging from diagnosis establishment to medicines access for optimal disease control. Most RD patients' symptoms are chronic and, in some cases, persist regardless of the therapy used. RD patients are lacking solutions for effective relief of symptoms of their disease.

The study helps to identify the potential of MC use in RD patients supporting it by literature evidence and attenuating HCPs and RD patient experiences. The research suggests that MC can be used in RD that are associated with chronic symptoms, such as pain, muscle spasticity, seizures and anxiety. In lack of efficacious treatment options for RD patients, MC should be considered an alternative therapy for symptom relief.

Education and awareness programmes, and support of the development of new effective MC treatments by establishing optimal regulatory and policy solutions should be provided to help overcome challenges related to treatment with MC.

REFERENCES

Achenbach J, Thiels C, Lücke T, Saft C. Clinical Manifestation of Juvenile and Pediatric HD Patients: A Retrospective Case Series. Brain sciences. 2020;10(6):340.

An D, Peigneur S, Hendrickx LA, Tytgat J.Targeting cannabinoid receptors:current status and prospects of natural products.International Journal of Molecular Sciences. 2020;21(14):5064.

Anekar AA, Cascella M. WHO Analgesic Ladder. StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.

Aran A, Cayam-Rand D. Medical cannabis in children. Rambam Maimonides Medical Journal. 2020;11(1): e0003.

Aso E, Andrés-Benito P, Grau-Escolano J, Caltana L, Brusco A, Sanz P, et al. Cannabidiol-Enriched Extract Reduced the Cognitive Impairment but Not the Epileptic Seizures in a Lafora Disease Animal Model. Cannabis and cannabinoid research. 2020;5(2):150-63.

Atakan Z. Cannabis, a complex plant: different compounds and different effects on individuals. Therapeutic advances in psychopharmacology. 2012;2(6):241-54.

Auvin S, Damera V, Martin M, Holland R, Simontacchi K, Saich A. The impact of seizure frequency on quality of life in patients with Lennox-Gastaut syndrome or Dravet syndrome. Epilepsy & Behavior. 2021;123:108239.

Baratta F, Simiele M, Pignata I, Ravetto Enri L, D'Avolio A, Torta R, et al. Cannabis-based oral formulations for medical purposes: preparation, quality and stability. Pharmaceuticals. 2021;14(2):171.

Baron EP. Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been. Headache. 2015;55(6):885-916.

Baswan SM, Klosner AE, Glynn K, Rajgopal A, Malik K, Yim S, et al. Therapeutic Potential of Cannabidiol (CBD) for Skin Health and Disorders. Clinical Cosmetic and Investigational Dermatology. 2020;13:927-42.

Black N, Stockings E, Campbell G, Tran LT, Zagic D, Hall WD, et al. Cannabinoids for the treatment of mental disorders and symptoms of mental disorders: a systematic review and meta-analysis. Lancet Psychiatry. 2019; 6(12):995-1010.

Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology. 2006;45(1):50-2.

Blessing EM, Steenkamp MM, Manzanares J, Marmar CR. Cannabidiol as a potential treatment for anxiety disorders. Neurotherapeutics. 2015;12(4):825-36.

Boutron I, Hoffmann T, Mulrow C, Shamseer L, Tetzlaff J, Akl E, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.

Bowling A. Research Methods in Health. Fourth Edition ed. England: Open University Press; 2014.

Bridgeman MB, Abazia DT. Medicinal Cannabis: History, Pharmacology, And Implications for the Acute Care Setting. Pharmacy and Therapeutics. 2017;42(3):180-8.

Bura SA, Almada RC, Lutz B, Marsicano G, Wotjak CT. Role of Endocannabinoids in Synaptic Plasticity and Memory. Group Endocannabinoids and Neuroadaptation. France. Elsevier Inc. 2017.

Busse JW, Vankrunkelsven P, Zeng L, Heen AF, Merglen A, Campbell F, et al. Medical cannabis or cannabinoids for chronic pain: a clinical practice guideline. BMJ. 2021;374:n2040.

Campbell CT, Phillips MS, Manasco K. Cannabinoids in pediatrics. The Journal of Pediatric Pharmacology and Therapeutics. 2017;22(3):176-85.

Carlson CL. Effectiveness of the World Health Organization cancer pain relief guidelines: An integrative review. Journal of Pain Research. 2016;9:515-34.

Chiu V, Leung J, Hall W, Stjepanović D, Degenhardt L. Public health impacts to date of the legalization of medical and recreational cannabis use in the USA. Neuropharmacolo gy. 2021;193:108610.

Christenson RH, Snyder SR, Shaw CS, Derzon JH, Black RS, Mass D, et al. Laboratory medicine best practices: systematic evidence review and evaluation methods for quality improvement. Clinical Chemistry. 2011;57(6):816-25.

Clobes Ta P, M Gagnon, C Klaiman. The impact of education on attitudes toward medical cannabis. PEC Innovation. 2022;1:100009.

Collin C, Davies P, Mutiboko IK, Ratcliffe S, Sativex Spasticity in MS Study Group. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. European journal of neurology. 2007;14(3):290-6.

Corey-Bloom J, Wolfson T, Gamst A, Jin S, Marcotte TD, Bentley H, et al. Smoked cannabis for spasticity in multiple sclerosis: a randomized, placebo-controlled trial. The Canadian Medical Association Journal. 2012;184(10):1143-50.

Costa B, Giagnoni G, Franke C, Trovato AE, Colleoni M. Vanilloid TRPV1 receptor mediates the antihyperalgesic effect of the nonpsychoactive cannabinoid, cannabidiol, in a rat model of acute inflammation. British Journal of Pharmacology. 2004;143(2):247-50.

Crocq MA. History of cannabis and the endocannabinoid system. Dialogues in clinical neuroscience. 2022;3:223-228.

Crow RA, Hart KA, McDermott MP, Tawil R, Martens WB, Herr BE. A checklist for clinical trials in rare disease: obstacles and anticipatory actions-lessons learned from the FOR-DMD trial. Trials. 2018;19(1):291.

Davey HM, Barratt AL, Butow PN, Deeks JJ. A one-item question with a Likert or Visual Analog Scale adequately measured current anxiety. Journal of Clinical Epidemiology. 2007;60(4):356-60.

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.

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.

Donnelly J, Young M, Marshall B, Hecht ML, Saldutti E. Public health implications of cannabis legalization: an exploration of adolescent use and evidence-based interventions. International journal of environmental research and public health. 2022;19(6):3336.

Du Q, Liao Q, Chen C, Yang X, Xie R, Xu J. The role of transient receptor potential vanilloid 1 in common diseases of the digestive tract and the cardiovascular and respiratory system. Frontiers in Physiology. 2019:1064.

Eljaschewitsch E, Witting A, Mawrin C, Lee T, Schmidt PM, Wolf S, Hoertnagl H, Raine CS, Schneider-Stock R, Nitsch R, Ullrich O. The endocannabinoid anandamide protects neurons during CNS inflammation by induction of MKP-1 in microglial cells. Neuron. 2006;49(1):67-79.

Fattorusso A, Matricardi S, Mencaroni E, Dell'Isola GB, Di Cara G, Striano P, et al. The Pharmacoresistant Epilepsy: An Overview on Existant and New Emerging Therapies. Frontiers in Neurology. 2021;12:674483.

Ferber SG, Namdar D, Hen-Shoval D, Eger G, Koltai H, Shoval G, et al. The “entourage effect”: terpenes coupled with cannabinoids for the treatment of mood disorders and anxiety disorders. Current neuropharmacology. 2020;18(2):87-96.

Field MJ, Boat TF. Profile of rare diseases. Rare Diseases and Orphan Products: Accelerating Research and Development: National Academies Press (US); 2010.

Flanagan S, Damery S, Combes G. The effectiveness of integrated care interventions in improving patient quality of life (QoL) for patients with chronic conditions. An overview of the systematic review evidence. Health and quality of life outcomes. 2017;15(1):1-11.

Gibbard M, Mount D, Rassekh SR, Siden HH. Family attitudes about and experiences with medical cannabis in children with cancer or epilepsy: an exploratory qualitative study. The Canadian Medical Association Journal Open. 2021;9(2):E563-E9.

Goldenberg MM. Multiple sclerosis review. Physical Therapy. 2012;37(3):175-84.

Grotenhermen F. Pharmacokinetics and pharmacodynamics of cannabinoids. Clinical pharmacokinetics. 2003;42(4):327-60.

Hadi MA, McHugh GA, Closs SJ. Impact of Chronic Pain on Patients' Quality of Life: A Comparative Mixed-Methods Study.Journal of Patientient Experience. 2019;6(2):133-41.

Haefeli M, Elfering A. Pain assessment. European Spine Journal. 2006;15(1):S17-S24.

Halpin A, Huckabay LM, Kozuki JL, Forsythe D. Weigh the benefits of using a 0-to-5 nausea scale. Nursing2022. 2010;40(11):18-20.

Hartung B, Kauferstein S, Ritz-Timme S, Daldrup T. Sudden unexpected death under acute influence of cannabis. Forensic Sci Intern. 2014;237:e11-3.

Haugh O, Penman J, Irving AJ, Campbell VA. The Emerging Role of the Cannabinoid Receptor Family in Peripheral and Neuro-immune Interactions. Current Drug Targets. 2016;17(16):1834-40.

Heale R, Twycross A. What is a case study? Evidence based nursing. 2018;21(1):7-8.

Heuyer T, Pavan S, Vicard C. The health and life path of rare disease patients: results of the 2015 French barometer. Patient Related Outcome Measures. 2017; 8:97-110.

Hossain MZ, Hasan GZ, Siddiqui TH. Congenital bladder diverticulum causing acute urinary retention in an infant. Mymensingh Medical Journal. 2012;21(2):360-2.

Hossain MZ, Ando H, Unno S, Kitagawa J. Targeting Peripherally Restricted Cannabinoid Receptor 1, Cannabinoid Receptor 2, and Endocannabinoid-Degrading Enzymes for the Treatment of Neuropathic Pain Including Neuropathic Orofacial Pain. International Journal of Molecular Sciences. 2020;21(4):1423.

Iannone LF, Arena G, Battaglia D, Bisulli F, Bonanni P, Boni A, et al. Results From an Italian Expanded Access Program on Cannabidiol Treatment in Highly Refractory Dravet Syndrome and Lennox-Gastaut Syndrome. Frontiers in Neurology. 2021;12:673135.

Johal H, Devji T, Chang Y, Simone J, Vannabouathong C, Bhandari M. Cannabinoids in Chronic Non-Cancer Pain: A Systematic Review and Meta-Analysis. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders. 2020;13:11.

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):167-79.

Jones TL, Baxter MA, Khanduja V. A quick guide to survey research. Annals of Royal College of Surgeons of England. 2013;95(1):5-7.

Kachru R, Perry-Lunardo C, Thompson LA. CBD Use in Children—Miracle, Myth, or Mystery? The Journal of the American Medical Association, pediatrics. 2021;175(6):652.

Karch SB. Cannabis and cardiotoxicity. Forensic science, medicine, and pathology. 2006;2(1):13-8.

Karila L, Roux P, Rolland B, Benyamina A, Reynaud M, Aubin H-J, et al. Acute and long-term effects of cannabis use: a review. Current pharmaceutical design. 2014;20(25):4112-8.

Katz N. The impact of pain management on quality of life. Journal of pain and symptom management. 2002;24(1):S38-S47.

Knani I, Earley BJ, Udi S, Nemirovski A, Hadar R, Gammal A, et al. Targeting the endocannabinoid/CB1 receptor system for treating obesity in Prader-Willi syndrome. Molecular Metabolism. 2016;5(12):1187-99.

Kosiba JD, Maisto SA, Ditre JW. Patient-reported use of medical cannabis for pain, anxiety, and depression symptoms: Systematic review and meta-analysis. Social Science & Medicine. 2019;233:181-92.

Koturbash I, MacKay D. Cannabidiol and Other Cannabinoids: From Toxicology and Pharmacology to the Development of a Regulatory Pathway. The Journal of Dietary Supplements. 2020;17(5):487-92.

Kuhlen M, Hoell JI, Gagnon G, Balzer S, Oommen PT, Borkhardt A, et al. Effective treatment of spasticity using dronabinol in pediatric palliative care. European Journal of Paediatric Neurology. 2016;20(6):898-903.

Lim F. Interpreting comparisons between clinical trials. ASAIO Journal. 2019;65(7):E80.

Lipscomb CE. Medical Subject Headings (MeSH). Bulletin of the Medical Library Association. 2000;88(3):265-6.

Lowe H, Toyang N, Steele B, Bryant J, Ngwa W. The Endocannabinoid System: A Potential Target for the Treatment of Various Diseases. The International Journal of Molecular Sciences. 2021;22(17):9472.

Lynch ME, Watson CPN. The pharmacotherapy of chronic pain: a review. Pain Research & Management. 2006;11(1):11-38.

Ma Y, Xiang Q, Yan C, Liao H, Wang J. Relationship between chronic diseases and depression: the mediating effect of pain. BMC psychiatry. 2021;21(1):1-11.

Mack A. Marijuana and pain. Marijuana as Medicine? The Science Beyond the Controversy. Washington (DC): National Academies Press (US); 2000.

Mandolini G, Lazzaretti M, Pigoni A, Oldani L, Delvecchio G, Brambilla P. Pharmacological properties of cannabidiol in the treatment of psychiatric disorders: a critical overview. Epidemiology and psychiatric sciences. 2018;27(4):327-35.

Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. Current Neuropharmacology. 2006;4(3):239-57.

Maresz K, Carrier EJ, Ponomarev ED, Hillard CJ, Dittel BN. Modulation of the cannabinoid CB2 receptor in microglial cells in response to inflammatory stimuli. Journal of Neurochemistry. 2005;95(2):437-45.

Martins-Welch D NC, Kline M, Modayil S. Health providers' perspectives on medical marijuana use. Journal of Clinical Oncology. 2017;35(31):235.

Mastinu A, Premoli M, Ferrari-Toninelli G, Tambaro S, Maccarinelli G, Memo M, et al. Cannabinoids in health and disease: pharmacological potential in metabolic syndrome and neuroinflammation. Hormone Molecular Biology and Clinical Investigation. 2018;36(2).

Meng H, Dai T, Hanlon JG, Downar J, Alibhai SMH, Clarke H. Cannabis and cannabinoids in cancer pain management. Current Opinion Support Palliative Care. 2020;14(2):87-93.

Millar SA, Stone NL, Yates AS, O'Sullivan SE. A systematic review on the pharmacokinetics of cannabidiol in humans. Frontiers in pharmacology. 2018;9:1365.

Morales P, Isawi I, Reggio PH. Towards a better understanding of the cannabinoid-related orphan receptors GPR3,GPR6,and GPR12.Drug Metabolism Reviews.2018;50(1):74-93.

Morales P, Reggio PH. An Update on Non-CB1, Non-CB2 Cannabinoid Related G-Protein-Coupled Receptors. Cannabis and Cannabinoid Research. 2017;2(1):265-73.

Mücke M, Weier M, Carter C, Copeland J, Degenhardt L, Cuhls H, et al. Systematic review and meta-analysis of cannabinoids in palliative medicine. Journal of cachexia, sarcopenia and muscle. 2018;9(2):220-34.

Mueller T, Jerrentrup A, Bauer MJ, Fritsch HW, Schaefer JR. Characteristics of patients contacting a center for undiagnosed and rare diseases. Orphanet Journal of Rare Diseases. 2016;11(1):81.

Nabbout R, Thiele EA. The role of cannabinoids in epilepsy treatment: a critical review of efficacy results from clinical trials. Epileptic Disorders. 2020;22(S1):23-8.

National Academies of Sciences, Engineering, and Medicine. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research. The National Academies Collection: Reports funded by National Institutes of Health. Washington (DC); National Academies Press (US); 2017.

Newton M, Newton DW. Cannabidiol or CBD Oil: Help, Hope, and Hype for Psychiatric and Neurologic Conditions. Journal of American Psychiatric Nurses Association. 2020;26(5):447-57.

Nicotera AG, Spanò M, Decio A, Valentini G, Saia M, Di Rosa G. Epileptic Phenotype and Cannabidiol Efficacy in a Williams-Beuren Syndrome Patient With Atypical Deletion: A Case Report. Frontiers in Neurology. 2021;12:659543.

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):1122-31.

Nurmikko TJ, Serpell MG, Hoggart B, Toomey PJ, Morlion BJ, Haines D. Sativex successfully treats neuropathic pain characterised by allodynia: A randomised, double-blind, placebo-controlled clinical trial. Pain. 2007;133(1-3):210-20.

O'Donnell B, Meissner H, Gupta V. Dronabinol. StatPearls: Treasure Island (FL): StatPearls Publishing; 2021.

Patzke C, Dai J, Brockmann MM, Sun Z, Fenske P, Rosenmund C, Südhof TC. Cannabinoid receptor activation acutely increases synaptic vesicle numbers by activating synapsins in human synapses. Molecular psychiatry. 2021;26(11):6253-68.

Pérez-Gómez E, Andradas C, Flores JM, Quintanilla M, Paramio JM, Guzmán M, et al. The orphan receptor GPR55 drives skin carcinogenesis and is upregulated in human squamous cell carcinomas. Oncogene. 2013;32(20):2534-42.

Pertwee RG. Handbook of Cannabis. Iversen PL, editor. United Kingdom: Oxford University Press; 2014.

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;20:17.

Porter BE, Jacobson C. Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. Epilepsy & Behavior. 2013;29(3):574-7.

Press CA, Knupp KG, Chapman KE. Parental reporting of response to oral cannabis extracts for treatment of refractory epilepsy. Epilepsy & Behavior. 2015;45:49-52.

Rahn EJ, Hohmann AG. Cannabinoids as pharmacotherapies for neuropathic pain: from the bench to the bedside. Neurotherapeutics. 2009;6(4):713-37.

Ranganathan P, Aggarwal R. Study designs: Part 1 - An overview and classification. Perspectives in Clinical Research. 2018;9(4):184-6.

Rieder MJ, Canadian Paediatric Society, Drug Therapy Hazardous Substances C. Is the medical use of cannabis a therapeutic option for children? Paediatrics & Child Health. 2016;21(1):31-4.

Rodríguez-Cueto C, Hernández-Gálvez M, Hillard CJ, Maciel P, García-García L, Valdeolivas S, et al. Dysregulation of the endocannabinoid signalling system in the cerebellum and brainstem in a transgenic mouse model of spinocerebellar ataxia type-3. Neuroscience. 2016;339:191-209.

Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology. 2005;65(6):812-9.

Ronne ST, Rosenbaek F, Pedersen LB, Waldorff FB, Nielsen JB, Riisgaard H, et al. Physicians' experiences, attitudes, and beliefs towards medical cannabis: a systematic literature review. BMC Family Practice. 2021;22(1):212.

Rosenthal MS, Pipitone RN. Demographics, Perceptions, and Use of Medical Marijuana among Patients in Florida. Medical Cannabis and Cannabinoids. 2021;4:13-20.

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):154-65.

Russo EB. Cannabinoids in the management of difficult to treat pain. Therapeutics and Clinical Risk Management. 2008;4(1):245-59.

Santiago M, Sachdev S, Arnold JC, McGregor IS, Connor M. Absence of Entourage: Terpenoids Commonly Found in Cannabis sativa Do Not Modulate the Functional Activity of Δ(9)-THC at Human CB(1) and CB(2) Receptors. Cannabis and Cannabinoid Research. 2019;4(3):165-76.

Sarris J, Sinclair J, Karamacoska D, Davidson M, Firth J. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry. 2020;20(1):24.

Sartori SB, Singewald N. Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacology & Therapeutics. 2019;204:107402.

Schräder NHB, Gorell ES, Stewart RE, Duipmans JC, Harris N, Perez VA, et al. Cannabinoid use and effects in patients with epidermolysis bullosa: an international cross-sectional survey study. The Orphanet Journal of Rare Diseases. 2021;16(1):377.

Seltzman HH, Shiner C, Hirt EE, Gilliam AF, Thomas BF, Maitra R, et al. Peripherally Selective Cannabinoid 1 Receptor (CB1R) Agonists for the Treatment of Neuropathic Pain. The Journal of Medicinal Chemistry. 2016;59(16):7525-43.

Serra I, Scheldeman C, Bazelot M, Whalley BJ, Dallas ML, de Witte PAM, et al. Cannabidiol modulates phosphorylated rpS6 signalling in a zebrafish model of Tuberous Sclerosis Complex. Behavioural brain research. 2019;363:135-44.

Shourick J, Wack M, Jannot AS. Assessing rare diseases prevalence using literature quantification. The Orphanet Journal of Rare Diseases. 2021;16(1):139.

Simon G, Tóth D, Heckmann V, Kuzma M, Mayer M. Lethal case of myocardial ischemia following overdose of the synthetic cannabinoid ADB-FUBINACA. Legal Medicine. 2022;54:102004.

Singer L, Tokish H, Park F, Campisi C, Milanaik RL. The cannabidiol conundrum: potential benefits and risks of cannabidiol products for children. Current Opinion in Pediatrics. 2020;32(1):198-205.

Sisay S, Pryce G, Jackson SJ, Tanner C, Ross RA, Michael GJ, et al. Genetic background can result in a marked or minimal effect of gene knockout (GPR55 and CB2 receptor) in experimental autoimmune encephalomyelitis models of multiple sclerosis. PLoS One. 2013;8(10):e76907.

Shegokar R. Preclinical testing—Understanding the basics first. Drug Delivery Aspects: Elsevier; 2020:19-32.

Skrabek RQ, Galimova L, Ethans K, Perry D. Nabilone for the Treatment of Pain in Fibromyalgia. Journal of Pain. 2008;9(2):164-73.

Slade A, Isa F, Kyte D, Pankhurst T, Kerecuk L, Ferguson J, et al. Patient reported outcome measures in rare diseases: a narrative review. The Orphanet Journal of Rare Diseases. 2018;13(1):61.

Smith SC, Wagner MS. Clinical endocannabinoid deficiency (CECD) revisited: can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinology Letters. 2014;35(3):198-201.

Snyder H. Literature review as a research methodology: An overview and guidelines. Journal of Business Research. 2019;104:333-9.

Stanciu CN, Brunette MF, Teja N, Budney JB. Evidence for Use of Cannabinoids in Mood Disorders, Anxiety Disorders, and PTSD: A Systematic Review. Psychiatric Services. 2021;72(4):429-36.

Starowicz K, Finn DP. Cannabinoids and pain: Sites and mechanisms of action. Advances in Pharmacology. 2017;80:437-75.

Stasiłowicz A TA, Podolak I, and Cielecka-Piontek J. Cannabis sativa L. as a Natural Drug Meeting the Criteria of a Multitarget Approach to Treatment. International Journal of Molecular Sciences. 2021;22(2):778.

Stella B, Baratta F, Della Pepa C, Arpicco S, Gastaldi D, Dosio F. Cannabinoid Formulations and Delivery Systems: Current and Future Options to Treat Pain. Drugs. 2021;81(13):1513-57.

Stockings E, Campbell G, Hall WD, Nielsen S, Zagic D, Rahman R, et al. Cannabis and cannabinoids for the treatment of people with chronic noncancer pain conditions: A systematic review and meta-analysis of controlled and observational studies. Pain. 2018;159:1932-54.

Stoller JK. The challenge of rare diseases. Chest. 2018;153(6):1309-14.

Svendsen KB, Jensen TS, Bach FW. Does the cannabinoid dronabinol reduce central pain in multiple sclerosis? Randomised double blind placebo controlled crossover trial. BMJ. 2004;329(7460):253-.

Tharumia Jagadeesan C, Wirtz VJ. Geographical accessibility of medicines: a systematic literature review of pharmacy mapping. Journal of Pharmaceutical Policy and Practice. 2021;14(1):28.

Thiele EA, Bebin EM, Bhathal H, Jansen FE, Kotulska K, Lawson JA, et al. Add-on Cannabidiol Treatment for Drug-Resistant Seizures in Tuberous Sclerosis Complex: A Placebo-Controlled Randomized Clinical Trial. JAMA neurology. 2021;78(3):285-92.

Tian N, Boring M, Kobau R, Zack MM, Croft JB. Active Epilepsy and Seizure Control in Adults - United States, 2013 and 2015. The Morbidity and Mortality Weekly Report. 2018;67(15):437-42.

Tiwari J. Navigating through orphan medicinal product regulations in EU and US–Similarities and differences. Regulatory Toxicology and Pharmacology.2015;71(1):63-7.

Turcotte C, Blanchet M-R, Laviolette M, Flamand N. The CB2 receptor and its role as a regulator of inflammation. Cellular and Molecular Life Sciences. 2016;73(23):4449-70.

Turgeman I, Bar-Sela G. Cannabis use in Palliative Oncology: A Review of the Evidence for Popular indications. The Israel Medical Association Journal. 2017;19(2):85-8.

Turner AR, Spurling BC, Agrawal S. Marijuana toxicity. StatPearls. Treasure Island (FL): StatPearls Publishing; 2021.

van den Beuken-van Everdingen MHJ, de Graeff A, Jongen JLM, Dijkstra D, Mostovaya I, Vissers KC. Pharmacological Treatment of Pain in Cancer Patients: The Role of Adjuvant Analgesics, a Systematic Review. Pain Practice. 2017;17:409-19.

Vandamme T. Use of rodents as models of human diseases. Journal of Pharmacy and Bioallied Sciences. 2014;6(1):2-9.

Vanti G, Grifoni L, Bergonzi MC, Antiga E, Montefusc F, Caproni M, et al. Developme nt and optimization of biopharmaceutical properties of a new microemulgel of cannabid iol for locally acting dermatological delivery. International Journal of Pharmaceutics. 2021;607:121036.

Vigli D, Cosentino L, Pellas M, De Filippis B. Chronic Treatment with Cannabidiolic Acid (CBDA) Reduces Thermal Pain Sensitivity in Male Mice and Rescues the Hyperalgesia in a Mouse Model of Rett Syndrome. Neuroscience. 2021;453:113-23.

Villa F, Di Filippo A, Pierantozzi A, Genazzani A, Addis A, Trifiro G, et al. Orphan Drug Prices and Epidemiology of Rare Diseases: A Cross-Sectional Study in Italy in the Years 2014-2019. Front Med (Lausanne). 2022;9:820757.

Vinton AB, Carne R, Hicks RJ, Desmond PM, Kilpatrick C, Kaye AH, et al. The extent of resection of FDG-PET hypometabolism relates to outcome of temporal lobectomy. Brain. 2007;130(2):548-60.

Virgilio E, Vecchio D, Naldi P, Cantello R. Efficacy of Cannabinoids on Spasticity and Chronic Pain in a Patient with Co-occurrence of Multiple Sclerosis and Neurofibromatosis Type 1. European journal of case reports in internal medicine. 2021;8(5):002424.

Wade DT, Makela P, Robson P, House H, Bateman C. Do cannabis-based medicinal extracts have general or specific effects on symptoms in multiple sclerosis? A double-blind, randomized, placebo-controlled study on 160 patients. Multiple Sclerosis Journal. 2004;10(4):434-41.

Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. European Journal of Human Genetics. 2020;28(2):165-73.

Wang L, Hong PJ, May C, Rehman Y, Oparin Y, Hong CJ, et al. Medical cannabis or cannabinoids for chronic non-cancer and cancer related pain: a systematic review and meta-analysis of randomised clinical trials. BMJ. 2021;374.

Wang Y, Mukhopadhyay P, Cao Z, Wang H, Feng D, Haskó G, et al. Cannabidiol attenuates alcohol-induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury. Scientific reports. 2017;7(1):12064.

Ware MA, Beaulieu P. Cannabinoids for the treatment of pain: an update on recent clinical trials. Pain Research & Management. 2005;10:27A-30A.

Ware MA, Wang T, Shapiro S, Robinson A, Ducruet T, Huynh T, et al. Smoked cannabis for chronic neuropathic pain: a randomized controlled trial. Canadian Medical Association Journal. 2010;182(14):E694-701.

Washabau R. Antiemetic Agents. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012; 450-4.

Watson SJ, Benson JA, Jr., Joy JE. Marijuana and medicine: assessing the science base: a summary of the 1999 Institute of Medicine report. Archives Of General Psychiatry. 2000;57(6):547-52.

Weisman JM, Rodríguez M. A systematic review of medical students' and professionals' attitudes and knowledge regarding medical cannabis. Journal of Cannabis Research. 2021;3(1):1-20.

Wilsey B, Marcotte T, Tsodikov A, Millman J, Bentley H, Gouaux B, et al. A Randomized, Placebo-Controlled, Crossover Trial of Cannabis Cigarettes in Neuropathic Pain. Journal of Pain. 2008;9(6):506-21.

Woo AK. Depression and Anxiety in Pain. Reviews in Pain. 2010;4(1):8-12.

Yang G, Cintina I, Pariser A, Oehrlein E, Sullivan J, Kennedy A. The national economic burden of rare disease in the United States in 2019. Orphanet journal of rare diseases. 2022;17(1):1-11.

Yaribeygi H, Panahi Y, Sahraei H, Johnston TP, Sahebkar A. The impact of stress on body function: A review. EXCLI J. 2017;16:1057-72.

Zajicek JP, Hobart JC, Slade A, Barnes D, Mattison PG, MUSEC Research Group. Multiple sclerosis and extract of cannabis: results of the MUSEC trial. Journal of neurology, neurosurgery & psychiatry. 2012;83(11):1125-32.

Zamora B, Maignen F, O'Neill P, Mestre-Ferrandiz J, Garau M. Comparing access to orphan medicinal products in Europe. The Orphanet Journal of Rare Diseases. 2019;14(1):95.

Zemrani B, Lambe C, Goulet O. Cannabinoids Improve Gastrointestinal Symptoms in a Parenteral Nutrition-Dependent Patient With Chronic Intestinal Pseudo-Obstruction. The Journal of Parenteral and Enteral Nutrition. 2021;45(2):427-9.

Zeng L, Wang X, Kithulegoda N, Agterberg S, Shergill Y, Esfahani MA, Heen AF, Agoritsas T, Guyatt GH, Busse JW. Values and preferences towards medical cannabis among people living with chronic pain: a mixed-methods systematic review. BMJ open. 2021;11(9):e050831.

Appendix 1

Questionnaire for Healthcare Professionals

Date:
Respondent No:

CANNABIS FOR MEDICINAL USE

IN PATIENTS WITH RARE DISEASES

Questionnaire for medical practitioners

SECTION A – Demographic information

Please select the relevant.

1. Gender: □ Male

□ Female

□ Prefer not to say

2. Age group (years): □ 20-29

□ 30-38

□ 39-47

□ 48-56

□ 57+

3. Profession:

□ Medical doctor in general practice

□ Pediatrics

□ Internal medicine

□ Dermatology

□ Pathology

□ Physical medicine and rehabilitation

□ Psychiatry

□ Neurology

□ Nurse

□ Pharmacist

□ Physiotherapist

□ Psychotherapist

□ Occupational therapist

□ Speech therapist

□ If other, please specify:

……..

4. Area of practice:

□ Academia

□ Hospital

□ Regulatory

□ Community pharmacy

□ Nursing Home

□ Private Medical Clinic

□ Public Health centre

□ Health policy/reimbursement

□ If other, please specify:

.....

5. Years of practice:

□ 0-2

□ 3-5

□ 6-10

□ 11-15

□ >15

6. How often do you encounter rare disease (RD) patients in your practice? □ Never

□ Once a year

□ 2-4 patients a year

□ 2-4 patients a month

□ Every week

□ If other, please specify:

……

……

7. Which RDs have you encountered?

Please specify:
……
……

SECTION B – Clinical presentation of the RDs

8. Which of the following symptoms were experienced by RD patients, that you encountered in your practice? □ Pain

□ Muscle spasticity

□ Seizures

□ Nausea and/or vomiting

□ Appetite alterations

□ Anxiety

□ Sleep disorder

□ Respiratory disorder

□ Visual disturbance

□ Skin disorder

□ Psychiatric disorder / behavioural changes

□ If other, please specify:

Select all that applies.
……

9. If the patient was in pain, please specify the type of pain experienced

□ Acute pain

□ Chronic nociceptive/inflammatory pain

□ Chronic neuropathic pain

 Malignant pain

 Not applicable

 If other, please specify:
…….

10. If the patient was in pain, what was the duration of pain episode?

 Acute pain (1-7 days)

 Acute lasting pain (8 days – 3 months)

 Persistent chronic pain (>3months)

 Pain caused by activity

 Breakthrough pain (pain attack)

 Sporadic (intermittent /episodic pain)

 Not applicable

11. If the patient had seizures, how often did the patient experience it?

 Daily

 x 1

 x 2

 x 3

 x 4

 more than 4

Weekly

 x 1

 x 2

 x 3

 x 4

 x 5
 more than 5

Monthly

 x 1

 x 2

 x 3

□ x 4

□ x 5

□ more than 5

□ Several times a year

□ x 1

□ x 2

□ x 3

□ x 4

□ x 5

□ more than 5

□ Never, seizures are well-controlled

□ Not applicable

12. If the patient experienced nausea and/or vomiting, how strong were the symptoms?

0	**1**	**2**	**3**	**4**	**5**
No symptoms	Light symptoms Sometimes feeling nausea	Discomfortin g symptoms Frequent nausea	Mild symptoms Feeling strong nausea	Strong symptoms Severe nausea, vomiting	Unbearable symptoms Frequent vomiting

13. How often the patient experienced nausea and/or vomiting?

□ Every day

□ Every week

□ Once a month

□ Several times a year

□ Not relevant

14. If the patient complained of feeling nervous, anxious or altered stress level, how strong were the symptoms?

0	1	2	3	4	5
Feeling calm	Light stress. Feeling worried some days a week	Mild stress. Feeling worried most of the days	Increased emotional and/or physical stress. Feeling worried every day	Severe stress. Feeling anxious most of the day	Extremely anxious

15. Did the patient experience any of these stress-related symptoms?

- ☐ Anxious mood
- ☐ Tension
- ☐ Fears
- ☐ Insomnia
- ☐ Difficulties in concentration and memory
- ☐ Weakness and/or dizziness
- ☐ Depressed mood
- ☐ Cardiovascular symptoms
- ☐ Gastro-intestinal symptoms
- ☐ Genito-urinary symptoms
- ☐ Not relevant
- ☐ If other, please specify:

.....

Section C - Management of symptoms of RD patients

16. What pain management medications are used in your practice for rare disease patients?

Select all that applies.

- ☐ Not applicable
- ☐ Paracetamol
- ☐ NSAIDs
  - ☐ Ibuprofen
  - ☐ Aspirin
  - ☐ Naproxen
  - ☐ Ketoprofen
  - ☐ Diclofenac
  - ☐ Indomethacin
  - ☐ Celecoxib
- ☐ Antidepressants
  - ☐ Tricyclic antidepressants, such as amitriptyline, imipramine, nortriptyline
  - ☐ Selective serotonin/norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, venlafaxine
  - ☐ Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline
- ☐ Anticonvulsants
  - ☐ Gabapentin
  - ☐ Carbamazepine
  - ☐ Phenytoin
  - ☐ Pregabalin
  - ☐ Topiramate
- ☐ Narcotics
  - ☐ Codeine
  - ☐ Fentanyl

- Morphine
- Oxycodone Hydrochloride
- Tramadol

- Codeine + Caffeine + Paracetamol
- Tramadol + Dexketoprofen
- Tramadol + Paracetamol
- If other, please specify:

……..

17. What alternative therapy options used in your practice for <u>pain management</u> in RD patients?
    - Not applicable
    - Acupuncture
    - Aromatherapy
    - Ayurvedic medicine
    - Homeopathy
    - Hypnotherapy
    - Massage
    - None of the above
    - If other, please specify:

……..

18. What medications are used in your practice for <u>muscle spasticity management</u> in rare disease patients?
    - Not applicable
    - Baclofen
    - Dantrolene
    - Riluzole
    - Orphenadrine
    - If other, please specify:

19. What therapeutic options do you use in your practice for <u>anxiety management</u> in rare disease patients?
    - Not applicable
    - Psycholeptics

- Antipsycotics
  - Chlorpromazine
  - Levomepromazine
  - Trifluoperazine
  - Haloperidol
  - Flupentixol
  - Zuclopenthixol
  - Pimozide
  - Clozapine
  - Quetiapine
- Anxiolytics
  - Benzodiazepines
    - Mexazolam
    - Diazepam
    - Chlordiazepoxide
    - Lorazepam
    - Bromazepam
    - Clobazam
    - Alprazolam
  - Buspirone
  - Hydroxyzine
  - Etifoxine
- Antidepressants
  - Tricyclic antidepressants (TCAs), such as amitriptyline, imipramine, nortriptyline, Maprotiline
  - Monoamine oxidase inhibitors (MAOIs), such as isocarboxazid
  - Selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, sertraline
- Herbal medicines
  - Gentian, humulus lupulus, valeriana officinalis
  - Valeriana officinalis
  - Chamomille tea
  - Melatonin
- Aromatherapy

- Physiotherapy
- Psychotherapy (Cognitive Behavioural Therapy)
- Aromatherapy
- Homeopathy
- If other, please specify:

……..

20. What therapeutic options do you use for nausea and/or vomiting management in rare disease patients?
    - Not applicable
    - Propulsives
        - Metoclopramide
        - Domperidone
        - Isopride
    - Antihistamines (eg, cyclizine, promethazine, dimenhydrinate, hydroxyzine)
    - Serotonin (5HT3) antagonists (eg, ondansetron , granisetron, palonosetron)
    - Other antiemetics
        - Aprepitant
        - Hyoscine hydrobromide
        - Dexamethasone
        - Levosulpiride
        - Prochlorperazine maleate
    - Herbal preparations
        - Ginger
        - Chamomile
        - Fennel
        - Peppermint
        - Liquorice
    - If other, please specify:

……

21. What therapeutic options are used in your practice for management of seizures in RD patients?

- Not applicable
- Phenobarbital
- Primidone
- Phenytoin
- Ethosuximide
- Clonazepam
- Carbamazepine
- Oxcarbamazepine
- Valproate Sodium
- Vigabatrin
- Lamotrigin
- Topiramate
- Gabapentin
- Levetiracetam
- Zonisamide
- Pregabalin
- Lacosamide
- If other, please specify:

  ……

Section D – Issues to therapy

22. In your opinion, what are the issues associated with the rare disease (RD) patient symptom management?

Select all that applies.

- No issues
- Diagnosis of the medical condition
- No appropriate medication for RD
- Insufficient symptom relief with the current available therapeutic options
- Drug accessibility issues due to drug shortages

- ☐ Drug accessibility issues due to financial burden caused by the cost of the medicines
- ☐ Drug accessibility issues due to complex import / permission requirements
- ☐ Side-effects associated with use of current medicines
- ☐ Contraindication to medicines
- ☐ Others, *please specify:*

  ……..

23. How easy it is to access the necessary medications for patients with RDs?
    - ☐ Very easy
    - ☐ Somewhat easy
    - ☐ Somewhat hard
    - ☐ Very hard
    - ☐ Almost impossible

Section E - Medicinal Cannabis

24. Do you have experience with the use of medicinal cannabis (MC) in your practice?
    - ☐ Yes
    - ☐ No

    <u>If yes, proceed to question 25, if no, proceed to question 26</u>

25. In your practice, for which indications was MC used?
    - ☐ Chronic Pain:

    a. Neuropathic pain in multiple sclerosis
    b. Neuropathic pain in cancer
    c. Fibromyalgia
    d. Mixed aetiology neuropathies
    e. Chemotherapy induced pain
    f. Pain of not classified aetiology

    - ☐ Muscle spasticity
    - ☐ Anxiety

- Insomnia
- Chemotherapy induced nausea and/or vomiting
- Epilepsy
- Anorexia associated with HIV/AIDS
- Anorexia associated with Cancer If other, please specify:

  …….

26. Do you consider that MC can be effective for treatment and/or prevention of the following symptoms, possibly experienced by patients with RDs?

    Select all that applies.

    - Pain (including neuropathic pain)
    - Muscle spasticity
    - Seizures
    - Nausea and/or vomiting
    - Appetite alterations
    - Anorexia
    - Anxiety
    - Sleep disorder
    - Respiratory disorders
    - Visual disturbances
    - Skin disorders
    - If other, please specify:

      ……..

27. Would you consider the use of MC in your practice for RD patients?

    - Strongly agree
    - Agree
    - Neutral
    - Disagree
    - Strongly disagree

      IF NO, please specify the reasoning:

……..

……..

28. On a scale from 1 to 5, where 1 represents the least and 5 represents the most, how confident are you with the use of MC in RD patients?

1	**2**	**3**	**4**	**5**
Not confident at all	Slightly confident	Somewhat confident	Fairly confident	Completely confident

Please specify the reasoning

……

……

……

29. What side-effects of MC are of your concern?

Select all that applies.

- □ Drowsiness
- □ Feeling tired or lethargic
- □ Confusion
- □ Change in appetite
- □ Mood swings
- □ Reduced level of memory or concentration
- □ Experience of mild hallucinations
- □ Anxiety or paranoia
- □ Addiction to MC
- □ Other

……

30. On a scale from 1 to 5, what is your concern on the MC possible side-effects?

1	**2**	**3**	**4**	**5**
No concern at all	Low concern	Undecided	High concern	Very high concern

Please specify the reasoning

……

……

……

31. Please leave any additional comments on the topic

……

……

……

Appendix 2

Questionnaire for Rare Disease patients

CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES

QUESTIONNAIRE FOR PATIENTS

Demographic information

Please select the relevant

* 1. Gender

- ◯ Male
- ◯ Female
- ◯ Prefer not to say

* 2. Age group (years):

- ◯ 0 - 5
- ◯ 1-5
- ◯ 5 - 11
- ◯ 12-18
- ◯ 20-25
- ◯ 26-30
- ◯ 31-40
- ◯ 41-50
- ◯ 51-65
- ◯ 65-80
- ◯ 80+

* 3. Please state your country of residence:

* 4. Do you smoke?

- ◯ No
- ◯ Yes

* 5. Please state the name of your Rare Disease:

CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES

QUESTIONNAIRE FOR PATIENTS

Presentation of the disease

Select all that applies

* 6. Which symptoms associated with the disease do you experience?

- [ ] Pain
- [ ] Muscle spasticity
- [ ] Seizures
- [ ] Nausea and/or vomiting
- [ ] Appetite alterations
- [ ] Stress and anxiety
- [ ] Sleep disorder
- [ ] Respiratory disorders
- [ ] Visual disturbances
- [ ] Skin disorders
- [ ] Psychiatric disorder / behavioral changes
- [ ] Inflammation
- [ ] Other (please specify)

* 7. If you are in pain, please specify the type of pain:

- ( ) Pain in joint(s)
- ( ) Muscle pain
- ( ) Headache
- ( ) Abdominal pain
- ( ) Other (please specify)
- ( ) Full body pain
- ( ) Localised pain in a single extremity
- ( ) Nerve-related (neuropathic pain)
- ( ) Not relevant

* 8. If you are in pain, please rate how strong is the pain, on a scale from 0 to 10, 0 being no pain and 10 being the worst pain possible

- 0 No pain
- 1 Very mild possible
- 2 Tolerable
- 3 Discomforting
- 4 Mild
- 5 Moderate
- 6 Distressing
- 7 Severe
- 8 Very severe
- 9 Unbear able
- 10 Worst pain possible

* 9. If you are in pain, what is the duration of the pain episode?

- Acute pain (1 - 7 days)
- Acute lasting pain (8 days – 3 months)
- Persistent chronic pain (more than 3 month)
- Pain caused by activity
- Breakthrough pain (unpredictable attack)
- Sporadic (intermittent / episodic pain)
- Not relevant

* 10. If you experience seizures, how often do you experience them?

- 0 Seizure-free, no AEDs
- 1 Seizure -free, need for AEDs unknown
- 2 Seizure -free, needs AEDs
- 3 Non-disabling simple partial seizures
- 4 Non-disabling nocturnal seizures only
- 5 1-3 disabling seizures per year
- 6 4-11 disabling seizures per year
- 7 1-3 disabling seizures per month
- 8 1-6 disabling seizures per week
- 9 1-3 disabling seizures per day
- 10 4-10 disabling seizures per day
- 11 >10 disabling seizures per year
- 12 Status epilepticus
- Not relevant

* 11. If you experience **nausea and/or vomiting**, how strong are the symptoms?

- ◯ **0** No nausea
- ◯ **1** Light symptoms Anticipated nausea, prophylaxis medications may be given
- ◯ **2** Mild symptoms Reported nausea
- ◯ **3** Moderate symptoms Persisting nausea, loss of appetite
- ◯ **4** Great symptoms Ongoing nausea, unable to tolerate food/medications by mouth
- ◯ **5** Severe symptoms Nausea and vomiting

* 12. How often do you experience nausea and/or vomiting?

- ◯ Every day
- ◯ Every week
- ◯ Once a month
- ◯ Several times a year
- ◯ Not relevant

* 13. If you feel **nervous or anxious**, how strong are the symptoms?

- ◯ **1** Not at all anxious
- ◯ **2** A little anxious
- ◯ **3** Moderately anxious
- ◯ **4** Very anxious
- ◯ **5** Extremely anxious

* 14. Do you experience any of these stress-related symptoms?

- ☐ Anxious mood
- ☐ Tension
- ☐ Fears
- ☐ Insomnia
- ☐ Difficulties in concentration and memory
- ☐ Weakness and/or dizziness
- ☐ Depressed mood
- ☐ Cardiovascular symptoms
- ☐ Gastro-intestinal symptoms
- ☐ Genito-urinary symptoms
- ☐ Not relevant
- ☐ Other (please specify)

CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES

QUESTIONNAIRE FOR PATIENTS

Therapy for the Rare Disease

* 15. Are you taking any medications?

- ◡ Yes
- ◡ No

If YES, proceed to question 16, if NO, proceed to question 20.

16. Please state the name of the medicine(s) you are taking for your rare disease:

17. Are you following the treatment plan scheduled by your doctor?

- ◡ Yes, I take medications regularly as prescribed
- ◡ Yes, but I do not take all medications regularly
- ◡ No, I take medications only when needed
- ◡ No, I don't take medications prescribed by my doctor
- ◡ Not relevant

18. If NO, why?

- ◡ Cost of the medicine
- ◡ Potential side-effects
- ◡ Too many medications
- ◡ No need for the medicine (no symptoms)
- ◡ Other (please specify)

* 19. Are you taking any other medications for symptom relief?

- ◡ Yes
- ◡ No

20. If YES in question 19, please state the name of the medicine(s) you are taking

21. If YES in question 19, please select the symptoms for which you are taking these medicines.

- [ ] Pain
- [ ] Muscle spasticity
- [ ] Seizures
- [ ] Nausea or vomiting
- [ ] Appetite alterations
- [ ] Stress and anxiety
- [ ] Other (please specify)
- [ ] Sleep disorder
- [ ] Respiratory disorders
- [ ] Visual disturbances
- [ ] Skin disorders
- [ ] Psychiatric disorder / behavioral changes
- [ ] I don't know

* 22. Are you taking any food supplements or herbal preparations?

- ◯ No
- ◯ Yes

23. If yes in question 22, please specify the name of the medicine(s):

* 24. Do you undergo any other treatment?

- [ ] Physiotherapy
- [ ] Homeopathy
- [ ] Speech therapy
- [ ] Occupational therapy
- [ ] Psychotherapy
- [ ] Other (please specify)
- [ ] Acupuncture
- [ ] Aromatherapy
- [ ] Ayurvedic medicine
- [ ] Relaxation techniques
- [ ] No

CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES

QUESTIONNAIRE FOR PATIENTS

Issues related to therapy

If you do not take any medications, proceed to section D

25. Finding your medicine available at the pharmacy for you is:

- ◯ Easy
- ◯ Easy most of the times
- ◯ Sometimes difficult
- ◯ Difficult
- ◯ Very difficult
- ◯ There is currently no treatment for my condition

26. Do you struggle financially due to the price of medications/treatment?

- ◯ Yes
- ◯ No

27. Do you experience side-effects associated with the use of your medications?

- ◯ Yes
- ◯ No
- ◯ Not sure

28. If yes in question 27, please specify the side-effects you experience:

_____

29. Do you experience symptoms associated with your disease that persist irrespective of the use of the medications? Select all that apply.

- ☐ Pain
- ☐ Muscle spasticity
- ☐ Seizures
- ☐ Nausea or vomiting
- ☐ Appetite alterations
- ☐ Stress and anxiety
- ☐ Sleep disorder
- ☐ Respiratory disorders
- ☐ Visual disturbances
- ☐ Skin disorders
- ☐ Psychiatric disorder / behavioral changes
- ☐ No symptoms
- ☐ Other (please specify)

_____

_____

CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES

QUESTIONNAIRE FOR PATIENTS

Select all that apply

* 30. Have you ever been prescribed Medicinal Cannabis by a medical professional?

- ◡ Yes
- ◡ No

* 31. Do you consider medicinal cannabis may be used for any of these symptoms?

- ☐ Pain
- ☐ Muscle spasticity
- ☐ Seizures
- ☐ Nausea or vomiting
- ☐ Appetite alterations
- ☐ Stress and anxiety
- ☐ Other (please specify)
- ☐ Sleep disorder
- ☐ Respiratory disorders
- ☐ Visual disturbances
- ☐ Skin disorders
- ☐ Psychiatric disorder / behavioral changes

* 32. Would you consider the use of medicinal cannabis to treat your condition or relieve the symptoms of your disease?

- ◡ Yes
- ◡ No
- ◡ Not sure

* 33. If YES in question 28, would you consider taking medicinal cannabis in any of these forms?

- ☐ Oil drops
- ☐ Mouth spray
- ☐ Smoked/vaporised cannabis flowers
- ☐ Other (please specify)
- ☐ Oral capsules
- ☐ Syrup
- ☐ Topical cream

* 34. If NO in question 28, please state why.

- [ ] Cost of the medicinal cannabis
- [ ] Never recommended by medical professional
- [ ] Pressure by social stigma
- [ ] Side-effects
- [ ] It is not effective
- [ ] Difficult to obtain medicinal cannabis for regular use
- [ ] Lack of the experience in medicinal cannabis use
- [ ] Contemporary medications preferred
- [ ] Other (please specify)

* 35. What side-effects of medicinal cannabis are of concern to you?

- [ ] Drowsiness
- [ ] Reduced level of memory or concentration
- [ ] Feeling tired or lethargic
- [ ] Experience of mild hallucinations
- [ ] Confusion
- [ ] Anxiety or paranoia
- [ ] Change in appetite
- [ ] Addiction
- [ ] Mood swings
- [ ] I am not concerned about the side effects associated with the use of medicinal cannabis

36. Please leave any additional comments on the topic

THANK YOU FOR YOUR PARTICIPATION!

Appendix 3

Validation Tool

VALIDATION FORM FOR THE RESEARCH QUESTIONNAIRES:

QUESTIONNAIRE FOR HEALTHCARE PROFESSIONALS AND QUESTIONNAIRE FOR PATIENTS WITH RARE DISEASES

I am currently on the 2nd year of the Doctorate in Pharmacy course at the University of Malta. As part of course requirements I am currently conducting a study titled "CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES" under the supervision of Dr. Janis Vella Szijj and Professor Anthony Serracino Inglott.

The aims of the study are to identify (1) disease related symptoms encountered by rare disease (RD) patients, (2) identify current therapeutic options for the symptom relief, (3) issues encountered by RD patients and (3) the perception on the use of medicinal cannabis in rare disease patients.

Two questionnaires were developed - for healthcare professionals and RD patients. I am asking you to be a part of the panel for face and content validation of these questionnaires by using the attached rating tool.

Thank you for your time.

To the Evaluator:

Occupation: _____

Degree: _____

Number of Years in Practice: _____

Direction:

This tool asks for your evaluation of the questionnaires to be used in the data gathering for the research titled "CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES". You are kindly requested to give your honest assessment using the criteria stated below. Please fill-in a different evaluation form for each questionnaire.

Scale	**Interpretation**
1	Strongly Disagree
2	Disagree
3	Neutral
4	Agree
5	Strongly Agree

Please check the appropriate box for your ratings:

Criteria	**Scale**				
	1	**2**	**3**	**4**	**5**
1. Clarity of questions Text is written in a clear and understandable manner. The vocabulary level, language structure and concept of the questions suit the level of the respondents.					
2. Presentation / Organization of the questions The questionnaire is presented and organized in a logical matter.					
3. Suitability of questions Questions are adequate to address study aims.					
4. Objectivity Questions do not lead the participants to a response. No aspect of the questionnaire suggests bias on the part of the research.					
5. Scale and Evaluation Specific question answer or measure only one behaviour. The scale adopted is appropriate for the items.					
6. The Purpose The questionnaire as a whole fulfils the objective for which it was constructed.					

Remarks:

_____

_____

_____

_____

_____

_____

Appendix 4

The Faculty Research Ethics Committee (FREC) 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: MED-2021-00020

2 March 2022

Ms Jekaterina Parovincaka

Birkirkara Road,
Dion court 7,
STJ 1300 St.Julians, Malta.

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

CANNABIS FOR MEDICINAL USE IN RARE DISEASES

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application.

Professor Anthony Serracino Inglott
Chair
Faculty Research Ethics Committee

Appendix 5

Approval for distribution of the questionnaires among Health Care Professionals in Mater Dei Hospital

Data Protection Clearance Declaration Form

REF: 60/2022

I hereby declare that I will respect the confidentiality and privacy of any personal data or information that I will come across at Mater Dei and will in no circumstance disclose any such information to third parties.

I confirm that information submitted for Data Protection Clearance is correct and that I will abide with conditions issued in same clearance notice.

- **This clearance does not cover ethical approval.**
- **This clearance applies only for your online questionnaire to be conducted at MDH and not at any other institution / department / unit.**
- **This clearance is only valid for your questionnaire to be distributed online and not paper-based.**
- **What was declared during this clearance process is what you will abide to.**
- **Your submitted documentation and declarations must remain unchanged.**
- **You must abide with all the articles of the GDPR (EU) 2016 / 679 throughout the data collection process and thereafter.**
- **You are requested to submit a copy of your findings to this office at the end of your study.**
- **Please present this email to Ms Marika from Customer Care MDH.**

I also declare that I am aware of the provisions of the:

General Data Protection Regulation (2016)
(ref: https://idpc.org.mt/en/Pages/gdpr.aspx),
Computer misuse provisions of the Criminal Code
(ref: http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8574),
and, the Professional Secrecy Act
(ref: http://www.justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8844&l=1)

and that I will abide by all Government and Hospital regulations related to data, information and use of IT Systems and services (ref: http://ictpolicies.gov.mt , http://www.kura.gov.mt).

Full Name: Iekaterina Parovincaka

ID/ Passport: 0246086A

Approval Date from DPO: 23rd February 2022

Approval Date from CEO: 01st March 2022

Data Collection Period (From – To): March 2022 – March 2022

MDH Official Approval Names: Mr J Debono

Name of Study / Audit: Cannabis for Medicinal use in Rare Diseases

Applicant's Signature: _____

Data Protection Approval Form - Jekaterina Parovincaka

Final Audit Report 2022-03-02

Created:	2022-03-02
By:	Data Protection Approval Form (dpaform.mdh@gov.mt)
Status:	Signed
Transaction ID:	CBJCHBCAABAARKTaAKXqQaUI7tXPrkYSaen28xmPtxZ

"Data Protection Approval Form - Jekaterina Parovincaka" History

Document created by Data Protection Approval Form (dpaform.mdh@gov.mt)
2022-03-02 - 8:06:21 AM GMT

Document emailed to Jekaterina Parovincaka (jekaterina.parovincaka.19@um.edu.mt) for signature
2022-03-02 - 8:07:09 AM GMT

Email viewed by Jekaterina Parovincaka (jekaterina.parovincaka.19@um.edu.mt)
2022-03-02 - 12:10:45 PM GMT

Document e-signed by Jekaterina Parovincaka (jekaterina.parovincaka.19@um.edu.mt)
Signature Date: 2022-03-02 - 12:12:18 PM GMT - Time Source: server

Agreement completed.
2022-03-02 - 12:12:18 PM GMT

Adobe Sign

Appendix 6

Tabulated summary of the literature review on Medicinal Cannabis use in Rare Diseases

Case reports					
	Rare Disease	**Case description**	**Cannabinoid used**	**Main outcomes**	**Citation**
1	**Juvenile and/ or pediatric Huntington's disease (HD) cases**	Retrospective cohort (N=32) patients with HD, presenting progressive movement disorders with hypokinetic-rigid aspects and critical illness polyneuropathy. Initially receiving Madopar and memantine and Deep brain stimulation (DBS) without beneficial effect.	Oromucosal cannabinoid spray THC: CBD in 1:1 ratio ("Sativex-Spray")	Addition of cannabinoids led to marked improvement of motor symptoms in patients with severe cases of generalised dystonia.	Achenbach et al, 2020
2	**Neurofibromatosis type 1 (NF1)**	Caucasian man 30 y.o. with NF1. Chronic sensory and motor symptoms (sensory paraesthesia, chronic pain with dysesthesia and progressive development of spasticity particularly in the lower limbs.	Oromucosal cannabinoid spray THC: CBD in 1:1 ratio ("Sativex-Spray")	After a poor response to traditional treatments, a patient with NF1 and MS was successfully treated for chronic neurogenic pain and spasticity. Subjective and objective Improvement in quality of life and walking independence, as well as a reduction in neuropathic pain and dysesthesia (VAS scale)	Virgilio et al, 2021

Case reports					
	Rare Disease	**Case description**	**Cannabinoid used**	**Main outcomes**	**Citation**
3	**Chronic intestinal pseudo-obstruction (CIPO)**	19-year-old female with enteral feeding intolerance. Presenting abdominal pain and receiving partial parenteral nutrition (PN).	Synthetic THC (dronabinol) 2.5 mg twice a day	Successful usage of MC resulting in cessation of subocclusive episodes and a significant cessation of GI complaints (abdominal pain, vomiting), and subjective improvement of QOL in a patient with CIPO, Improvement in appetite and food tolerance. No major adverse events reported. Fatigue reported with increased dose 35mg/week.	Zemrani et al, 2021
4	**Williams–Beuren syndrome (WBS)**	13-year-old female with WBS and pharmacoresistant epilepsy. Antiepileptic drugs (AEDs) on many labels and off labels were prescribed with no clinical effects. Patient present seizures (4 to 5 per day), of varying semiology (focal seizures or flexion–extension spasms), most of which were accompanied by cyanosis, bradycardia, and desaturation.	Oral CBD extract 99% ("Epidiolex") 50 mg twice daily, then titrated up to 200 mg twice daily (20 mg/kg)	Seizure frequency and seizure intensity was significantly reduced (to 1 - 3 seizures/week). Improvement in cerebral activity (EEG) improved posture and gross motor abilities, enriched vocalization and improved social skills. No major adverse events reported.	Nicotera et al, 2021

Case reports					
	Rare Disease	**Case description**	**Cannabinoid used**	**Main outcomes**	**Citation**
5	**Febrile infection-related epilepsy syndrome (FIRES)**	7 children with FIRES and promptly progressing to refractory status epilepticus (RSE), refractory to standard antiseizure drugs.	Oral CBD extract 99% ("Epidiolex"). Initiated in emergency or acute or chronic phase of disease 5/7 subjects titrated to 25 mg/kg/day, 1 stopped at 15 mg/kg/day due to a considerable decrease in seizures. 1 titrated to 20 mg/kg/day.	Improvement in frequency and duration in focal seizures with impaired consciousness, 90% reduction after four weeks (in 6/7 cases) and 65% reduction in 48 weeks (in 6/7 cases). In 1 patient, seizures completely resolved after 2 days. Marked improvements in motor, verbal and cognitive abilities.	Koh et al, 2021 +

Surveys					
	Rare Disease	**Survey type and study population**	**Cannabis product used**	**Main outcomes**	**Citation**
1	**Epidermolysis Bullosa (EB)**	An online international, anonymous, cross-sectional survey. EB patients or caregivers from 5 continents (N=71).	Cannabinoid-based medicines (CBMs, mostly topical or ingested)	Pain and pruritus decreased by 3 points (scale: 0-10; $p < 0.001$ for both). Improvement in overall EB symptoms (95%), pain (94%), pruritus (91%) and wound healing (81%), reduction of concomitant medication use (79%). Most used more than one CBM preparation and route of administration.	Schräder et al, 2021

Surveys					
	Rare Disease	**Survey type and study population**	**Cannabis product used**	**Main outcomes**	**Citation**
2	**Dravet syndrome, Doose syndrome, Lennox-Gastaut syndrome**	Survey of 24 questions presented to a Facebook group. Children with treatment-resistant epilepsy (N=19): Dravet syndrome (N=13), Doose syndrome (N=4), Lennox-Gastaut syndrome (N=1).	CBD-enriched cannabis	16 of 19 reported reduction seizure frequency. Of 16, two had complete seizure freedom, 8 reduction in seizures greater than 80%, and 6 seizure reduction 25-60%. Also, greater alertness, improved mood, and better sleep Drowsiness and exhaustion were among the side effects.	Porter et al, 2013
3	**Dravet syndrome, Lennox-Gastaut syndrome**	A group of paediatric epilepsy patients who received OCE and were tracked in a single tertiary epilepsy centre (N=75): Dravet syndrome (23%), Lennox-Gastaut syndrome (N=88.9%).	Oral cannabis extracts (OCEs)	In 57% improvement in seizure control and in 33% >50% reduction in seizures. Adverse events in 44% of patients: increase in seizures (13%), somnolence or fatigue (12%).	Press et al, 2015

Pre-clinical studies					
	Rare Disease	**Animal model**	**Cannabis product used and intervention**	**Main outcomes**	**Citation**
1	**Lafora disease (LD)**	Malin knockout (KO) mice (homozygous for the EPM2B deletion) as an animal model of LD and the wild-type (WT) littermates. 6-11 animals per group.	Cannabis extract highly enriched in cannabidiol (CBD) 98.5 mg/kg/day, containing 35 mg/kg/day of CBD and 4.8 mg/kg/day of THC, and other minor cannabinoids Chronic treatment. 5 days/week for 2 months from 4 months of age (early symptomatic phase) and 10 months of age (advanced symptomatic phase)	Reduction in cognitive impairment (two-object recognition test, $p<0.01$) and spontaneous locomotor activity (coat hanger test). No reduction in the severity of the epileptic seizures. Cannabinoid receptors alterations suggest that ECS might play a role in LD. When administered to WT mice at the age of four months, there was a significant decline in their memory function.	Aso et al, 2020

Pre-clinical studies					
	Rare Disease	**Animal model**	**Cannabis product used and intervention**	**Main outcomes**	**Citation**
2	**Rett Syndrome (RTT)**	8 month-old MeCP2-308 hemizygous male mice and wild-type (wt) littermates N=83	Cannabidiolic acid (CBDA) 0.2, 2, 20 mg/kg 1 x daily intraperitoneally injections for 14 consecutive days	Reduction in pain sensitivity in wild type mice ($p<0.001$); In low doses rescue the thermal hyperalgesia of a Rett mouse model; No improvement in the motor, anxiety-like and cognitive deficits of Rett mice; no effect on the aberrant neurobiological profile of Rett mouse brains.	Vigli et al, 2021
3	**Systemic sclerosis (SSc); scleroderma**	Murine model of dermal fibrosis induced by bleomycin (six- to eight-week-old female BALB/c mice)	Derivative of the CBD quinol (VCE-004.8), a dual agonist of PPARγ and CB2 receptors (10 and 20 mg/kg intraperitoneal injection)	VCE-004.8 reduced TGF-mediated myofibroblast development and hindered wound-healing capability by downregulating the expression of numerous critical genes related with fibrosis. VCE-004.8 inhibited mast cell degranulation and macrophage infiltration in the skin by reducing dermal thickness, blood vessel collagen build-up, and preventing mast cell degranulation.	Del Río et al, 2016

Pre-clinical studies					
	Rare Disease	**Animal model**	**Cannabis product used and intervention**	**Main outcomes**	**Citation**
4	**Spinocerebellar ataxia type-3 (SCA-3) or Machado-Joseph disease**	Transgenic mouse model of SCA-3	Cannabinoid-based therapy	Study discovered a dysregulation in the endocannabinoid system in the brain structures affected by disease and change of the endocannabinoid signalling system's current state (CB1 and CB2) in cerebellum and brainstem, which suggests that cannabinoid-based therapy can delay the disease progression. *(CB1 receptors increased in the Purkinje cell layer, reductions in anandamide in the brainstem, crease in the FAAH enzyme in*	Rodriguez-Cueto et al, 2016
5	**Prader-Willi syndrome (PWS)**	Obese Magel2-null mice and littermate wild-type controls	Peripherally restricted CB1R antagonist (JD5037, rimonabant) 3 mg/kg/d for 28 days	Reduction of body weight, hyperphagia eversion, and improvement in metabolic parameters related to obese phenotype.	Knani et al, 2016

Pre-clinical studies					
	Rare Disease	**Animal model**	**Cannabis product used and intervention**	**Main outcomes**	**Citation**
6	**Tuberous Sclerosis Complex (TSC)**	Zebra fish, mTOR signalling model	CBD in concentrations 0.3 µM to 125 µM	Effect of CBD on TSC pathology: mTOR signalling disruption causes neurological and neuropsychiatric complications By modulating aberrant mTOR signalling, and selectively modulating levels of phosphorylated rpS6 in the brain CBD produces substantial anxiolytic effects without causing sedation.	Serra et al, 2019
7	**Multiple Sclerosis (MS)**	CB2 and GPR55 gene knockout mouse	Medicinal cannabis	CB1 receptor-mediated effect could induce immunosuppression and influence the immune response in MS	Sisay et al., 2013

Clinical trials					
	Rare Disease	**Study design and study population**	**Cannabis product used**	**Main outcomes**	**Citation**
1	**Dravet syndrome (DS), Lennox–Gastaut (LGS) syndrome**	Open-label prospective trial. 30 sites. Paediatric and adult patients. 12 months of treatment. Effectiveness analysis: N=82 Safety analysis: N=93	CBD 14 mg/kg/day medium (100 mg/ml; Epidyolex) Add-on therapy to ASMs.	Effectiveness: 40.2% had at least a 50% reduction in seizure frequency (plus 1.2% seizure-free) in the 1st 3 months. At 12-month follow-up - 49.0% (and 3.9% seizure-free), 9.8% experienced seizures worsening Safety: most common AEs were somnolence (22.6%) and diarrhea (11.9%). 8 AEs (8.6%) classified as serious (status epilepticus or vomiting)	Iannone et al, 2021

2	**Tuberous Sclerosis Complex (TSC)**	Double-blind, placebo-controlled randomized clinical trial 46 sites. Pediatric and adult patients. 16 weeks of treatment. N=224: CBD25 (n=75); 73 to CBD50 (n=73); and placebo (n=76);	Cannabidiol (25 or 50 mg/kg/day) or matched placebo. (100 mg/ml; Epidyolex Add-on therapy to ASMs	Reduction (%) in the type of seizures was equal in groups: CBD25 (49%), CBD50 (n=48%) and lower in placebo (n=27%). CBD25 associated with fewer AEs than CBD50. The most common AEs in CBD50 group were diarrhea (56%) and somnolence (26%). Elevated liver transaminase levels (both CBD groups 18.9% vs placebo 0%)	Thiele et al, 2021

Appendix 7

List of Rare Diseases Included in the Literature Review

1. Tuberous Sclerosis Complex (TSC)
2. Dravet Syndrome (DS)
3. Lennox-Gastaut Syndrome (LGS)
4. Prader-Willi Syndrome (PWS)
5. Huntington's Disease (Juvenile and Paediatric manifestation, HD)
6. Amyotrophic Lateral Sclerosis (ALS)
7. Febrile Infection-Related Epilepsy Syndrome (FIRES)
8. Williams-Beuren Syndrome (WBS)
9. Neurofibromatosis Type 1 (NF1)
10. Chronic Intestinal Pseudo-Obstruction (CIPO)
11. CDKL5 Deficiency Disorder
12. Rett syndrome (RTT)
13. Multiple Sclerosis (MS)
14. Infantile spasms (West syndrome)
15. Lafora Disease (LD)
16. Scleroderma (Systemic sclerosis, SC)
17. Spinocerebellar ataxia type-3
18. Myoclonic atonic epilepsy (MAE, Doose syndrome)
19. Epidermolysis bullosa (EB)
20. Cystic fibrosis
21. Dermatomyositis
22. Systemic lupus erythematosus (SLE)

Appendix 8

RDs, disease symptoms and cannabis formulation used in the individual studies included in the current literature review

Rare Disease	Symptoms addressed by cannabis treatment	Cannabis formulation used	Citation
Chronic intestinal pseudo-obstruction (CIPO)	GI complaints (abdominal pain, vomiting)	Synthetic THC (dronabinol)	Zamrani et al, 2021
Dravet Syndrome, Lennox-Gastaut Syndrome and Doose syndrome	Pharmaco-resistant seizures	CBD enriched cannabis	Porter et al, 2013
Dravet Syndrome, Lennox-Gastaut Syndrome	Pharmaco-resistant seizures	Oral cannabis extracts (OCEs)	Press et al, 2015
Dravet syndrome (DS), Lennox–Gastaut (LGS) syndrome	Pharmaco-resistant seizures	Oral CBD extract 99% ("Epidiolex")	Iannone et al, 2021
Epidermolysis bullosa (EB)	EB symptoms (pain and pruritus), impact on disease progress	Cannabinoid-based medicines (CBMs)	Schräder et al, 2021
Febrile infection-related epilepsy syndrome (FIRES)	Pharmaco-resistant seizures. improvements in motor, cognitive and verbal abilities	Oral CBD extract 99% ("Epidiolex")	Koh et al, 2021 +
Juvenile and/ or paediatric Huntington's disease (HD)	Motor symptoms, severe generalised dystonia	Oromucosal cannabinoid spray THC: CBD in 1:1 ratio ("Sativex-Spray")	Achenbach et al, 2020
Lafora disease (LD)	Cognitive impairment, Epileptic seizures	CBD enriched extract	Aso et al, 2020

Rare Disease	Symptoms addressed by cannabis treatment	Cannabis formulation used	Citation
Multiple Sclerosis (MS)	Immunosuppression and impact on immune response in MS	Non-psychoactive doses of medicinal cannabis	Sisay et al., 2013
Neurofibromatosis type 1 (NF1)	Neuropathic pain, spasticity, dysesthesia, improvement in QoL	Oromucosal cannabinoid spray THC: CBD in 1:1 ratio ("Sativex-Spray")	Virgilio et al, 2021
Prader-Willi syndrome (PWS)	Obesity treatment	CB1R antagonist (JD5037, rimonabant)	Knani et al, 2016
Rett Syndrome (RTT)	Chronic pain, thermal hyperalgesia, motor symptoms and anxiety-like symptoms and cognitive deficits	Cannabidiolic acid (CBDA)	Vigli et al, 2021
Scleroderma (SSc)	Antifibrotic effects, impact on wound-healing	Synthetic CBD derivative (Quinol, VCE-004.8)	Del Río et al, 2016
Spinocerebellar ataxia type-3 (SCA-3)	Potential effects on disease progression	Cannabinoid-based medicines (CBMs)	Rodriguez-Cueto et al, 2016

Rare Disease	Symptoms addressed by cannabis treatment	Cannabis formulation used	Citation
Tuberous Sclerosis Complex (TSC)	Effect on mTOR signalling associated with neurological and neuropsychiatric complications	CBD	Serra et al, 2019
Tuberous Sclerosis Complex (TSC)	Pharmaco-resistant seizures	Oral CBD extract 99% ("Epidiolex")	Thiele et al, 2021
Williams–Beuren syndrome (WBS)	Pharmaco-resistant seizures	Oral CBD extract 99% ("Epidiolex")	Nicotera et al, 2021

Appendix 9

Rare Diseases, indications for Medicinal Cannabis use and cannabis formulations used in the review studies

Rare disease	Indication	Cannabis formulation used	Citation
Dravet syndrome	Refractory seizures	CBD	Strzelczyk and Schubert-Bast, 2020
Dravet Syndrome, Lennox-Gastaut Syndrome and CDKL5 Deficiency Disorder	Refractory seizures	CBD	Chin et al, 2021
Lennox-Gastaut syndrome, Dravet syndrome and Tuberous sclerosis complex, CDKL5 deficiency disorder, Doose syndrome	Severe epilepsy	CBD	Arzimanoglou et al, 2020
Lennox-Gastaut or Dravet syndrome	Seizures	CBD (Epidiolex), agents targeting TRPV1, GPR55 ENT-1 receptors	Gray and Whalley, 2020
Lennox-Gastaut or Dravet syndrome	Seizures	CBD	Pacher et al, 2020
Lennox-Gastaut or Dravet syndrome	Refractory seizures (in paediatric patients)	CBD	Raucci et al, 2020
Lennox-Gastaut or Dravet syndrome	Refractory seizures (in paediatric patients)	CBD	Singer et al, 2020
Lennox-Gastaut or Dravet syndrome	Refractory seizures (in paediatric patients)	CBD	Specchio et al, 2020
Lennox-Gastaut or Dravet syndrome	Refractory seizures (in paediatric patients)	CBD	Steriade et al, 2020

Rare disease	Indication	Cannabis formulation used	Citation
Lennox-Gastaut syndrome, Dravet syndrome and Tuberous sclerosis complex	Seizures in severe epilepsy	CBD	Johannessen Landmark et al, 2021
Lennox-Gastaut or Dravet syndrome	Refractory Epilepsy (in paediatric patients)	CBD	Zürcher et al, 2021
Multiple Sclerosis (MS)	Difficult to treat pain, spasticity	Cannabinoids	Stasiłowicz et al, 2021
Multiple Sclerosis (MS)	MS associated spasticity and central pain	Cannabinoids	Rice and Cameron, 2018
Multiple Sclerosis (MS)	Difficult to treat pain, spasticity	Cannabinoids	Russo, 2008
Prader-Willi syndrome (PWS)	Obesity in PWS	Agents (JD5037, KAL671, HU-671, OEA, CBD, rimonabant) targeting endocannabinoid and CB1 receptor system	Carias and Wevrick, 2019
Rett syndrome	Epileptic seizures	Cannabinoids, in particular Cannabidivarin (CBDV), cannabidiol (CBD)	Mouro et al, 2019

Rare disease	Indication	Cannabis formulation used	Citation
Rare forms of Alzheimer's, Parkinson's, and Huntington's Diseases e.g., Posterior cortical atrophy (PCA), also called Benson's syndrome Kufor Rakeb syndrome (KRS)	Neurodegenerative processes	Cannabinoids	Pérez-Olives et al, 2021
Systemic sclerosis (SSc), cystic fibrosis, dermato-myositis (DM), systemic lupus erythematosus (SLE)	Suppression of tissue scarring and stimulation of endogenous eicosanoids that resolve chronic inflammation and fibrosis	Ajulemic acid, synthetic, cannabinoid-derived drug	Burstein, 2018
West syndrome	Infantile spasms	CBD	Velíšek and Velíšková, 2020

Appendix 10

Short summaries of the studies included in the literature review on Medicinal Cannabis use in Rare Diseases

Case studies

1. In the study by Achenbach et al, cannabinoids (combination therapy with deep brain stimulation and botulinum toxin injections) were used for the improvement of movement disorders in patients with juvenile and/ or paediatric **Huntington's disease (HD).** It was reported that a patient with paediatric onset of Huntingtons disease, presenting "progressive movement disorders with hypokinetic-rigid aspects" as well as "motoric axonal polyneuropathy" was additionally receiving cannabinoids ("Sativex") which lead to "marked improvement of dystonia" (Achenbach et a,. 2020).

2. A case study by Virgilio et al. 2021, report a successful use of oromucosal cannabinoid spray in **Neurofibromatosis type 1 (NF1),** a "rare autosomal dominant disease" which affects the skin and central nervous system (CNS), and may cause chronic neurogenic pain. A Caucasian man was diagnosed with NF1 at 30 years of age, proven by genetical testing and diagnostic brain and spinal magnetic resonance imaging. At the age of 55 he was first evaluated for multiple sclerosis (MS). Patient experienced chronic sensory and motor symptoms - sensory paraesthesia, chronic pain with dysesthesia and progressive development of spasticity particularly in the lower limbs. Patient was moderately disabled, neuropathic pain was accessed with standard treatments, such as pregabalin, carbamazepine, gabapentin, which resulted with frequent side-effects and inefficient suppression of sensory manifestations in patients. (THC:CBD 1:1) Oromucosal cannabinoid spray was initiated. Patients had "subjective and objective reduction in hypertonia (MAS 6/48), in neuropathic pain and dysesthesia (VAS 2/10), improvement in quality of life and walking

independence". The authors conclude that it can not be excluded that neuropathic pain in this patient was caused primary by MS but the report of successful treatment of chronic neuropathic pain and spasticity in patients with NF1 (Virgilio et al. 2021).

3. A 19-year-old female diagnosed with **chronic intestinal pseudo-obstruction (CIPO)** had significant reduction in gastrointestinal (GI) complaints upon administration of synthetic dronabinol for 15 months. CIPO causes intestinal failure and is associated with challenging treatment. The patient was diagnosed with CIPO in the neonatal period and since her first month of life was started on parenteral nutrition (PN). Since 16 years old, 3 nights a week patient was administered PM with small oral intake. Patient experienced frequent, mild abdominal pain and "2–3 moderate subocclusive episodes per year". She initiated smoked cannabis on her own for the knee pain which led to remarkable improvement in GI symptoms. She was then indicated synthetic THC (dronabinol) 2.5 mg twice a day, for 15 months. Cannabinoid therapy led to improvement of GI symptoms - abdominal pain, distension, and vomiting, cessation of subocclusive episodes and improvement in appetite and food tolerance. No major adverse events, including psychoactive effects were reported. Fatigue reported with increased dose of 35mg/week. The dose reduction from 35 to 25 mg/week reduced fatigue but also a decreased of efficacy of the treatment. Weight fluctuated but improved overall, stools frequency and consistency was unchanged. QOL subjectively improved as patient was able to maintain an oral diet without experiencing any abdominal pain. Authors conclude that cannabinoids could be "considered in cases of

chronic abdominal pain refractory to routine treatment and impacting the QOL, an option before considering intestinal transplant" (Zemrani et al, 2021).

4. **"Williams–Beuren syndrome (WBS)** is a genetic neurodevelopmental disorder characterized by typical facial dysmorphisms, congenital cardiac defects, weakness of connective tissue, and mild-to-moderate intellectual disability (ID). Epilepsy is a rare clinical manifestation in WBS patients. Nicotera et al, 2021, describe a female patient of a 13-year-old with WBS and pharmacoresistant epilepsy. Patient was born preterm, showed facial dysmorphisms, microcephaly, recurrent kidney stones, as well as neonatal seizures at birth. From 10 months of age, she presented infantile spasms, seizures of high variability in intensity and semeiology and severe developmental delay, which suggested a diagnosis of drug-resistant epileptic encephalopathy.

   Patients was receiving antiepileptic drugs (AEDs) (primidone, carbamazepine, diazepam, and levetiracetam) as well as clobazam and pregabalin in maximum daily doses were prescribed without clinical benefit. Patient was started on 99% CBD extract ("Epidiolex") mg x 2 day, then titrated up to 20 mg/kg (200 mg x 2 day). "After 3 months, seizure frequency reduced to one to three attacks/week and characterized by sporadic and brief clusters of flexor-extensor spasms". No episodes of bradycardia, cyanosis, and desaturation were reported. EEG revealed an "improvement in cerebral activity and a mild reduction of EEG abnormalities". Patient showed "better postural and gross motor skills" and enriched vocalization. Patient died unexpectedly due to complicated pneumonia (Nicotera et al. 2021).

5. **Febrile infection-related epilepsy syndrome (FIRES)** is characterised by explosive appearance of seizures and promptly progressing to refractory status epilepticus (RSE), after experiencing a febrile disease. FIRES is a rare epileptic encephalopathy that is observed in otherwise healthy children and young adults. This rare disease is associated with chronic epilepsy, significant neurological disability, and often mortality. Over 90% of patients develop refractory epilepsy. The current case series describe patients with FIRES and refractory epilepsy who had started with CBD ("Epidiolex") in the acute or chronic phase of the disease. All five patients, who initiated CBD treatment in the subacute/chronic phase had improvements in motor, cognitive and verbal abilities and showed marked reduction in seizure frequency. In 6/7 patients four weeks of treatment resulted in 90% improvement in seizure frequency and duration, and in 65% reduction after 48 weeks of treatment. CBD treatment was reported to be very well tolerated (Nabbout and Thiele 2020).

Surveys

1. **Epidermolysis bullosa (EB)** is a group of disorders of genetic origin, associated with fragility in the epithelial lining. EB patients are susceptible to painful repeated blistering and wounding of skin and other tissues even with minor traction or trauma and secondary, to infections and extracutaneous symptoms. "Pain and pruritus have a significant impact on QOL in EB patients". CBMs affects CB1/CB2 ligation and are proved to have therapeutic effects on pain and pruritus. In a survey by Schräder et al in 2021 EB patients from 5 continents (N=71) reported using or having used CBMs and improvement in their disease symptoms – "overall EB symptoms (95%), pain (94%), pruritus (91%) and

wound healing (81%)", as well as reduction of concomitant medication use. The most prevalent CBM preparations used by EB patients are topical (oil/paste), and ingested (smoking, infused or cooked). Most commonly, CBMs contained both THC and CBD (34.7%), CBD-only (20.3%) and THC-only (15.3%). It was reported that patients start using a CBM to relieve EB symptoms (e.g.pain n = 40), and as an alternative treatment option to opiates. The majority (62/71, 87.3%) were still currently using CBMs in their therapy (Schräder et al. 2021).

2. A survey by Porter and Jacobson in 2013 on the use of CBD-enriched cannabis was conducted in children (2 to 16 years old) with refractory epilepsy. Sixteen (84%) of the 19 patients with severe childhood epilepsies (**Lennox-Gastaut syndrome, Dravet syndrome,** idiopathic epilepsy **and Doose syndrome**), had a reduction in seizure frequency, of these, two had complete relief of seizures. Before treatment with CBD-enriched cannabis patients had received on average 12 anti-epileptic drugs (AEDs) (Porter and Jacobson 2013).

3. A retrospective review of children with epilepsy 30 days to 18 years old who received oral cannabis extracts (OCEs), revealed a significant improvement in their seizure control (33% had 50% reduction in seizures) and improvement in other disease-associated symptoms: "behaviour/alertness (33%), improved language (10%), and motor skills (10%). Adverse events (AEs) occurred in 44% of patients including increased seizures (13%) and somnolence/fatigue (12%)". The most response rate was in children with **Lennox–Gastaut syndrome (LGS)** 88.9% and **Dravet syndrome 23%** (Press, Knupp, and Chapman 2015).

Pre-clinical studies

1. **Lafora disease (LD)** is an inherited rare and fatal disease which is presented as rapid progression of cognitive impairment and progressive myoclonus epilepsy. The underlying disease pathophysiology is genetic mutation and only palliative treatment is available. Malin KO mice models exhibit a severe phenotype of the LD which is used as this study. Chronic treatment (for 2 months) with a cannabis extract highly enriched in CBD improved cognitive performance but did not have impact on the severity of the epileptic seizures. Based on the alterations endocannabinoid degradative enzymes, and on the G protein-coupled receptor 55 (GPR55) as well as CB1, CB2 receptors overexpression (In the hippocampus ($p<0.001$) and in the cortex ($p<0.05$)) at different stages of the neurodegenerative process the authors conclude that ECS may contribute in disease pathophysiology (Aso et al. 2020).

2. **Rett syndrome (RTT)** is caused mainly by genetic X-linked mutations, expressed in females. RTT is a neurodevelopmental disorder and epilepsy is presented in up to 80% patients). The cannabidiolic acid (CBDA) was administered intraperitoneally for 14 consecutive days (0.2, 2, 20 mg/kg) which lead to a reduction in pain sensitivity in wild type mice Rett mouse model ($p<0.001$) and rescue of the thermal hyperalgesia. The study outcomes show no improvement in cognitive deficits, motor and anxiety-like symptoms and no impact on the aberrant neurobiological profile (Vigli et al. 2021).

3. **Systemic sclerosis (SSc; scleroderma)** is characterized by "progressive thickening and fibrosis of skin secondary to excessive collagen accumulation, that can be limited to the skin (limited cutaneous SSc) or extended to internal

organs (diffuse cutaneous SSc)". Cannabinoid PPARγ and CB2 receptors have the potential impact in modulation of fibrotic and inflammatory responses. Rio et al studied the effects of VCE-004.8 – a dual agonist of PPARγ and CB2 receptors in bleomycin induced progressive fibrosis with early inflammatory reaction in murine model (Six- to eight-week-old female BALB/c mice). "Administration of VCE-004.8 during the last three weeks of bleomycin injections reduced dermal thickness and accumulation of blood vessels collagen. VCE-004.8 inhibited collagen gen transcription and prevented cell differentiation into myofibroblast and remarkably impaired wound healing". Authors conclude, that CBD quinol (VCE-004.8) may have potential for the treatment of fibrotic diseases, such as SSc (del Río et al. 2016).

4. **Spinocerebellar ataxia type-3 (SCA-3)** is a dominant neurodegenerative disorder also called **Machado-Joseph disease**. Patients present a neurological abnormalities (intracted motor coordination, spasticity and extrapyramidal symptoms such as oculomotor impairment, muscle dystonia and peripheral amyotrophy (muscle atrophy). Patients with SCA-3 lack "an effective treatment to alleviate major symptoms and to modify disease progression". The study reports on the observed dysregulation in the ECS in the brain of SCA-3 mutant mice (increase in CB1 in the Purkinje cell layer, reductions in anandamide andoleoylethanolamide in the brainstem, crease in the FAAH enzyme in the brainstem). Study authors suggest that a pharmacological manipulation on ECS may be a promising treatment option in delaying the SCA-3 disease progression (Rodríguez-Cueto et al. 2016).

5. **Prader–Willi syndrome (PWS)** is a childhood-onset neurogenetic disorder. Patients present complex symptoms - intellectual disability, hypogonadism, obesity, disturbances of thermoregulation and sleep. Endocannabinoid (eCB) system has critical involvement in controlling energy metabolism and body weight. Knani et al in 2016 reported that dysregulation of the ECS may lead to obesity and hyperphagia in individuals with PWS and in *Magel2*-null mice. The first-in-class CB1R antagonist rimonabant is effective in reversing obesity both in animals and humans with PWS, however, because of its neuropsychiatric adverse effects not efficient for clinical implications (Knani et al. 2016).

6. **Tuberous Sclerosis Complex (TSC)** is a genetic rare disease caused by mutations in the TSC1 or TSC2 genes. Most common manifestations of the disease are intractable epilepsy, multiple progressive tumours, and cognitive impairment. Overactivation of mammalian target of rapamycin (mTOR) is evident in the majority of TSC patients and is associated with benign tumours, and neurological and neuropsychiatric complications in 85% of TSH patients. Using a TSC zebrafish model, it has been reported that CBD modulate a suppression of mTOR signalling, which is associated with decrease in seizures and inhibition of tumour cell progression (Goldenberg 2012).

7. **"Multiple sclerosis (MS)** is a chronic immune-mediated neurological disease" which is associated with inflammation and demyelination of the central nervous system. Initially MS patients are presenting sensory disturbances - dysesthesias ("pins and needles", burning), paresthesias (numbness and

tingling), ataxia, bladder disturbances (90% have incontinence), diplopia and vertigo. Patients present with chronic neuropathic pain, and moderate-to-severe spasticity (in 30% of patients) (Serra et al. 2019). Δ9-tetrahydrocannabinol has been reported to control spasticity, associated with nerve damage in MS by regulating aberrant synaptic neurotransmission. There is increasing evidence that the CB1 and CB2 distribution on immune and nerve cells my play a role in disease control. Cannabinoids interfere on the CB1 receptors play role in the immune and neurodegenerative mechanisms of disease and that may control the relapsing of the MS symptoms (Sisay et al. 2013).

Clinical trials

1. The open-label prospective expanded access 12 months program was performed in 30 sites, where 93 patients with highly refractory **Dravet (DS) or Lennox–Gastaut (LGS)** syndromes received purified CBD ("Epidyolex" 100 mg/ml) from 2 and 5 mg/kg per day to 18–25 mg/kg per day. Patients were allowed dose modifications and concomitant use of antiseizure medications (ASMs) as clinically appropriated. ASMs previously failed before CBD treatment was 8 (median). The study efficacy endpoints were the reduction in seizures (≥50 and 100%) compared to baseline. Assessment of AEs and laboratory parameters was performed after 2 weeks; 1, 3, and 6 months. At 3 months follow up 40.2% patients had at least 50% reduction in seizure frequency (and 1.2% seizure-free) and at 12-month follow-up - 49.0% (and 3.9% seizure-free), 9.8% experienced seizures worsening. The cotreatment with clobazam resulted in greater clinical response. 51.6% of patients have experienced at least 1 AE, most common were

somnolence (22.6%), diarrhea (11.9%), elevated liver enzymes (10.7%) and loss of appetite (8.6%), with 8 AEs classified as serious - status epilepticus (9.6%) and vomiting (2.1%). The overall AEs incidence was higher in the <10 mg/kg per day group (Iannone et al. 2021).

2. Double-blind randomized clinical trial by Thiele et al in 2021 included 224 patients with diagnosis of **Tuberous Sclerosis Complex (TSC)** and drug-resistant epilepsy, where patients received CBD (25 or 50 mg/kg/day) or placebo during 16 weeks. Study was conducted internationally at 46 sites. The primary end point, reduction in the type of seizures, was achieved in all groups, equal in CBD25 (49%) and CBD50 (n=48%) groups and lower in placebo (n=27%). CBD25 associated with fewer AEs than CBD50. The most common AEs in CBD50 group were diarrhea (56%) and somnolence (26%). Liver transaminase levels were elevated in CBD groups (18.9%) vs placebo (0%) (Thiele et al. 2021).

Appendix 11

Poster presentation at the

“Pharmacy practice research summer meeting for PhD students, postdoctoral fellows and supervisors” 4th - 5th July 2022, Utrecht, Netherlands.

Title: "CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES"

Background information: Rare diseases (RDs) are severe, progressive and usually chronically debilitating. About 4%–6% of the world population is affected by a rare disease[1]. Despite the improvement in diagnostic procedures and advancements in research and development, RD patients are facing unmet medical needs[2]. Medicinal Cannabis (MC) is used for management of symptoms such as pain, spasticity, nausea and vomiting, seizures, and anxiety[3] which may be experienced by RD patients.

Purpose: To identify potential use of MC in RDs and issues related to its use.

Method: Two questionnaires were developed for: (1) RD patients and (2) healthcare professionals (HCP). Questionnaires contained questions related to: treatment of RD patients, issues related to treatment and use of medicinal cannabis. Questionnaires were validated and disseminated physically and online.

Results: Respondents of the questionnaire for HCP (n=101) were mostly pharmacists (n=40), general practitioners (n=17) and occupational therapists (n=13), with more than

[1] Bruckner-Tuderman L. Epidemiology of rare diseases is important. Journal of the European Academy of Dermatology and Venereology. 2021;35(4):783-4.

[2] Groft SC, Posada M, Taruscio D. Progress, challenges and global approaches to rare diseases. Acta Paediatrica. 2021 Oct;110(10):2711-6.

[3] National Academies of Sciences, Engineering, and Medicine. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.

11 years of practice (n=46). HCP encounter 2-4 RD patients a year on average. Symptoms experienced by RD patients were pain (n=51), mainly chronic neuropathic pain n=38), anxiety (n=34) and muscle spasticity (n=33).

Fifty-nine HPC agreed to reply to MC related questions. Twenty-six of 59 HCP used MC in their practice. Forty eight out of 59 HCPs consider it to be effective for pain relief, 38 for anxiety and for muscle spasticity. Thirty six out of 59 HCP agreed on the use of MC in their practice. Regarding the side-effects of MC, confusion (n=30) and addiction (n=29) are reported to be of the most concern.

The majority of patients with RDs (n=38) were 41-50 years old (n=11) and reported anxiety (n=20), pain (n=20) and muscle spasticity (n=10) as commonly experienced symptoms. Seven reported experiencing side-effects associated with the use of medications. Two respondents have been prescribed MC by a HCP, though 20 would consider MC use to relieve symptoms of their disease. Eighteen patients are not concerned of MC side-effects. Confusion possibly associated with MC use was a side-effect reported of the most concern (n=8).

Conclusion: MC can be effective to relief pain, anxiety and muscle spasticity possibly experienced by RD patients. HCP and RD patients consider that MC can be used in management of RD symptoms.

Key words: medicinal cannabis, rare diseases, CBD, THC, orphan diseases

Authors: Jekaterina Parovincaka, Dr. Janis Vella Szijj, Prof. Anthony Serracino Inglott

Appendix 12

Accepted abstract

“80th FIP world congress of pharmacy and pharmaceutical sciences” 18 to 22 September 2022 in Seville, Spain.

Title: "CANNABIS FOR MEDICINAL USE IN PATIENTS WITH RARE DISEASES"

Background information:

Rare diseases (RDs) affect over 300 million people worldwide. There are approximately 7,000 recognised RDs[1]. RDs are usually genetic, with childhood or adulthood onset and are associated with severe debilitating symptoms which persist for a patient's lifetime[2]. RD patients often face multiple issues, ranging from difficulty in establishing an accurate diagnosis to lack accessible treatment options.[3] Medicinal Cannabis (MC) is used to relieve symptoms, such as pain, anxiety and muscle spasticity, which may be commonly experienced by patients with RDs.

Purpose:

To identify RDs for which MC is of interest.

[1] Nguengang Wakap S, Lambert DM, Olry A, Rodwell C, Gueydan C, Lanneau V, et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. Eur J Hum Genet. 2020;28(2):165-73.

[2] Orphanet. About rare disease. [Cited on 30 Jan 2022]. Can be accessed from URL: http://www.orpha.net/consor/cgibin/Education_AboutRareDiseases.php?lng=EN

[3] National Institutes of Health (NIH). Rare Disease Day: Frequently Asked Questions. National Organization for Rare Disorders (NORD). [Cited 02.06.2022]. Can be accessed from URL: https://rarediseases.org/wp-content/uploads/2019/01/RDD-FAQ-2019.pdf

Method:

A systematic literature review was carried out. Open access peer review journal articles, published in English in PubMed Central or MEDLINE databases between January 2011 – September 2021 were included.

Results:

Thirty-eight identified articles describe the use of MC as a possible therapeutic option in 22 RDs: epileptic conditions (n=7), neurodegenerative diseases (n=6) and skin disorders (n=4), a number of them of early childhood onset (n=12). Literature suggests that MC can be used in RDs which are associated with pharmaco-resistant seizures, such as Dravet Syndrome (n=14), Lennox-Gastaut Syndrome (n=13), Tuberous sclerosis complex (n=4); in neuropathic pain and spasticity (Neurofibromatosis type 1 (n=1), Multiple Sclerosis (n=4)); in skin disorders (Epidermolysis bullosa (n=1), Scleroderma (n=1)); also obesity in Prader-Willi syndrome (n=1), gastrointestinal symptoms in chronic intestinal pseudo-obstruction **(**n=1). Studies show improvement in patients' Quality of Life (QOL) and low incidence of severe adverse events associated with MC use. Studies reported the use of CBD (Cannabidiol, n=16), Cannabinoid-based medicines (CBMs, n=7), synthetic derivates of MC (n=4) or "Sativex" (THC: CBD in 1:1 ratio, n=2) in patients with RDs. The number of publications in 2020 and 2021 on the MC use in RDs has increased, demonstrating that research on the use of MC as a therapeutic option in RDs is emerging.

Conclusion:

Literature suggests that MC can be used in certain RDs. In lack of efficacious treatment options, MC can be an alternative therapy for symptom relief. There is need for further studies involving academia and industry investigating the use of MC therapies in RDs.

Authors: Jekaterina Parovincaka, Dr. Janis Vella Szijj, Prof. Anthony Serracino Inglott