ANALYSIS OF THE SAFETY PROFILE OF CANNABIS-DERIVED PRODUCTS USING THE FDA ADVERSE EVENT REPORTING SYSTEM DATABASES

Priscilla Orechio de Morais Victor Lopes

Thesis submitted to the University of Ottawa
in partial fulfillment of the requirements for the
Master of Science in Biology degree

Department of Biology
Faculty of Science
University of Ottawa

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ABSTRACT

In many parts of the United States (U.S.) and other countries, including Canada, evolving changes in the legalization and regulation of cannabis use have led to expanding access to a wide variety of cannabis-derived products (CDPs). CDPs, which can range from highly regulated pharmaceutical formulations to less controlled or illicit products, have become increasingly popular among diverse populations for both medical and recreational purposes. As CDP consumption increases, particularly across a heterogeneous population with varying demographics, health conditions, and usage patterns, the potential for unknown or unexpected adverse drug reactions (ADRs) also increases. This heterogeneity in both CDPs and population creates a complex landscape where the safety profile of these products may differ from those observed in pre-marketing safety assessments of standardized CDPs. The use of spontaneous reporting systems (SRSs) such as the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) is a valuable tool for the rapid detection of unexpected emerging safety signals using real-world data. We conducted a descriptive analysis and a disproportionality analysis of CDP-related spontaneous adverse event reports (AERs) queried from FAERS from the first quarter of 1999 to the first quarter of 2023. While we identified unique challenges in the post-marketing surveillance process for CDPs, with heterogeneous reporting patterns and trends across all products, we also demonstrated that FAERS data followed expected temporal and regulatory trends and can thus be applied for signal detection research. We then demonstrated that CDPs containing similar active ingredients may produce different signal detection safety profiles. Therefore, this work provided insights into the design of future cannabis safety assessment studies.

RÉSUMÉ

Dans de nombreuses régions des États-Unis et d'autres pays, dont le Canada, l'évolution de la légalisation et de la réglementation de la consommation de cannabis a conduit à un accès accru à une grande variété de produits dérivés du cannabis (PDC). Les PDC, qui peuvent aller de formulations pharmaceutiques hautement réglementées à des produits moins contrôlés ou illicites, sont devenus de plus en plus populaires parmi diverses populations, à des fins médicales et récréatives. L'augmentation de la consommation de PDC, en particulier au sein d'une population hétérogène dont les caractéristiques démographiques, l'état de santé et les modes d'utilisation varient, accroît également le risque d'effets indésirables inconnus ou inattendus des médicaments. Cette hétérogénéité des PDC et de la population crée un paysage complexe dans lequel le profil de sécurité de ces produits peut différer de celui observé dans les évaluations de sécurité des PDC standardisés avant leur mise sur le marché. L'utilisation de systèmes de notifications spontanées tels que le système de notification des événements indésirables de la U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) est un outil précieux pour la détection rapide de signaux de sécurité émergents inattendus à l'aide de données du monde réel. Nous avons effectué une analyse descriptive et une analyse de disproportionnalité des rapports spontanés d'événements indésirables liés à la PDC, à partir du FAERS entre le premier trimestre de 1999 et le premier trimestre de 2023. Bien que nous ayons identifié des défis uniques dans le processus de surveillance post-commercialisation des PDC, avec des modèles et des tendances de notification hétérogènes pour tous les produits, nous avons également démontré que les données du FAERS suivaient les tendances temporelles et réglementaires attendues et qu'elles pouvaient donc être utilisées pour la recherche sur la détection des signaux. Nous avons ensuite démontré que les PDC contenant des ingrédients actifs similaires peuvent produire des profils de sécurité différents en

matière de détection des signaux. Par conséquent, ce travail a permis de mieux comprendre la conception des futures études d'évaluation de la sécurité du cannabis.

ACKNOWLEDGEMENTS

I would like to begin by expressing my deepest gratitude to my supervisor, Dr. Cory Harris, for taking a chance on a 'mature' student and giving me the opportunity to pursue a long-held dream of earning an M.Sc. in Biology. His guidance and advice have been invaluable, and I sincerely appreciate all the effort and time he dedicated to keeping me on track and motivated to complete this degree.

I extend the same heartfelt thanks to my co-supervisor, Dr. Christopher Gravel. This degree would not have been possible without his guidance and support throughout the process. I will be forever grateful for the encouragement and help he provided, especially for the regular (and sometimes long) meetings and R training sessions.

I would also like to extend my gratitude to my examining committee members, Dr. Adam Shuhendler and Dr. Laurie Chan, for taking the time to review my work on short notice. Your feedback and insights are greatly appreciated.

I would like to thank my team in Harris' lab for their support from day one. Special thanks go to Corrine, who served as my mentor during my Health Canada internship, providing invaluable guidance and support. I also want to thank my colleagues in Dr. Gravel's lab for their help with statistics and coding. I would like to thank Dr. Jordana Oliveira for her valuable assistance and insights, especially with R. I want to thank Lin for her amazing partnership during TA sessions, the fun times in the lab, and for helping me stay motivated. Finally, I want to express my appreciation to Anthony, my parents and sister for their endless encouragement and support, especially during the most challenging and stressful times of my degree.

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LIST OF ABBREVIATIONS

ACMPR	Access to cannabis for medical purporses regulations
ADR	Adverse drug reaction
AE	Adverse event
AEA	N-arachidonoyl ethanolamine
AER	Adverse event report
BCPNN	Bayesian confidence propagation neural network
CB_1	Cannabinoid Receptor Type 1
CB_2	Cannabinoid Receptor Type 2
CBC	Cannabichromene
CBCA	Cannabichromenic acid
CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBDV	Cannabidivarin
CBG	Cannabigerol
CBGA	Cannabigerolic acid
CBGV	Cannabigerovarin
CBN	Cannabinol
CDP	Cannabis-derived product
CI	Confidence interval
CNS	Central nervous system
CrI	Credible interval
CSA	Controlled Substance Act
D8-THC	Delta-8-tetrahydrocannabinol
D9-THC	Delta-9-tetrahydrocannabinol
D10-THC	Delta-10-tetrahydrocannabinol
DEC	Drug event combination
DDI	Drug-drug interaction
DME	Designated medical events
ECS	Endocannabinoid system
EMA	European Medicines Agency
FAERS	FDA Adverse Event Reporting System
FDA	U.S. Food and Drug Administration
GPCR	G protein-coupled receptors
HHC	Hexahydrocannabinol
HLT	High level term
HLGT	High level group term
IC	Information component
MedDRA	Medical dictionary for regulatory activities

MHRA	United Kingdom Medicines and Healthcare Products Regulatory Agency
MMAR	Marihuana Medical Access Regulations
MMPR	Marihuana for Medical Purposes Regulations
MS	Multiple sclerosis
PPAR	Peroxisome proliferator-activated receptors
PRR	Proportional reporting ratio
PT	Preferred term
PV	Pharmacovigilance
RCT	Randomized controlled trial
ROR	Reporting odds ratio
RR	Risk ratio
Rx THC	Pharmaceutical-grade THC
SOC	System organ class
SRS	Spontaneous reporting system
TGA	Australian Therapeutic Goods Administration
THC	Delta-9-tetrahydrocannabinol
THCA	Delta-9-tetrahydrocannabinolic acid
THCV	Tetrahydrocannabivarin
TNFα	Tumor necrosis factor-alpha
TRPV	Transient receptor potential vanilloid channel
U.S.	The United States
WHO	World and Health Organization

CHAPTER 1: GENERAL INTRODUCTION

1.1 Legal Status of Cannabis

Cannabis sativa L., also known as marijuana, is considered the most-used illicit substance worldwide [1], with an estimated 268 million people who consumed cannabis at least once in 2020 [2]. The drug's legal status varies greatly between and within countries, with many having legalized some form of cannabis for medical or recreational use [3]. In the United States (U.S.), the legalization of cannabis is marked by a long history of gradual changes. In the early 20th century, cannabis was widely used for medicinal and industrial purposes [4]. However, in the 1930s, anti-drug campaigns resulted in the prohibition of its use in many states. Consequently, in 1937, the federal Marihuana Tax Act was enacted, criminalizing cannabis by imposing strict regulations and taxes on its production, sale, and possession [5]. In the subsequent years, interest in the therapeutic uses of cannabis emerged, accompanied by a concomitant increase in safety concerns related to the psychoactive effects of delta-9-tetrahydrocannabinol (D9-THC). In 1970, cannabis was classified by the Controlled Substances Act (CSA) as a Schedule I drug and remains illegal at the federal level to this day [6]. The year of 1996 marked the beginning of a shift in public perception and policy toward cannabis legalization after California became the first state to legalize medical cannabis, exempting certain patients and their primary caregivers from criminal penalties for the possession and cultivation of cannabis for medical use [7]. In the following years, particularly the past decade, more states followed the trend and, as of April of 2023, 38 states, three territories and the District of Columbia allowed cannabis for medical use. In 2012, Colorado and Washington became the first states to legalize cannabis for recreational use, and 10 years later, 24 states, three territories and the District of Columbia legalized cannabis for non-medical adult use [8, 9]. A milestone in cannabis policy was the enactment of the 2018 Farm Bill, which legalized the production and

sale of hemp (defined as the cannabis plant or any part of it, including its extract and cannabinoids, that contains less than 0.3% THC concentration on a dry weight basis). The bill removed hemp from the Schedule I classification under the CSA, thus resulting in the expansion of the cannabidiol (CBD) market and that of its derivates (e.g. delta-8-tetrahydrocannabinol, D8-THC) [10].

In Canada, access to medical cannabis was first implemented with the Marihuana Medical Access Regulations (MMAR) in 2001 [11]. Upon authorization of health care practitioners, patients could obtain cannabis solely as dried plant material by cultivating their plants, having someone to produce for them, or purchasing from Health Canada supply. In 2013, the MMAR was replaced by the Marihuana for Medical Purposes Regulations (MMPR), allowing those with medical conditions access to quality-controlled dried cannabis and initiating the development of a regulated cannabis industry. In 2015, the Supreme Court of Canada authorized licensed producers to expand the different forms of cannabis allowed to medical patients, adding cannabis oils and fresh cannabis buds and leaves to the list of dried plant materials [11]. In August 2016, the MMPR was replaced by the Access to Cannabis for Medical Purposes Regulations (ACMPR), and finally, in 2018, Canada implemented the *Cannabis Act,* creating a legal framework for regulating the production, distribution, sale, and possession of cannabis for non-medical use [12]. Through the *Cannabis Act*, the federal government prioritizes a public health approach, with the objective of limiting access to cannabis to the youth public, diminishing the illegal cannabis revenue from criminality, and protecting the safety and public health by permitting adults 18 years and older to consume legal quality-controlled cannabis products [12]. In 2018, Canada became the first G7 country to allow adult access to cannabis-

based products and represents one of the largest demographics of users in the world [13], with an estimated 5 million cannabis consumers [14].

The legal status of cannabis in Europe varies widely. Some countries have adopted a policy of legalization for recreational use, while others have implemented medical or decriminalization measures. Malta was the first country to legalize cannabis for recreational use in 2021. In 2023, Germany was considered the largest national medical cannabis market in Europe, and in 2024, it became the third European Union country (after Malta and Luxembourg) to legalize cannabis for non-medical adult use [8].

1.2 Cannabis and Cannabinoids

Cannabis for medical and non-medical uses includes a wide range of complex and variable mixtures of bioactive compounds. *Cannabis sativa* is an annual, dioecious flowering plant of the family *Cannabaceae*. It is typically cultivated in temperate and tropical regions, although it is also grown indoors worldwide [15]. The cannabis plant exhibits a diverse phytochemical profile. Over 500 distinct compounds have been identified in the leaves and inflorescences of the cannabis plant [16]. These include a variety of terpenes, flavonoids, alkaloids, and over 100 unique phytocannabinoids [17]. Cannabinoids can occur naturally in the cannabis plant as phytocannabinoids or be synthesized in the laboratory as synthetic cannabinoids [18]. The two most abundant and extensively studied cannabinoids are the psychoactive delta-9-tetrahydrocannabinol (D9-THC) and the non-psychoeuphoric cannabidiol (CBD) [19]. In the cannabis plant, these cannabinoids are synthesized as carboxylic acids (e.g., tetrahydrocannabinolic acid - THCA and cannabidiolic acid - CBDA, respectively). When submitted to high temperatures above 120°C, they decarboxylate into their neutral and more

bioactive forms. As an example, when cannabis is smoked or vaporized, THCA is converted to THC [20]. In addition to these two major cannabinoids, other cannabinoids found at lower concentrations – known as minor cannabinoids – include (but are not limited to) the acid and neutral forms of cannabigerol (CBG), cannabinol (CBN), cannabidivarin (CBDV), tetrahydrocannabivarin (THCV), and cannabichromene (CBC) and cannabichromvarin (CBCV) [21, 22]. Recently, research has also focused on the emerging cannabinoid D8-THC, which is a natural cannabinoid found in low concentrations in the cannabis plant, considered an isomer of D9-THC. Since the approval of the Farm Bill in 2018, D8-THC has been growing in popularity in the U.S., with most of the commercially available D8-THC synthesized from CBD extracted from hemp [23]. In fact, semi-synthetic cannabinoids derived from hemp/CBD emerged in products in the last years, including hexahydrocannabinol (HHC) and delta-10-tetrahydrocannabinol (D10-THC) [24]. Synthetic cannabinoids also gained popularity with advances in research and political and social acceptance of cannabis use [25].

1.3 Cannabis Derived Products

Over recent years, the global shift toward cannabis legalization has impacted the accessibility and diversity of cannabis-derived products (CDPs) that have emerged in the U.S. and abroad. This shift has enabled the expansion of both pharmaceutical-grade cannabis-derived drugs and a broader range of non-pharmaceutical CDPs. Pharmaceutical CDPs are formulations that undergo rigorous development, testing, and approval processes, similar to those of conventional pharmaceuticals [26]. These highly standardized drugs must adhere to strict manufacturing, labelling, and quality control standards to ensure the safety and efficacy required for federal approval. To date, the U.S. Food and Drug Administration (FDA) has approved

Epidiolex® (cannabidiol) [27], dronabinol (Marinol® and Syndros® – synthetic forms of D9-THC) [28, 29], and Cesamet® (nabilone – a synthetic analogue of THC) [30]. Sativex® (nabiximols – a standardized botanical extract with slightly more THC than CBD (2.7:2.5 mg per spray) is also a pharmaceutical CDP. However, it has not been approved by the FDA in the U.S. Instead, it has gained approval in several European countries and in Canada [31].

Epidiolex (marketed as Epidyolex® in Europe) is a 98% pure plant-derived CBD solution for oral administration, approved by the FDA, European Medicines Agency (EMA), the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA), and the Australian Therapeutic Goods Administration (TGA) for "the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in pediatric patients two years of age and older" [27]. Dronabinol, a synthetic form of D9-THC, is available in two formulations, as either an oral capsule (Marinol) or an oral solution (Syndros). They received federal approval from the FDA, Health Canada, and TGA for "the treatment of adults with anorexia associated with weight loss in AIDS and for the treatment of adults with nausea and vomiting associated with cancer chemotherapy who have failed to respond adequately to conventional antiemetic treatments" [28, 29]. Nabilone, marketed as Cesamet, is a synthetic analogue of D9-THC, available as an oral capsule. It was approved by regulatory agencies, including the FDA, Health Canada, MHRA, and TGA. Approval indications include "treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments" [30]. Nabiximols, marketed as Sativex®, is a plant-derived buccal spray formulation (27mg/ml of D9-THC and 25mg/ml CBD per spray) approved as "an adjunctive treatment for symptomatic relief of spasticity in patients with multiple sclerosis (MS) who have not responded adequately to other therapy and who demonstrate meaningful improvement during

an initial trial of therapy". It was approved in more than 25 countries by regulatory agencies such as EMA, Health Canada, MHRA, and TGA [31].

Non-pharmaceutical CDPs include diverse products available outside of the regulated pharmaceutical framework. Their composition, potency, and quality can vary widely [21]. The profile of cannabinoids and other compounds may differ both qualitatively and quantitatively based on plant genetics, environmental factors, time of harvesting and post-harvesting practices [32]. Moreover, crossbreeding of cannabis plants has resulted in multiple strains with varying amounts and ratios of cannabinoids, often with very high THC content. While the major chemotypes (and labelling regulations) focus on THC and CBD, leading to broad classification as THC-dominant, CBD-dominant, or balanced (1:1 THC/CBD ratio), different strains and processing methods will generate different complements of minor cannabinoids and terpenes [33].

Non-pharmaceutical CDPs vary in their formulations and routes of administration, which may include the use of accessories. Some products can be inhaled through smoking (cigarettes, pipes, water pipes) or via vaping, dabbing, and nebulizing. Formats for oral administration include capsules, oils, tinctures, solutions, and edibles such as beverages, cookies, and gummies. CDPs can also be administered sublingually or buccally as lollipops, lozenges, or sprays, or applied topically as gels, creams, ointments, patches, or inserted as suppositories [34]. Non-pharmaceutical CDP use is evolving rapidly and can also include illicit and unregulated products sold as drugs, foods, beverages, cosmetics, and dietary supplements [35].

1.4 Broad Therapeutic Potential of Cannabis Derived Products

The cannabis plant, one of the earliest cultivated plant species by humans, has significantly influenced numerous civilizations throughout history. Historical evidence traces its initial use back to 4000 B.C. in China [36]. For centuries, cannabis has been broadly utilized for diverse applications, including the production of textiles, paper, food, biofuels, medicinal products, and recreational substances [37]. More recently, the growing interest in CDPs for treating and managing various diseases and disorders is primarily attributed to their pharmacological effects, which result from the cannabinoids' interaction with specific receptors in the endocannabinoid system (ECS) [38].

The ECS is a cell-signalling system that plays a crucial role in a wide range of pathophysiological processes in the body, such as homeostasis, anxiety, feeding behaviour/appetite, emotional behaviour, depression, nervous functions, neurogenesis, neuroprotection, reward, cognition, learning, memory, pain sensation, fertility, pregnancy, and pre-and post-natal development [39]. The ECS consists of receptors, ligands, and enzymes distributed across diverse tissues and cells [40]. The receptors are classified into three classes and include (i) G protein-coupled receptors (GPCRs) (e.g., Cannabinoid Receptor 1 (CB_1) and Cannabinoid Receptor 2 (CB_2) [41], (ii) Ligand-sensitive ion channels (e.g., Transient Receptor Potential Vanilloid 1 (TRPV1), and (iii) Nuclear receptors such as peroxisome proliferator-activated receptors (PPARs) [42]. The endogenous ligands (endocannabinoids) are anandamide or N-arachidonoyl ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes responsible for endocannabinoid metabolism are diacylglycerol lipase isozymes α and β, fatty

acid amide hydrolase, monoacylglycerol lipase, and N-acylphosphatidylethanolamine-selective phospholipase D [40].

Cannabinoids exert their pharmacological effects by binding to specific receptors located within the ECS. Cannabinoid receptors, CB_1 and CB_2, are located throughout the body. CB_1 is expressed primarily in the central nervous system (CNS) (e.g., brain and spinal cord) but is also found in some peripheral organs and tissues. CB_2 is mainly expressed in the peripheral nervous system, particularly in the immune cells, spleen, and thymus [43]. D9-THC acts as a partial agonist at both CB_1 and CB_2 receptors [44]. The precise pharmacodynamic mechanism of CBD is still being elucidated, but it is proposed that CBD interacts with multiple targets, including other receptor systems. Potential mechanisms include antagonistic effect at CB_1 receptors, antagonistic effect at TRPV1 and TRPV2, inhibition of the hydrolysis of anandamide, binding to the equilibrative nucleoside transporter-1, and biding to the G-protein coupled receptor (GPR55). Additionally, CBD is known to inhibit adenosine uptake, enhance the suppression of tumor necrosis factor-alpha (TNFα), and interact with calcium and sodium channels [45].

Cannabinoids have increasingly emerged as potential therapeutic agents for the treatment of various diseases due to their multiple targets and interactions with the ECS [39]. In addition to the demonstrated efficacy of standardized THC in stimulating appetite, treating nausea and vomiting, and reducing spasticity in MS [28-31], and of standardized CBD in managing pediatric seizure disorders [27], there is growing preclinical and clinical evidence suggesting the potential of CDPs for treating and/or managing a broader array of diseases [46, 47].

D9-THC has exhibited potential as an anticancer, anti-microbial, anti-inflammatory, and analgesic agent, with additional therapeutic applications in the treatment of mood and anxiety

disorders, as well as in managing frontal lobe strokes [48]. CBD has exhibited potential for its anxiolytic, panicolytic, and anti-compulsive effects, with promising applications in treating chronic pain conditions such as rheumatoid arthritis, fibromyalgia, cancer-associated pain, chronic back pain, chronic abdominal pain, chronic pancreatitis, headache, and facial pain [49]. CBD has also exhibited neuroprotective and anti-inflammatory properties, making it a potential treatment for post-stroke spasticity, neurological disorders, and psychotic conditions such as schizophrenia. CBD has further demonstrated therapeutic potential in managing inflammatory bowel diseases, with advantages over D9-THC due to the absence of psychoactive effects [49]. CBD has also shown properties to alleviate symptoms associated with HIV/AIDS, such as wasting syndrome, and has shown inhibitory effects against Viral Hepatitis C *in vitro* [50].

Cannabinoids, in general, have demonstrated potential therapeutic properties in decreasing opioid withdrawal symptoms, on forms of substance abuse, such as opioid-, cocaine-, tobacco- and alcohol addiction and their symptoms [51]. Clinical evidence has also demonstrated the therapeutic effects of cannabinoids against skin lesions, skin burns, and pruritus in several dermatologic diseases, such as allergic contact dermatitis, atopic dermatitis, asteatotic eczema, and prurigo nodularis [52].

1.5 Safety Concerns Related to Cannabis Derived Products Use

With this rising interest in the therapeutic use of CDPs, the safety of cannabinoids is an emerging source of concern for all the involved stakeholders, including healthcare professionals, policymakers, manufacturers, and the general public [53]. The most frequently reported adverse drug reactions (ADRs) associated with pharmaceutical CDPs, as outlined in their product

monographs, are well-documented and supported by a wide range of preclinical and clinical evidence (Table 1).

Table 1. Most reported ADRs associated with pharmaceutical CDP use

CDP	Most reported ADRs
Epidiolex	somnolence
	decreased appetite
	diarrhea
	transaminase elevations
	fatigue
	malaise
	asthenia
	rash
	insomnia
	sleep disorder
	poor quality sleep
	infection
Dronabinol	abdominal pain
	dizziness
	euphoria
	nausea
	paranoid reaction
	somnolence
	thinking abnormal
	vomiting
Nabilone	drowsiness
	vertigo
	psychological high
	dry mouth
	depression
	ataxia
	blurred vision
	sensation disturbance
	anorexia
	asthenia
	headache
	orthostatic hypotension
	euphoria
	hallucinations
Sativex	palpitations
	tooth discoloration
	oral mucosal disorder
	oral mucosal discoloration
	oral mucosal exfoliation
	stomatitis
	hypertension
	delusional perception
	syncope

Adapted from products' monographs [27-31]

In contrast, the safety profile of non-pharmaceutical CDPs is widely variable and depends on several factors, including the specific cannabinoids present in the product (such as THC, CBD, and/or other cannabinoids), the dose, the method of consumption, the individual health conditions and characteristics, and concomitant use of other substances or medications [54]. The safety risks are generally dose-dependent, with higher doses of cannabinoids, particularly THC, posing greater risks [55]. Reported AEs associated with non-pharmaceutical CDP use are primarily linked to THC content. At higher doses, it may induce psychoactive effects, including dysphoria, anxiety, panic, schizophrenic psychosis, impairment of memory, reductions in psychomotor and cognitive performance, and sensation of slowed time. Frequent physical effects are also related to THC consumption, including tiredness, dizziness, tachycardia, postural hypotension, xerostomia, decreased lacrimation, muscle relaxation, and increased appetite [46]. In contrast to THC, CBD's safety profile is underestimated due to the absence of euphoric and psychoactive properties. However, preclinical and clinical evidence suggests that AEs and toxicity associated with CBD intake include hepatic dysfunction, diarrhea, fatigue, vomiting, and somnolence [56].

The route of administration of the CDP may influence adverse outcomes. Each method (oral, inhalation, sublingual, topical, or rectal) affects the pharmacokinetics of cannabinoids and bioavailability of CDP, thereby impacting the onset, duration, and intensity of AEs [57]. Oral ingestion through capsules or edibles provides a slower onset of action and lower bioavailability when compared to inhalation but may produce longer-lasting effects. Research has shown that drugs administered orally undergo first-pass metabolism in the liver, and the secondary metabolites produced during this process, such as 11-hydroxy-THC from THC, may also have additional pharmacological effects. Therefore, these cannabinoid metabolites may contribute to

the CDP's overall effects and result in potential AEs [58, 59]. Inhalation through smoking or vaping has been associated with a higher risk of respiratory events [60]. Sublingual administration via tinctures results in a faster onset of action and higher bioavailability than oral, as cannabinoids bypass the liver. Topical administration of creams or ointments leads to local effects with lower systemic bioavailability and reduced intoxication risk [61].

Individual factors such as age, gender, genetics, pre-existing medical conditions, and concomitant use of substances or medications may impact the safety profile of non-pharmaceutical CDPs. Adolescents and young adults are more vulnerable to developing cognitive and psychiatric effects of THC, especially with early and heavy use [62]. Conversely, the elderly may be more sensitive to the sedative effects of CDPs, with a higher risk of falls, cognitive decline, and drug-drug interactions (DDI) with other medications, which have their own safety profiles [63]. Concomitant use of medications increases the potential of experiencing DDIs potentially occurring via metabolic or transport pathways [64]. Gender differences may influence body morphology and function. Genetic differences, particularly in CB_1 and enzymes involved in cannabinoid metabolism, can result in different therapeutic effects and potential AEs [54].

Product quality issues may lead to undesirable AEs. Contamination with pesticides, heavy metals, molds, microbes and other substances may occur at various stages of the production, cultivation, processing, packaging and distribution processes [65]. Labelling issues, such as inaccurate concentration of the cannabinoid, undisclosed contaminants, and inadequate use instructions, can also result in potential accidental misuse, toxicity, and AEs. Individuals may also purchase CDPs from the illicit market without quality control measures [66].

Given the diversity of non-pharmaceutical CDPs available in the market, identifying and generalizing potential safety risks, such as ADRs, is challenging, especially when considering the heterogeneity of patients and consumers, which also present distinct safety profile risks. In addition, the evolving cannabis regulatory and legislation frameworks vary considerably between and within countries, with many having reduced regulatory oversight on CDPs. As cannabis use continues to rise, ADR monitoring is a crucial process for the rapid detection of previously unknown safety signals. Post-marketing safety surveillance is an ongoing process in the cannabis pharmacovigilance (PV) routine and is an essential aspect of the public health approach to the legalization and regulation of CDPs [67].

1.6 Signal Detection in Pharmacovigilance

1.6.1 Overview of Pharmacovigilance

PV is a pivotal, indispensable science for all medications, including CDPs. The World Health Organization (WHO) defines PV as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems." PV aims to identify and confirm safety signals that may indicate potential risks of ADRs under real-world conditions [68].

1.6.2 Signal Detection in Pharmacovigilance

A signal in PV has been defined as "information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify

verificatory and, when necessary, remedial actions" [69]. Once a signal is identified, for example, through signal detection methods, it undergoes rigorous evaluation to determine its validity and the need for regulatory action. A signal can be classified as "verified," "refuted," or "indeterminate." A signal is considered an identified risk (i.e., "verified") when the association between the drug and the AE has been confirmed, and the probability of this association has been established through the activities within the frame of the signal management process. A signal classified as "refuted" will likely indicate a "false-positive" finding and an "indeterminate" signal represents a "potential risk" where the likelihood of this association has not yet been verified [69].

Signals can derive from multiple types of evidence that emerge throughout a drug's life cycle, including (but not limited to) systematic reviews and meta-analysis, experimental studies (e.g., RCTs), disproportionality analyses in spontaneous reporting systems (SRSs) (e.g., adverse events reports), and observational studies conducted using administrative healthcare data (e.g., electronic health records or administrative claims) [70].

1.6.3 Spontaneous Reporting Systems

The collection of spontaneous reports began in the 1960s in response to the thalidomide tragedy, which highlighted the need for robust post-marketing surveillance systems to detect and monitor ADRs associated with medicinal products [71], leading to the development and implementation of SRSs worldwide. Since then, SRSs have been used for the early detection, and hypothesis generation, of previously unknown safety signals not identified in clinical trials before marketing authorization [72]. A spontaneous report is an unsolicited communication by a healthcare provider, or consumer/patient to a company, regulatory authority or other organization

that describes one or more suspected ADR in a patient who has received one or more medicinal products [73]. Adverse event reports (AERs) are compiled into databases such as Canada Vigilance (maintained by Health Canada) [74], the EudraVigilance (maintained by the European Medicines Agency, EMA) [75], and the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) [76].

1.6.4 The U.S. FDA Adverse Event Reporting System

FAERS, formerly known as AERS, is an electronic database maintained by the FDA that consists of AERs and provides information on suspected ADRs, medication errors, and product quality complaints [76]. The database is designed to support the FDA's post-marketing safety surveillance program for drugs and therapeutic biologic products. Its structure adheres to the international safety reporting guidance issued by the International Council of Harmonisation (ICH) [77]. Suspected ADRs and medication errors are coded using terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. MedDRA is a standardized medical terminology used throughout the development and regulatory phases of medical products for humans. It encompasses a range of terms such as signs, symptoms, diseases, therapeutic indications, and procedural terms, supporting accurate data entry, retrieval, and evaluation in clinical studies, adverse event reporting, and regulatory submissions [78]. The MedDRA terminology is categorized into a five-level hierarchy structure, allowing for data retrieval through specific or broad groupings (Figure 1) [79]. The basic units are the ‘preferred terms’ (PTs) level, which are distinct descriptors (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristic. Each PT is linked to a ‘lowest level term’ (LLT), which is considered synonym, lexical variant or alternative spelling of PT. PTs are subordinate to

‘high level term’ (HLT), which links PTs related to it by anatomy, pathology, physiology, etiology, or function. ‘High level group term’ (HLGTs) group HLTs to aid retrieval by broader concepts and are subordinate to a ‘system organ class’ (SOC), which is the highest level of the hierarchy that groups terms by etiology, manifestation site and purpose [79];

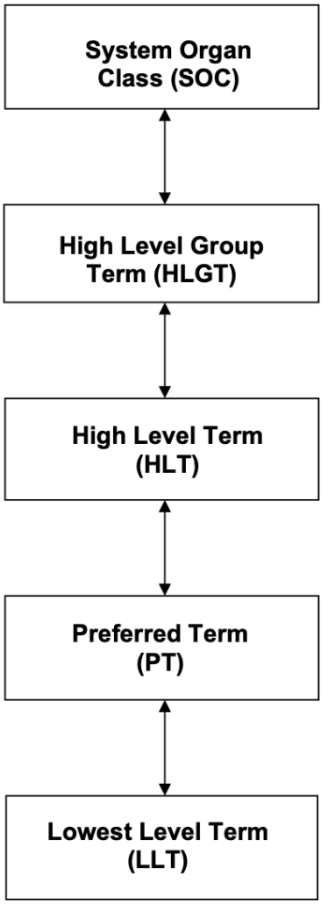

Figure 1. Structural Hierarchy of the MedDRA Terminology [79]

Reporting to the FDA is mandatory for product manufacturers and voluntary for healthcare professionals, patients, and consumers through the "MedWatch" program [80]. The FDA uploads raw AERs on a quarterly basis and provides public access to the data, enabling experts to conduct pharmacovigilance analyses.

FAERS consists of seven distinct databases with anonymous information on (i) demographic characteristics, including age, sex, weight, reporter country, and reporter's type by occupation; (ii) drug data, including the drug's name, dose, frequency, route of administration, the active ingredient, and its suspected role in the adverse event (coded as primary suspect drug, secondary suspect drug, concomitant drug, or interacting drug); (iii) reactions, which are suspected ADRs coded using the MedDRA terminology at the PT level; (iv) outcomes of the report (death, disability, life-threatening, hospitalization, congenital abnormality, required intervention, and others); (v) report sources; (vi) therapy with start and end dates for the reported drugs, and (vii) indications, also coded using MedDRA PTs [76].

1.6.5 Disproportionality Analysis

Several validated quantitative methods are used for early signal detection of safety signals in SRSs and are widely employed by pharmaceutical industries, health authorities, and the medical community [81]. Disproportionality analysis (DA) is one of the most used statistical approaches to identify safety signals. Three of the most frequently used measures of DA are the proportional reporting ratio (PRR) [82], reporting odds ratio (ROR) [83], and the information component (IC), which is the log base 2 of the relative reporting ratio (RRR), estimated by a Bayesian confidence propagation neural network (BCPNN) [84]. These methods compare observed reporting rates of drug-event combinations (DECs) of interest against a comparator or

"reference set" reporting within a given time frame. These algorithms are designed to identify disproportionately higher-than-expected reporting of suspected ADRs in SRSs for signal detection purposes, and the identified signals serve as generated drug safety hypotheses, which can then be followed up on in pharmacoepidemiologic studies or RCTs [85]. Note that the triaging process for follow-up incorporates additional evidence beyond the results of DA. The estimates of disproportionate reporting are calculated based on a contingency table representation of a DEC - it cross-classifies the AERs according to the presence or absence of a drug and AE of interest (Table 2).

Table 2. A contingency table used in disproportionality analysis

	With the adverse event	**Without the adverse event**
Reports mentioning the drug of interest	a	b
Reports not mentioning the drug of interest	c	d

Adapted from van Manen *et al*., 2007 [86]

The PRR is a reporting-based version of a risk ratio (RR) that compares the frequency of reporting of an AE with a given drug with the frequency of reporting of that AE in reports that do not mention the drug. A signal is flagged if the lower bound of the confidence interval (95% CI) exceeds 1, or 0 on the log scale. PRR is defined as below [82].:

$$\mathrm{PRR} = \frac{\mathrm{a} / (\mathrm{a} + \mathrm{b})}{\mathrm{c} / (\mathrm{c} + \mathrm{d})}$$

$$PRR\ (95\%\ CI) = \mathrm{e}^{\ln(PRR) \pm 1.96 \sqrt{\frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}}}$$

The ROR is the reporting version of an odds ratio. It represents the odds of an AE being reported with a specific drug or drug class against the odds of the same AE being reported with all other drugs. A signal is flagged if the lower bound of a 95% CI of the point estimate exceeds 1, or 0 on the log scale. It is defined as [83]:

$$\mathrm{ROR} = \frac{\mathrm{a/c}}{\mathrm{b}/d} = \frac{a \times d}{b \times c}$$

$$ROR\ (95\%\ CI) = \mathrm{e}^{\ln(ROR) \pm 1.96\sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}}$$

The IC compares the reporting rate of a drug-AE combination being reported against the reporting rate under the assumption of independence or no reporting relationships between the drug and the AE. The BCPNN is an algorithm that employs prior distributions to 'shrink' the signal detection estimates towards independent reporting to reduce false positive rates, a known concern with the PRR and ROR. A positive IC value, with the lower bound 95% credible interval (95 % CrI) greater than 0, suggests a safety signal [84].

$$IC = \log_2 \frac{a + 0.5}{a_{exp} + 0.5}$$

$$a_{exp} = \frac{(a+b) \times (a+c)}{(a+b+c+d)}$$

$$IC_{025} = IC - 3.3 \times (a+0.5)^{-1/2} - 2 \times (a+0.5)^{-3/2}$$

$$IC_{075} = IC - 2.4 \times (a+0.5)^{-1/2} - 0.5 \times (a+0.5)^{-3/2}$$

Statistical analyses have proven valuable in supporting signal detection within SRSs. Several studies have compared these methods using real spontaneous reporting data and simulated data, and no definitive 'gold standard' method has been identified [87]. The strengths and limitations of each depend on factors such as the type and size of the dataset, the specific research question, the background frequency of the events, and the characteristics of the drug and AE under study. Overall, PRR is valued for its ease of interpretation and applicability in large datasets, but it tends to generate more false positives compared to IC, and its estimates can be affected by a small number of reports or rare events. Similarly, ROR is easily applicable and effective in large datasets, but it is also prone to false positives in situations with low counts or rare events. In contrast, BCPNN accounts for the high sampling variability in the data, which is quite sparse, by incorporating independent prior beliefs about the nature of reporting, which is a conservative modelling assumption and reduces the likelihood of false positives. In addition, it supports large numbers of calculations efficiently, is better suited for rare events and sparse data, and can be used for pattern recognition in higher dimensions [87].

The FAERS database is a well-established system for monitoring potential ADRs related to pharmaceutical products. In addition, international efforts to capture large volumes of spontaneous reports have resulting in domestic requirements for market authorization holders to regularly collect and report to drug regulators [88]. However, as cannabis consumption continues to increase, the applicability of FAERS to the safety surveillance of non-pharmaceutical substances, such as cannabis, remains unclear due to both limitations in the motivation to spontaneously report (e.g. legality/regulations, stigma) and the inherent heterogeneity of CDPs in both their chemical complexity and their broad therapeutic uses. Unlike prescription and over-

the-counter medications, CDPs may pose unique challenges that complicate the use of FAERS data and standard signal detection methods for their safety surveillance.

1.7 Thesis Objectives

Chapter 2. A feasibility assessment of the FDA Adverse Event Reporting System for the detection of cannabis-related safety signals

General objective: To assess the feasibility of using FAERS for cannabis safety surveillance, we conducted a descriptive analysis of adverse event reports related to seven CDPs queried from FAERS.

Specific objectives:

1. To assess the self-reported terminology used to describe cannabis products;
2. To identify reporting patterns among different populations and CDPs, with a focus on whether the same demographic groups are reporting at similar rates for those CDPs that share the same active ingredient;
3. To evaluate reporting trends over time in the context of evolving regulatory and legal status.

Chapter 3. Signal detection in pharmacovigilance of cannabis-derived products using the FDA Adverse Event Reporting System databases

General objective: To investigate CDP-related ADR in FAERS and identify safety signals associated with different CPDs and terminologies, we conducted a broad signal detection study

using disproportionality analysis of adverse event reports related to five CDPs queried from FAERS.

Specific objectives:

1. To characterize the nature and frequency of signals of disproportionate reporting;
2. To assess the impact of disproportionality analysis in detecting safety signals among CDPs with similar active ingredients but distinct pharmaceutical classifications.

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CHAPTER 2: A FEASIBILITY ASSESSMENT OF THE FDA ADVERSE EVENT REPORTING SYSTEM FOR THE DETECTION OF CANNABIS-RELATED SAFETY SIGNALS

Priscilla. O. M. V. Lopes[1]; Christopher. A. Gravel[2]; Cory. S. Harris[1]

[1] Department of Biology, University of Ottawa, Ottawa, Canada

[2] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

ABSTRACT

The evolving legal and regulatory frameworks surrounding cannabis use have led to a rapid increase in the availability and diversity of cannabis-derived products (CDPs) for both medical and recreational purposes. This emergence has drawn the interest of a diverse range of patient and consumers and heightened public health safety concerns, particularly regarding potential risks, such as adverse drug reactions (ADRs) associated with CDP use. As cannabis consumption continues to increase, ADR monitoring using spontaneous reports systems (SRSs), such as the United States (U.S.) Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS), represent a valuable tool for the rapid detection of previously unknown safety signals. However, FAERS applicability for CDP safety surveillance remains unclear. CDPs, in contrast to prescription and over-the-counter drugs, present unique challenges that may impact the use of both FAERS and signal detection methods. This project assessed the feasibility of using FAERS for CDP safety surveillance. We conducted a descriptive analysis of adverse events reports (AERs) related to CDPs queried from FAERS from the first quarter of 1999 to the first quarter of 2023. We explored the terminology used to report CDPs, identified reporting patterns across different populations, and evaluated reporting trends over time. Among the 1,160 unique terms identified to describe CDPs, those referring to CBD were the most variable. Of the 42,530 reports identified for CDPs, Cannabis and Epidiolex were the most frequently reported products. We identified heterogenous demographic reporting patterns and trends, with women and older adults more frequently reporting CBD, while THC and Cannabis reports were predominantly associated with younger individuals and males subjects. We also noted reporting trends reflective of the availability of CDPs in the context of regulatory and legal status. Our project identified mixed results regarding the potential feasibility of using FAERS for a similar purpose as with

pharmaceutical safety signal detection and highlighted the uniqueness of cannabis-related adverse events and suggested that additional aspects need to be considered when collecting, coding, and assessing self-reports of ADR regarding cannabis use.

2.1 INTRODUCTION

Cannabis sativa L., also known as marijuana, is considered the most-used illicit substance worldwide [1], with an estimated 268 million people who consumed cannabis at least once in 2020 [2]. The drug's legal status varies greatly between and within countries, with many having legalized some form of cannabis for medical or adult recreational use [3]. Currently, access to cannabis in the United States (U.S.) remains illegal at the federal level but is fully legal for both medical and adult recreational use in 24 states [4]. In 2018, Canada became the first G7 country to allow adults access to cannabis-derived products (CDPs) representing one of the largest demographics of users in the world [5]. In 2023, Germany became the largest national medical cannabis market in Europe, followed by the United Kingdom [6]. Despite the long history of prohibition worldwide, the global shift toward cannabis legalization has motivated research and innovation, resulting in a highly diverse and rapidly evolving CDP landscape [7].

CDPs for medical and non-medical purposes include a wide range of complex and variable mixtures of bioactive compounds. Cannabinoids are the active ingredients responsible for the pharmacological effects of cannabis. They can occur naturally in the cannabis plant as phytocannabinoids or be synthesized in the laboratory as synthetic cannabinoids [8]. Over 500 compounds have been detected in the leaves and inflorescences of the plant [9], including terpenes, flavonoids, alkaloids, and over 100 phytocannabinoids [10], which are considered the most dominant and active compounds [11]. The prevalent and most researched phytocannabinoids include the psychoactive constituent delta-9-tetrahydrocannabinol (D9-THC) and the non-psychoeuphoric constituent cannabidiol (CBD) [12]. Recently, research has also focused on emerging cannabinoids, such as THC isomers delta-8- and delta-10-tetrahydrocannabinol (D8-THC and D10-THC), cannabichromene (CBC), cannabigerol (CBG),

cannabinol (CBN), hexahydrocannabinol (HHC), tetrahydrocannabinolic acid (THCA), and cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), cannabidivarin (CBDV), tetrahydrocannabivarin (THCV), and cannabichromevarin (CBCV) [13]. Synthetic cannabinoids include the pharmaceutical-grade CDPs, dronabinol (Marinol®, Syndros®), considered synthetic of D9-THC, and nabilone (Cesamet®), a synthetic analogue of D9-THC [14].

The potency and composition of CDPs can vary widely [15]. For cannabis-based products (e.g., dried flower, concentrates), the profile of cannabinoids and other compounds vary both qualitatively and quantitatively based on plant genetics, environmental factors, time of harvesting and post-harvesting aspects [16]. In addition, crossbreeding of cannabis plants has resulted in a wide variety of strains with different amounts and ratios of cannabinoids, often with very high THC content. While the major chemotypes (and labelling regulations) focus on THC and CBD, leading to broad classification as THC-dominant, CBD-dominant, or balanced (1:1 THC/CBD ratio), different strains and processing practices will generate different complements of minor cannabinoids and terpenes [17].

Increasingly, consumers and patients have access to a diversity of CDPs, including dried flower, concentrates, edibles, beverages, topicals and other novel formulations (in addition to synthetic cannabinoids). These can differ in their routes of administration and may include the use of accessories, including oral use (ingestion, sublingual or buccal), inhalation (smoking or vaping), topical administration, and others. CDP use is evolving rapidly and can also include illicit and unregulated products sold as drugs, foods, beverages, cosmetics, and dietary supplements [18].

Prescription treatments containing THC, CBD and a standardized cannabis extract have exhibited therapeutic potential for certain indications and are supported by clinical evidence. Pharmaceutical CDPs prescribed to individuals with serious chronic diseases include (i) Dronabinol, whose approved indications are AIDS-related anorexia associated with weight loss and severe nausea and vomiting associated with cancer chemotherapy [19, 20], (ii) Nabilone, also approved for chemotherapy-induced nausea and vomiting [21], (iii) Epidiolex® (cannabidiol), approved for use in patients two years of age and older for the treatment of resistant seizures associated with Dravet syndrome, Lennox-Gastaut syndrome or Tuberous Sclerosis Complex [22], and (iv) Sativex® (nabiximols), a standardized botanical extract with slightly more THC than CBD (2.7:2.5 mg per spray) indicated as an adjunctive treatment for symptomatic relief of spasticity in patients with multiple sclerosis [23]. Non-pharmaceutical CDP use is not necessarily based on evidence nor limited to symptoms and conditions suitable for medical supervision. CDP's growing popularity as a potential treatment for managing diverse symptoms, diseases and disorders is increasingly adopted by the general public and clinicians [24].

Globally, cannabis has been used by a range of individuals for both acute and chronic conditions. Many CDPs are purchased to enhance general well-being and to alleviate symptoms such as pain, anxiety, depression, and sleep disorders [25]. In recent years, the distinction between medical and recreational use of CDPs has begun to converge. Certain CDP formulations that were initially developed for medical use, particularly those high in CBD and low in THC, have gained popularity among consumers seeking the potential benefits of cannabinoids without the pronounced psychoactive effects associated with higher THC levels. Conversely, some non-pharmaceutical CDPs are marketed for their potential therapeutic properties, resulting in an

overlap between markets [26]. As a result, CDPs consumers are heterogeneous and represent diverse demographic groups, ranging from infants to aging adults, with complex medical records including chronic conditions, comorbidities, and polypharmacy [27].

The rapid emergence and diversification of CDPs raises public health and safety concerns regarding their use, including potential risks such as possible adverse drug reactions (ADRs) and potential CDP-drug interactions [28]. The safety risks of cannabis may vary depending on the type of product, its chemical complexity, and the route of administration [29], as well as consumer health and use of other substances/medications. In general, risks are dose-dependent and proportional to the amount of cannabinoids in the product, where higher doses constitute greater risks. Moreover, due to the complexity of cannabinoids present in a single product, identifying which compound or combination of compounds may be associated with a safety concern is difficult, as is predicting the product's precise pharmacokinetics, pharmacodynamics, and toxicology. CDP-related ADRs may involve toxic responses to cannabinoids but may also be due to CDP-drug interactions or contaminants [30].

The timely collection, monitoring, detection, and assessment of ADRs is an ongoing process in the cannabis pharmacovigilance (PV) routine and is an essential component of the public health approach to the legalization and regulation of CDPs [31]. Spontaneous reporting systems (SRSs) are an important source of information for the early detection, and hypothesis generation, of previously unknown safety signals not identified in clinical trials before marketing authorization [32]. Adverse events reports (AERs) are gathered in databases such as Canada Vigilance (maintained by Health Canada), the EudraVigilance (maintained by the European Medicines Agency, EMA), and the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). These reports are initiated by the consumer who directly, or

indirectly via their health care provider or through a pharmaceutical company, describe their adverse experiences with therapeutic products. AERs are analyzed using quantitative data mining algorithms to search for early evidence of emerging safety signals that reflect real-world use in specific populations and clinical practice [33] and are used for drug safety surveillance monitoring. Due to the limitations and potential biases associated with spontaneous reporting, SRSs are primarily used to generate drug safety hypotheses which are followed up in more robust confirmatory studies based on pharmacoepidemiologic or randomized trials [34].

As cannabis consumption continues to increase, PV processes, including ADR monitoring, represent a valuable tool for the rapid detection of previously unknown risks. Unlike prescription and over-the-counter drugs, cannabis presents numerous challenges that complicate the use of both FAERS data and standard signal detection methods. Besides the unique complexities of CDPs as described here, it is not clear whether the variables captured by SRSs, such as FAERS, are sufficient to differentiate between distinct types of CDPs and identify related safety signals. It is important to note that SRSs have inherent limitations that affect the representativeness of the data collected, including, but not limited to, selection and reporting biases, most often represented as underreporting [35]. Furthermore, in the context of the CDPs, other variables such as criminality and social stigma may exacerbate these reporting patterns, impacting the validity of AER assessment beyond current understanding [36, 37].

The FAERS database is a well-established system for monitoring ADRs related to pharmaceutical drugs [38]. Its applicability, however, to the safety surveillance of non-pharmaceutical substances such as cannabis remains unclear due to the inherent heterogeneity of non-pharmaceutical CDPs, both in their chemical complexity and the reasons for their use. In addition, the same CDP can be used for both prescribed indications and recreational purposes.

Therefore, these duo scenarios create distinct pathways for the ‘same’ product to be represented in SRSs, which may result in different reporting patterns. To assess the feasibility of using FAERS for cannabis safety surveillance, we conducted a descriptive analysis of AERs related to seven CDPs queried from FAERS to: a) assess the self-reported terminology used to describe cannabis products; b) identify reporting patterns among different populations and CDPs, with a focus on whether the same demographic groups are reporting at similar rates for CDPs that share the same active ingredient; and c) evaluate reporting trends over time in the context of evolving regulatory and legal status.

2.2 METHODS

2.2.1 Data Source

The data for this study was extracted from the FAERS database between the first quarter (Q1) of 1999 and Q1 2023 [39], a period marked by increasing changes in U.S. cannabis regulations followed the legalization of medical cannabis use in California in 1996. In 1999, several states, including Alaska, Oregon, and Washington adhered to this shift toward legalization [40].

FAERS is an electronic database hosted by the FDA that consists of over nine million AERs. This post-marketing safety surveillance program for drugs and therapeutic biological products consists of medication error reports and product quality complaints leading to ADRs. Reporting to the FDA is voluntary for healthcare professionals, patients, and consumers and is mandatory for product manufacturers [41]. The FDA uploads raw AERs on a quarterly basis and it consists of seven distinct databases that can be merged via a unique case ID number. The information in an AER is anonymous and includes details on (i) demographic characteristics, including age, sex, weight, reporter country, and reporter's type by occupation; (ii) drug data, including the drug's name, dose, frequency, route of administration, the active ingredient, and its suspected role in the adverse event (coded as primary suspect drug, secondary suspect drug, concomitant drug, or interacting drug); (iii) reactions, which are suspected ADRs coded using the Medical Dictionary for Regulatory Activities (MedDRA) [42] terminology at the level of 'preferred terms' (PT); (iv) outcomes of the report (death, disability, life-threatening, hospitalization, congenital abnormality, required intervention, and others); (v) report sources; (vi) therapy with start and end dates for the reported drugs, and (vii) indications, also coded

using MedDRA PTs. The quarterly raw data was linked by primaryid (earlier known as LAERS) and caseid (FAERS), deleted duplicated reports, and retained the most recent updated case version timestamped to the date the FDA first made the report available.

2.2.2 Exposure

As cannabis nomenclature lacks uniformity and several types of names and products are currently in use, we searched for matches in characters or sequences of characters present in the plant species name, plant common names, active ingredients, and brand and generic names of pharmaceutical cannabis-derived drugs. This process was done to increase the specificity of exposure definitions, and we included 14 search terms: “cannab”, “canab”, “mariju”, “marih”, “thc”, “cbd”, “nabixi”, “dronab”, “nabilo”, “cesam”, “syndros”, “marino”, “epidiol”, and “sative”. We included reports regardless of the suspected role that the reporter assigned to the cannabis-related term (e.g., primary suspect drug, secondary suspect drug, concomitant drug or interacting drug). Further, to ensure the accuracy and completeness of the data, we conducted a second rigorous data cleaning, by manually sorting CDPs into groups for descriptive analysis.

We classified the terms into three high-level categories: (i) Federally Approved Drugs, (ii) Major Cannabinoids, and (iii) Cannabis. The Federally Approved Drugs category included the pharmaceutical CDPs: dronabinol (Marinol®, Syndros®), nabilone (Cesamet®), Epidiolex, and nabiximols (Sativex®). We then merged the drugs into groups based on their chemical similarities. The Rx THC group included the brand and generic dronabinol and nabilone terms, the Epidiolex group included terms where the brand name (e.g., Epidiolex® or Epidyolex®) was mentioned, and the Sativex group included the brand and generic names for nabiximols (Sativex®). The Major Cannabinoids category contained the THC group (e.g., D8-THC and D9-

THC), the THC/CBD group, where both cannabinoids were mentioned, and the CBD group, which included terms mentioning CBD and not Epidiolex. Finally, the group Cannabis was comprised of generic terms such as cannabis, cannabinoids, or marijuana (Figure 2).

2.2.3 Data Analysis

A descriptive analysis of the CDP reports was conducted using the cleaned FAERS data and the CDP groups. The distribution of reporter demographics was characterized, including age, sex, reporting country, reporter source, outcome, and role of the suspected CDP. Furthermore, the 15 most frequently reported PTs were evaluated based on MedDRA at the PT level.

We conducted two temporal analyses of CDP reports to evaluate reporting trends and patterns over time. For the temporal analysis in the context of evolving legalization status, the study period was limited to Q1 1999 to Q4 2022 to include full years only. Finally, stratified analyses by age and sex, the study period was restricted from Q1 2012 to Q4 2022, corresponding to the last decade of notable changes towards cannabis legalization worldwide. The analyses were performed using the statistical software R version 4.2.3 (see Appendix 1 for R code).

2.3 RESULTS

2.3.1 Cannabis Derived Product Terminology

AERs that contained any of the 14 CDPs search terms were retrieved from FAERS from Q1 1999 through Q1 2023. We identified a total of 1204 unique terms that were used to report CDP, of which 19 were related to emerging minor cannabinoids (e.g., HHC, CBG, CBN, THCA, CBDA), and 25 were related to THC homologs or synthetics (e.g., THC homolog, AM2201). Due to their limited representativeness, they were excluded from the descriptive analysis. Among the remaining 1160 unique terms of interest, those referring to CBD were the most variable, accounting for 339 (29.2%) of all terms, followed by Cannabis (319 terms, 27.5%) and THC (244 terms, 21.0%) (Figure 2). We noted that, generally, the terms lacked uniformity and included the names of cannabis botanical species – with and without – the plant part (e.g., "*Cannabis sativa"* and "*Cannabis sativa* flower"*)*, manufacturers' products including the brand and generic nomenclatures, common or vernacular names that often included the methods of consumption (e.g., "vaping cannabis" and "cannabis smoking"), the legal status of the product (e.g., "illegal marijuana" and "legal cannabis"), the intended use (e.g., "recreational marijuana" and "medical cannabis"), the formulation (e.g., "CBD oil" and "THC gummy") and the cultivar and chemical variant (e.g., "low Indica THC"). In addition, we encountered terms that were incomplete, incorrect, misspelled or lacked specificity (e.g., "THC free"). A complete list of the self-reported terminology by the CDP group used in this study can be found in Appendix 2.

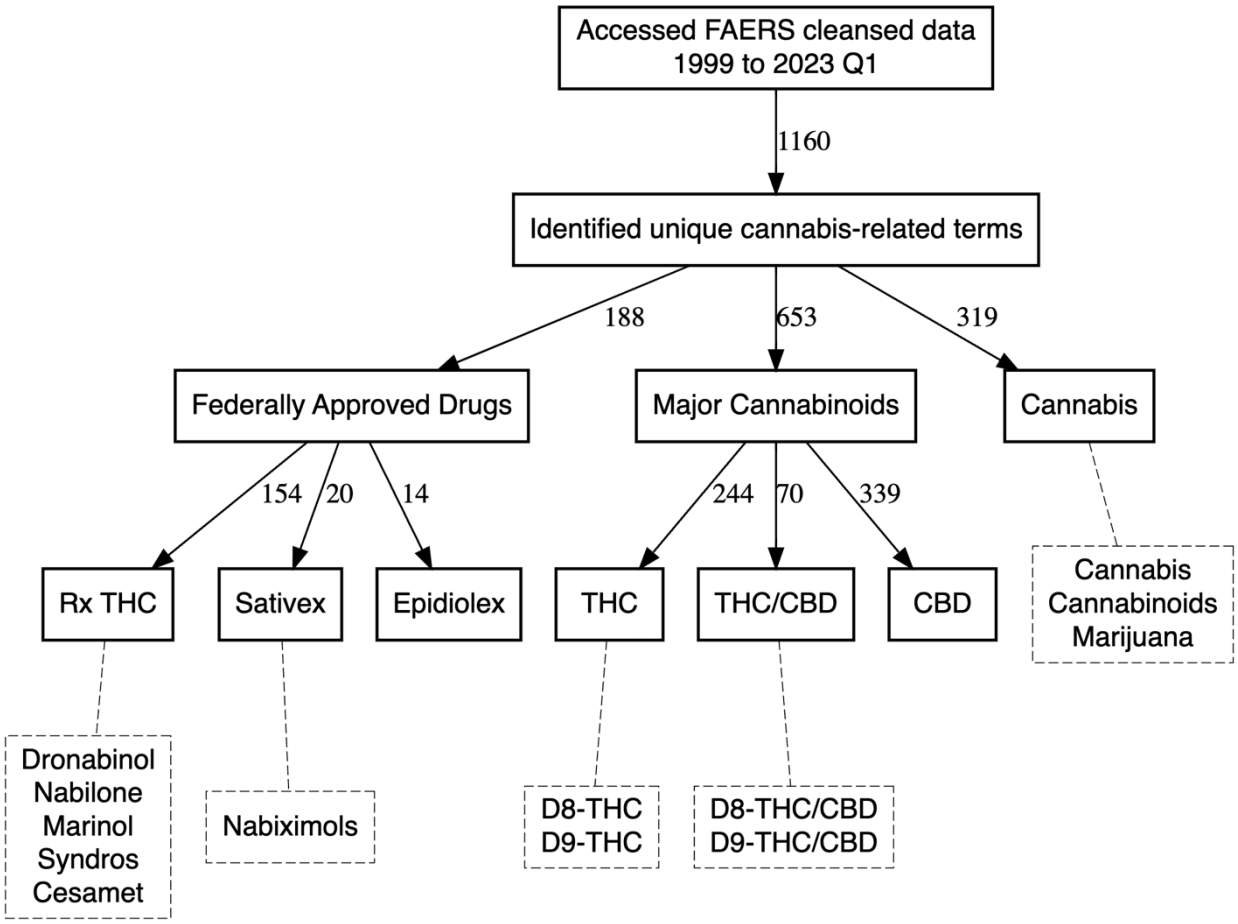

Figure 2. Schematic representation of the cannabis-related search terms and categorization of groups used to filter AER and utilized for descriptive analysis. The diagram categorizes identified terms into three high-level categories: Federally Approved Drugs, Major Cannabinoids, and Cannabis. The numbers displayed next to each arrow represent the total number of unique terms identified for each CDP group. Dotted boxes indicate the products included within each CDP group.

2.3.2 Characteristics of Cannabis Derived Product Reports

We identified 42,530 unique reports linked to CDPs, of which the most frequently reported was Cannabis (n = 14,653; 33.9%), followed by Epidiolex (n = 13,758; 31.8%), Rx THC (n = 8,637; 20.0%), CBD (n = 3,976; 9.2%), and THC (n = 1,433; 3.3%) (Table 3). Pharmaceutical CDPs (Rx THC, Epidiolex, and Sativex) accounted for more than half of the total CDP reports (53.2%), while non-pharmaceuticals (THC, THC/CBD, CBD, and Cannabis) constituted 46.8%.

Overall, the demographic characteristics varied across CDPs, although some similarities were noted. Nearly 93% of the Epidiolex reports were flagged as the primary suspect drug (n = 12,788; 92.9%), and among the total number of reports, the majority involved infants aged 0-12 years old (n = 638; 4.6%), despite a large amount of missing data. Reports for CBD, Rx THC, and Sativex predominantly involved women and adults aged 36 to 70+, and often flagged as concomitant drugs in most reports. Conversely, THC and Cannabis were mostly reported by men and adults aged 18 to 54 years, with both products mostly reported as secondary suspects.

In terms of serious outcomes, the “Other” category was the most reported across all CDPs (n = 18,008; 44.9%), followed by hospitalization (n = 12,588; 31.4%). Notably, death was flagged in more than 20% of THC and Cannabis reports (28.3% and 21.2%, respectively). Reporting trends reflected the availability of marketed CDP by geographic location. Most CDP-AERs originated from the U.S. (n = 29,867; 70.2%), except for Sativex, where 92.5% (n = 571) of the reports were identified from Europe. Finally, CDP reports were predominantly submitted by healthcare professionals (n = 1,779; 4.2%) and consumers (n = 1,429; 3.4%).

Table 3. Patient demographics characteristics with reported use of CDPs queried from FAERS between Q1 1999 and Q1 2023

Characteristic	All terms (n = 42,530)	Federally Approved Drugs			Major Cannabinoids			Cannabis
		Rx THC (n = 8,637)	Epidiolex (n = 13,758)	Sativex (n = 617)	THC (n = 1,433)	THC/CBD (n = 127)	CBD (n = 3,976)	Cannabis (n = 14,653)
Age in years, n (%)								
0-12	1249 (2.9)	118 (1.4)	638 (4.6)	4 (0.6)	16 (1.1)	5 (3.9)	328 (8.2)	155 (1.1)
13-17	1440 (3.4)	201 (2.3)	230 (1.7)	0 (0)	61 (4.3)	4 (3.1)	96 (2.4)	856 (5.8)
18-35	6837 (16.1)	764 (8.8)	424 (3.1)	54 (8.8)	605 (42.2)	29 (22.8)	395 (9.9)	4713 (32.2)
36-54	6607 (15.5)	1695 (19.6)	180 (1.3)	328 (53.2)	395 (27.6)	41 (32.3)	698 (17.6)	3437 (23.5)
55-69	4530 (10.7)	1970 (22.8)	72 (0.5)	123 (19.9)	115 (8.0)	19 (15.0)	684 (17.2)	1666 (11.4)
70+	2283 (5.4)	1249 (14.5)	17 (0.1)	16 (2.6)	34 (2.4)	8 (6.3)	475 (11.9)	515 (3.5)
Missing	19,584 (46.0)	2640 (30.6)	12,197 (88.7)	92 (14.9)	207 (14.4)	21 (16.5)	1300 (32.7)	3311 (22.6)
Sex, n (%)								
Female	14,228 (33.5)	4190 (48.5)	1678 (12.2)	394 (63.9)	524 (36.6)	69 (54.3)	2131 (53.6)	5520 (37.7)
Male	15,866 (37.3)	3918 (45.4)	1990 (14.5)	204 (33.1)	762 (53.2)	49 (38.6)	1234 (31.0)	7996 (54.6)
Missing	12,436 (29.2)	529 (6.1)	10,090 (73.3)	19 (3.1)	147 (10.3)	9 (7.1)	611 (15.4)	1137 (7.8)
Role, n (%)								
Primary suspect drug	14,408 (33.9)	775 (9.0)	12,788 (92.9)	7 (1.1)	346 (24.1)	61 (48.0)	353 (8.9)	78 (0.5)
Secondary suspect drug	9729 (22.9)	649 (7.5)	157 (1.1)	68 (11.0)	736 (51.4)	16 (12.6)	637 (16.0)	7656 (52.2)
Interacting drug	474 (1.1)	55 (0.6)	40 (0.3)	5 (0.8)	54 (3.8)	6 (4.7)	148 (3.7)	189 (1.3)
Concomitant drug	17919 (42.1)	7158 (82.9)	773 (5.6)	537 (87.0)	297 (20.7)	44 (34.6)	2838 (71.4)	6730 (45.9)
Outcome, n (%)								
Hospitalization	12,588 (31.4)	3459 (36.7)	2942 (42.5)	281 (42.6)	409 (22.0)	46 (30.3)	915 (25.6)	4703 (25.8)
Life-threatening	1287 (3.2)	338 (3.6)	47 (0.7)	32 (4.8)	105 (5.6)	16 (10.5)	123 (3.4)	650 (3.6)
Death	6863 (17.1)	1527 (16.2)	837 (12.1)	17 (2.6)	526 (28.3)	1 (0.7)	188 (5.3)	3869 (21.2)
Other	18,008 (44.9)	3839 (40.7)	3056 (44.2)	308 (46.7)	650 (34.9)	59 (38.8)	2123 (59.5)	8363 (45.8)
Disability	879 (2.2)	188 (2.0)	27 (0.4)	22 (3.3)	54 (2.9)	11 (7.2)	156 (4.4)	441 (2.4)
Congenital Abnormality	189 (0.5)	20 (0.2)	5 (0.1)	0 (0)	9 (0.5)	0 (0)	4 (0.1)	152 (0.8)
Required Intervention	320 (0.8)	58 (0.6)	4 (0.1)	0 (0)	107 (5.8)	19 (12.5)	59 (1.7)	79 (0.4)
Reporting country, n (%)								
Canada	4507 (10.6)	1426 (16.5)	12 (0.1)	22 (3.6)	59 (4.1)	20 (15.7)	793 (19.9)	2359 (16.1)
United States	29,867 (70.2)	6066 (70.2)	13,355 (97.1)	9 (1.5)	803 (56.0)	93 (73.2)	2407 (60.5)	7446 (50.8)
Europe	6012 (14.1)	675 (7.8)	219 (1.6)	571 (92.5)	358 (25.0)	13 (10.2)	581 (14.6)	3745 (25.6)
Other	836 (2.0)	45 (0.5)	125 (0.9)	12 (1.9)	104 (7.3)	1 (0.8)	130 (3.3)	425 (2.9)
Missing	1308 (3.1)	425 (4.9)	47 (0.3)	3 (0.5)	109 (7.6)	0 (0)	65 (1.6)	678 (4.6)
Reporter Source, n (%)								
Consumer	1429 (3.4)	185 (2.1)	23 (0.2)	0 (0)	249 (17.4)	55 (43.3)	387 (9.7)	559 (3.8)
Health Professional	1779 (4.2)	718 (8.3)	137 (1.0)	1 (0.2)	204 (14.2)	10 (7.9)	80 (2.0)	642 (4.4)
Others	636 (1.4)	138 (1.7)	3 (0.02)	5 (0.8)	61 (4.3)	0 (0)	3 (0.1)	428 (2.9)
Missing	38,686 (91.0)	7596 (87.9)	13,595 (98.8)	611 (99.0)	919 (64.1)	62 (48.8)	3506 (88.2)	13,024 (88.9)

Note: The estimated numbers of CDP reports are not mutually exclusive because people could have reported more than one suspected CDP in FAERS. Percentages were calculated using the total number of reports for each specific CDP as the denominator.

2.3.3 Preferred Terms Reported with Cannabis Derived Products

Table 4 presents the 15 most reported PTs stratified by CDP and ranked by occurrence at the PT level. Overall, the most reported PTs for all CDPs included seizure (n = 4,787; 11.3%), drug abuse (n = 3,190; 7.5%), fatigue (n = 2,928; 6.9%), diarrhea (n= 2,829; 6.7%), and nausea (n = 2,701; 6.4%). Although this ranking varied by group, we noted some similarity between pharmaceutical CDPs and their non-pharmaceutical CDPs. Amongst the top 15 PTs, commonly PTs among Rx THC and THC, included nausea, vomiting, fatigue, and dyspnoea. Similarly, we also observed similar PTs reported with Epidiolex and CBD, such as drug ineffective, off-label use, seizure, diarrhea, condition aggravated, vomiting, somnolence, and fatigue. Among the non-pharmaceutical CDPs, more than half of the THC and Cannabis PTs were drug use-related effects. Conversely, PTs reported with pharmaceutical CDPs were mostly related to the pathophysiology of a related medical condition rather than drug abuse-related events.

Table 4. The top 15 PTs and number of cases displayed by CDP

All terms (n = 42,530)		Rx THC (n = 8,637)		Epidiolex (n = 13,758)		Sativex (n = 617)		THC (n = 1,433)		THC/CBD (n = 127)		CBD (n = 3,976)		Cannabis (n = 14,653)	
Seizure	4787 (11.3)	Nausea	1002 (11.6)	Seizure	4170 (30.3)	Fatigue	115 (18.6)	Toxicity to various agents	298 (20.8)	Nausea	20 (15.7)	Fatigue	482 (12.1)	Drug abuse	2936 (20.0)
Drug abuse	3190 (7.5)	Pain	779 (9.0)	Product use in unapproved indication	1674 (12.2)	Covid-19	99 (16.0)	Drug abuse	165 (11.5)	Anxiety	16 (12.6)	Drug ineffective	474 (11.9)	Nausea	1029 (7.0)
Fatigue	2928 (6.9)	Fatigue	774 (9.0)	Diarrhoea	1183 (8.6)	Headache	77 (12.5)	Overdose	118 (8.2)	Dyspnoea	16 (12.6)	Off label use	406 (10.2)	Toxicity to Various Agents	1022 (7.0)
Diarrhoea	2829 (6.7)	Diarrhoea	682 (7.9)	Somnolence	832 (6.0)	Multiple sclerosis relapse	76 (12.3)	Drug interaction	104 (7.3)	Vomiting	15 (11.8)	Nausea	375 (9.4)	Pain	1012 (6.9)
Nausea	2701 (6.4)	Vomiting	672 (7.8)	Product dose omission issue	782 (5.7)	Muscle spasticity	61 (9.9)	Vomiting	100 (7.0)	Dizziness	13 (10.2)	Diarrhoea	336 (8.5)	Drug ineffective	968 (6.6)
Off label use	2532 (6.0)	Death	620 (7.2)	Off label use	731 (5.3)	Gait disturbance	57 (9.2)	Nausea	82 (5.7)	Feeling abnormal	12 (9.4)	Pain	295 (7.4)	Fatigue	968 (6.6)
Drug ineffective	2515 (5.9)	Off label use	591 (6.8)	Death	635 (4.6)	Urinary tract infection	56 (9.1)	Dyspnoea	79 (5.5)	Headache	12 (9.4)	Arthralgia	361 (6.6)	Drug dependence	920 (6.3)
Pain	2169 (5.1)	Drug ineffective	521 (6.0)	Weight increased	616 (4.5)	Fall	55 (8.9)	Pulmonary oedema	74 (5.2)	Heart rate increased	12 (9.4)	Headache	258 (6.5)	Substance abuse	823 (5.6)
Vomiting	2053 (4.8)	Decreased appetite	502 (5.8)	Fatigue	610 (4.4)	Asthenia	52 (8.4)	Dizziness	70 (4.9)	Off label use	9 (7.1)	Dizziness	243 (6.1)	Off label use	781 (5.3)
Product Use in Unapproved Indication	2021 (4.8)	Weight decreased	486 (5.6)	Hospitalization	553 (4.0)	Nasopharyngitis	52 (8.4)	Anxiety	69 (4.8)	Tremor	9 (7.1)	Drug interaction	233 (5.9)	Headache	732 (5.0)
Death	1813 (4.3)	Asthenia	450 (5.2)	Drug ineffective	551 (4.0)	Pain	50 (8.1)	Tremor	66 (4.6)	Arthralgia	8 (6.3)	Seizure	217 (5.5)	Overdose	705 (4.8)
Somnolence	1785 (4.2)	Dyspnoea	445 (5.2)	Weight decreased	525 (3.8)	Pain in Extremity	48 (7.8)	Heart rate increased	65 (4.5)	Blood pressure increased	8 (6.3)	Vomiting	200 (5.0)	Vomiting	688 (4.7)
Weight decreased	1655 (3.9)	Headache	401 (4.6)	Decreased appetite	458 (3.3)	Muscular weakness	45 (7.3)	Drug screen positive	64 (4.5)	Loss of consciousness	8 (6.3)	Cough	198 (5.0)	Arthralgia	686 (4.7)
Headache	1563 (3.7)	Insomnia	398 (4.6)	Condition aggravated	418 (3.0)	Pyrexia	42 (6.8)	Fatigue	60 (4.2)	Condition aggravated	7 (5.5)	Somnolence	194 (4.9)	Anxiety	671 (4.6)
Toxicity to various agents	1516 (3.6)	Pneumonia	350 (4.1)	Vomiting	338 (2.5)	Off label use	41 (6.6)	Aggression	59 (4.1)	Drug ineffective	7 (5.5)	Condition aggravated	178 (4.5)	Diarrhoea	617 (4.2)

Note: CDP reports can contain more than one PT. Percentages were calculated using the total number of reports for each specific CDP as the denominator.

2.3.4 Reporting Trends Over Time

We observed a consistent increasing of total number of reports for all CDPs (n = 42,530) throughout the study period, of which, 93% (n = 39,545) were identified between Q1 2013 and Q1 2023. Figure 3 presents the reporting rates for CDPs identified during the same study period. Reporting rates were calculated as the ratio of the number of reports for each CDP in a given year to the total number of all CDP reports in the same year (e.g., number of reports for Cannabis in 1999 divided by the total number of all CDP reports in 1999). Reporting rates during the first 15-17 years of the study period (1999-2016) were dominated by Cannabis followed by Rx THC-related AERs and increased gradually from <50/year to ~500/year. During the subsequent five years (2017-2022), reporting rates stabilized for Rx THC whereas those for Cannabis nearly tripled and those for newly emerging Epidiolex and CBD groups increased sharply (Figure 3).

The reporting rates for CDPs demonstrated notable trends and shifts. Cannabis consistently showed the highest reporting rates among all CDPs throughout the study period, with higher rates, in 2002 (0.70) and in 2003 (0.67). However, a notable decline occurred after 2018, with the rate dropping to 0.23 in 2019, the lowest rate observed for Cannabis during the study period. Rx THC started with a relatively high reporting rate at 0.45 in 1999, followed by a decline after 2018. In contrast, no case reports for Epidiolex were identified until 2017, after which reporting rates peaked in 2019 (0.49) and 2021 (0.51), before slightly declining in 2022 (0.41) (Table 5).

CBD showed a consistent increase in reporting rates, with spikes from 2014 to 2018 (0.001 to 0.10), and from 2019 to 2022 (0.09 to 0.13). THC demonstrated a variable pattern, with

peaks in 2002 (0.15) and 2010 (0.14), but reporting rates remained relatively low over the years. Sativex and THC/CBD showed minor increases, presenting low reporting rates.

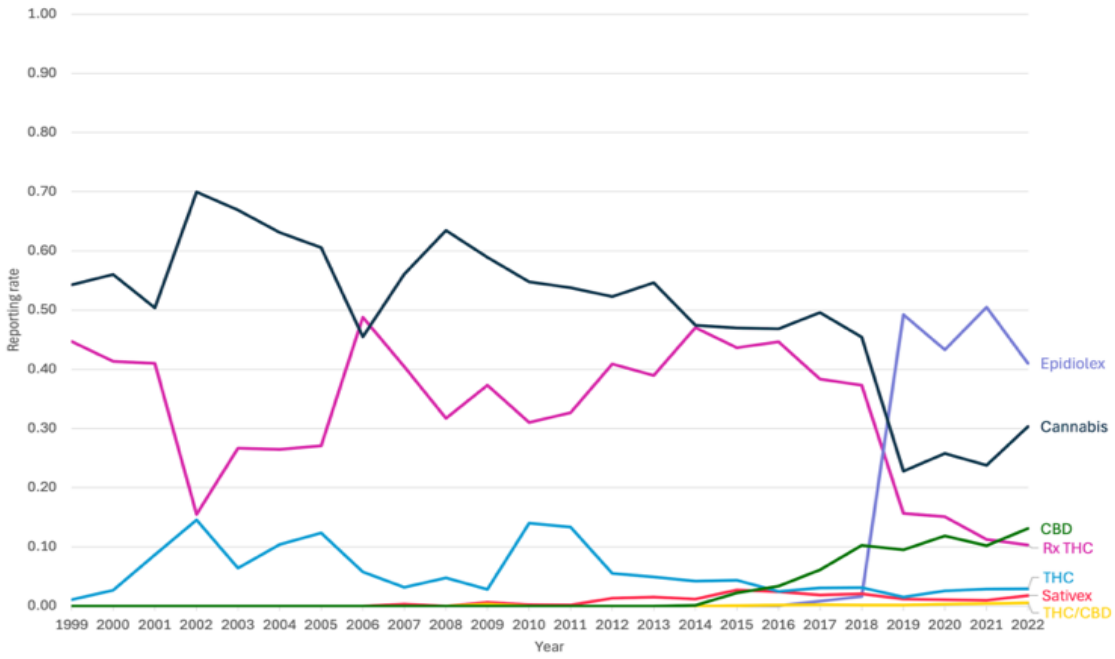

Figure 3. Reporting rates for CDPs (Q1 1999 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

Table 5. Key dates of CDP reports identified in FAERS and regulatory approvals

	CDP	FAERS 1st Year (cases)	Medical Approval 1st Year (region)	Recreational Approval 1st Year (region)
Non-Rx	Cannabis	1999 (51)	1996 (U.S.) 2001 (Canada) 2013 (Europe)	2012 (U.S.) 2018 (Canada) 2021 (Europe)
	THC	1999 (1)		
	CBD	2014 (1)		
	THC/CBD	2015 (1)		
Rx	Sativex	2007 (2)	2005 (HC) 2010 (EMA)	NA
	Epidiolex	2017 (14)	2018 (FDA) 2019 (EMA)	NA
	Rx THC	1999 (42)	1981 (HC) 1985 (FDA) 2010 (EMA)	NA

The table displays the first year a CDP report was identified in FAERS, the number of cases, and the first year and region where CDP was approved by a regulatory agency or legalized for medical or recreational use.
Abbreviations: *EMA* European Medicines Agency, *FDA* U.S. Food and Drug Administration, *HC* Health Canada, *NA* not applicable, *Non-Rx* non-pharmaceutical CDP, *Rx* pharmaceutical CDP

2.3.5 Temporal Analysis by Age and Gender of Non-Pharmaceutical Cannabis Derived Products

From Q1 2012 to Q4 2022, we observed a trend in reporting rates for gender for THC, with men consistently reporting at higher rates relative to women (Figure 4). However, notable shifts were observed in 2014, 2015, and 2022 with women's reporting surpassing men's. Surprisingly, reporting rates for men decreased by one-third from 2012 (0.09) to 2022 (0.03), whereas rates for women doubled (from 0.02 to 0.04) over the same period.

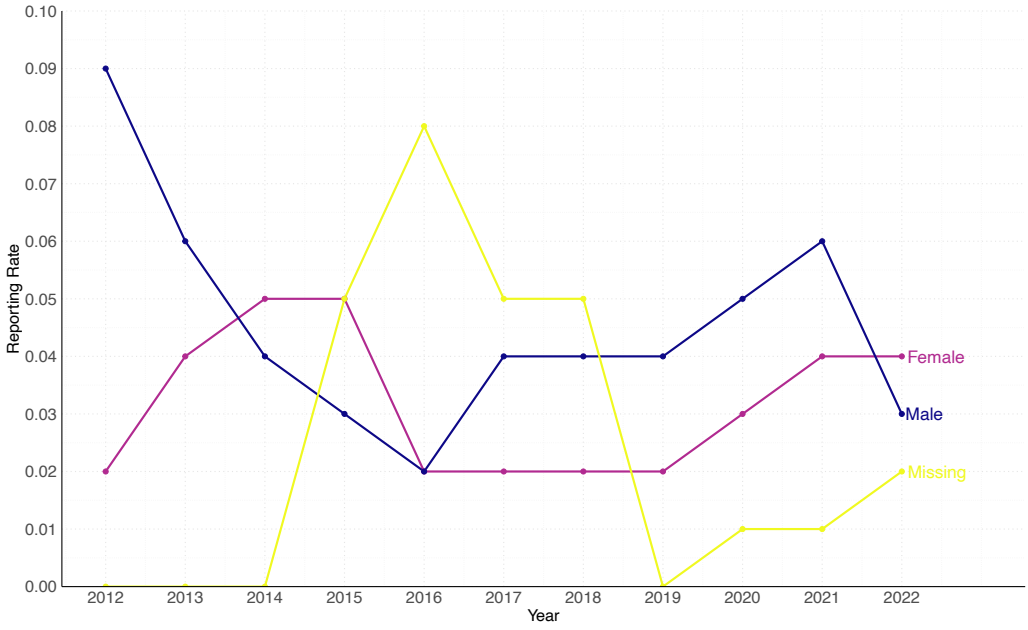

Figure 4. Reporting rates for THC stratified by gender (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

The stratification analysis by age for THC demonstrated distinct reporting trends across all demographic groups (Figure 5). The 18-35 age group consistently showed the highest reporting rates throughout the study period, with peaks observed in 2013 and 2021 (0.11 for both years). Adults aged 36-54 also showed relatively high rates, following behind the 18-35 group. Interestingly, in 2015, we noted spikes in reporting rates for infants (0-12) and older adults (70+) with rates at 0.14 and 0.07, respectively. However, these rates declined in the subsequent years, with no reports observed for the 0-12 group by 2022 and a 43% decrease in the rate for 70+ group by the same year.

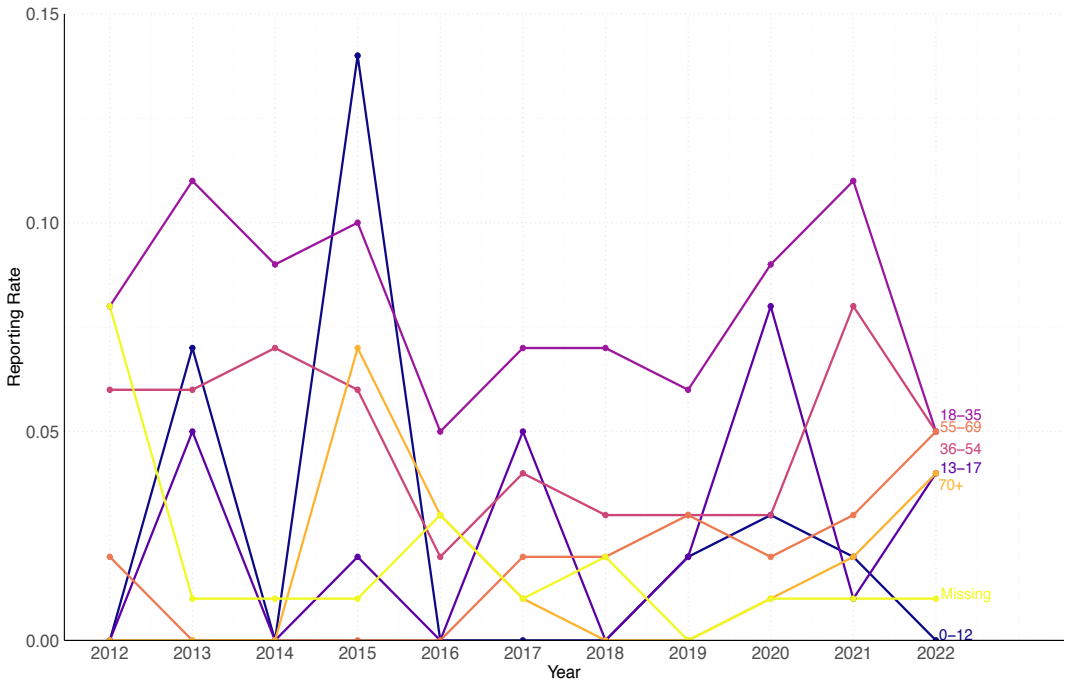

Figure 5. Reporting rates for THC stratified by age (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

Between 2014 to 2022, CBD reporting rates steadily increased for both genders (Figure 6), with women consistently reported at higher rates than men. From 2018 to 2020, we noted a 1.7-fold increase in the rates for women (from 0.14 to 0.24) and a 2.3-fold increase for men (from 0.06 to 0.14). Notably, the highest reporting rates for both genders were observed in 2020, with women's rate at 0.24 and men's at 0.14. After 2020, reporting rates stabilized and slightly declined for both groups by 2022.

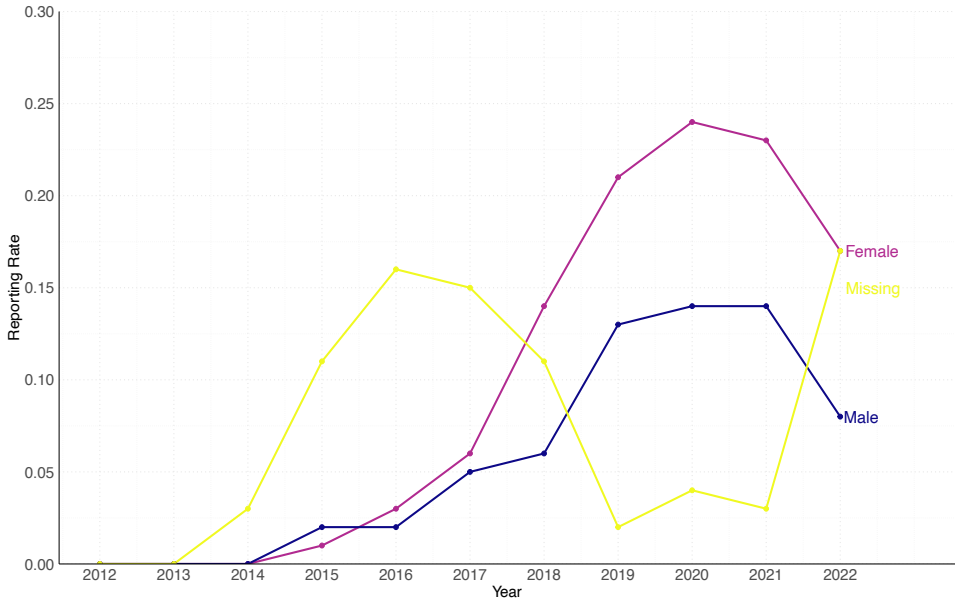

Figure 6. Reporting rates for CBD stratified by gender (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

We observed a consistent upward trend in reporting rates for all CBD demographic groups (Figure 7). Infants (0-12) showed a 1.6-fold increase (from 0.29 to 0.46) from 2015 to 2020, with the highest rate observed in 2018 (0.47). However, a decline was noted after 2020. The 70+ group demonstrated the second highest reporting rates during this period, surpassing infants in 2021 (0.37) and 2022 (0.27). We also noted a marked increase in the reporting rates for middle-aged adults (55-69), with rates increasing twofold from 0.12 in 2018 to 0.24 in 2022.

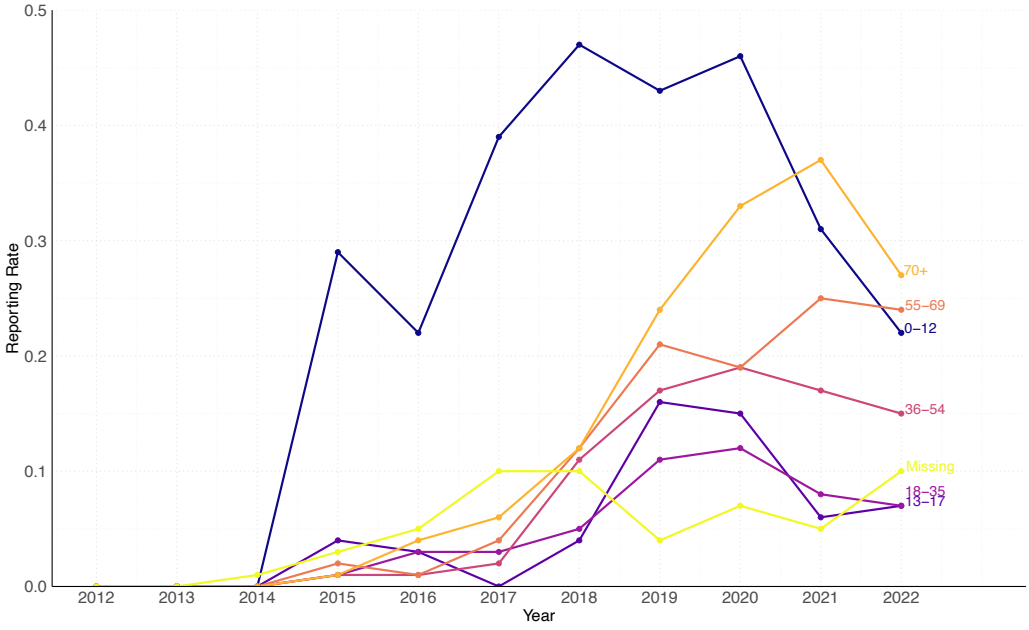

Figure 7. Reporting rates for CBD stratified by age (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

A downward trend in Cannabis reporting rates for both genders was observed from Q1 2012 to Q4 2022 (Figure 8). Throughout this period, men consistently reported at higher rates relative to women. The peak reporting rates was observed early in the decade, with the highest rate for men in 2013 (0.58) and women in 2012 (0.52).

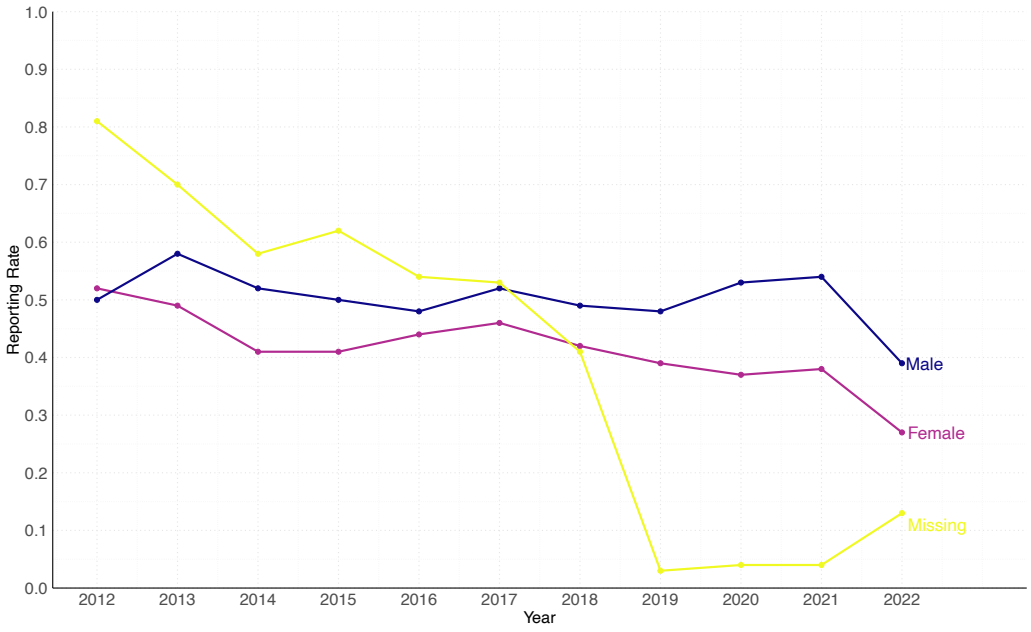

Figure 8. Reporting rates for Cannabis stratified by gender (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

The stratification by age for Cannabis indicated considerable fluctuations across all age groups (Figure 9). Adults aged 18-35 years consistently demonstrated the highest reporting rates throughout the period, with a peak in 2013 (0.77). A remarkable shift was noted for older adults (70+), who showed a steady rise in reporting rates, resulting in a 9.6-fold increase in reporting rates over 10 years. The 55-69 age group also showed a rise, with rates increasing from 0.22 in 2012 to 0.38 in 2022, representing a 73% increase. In contrast, reporting rates declined in the 0-12, 13-17, 18-35, and 36-54 age groups, with a notable decrease observed among infants and youth.

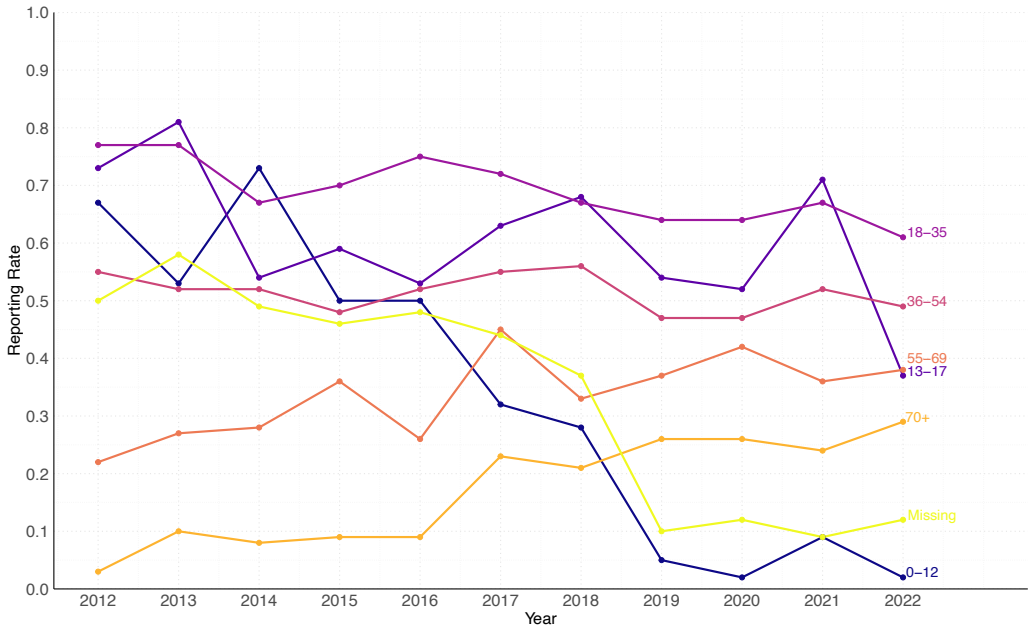

Figure 9. Reporting rates for Cannabis stratified by age (Q1 2012 to Q4 2022). Reporting rates for each product were standardized to the total number of all CDP reports for a given year and are presented with their proportions.

2.4 DISCUSSION

Our descriptive study assessed the feasibility of using FAERS for CDP safety surveillance by evaluating AERs related to seven CDPs from Q1 1999 to Q1 2023. We evaluated the self-reported terminologies used to describe CDP reports and identified a total of 1160 unique terms, of which the majority (77.7%) were non-pharmaceutical CDPs (e.g., THC, THC/CBD, CBD, and Cannabis). Multiple names were employed to describe these products, encompassing a range of categories, including botanical species nomenclatures, legal status of the products, and chemical variants. The extensive use of disparate terminology, frequently lacking uniformity and specificity, may result in ambiguity, thereby posing challenges in coding and classifying CDPs into the appropriate groups. This, in turn, may limit the validity of signal detection screening for CDP safety surveillance. It is, therefore, incumbent upon professionals to consider the potential for ambiguity in the identification of CDPs in SRSs when contemplating their utility.

Assessing self-reported terminology of pharmaceutical CDPs may also require a higher amount of data cleaning than is standard, as a variety of terms can also be used to describe a single product (herbal or pharmaceutical), and terms for the same compound (active ingredient) may be used interchangeably (e.g., Epidiolex and CBD), making it difficult to establish a direct link between specific products and their unique features. In addition, the same active compound (e.g. THC) may be listed in reference to different types of products (e.g. flower, oil, concentrate, edible, pharmaceutical) and consumed in different ways (e.g. inhalation, oral, topical, intranasal). Therefore, our terminology analysis reflects the heterogeneity, complexity and ambiguity of CDPs highlighting the importance of considering how cannabis nomenclatures relate to variables

of importance when coding, cleaning and evaluating case reports related to CDP use for signal detection studies, as emphasized by previous research [43].

We identified a total of 42,530 unique CDP reports queried from FAERS from Q1 1999 to Q1 2023. Of the total number of CDP reports, 53.2% were associated with pharmaceutical CDPs, including Rx THC, Epidiolex, and Sativex. Given that FAERS is a well-established post-marketing surveillance system for pharmaceutical drugs [38], which are subject to legislative requirements for mandatory reporting, the predominance of AERs related to pharmaceutical CDPs was aligned with expectations.

Our descriptive analysis demonstrated a consistent temporal increase in reporting across all CDPs and reflected similar heterogeneous reporting patterns and trends that would be expected with established demographic profiles of CPD use. For pharmaceutical CDPs, such as Epidiolex, we observed the predominance of reports among infants (0-12), consistent with its FDA-approved indication for the treatment of refractory seizures in individuals two years of age and older [22]. Sativex is approved for the treatment of spasticity in patients with multiple sclerosis, and research has shown that women are more highly susceptible to developing this condition [44]. Reflecting this susceptibility, our analysis showed that nearly 64% of the total reports of Sativex were submitted by female subjects. These findings suggested that FAERS highlighted well-known patient population patterns for pharmaceutical CDP use, which can be related as to ‘positive controls’.

Our study demonstrated the potential for FAERS to accrue AERs for non-standardized and unregulated CDPs, which represented 46.8% of the total CDP reports, including THC, THC/CBD, CBD, and Cannabis. Heterogenous reporting patterns were observed among

chemically distinct non-pharmaceutical CDPs (e.g., THC versus CBD), as well as among CDPs that share the same active ingredient (e.g., Epidiolex versus CBD and Rx THC versus THC). Despite this heterogeneity, the reporting patterns and trends identified in our study for non-pharmaceutical CDPs, may reflect the expected usage patterns within the population. The demographic trends in CBD reporting demonstrated that women consistently reported CBD at higher rates compared to men. Recent studies demonstrated that women are more likely to use CBD for its therapeutic potential in managing conditions such as premenstrual pain, anxiety, depression and sleep disorders [45, 46]. In terms of age, our analysis identified a 1.6-fold increase in reporting rates among infants from 2015 to 2020, with the highest rate observed in 2018. Interestingly, Epidiolex was approved by the FDA in 2018, suggesting that this increase may be linked to therapeutic potential of CBD in this population or may be also influenced by reporting bias. Older adults (70+) and middle-aged adults (55-69) also emerged as significant groups reporting CBD. A cross-sectional study demonstrated an increase in CBD use by middle-aged and older adults to treat diverse medical conditions, particularly pain, anxiety and depression [45].

We identified gender and age trends in THC reporting. Surprisingly, these patterns were not observed in Rx THC, instead, demographic characteristics of THC were more congruent with those of Cannabis. Previous studies demonstrated that commercially available cannabis products contain higher amounts of THC relative to CBD and other compounds [46,48]. In addition, a systematic and meta-analysis study showed that the concentrations of THC in cannabis products increased by approximately 0.29% each year from 1970 to 2017 [49]. Moreover, published evidence on the population characteristics and prevalence of THC use is often confounded by

studies that broadly assess ‘cannabis for non-medical use’ without distinguishing which specific cannabinoids were involved [48].

Overall gender reporting patterns for both THC and Cannabis indicated that men consistently reported at higher rates than women from Q1 2012 to Q4 2022. Studies of cannabis use found that past-months use is higher in males than females [50]. The trends for THC among females showed remarkable shifts, with reporting rates increasing twofold from 2012 to 2022, surpassing those of men in 2022. This shift was not observed in Cannabis, where female reporting rates consistently remained lower than men’s. Interestingly, previous studies demonstrated an increase in cannabis use prevalence among US women of reproductive age from 2002 to 2014 [51], including among pregnant [52]. In addition, Cuttler et al (2016) showed a higher percentage of women reporting using cannabis for medical purposes [53]. Evidence showed that women are using medical and recreational cannabis for the treatment of menstrual-related cramps, mood symptoms, and endometriosis-related pain, which may contribute to reduction of perceived risk [54].

Regarding age, heterogenous reporting trends were identified for both CDPs, yet common patterns were observed that may reflect patterns of use among real population. Adults aged 18-35 years consistently demonstrated the highest reporting rates throughout the period with a peak in 2013. A recent survey conducted from 2016 and 2019 evaluated the frequency of cannabis use and related sociodemographic characteristics among U.S. adults and demonstrated that higher frequency cannabis use is more prevalent among young adults (18-34) [55]. Our results demonstrated that while reporting rates for Cannabis increased among older adults (70+), there was a decrease in reporting rates for THC within this age group. A secondary analysis of

the National Survey on Drug Use and Health data showed a 75% relative increase in the prevalence of past-year cannabis use among adults aged 65+ between 2015 and 2018 [56]. Overall, this heterogeneity may reflect motivations or indications for cannabis use. Haug et al (2017) compared cannabis patterns and motives among three age groups (18–30, 31–50, and 51–72) and found that the motives of cannabis use for each demographic differed, with the 31-50 age group more likely to use cannabis for insomnia, older adults use it for chronic conditions, such as cancer, glaucoma, and HIV/AIDS, and younger adults for recreational use [50]. In summary, while chemically similar CDPs (e.g., Epidiolex versus CBD and Rx THC versus THC) may share the same active ingredient, a combination of factors related to ambiguity of terms, indications, patient demographics, and reporting behaviors can lead to distinct reporting trends and patterns. Similarly, while Cannabis and THC exhibited comparable patterns and behaviors, these factors may also influence the validity for signal detection studies. Therefore, tailored approaches that accounts for the CPD-specific context, terminology, and demographic characteristics demonstrated to be crucial steps for using FAERS for CDP safety surveillance.

The rise in CDP reporting and the observed trends highlighted the evolving and increasingly diverse landscape of CDPs in the context of changing legal frameworks in the U.S. and abroad. We observed that 93% of the total number of CDP reports were dated from 2013 to 2023, and only 7% from 1999 to 2012. Legal status, stigma, and social environment may have limited CDP reporting historically [40]. However, a turning point in 2012, followed by the legalization of recreational cannabis in the U.S., might have contributed to broader CDP use in diverse demographic groups [12]. Compton et al. (2016) demonstrated that cannabis use increased from 10.4% to 13.3% in adults in the U.S. from 2002 to 2014, and the prevalence of perceived great risk of harm from smoking cannabis decreased from 50.4% to 33.3% [13]. The

upward trend identified in the CDP reporting after 2012 might have reflected the progressive shift from medical cannabis legalization in one U.S. state in 1996, to medical cannabis being legal in 23 states by 2015, and by 2023, cannabis was legalized for medical in 38 states and recreational use in 24 states, perhaps contributing to a steep rise in increasing reporting rates for cannabis and major cannabinoid groups [10]. This temporal trend observed in our study, might also suggest increased awareness of the cannabinoids' therapeutic benefits and reduced perceived risks [14]. The loosened regulatory enforcement and reduced stigma and criminality, possibly reflected in behavioral changes within the population, resulting in more widespread use and a rise in reporting of CDPs.

The introduction of novel cannabis legislation and policies, such as the legalization of recreational cannabis in Canada and the enactment of 2018 Farm Bill in U.S., which effectively legalized the outdoor cultivation of hemp and the sale of related products likely played a role in the expansion of CDPs, including CBD and its derivates, such as the emerging D8-THC [57]. Our findings indicated a 1.3-fold-increase in reporting rates for CBD between 2018 and 2022. A recent cross-sectional study identified a 50% increase in past-year prevalence of CBD use between 2019 and 2023 [58].

In addition, 2018 marked a period of considerable changes in reporting rates for individual CDPs. Epidiolex was approved by the FDA in 2018 and by the EMA in 2019 [22]. Remarkable increasing in reporting rates were observed in 2019 and 2021. Following the release of a new drug, there might be heightened reporting of ADRs as healthcare providers, patients, and other stakeholders become more familiar with its use. This phenomenon is known as the Weber Effect [59]. Conversely, reporting rates for Rx THC, THC and particularly Cannabis,

which consistently showed the highest reporting rates throughout the study period, all declined after 2018. This decline may reflect shifts in the context of evolving cannabis industry, which has allowed the introduction of new products into the market. CDPs such as Cannabis, which previously dominated the market, are now sharing market space with newer variety of products [60]. This shift may impact the distribution of consumer use and reporting behaviors.

The analysis of the 15 most reported PTs revealed heterogenous patterns across CDPs. Despite this variability, several similarities and differences emerged between pharmaceutical CDPs and their non-pharmaceutical equivalents. While Rx THC and THC shared common PTs like nausea, vomiting, fatigue, and dyspnoea, which may reflect pharmacological effects related to the consumption of D9-THC [25], Rx THC AEs were more associated with health conditions. In contrast, THC showed a higher reporting for drug use related events, likely reflecting its recreational use. Interestingly, we noted that PTs reported for Cannabis were similarly drug use related, suggesting predominant recreational use, potential overlapping usage patterns or reporting bias. Epidiolex and CBD demonstrated several similarities in the reported PTs, including seizure. As shown in our demographic analysis, a higher proportion of infants are reporting CBD, which may reflect that both products are being used for the same indication by the same patient population.

Reported AEs are related to the patterns of use of CDPs by individuals directly [61]. Therefore, the discrepancies observed for PTs across CDP groups may be attributed to the varying user profiles, in terms of both demographics reason for use (medical or adult purposes). Overall, we noted that PTs for pharmaceutical CDPs were related to the underlying medical condition being treated, whereas non-pharmaceutical CDPs were more drug use related.

The information in these reports reflects only the reporter's observations and opinions [38]. It is therefore necessary to conduct signal detection studies using advanced statistical methods in order to quantify ADRs and identify potential safety signals associated with the use of CDPs. Disproportionality analysis methods must be employed in order to evaluate the potential excess of reported adverse events in comparison to what would be expected to be associated with the use of a cannabinoid product. These findings are worthy of further exploration and continued surveillance.

Pharmacovigilance studies based on SRSs have several inherent biases that include confounding by indication, which occurs when the adverse event is related to the disease being treated [62]. This is noted in the seizure reports with Epidiolex and CBD. Another challenge in the use of SRSs is potential for stimulated reporting, which could result from several factors, including new safety warnings by regulators or occur after prominent publications and is commonly known as notoriety bias in signal detection studies [63].

We identified a large proportion of missing data on patient demographics, particularly related to age, gender, and reporter source. Incompleteness and inaccuracies in FAERS contribute to data quality concerns which may result in selection bias, thus limiting its interpretation [64]. Additionally, FAERS cannot be used to estimate incidence rates, as it lacks detailed information on drug utilization, including the absence of a denominator [65]. The voluntary nature of SRS relies solely on the individual’s motivation to report a perceived experience of an ADR [66], hence resulting in underreported AEs and potentially leading to reporting bias [67]. Additional variables may impact the validity of reporting and influence underreporting, including social stigma, social environment and legal status associated with CDP

use [36]. In addition, in the case of psychoactive CDP use, altered cognitive function and memory impairment may limit accurate reporting.

We observed that patients' characteristics varied between CDPs, and since FAERS does not collect risk factors or comorbidities, this could result in unmeasured confounding factors when designing a signal detection study [68]. Moreover, we noted that the second-highest reported PT for all the CDPs was drug abuse, implying the presence of selection bias. Previous research has suggested that serious events tend to be reported more often than non-serious events [69], which can vary by drug and PT and affect the estimates [70].

Our analysis showed concordance with the PTs reported for pharmaceutical CDPs on product labels and in previous studies, but differences noted for PTs could also result from distinct coding strategies. Here, we presented the diversity and complexity of terminologies used to describe CDPs, which can make it difficult to distinguish between pharmaceutical and non-pharmaceutical products, particularly when two CDPs contain the same active ingredient (e.g., Epidiolex and CBD). Therefore, understanding the variety of biases involved in CDP spontaneous reporting is important for designing and interpreting pharmacovigilance studies using SRSs.

2.5 CONCLUSION

The post-marketing surveillance process for CDPs poses unique challenges relative to pharmaceutical drugs, driven by the distinct characteristics of these diverse cannabinoid-containing products and the manner in which they are reported. In our descriptive analysis of CDPs reporting in FAERS from Q1 1999 to Q1 2023, we identified mixed results regarding the potential feasibility of using this SRS for a similar purpose as with pharmaceutical safety signal detection. The results of our study demonstrated a consistent increase in reporting over time, reflecting heterogeneous reporting patterns and trends that align with established demographic patterns of CPD use. Furthermore, our study encompassed the diversity of pharmaceutical and non-pharmaceutical CDPs within the context of changes to the legal status of cannabis in the U.S. and abroad. Finally, this project underscores the uniqueness of CDP-related AERs and provides insights into the design of signal detection studies for CDP, including additional factors that must be considered when collecting, coding, and assessing individual case reports related to CDP use.

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CHAPTER 3: SIGNAL DETECTION IN PHARMACOVIGILANCE OF CANNABIS-DERIVED PRODUCTS USING THE FDA ADVERSE EVENT REPORTING SYSTEM DATABASES

Priscilla. O. M. V. Lopes[1]; Christopher. A. Gravel[2]; Cory. S. Harris[1]

[1] Department of Biology, University of Ottawa, Ottawa, Canada

[2] School of Epidemiology and Public Health, University of Ottawa, Ottawa, Canada

ABSTRACT

In the U.S. and abroad, changes in the legal and regulatory frameworks of cannabis use have enabled the expansion and the increased accessibility to a variety of cannabis-derived products (CDPs), including both pharmaceutical-grade CDPs and non-pharmaceutical CDPs. This emerging industry has influenced patterns of cannabis consumption across diverse populations, resulting in distinct reporting behaviors of potential adverse drug reactions (ADRs) associated with CDP use. This study assessed whether heterogenous reporting patterns, different CDPs and terminologies impacted the detection and interpretation of safety signals regarding CDP use. We conducted a broad signal detection study using disproportionality analysis on CDPs queried from FAERS between the first quarter of 1999 and the first quarter of 2023. Three algorithms were employed to quantify the signals of CDP associated adverse events, including reporting odds ratio (ROR), proportional reporting ratio (PRR) and Bayesian confidence propagation neural network (BCPNN) of information components (IC). A total of 42,109 CDP-related AERs were identified, and results indicated an overall distinct signal safety profiles between pharmaceutical and non-pharmaceutical CDPs, influenced by the unique characteristics of each CDP, patient demographics, and distinct reporting behaviors. CDPs containing similar cannabinoids demonstrated heterogenous safety signals, while having some notable similarities. Epidiolex and cannabidiol (CBD) shared some seizure-related signals, although the nature and strength of signals differed. This project may validate that signal detection using FAERS has some potential feasibility for CPD safety surveillance and highlighted the need for signal confirmation, incorporating any actionable insights or complex relationships relevant to the signal to provide a solid basis for decision-making.

3.1 INTRODUCTION

Over the past two decades, changes in legal and regulatory status of cannabis significantly impacted the accessibility and diversity of cannabis-derived products (CDPs) in the United States (U.S.) and abroad. This shift has enabled the expansion of both pharmaceutical-grade cannabis-derived drugs as well as a wider range of non-pharmaceutical cannabis products. Pharmaceutical CDPs refer to formulations that have been developed, tested, and approved through rigorous clinical trials and regulatory processes, similar to conventional pharmaceutical drugs [1]. These highly standardized drugs, such as the Food and Drug Administration (FDA)-approved Epidiolex® (cannabidiol) [2] and Marinol® (dronabinol – a synthetic of delta-9-tetrahydrocannabinol, D9-THC) [3], must meet stringent manufacturing, labelling, and quality control standards to ensure safety and efficacy. Other federally approved CDPs include Syndros® (dronabinol) [4], Cesamet® (nabilone – a synthetic analogue of THC) [5], and Sativex® (nabiximols) [6]. In contrast, non-pharmaceutical CDPs encompass a broader range available outside of the regulated pharmaceutical framework. These CDPs can include dried flower material, concentrates, edibles, tinctures, topicals and other formulations sold in legal, unregulated and illicit cannabis markets [7]. Their composition, potency, and quality can vary widely, as they are not subject to the same degree of standardization, testing, and oversight as their pharmaceutical counterparts [8]. The most common cannabinoids present in these products include the psychoactive compound D9-THC and the non-psychoeuphoric cannabidiol (CBD) [9]. Additionally, some other compounds and cannabinoids may also be present in varying concentrations, such as the emerging delta-8-tetrahydrocannabinol (D8-THC), minor cannabinoids, terpenes, and flavonoids, among others [10].

While non-pharmaceutical CDPs also demonstrate comparable potential for therapeutic benefit to that of the standardized products, their efficacy and safety profiles remain less well characterized than those of the approved pharmaceutical CDPs. The relative shortage of comprehensive data on the safety aspects of CDPs has historically been constrained by stringent regulatory barriers, scheduling classifications, and funding limitations [11]. In addition, most of the available sources of safety data are from randomized controlled trials (RCTs) conducted on pharmaceutical CDPs. These RCTs provide the most rigorous cannabis safety evidence to date, although they are often not the predefined primary objectives of these studies and may be underpowered as a result. In addition, they may be conducted in a limited and controlled population that may not fully represent the diverse demographics, health conditions, and use patterns in real-world settings. As a result, these RCT data may not provide an accurate characterization of the safety profile for the variety of CDPs available on the market [12]. Consequently, pharmaceutical CDPs, as conventional pharmaceutical drugs, are subject to post-marketing requirements after their authorization using statistical pharmacovigilance methods [13].

Pharmacovigilance is a pivotal, indispensable science for all medications, including CDPs. The World Health Organization (WHO) defines pharmacovigilance as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems” [14]. Pharmacovigilance aims to identify and confirm safety signals that may indicate potential risks of adverse drug reactions (ADRs) under real-world conditions of use outside of controlled clinical trial settings. Post-market surveillance is an important component of the pharmacovigilance of cannabis products [15], and the analysis of data from spontaneous reporting systems (SRSs) is one of the most common methods and

relevant tools for the early detection of unexpected safety signals [16]. Spontaneous reports are unsolicited reports that describes one or more suspected ADR in a patient who was given one or more medicinal products. They are voluntarily submitted by healthcare professionals, patients, or consumers to regulatory authorities or pharmaceutical companies. Spontaneous reports of suspected ADRs are compiled in databases such as the FDA Adverse Events Reporting System (FAERS) maintained by the U.S. Food and Drug Administration (FDA) [17], and through data mining methods, these spontaneous reports data are primarily used for signal detection, or to generate novel drug safety hypotheses for follow-up study [18].

Disproportionality analysis is based on statistical methods designed to identify heightened reporting rates of drugs and adverse events than what would be expected under independence and are used for the quantitative detection of signals [19]. Several signal detection methods can be applied in the analyses of these data and they have been extensively reviewed [20], the most widely used being the proportional reporting ratio (PRR) [21], the reporting odds ratio (ROR) [22], and the information component (IC), the log base 2 of the relative reporting ratio (RRR), which is estimated by a Bayesian confidence propagation neural network (BCPNN) [23]. These algorithms calculate signal scores (i.e., the lower bound of interval estimates of PRR, ROR, and IC) to assess evidence of disproportionate reporting of a potential drug event combination (DEC) [24].

Pharmacovigilance for non-pharmaceutical CDPs may benefit from the screening of SRSs using disproportionality analysis in databases such as FAERS. FAERS is a well-established post-marketing safety surveillance system for monitoring ADRs associated with pharmaceutical drugs, however, its utility for CDP monitoring is still in its infancy. A disproportionality analysis study of Epidiolex using FAERS from Q3 2018 to Q1 2023 identified

potential new safety signals not previously listed on the product's label that warranted further investigation, including seizure cluster, blood ketone body decrease, cortical visual impairment, hyperactive pharyngeal reflex, and poverty of speech [25]. Another study using FAERS from Q3 2018 to Q1 2020 compared the older generation of antiepileptic drugs with newer medications and concluded that, unlike older generations, Epidiolex was not disproportionately reported with hepatotoxicity [26]. Post-marketing surveillance studies of non-pharmaceutical CDPs in FAERS have also been conducted. Simon et al. (2023) evaluated D8-THC AERs in FAERS from 2011 to Q2 2021 and identified potential safety signals, including dyspnea, respiratory disorder, and seizure [27], and Leas et al. (2023) characterized AERs associated with D8-THC, and their findings suggested that the detected ADRs with D8-THC use are typically similar to those experienced during an acute cannabis intoxication [28].

Applying the existing pharmacovigilance model and its tools to monitor ADRs of CDPs poses unique challenges [29] given their unique reporting characteristics including the ambiguous terminologies used to identify these products, how the reporting rates are influenced by their public perception, the heterogeneity in their method of utilization, and temporally changing regulations raise considerations that need to be recognized and carefully addressed when designing disproportionality analyses, as highlighted in the Chapter 2. This descriptive analysis of spontaneous reports related to the use of different CDPs (pharmaceuticals and non-pharmaceuticals) submitted to FAERS from the first quarter (Q1) 1999 to Q1 2023 identified mixed results regarding the potential feasibility of using FAERS for monitoring CDPs-related adverse events (AEs).

Building from these descriptive results we conducted a broad signal detection study of Epidiolex, pharmaceutical THC-based products (Rx THC), THC, CBD, and Cannabis in FAERS

to characterize the nature and frequency of signals detected using standard disproportionality analysis methods to evaluate the relationship between pharmaceutical CDPs' safety profiles and non-pharmaceutical CDPs' involvement in potential signals. In particular, we explored the ambiguity of terms used to report CDPs with similar active ingredients, but distinct pharmaceutical classifications.

3.2 METHODS

3.2.1 Data Source

The data for this study was extracted from the FAERS database [30] between Q1 1999 and Q1 2023, which was the same study period used in Chapter 2. This timeframe captures the early expansion of medical cannabis legalization in the U.S., marked by three states legalizing cannabis for medical use [31]. FAERS is considered a post-marketing safety surveillance program that supports the drug safety evaluation process for drug and biological products. It consists of seven databases that contain individual case safety reports (ICSRs) of suspected ADRs and medication errors. The FDA receives the ICSRs on a mandatory basis from the regulated industry (e.g., manufacturers, distributors, or packers) or on a voluntary basis by the general public (e.g., healthcare professionals, patients, or consumers). The seven database files include anonymous information on demographic characteristics, drug data, reactions, outcomes, report sources, therapy information, and indications. The reactions are the adverse events, which are coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology at the level of 'preferred terms' (PT). A PT is a distinct descriptor (single medical concept) for a symptom, sign, disease, diagnosis, therapeutic indication, investigation, surgical, or medical procedure, and medical, social, or family history characteristic. PTs must be linked to a System Organ Class (SOC), which is the highest level of the hierarchy that groups terms by etiology, manifestation site and purpose [32].

FAERS databases are publicly available and the raw quarterly data files were extracted, linked and submitted to rigorous data cleaning. This included deleting duplicate reports, correcting misspelled CDPs names, and retaining the most recent updated case version assigned

to the date the FDA first made the report available. The analyses were not restricted to CDPs reports only, rather, we used the full FAERS database as the reference set for disproportionality analysis.

3.2.2 Exposure

In chapter 2, particular challenges were identified in establishing exposure definitions for the CDPs of interest. Multiple manufacturers' cannabis-related products and other types of CDP formulations may contain the same ingredients but vary in the profile of their chemical constituents [33]. Given that we were interested in the potential for toxicity suspected to be related to a specific chemical compound in the cannabis product, we grouped CDP reports involving the same active ingredient and product quality control standards, which is similar to investigating a "therapeutic class" with conventional pharmaceutical drugs [34]. To this end, we defined two groups of pharmaceutical CDPs (e.g., Epidiolex and Rx THC) and three groups of non-pharmaceutical CDPs (THC, CBD, and Cannabis). Epidiolex included terms where the brand name (e.g., Epidiolex® or Epidyolex®) was mentioned, Rx THC included the brand and generic dronabinol and nabilone terms, THC included D9-THC only and not D8-THC, CBD included terms mentioning CBD and not Epidiolex. Finally, the Cannabis was comprised of generic terms such as cannabis, cannabinoids, or marijuana (see Appendix 2 for the complete list of terms). We included all reports regardless of the suspected role assigned to the AER by the individual reporter (e.g. primary suspect drug, secondary suspect drug, concomitant drug, or interacting drug).

For the disproportionality analyses of Epidiolex and CBD, we restricted the study period from Q2 2018 onwards to reflect the later approval of Epidiolex by the FDA [2], which allowed

us to conduct signal detection studies in similar time intervals to investigate the ambiguity of terminologies used for these CDPs. Finally, for the Rx THC, THC, and Cannabis analyses, we used the full study period from Q1 1999 to Q1 2023 as these products were available throughout.

3.2.3 Statistical Analysis

We estimated the ROR, PRR and IC, along with their estimated confidence interval (CI) and credible intervals (CrI), for all CDP-AE pairs using the non-CDPs-AE pairs for comparison. For example, Epidiolex-AE combinations were compared with all non-Epidiolex-AE in FAERS and similarly were done for Rx THC, THC, CBD, and Cannabis. For these analyses, the reports were summarized based on a contingency table representation (Table 6).

The ROR is the reporting version of an odds-ratio, and represents the odds of an AE being reported for a specific drug or drug class against the odds of the same AE occurring with all other drug reports [35]. A signal was flagged if the lower bound of a 95% CI of the point estimate exceeded 1. The PRR, is the reporting version of a relative risk, and corresponds to the proportion of reports of the AE with the drug under the study, divided by the corresponding proportion of all the other drugs [21]. A signal is flagged if the lower bound of the 95% CI exceeded 1 [22]. Finally, the IC is a Bayesian method, estimated using the BCPNN and this method compares the probability of observing a drug-AE combination with the same probability of the expected drug-AE pair under the assumption of independence or no association between the drug and the AE. The BCPNN employs prior distributions to ‘shrink’ the signal detection estimates towards independent reporting to reduce false positive rates, which are a known concern with the PRR and ROR [23]. A positive IC value, with the lower bound 95% CrI greater than 0, suggests a safety signal. Detailed calculations and specific detection criteria are displayed

in Table 7. The analyses were performed using the statistical software R version 4.2.3. The codes can be found in Appendix 3.

Table 6. A contingency table reporting event counts for each specific CDP and all other drugs

	With the adverse event	Without the adverse event
Reports mentioning a cannabis product	a	b
Reports not mentioning a cannabis product	c	d

Table 7. Common measures of association used in disproportionality analysis

Algorithm	Formula	Detection criteria
PRR	$\mathrm{PRR} = \frac{a/(a+b)}{c/(c+d)}$	95% CI lb > 1
ROR	$\mathrm{ROR} = \frac{a/c}{b/d} = \frac{a \times d}{b \times c}$	95% CI lb > 1
BCPNN	$\mathrm{IC} = \log_2 \frac{a(a+b+c+d)}{(a+b)(a+c)}$	95% CrI lb > 0

BCPNN Bayesian Confidence Propagation Neural Network, *CI* confidence interval, *CrI* credible interval, *IC* information component, *lb* lower bound, *PRR* proportional reporting ratio, *ROR* reporting odds ratio

3.3 RESULTS

We identified 42,109 AERs related to the five CDPs. The demographic characteristics varied across each group, and the reporting patterns were similar to those observed in Chapter 2 (see Table 8 for frequency and percentages of reporting per CDP in detail).

Table 8. Patient demographics characteristics with reported use of CDPs queried from FAERS

Characteristic	Pharmaceutical CDPs		Non-Pharmaceutical CDPs		
	Rx THC[a] (n = 8637)	**Epidiolex[b] (n =13,743)**	**THC[a] (n = 1433)**	**CBD[b] (n = 3769)**	**Cannabis[a] (n = 14,653)**
Age in years, n (%)					
0-12	118 (1.4)	637 (4.6)	16 (1.1)	304 (8.1)	155 (1.1)
13-17	201 (2.3)	230 (1.7)	61 (4.3)	92 (2.4)	856 (5.8)
18-35	764 (8.8)	424 (3.1)	605 (42.2)	372 (9.9)	4713 (32.2)
36-54	1695 (19.6)	180 (1.3)	395 (27.6)	682 (18.1)	3437 (23.5)
55-69	1970 (22.8)	72 (0.5)	115 (8.0)	665 (17.6)	1666 (11.4)
70+	1249 (14.5)	17 (0.1)	34 (2.4)	457 (12.1)	515 (3.5)
Missing	2640 (30.6)	12,183 (88.6)	207 (14.4)	1197 (31.8)	3311 (22.6)
Sex, n (%)					
Female	4190 (48.5)	1677 (12.2)	524 (36.6)	2049 (54.4)	5520 (37.7)
Male	3918 (45.4)	1990 (14.5)	762 (53.2)	1157 (30.7)	7996 (54.6)
Missing	529 (6.1)	10,076 (73.3)	147 (10.3)	563 (14.9)	1137 (7.8)
Role, n (%)					
Primary suspect drug	775 (9.0)	12,788 (93.1)	346 (24.1)	329 (8.7)	78 (0.5)
Secondary suspect drug	649 (7.5)	157 (1.1)	736 (51.4)	601 (15.9)	7656 (52.2)
Interacting drug	55 (0.6)	26 (0.2)	54 (3.8)	126 (3.3)	189 (1.3)
Concomitant drug	7158 (82.9)	772 (5.6)	297 (20.7)	2713 (72.1)	6730 (45.9)
Outcome, n (%)					
Hospitalization	3459 (36.7)	2942 (42.5)	409 (22.0)	869 (25.6)	4703 (25.8)
Life-threatening	338 (3.6)	47 (0.7)	105 (5.6)	116 (3.4)	650 (3.6)
Death	1527 (16.2)	837 (12.1)	526 (28.3)	179 (5.3)	3869 (21.2)
Other	3839 (40.7)	2942 (42.5)	650 (34.9)	2034 (59.8)	8363 (45.8)
Disability	188 (2.0)	27 (0.4)	54 (2.9)	140 (4.1)	441 (2.4)
Congenital Abnormality	20 (0.2)	5 (0.1)	9 (0.5)	4 (0.1)	152 (0.8)
Required Intervention	58 (0.6)	4 (0.1)	107 (5.8)	57 (1.7)	79 (0.4)

Note: The estimated numbers of CDP reports are not mutually exclusive because people could have reported more than one suspected product in FAERS. Percentages were calculated using the total number of reports for each specific CDP as the denominator.

Abbreviations: *CBD* cannabidiol, *Rx THC* pharmaceuticals THC, *THC* delta-9-tetrahydrocannabinol

[a] Study period from Q1 1999 to Q1 2023

[b] Study period restricted from Q2 2018 to Q1 2023

The number of detected signals are displayed in Table 9. Given the propensity for false positives expected with the PRR and ROR, we used the IC results to select signals for further analyses and discussion (see Appendix 4 for the top 30 disproportionality analysis estimates for PRR, ROR, and IC by CDP at the SOC and PT levels).

Table 9. Number of signals of disproportionate reporting detected by the PRR, ROR and IC for each CDP grouping

	PRR	ROR	IC
Epidiolex	368	368	176
CBD	1243	1243	638
Rx-THC	1904	1904	907
THC	634	634	220
Cannabis	2091	2091	1204

CBD cannabidiol, *IC* information component, *PRR* proportional reporting ratio, *ROR* reporting odds ratio, *Rx THC* Pharmaceuticals THC, *THC* delta-9-tetrahydrocannabinol

3.3.1 Characteristics of the detected signals for Epidiolex and CBD

For the disproportionality analyses of Epidiolex and CBD, the study period was restricted from Q2 2018 to Q1 2023 (Table 10). Epidiolex had 3.6 times more reports (n = 13,743) compared to CBD products (n = 3,769) but a lower number of detected signals (176 and 638, respectively). The signals for Epidiolex were distributed across 18 SOC, of which the nervous system disorders accounted for the majority of the signals (18.75%), followed by psychiatric disorders (16.48%) and injury, poisoning and procedural complications (10.23%). Out of the 30 strongest signals at the PT level, 11 were seizure-related events, with IC ranging from 3.59 to 6.36, such as seizure cluster (IC, 6.36; 95% CrI 6.05-6.68), change in seizure presentation (IC,

6.07; 95% CrI 5.68-6.45), atonic seizures (IC, 6.02; 95% CrI 5.64-6.41), seizure (IC, 5.47; 95% CrI 5.43-5.51), and weight abnormal (IC, 5.67; 95% CrI 5.40-5.93) (Table 10, left panel).

CBD signals were predominantly categorized as nervous system disorders (13.79%), investigations (11.13%), and general disorders and administration site conditions (10.03%). In contrast to Epidiolex, CBD's highest estimates were not seizure-related but rather neoplasm-associated events, with ICs ranging from 3.5 to 5.1 (Table 10, right panel). The strongest signals for CBD included multiple-drug resistance (IC, 5.73; 95% CrI 5.35-6.12), blood pressure diastolic decreased (IC, 4.88; 95% CrI 4.49-5.27), device related thrombosis (IC, 5.00; 95% CrI 4.36-5.65), malignant cranial nerve neoplasm (IC, 5.1; 95% CrI 4.33-5.87), and retro-orbital neoplasm (IC, 5.08; 95% CrI 4.31-5.85).

We observed that nervous system disorders were the most predominant SOC category of the ADRs detected for both CPDs. The nature of these signals, however, differed between both groups. Of the 33 signals detected for Epidiolex, 13 (39.4%) contained seizure or convulsion in the PT description, with ICs ranging from 1.62 to 6.36. In fact, many ADRs were related to pre- or post-epilepsy episodes, such as postictal state, hypotonia, and head titubation, among others. In contrast, CBD reports showed nearly 2.6-fold more ADRs (88 signals) linked to the nervous system category, however, only 12 (13.6%) were seizure/convulsion related, with ICs ranging from 1.97 to 4.81. The majority of the CBD-related signals in this SOC were connected to diverse medical conditions, such as multiple sclerosis, Parkinson's, and neuralgia. These differences were represented in a sector map, which visually demonstrated the disproportionality signals for ADRs associated with Epidiolex and CBD within the nervous system disorders (Figure 10). Each square in the map corresponds to a unique AE at the PT level within this SOC. The color gradient from dark purple to bright yellow indicates the IC estimates, with darker

shades representing absent signals and brighter shades indicating stronger associations. Therefore, we observed 33 highlighted ‘squares’ (i.e., signals) for Epidiolex and 88 for CBD. These comparisons are exploratory and designed to highlight the impact of reporting behaviors resulting in the use of ambiguous terminology and should not be used to infer a comparative safety profile between Epidiolex and CBD.

Table 10. The top 30 IC estimates for Epidiolex (left panel) and CBD (right panel) at the PT level (Q2 2018 to Q1 2023)

Epidiolex® TOP 30 PTs	Epidiolex IC (95% CrI)	CBD IC (95% CrI)	CBD TOP 30 PTs	CBD IC (95% CrI)	Epidiolex IC (95% CrI)
Seizure cluster	6.36 (6.05-6.68)	2.43 (0.44-4.42)	Multiple-drug resistance	5.73 (5.35-6.12)	1.04 (-0.31-2.38)
Change in seizure presentation	6.07 (5.68-6.45)	2.88 (1.19-4.57)	Blood pressure diastolic decreased	4.88 (4.49-5.27)	-2.15 (-5.88-1.58)
Atonic seizures	6.02 (5.64-6.41)	2.51 (0.52-4.5)	Device related thrombosis	5 (4.36-5.65)	NA
Seizure	5.47 (5.43-5.51)	2.89 (2.68-3.1)	Malignant cranial nerve neoplasm	5.1 (4.33-5.87)	NA
Weight abnormal	5.67 (5.4-5.93)	NA	Retro-orbital neoplasm	5.08 (4.31-5.85)	NA
Product supply issue	5.31 (5.14-5.48)	0.53 (-1.46-2.52)	Neuroblastoma recurrent	4.96 (4.17-5.76)	NA
Anticonvulsant drug level increased	5.56 (5.14-5.99)	2.8 (1.12-4.49)	Blood pressure diastolic abnormal	4.65 (4.12-5.18)	-1.35 (-5.08-2.38)
Emergency care	5.39 (5.12-5.65)	1.08 (-1.43-3.6)	Tonic convulsion	4.81 (4.09-5.54)	3.94 (3.19-4.69)
Product administration interrupted	4.97 (4.77-5.18)	1.8 (0.56-3.03)	Metal poisoning	4.78 (3.96-5.6)	NA
Sudden unexplained death in epilepsy	4.66 (3.95-5.36)	3.47 (2.13-4.82)	Urine leukocyte esterase positive	4.42 (3.6-5.24)	NA
Drooling	4.2 (3.86-4.54)	1.76 (0.27-3.25)	Behaviour disorder	4.08 (3.54-4.61)	3.01 (2.57-3.46)
Prescribed overdose	3.94 (3.72-4.16)	0.75 (-0.6-2.1)	Sinus headache	4.18 (3.49-4.87)	-1 (-4.73-2.73)
Product distribution issue	3.93 (3.59-4.27)	-0.33 (-4.06-3.4)	Blood pressure systolic abnormal	4.12 (3.45-4.79)	-1.18 (-4.91-2.55)
Therapy responder	4.45 (3.56-5.33)	NA	Blood pressure systolic increased	3.76 (3.38-4.14)	-2.77 (-5.29- -0.26)
Generalised tonic-clonic seizure	3.78 (3.55-4.01)	3.06 (2.51-3.6)	Post viral fatigue syndrome	4.33 (3.36-5.3)	NA
Aggression	3.61 (3.43-3.79)	2.2 (1.63-2.76)	Large intestine polyp	3.92 (3.36-4.48)	NA
Brain operation	3.85 (3.24-4.45)	NA	Finger deformity	3.99 (3.3-4.68)	NA
Status epilepticus	3.55 (3.22-3.89)	3.66 (3.09-4.24)	Metastases to spine	4.04 (3.27-4.81)	NA
Tonic convulsion	3.94 (3.19-4.69)	4.81 (4.09-5.54)	Infusion site pruritus	3.98 (3.21-4.75)	NA
Product administered to patient of inappropriate age	3.45 (3.09-3.82)	-0.54 (-4.27-3.19)	Infusion site scar	4.17 (3.15-5.19)	NA
Petit mal epilepsy	3.5 (2.99-4.02)	3.51 (2.66-4.37)	Nail disorder	3.73 (3.09-4.38)	NA
Vagal nerve stimulator implantation	4 (2.92-5.08)	1.51 (-2.22-5.24)	Status epilepticus	3.66 (3.09-4.24)	3.55 (3.22-3.89)
Drug withdrawal convulsions	3.59 (2.86-4.31)	2.12 (0.13-4.11)	Psychomotor hyperactivity	3.58 (3.04-4.12)	3.04 (2.68-3.4)
Head banging	3.83 (2.86-4.8)	1.36 (-2.37-5.09)	Product formulation issue	3.74 (3.03-4.44)	-0.78 (-3.29-1.74)
Inappropriate affect	3.65 (2.86-4.45)	3.17 (1.82-4.52)	Culture urine positive	4.04 (3.02-5.06)	NA
Myoclonic epilepsy	3.59 (2.79-4.38)	3.52 (2.37-4.67)	Metastases to liver	3.5 (3.01-3.98)	-3.01 (-6.74-0.72)
Abnormal behaviour	3.01 (2.74-3.27)	2.45 (1.84-3.05)	Body temperature decreased	3.53 (2.99-4.08)	-0.75 (-2.24-0.74)
Sedation	3.01 (2.73-3.3)	1.39 (0.42-2.36)	Microsporidia infection	4.04 (2.97-5.12)	0.95 (-2.78-4.68)
Product use in unapproved indication	2.79 (2.72-2.86)	0.23 (-0.12-0.59)	Urine abnormality	3.63 (2.86-4.4)	0.52 (-0.97-2.01)
Screaming	3.27 (2.71-3.84)	3.2 (2.23-4.16)	Pyelonephritis chronic	3.97 (2.82-5.12)	NA

CBD cannabidiol*, CrI* credible interval, *PTs* preferred terms, NA denotes a disproportionality score below the signal detection threshold. IC estimates were computed by comparing the observed drug event combination against the marginal counts of a reference set comprised of all other entries in the database.

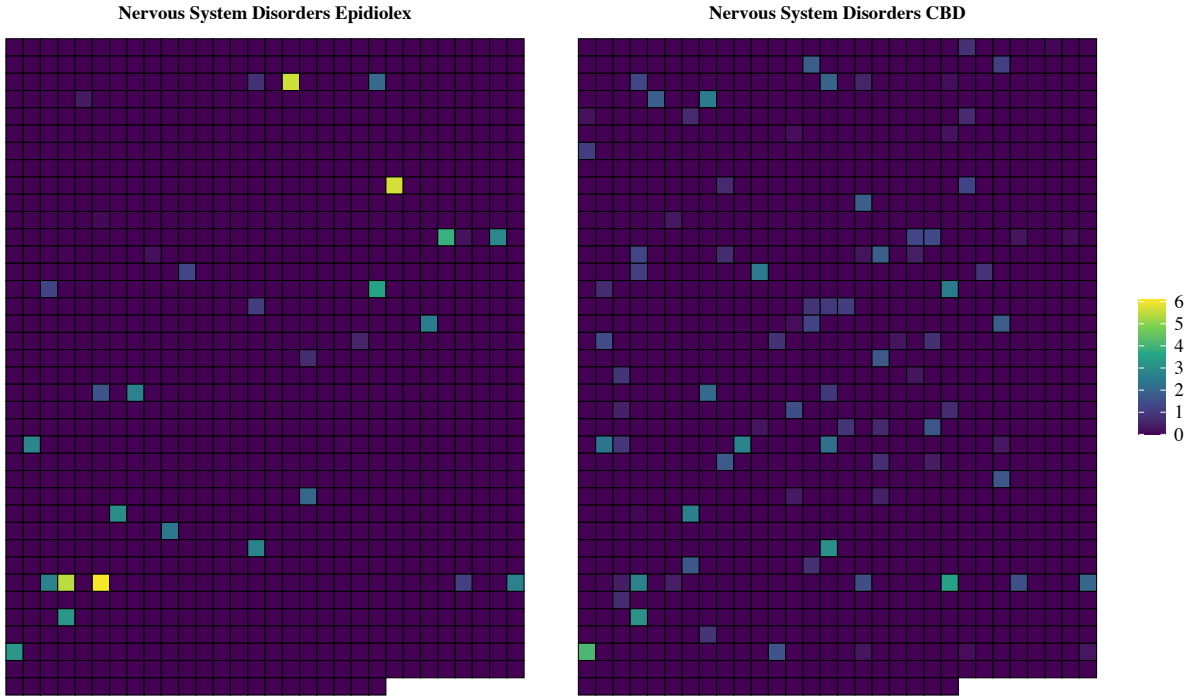

Figure 10. Sector map of potential signals identified in the Nervous System Disorders for Epidiolex (left) and CBD (right). Each square represents a unique adverse event classified by MedDRA at the Preferred Term level, arranged by system organ class. The colors in this diagram display the strengths of signals of disproportionality, ranging from dark purple, where the IC value is equal to zero, illustrating no signal detected, to bright yellow, representing a strong association between the cannabinoid and the adverse event.

3.3.2 Characteristics of the detected signals for Rx THC and THC

The study period for the disproportionality analysis of Rx THC and THC was Q1 1999 to Q1 2023. Rx THC had eight times more cases (n = 8637) compared to THC (n = 1085) and a higher number of signals (907 and 220, respectively). ADRs for Rx THC targeted all 27 SOCs, of which investigations (14.11%), infections and infestations (10.03%), and nervous system disorders (8.93%) accounted for the most reported SOC categories. At the PT level, the highest estimates were associated with underlying medical conditions, such as somatic symptom disorder (IC, 6.13; 95% CrI 5.73-6.52), white blood cell count abnormal (IC, 5.89, 95% CrI 5.66-6.11), sacroiliitis (IC, 5.71; 95% CrI 5.32-6.1), Parkinson's disease psychosis (IC, 5.85; 95% CrI 5.29-6.4), and failure to thrive (IC, 4.41 95% CrI 4.01-4.81) (Table 11, left panel).

In contrast, THC related signals were categorized into 23 SOCs, of which investigations (17.73%), psychiatric disorders (15.91%) and nervous system disorders (12.73%) were the most predominant SOC categories. At the PT level, drug use/abuse-related events accounted for the strongest signals, with IC ranging from 3.03 to 5.97, such as drug screen positive (IC, 5.97; 95% CrI 5.57-6.38), multiple drug overdose (IC, 5.66; 95% CrI 5.19-6.14), polysubstance abuse (IC, 5.72; 95% CrI 5.13-6.31), drug toxicity (IC, 5.23; 95% CrI 4.79-5.66), and toxicity to various agents (IC, 4.85; 95% CrI 4.68-5.03) (Table 11, right panel).

Notably, the PTs with the highest estimates for Rx THC were not flagged as potential signals in THC (Table 11). In fact, only two ADRs emerged as common signals, including white blood cell count abnormal and muscle mass. Conversely, among the top 30 estimates for THC, more than half of the ADRs were also identified as potential signals for Rx THC, including

several drug use-related events and respiratory disorders, such as respiratory depression, pulmonary congestion, pulmonary eodema, and asphyxia.

Although the overall distribution of ADRs reported for both CDPs was not similar, investigations were the most predominant SOC category for both groups. We identified 128 signals within this SOC for Rx THC, which were mostly related to alterations in laboratory test results related to a clinical condition, as opposed to THC, where 39 signals were identified, the highest signals related to drug abuse/use events. These differences were illustrated in a sector map, which displays the disproportionality signals for ADRs associated with Rx THC and THC within the investigations SOC. A total of 128 highlighted ‘squares’ (i.e., signals) for Rx THC and 39 for THC (Figure 11).

Table 11. The top 30 IC estimates for Rx THC (left panel) and THC (right panel) at the PT level (Q1 1999 to Q1 2023)

Rx THC TOP 30 PTs	Rx THC IC (95% CrI)	THC IC (95% CrI)	THC TOP 30 PTs	THC IC (95% CrI)	Rx THC IC (95% CrI)
Somatic symptom disorder	6.13 (5.73-6.52)	NA	Drug screen positive	5.97 (5.57-6.38)	2.14 (1.4-2.89)
White blood cell count abnormal	5.89 (5.66-6.11)	2.07 (0.08-4.06)	Multiple drug overdose	5.66 (5.19-6.14)	-0.49 (-3-2.03)
Sacroiliitis	5.71 (5.32-6.1)	NA	Polysubstance abuse	5.72 (5.13-6.31)	NA
Parkinson's disease psychosis	5.85 (5.29-6.4)	NA	Drug toxicity	5.23 (4.79-5.66)	0.35 (-0.73-1.43)
Failure to thrive	4.41 (4.01-4.81)	0.91 (-2.83-4.64)	Toxicity to various agents	4.85 (4.68-5.03)	1.31 (1.07-1.55)
Acute psychosis	4.33 (3.77-4.89)	NA	Drug abuse	4.9 (4.65-5.14)	1.63 (1.33-1.93)
Mean cell haemoglobin concentration abnormal	4.62 (3.73-5.5)	NA	Respiratory depression	4.88 (4.35-5.4)	2.65 (2.14-3.15)
Infective pulmonary exacerbation of cystic fibrosis	3.87 (3.38-4.35)	NA	Drug abuser	4.89 (4.33-5.45)	-1.73 (-5.46-2)
Immune-mediated hepatitis	3.97 (3.12-4.82)	NA	Substance abuse	4.86 (4.26-5.47)	2.19 (1.45-2.94)
Occult blood	4.02 (3.1-4.95)	NA	Brain oedema	4.77 (4.22-5.31)	2.68 (2.19-3.18)
Terminal insomnia	3.87 (3.05-4.7)	NA	Pulmonary congestion	4.74 (4.19-5.28)	1.72 (1.03-2.41)
Nocturnal dyspnoea	3.82 (2.97-4.67)	NA	Pulmonary oedema	4.43 (4.07-4.79)	1.78 (1.42-2.14)
Pancreatic carcinoma metastatic	3.59 (2.9-4.28)	1.18 (-2.55-4.91)	Toxicologic test abnormal	4.74 (3.95-5.54)	0.81 (-1.71-3.33)
Cannabinoid hyperemesis syndrome	4.05 (2.9-5.2)	NA	Accidental overdose	4.32 (3.87-4.77)	0.63 (-0.02-1.27)
Fibromyalgia	3.17 (2.84-3.51)	NA	Aspiration	4.5 (3.86-5.14)	1.4 (0.51-2.28)
Malnutrition	3.26 (2.81-3.71)	0.48 (-3.25-4.21)	Serotonin syndrome	4.4 (3.83-4.97)	0.95 (0.13-1.77)
Hangover	3.45 (2.77-4.12)	NA	Accidental poisoning	4.62 (3.74-5.51)	1.98 (-0.01-3.97)
Muscle mass	3.81 (2.73-4.89)	2.74 (0.75-4.73)	Intentional misuse	4.44 (3.55-5.32)	0.02 (-3.71-3.76)
Economic problem	3.08 (2.7-3.46)	NA	Sinus tachycardia	4.14 (3.49-4.8)	1.6 (0.91-2.29)
Gastric infection	3.37 (2.66-4.08)	NA	Aggression	3.82 (3.37-4.27)	1.06 (0.61-1.5)
Anhedonia	2.95 (2.64-3.25)	NA	Coma	3.81 (3.37-4.26)	-0.12 (-0.8-0.55)
Hyposplenism	3.87 (2.63-5.11)	NA	Asphyxia	3.96 (3.11-4.82)	2.46 (1.77-3.15)
Musculoskeletal stiffness	2.83 (2.63-3.02)	0.15 (-1.34-1.64)	Blood pH decreased	4.02 (3-5.04)	1.44 (-0.25-3.13)
Contraindicated product administered	2.95 (2.6-3.29)	-0.23 (-3.96-3.5)	Depressed level of consciousness	3.55 (3-4.09)	1.17 (0.69-1.64)
Cystic fibrosis	3.2 (2.59-3.82)	NA	Drug Interaction	3.22 (2.91-3.54)	0.87 (0.6-1.15)
Lip and/or oral cavity cancer	3.51 (2.58-4.43)	NA	Unresponsive to stimuli	3.57 (2.88-4.26)	1.7 (1.17-2.23)
Blood pressure systolic abnormal	3.41 (2.56-4.27)	NA	Dysarthria	3.44 (2.84-4.03)	1.35 (0.88-1.82)
Asplenia	3.8 (2.56-5.03)	NA	Substance use	3.94 (2.79-5.09)	2.81 (1.47-4.16)
Bronchial wall thickening	3.64 (2.56-4.71)	NA	Cardiomegaly	3.58 (2.79-4.38)	0.74 (-0.18-1.66)
Vascular device infection	3.3 (2.53-4.07)	NA	Overdose	3.03 (2.74-3.33)	-0.27 (-0.63-0.09)

CrI credible interval, IC information component, PT preferred term, THC delta-9-tetrahydrocannabinol, NA denotes a disproportionality score below the signal detection threshold. IC estimates were computed by comparing the observed drug event combination against the marginal counts of a reference set comprised of all other entries in the database.

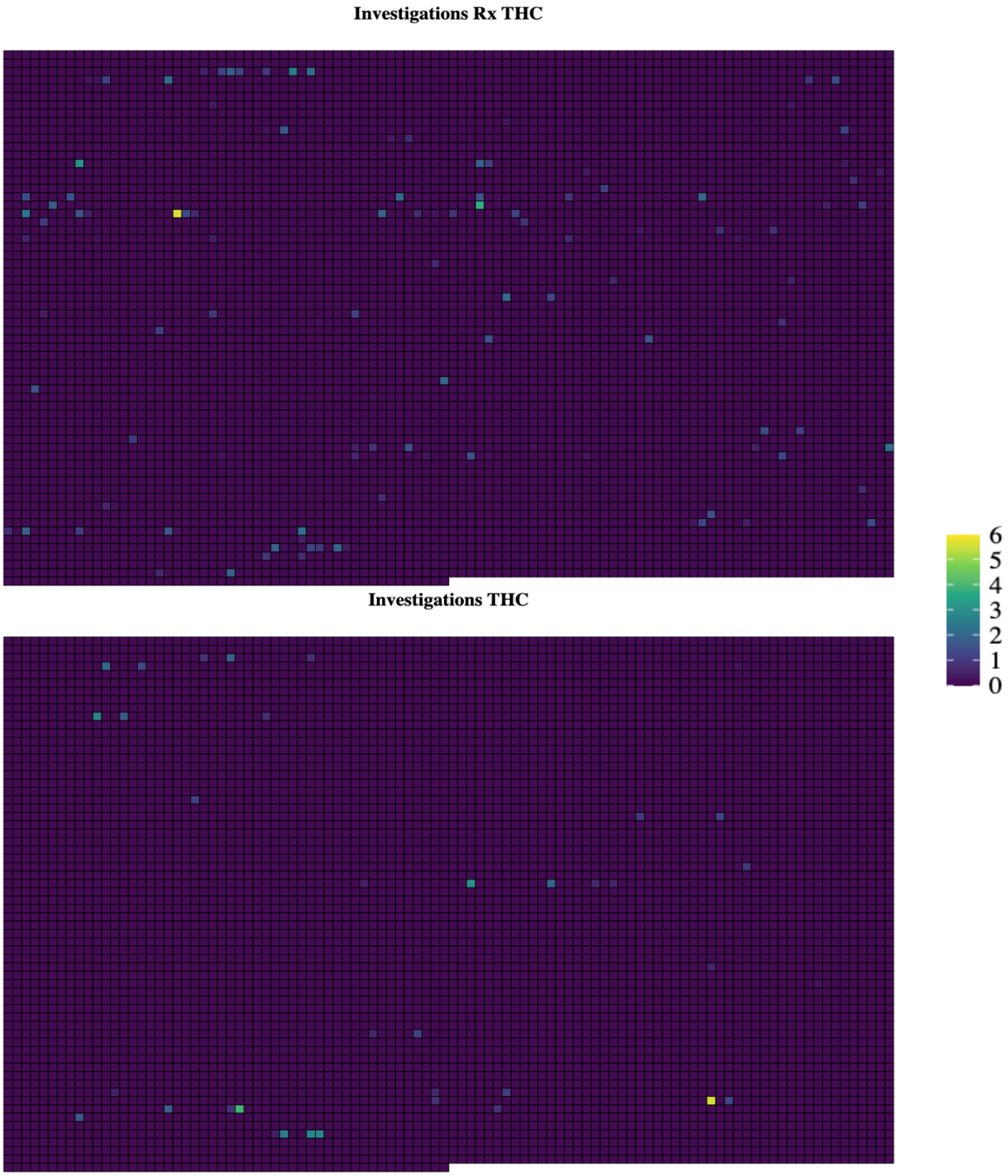

Figure 11. Sector map of potential signals identified in the Investigations for Rx THC (top) and THC (bottom). Each square represents a unique adverse event classified by MedDRA at the Preferred Term level, arranged by system organ class. The colors in this diagram display the strengths of signals of disproportionality, ranging from dark purple, where the IC value is equal to zero, illustrating no signal detected, to bright yellow, representing a strong association between the cannabinoid and the adverse event.

3.3.3 Characteristics of the detected signals for Cannabis

The study period for the signal detection analysis of Cannabis was from Q1 1999 to Q1 2023. Cannabis represented the largest group in case reports compared to the other CDPs (n = 14,653). A total of 1204 signals were identified, involving 27 SOC. The predominant SOC was psychiatric disorders (14.04%), followed by investigations (12.54%) and nervous system disorders (10.38%). At the PT level, we noticed a diversity of ADRs ranging from drug use/abuse-related events to physiopathology of an underlying medical condition. The highest estimates were substance abuse (IC, 6.98; 95% CrI 6.88-7.08), substance dependence (IC, 6.67; 95% CrI 6.37-6.97), polysubstance abuse (IC, 6.43; 95% CrI 6.12-6.74), red blood cell sedimentation rate (IC, 6.34; 95% CrI 5.96-6.73), and C-reactive protein abnormal (IC, 6.04; 95% CrI 5.84-6.24) (Table 12).

Table 12. The top 30 IC estimates for Cannabis at the PT level (Q1 1999 - Q1 2023)

Cannabis TOP 30 PTs	Cannabis IC (95% CrI)	THC IC (95% CrI)	CBD IC (95% CrI)
Substance abuse	6.98 (6.88-7.08)	4.86 (4.26-5.47)	0.97 (-0.72-2.66)
Substance dependence	6.67 (6.37-6.97)	NA	NA
Polysubstance abuse	6.43 (6.12-6.74)	5.72 (5.13-6.31)	NA
Red blood cell sedimentation rate	6.34 (5.96-6.73)	1.14 (-1.38-3.65)	2.3 (1.37-3.22)
C-reactive protein abnormal	6.04 (5.84-6.24)	NA	NA
Substance use disorder	5.97 (5.63-6.3)	1.43 (-2.3-5.17)	0.79 (-2.94-4.52)
Substance use	5.97 (5.63-6.31)	3.94 (2.79-5.09)	3.31 (2.07-4.54)
Drug abuse	5.64 (5.59-5.7)	4.9 (4.65-5.14)	0.9 (0.38-1.42)
Alanine aminotransferase abnormal	5.71 (5.39-6.02)	1.32 (-2.41-5.05)	NA
Alcohol abuse	5.6 (5.32-5.88)	1.94 (-0.57-4.46)	0.57 (-3.16-4.3)
Red blood cell sedimentation rate abnormal	5.57 (5.24-5.89)	NA	NA
Drug abuser	5.39 (5.22-5.56)	4.89 (4.33-5.45)	NA
Enthesopathy	5.56 (5.19-5.94)	NA	3.43 (2.41-4.45)
Intestinal sepsis	5.66 (5.11-6.22)	NA	NA
Miosis	5.28 (5.07-5.48)	3.05 (1.81-4.28)	-0.3 (-4.03-3.43)
Tenosynovitis	5.34 (5.03-5.64)	NA	2.93 (1.78-4.08)
Synovial fluid analysis	5.6 (4.99-6.22)	NA	NA
Blood parathyroid hormone decreased	5.37 (4.98-5.77)	NA	NA
Granuloma skin	5.44 (4.98-5.91)	NA	NA
Rheumatoid nodule	5.19 (4.87-5.52)	NA	NA
Drug use disorder	5.09 (4.82-5.36)	2.87 (1.38-4.36)	1.12 (-0.88-3.11)
Joint ankylosis	5.21 (4.66-5.75)	NA	NA
Victim of chemical submission	5.27 (4.66-5.87)	NA	1.29 (-2.44-5.02)
Panniculitis	5 (4.62-5.38)	NA	0.55 (-3.19-4.28)
Asphyxia	4.81 (4.58-5.04)	3.96 (3.11-4.82)	1.6 (0.26-2.95)
Tenosynovitis stenosans	5.12 (4.54-5.69)	NA	NA
Poisoning deliberate	4.78 (4.53-5.04)	1.53 (-0.98-4.05)	NA
Poisoning	4.71 (4.51-4.91)	2.86 (1.71-4)	1.77 (0.42-3.11)
Multiple drug overdose accidental	5.08 (4.51-5.65)	3.38 (1.89-4.87)	NA
Rheumatoid lung	5.01 (4.51-5.51)	NA	1.13 (-2.6-4.86)

CBD cannabidiol, *CrI* credible interval, *IC* information component, *PT* preferred term, *THC* delta-9-tetrahydrocannabinol, *NA* denotes a disproportionality score below the signal detection threshold. IC estimates were computed by comparing the observed drug event combination against the marginal counts of a reference set comprised of all other entries in the database.

3.4 DISCUSSION

We conducted a disproportionality analysis on CDPs queried from FAERS between Q1 1999 and Q1 2023. We identified a total of 42,109 AERs mentioning five CDPs, including pharmaceutical CDPs (Epidiolex and Rx THC) and non-pharmaceutical CDPs (THC, CBD, Cannabis). Overall, the nature and signal strengths reported with pharmaceutical-grade CDPs were different from non-pharmaceutical CDPs noting the influence of different reporting patterns for products with similar active ingredients.

In the last decades, interest in the therapeutic value of the active ingredient, ‘cannabidiol’, as anti-inflammatory, anti-emetic, anti-psychotic, and anti-epileptic treatments has emerged for a wide range of conditions [36]. However, its safety profile varied depending on whether ‘cannabidiol’ is used as a pharmaceutical-grade CDP, such as Epidiolex, or as a non-pharmaceutical CDP, such as CBD. Despite sharing the same cannabinoid, these two CDPs presented distinct demographic characteristics, reporting patterns, and ADRs. These differences, observed in multiple layers and analyses, raised challenges in the interpretation of the safety signals that are related to the pharmacological effect of the cannabinoid itself versus those influenced by external factors such as product formulation, patient population, and reporting patterns.

The strongest signals of disproportionate reporting for Epidiolex were predominantly related to seizure events. Given that quantitative signal detection methods cannot eliminate confounding by indication [19], these seizure-related ADRs were expected as Epidiolex is indicated for the treatment of seizures [2]. Surprisingly, CBD also showed signals related to seizure events, however, to a much lesser extent. Given promising results of RCTs and open-

label extended-access studies demonstrating improvement in seizure frequency and severity with a relatively well-tolerated side effect profile, there is emerging literature in the pipeline surrounding the potential use of CBD for other indications, including other medically refractory epilepsy syndromes [37]. Anecdotal reports also demonstrated the beneficial effects of artisanal CBD formulations in the reduction of seizures and may motivate individuals to seek CBD for the treatment of drug-resistant epilepsy [38]. A well-documented case was reported in 2013 in the U.S., where a five-year-old girl was diagnosed with Dravet syndrome, with up to 50 generalized tonic-clonic seizures per day. Following three months of treatment with high-CBD-strain cannabis extract, the seizures were reported to have reduced by more than 90% [39]. In addition, we observed a higher reporting rate (0.24) for CBD among infants (0-12 years old), the second highest rate after Epidiolex. Therefore, given the nature and strength of seizure-related signals for CBD, and its reporting pattern, we might hypothesize that CBD is being used by individuals for seizure management.

While the seizure events observed for both Epidiolex and CBD may be, in part, related to confounding by indication, there is also potential for a pharmacologically plausible association. First, a pharmacokinetic mechanism based on the induction or inhibition of Cytochromes (CYP) enzymes involved in the metabolism of ‘cannabidiol’ has been suggested. Recent studies demonstrated that cannabidiol is a potent inhibitor of CYP450 enzymes such as CYP3A4 and CYP2C19 [40]. Therefore, there is a risk of drug-drug interactions (DDIs) between cannabidiol and concomitant medications. Epileptic patients often administer Epidiolex concomitantly with other anti-seizure medications, such as clobazam. Thus, a DDI between these two drug classes resulting in increased benzodiazepine toxicity could be of high clinical relevance. Decreased clobazam elimination via cannabidiol-mediated inhibition could lead to elevated clobazam

plasma levels and potentially lead to AEs such as somnolence, lethargy, fatigue, and sedation. In some cases, it is necessary to adjust the dose of 'cannabidiol' or antiseizure medication, as overdosing or sub-dosing may alter the optimal therapeutic dose, which could result in epilepsy relapse [41]. Second, a pharmacodynamic mechanism, where the affinity of 'cannabidiol' for multiple targets, has also been proposed. Potential mechanisms could involve 'cannabidiol' interacting with cannabinoid receptor 1 (CB_1), GABA receptors, serotonin receptors, and GPR55 receptors. 'Cannabidiol' also inhibits adenosine uptake, enhances suppression of TNFα, and interacts with calcium or sodium channels in networks that are involved in seizure generation [42]. The combination of Epidiolex with other antiseizure medications is common in epilepsy treatment. However, evidence has shown that many anticonvulsants can contribute to the aggravation of existing epilepsy, the emergence of new seizure types, or the occurrence of status epilepticus. This effect is known as the "inverse pharmacodynamic effect," in which the drug's specific effects on its antiseizure target worsen seizures rather than improve [43].

In the CBD reports, we also identified multiple ADRs related to neoplasm events and linked to medical conditions, such as multiple sclerosis, Parkinson's, and neuralgia. Given CBD's growing popularity as a potential treatment for managing diverse symptoms and reporting patterns showed a heterogenous population, we might hypothesize that CBD is also being used by individuals to alleviate and manage multiple health conditions. An abundance of CBD products is currently available in the market, ranging extensively in purity and content of bioactive compounds. The content of these products (also applicable to other non-pharmaceutical CDPs) depends on the type of cannabis plant, plant parts used, growing and harvesting conditions, and post-harvest processing and formulation practices [44]. In addition, the exact composition and amounts of ingredients are not always measured and reported by the producers

and may be inconsistent between batches. Therefore, heterogenous CBD preparations likely elicit variable pharmacological effects, thereby affecting clinical response and leading to confusion regarding the safety of the product [45].

We also identified common PTs reported with Epidiolex and CBD that are disclosed on the Epidiolex's monograph [2], which involved mostly psychiatric disorders (e.g., aggression, agitation, anger, insomnia, irritability, and sleep disorder), neurological disorders (e.g., drooling, lethargy, sedation, and somnolence), and gastrointestinal disorders (e.g., diarrhoea and salivary hypersecretion). Overall, our findings were also in alignment with recent disproportionality studies that evaluated the spontaneous reporting of Epidiolex [26, 46, 47].

Similarly in Rx THC and THC analysis, the characteristics of the products, their indications, their patient population, and their reporting patterns may have influenced the outputs of disproportionality analysis. The highest estimates for Rx THC included multiple events ranging from musculoskeletal to gastrointestinal and neuropsychiatric symptoms. Many of these ADRs may have reflected the underlying disease states or conditions for which Rx THC is indicated, such as failure to thrive in patients with AIDS-related anorexia or nausea and vomiting associated with cancer chemotherapy [3,5]. Conversely, THC highest signals were primarily related to drug use/abuse events, likely reflecting its recreational use, which may involve a variety of formulations, differing in methods of consumption and dosing. Evidence demonstrated a 212% increase in THC content in the cannabis flower between 1995 and 2015, and as the market expands into novel formulations, customers/patients have access to wide variability and increasing potency of THC products [48]. In addition, a chemotaxonomic analysis demonstrated that cannabis products contain high variability in the cannabinoid and terpene profiles, with

96.5% being classified as THC-dominant [49]. As a result, individuals might be at higher risk of negative physical and psychological outcomes.

The target population for Rx THC is highly heterogeneous and include individuals with comorbities and in polypharmacy. Similarly, the characteristics of THC users differ in etiology, with ages ranging from infants to aging adults, with many showing addictive behaviors and polysubstance use/abuse. Therefore, there is potential for DDIs occurring via pharmacodynamic or pharmacokinetics processes [50]. Research has shown that inhibitors and inducers of CYP2C9 and CYP3A4 may affect the levels of 'THC' (active ingredient) if orally administered. In addition, 'THC' is highly protein-bound and may displace other protein-bound drugs, increasing their plasma levels (e.g., warfarin and cyclosporine) [51].

Although overall the safety profile of Rx THC and THC were different, common ADRs associated with drug use and respiratory events were identified in both CDPs. Several studies showed that HIV patients use cannabis to relieve symptoms associated with a medical condition, to reduce stress and anxiety, and for recreational purposes [52]. In addition, the prevalence of cannabis use among this patient population is high, with many preferring smoking cannabis to taking Rx THC [53]. This cannabis smoking behavior is significant because respiratory events were not expected with the oral administration of Rx THC. Therefore, these evidences might support our hypothesis that Rx THC and THC are being used concomitantly. Finally, we also identified common signals related to nervous system disorders, such as sedation, anxiety, and euphoria. These ADRs might indicate potential for a pharmacologically plausible association, given that Rx THC and THC contain the same active ingredient, therefore, exhibit equivalent mechanism of action, with most pharmacological effects occurring via partial agonism at the CB_1

receptor [54]. Consequently, some biological responses in the central nervous system can be expected, such as affective, sensory, somatic, and cognitive effects [50].

Cannabis reports demonstrated a unique safety profile relative to the other CDPs. We identified a diversity of signals ranging from drug use/abuse-related events to pathophysiology of an underlying medical condition, with the highest estimates for substance abuse, substance dependence and polysubstance abuse. The Cannabis group in our study lacked active ingredient specificity and included general terms such as cannabis sativa, medical cannabis, and illegal marijuana. The term "cannabis" is used by the general population to refer to a variety of compounds derived from the *Cannabis sativa* plant, which exhibits genomic and phenotypic variations [55]. To date, over 545 compounds and 140 distinct phytocannabinoids have been identified in the cannabis plant. The most abundant and researched of these are THC and CBD [56]. However, other secondary metabolites and minor cannabinoids are often present at much lower concentrations in cannabis products, with ratios that vary within and across different batches [57]. The legal framework surrounding cannabis has enabled a broad classification of these products based on the ratios of THC to CBD present in the cannabis product, with them falling into one of three categories: THC-dominant, CBD-dominant, or balanced (with a ratio of 1:1 THC to CBD) [58]. Therefore, as the composition of Cannabis products in our study was unclear and it is well-established that commercial cannabis products are highly variable, it can be challenging to determine a direct correlation between AEs and specific cannabinoids. However, based on the characteristics of the signals identified for drug use/abuse events and the associated reporting demographics, it may be possible that these products are more likely to contain higher levels of THC than CBD. This hypothesis might be supported by several studies, which

demonstrated the variability in cannabinoids levels in cannabis products, with the majority being high in THC [49].

We also identified AEs related to a medical condition/disease state, which were also assigned to CBD products as potential signals, including red blood cell sedimentation rate, enthesopathy, and tenosynovitis. The underlying pathophysiology of these conditions is associated with an inflammatory process, which could have been considered an indication for the use of the cannabis product. This hypothesis is supported by a substantial body of evidence, including the most recent Canadian Cannabis Survey, which has demonstrated that sleeping disturbances, chronic pain, and anxiety are the most commonly reported symptoms for which individuals seek cannabis use [59].

SRSs, such as FAERS, remain an important source of signals and safety information once a drug is launched in the market, including CDPs. Given the evolving changes in CDP legislation and the constant launch of new products into the marketplace, FAERS' ability to quickly gather and analyze data is valuable in the CDP safety surveillance process. However, caution must be taken when interpreting signals of disproportionate reporting of CDPs. Such ADRs can be a result of a previously unrecognized pharmacological effects of the cannabinoid, idiosyncratic effects, DDIs, CDP-food interactions, CDP-disease interactions, factors related to specific patient populations, individual patient factors, and the potential reporting biases inherent in SRSs [14].

Several sources of bias specific to drug safety signal detection may affect the estimators and must be considered when interpreting signals of disproportionality analysis. That includes under-reporting and notoriety bias, which might impact the accuracy of estimates of rates of adverse events reporting [60], and lack of detailed information on the quantity of the actual

population exposure to the drug (e.g., lack of a denominator). Therefore, FAERS cannot be used to estimate AE incidence rates [61]. Additionally, it does not take into account external factors that might influence the joint occurrence of a particular cannabinoid and a particular AE, such as population demographics. As our previous work and numerous studies have demonstrated, the diversity in demographic characteristics and age-sex-specific reporting trends associated with CDP use is widely variable, accounting for multiple and diverse patient risk profiles. Consequently, if an AE is more prevalent in a subgroup of individuals who are also more likely to be exposed to a certain cannabinoid (e.g., infants and Epidiolex use), the disproportionality estimates may be influenced by unmeasured confounding.

Confounding by indication occurs when the AE is related to the disease being treated or with comorbidity associated with the disease [62]. For each CDP group, we identified multiple cases possibly associated with confounding by indication, such as the findings of seizure-related events reported with Epidiolex and CBD, failure-to-thrive reported with Rx THC, sleep disorder with THC, and pain reported with cannabis. Confounding by association or signal leakage occurs when the AE is related to a co-administered drug, and the drug-event combination is then misclassified as a potential signal [63]. Masking, also known as drug and/or event-competition bias, is characterized when another drug or AE has a stronger or weaker risk than the study drug-event pair, leading to the underestimation of the signal [64]. Reporting bias can also impact the disproportionality analysis estimates. In fact, reporting bias in our study was demonstrated by different signals being identified for the same compound (e.g., Epidiolex versus CBD). In other words, reporting bias associated with in non-pharmaceutical CDPs differ from biases associated with pharmaceutical products. From a methodology standpoint, some limitations of our study

may include the selection of specific comparators, which are known to have a considerable impact on the estimates [65, 66].

Therefore, the CDP signals here described merely provided another perspective on reporting behaviour at a point in time. They cannot be used to explain the cause of distinctive reporting behaviour, which may reflect causality, but could also reflect chance, recorded or unrecorded confounding factors. The interpretation of the signals should always consider the safety data of multiple and relevant sources, including knowledge of the target drug, the target population, biological plausibility, and alternative etiologies for the ADR of interest [23].

3.5 CONCLUSION

Our study evaluated a broad-screen method for signal detection of CPDs on a large scale within a well-established SRS. We showed that CDPs containing similar cannabinoids may produce different signal detection safety profiles, while having some notable similarities. Specifically, we demonstrated the detected safety signals differed among chemically distinct CDPs (e.g., THC versus CBD) and among chemically similar CDPs (e.g., Epidiolex versus CBD and Rx THC versus THC). In addition, our results highlighted the unique ADR profile of cannabis products, which appeared to be more congruent with THC profile. These findings may validate that signal detection using spontaneous reporting has some potential feasibility for CPD safety surveillance, but care must be taken in the design of these studies noting the potential heterogeneity in reporting biases that are unique to products in which both pharmaceutical and non-pharmaceutical versions exist in the marketplace simultaneously. Finally, our study highlighted the multiple variables and dimensions that should be addressed when evaluating AERs of CDPs. Future research is now needed for signal confirmation, incorporating any actionable insights or complex relationships relevant to the signal in order to provide a solid basis for decision-making. Therefore, this project represented a valuable source of knowledge for the design of follow-up cannabis safety assessment studies and supported knowledge translation and communication of cannabis safety to the public.

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CHAPTER 4: GENERAL DISCUSSION

4.1 Synthesis of Results and General Discussion

We conducted a comprehensive analysis of the safety profile of pharmaceutical and non-pharmaceutical cannabis-derived products (CDPs) by evaluating spontaneous adverse event reports (AERs) queried from the FAERS database between Q1 1999 and Q1 2023. Our study was divided into two parts: a descriptive analysis and a disproportionality analysis. The descriptive analysis of seven CDPs and their related AERs assessed the feasibility of using this tool for CDP safety surveillance. The post-marketing surveillance process of CDPs presented unique challenges relative to traditional pharmaceutical drugs. Specifically, a wide variety, often ambiguous and interchangeable terminologies were identified to describe CDPs and reflected the diversity of products available in the market (pharmaceutical, non-pharmaceutical, regulated, and illegal). The accuracy and consistency of data entry, which means, the way adverse events (AEs) are reported in FAERS, directly affects the efficiency and quality of subsequent data extraction, processing, and analysis for signal detection purposes [1]. Poor data entry practices, such as observed with CDPs, required manual intervention, standardization efforts and contextual understanding compared to standardized formulations and pharmaceutical drugs.

We identified 42,530 unique CDP reports queried from FAERS during the study period. Our findings showed a consistent temporal increase in reporting across all CDPs and both pharmaceutical and non-pharmaceutical CDPs exhibited varied reporting patterns that appear to reflect known usage trends within a population that is itself diverse. The diversity in the reporting of these CDPs may reflect the variability in their usage.

We also observed additional reporting patterns that complemented and extended the findings from previous chapters. The FDA recognized delta-8-tetrahydrocannabinol (D8-THC)

as having psychoactive and intoxicating effects similar to D9-THC [2] and pharmacologically, both act as a partial agonist to CB_1 and CB_2 cannabinoid receptors [3]. Given those similarities and the lower representativeness of D8-THC in FAERS (n = 358), we grouped both cannabinoids into the same category (i.e., THC). However, we noticed that demographic reporting patterns slightly varied among both products, with D8-THC showing higher reporting rates as primary suspect drug (0.01 versus 0.008, respectively) and D9-THC exhibited nearly 1.3 times higher reporting rates for death compared to D8-THC (0.07 versus 0.008, respectively). Research has shown that the psychoactivity of D8-THC are about 75% that of D9-THC [4] and D8-THC seems to be more effective and better tolerated than D9-THC [5]. In addition, a recent survey investigated individuals experiences with D8-THC relative to D9-THC and demonstrated that participants generally compared D8-THC favorably with both D9-THC and pharmaceutical drugs, with most participants reporting substitution for D9-THC and pharmaceutical drugs [6]. Although research indicates that D8-THC shares a comparable psychoactive effect with D9-THC, D8-THC products are not approved nor evaluated for safety and/or analyzed for content [7]. Therefore, considering distinct reporting patterns and safety signals across all CDPs, including between chemically similar CDPs (e.g., Epidiolex versus CBD, and potentially D8-THC versus D9-THC), our study demonstrated that the diversity of CDP terms may reflect different products and consumer populations that cannot simply be grouped together for analysis.

The increase in CDP reporting and the observed trends highlighted the evolving and increasingly diverse landscape of CDPs in the context of changing legal frameworks in the U.S. and abroad. Our findings indicated increased reporting rates for CBD between 2018 and 2022, which marked the period when these products became more popular and available, after the enactment of Farm Bill in 2018 [8]. We also identified reports for minor cannabinoids, such as

hexahydrocannabinol (HHC), which we did not explore due to their low number of reports in FAERS. The global illicit cannabinoid market has been changing since the early 2000s, with the emergence of synthetic and semi-synthetic cannabinoids following legal shifts in cannabis regulations. HHC is a semi-synthetic cannabinoid, derived from hemp through chemical transformations, and exhibits similar effects as D9-THC. It first appeared on the drug market in U.S in 2021 [9]. Interestingly, we identified two HHC reports in 2022, further reflecting reporting trends that corresponded with the availability of CDPs in the market. The introduction of novel cannabis legislation and policies, such as the Farm Bill in 2018, likely played a role in the expansion of both CBD and minor cannabinoids market, including the emerging D8-THC in the U.S [8].

The disproportionality analysis conducted on five CDPs (e.g., Rx THC, Epidiolex, THC, CBD, and Cannabis) characterized the nature and frequency of signals of disproportionate reporting and assessed the impact of reporting behaviors on potential safety signals. We observed heterogenous safety signals across all CDPs, including among similar CDPs. Epidiolex's strongest signals were predominantly related to seizure events, while CBD's highest estimates were associated with neoplasm-related events and other medical conditions. Some similarities were observed, which may reflect the intended use of the cannabinoid. Our results may suggest that CBD is being used by infants (due to the higher reporting demonstrated in our descriptive analysis) for seizure treatment (due to the nature of signals identified in our disproportionality analysis).

We noted common demographic characteristics and safety signals among THC and Cannabis, which may suggest that cannabis products potentially contain high levels of THC, as

demonstrated by several studies [10, 11]. In addition, most of the signals were related to drug use events, likely reflecting its recreational use. We also identified signals related to medical conditions for Cannabis reports, such as enthesopathy and tenosynovitis, possibly reflecting potential use of cannabis for managing symptoms associated with these conditions. The Canadian Cannabis Survey showed that sleeping disturbances, chronic pain, and anxiety are the most commonly reported symptoms for which individuals seek cannabis use [12].

The comparisons between CPD groups are based on exploratory studies designed to highlight the potential impact of reporting behaviors on disproportionality analyses introduced by the use of ambiguous terminology for similar compounds. It should not be used to infer a comparative safety profile between pharmaceutical CDPs and non-pharmaceutical CDPs.

4.2 Contributions of the Research to the Field of Study

Spontaneous reporting systems (SRSs), such as FAERS, remain an important source of signals and safety information once a drug is launched in the market, including CDPs. These surveillance tools are designed to collect and analyze AERs, allowing for the rapid detection of unexpected emerging safety signals that might not have been evident during pre-marketing safety assessment. Safety signals may emerge in SRSs faster than other types of data, such as longitudinal studies or clinical trials, given that the consumer directly initiates the report relative to a potential drug safety concern and that identifying trends in these data sources may take longer due to the time required to accrue sufficient data. However, this also results in a large propensity for reporting biases that may impact signal detection efforts and given the evolving changes in CDP legislation and the constant launch of new products into the marketplace,

FAERS' ability to quickly gather and analyze CDP safety data is a valuable tool for public health.

Previous cannabis-related signal detection studies using SRSs focused solely on individual cannabinoids, relying on established methods for typical pharmaceutical drugs and neglecting the complexity of CDP terms and their associated chemical contents. Our study was the first to evaluate a large dataset of spontaneous AERs over an extended period and provide a robust analysis of the safety profiles of pharmaceutical and non-pharmaceutical CDPs using real-world data. Our results highlighted some of the challenges in monitoring the ADR of cannabinoids, addressing the differences in reporting of pharmaceutical CDPs and non-pharmaceutical CDPs. Our findings showed a few complexities of the CDP safety surveillance process in FAERS, which has not been extensively studied, thereby filling a gap in the literature. We identified temporal trends and demographic reporting patterns aligned with both legal and regulatory changes and expected patient populations. These results offer novel insights into the design of follow-up CDP surveillance studies, where sensitivity analysis or special population analysis may be required. Our descriptive analysis also demonstrated that FAERS captured non-pharmaceutical CDP-related AERs in specific patient populations and flagged the diversity of products currently available on the market, including recently emerged minor cannabinoids.

We demonstrated that ADR profiles and detected signals differed among chemically distinct CDPs (e.g., THC versus CBD) and among chemically similar CDPs (e.g., Epidiolex versus CBD and Rx THC versus THC). In addition, our results highlighted the unique ADR profile of cannabis products, which resembled most of the THC profile.

Signal detection in SRSs is considered the first step of an analysis to detect the safety profile of drugs. Further research is required for an investigation to confirm or refute the detected signals [13]. A traditional signal management approach involves signal detection, signal validation (signal should represent a novel causal relationship between a drug and an event, or a new aspect of known association, and therefore justifies further assessment), and signal prioritization (evaluation of the clinical impact of the safety issue) [13]. We conducted the first step of the analysis to detect the safety profile of cannabinoids. Future research is now needed for signal validation, incorporating any actionable insights or complex relationships relevant to the signal, which can then be tested in pharmacoepidemiologic studies or randomized controlled studies.

4.3 Limitations of the Research

Our study has several limitations that could impact the interpretation of reporting patterns and signals of disproportionate reporting. These limitations should be considered when interpreting the results of this research. SRSs are well-known for their inherent limitations, which include (but are not limited to) reporting biases, underreporting, and confounding by indication [14]. Given the long history of prohibition of cannabis, the stringent regulatory barriers, and social stigma, reporting biases and underreporting are expected with CDP reporting [15]. Confounding by indication could be attributed to seizure events identified with Epidiolex and CBD reports, although it was also observed in all CDP reports. We also identified a large proportion of missing data on patient's demographics, contributing to data quality bias. FAERS cannot be used to estimate adverse event incidence rate due to the lack of detailed information on the quantity of the actual population exposure to the drug [16]. The diverse and inconsistent terminology used to describe CDPs in AERs may limit the validity of the data.

4.4 General Conclusions

The post-marketing surveillance process for CDPs poses unique challenges in comparison to conventional pharmaceutical drugs. We demonstrated that CDPs containing similar active ingredients may produce different signal detection safety profiles. Our findings may validate that signal detection using spontaneous reporting has some potential feasibility for CPD safety surveillance, but care must be taken in the design of these studies noting the potential heterogeneity in reporting biases that are unique to products in which both pharmaceutical and non-pharmaceutical versions exist in the marketplace simultaneously. This project underscores the uniqueness of CDP-related AERs and provides insights into the design of signal detection for CDP studies, suggesting that additional factors should be considered when collecting, coding, and assessing individual case reports related to CDP use. Therefore, this project represents a valuable source of knowledge for the design of follow-up cannabis safety assessment studies and supports knowledge translation and communication of cannabis safety to the public.

4.5 Recommendations for future CDP Safety Surveillance using FAERS

The FAERS database has the potential to be a viable resource for monitoring the safety of CDPs. However, to ensure the accurate detection of signals, it is essential to consider certain key factors. Although FAERS offers valuable insights into CDP-related AERs, the unique characteristics of CDPs—such as product heterogeneity and diverse usage patterns—present challenges that must be addressed. Careful adjustments and considerations are essential to enhance the system's efficacy in monitoring the safety of these products. This aligns with the general conclusion that, despite the feasibility of using FAERS for CDP surveillance, targeted approaches must be implemented to account for the complexity and diversity of CDPs.

It is crucial to recognize that grouping all CDPs together under one category is not feasible because CDPs with the same cannabinoid can present different reporting profiles depending on how they are used and the populations using them. For example, pharmaceutical THC used for medical conditions may present AEs related to the underlying health condition itself, whereas recreational THC may elicit more reports of misuse or drug-related behaviors. By analyzing CDPs separately, researchers can better understand the unique safety profiles of each CDP. This also applies to regulatory variability, as non-pharmaceutical CDPs—especially those from unregulated markets—may have inconsistent quality or contamination, which must be accounted for separately from regulated pharmaceutical-grade products.

Addressing heterogeneity of CDP reporting behaviours in FAERS is critical to refining signal detection, reducing noise in the data, and generating more accurate safety assessments tailored to specific CDPs and user populations. One important strategy is categorizing CDPs by type, composition, and route of administration. CDPs should be grouped based on factors such as cannabinoid content (e.g., THC-dominant vs. CBD-dominant), product type (pharmaceutical vs. non-pharmaceutical), and method of consumption (e.g., THC vape vs. CBD oil). Different formulations and uses can lead to distinct safety profiles, and this differentiation helps ensure that signals are detected more precisely. In addition, classifying CDP use by medical and recreational purposes may enhance signal detection, as these uses can lead to very distinct AE profiles due to variations in dosage, patient health conditions, and possible polysubstance use.

Signal detection for CDPs in FAERS requires a targeted approach, necessitating a specific understanding of the CDP in question, its intended use, and the population for which it is indicated. CDPs exhibit considerable variation in formulation, potency, and context of use.

Consequently, lumping all CDPs together could obscure meaningful signals. The implementation of stratified signal detection and subgroup-based analysis, such as the concentration on particular populations or CDP categories, may be required for the identification of safety signals within more homogeneous subgroups. This approach helps to reduce the impact of the overall diversity of CDPs, ensuring the accurate detection of signals within the appropriate context.

The presence of reporting bias and unmeasured confounding represents a significant challenge, particularly when analyzing CDPs that share similar cannabinoids, such as Epidiolex and over-the-counter CBD products. The utilization of these products may vary across different populations for distinct purposes, which can result in disparate AE patterns. Reporting bias can skew safety signals, especially when one CDP is used under medical supervision and the other is consumed in a more informal manner. Adjusting for these biases, as well as for variability in usage patterns (e.g., different doses and frequencies of use), may be required to ensure that signal detection remains valid. In addition, the complexity introduced by the heterogeneity of CDPs captured in AERs, suggests that a more tailored data collection approach may be necessary. For instance, modifying FAERS reporting forms to include a specific field for CDPs could help capture critical details, such as product formulation, route of administration, and usage context, ultimately improving the precision of safety surveillance.

Finally, interpreting CDP safety signals with complementary data sources, such as electronic health records, patient registries, and observational studies, may reduce the inherent CDP complexities and challenges and provide additional context for validating signals detected in FAERS. These data sources enable a more comprehensive assessment of CDP safety,

complementing the spontaneous reporting data from FAERS, especially regarding the biological plausibility of the CDP-related ADR.

The implementation of these strategies will enable FAERS to serve as a valuable tool for CDP safety surveillance, despite the inherent heterogeneity and bias derived from CDPs and the spontaneous reporting system. These approaches are essential to improving the accuracy of safety assessments and contributing to FAERS's greater effectiveness in detecting safety signals in the diverse and evolving CDP landscape.

4.6 References

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APPENDIX

APPENDIX 1. Codes for Descriptive Analysis

```
#TABLE 1 DEMO CHAPTER 2#

#SET PACKAGES AND LOAD DATABASES####

library(data.table)

setwd("/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Table 01 Coding")

#DRUG DATABASES
drug2012<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641687/drug1688641687.csv",
                                 allowEscapes = FALSE,
                                 colClasses="character",
                                 encoding = "latin1"))

drug1999<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641629/drug1688641629.csv",
                                 allowEscapes = FALSE,
                                 colClasses="character",
                                 encoding = "latin1"))

drug2012<-drug2012[,.(source,primaryid,caseid,role_cod,drugname)] #48118975 obs.
drug1999<-drug1999[,.(source,primaryid,caseid,role_cod,drugname)] #13367151 obs.

drugtotal<-rbind(drug1999,drug2012, fill = TRUE) #61486126 obs.
rm(drug1999,drug2012)

#DEMO DATABASES
demo2012<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641687/demo1688641687.csv",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))

demo1999<-as.data.table(fread("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641629/demo1688641629.csv"))

demo2012<-demo2012[,.(source,primaryid,caseid,age_years,sex,reporter_country)] #13208968 obs.
demo1999<-demo1999[,.(source,primaryid,caseid,age_years,sex,reporter_country)] #3878857 obs.

demototal <- rbind(demo1999,demo2012, fill = TRUE) #17087825 obs.
rm(demo1999,demo2012)

#OUTCOMES DATABASES
outc2012<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641687/outc1688641687.csv",
                                 colClasses="character",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))

outc2012<-outc2012[,.(source,primaryid,caseid,outc_cod)] #9342881 obs.

outc1999<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641629/outc1688641629.csv",
                                 colClasses="character",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))

outc1999<-outc1999[,.(source,primaryid,caseid,outc_cod)] #3359942 obs.
```

```
outctotal<- rbind(outc1999,outc2012, fill = TRUE) #12702823 obs.
rm(outc1999,outc2012)

#REPORTER SOURCE DATABASES
rpsp1999 <- as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641629/rpsr1688641629.csv",
                                   colClasses="character",
                                   allowEscapes = FALSE,
                                   encoding = "latin1"))

rpsp2012 <- as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641687/rpsr1688641687.csv",
                                   colClasses="character",
                                   allowEscapes = FALSE,
                                   encoding = "latin1"))

rpsp1999 <- rpsp1999[,.(source,primaryid,caseid,rpsr_cod)] #2357047 obs.
rpsp2012 <- rpsp2012[,.(source,primaryid,caseid,rpsr_cod)] #752591 obs.

rpsptotal<- rbind(rpsp1999,rpsp2012, fill = TRUE) #3109638 obs.
rm(rpsp1999,rpsp2012)

#REACTIONS DATABASES
reac2012<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641687/reac1688641687.csv",
                                 colClasses="character",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))

reac1999<-as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive analysis/Gravel cleaned data (1999-
2023)/1688641629/reac1688641629.csv",
                                 colClasses="character",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))

reac2012<-reac2012[,.(source,primaryid,caseid,pt)] #37947388
reac1999<-reac1999[,.(source,primaryid,caseid,pt)] #13042597

reactotal<-rbind(reac1999,reac2012, fill = TRUE) #50989985
rm(reac1999,reac2012)

#Old_All terms####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/reltableallterms.csv"

#Dronabinol####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/dronabinol terms.csv"

#Sativex####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/sativex terms.csv"

#Epidiolex####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/epidiolex terms.csv"

#D8-THC####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/d8thc terms.csv"

#D9-THC####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/d9thc terms.csv"
```

```
#D8-THC/CBD####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/d8thccbd terms.csv"

#D9-THC/CBD####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/d9thccbd terms.csv"

#CBD####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/CBD terms.csv"

#Minor Cannabinoids####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/minor cannabinoids terms.csv"

#Cannabis####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/cannabis terms.csv"

#THC Homologs####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Relational Tables_Terms/thc homologs terms.csv"

#New All terms####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/All terms condensed.csv"
#New THC####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/THC terms.csv"
#New THC/CBD####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/THCCBD terms.csv"
#New Nabilone####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/nabilone terms.csv"

#New Dronabinol only####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/dronabinol only terms.csv"

#New All 5 CDPs Signal detection####
csv_path <- "/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1
Descriptive analysis/Final Files/5cdps terms.csv"

#All quarters####
quarters <- c(
              19991,19992,19993,19994,
              20001,20002,20003,20004,
              20011,20012,20013,20014,
              20021,20022,20023,20024,
              20031,20032,20033,20034,
              20041,20042,20043,20044,
              20051,20052,20053,20054,
              20061,20062,20063,20064,
              20071,20072,20073,20074,
              20081,20082,20083,20084,
              20091,20092,20093,20094,
              20101,20102,20103,20104,
              20111,20112,20113,20114,
              20121,20122,20123,20124,
              20131,20132,20133,20134,
              20141,20142,20143,20144,
              20151,20152,20153,20154,
              20161,20162,20163,20164,
              20171,20172,20173,20174,
              20181,20182,20183,20184,
```

```
              20191,20192,20193,20194,
              20201,20202,20203,20204,
              20211,20212,20213,20214,
              20221,20222,20223,20224,
              20231)

#1999-2003####
quarters <- c(
              19991,19992,19993,19994,
              20001,20002,20003,20004,
              20011,20012,20013,20014,
              20021,20022,20023,20024,
              20031,20032,20033,20034)
#2004-2008####
quarters <- c(20041,20042,20043,20044,
              20051,20052,20053,20054,
              20061,20062,20063,20064,
              20071,20072,20073,20074,
              20081,20082,20083,20084)

#2009-2013####
quarters <- c(20091,20092,20093,20094,
              20101,20102,20103,20104,
              20111,20112,20113,20114,
              20121,20122,20123,20124,
              20131,20132,20133,20134)

#2014-2018####
quarters <- c(20141,20142,20143,20144,
              20151,20152,20153,20154,
              20161,20162,20163,20164,
              20171,20172,20173,20174,
              20181,20182,20183,20184)

#2019-2023####
quarters <- c(20191,20192,20193,20194,
              20201,20202,20203,20204,
              20211,20212,20213,20214,
              20221,20222,20223,20224,
              20231)


#2011-2013####
quarters <- c(20111,20112,20113,20114,
              20121,20122,20123,20124,
              20131,20132,20133,20134)
#2014-2016####
quarters <- c(20141,20142,20143,20144,
              20151,20152,20153,20154,
              20161,20162,20163,20164)
#2017-2019####
quarters <- c(20171,20172,20173,20174,
              20181,20182,20183,20184,
              20191,20192,20193,20194)
#2020-2022####
quarters <- c(20201,20202,20203,20204,
              20211,20212,20213,20214,
              20221,20222,20223,20224)

#1999####
quarters <- c(19991,19992,19993,19994)
#2000####
quarters <- c(20001,20002,20003,20004)

#2001####
quarters <- c(20011,20012,20013,20014)

#2002####
```

```
quarters <- c(20021,20022,20023,20024)

#2003####
quarters <- c(20031,20032,20033,20034)

#2004####
quarters <- c(20041,20042,20043,20044)

#2005####
quarters <- c(20051,20052,20053,20054)

#2006####
quarters <- c(20061,20062,20063,20064)

#2007####
quarters <- c(20071,20072,20073,20074)

#2008####
quarters <- c(20081,20082,20083,20084)

#2009####
quarters <- c(20091,20092,20093,20094)

#2010####
quarters <- c(20101,20102,20103,20104)

#2011####
quarters <- c(20111,20112,20113,20114)

#2012####
quarters <- c(20121,20122,20123,20124)

#2013####
quarters <- c(20131,20132,20133,20134)

#2014####
quarters <- c(20141,20142,20143,20144)

#2015####
quarters <- c(20151,20152,20153,20154)

#2016####
quarters <- c(20161,20162,20163,20164)

#2017####
quarters <- c(20171,20172,20173,20174)

#2018####
quarters <- c(20181,20182,20183,20184)

#2019####
quarters <- c(20191,20192,20193,20194)

#2020####
quarters <- c(20201,20202,20203,20204)

#2021####
quarters <- c(20211,20212,20213,20214)

#2022####
quarters <- c(20221,20222,20223,20224)

#2023####
quarters <- c(20231)

#Quarters Epidiolex & CBD Signal Detection####
quarters <- c(20182,20183,20184,
              20191,20192,20193,20194,
```

```
              20201,20202,20203,20204,
              20211,20212,20213,20214,
              20221,20222,20223,20224,
              20231)

#DRUG PROCESSING ROLE####
drug_processing <- function(csv_path,quarters) {

  reltableallterms <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))

  allterms <- reltableallterms[,TERMS] #1204 terms

  alltermstotal <- drugtotal[toupper(drugname) %in% toupper(allterms)]

  source_quarters <- alltermstotal[source %in% quarters]

  alltermscaseids <- unique(source_quarters[,.(primaryid,caseid)]) #42654 obs.

  alltermstotal <- source_quarters[,ROLE:=ifelse(role_cod=="PS",4,
                                                 ifelse(role_cod=="SS",3,
                                                        ifelse(role_cod=="I",2,

ifelse(role_cod=="C",1,NA)))),by=.(primaryid,caseid)]

  alltermsROLE_COD <- unique(alltermstotal[,.(primaryid,caseid,ROLE)])

  cols <- c("ROLE")
  alltermsROLE_COD <-
unique(alltermsROLE_COD[,(cols):=lapply(.SD,max),.SDcols=cols,by=.(primaryid,caseid)])

  alltermsPS <- alltermsROLE_COD[ROLE==4] #14412 obs.
  alltermsSS <- alltermsROLE_COD[ROLE==3]
  alltermsI <- alltermsROLE_COD[ROLE==2]
  alltermsC <- alltermsROLE_COD[ROLE==1]

  n <- dim(alltermsROLE_COD)[1]

  percPS <- round(nrow(alltermsPS) / n * 100, 1)
  percSS <- round(nrow(alltermsSS)/n*100, 1)
  percI <- round(nrow(alltermsI) / n * 100, 1)
  percC <- round(nrow(alltermsC) / n * 100, 1)

  total_cases <- nrow(alltermsPS) + nrow(alltermsSS) + nrow(alltermsI) + nrow(alltermsC)

  ALLTERMS <-paste("DRUG ROLE (n=", total_cases, ")",sep = "")

  output <- matrix(
    c(
      paste(nrow(alltermsPS), " (", percPS, "%)",sep = ""),
      paste(nrow(alltermsSS), " (", percSS, "%)",sep = ""),
      paste(nrow(alltermsI), " (", percI, "%)",sep = ""),
      paste(nrow(alltermsC), " (", percC, "%)",sep = "")),
    nrow = 4,
    dimnames = list(
      c("Primary suspect drug", "Secondary suspect drug", "Interacting drug", "Concomitant drug"),
      ALLTERMS),
    byrow = TRUE
  )

  return(output)
}

finaloutput_drugprocessing <- print(drug_processing(csv_path,quarters))

#DEMO_AGE####
demo_processing_age <- function(csv_path,quarters) {

  reltabledronab <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))
```

```
  dronabterms <- reltabledronab[,TERMS] #154 terms

  dronabtermstotal <- drugtotal[toupper(drugname) %in% toupper(dronabterms)] #9662 obs.

  source_quarters <- dronabtermstotal[source %in% quarters] #9662 obs.

  dronabtermscaseids <- unique(source_quarters[,.(primaryid,caseid)]) #8637 unique caseid/primaryid

  dronabtermsprimaryid <- dronabtermscaseids[,primaryid] # obs.

  dronabtermscaseid <- dronabtermscaseids[,caseid] # obs.

  dronabtermsage<-unique(demototal[primaryid %in% dronabtermsprimaryid]) # obs.

  dronabtermsage<-dronabtermsage[!which(duplicated(dronabtermsage[,primaryid])),] # obs. same as unique
caseid in drug processing

  dronabtermsage<-dronabtermsage[,.(caseid,ceiling(age_years))] # obs.

  summary(dronabtermsage[,V2], na.rm=TRUE) # NA
  mean(dronabtermsage[,V2], na.rm=TRUE) #
  sd(dronabtermsage[,V2], na.rm=TRUE) #

  dronabtermsage0<-dronabtermsage[V2>=0 & V2<=12] # obs.
  dronabtermsage13<-dronabtermsage[V2>12 & V2<=17] # obs.
  dronabtermsage18<-dronabtermsage[V2>17 & V2<=35] # obs.
  dronabtermsage36<-dronabtermsage[V2>35 & V2<=54] # obs.
  dronabtermsage55<-dronabtermsage[V2>54 & V2<=69] # obs.
  dronabtermsage70<-dronabtermsage[V2>69] #  obs.
  dronabtermsmissing<-sum(is.na(dronabtermsage[,V2])) # obs.

  n <- dim(dronabtermsage)[1]

  percage0 <- round(nrow(dronabtermsage0) / n * 100, 1)
  percage13 <- round(nrow(dronabtermsage13)/n * 100, 1)
  percage18 <- round(nrow(dronabtermsage18) / n * 100, 1)
  percage36 <- round(nrow(dronabtermsage36) / n * 100, 1)
  percage55 <- round(nrow(dronabtermsage55) / n * 100, 1)
  percage70 <- round(nrow(dronabtermsage70) / n * 100, 1)
  percagemissing <- round(dronabtermsmissing / n* 100, 1)

  total_cases <- nrow(dronabtermsage0) + nrow(dronabtermsage13) + nrow(dronabtermsage18) +
nrow(dronabtermsage36) +
    nrow(dronabtermsage55) + nrow(dronabtermsage70) + dronabtermsmissing

  DRONAB_AGE <-paste("AGE (n=", total_cases, ")",sep = "")

  output <- matrix(
    c(paste(nrow(dronabtermsage0), " (", percage0, "%)", sep = ""),
      paste(nrow(dronabtermsage13), " (", percage13, "%)", sep = ""),
      paste(nrow(dronabtermsage18), " (", percage18, "%)", sep = ""),
      paste(nrow(dronabtermsage36), " (", percage36, "%)", sep = ""),
      paste(nrow(dronabtermsage55), " (", percage55, "%)", sep = ""),
      paste(nrow(dronabtermsage70), " (", percage70, "%)", sep = ""),
      paste(dronabtermsmissing, " (", percagemissing, "%)", sep = "")),
    nrow = 7,
    dimnames = list(c("0-12", "13-17", "18-35", "36-54", "55-69", "70+", "Missing"), DRONAB_AGE),
    byrow = TRUE)

  return(output)
}

finaloutput_age<- print(demo_processing_age(csv_path,quarters))

#DEMO_SEX####
demo_processing_sex <- function(csv_path,quarters) {
```

```
  reltabledronab <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))

  dronabterms <- reltabledronab[,TERMS] #154 terms

  dronabtermstotal <- drugtotal[toupper(drugname) %in% toupper(dronabterms)] #9662 obs.

  source_quarters <- dronabtermstotal[source %in% quarters] #9662 obs.

  dronabtermscaseids <- unique(source_quarters[,.(primaryid,caseid)]) #8637 unique caseid/primaryid

  dronabtermsprimaryid <- dronabtermscaseids[,primaryid] # obs.

  dronabtermscaseid <- dronabtermscaseids[,caseid] # obs.

  dronabtermssex<-unique(demototal[primaryid %in% dronabtermsprimaryid]) # obs.

  dronabtermssex<-dronabtermssex[!which(duplicated(dronabtermssex[,primaryid])),] # obs. same as unique
caseid in drug processing

  dronabtermssex<-dronabtermssex[,.(caseid,sex)] # obs.

  sexF<-dronabtermssex[sex=="F"]
  sexM<-dronabtermssex[sex=="M"]
  sexNA<-dronabtermssex[sex==""]
  sexNS<-dronabtermssex[sex=="NS"]
  sexP<-dronabtermssex[sex=="P"]
  sexT<-dronabtermssex[sex=="T"]
  sexUNK<-dronabtermssex[sex=="UNK"]
  sexmissing<-nrow(sexNA) + nrow(sexNS) + nrow(sexP) + nrow(sexT) + nrow(sexUNK)

  n <- dim(dronabtermssex)[1]

  percsexF <- round(nrow(sexF) / n * 100, 1)
  percasexM <- round(nrow(sexM)/n * 100, 1)
  percsexmissing <- round(sexmissing / n * 100, 1)

  total_cases <- nrow(sexF) + nrow(sexM) + sexmissing

  DRONAB_SEX <-paste("SEX (n=", total_cases, ")",sep = "")

  output <- matrix(
    c(paste(nrow(sexF), " (", percsexF, "%)", sep = ""),
      paste(nrow(sexM), " (", percasexM, "%)", sep = ""),
      paste(sexmissing, " (", percsexmissing, "%)", sep = "")),
    nrow = 3,
    dimnames = list(c("Female", "Male", "Missing"), DRONAB_SEX),
    byrow = TRUE)

  return(output)
}

finaloutput_sex<- print(demo_processing_sex(csv_path,quarters))

#FINAL DRUG AND DEMO OUTPUTS####

print(list(finaloutput_drugprocessing,finaloutput_age,finaloutput_sex))

#OUTCOMES####
reltableallterms <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))
allterms <- reltableallterms[,TERMS]
alltermstotal <- drugtotal[toupper(drugname) %in% toupper(allterms)]
source_quarters <- alltermstotal[source %in% quarters]
alltermscaseids <- unique(source_quarters[,.(primaryid,caseid)]) #42654
alltermsprimaryid <-alltermscaseids[,primaryid] #42654
outctotal2<-outctotal[,.(source,primaryid,outc_cod)]
tempoutc <- unique(outctotal2[primaryid%in%alltermsprimaryid]) #40289 obs. 152
tempoutc <- tempoutc[,outc_cod]
tempoutc <- as.factor(tempoutc)
```

```
print(summary(tempoutc))
percentage_tempoutc <- round(prop.table(table(tempoutc)) * 100, 1)
factor_counts <- table(tempoutc)
factor_percentage <- paste0(names(percentage_tempoutc), " (", factor_counts, ", ", percentage_tempoutc,
"%)")
print(factor_percentage)

#REPORTING COUNTRY####
reltableallterms <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))
allterms <- reltableallterms[,TERMS]
alltermstotal <- drugtotal[toupper(drugname) %in% toupper(allterms)]
source_quarters <- alltermstotal[source %in% quarters]
alltermscaseids <- unique(source_quarters[,.(primaryid,caseid)])
alltermsprimaryid <-alltermscaseids[,primaryid]
demototal2<-demototal[,.(source,primaryid,reporter_country)] #17087825 obs.
repcountry<-unique(demototal2[primaryid%in%alltermsprimaryid]) #42675 and not 42654 as drug processing
repcountry<-repcountry[!which(duplicated(repcountry[,primaryid])),] #42654 same as drug processing
repcountry<-repcountry[,reporter_country]
repcountry<-as.factor(repcountry)
repcountry<-print(summary(repcountry))
write.csv(repcountry,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 1 Descriptive
analysis/thccbdcondensedrepcountry.csv")

#REPORTER SOURCE####
reltableallterms <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))
allterms <- reltableallterms[,TERMS]
alltermstotal <- drugtotal[toupper(drugname) %in% toupper(allterms)]
source_quarters <- alltermstotal[source %in% quarters]
alltermscaseids <- unique(source_quarters[,.(primaryid,caseid)])
alltermsprimaryid <-alltermscaseids[,primaryid]
rpsptotal2<-rpsptotal[,.(source,primaryid,rpsr_cod)] #3109638 obs.
rpsp<-unique(rpsptotal2[primaryid%in%alltermsprimaryid]) #6060 obs.
rpsp<-rpsp[!which(duplicated(rpsp[,primaryid])),] #3857 obs.
rpsp<-rpsp[,rpsr_cod]
rpsp<-as.factor(rpsp)
rpsp<-print(summary(rpsp))

#REACTIONS####
reltableallterms <- as.data.table(read.csv(csv_path, allowEscapes = FALSE, colClasses='character'))
allterms <- reltableallterms[,TERMS]
alltermstotal <- drugtotal[toupper(drugname) %in% toupper(allterms)]
source_quarters <- alltermstotal[source %in% quarters]
alltermscaseids <- unique(source_quarters[,.(primaryid,caseid)]) #42654 obs.
alltermsprimaryid <-alltermscaseids[,primaryid] #42654 obs.
reactotal2<-reactotal[,.(source,primaryid,pt)] #50989985 obs.
reac<-unique(reactotal2[primaryid%in%alltermsprimaryid]) #203017 obs.
reac<-toupper(reac$pt)
reac<-as.factor(reac) #6524 levels
write.csv(reac,"/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter
1 Descriptive analysis/thccbdcondensedreac.csv")
reac<-print(summary(reac))
write.csv(reac,"/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter
1 Descriptive analysis/thccbdcondensedsummaryreac.csv")
```

APPENDIX 2. Self-reported Terminologies for CDPs

2.1 Rx THC Terminology

MARINOL /00897601/

MARINOL

Marinol

DRONABINOL

MARINOL (UNITED STATES)

CESAMET

DRONABINOL.

MARINOL (DRONABINOL)

NABILONE

MARTINOL (DRONABINOL) (DRONABINOL)

MARINOL /00003301/

MARINOL (DRONABINOL) (2.5 MILLIGRAM, CAPSULES)
DRONABINOL (DRONABINOL) (UNKNOWN)

MARINOL (DRONABINOL) (UNKNOWN)

DRONABINOL (DRONABINOL) (10 MILLIGRAM, CAPSULES)
DRONABINOL (DRONABINOL) (CAPSULES)

DRONABINOL(DRONABINOL)

DRONABINOL(DRONABINOL)(UNKNOWN)

dronabinol

nabilone

DRONABINOOL

DRONABINOL CAPSULES

CESAMET (NABILONE)

marinol

MARINIOL (DRONABINOL)

DRONABINOL (DRONABINOL)

MARINOL (DRONABINOL) (DRONABINOL)

MARINOL (mecobalamin)

Dronabinol

MARINOL (dronabinol)

Dronabinol Capsules

MARINOL /00897601/

MARINOL (DRONABINOL) (CAPSULES)

MARIINOL (DRONABINOL)

DRONABINOL (UNKNOWN)

DRONABINOL CAPSULES USP

Marinol/Dronabinol/THC

Nabilone

Dronabinol (THC)

Dronabinol Softgel Caps

MARINOL(DRONABINOL)

MARINOL 2.5MG

MARINOL (DRONABINOL) (CAPSULES) (DRONABINOL)
MARINOL (UNITED STATES) (DRONABINOL)

DRONABINOL (MEDICAL MARIJUANA)

DRONABINOL (MARINOL)

DRONABINOL 2.5MG

MARINOL [ALLOPURINOL]

DRONABINOL Capsule

MARINOL /00003301/

DRONABINOL (IMARINOL)

DRONABINAL

DRONABINOL 5MG

Marinot

NABILONE 250 MCG

DRONABINOL (MARINOL PO)

DRONABIHOL

RAN-NABILONE

MARINOL (ALLOPURINOL)

Dronabinol w/ Aspirin

MARINOL CAP

DRONABINAL (MARINAL)

DRONABINOL (MSTINOL)

DRONABINOL CAPSULE, USP CIII

TEVA NABILONE

Dronabinol Capsule, USP CIII

SYNDROS

MARINORL

NIDA CANNABIS/DRONABINOL

DRONABI NCL

NABILON

Marinol 5 mg.

Dronabinoloel

Dronabinol 5mg

Dronabinol j5mg

DRONABINOL CAP 10MG

dronabinol 2.5

MARINOL [DRONABINOL]

dronabinol cap 10mg

NABILONE CAPSULE

NABILONE CAPSULES

DRONABINOL CAP 2.5MG

DRONABINOL 2.5 MG CAPSULE CIII

Dronabinol, Dulera, Montelukast

dronabinole

NABILONE MYLAN

DRONABOL

Dronabinol capsules

DRONABINOL CAPSULES, USP 2.5 MG. RX ONLY

dronabinal cap 5mg

MARINOL [MECOBALAMIN]

BEDIOL (CANNABIDOL\DRONABINOL)

dronabinol 2.5 mg

marinol cap 5 mg

dronabinol 2.5mg

DRONABINOL 5MG CAPSULES

MARINOL CAP 5MG

Dronabinol 2.5 mg, oral

Dronabinol 2.5mg

DRONABINOL (DRONABINOL 2.5MG CAP)

Marinol 2.5mg

DRONABINOL 5 MG

DRONABINOL CAPSULE CIII

MARINOL 5MG

DRONABINOL 10MG

MARINOL 10MG

DRONABINOL 2.5MG CAPSULES

Marinol 10mg

Dronabinol 2.5MG capsules

^MARINOL^

dronabinol 5?10

DARUNAVIR , GENERIC FOR MARINOL

Dronabinol 5MG capsules

THC (DRONABINOL)

DRONABINOL (Medical Marijuana)

MARINOL OMEGA 3

dronabinol 5 mg

RAN NABILONE

Marinol 5mg

NABILONA

Dronabino

Dronabinol 5mg BID

Cetirizine DronabinoL

MARINOL 10 MG

Dronabinol 2.5 mg

DRONABIN OL

Dronabinol Oral Capsule 2.5 MG

Marinol 5 mg

DRONABINOL CAP 5MG

MAG-OXIDE MARINOL

MARINOL (DRONABINOL (DELTA-9-TETRAHYDROCANNABINOL))
COMPASSIA (DRONABINOL)

NABILONE (NABILONE)

MARINOL (ALGAE/CALCIUM PHOSPHATE, MONOBASIC/IODINE NOS/PHOSPHORIC ACID
DRONABINOL 2.5 MG

NARINOL (DRONABINOL)

MARIOL (DRONABINOL)

DRONABINOAL

MARNOL (DRONABINOL)

MARINOL (DRONABINAOL)

MARINOL TABLETS

MARINOL 2.5

MARINOL (DRONABINOL) TABLET

MARINOL (DRONABINOL),(2.5 MILLIGRAM, CAPSULES)
MARINOL (BRONABINOL)

MARINOL (DRONABINOL) (10 MILLIGRAM, CAPSULES)
NABILONE (CESAMET)

MARINOL (*ALGAE/*ALLOPURINOL/*CALCIUM PHOSPHATE, MONOBASIC/*DROABINNOL
MARINOL (ALGAE/ALLOPURINOL/CALCIUM PHOSPHATE MONOBASIC/*DRONABINOL/*IO
MARINOL(ALGAE/ALLOPURINOL/CALCIUM PHOSPHATE
(NABILONE)

DRONABINOL 2.5 G

DRONABIONL

DELTA(9)- TETRAHYDROCANNABINOL (DRONABINOL)

2.2 Sativex Terminology

SATIVEX SPRAY

SATIVEX

NABIXIMOLS

Sativex

BLINDED SATIVEX

NABIXIMOLS (SATIVEX) OROMUCOSAL SPRAY

SATIVEX (NABIXIMOLS)

sativex

SATIVEX - SPRAY PER MUCOSA ORALE

DELTA?SATIVEX

nabiximols

Sativex Spray zur Anwendung in der Mundhoehle

Sativex Spray

Sativex Spray zur Anwendung in der Mundhohle

FM2 OIL (MAGISTRAL PREPARATION) (NABIXIMOLS)

Sativex Spray 38.5/41 mg

Nabiximols

MEVATYL

sativex spray for application in the oral cavity

sativex Spray zur Anwendung in der Mundhohle

2.3 Epidiolex Terminology

Epidiolex

EPIDIOLEX ODT

EPIDIOLEX

EPIDIOLEX CBD OIL

EPIOLEX

Epidolex

Epidolex oral solution

EPIDOLEX

EPIDIOLEX (CBD)

EPIDYOLEX (CANNABIDIOL) IN GERMAN CLINICAL PRACTICE

EPIDIOLEX (RETAIL0

EPIDIOLEX (RETAIL)

cannabidiol (Epidiolex)

EPIDIOLEX SOL

2.4 THC Terminology

TETRAHYDROCANNABINOL

Tetrahydrocannabinol

THC

TETRAHYDROCANNABINOL (THC)

CANNABIS (CANNABIS-TETRAHYDROCANNABINOL)
8-TETRAHYDROCANNABINOL

DELTA-9-TETRAHYDROCANNABIONOL

Delta-9-tetrahydrocannabinol

DELTA-9-TETRAHYDROCANNABINOL

9-TETRAHYDROCANNABINOL

UNSPECIFIED FORMULATIN OF TETRAHYDROCANNASINOL (THC)
TETRAHYDROCANNABINOL (MARIJUANA,HASH)
Marijuana/ THC/ hemp/Hash

DELTA-9-CARBOXY-TETRAHYDROCANNABINOL
8-THC

TETRANHYDROCANNABINOL

tetrahydrocannabinol

11-NOR-9-TETRAHYDRO-9-CANNABINOLIC ACID
DELTA(9)-TETRAHYDROCANNABINOL

THC (PURE MARIJUANA IN PILL FORM) PRN

TETRAHYDROCANNABINOL-THC

THC (NOS)

8-Tetrahydrocannabinol

11-nor-9-carboxy-delta-9-tetrahydrocannabinol

DELTA 9 THC

TETRAHYDRO CANNABIDIAOL

TETRAHYDRO CANNABIDIOL

HYDROXY-THC

DELTA-9 CARBOXY TETRAHYDROCANNABINOL

9-THC

THC-COOH

Carboxy- tetrahydrocannabinol

8?TETRAHYDROCANNABINOL

Delta-9-Tetrahydrocannabinol

thc

Delta-9 THC

Delta-9-carboxy THC

THC TETRAHYDROCANNABINOL

TETRAHYDROCANNABINOLS

11-NOR-9-CARBOXY-DELTA-9-TETRAHYDROCANNABINOL
THC (9 TETRAHYDROCANNABINOL)

THC (9 Tetrahydrocannabinol)

low Indica thc

.DELTA.8-TETRAHYDROCANNABINOL\HERBALS

THC 3.4g Gummies

THC Vaping

DELTA 9-TETRAHYDROCANNABINOL

11-NOR-9-CARBOXY-?-9-TETRAHYDROCANNABINOL
DELTA-9 CARBOXY THC

11-HYDROXY DELTA-9 THC

DELTA-9 TETRAHYDROCANNABINOL

11-HYDROXY DELTA-9 TETRAHYDROCANNABINOL
DELTA-9-CARBOXY-THC

11-HYDROXY-DELTA-9-TETRAHYDROCANNABINOL
Delta-9-thc

11-NOR-9-CARBOXY-THC

9?TETRAHYDROCANNABINOL

LEGAL LOQ THC CANNABIS

[NO NAME] THC REFILL CARTRIDGE

11-Nor-9-carboxy-THC

11-COOH-THC (11-NOR-9-CARBOXY-.DELTA.9-TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL CARBOXYLIC ACID
CANNABIS EKSTRACT (THC)

Medical THC

THC MARIJUANA

SNOW SHARK 100MG THC CAPSULES

100MG THC

TETRAHYDROCANNABINOL-CARBOXYLIC ACID
Tetrahydrocannabin OL

THC VAPE PEN

VAPE DEVICE (THC OIL)

THC OIL

THC VAPING

THC (Tetrahydrocannabinol)

THC VAPING LIQUID

PLATINUM AND DANK BRAND MARIJUANA CARTRIDGES (VAPE THC\NICOTINE)
THE KIND PEN (USING GENERIC THC CARTRIDGE)
DR. ZODIAKS (THC VAPING)

HAVEY HITTERS (THC VAPING)

THC VAPE

HERBALS\TETRAHYDROCANNABINOL UNSPECIFIED
Delta 9-tetrahydrocannabinol

THC DROPS

THC CARTRIDGE

THC vape pen

MARIJUANA HERB, THC OILS

VAPE THC

THC CARTRIDGES

THC POWDER TO MIX WITH WATER FOR VAPING

SUPREME CART THC DEVICE

CARTNITE THC DEVICE

SMOK NOVO THC VAPES

VAPING THC OIL

THC VAPE, DANK VAPES, EXOTIC CARTS, KING PEN, COOKIES, VAPURRR EXTRACT
RYTHM SINGLE (DISPOSABLE THC VAPE) WWW.RYTHM.COM
THC VAPE DANK STRAWBERRY

THC DANK VAPES-HARDCORE OG

Tetrahydrocannabinol Carboxylic Acid

VAPE PEN WITH THC

THC CONCENTRATES WAX

DANK KING LOUIE [.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS]
DANK STRAW-NANA FLAVORS [.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS]
STIG THC-DANK VAPES, GLOW, CALIFORNIA CONFIDENTIAL
TKO THC, FRUIT FLAVORING

^THC TOPPERS^ [.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS]
^THC TOPPERS-DANK, SUPREME, VSOP, COOKIE CART, ROVE, SMART CART AND MARIO CART [.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS]
^DABWOOD, ROVE, AND SUPREME G THC CARTRIDGES.
DANK VAPES THC CARTRIDGES

MEDICINAL THC 5

THC CARTRIDGE BRANDS: DANK VAPES. DOUGHBOY. GAS TANK
thc -

THC VAPE CARTRIDGE

THC OIL VAPE PEN

VALLEY LABS THC CARTRIDGES

STRAIGHT FIRE VACUUM SEALED CARTS [THC]

DABS, DAB WAX, DAB CARDS, WAX (THC VAPING)
THC/NICOTINE VAPE CARTRIDGE

CEREAL CARTS IN CEREAL FLAVORS [THC]

DANK VAPES [THC]

THC VAPING CARTRIDGES ARE UNFLAVORED: PINGS PENS, 1% TKO^
STRAINLY INTERNET SIGHT THC PLANTS (HEMP)
VAPING THC

DANK VAPES THC

THC VAPES DANK

THC [.DELTA.8-TETRAHYDROCANNABINOL]

BRASS KNUCKLE [THC VAPE]

THC VAPE JUICE

DANK THC VAPE

MEDICAL THC

BIOTIN THC

THC VAPE PENS

DANK VAPES THC INFUSED E-LIQUID CARTS

ROVE, DANK VAPES, AND CHRONIC BRANDS OF THC INFUSED E-LIQUIDS
THC WAX MIXED WITH VAPEYOURWAX JUICE

.DELTA.9-TETRAHYDROCANNABINOL\CANNABIDIOL\HERBALS

.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS
THC oil

delta?9?tetrahydrocannabinol

9?TETRAHYDROCANNABIN OL

8?THC

9?THC

Delta?9 Carboxy THC

THC DROPS STENOCARE

THC (9-CARBOXY THC)

THC AND METABOLITES (TETRAHYDROCANNABINOL)
THC (TETRAHYDROCANNABINOL) (THC-COOH)

CANNTRUST THC DROPS

2600MG D8 SPECIAL EDITION EXTREME BROWNIE [.DELTA.8-TETRAHYDROCANNABINOL]
THC?dominant cannabis

THC?COOH

TETRAHYDRO [TETRAHYDROCANNABINOL]

Thc drops stenocare

KOI DELTA 8 GUMMIES BLUE?RAZZ FLAVORED KOICBD.COM
BEDROCAN (THC_PREDOMINANT)

11?NOR?9?CARBOXY?DELTA(9)?TETRAHYDROCANNABINOL
CANNABURST THC GUMMY SOURS

11?nor?9?carboxy?delta?9?tetrahydrocannabinol

Delta?9?tetrahydrocannabinol

YOUR CURE CBD ? DELTA 8 VAPE TANK

DELTA(9)?TETRAHYDROCANNABINOL

THC PROSTAFLO [HERBALS]

RAW GARDEN, THC VAPE PEN

TETRAHYDROCANNABINOL CARBOXYLIC ACID (THC?COOH)
Tetrahydrocannabinol (THC)

UNKNOWN DELTA 8 THC GUMMY

DELTA 8 THC

THC BUTTERSCOTCH CHOCOLATE [DELTA 8 THC]
11-NOR-9-CARBOXY-.DELTA-9-TETRAHYDROCANNABINOL
11?NOR?9?CARBOXY?TETRAHYDROCANNABINOL
11?nor?9?carboxy?tetrahydrocannabinol

DELTA?9 THC

DELTA 8 THC GUMMIES

DELTA 8 THC EDIBLE

ZAR COSMIC CHOCOLATE CANDY BAR WITH PEANUT BUTTER [DELTA?8?THC]
Delta 8 THC edible

THC vape

THC PROSTAFLO

DELTA 8 THC CHOCOLATE

1000 MG THC DELTA 8 BROWNIE

GALAXY TREATS MOON BABIES DELTA 8 THC GUMMIES 50 MG STARBERRY
8?Tetrahydrocannabinol

THC CHOCOLATE BAR

JAH GUMMIES WHAT?A?MELON [DELTA?8 THC]

DELTA?8 CANNABIS

BITES DELTA?8 THC PINK LEMONADE GUMMIS

CANNAAID DELTA 8 OIL [.DELTA.8?TETRAHYDROCANNABINOL\HERBALS]
.DELTA.8-TETRAHYDROCANNABINOL

UNKNOWN THC GUMMY

KUSH BURST THC GUMMIES PINEAPPLE PUNCH (DELTA 8) ?

THC?0

THC EDIBLE

THC W CANNABIS

THC MARIJUANA

11-NOR-9-CARBOXY-.DELTA.9-TETRAHYDROCANNABINOL
11-HYDROXY-.DELTA.9-TETRAHYDROCANNABINOL
.DELTA.9-TETRAHYDROCANNABINOL\HERBALS

TETRAHYDROCANNABINOLS NOS

HERBALS\TETRAHYDROCANNABINOL MIXED

.DELTA.9-TETRAHYDROCANNABINOL ACETATE\HERBALS
TETRAHYDROCANNABINOL UNSPECIFIED\HERBALS
THC GUMMY

TETRAHYDROCANNABINOLS NOS (TETRAHYDROCANNABINOLS NOS)
THC Tincture

DELTA 8 CBD

THC W CANNIBIS

Tetrahydrocannabinol nos

Delta8THCDeath by GummyBear

Tetrahydrocannabinol dab pen

THC GUMMIES

THC (CANNABIS)

TETRAHDROCANNABINOL

DELTA-9-CARBOXY THC

TETRAHYDROCANNABIONAL

TETRAHYDROCANNABINOL (TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL(TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYDROCANNABINOL) CAPSULE, UNKNOWN

TETRAHYDROCANNABINOL (TETRAHYDRACANNIBONOL)
TETRAHYDROCANNABINOL (TETRATHYDROCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYROCANNABINOL)
TETRAHYDROCANABINOL (TETRAHYDROCANNABINOL)
TETRAHYDROCOANNABINOL (TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYDROCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYDROCANNABIMOL)
TETRAHYDROCANNABINOL(TETRAHYDRCANNABINOL)
TETRAHYDROCANNABINOL (TETRAHYDROCANNIBOL)
TETRAHYDROCANNANBINOL(TETRAHYDROCANABINOL)
TETRAHYDROCANNABINOL (TETAHYDROCANNABINOL)
CARBOXY THC

THC (TETRAHYDROCANNABINOL) (TETRAHYDROCANNABINOL)
TETRAHYDROCANABINOL CARBOXY-ACID (TETRAHYDROCANNABINOL) (UNKNOWN)
TETRAHYDROCANNABINOL (CON.)

TETRAHYDROCANNABNIOL (TETRAHYDROCANNABINOL)
THC-COOH (CANNABIS)

THC (CANNABIS STAIVA)

THC (CANNABIS SATIVA)

DELTA-9-THC

DELTA(9)-TETRAHYDROCANNABITOL

DELTA (9) TETRA HYDRO CANNABINOL

DELTA 9 TETRA HYDRO CANNABINOL

THC (CANNABIS SATIVA) (INHALANT)

DELTA-9-THC (TETRAHYDROCANNABINOL)

THC (NO PREF. NAME)

D-9-THC (NO PREF. NAME)

2.5 THC/CBD Terminology

MARIJUANA SUPPLEMENTS (THC AND CBD)

THC/cbd oil

THC/CBD

CANNABID CBD/THC

TROKIE HYBRID CITRUS 0.98GR. 21.3MG THC, 19.9MG CBD, 20MG?

TROKIE HYBRID CITRUS 0.98GR.21.3MG THC, 19.9MG CBD, 20MG?

5.6%CBD/3.7%THC DRONABINOL (VAPOR)

CBD/THC oil

CBD HEMP FLOWER (CBD\THC)

BREEZ (CBD/THC)

CBD;THC

TETRAHYDROCANNABINOL 10MG; CANNABIDIOL 1MG

TETRAHYDROCANNABINOL/CANNABIDIOL

CANNABIDIOL, TETRAHYDROCANNABINOL

CANNABIDIOL;DRONABINOL (TETRAHYDROCANNABINOL AND CANNABIDIOL)

RELIEF VAPE PEN 1:9 CBD:THC

SHIFT (CANNABIDIOL\.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS)

CANNABIDIOL/DRONABINOL

WANA SOUR GUMMIES 50:1 CBD/THC

CANNTRUST 1:1 DROPS (CANNABIDOL/DRONABINOL)

THC/CBD CARTRIDGE

CBD/THC VAPING OIL

THC/CBD OIL

ORGANIC SMART CARTS (CBD\THC)

LEGENDARY CARTS [THC/CBD]

THC OIL, CANNABIDIOL FLAVORED WITH FRUIT PUNCH

STRAINLY INTERNET SIGHT THC POLLEN (CBD, THC)

THC VAPES DANK/VENOM/COOKIES/SMART KART/CALI PLUD [CANNABIDIOL\.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS]

CANNABIDIOL OG DRONABINOL

CANNABIDIOL;DRONABINOL

CANNIMED OIL (CBD\THC)

CBD/THC

CANNABIDIOL,TETRAHYDROCANNABINOL

DIAMOND STIXX [CBD\THC VAPE]

CBD/THC TINCTURE 5MG

Cannabidiol/tetrahydrocannabinol

Cannabidiol;Dronabinol

WANA SOUR GUMMIES EXOTIC YUZU CBD/THC

MEDICAL CANNABIS RED 500 MG DISTILLATE PREFILLED VAPORIZER (CBD/THC)

RED DISTILLATE PREFILLED VAPORIZER (CBD/THC)

RAZZ BERRY 100 MG [CBD\THC]

DELTA?8 50 MG CBD GUMMY

CANNABIS INFUSED GUMMIES PLUS?BALANCE (CBD\THC)

CBD WITH THC

50/50 edibles CBD/THC

CANNABIS (MINT CAKE) (CBD\THC)

DELTA 8 CBD FLOWER

.DELTA.8-TETRAHYDROCANNABINOL\CANNABIDIOL\HERBALS

COCOA PEBBLEZ TREATS (CBD\DELTA 8?THC)

7 G HYBRID TKO BY TERP NATION 8 HEMP FLOWER DELTA?8 (CANNABIDIOL\.DELTA.8?TETRAHYDROCANNABINOL\HERBALS)

NAXIVA?PANAXIR T25C25 [CANNABIDIOL/DRONABINOL]

DELTA 8 CBD GUMMIES 1000MG

CBD DELTA 8 GUMMIES

DELTA9 [CANNABIDIOL\.DELTA.8?TETRAHYDROCANNABINOL\DEVICE\HERBALS]

CANNABIDIOL\.DELTA.8-TETRAHYDROCANNABINOL\HERBALS

CANNABIDIOL\.DELTA.8-TETRAHYDROCANNABINOL

CBD AND THC

CANNABIDIOL\.DELTA.8-TETRAHYDROCANNABINOL\DEVICE\HERBALS

CBD/THC SUPPLEMENT

Cannabidiol;Tetrahydrocannabinols nos

THC edible and CBD

CANNABIDIOL\HERBALS\TETRAHYDROCANNABINOL MIXED

THC AND CBD

CANNABIDIOL\HERBALS\TETRAHYDROCANNABINOL UNSPECIFIED

THC CBD PATCH

CANNABIDIOL;TETRAHYDROCANNABINOL NOS

CANNABIDIOL;TETRAHYDROCANNABINOLS NOS

CANNABIDIOL + TETRAHYDROCANNABINOL

potassium tropical cbd/thc 20 MEQ twice daily

TETRAHYDROCANNABINOL AND CANNABIDIOL

2.6 CBD Terminology

CANNABIDIOL\HERBALS

CANNABIDIOL OIL

CBD

CANNABIDIOL

CBD DROPS 200MG, 30ML SOOTHEEN

CBD OIL

PALMETTO HARMONY (CBD OIL)

JUNGLE JUICE CBD OIL 1ML JUST CHILL PRODUCTS
CBD IN HEMP OIL 1800 MG, IN 60 ML ABLE DOC.COM OR PROHELAHADVISOR
Cannabidiol

VAPE OIL WITH CBD ALTERNATE VAPE 5 ML (25 MG OF CBD)
HAYLEIGHS HOPE CBD OIL

CANNABIDOL

CBD OIL/CANNABINOID

CBD FOOD SUPPLEMENTS

cannabidiol

CBD OILS

CBD OIL-PALMETTO HARMONY

CBD - OIL

CBD OIL (MEDICAL MARIJUANA)

Medical Cannabis CBD

Cannabidiol oil

CBD Oil

CBD HEMP OIL IN MCT

CANNABIDIOL DRUPPELS 100MG/ML

HEMP BASED CBD OIL

CBD oil (NOS)

PUFCBD REMEDY KIT (POWER)

CBD oil

CBD drops

DIAMOND CBD

ADVANCED CBD OIL WITH TERPENES (FROM HEMP)
PEACE + WELLNESS ELEVATE (CBD/HEMP OIL INFUSED)
INFUSED BODY BUDDERS; INGREDIENT: CBD

MIRACLE BUDDER: UNSCENTED INGREDIENT: CBD
KANNAWAY CBD OIL

20% CBD

CBD hemp oil

CANNABIDIOL ORAL SOLUTION (300MG/ML)

CBD, BATCH# TRU4720, PRODUCT# TRU4808, HARVEST# TRU4720
MEDICAL CANNABIS OIL VIOLET CBD

CBD ORAL DROPS

CBD TYPE OF CANNABIS

CBD oral drops

LAB BLENDS CBD PAIN RELIEVER (LIDOCAINE\MENTHOL)
CANNABIDIOL\CANNABIS SATIVA SEED OIL (INACTIVE INGREDIENTS)
CHILL GUMMIES DIAMOND CBD

COSMIC CLEANSE BODY BUDDER (CBD)

HERBALOGIX CBD ENHANCED BODY LOTION

CBD Oils

CBD Salve

CBD Hemp Oil

medical cbd

CBD HEMP OIL

CBD lotion

CHARLOTTE'S WEB (CBD)

cbd oil

RED DEVIL KRATOM WATER SOLUBLE CBD

CBD OIL CRYSTAL ISOLATE 1500MG (AND GUMMIES)
CBD OIL (CANNABIDIOL)

CBD OIL PLUS

CBD HEMP FLOWER

CANNABIDIOL (CBD oil)

CBD Vape and Balm

CBD CREAM

CBD CANDIES

HERBAL INSANITY'S CBD OIL FOR PAIN

KUSH MASCARA (CBD OIL)

CBD oil / Hemp Oil

cbd

CBD balm

CBD cream

FLEXALL420 (CANNABIDIOL)

CANNABIDIOL ORAL SOLUTION 300 MG/ML

BIO REMEDIES PUFCBD

PUREKANA PREMIUM CBD OIL DROPS

CBD TINCTURE

cbd 5mg

CREATING BETTER DAYS PEACH POPS TANGY ORANGE 50MG CBD INFUSED
MEDICAL MARIJUANA/CBD

CBD GUMMY BEAR

HEMPWORK 750 WITH PURE CBD OIL AND HERBAL DROPS PEPPERMINT FLAVOR 1OZ/

KOICBD PRODUCTS

CBDROP FULL SPECTRUM OIL

CBD OIL TABLET

Cannabidiol Oil

CANNABIDIOL ORAL SOLUTION 300MG/ML

EVOLUTION CBD OILS

LAZARUS NATURALS CBD CAPSULES 2000MG CBD
JUST CBD CANNABIDIOL GUMMIES GUMMY BEARS 250MG
optimacbd cbd 4%

CANNABIDIOL (CBD)

CBD WELLNESS CENTER DROPPER 1500MG

CBD paste

CBD EDIBLE

HEMPTRANCE NATURAL CBD GUMMIES

CBD OIL INA CREAM

CBD GUMMIES

QUEEN BEE NATURALS , CBD QUEEN

BATH BOMB [CANNABIDIOL]

CBD EXTRACT

CBD OIL 750 MG

CBD CANNABIS OIL (CANNABIDIOL)

CBD OIL,

CBD +STRESS DEFY

CBD HEMP

CBD hemp extract

CBD OIL (HEMP)

ULTRA CBD EXTRACT

CBD LOTION

CBD GUMMIES FROM HEMP 300 MG

PURE ALOE VERA GEL HEADACHE + SORE MUSCLES RUB [CBD]
PAIN STICK [CBD\MENTHOL]

CBD OIL

ELIXIR / CBD OIL TREATMENT

HEMP CBD

CBD ESSENTIAL OIL OINTMENT

MIRACLE LEAF CBD - EXTRA STRENGTH, 1200 MG
COOKIE INFUSED WITH CBD

CHILL RD VELVET TINCTURE CBD 1500 MG

CBD Alive

TRUORGANICS HIGH CBD OIL TINCTURE 900MG CBD
CBD Oil 50 mg

RELAX FULL SPECTRUM CBD OIL

SUNMED FULL SPECTRUM TINCTURE CBD OIL 750 MG
CBD KINGS

CBD TOBACCO TO RELAX

NATIVE LIPOSOMAL CBD EXTRACT SPRAY

RESET BIOSCIENCE BALANCE 300MG 99%+ NANO LIPOSOMAL ORGANIC HEMP CBD
CV SCIENCE CBD OIL

CBD CAPSULES

CBD VAPE PEN

PURIFIED CBD (CANNABIDLOL) ORA SOLUTION

DIAMOND CBD FULL SPECTRUM CBD OIL (TICLLOSENAC)
CBD (cannabidiol)

CBD SALVE

CBD OIL: 7MG CBD/1ML

CBD capsule

CBD TABLETS

KOI CBD

NEW LEAF CBD OIL

NOVO 2 VAPE PEN (CBD)

CBD EXTRACT OIL

CBD OIL 5M/DAY

ORGANABUS SILVER ORGANIC CBD VAPOR LIQUID
EVE'S MAGIC. HEMP REMEDY CBD OIL 750MG

AMOS HEMPS [CBD OIL IN MCT OIL]

CBD 35MG

CBD 25 MG

PLUS CBD OIL HEMP DROPS PEPPERMINT EXTRA STRENGTH
CBD FLAXSEES COMBO

CBD ADREXOL

LEAF AND FLOWER CBD SHAMPOO

LEAF AND FLOWER CBD CONDITIONER

CBDISTILLERY 33MG CBD PER SERVING FULL SPECTRUM HEMP SUPPLEMENT
HEMPLUCID CBD OIL 1000 MG VAPING

HEEL BALM WITH CBD AND MENTHOL

CHOCOLATE CHIP COOKIE [CBD]

JOY ORGANICS CBD OIL 500MG

CBD Kings

CTFO (CHANGING THE FUTURE OUTCOME) 10XPURE CBD HEMP OIL
CANNABIDIOL DRUPPELS, 50 MG/ML (MILLIGRAM PER MILLILITER)
JUST CBD GUMMIES

FEALS [CBD]

CBD OIL HEMP-DERIVED CANNABIDIOL FULL SPECTRUM HEMP SUPPL
JOINT VIBRANCE + CBD

CANNAVALLEY [CBD]

HEMP CLASSIC CBD

CTFO 10X PURE CBD GOLD 1000

CBD-olie

COLESVAM MEDICAL MARIJUANA (CBD)

VAPING CBD OIL

MAGIC LEAF STRAWBERRY 1000MG/3ML CBD VAPE CARTRIDGE
MAGIC LEAF OGKOSH 1000MG/3ML CBD VAPE CARTRIDGE
cbd drops

SKIN KUSHION BY MONAT BODY BUTTER (CBD)

RSO CBD 2:1

SOUL 500 [CANNABIDIOL\HERBALS]

CBD KINGS THC FREE

CTFO 10X GOLD CBD OIL AND 10X PURE ULTIMATE MULTI-VITAMIN
VAPORIZER CBD/MARIJUANA

CBD VAPING

QUEEN CITY HEMP 500MG (CBD)

queen city hemp cbd

Cbd

cbd hemp oil

CBD/CBD OIL VAPE

CHARLOTTE'S WEB STANLEY BROTHERS 17MG OLIVE OIL 30ML (CBD)
HEMPWORX CBD OIL

PREMIUM CBD DROPS

ORIGINAL FORMULA HEMP EXTRACT OIL MINT CHOCOLATE FLAVOR CHARLOTTES WEB [CBD]

ORIGINAL FORMULA HEMP EXTRACT OLIVE OIL FLAVOR CHARLOTTES WEB [CBD]
cbd kings

CBD BALM - EXTRA STRENGTH

NULEAF NATURALS FULL SPECTRUM CBD OIL

CBD DROPS (ONYX + ROSE BROAD SPECTRUM)

cannabidiol oil

CBD GUMMY

TURMERIC + CBD

RESCUE BLEND RAW ORGANIC HONEY WITH CBD 250 MG
FULL SPECTRUM CBD OIL 850MG

CBD Extract

Rescue Blend Raw Organic Honey with CBD 250 mg

ULTIMATE CBD VAPE ADDITIVE (CBD OIL)

CBD ointment

CBD CREAM (BRAND/FORMULATION UNKNOWN)
CBDFX HEMP GUMMIES

CBD DROPS

CANNABIDIOL.

CALM REST AND RELAX HEMP EXTRACT FORMULA (CBD)
ARTISANAL CANNABIDIOL

OPTIFORM CANNABIDIOL (CBD)

LIBERTY CBD TINCTURE, JACKSON'S COURAGE

NULEAF NATURALS CBD

WBRX METERED DOSE INHALER [CANNABIDIOL\DEVICE\HERBALS]
CBD Oil (NON-ABBVIE)

SUNMED VEGAN GUMMY BEARS WITH 5MG CBD
SOUR WORMS 10 PIECE [CBD]

Cbd kings

T?Relief CBD+13 Sublingual

CBD GUMMY 3MG

CYPRESS HEMP CBD OMEGAS

CANN I BE SO EXTRA TROP THE BEAT 1,000 MG FULL SPECTRUM CBD OIL
LIFE STREAMS CBD GUMMY

CRISP CBD

PRO RESTORE CBD+

CBD INTENSIVE CREAM

CANNABIDIOL (CBD) OIL

HAWAIIAN HAZE CBD 18.9%

EXTRA STRENGTH TABLETS CBD GEL

Cbd oil

INV cannabidiol 300mg/ml oral solution

CBD OINTMENT

CBD products

CBD Kings with Lidocaine

CBD (NO THC)

CBD KINGS EX

CANNABIDIOL CREAM

CBD salve

FULL SPECTRUM CBD CAPSULES

LEVEN CANNABIDIOL 1500MG CBD SERUM

Palmetto Harmony CBD Oil

Jade CBD Oil

Mary's CBD Oil

Charlottes Web CBD Oil

HI STEVIE CBD TINCTURE

Liberty CBD Tincture, Jackson's Courage

ADVEN (CANNABIDIOL)

CBD (Cannabidiol)

SWAG HEMP INFUSED NATURAL CBD GUMMIES

CBD Oil (Cannabidiol)

SWANSON ULTRA? CBD + SLEEP SUPPORT FULL SPECTRUM
CBD KINGS DIS W/LIDO

CBD stuff

^HARRELSON'S OWN^ CBD OIL

Charlotte's Web CBD

CBD (CANNABIDIOL)

CBD-KINGS WITH LIDOCAINE

CBD (CANNABIDIOL) OIL (DIETARY SUPPLEMENT)
CBD SUPPLEMENTS

CBD COMPLEX

CBD Liquid

NOT POT ORIGINAL CBD GUMMIES

CANNABLISS BALM

CBD GEL CAP

CBD PRODUCT

CBD INFUSED VAGINAL TIGHTENING OIL

CBD W/MELATONIN

CANNABIOL

CBD EDIBLE CINNAMON COOKIE BAR 475MG

Cannabiol

CBD DROPS LUCID BLOOD ORANGE 1000MG
CBD HEMP EXTRACT
MR. CBD OXYGENATED HEMP OIL

CHARLOTTE'S WEB ORIGINAL FORMULA CBD

cannabidiol (CBD) gummy candies

vaporized CBD

HEMP cbd

CBD WAX PRODUCT (CBD)

Mary's CBD

Palmetto Harmony CBD

Jade Nectar CBD

LEAF THERAPEUTICS CBD SLEEP BLEND (DIETARY SUPPLEMENT\HEMP)
CBD 25 MG

RADICAL RELEIF ANTI?INFLAMMATORY CBD PILLS
TILRAY CBD

CBD + MAGNESIUM

CBD TABLET

CANNABIDIOL EXTRACT

CBD product

CBD AND MELATONIN

CANNABIDIOL Powder

CBD Kings Dis W/Lido

UNKNOWN CBD GUMMY

CBD COOKIES

Melatonin/CBD

CBD Cream

Haleigh^s Hope CBD Oil

VAPORIZED CANNABIDIOL (CBD) OIL

CBD Oil cream

Medical marijuana and CBD

Hemp organic CBD

CBD CANNABIS

shikai CBD body lotion

CBD kings

CBD CAPSULE

CANNABIDIOL\CANNABIS SATIVA SEED OIL

CBD oil 1cc daily

CBD-KINGS

CBD whole plant

CBD Oil Kings

CBD PAIN RELIEF CREAM

Low-dose CBD oil

CBD OEL

canabediol

CBD gummies, 25 mg, 2, bid

CBD OILSUPLLIMENT

Melatonine with CBD

cbd oil tincture

CBD for sleep

CANABIDIOL

CANNABIDOLOL

CBD (NON-ABBVIE)

CBD softgel

cannabidoil

CBD rub

CBD tincture

CBD Kings THC Free

Cbdfx hemp gummie

CBD Balm

Cbdfx hemp gummies

Cannabidiol glostrup

CBD gummies(for pain)

OTHER THERAPEUTIC PRODUCTS (CBD king dis w/lido)
CBD gel caps

full-spectrum CBD

Cbd hemp

CBD PATCHES

CBD PATCH

CBD Cannabidiol

2.7 Cannabis Terminology

CANNABIS

CANNABIS SATIVA SUBSP. INDICA TOP

MEDICAL CANNABIS

MEDICAL MARIJUANA (MARIJUANA)

CANNABIS SATIVA

Cannabis

MARIJUANA

Medical Marijuana

Cannabis sativa

CANNABIS SATIVA (CANNABIS) (UNKNOWN)

MEDICAL MARIJUANA

CANNABIS (CANNABIS)

Marijuana

MARIJUANA (CANNABIS SATIVA) (CANNABIS SATIVA)
CANNABIS SATIVA OIL

MEDICINAL MARIJUANA

MARIJUANA (CANNABIS SATIVA)(CANNABIS SATIVA)
MARIJUANA (CANNABIS SATIVA)

MARIJUANA (CANNABIS) (PILL)

MARIHUANA

UNSPECIFIED ^CANNABINOIDS^

Oil with cannabis

MARIJUANA (MARIJUANA)

CANNABINOIDS

Cannabis Sativa

OIL MARIJUANA

CANNABIS\CANNABIS SATIVA L

WHITE RECLUSE MARIJUANA FLOWERS

Medical marijuana

MARIJUANA (CANNIBIS SATIVA)

CANNABIS (CANNABIS SATIVA) UNKNOWN

CANNABIS SATIVA SUBSP. SATIVA FLOWERING TOP
CANNABIS RESIN

Cannabinoids

marijuana

Marijuana Kush

MARIJUANA FOR MEDICAL USE

ILLEGAL MARIJUANA

Medicinal Marijuana

Cannabis oil

CANNABIS OILS

CANNABIS SATIVA FLOWERING TOP

MEDICAL MARIJUANA (PRESCRIPTION)

CANNABINOID

cannabis

MARIJUANA WAX

CANNABIS AND RESIN

MEDICINAL CANNABIS

medical marijuana

CANNABIS SATIVA FLOWER

CANNABINIODS

Vaporized Marijuana

CANNABIS SUBOXONE

CANNABINOIDS OIL

Cannabis inhalation

RECREATIONAL MARIJUANA

Medical Cannabis

CANNABIS DROPS

CANNABIS INDICA

Cannabis Oil

CANNABIS TEA

CANNABIS OIL

FULL CANNABIS OIL

LEGAL MARIJUANA

CANNABIS HERBAL EXPEC

MEDICAL MARIJUANNA

BEDROCAN MEDICINAL CANNABIS

CANNABIS (BEDROBINOL)

MEDICINAL RECREAT CANABIS HEMP F

CANNABIS SATIVA FRUIT

CANNABIS (CANNABIS SATIVA)

cannabis bedica olie

TART CHERRY JUICE AND NATURAL REMEDIES FOR PAIN SUCH AS CANNABIS
vaporized medicinal marijuana

cannabis oil

MARIJUANA OILS

cannabis bedica

CANNABIS COOKIE

INDIGO MARIJUANA

MARIJUANNA

Medical cannabis

HOMEMADE CANNABIS OIL

MARIJUANA TEA

61% Cannabis oil

CANABIS LOTION

medicinal marijuana

100% HEMP EXTRA VIRGIN NO THC

ACETAMINOPHEN/CODINE MEDICAL MARIJUANA
MEDICAL CANNABIS PATIENT CERTIFIED

CANNABIS PREPARATION

Cannabis indica

MEDICAL MARIJUANA OIL

MEDICAL GRADE CANNABIS

CANNABIS/CANNABIS SATIVA

CANNABANOIDS

CANNABIS INFUSED DARK CHOCOLATE

Marihuana

MARIJUANA EXTRACT

Cannabis sativa oil

medical cannabis

CANNABIS EXTRACT OIL

CANNABIS inflorescences

CANNABIS ET RESINE

CANNABIS, INDICA

BLACK MAMBA (CANNABIS SATIVA)

CANNABIS AND OIL

MEDICINAL CANNABIS OIL

Medicinal Cannabis

CANNABIS SATIVA SEED OIL\HERBALS

MEDICAL CANNABIS TINCTURE

MEDICAL CANABIS

CANNABIS and RESINE

Cannabis (cannabis sativa)

RICK SIMPSON CANNABIS OIL

medical Cannabis oil

MEDICAL MARIJUANA (RSO)

CANNABIS OIL, IN THE FORM OF A CHEWY GUMMY PRODUCT
medical marijuane

CANNABIS SATIVA SEED\HERBALS

Edible marijuana

CANNABINOID PRODUCT NOS

MARIJUANA OIL

MED MARIJUANA

Canabinoid Oil

cannabinoids

TOPICAL CANNABIS

MARIJUANA LIQUID

CANNABIS SATIVA OIL;COLECALCIFEROL

Canabis

Unspecified Medical Marijuana

Medical Marijuana Tincture Oils

CANNABIS BUD/FLOWER

TWEED CANNABIS OIL

^Marijuana cream^

medical cannabis

CANNABIS INDICA SMOKE

TRULIEVE [MEDICAL CANNABIS]

CANNABINOIDS NOS

VAPE PEN (MARIJUANA)

CANNABIS products

MARIJUANA FLOWER

CANNABIS SATIVA EXTRACT

CANNABIS OIL EXTRACT

PAX 3 VAPORIZER ^NOTHING WAS OBTAINED, BUT DRIED MARIJUANA WAS USED IN THE PAX 3 DEVICE
MARIJUANA OIL VAPING

DISPENSARY MARIJUANA PLANT AND WAX CARTRIDGES.
CANNABIS CARTRIDGE

CANNABIS VAPE CARTRIDGE WITH PHYTOL

VAPING MARIJUANA

MARIJUANA HERB DEVICE USED: LOKEE BRAND VAPE^
MARIJUANA VAPING LIQUID

CANNABIS VAPING

MARIJUANA VAPE

MARIJUANA VAPING PRODUCT

HASH OIL [CANNABIS OIL VAPING]

WAX, MARIJUANA

CLAW VAPE PEN ^THE POD^ ORANGE KUSH OIL STIX (CANNABIS OIL)
ABSOLUTE XTRACTS ^GSC^ CANNABIS OIL VAPE CARTRIDGE
Marijuana tincture

MARIJUANNA E-CIGARETTES

ARMOUR THYROID 60MG MEDICAL MARIJUANA PRN
edible marijuana

MEDICAL MARIJUANA CARD HOLDER

Apothecanna with cannabis

Cannabies

YELLOW CANNABIS SOFTGELS (HYBRID) BY SPECTRUM CANNABIS

HYBRID CANNABIS

MARIHUANA MEDICINE

MARIJUANA EDIBLES

60MG, PLANT?BASED CANNABINOIDS PER 1ML HEMP EXTRACT MINT CHOCOLATE FLA
Marijuana Gummies

cannabis sativa

BLUE CANNABIS SOFTGELS (HYBRID) BY SPECTRUM CANNABIS
Marijuana drops

MEDICAL MARIJUANA OIL VAPOR

Medical Marijuana Tinchur

CANNAB (MARIJUANA DROPS)

Medicinal cannabinoid extract

Cannabis spray

CANNABINOID OIL

CANNABIS OIL AND CREAM

Smoked cannabis

Vapes Cannabis

Smokes Marijuana

Smokes marijuana

smokes marijuana

CANNAB

CANNABIS SATIVA SEED OIL

MARIJUANA, N.O.S

MARIJUANA, N.O.S. (CANNABIS SATIVA)

CANNABIS FLOS BEDIOL (CANNABIS SATIVA FLOWER)
Marijuana oil

CANNABIS ? HEALTH CANADA

CANNABIS SATIVA E SEMINIBUS

Therpeutic cannabis

medical marijuanas

Marijuana Oil

MARIJUNAN

Smokes Cannabis

CANNABIS OEL

CANNABIS MEDICAL

CANNABIS FLOS

CANNABIS SATIVA SUBSP. INDICA

CANNABINOIDS(CANNABINOIDS)

CANNABIS SATIVA VAR. INDICA

Cannabis oel

CANNABIS OINTMENT

Marijuana edible

MEDICINAL CANNABIS CAPSULES

Recreational marijuana

Cannabis- smokes

cannabis cake

cannabis- smokes

Medical Indica Marijuana

Medical Sativa Marijuana

20164 (GLOBALC3Sep21): Medical Marijuana

CANNABIS VAPE OIL

Cannabinoid

MARIJUANA TINCTURE

CANNABIS SATIVA LEAF

MARIJUANA GUMMIES

medicinal cannabis

MEDICAL MARIJUANAS

MEDICAL MARIJUANA (RICK SIMPSON OIL)

MARIJUANA VAPOR

CANNABIS SATIVA FLOWER;CANNABIS SATIVA SEED OIL
CANNABINOLIC ACID

Medical-Marijuana

CANABIS

Canabis oil

Cannabis gummies

MARIJUANA (OPIATE UNSPEC.)

MARIJUANA USE

MARIJUANA (CANNABIS)

MARIJUANA UNKNOWN (CANNABIS)

MARIJUANA(OPIAT)

MARIJUANA(CANNABIS)

CANNABIS (FORMULATION UNKNOWN) (CANNABIS)
CANNABIS(CANNABIS) (UNK)

MARIJUANA (CANNABIS,)

CANNABIOIDS

MARIJUANA METABOLITES

MARIJUANA (CANNABIS

CANNABINODIS

CANNABNOIDS (CANNABIS)

CANNABOIDS

CANNABIS SATIVA(CANNABIS)

CANNABIS(CANNABIS)

MARIJUANA(CANNABIS) UNKNOWN

MARIJUANA (CANNABIS)

CANNABIS (CANNABIS)

MARIJUNA

MARIJUANA (CANNABIS) UNKNOWN

CANNABIS (CANNABIS, EXTENDED RELEASE)

CANNABINOIDS (CANNABIS)

CANNABINOIDS ()

CANNABIS (CAQNNABIS)

CANNABIS (CANNABIS,)

CANNABIS (CANNABIS, , 0)

MARKUUANA (CANNABIS)

MARIJUANA (CANNIBIS)

CANNABINOIDS()

MARIJUANA (CANNIBAS)

MARIJUANA (CANNABIS)UNKNOWN

CANABANOIDS (CANNABIS)

MARIJUANA (CANNABIS)

MARUANA (CANNABIS)

CANNABIS SMOKING

MARIJUANA(MARIJUANA)

MARIJUANA (CANNABIS SATIVA)

CANNABIS (FORMUATION UNKNOWN) (CANNABIS)
MARIJUAN (CANNABIS)

MARIJUANA (CANNABIS,)

MARIJUANA (CANNABIS SATIVA)

CANNABIS (CANNIABIS)

MARIJUANA (CANNABIS

MARIJUANA (MARIJUANA)

CANNABIS(CANNABIS, CANNABIS SATIVA)

CANNABIS (CANNABIS, 0)

CANNABIS (CANNABIS0

CANABIS (CANNABIS)

MARIJUNA (CANNABIS)

MARIJUANA (CANNABIS0

MEDICINAL MARIHUANA

CANNABIS (CANNABIS)

CANNABIS SATIVA(CANNABIS, CANNABIS SATIVA)
MARIJUANA (CANNABIS, CANNABIS SATIVA)

CANNABIS (CANNABIS, CANNABIS SATIVA)

2 HITS OF MARIJUANA

MARIJUANA (CANNABIS)

MARIJUANA (MEDICAL)

MEDICINAL MARIJUANA (CANNABIS SATIVA)

CANNABIS (CANNABIS SATIVA) (CON.)

LEGALIZED MARIJUANA

CANNABIS (HASHISH - CANNABIS)

MEDICAL MARIJUANA (CANNABIS SATIVA)

MARIJUANA/SYNTHETIC PILL FORM OF MARIJUANA (CANNABIS SATIVA)
CANNABIS (TABLETS)

MARIJUANA (CANNABIS, CANNABIS SATIVA)
MARIJUA

MARIJUANA (CANNABIS SATIVA) UNKNOWN

MARIJUANA TBD HERB MEDICAL CENTER, 12509 OXNARD ST. N.HOLLYW
MARIJUANA (MARIJUANA) UNKNOWN

CANNABIS PREPARATION (CANNABIS PREPARATION)
MARIJUANA (NO PREF. NAME)

CANNABIS TRANSPLACENTAL

DRUG - MARIJUANA

CANNABIS SATIVA (Hemp hearts)

CANNABIS LOTIONS

CANNABIS SATIVA (CANNABIS SATIVA)

CANNABIS (NO PREF. NAME)

CANNABIS (NONE)

CANNABIS (CANNABIS SATIVA

CANNABINOIDS (NO PREF. NAME)

CANNABIS (CANNIBIS SATIVA)

APPENDIX 3. Codes for Signal Detection Analysis

```
#Signal detection analysis

#SET PACKAGES AND LOAD DATABASES####

library(data.table)

setwd("C:\\Users\\Chris Lab\\Documents\\Priscilla")

#Drug database (20124 to 20231)

drug2012<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641687\\drug1688641687.csv",

                                 allowEscapes = FALSE,

                                 colClasses="character",

                                 encoding = "latin1"))

drug2012<-drug2012[,.(primaryid,caseid,drugname)] #48118975 obs.

drug2012 <- drug2012[, drugname := toupper(drugname)]

#Load corrected drug2012 terms

drug2012<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\drug2012_corrected_SD.csv",

                                 allowEscapes = FALSE,

                                 colClasses="character",

                                 encoding = "latin1"))  #48118975 obs.

drug2012 <- drug2012[,.(primaryid,caseid,drugname,final_drugname)]

#Drug database (1999 to 20123)

drug1999<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641629\\drug1688641629.csv",

                                 allowEscapes = FALSE,

                                 colClasses="character",

                                 encoding = "latin1"))

drug1999<-drug1999[,.(primaryid,caseid,drugname)] #13367151 obs.

drug1999 <- drug1999[, drugname := toupper(drugname)]

#Correct drug datable with terms

#Epidiolex

csv_path_epi <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\epidiolex terms.csv"

reltableepi <- as.data.table(read.csv(csv_path_epi, allowEscapes = FALSE, colClasses='character'))

epiterms <- toupper(reltableepi[,TERMS]) #14 terms

Epidiolex <- epiterms

#Cannabis

csv_path_cannabis <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\cannabis
terms.csv"
```

```
reltablecannabis <- as.data.table(read.csv(csv_path_cannabis, allowEscapes = FALSE,
colClasses='character'))

cannabisterms <- toupper(reltablecannabis[,TERMS]) #319 terms

Cannabis <- cannabisterms

#Dronabinol/Nabilone

csv_path_dronabinol <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\dronabinol
terms.csv"

reltabledronabinol <- as.data.table(read.csv(csv_path_dronabinol, allowEscapes = FALSE,
colClasses='character'))

dronabinolterms <- toupper(reltabledronabinol[,TERMS]) #154 terms

Dronabinol <- dronabinolterms

#Sativex

csv_path_sativex <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\sativex
terms.csv"

reltablesativex <- as.data.table(read.csv(csv_path_sativex, allowEscapes = FALSE, colClasses='character'))

sativexterms <- toupper(reltablesativex[,TERMS]) #20 terms

Sativex <- sativexterms

#D8-THC

csv_path_d8thc <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\d8thc terms.csv"

reltabled8thc <- as.data.table(read.csv(csv_path_d8thc, allowEscapes = FALSE, colClasses='character'))

d8thcterms <- toupper(reltabled8thc[,TERMS]) #34 terms

D8_THC <-d8thcterms

#D9-THC

csv_path_d9thc <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\d9thc terms.csv"

reltabled9thc <- as.data.table(read.csv(csv_path_d9thc, allowEscapes = FALSE, colClasses='character'))

d9thcterms <- toupper(reltabled9thc[,TERMS]) #210 terms

D9_THC <-d9thcterms


#D8-THC/CBD

csv_path_d8thccbd <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\d8thccbd
terms.csv"

reltabled8thccbd<- as.data.table(read.csv(csv_path_d8thccbd, allowEscapes = FALSE,
colClasses='character'))

d8thccbdterms <- toupper(reltabled8thccbd[,TERMS]) #13 terms

D8_THCCBD <- d8thccbdterms

#D9-THC/CBD

csv_path_d9thccbd <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\d9thccbd
terms.csv"
```

```
reltabled9thccbd<- as.data.table(read.csv(csv_path_d9thccbd, allowEscapes = FALSE,
colClasses='character'))

d9thccbdterms <- toupper(reltabled9thccbd[,TERMS]) #57 terms

D9_THCCBD <- d9thccbdterms

#CBD

csv_path_cbd <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\CBD terms.csv"

reltablecbd<- as.data.table(read.csv(csv_path_cbd, allowEscapes = FALSE, colClasses='character'))

cbdterms <- toupper(reltablecbd[,TERMS]) #339 terms

CBD <- cbdterms

#Minor Cannabinoids

csv_path_minor <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\minor cannabinoids
terms.csv"

reltableminor<- as.data.table(read.csv(csv_path_minor, allowEscapes = FALSE, colClasses='character'))

minorterms <- toupper(reltableminor[,TERMS]) #19 terms

Minor <- minorterms

#THC Homologs

csv_path_thchomologs <- "C:\\Users\\Chris Lab\\Documents\\Priscilla\\Relational Tables_Terms\\thc homologs
terms.csv"

reltablethchomologs<- as.data.table(read.csv(csv_path_thchomologs, allowEscapes = FALSE,
colClasses='character'))

thchomologsterms <- toupper(reltablethchomologs[,TERMS]) #25 terms

THCHomologs <- thchomologsterms

#Add new final_drugname column for corrected terms drug2012

drug2012 <- drug2012[, final_drugname := ifelse(drugname %in% Epidiolex, "EPIDIOLEX",

                                                ifelse(drugname %in% Cannabis, "CANNABIS",

                                                       ifelse(drugname %in% Sativex, "SATIVEX",

                                                              ifelse(drugname %in% Dronabinol,
"DRONABINOL",

                                                                     ifelse(drugname %in% CBD, "CBD",

                                                                            ifelse(drugname %in% D9_THC,
"D9-THC",

                                                                                   ifelse(drugname %in%
D8_THC, "D8-THC",

                                                                                          ifelse(drugname
%in% D8_THCCBD, "D8-THC/CBD",


ifelse(drugname %in% D9_THCCBD, "D9-THC/CBD",


ifelse(drugname %in% Minor, "Minor Cannabinoids",
```

```
ifelse(drugname %in% THCHomologs, "THC Homologs", drugname))))))))))]

write.csv(drug2012,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\drug2012_corrected_SD.csv")

#Add new final_drugname column for corrected terms drug 1999
drug1999 <- drug1999[, final_drugname := ifelse(drugname %in% Epidiolex, "EPIDIOLEX",
                                                ifelse(drugname %in% Cannabis, "CANNABIS",
                                                       ifelse(drugname %in% Sativex, "SATIVEX",
                                                              ifelse(drugname %in% Dronabinol,
"DRONABINOL",
                                                                     ifelse(drugname %in% CBD, "CBD",
                                                                            ifelse(drugname %in% D9_THC,
"D9-THC",
                                                                                   ifelse(drugname %in%
D8_THC, "D8-THC",
                                                                                          ifelse(drugname
%in% D8_THCCBD, "D8-THC/CBD",
ifelse(drugname %in% D9_THCCBD, "D9-THC/CBD",
ifelse(drugname %in% Minor, "Minor Cannabinoids",
ifelse(drugname %in% THCHomologs, "THC Homologs", drugname))))))))))]
write.csv(drug1999,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\drug1999_corrected_SD.csv")
#Restrict drug time frame for Epidiolex (20182 to 20231)####
source_epi <- c(20182,20183,20184,
                20191,20192,20193,20194,
                20201,20202,20203,20204,
                20211,20212,20213,20214,
                20221,20222,20223,20224,
                20231)
drug1823 <- drug2012[source %in% source_epi] #29593494 obs.
#Reactions database (20124 to 20231)#####
reac2012<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641687\\reac1688641687.csv",
                                 colClasses="character",
                                 allowEscapes = FALSE,
                                 encoding = "latin1"))
```

```
reac2012<-reac2012[,.(primaryid,caseid,pt)] #37947388 obs.

reac2012 <- reac2012[, pt := toupper(pt)]

#Reactions database (1999 to 20123)

reac1999<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641629\\reac1688641629.csv",

                                 colClasses="character",

                                 allowEscapes = FALSE,

                                 encoding = "latin1"))

reac1999<-reac1999[,.(primaryid,caseid,pt)] #13042597 obs.

reac1999 <- reac1999[, pt := toupper(pt)]

#Demo database 20124 to 20231

demo2012<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641687\\demo1688641687.csv",

                                 allowEscapes = FALSE,

                                 encoding = "latin1"))


demo1999<-as.data.table(fread("C:\\Users\\Chris Lab\\Documents\\Priscilla\\Gravel cleaned
data\\1688641629\\demo1688641629.csv"))

demo2012<-demo2012[,.(primaryid,caseid)] #13208968 obs.

demo1999<-demo1999[,.(primaryid,caseid)] #3878857 obs.

demo1999 <- demo1999[, primaryid := as.character(primaryid)]

demo2012 <- demo2012[, primaryid := as.character(primaryid)]

#Merge databases 1999 and 2012 by primaryid####

Dcases1999<-(unique(drug1999[,1])) #3875198 obs. unique primaryid

Rcases1999<-(unique(reac1999[,1])) #3875196 obs. unique primaryid

Dcases2012 <-(unique(drug2012[,1])) #13206775 obs.unique primaryid

Rcases2012<-(unique(reac2012[,1])) #13206728 obs.unique primaryid

temp_1999<-merge(drug1999,reac1999, by.x = "primaryid", by.y =
"primaryid",all.y=TRUE,allow.cartesian=TRUE) #65232651 obs.

length(unique(temp_1999$caseid.x)) #84835 obs.

length(unique(temp_1999$caseid.y)) #84835 obs.

setdiff(temp_1999$caseid.x,temp_1999$caseid.y) #0 obs.

temp_1999 <- temp_1999[,.(primaryid,caseid.x,final_drugname,pt)] #65232651 obs.

write.csv(temp_1999,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\temp_1999_drugreact_SD.csv")

temp_2012 <-merge(drug2012,reac2012, by.x = "primaryid", by.y =
"primaryid",all.y=TRUE,allow.cartesian=TRUE) #214618354 obs

length(unique(temp_2012$caseid.x)) #13206717 obs.

length(unique(temp_2012$caseid.y)) #13206717 obs.
```

```
setdiff(temp_2012$caseid.x,temp_2012$caseid.y) #0 obs.

temp_2012 <- temp_2012[,.(primaryid,caseid.x,final_drugname,pt)] #214618354 obs

write.csv(temp_2012,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\temp_2012_drugreact_SD.csv")

merged_full_data <- merge(temp_1999,temp_2012, by = "primaryid",all = TRUE) #279851005 obs.

temp <- merged_full_data[, drugname := ifelse(is.na(final_drugname.x), final_drugname.y,
final_drugname.x), by = primaryid]

temp1 <- temp[, AE := ifelse(is.na(pt.x), pt.y, pt.x), by = primaryid]

temp2 <- temp1[, id := ifelse(is.na(caseid.x.x), caseid.x.y, caseid.x.x), by = primaryid]

dt <- temp2[,.(primaryid,id,drugname,AE)]

setnames(dt, c("id", "AE"), c("caseid", "pt"))

write.csv(dt,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\dt2_1999_2023_corrected_SD.csv")


dt<-as.data.table(read.csv("C:\\Users\\Chris Lab\\Documents\\Priscilla\\dt2_1999_2023_corrected_SD.csv",

                                allowEscapes = FALSE,

                                colClasses="character",

                                encoding = "latin1")) #279851005 obs.

#merged_data_1999 <- drug1999[reac1999, on = "primaryid", allow.cartesian = TRUE] #65232651 obs.

#merged_data_1999 <- merged_data_1999[,.(primaryid,caseid,final_drugname,pt)]

#merged_data_2012 <- drug2012[reac2012, on = "primaryid", allow.cartesian = TRUE] #214618354 obs.

#merged_data_2012 <- merged_data_2012[,.(primaryid,caseid,final_drugname,pt)]

#demo_drug_1999 <- merge(demo1999, drug1999, by = "primaryid") #13399379 obs.

#demo_reac_1999 <- merge(demo1999, reac1999, by = "primaryid") #13069198 obs.

#merged_data2_1999 <- demo_drug_1999[demo_reac_1999, on = "primaryid", allow.cartesian = TRUE, nomatch =
0] #66112413 obs.

#demo_drug_2012 <- merge(demo2012, drug2012, by = "primaryid") #48167094 obs.

#demo_reac_2012 <- merge(demo2012, reac2012, by = "primaryid") #37958331 obs.

#merged_data2_2012 <- demo_drug_2012[demo_reac_2012, on = "caseid.x", allow.cartesian = TRUE, nomatch = 0]
#215712768 obs.

#merged_full_data <- merged_data_1999[merged_data_2012, on = "primaryid", allow.cartesian = TRUE]
#214618354 obs.

#temp <- merged_full_data[, drugname := ifelse(is.na(final_drugname), i.final_drugname, final_drugname),
by = primaryid]

#temp1 <- temp[, AE := ifelse(is.na(pt), i.pt, pt), by = primaryid]

#temp2 <- temp1[, id := ifelse(is.na(caseid), i.caseid, caseid), by = primaryid]

#dt <- temp2[,.(primaryid,id,drugname,AE)]

#setnames(dt, c("id", "AE"), c("caseid", "pt"))

#write.csv(dt,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\dt_1999_2023_corrected_SD.csv")

#Restrict reactions time frame for Epidiolex (20182 to 20231)####
```

```
source_epi <- c(20182,20183,20184,
                20191,20192,20193,20194,
                20201,20202,20203,20204,
                20211,20212,20213,20214,
                20221,20222,20223,20224,
                20231)


reac1823 <- reac2012[source %in% source_epi] #22187579 obs.

#Merge drug and reactions databases by caseid Epidiolex####

Dcases<-(unique(drug1823[,2])) #7562096 obs.

Rcases<-(unique(reac1823[,2])) #7562096 obs.

CASEIDS<-Dcases

temp<-CASEIDS[drug1823[,.(caseid,final_drugname)],on="caseid"] #29593494 obs.

temp1<-merge(temp,reac1823[,.(caseid,pt)],by.x = "caseid", by.y =
"caseid",all.y=TRUE,allow.cartesian=TRUE) #145909904 obs.

#Save wrangled databases Epidiolex####

write.csv(temp1,"/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter
2 Signal Detection/data1823_corrected_signadetection.csv")

dt <- temp1 #145909904 obs. Epidiolex

#Merge drug and reactions databases by caseid CBD#####

Dcases<-(unique(drug1423[,2])) #12266001 obs.

Rcases<-(unique(reac1423[,2])) #12266001 obs.

CASEIDS<-Dcases

temp<-CASEIDS[drug1423[,.(caseid,final_drugname)],on="caseid"] # obs.

temp1<-merge(temp,reac1423[,.(caseid,pt)],by.x = "caseid", by.y =
"caseid",all.y=TRUE,allow.cartesian=TRUE) #203977093 obs.

#Save wrangled databases CBD

write.csv(temp1,"/Users/priscillalopes/Library/Mobile Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter
2 Signal Detection/data1423_corrected_signadetection.csv")

dt <- temp1 #145909904 obs. Epidiolex

dt <- temp1 #203977093 obs. CBD

#Read data 14-23

dt <- as.data.table(read.csv("/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal
Detection/data1423_corrected_signadetection.csv",
                             allowEscapes = FALSE,
                             colClasses="character",
                             encoding = "latin1"))
```

```
#GENERATE CONTINGENCY TABLE#####

#input data in to this function, it returns a general contingency table for all drug-event pairs#

generate_contingency_table <- function(dt){


  result <- dt[, .(n11 = uniqueN(primaryid)), by = .(drugname, pt)] #in dt, count unique number of caseids
by combination of drugname and pt

  n1. <- dt[, .(n1. = uniqueN(primaryid)), by = .(drugname)]  #in dt, count unique number of caseids by
combination of drugname

  n.1 <- dt[, .(n.1 = uniqueN(primaryid)), by = .(pt)] #in dt, count unique number of caseids by pt

  result[n1., n1. := i.n1., on = "drugname"] #joining the column of n1. to n11(result)

  result[n.1, n.1 := i.n.1, on = "pt"] #joining the column of n.1 to n11(result)

  #subtractions to get the rest of the cell counts in 2x2 contingency

  result$n.. <- rep(length(unique(dt$primaryid))) #n.. cell count, total amount of reports

  result$n10 <- result$n1.-result$n11

  result$n01 <- result$n.1-result$n11

  result$n0. <- result$n..-result$n1.

  result$n00 <- result$n0.-result$n01

  result$n.0 <- result$n..-result$n.1

  return(result)}

#DATA MINING ALGORITHMS####

#ROR#

ROR_function <- function(n11, n10, n01, n00){

  ROR_hat <- (n11/n10) * (n00/n01)

  ROR_lb_hat <- exp(log(ROR_hat) - 1.96 * (sqrt((1/n11) + (1/n01) + (1/n10) + (1/n00))))

  ROR_ub_hat <- exp(log(ROR_hat) + 1.96 * (sqrt((1/n11) + (1/n01) + (1/n10) + (1/n00))))

  list(ROR_hat = ROR_hat, ROR_lb_hat = ROR_lb_hat,ROR_ub_hat=ROR_ub_hat)}

#PRR#

PRR_function <- function(n11, n1., n01, n0.){

  PRR_hat <- (n11/n1.) / (n01/n0.)

  VPRR_hat <- (1/n11)-(1/n1.)+(1/n01)-(1/n0.)

  PRR_lb_hat <- exp(log(PRR_hat) - (1.96 * sqrt(VPRR_hat)))

  PRR_ub_hat <- exp(log(PRR_hat) + (1.96 * sqrt(VPRR_hat)))

  list(PRR_hat = PRR_hat, PRR_lb_hat = PRR_lb_hat,PRR_ub_hat=PRR_ub_hat)

}


#BCPNN#
```

```
BCPNN<-function(n..,n1.,n0.,n.1,n.0,n10,n01,n11,n00) {

  q1.<-(n11+n01+0.5)/(n..+1)
  q0.<-(n10+n00+0.5)/(n..+1)
  q.1<-(n11+n10+0.5)/(n..+1)
  q.0<-(n01+n00+0.5)/(n..+1)

  a..<-0.5/(q1.*q.1)
  a11<-q1.*q.1*a..
  a10<-q1.*q.0*a..
  a01<-q0.*q.1*a..
  a00<-q0.*q.0*a..

  gam11<-a11+n11
  gam10<-a10+n01
  gam01<-a01+n10
  gam00<-a00+n00

  Ep11<-gam11/(gam11+gam10+gam01+gam00)                #expecation of p11
  Ep1.<-(gam11+gam10)/(gam11+gam10+gam01+gam00)               #expectation of p1.
  Ep.1<-(gam11+gam01)/(gam11+gam10+gam01+gam00)               #expectation of p.1

  ICmap<-log(Ep11/(Ep1.*Ep.1),base=2)                                 #map estimate of IC

  r<-round(gam11/pmin(gam11+gam10,gam11+gam01),1)            #used to determine delta

  id<-c(0,.1,.2,.3,.4,.5,.6,.7,.8,.9,1)

  Alist<-c(3.09,2.93,2.78,2.62,2.45,2.25,2.03,1.79,1.61,1.13,0.073)
  Blist<-c(2.22,2.27,2.26,2.25,2.15,2.12,2.05,1.93,1.89,1.15,-0.081)

  Ar<-Alist[which(id==r)]
  Br<-Blist[which(id==r)]
  delta<-Ar/sqrt(gam11)+Br*gam11^(-1.5)
  BCPNN.LB<-ICmap-delta
```

```
  BCPNN.UB<-ICmap+delta

  list(ic=ICmap, lb=BCPNN.LB, ub=BCPNN.UB)}

#Combined signal detection# This will generate all estimators (ROR/PRR/BCPNN)

#this will generate all disproportionality analysis results for each drug/ae based on cell counts
generated in contingency table#

generate_all_measures <- function(contingency) {

  contingency[, c("ROR_hat", "ROR_lb_hat","ROR_ub_hat") := ROR_function(n11 = n11, n10 = n10, n01 = n01,
n00 = n00)]

  contingency[, c("PRR_hat", "PRR_lb_hat","PRR_ub_hat") := PRR_function(n11 = n11, n1. = n1., n01 = n01,
n0. = n0.)]



  cat("Processing ic_hat", "\n")



  contingency[, ic_hat := apply(.SD, 1, function(x) {BCPNN(x["n.."], x["n1."], x["n0."], x["n.1"],
x["n.0"], x["n10"], x["n01"], x["n11"], x["n00"])$ic

  }), .SDcols = patterns("^n")] #the patterns("^n" makes sure only the n## columns are selected and passed
through the function, avoiding "non-numeric" arguments)#



  cat("Processing ic__lb_hat", "\n")



  contingency[, ic_lb_hat := apply(.SD, 1, function(x) {BCPNN(x["n.."], x["n1."], x["n0."], x["n.1"],
x["n.0"], x["n10"], x["n01"], x["n11"], x["n00"])$lb

  }), .SDcols = patterns("^n")] #the patterns("^n" makes sure only the n## columns are selected and passed
through the function, avoiding "non-numeric" arguments)#



  cat("Processing ic__ub_hat", "\n")



  contingency[, ic_ub_hat := apply(.SD, 1, function(x) {BCPNN(x["n.."], x["n1."], x["n0."], x["n.1"],
x["n.0"], x["n10"], x["n01"], x["n11"], x["n00"])$ub

  }), .SDcols = patterns("^n")] #the patterns("^n" makes sure only the n## columns are selected and passed
through the function, avoiding "non-numeric" arguments)#

  return(contingency)}

contingency_table <- generate_contingency_table(dt) #generating contingency table from data

#contingency_table <- contingency_table[n11 >= 5] #deleting rows with rare occurances, n11<5 will be
excluded



measures <- generate_all_measures(contingency_table) #calculating measures of disproportionality

write.csv(measures,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\measures1823_contingencytable.csv")

#DRUG OF INTEREST####

#Epidiolex####
```

```
measures_epi <- measures[final_drugname=="EPIDIOLEX"] #only looking at Epidiolex

measures_epi_seizure <- measures[final_drugname=="EPIDIOLEX"][pt=="SEIZURE"] #4169 Seizure with Epidiolex
(13743 caseids)

rankROR_Epi <- measures_epi[order(ROR_lb_hat, decreasing = TRUE)][,pt]

rankPRR_Epi <- measures_epi[order(PRR_lb_hat, decreasing = TRUE)][,pt]

rankIC_Epi <- measures_epi[order(ic_lb_hat, decreasing = TRUE)][,pt]

write.csv(rankROR_Epi,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankROR_Epi.csv")

write.csv(rankPRR_Epi,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankPRR_Epi.csv")

write.csv(rankIC_Epi,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankIC_Epi.csv")

rankROR_Epi_2 <- measures_epi[order(ROR_lb_hat, decreasing = TRUE)]

rankPRR_Epi_2 <- measures_epi[order(PRR_lb_hat, decreasing = TRUE)]

rankIC_Epi_2 <- measures_epi[order(ic_lb_hat, decreasing = TRUE)]

write.csv(rankROR_Epi_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankROR_Epi_2.csv")

write.csv(rankPRR_Epi_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankPRR_Epi_2.csv")

write.csv(rankIC_Epi_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankIC_Epi_2.csv")

#CBD####

#Did not run_Same time frame as Epidiolex_CBD2 (20183-20231)

measures_CBD <- measures[final_drugname=="CBD"] #only looking at CBD #2426 obs.

rankROR_CBD_2 <- measures_CBD[order(ROR_lb_hat, decreasing = TRUE)]

rankPRR_CBD_2 <- measures_CBD[order(PRR_lb_hat, decreasing = TRUE)]

rankIC_CBD_2 <- measures_CBD[order(ic_lb_hat, decreasing = TRUE)]

write.csv(rankROR_CBD_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankROR_CBD_2.csv")

write.csv(rankPRR_CBD_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankPRR_CBD_2.csv")

write.csv(rankIC_CBD_2,"/Users/priscillalopes/Library/Mobile
Documents/com~apple~CloudDocs/uOttawa/Thesis/Chapter 2 Signal Detection/rankIC_CBD_2")

#Dronabinol####

measures_dronabinol <- measures[drugname=="DRONABINOL"]

rankROR_dronabinol <- measures_dronabinol[order(ROR_lb_hat, decreasing = TRUE)]

rankPRR_dronabinol <- measures_dronabinol[order(PRR_lb_hat, decreasing = TRUE)]

rankIC_dronabinol <- measures_dronabinol[order(ic_lb_hat, decreasing = TRUE)]

write.csv(rankROR_dronabinol,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankROR_dronabinol.csv")

write.csv(rankPRR_dronabinol,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankPRR_dronabinol.csv")
```

```
write.csv(rankIC_dronabinol,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankIC_dronabinol.csv")
#D9-THc####
measures_d9thc <- measures[drugname=="D9-THC"]
rankROR_d9thc <- measures_d9thc[order(ROR_lb_hat, decreasing = TRUE)]
rankPRR_d9thc <- measures_d9thc[order(PRR_lb_hat, decreasing = TRUE)]
rankIC_d9thc <- measures_d9thc[order(ic_lb_hat, decreasing = TRUE)]
write.csv(rankROR_d9thc,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankROR_d9thc.csv")
write.csv(rankPRR_d9thc,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankPRR_d9thc.csv")
write.csv(rankIC_d9thc,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankIC_d9thc.csv")
#Cannabis####
measures_cannabis <- measures[drugname=="CANNABIS"]
rankROR_cannabis <- measures_cannabis[order(ROR_lb_hat, decreasing = TRUE)]
rankPRR_cannabis <- measures_cannabis[order(PRR_lb_hat, decreasing = TRUE)]
rankIC_cannabis <- measures_cannabis[order(ic_lb_hat, decreasing = TRUE)]
write.csv(rankROR_cannabis,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankROR_cannabis.csv")
write.csv(rankPRR_cannabis,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankPRR_cannabis.csv")
write.csv(rankIC_cannabis,"C:\\Users\\Chris Lab\\Documents\\Priscilla\\rankIC_cannabis.csv")
```

APPENDIX 4. The top 30 disproportionality analysis estimates of ROR, PRR, and IC for CPDs

Appendix 4.1 The top 30 disproportionality analysis estimates for Epidiolex ranked by IC at the PT and SOC levels from Q2 2018 to Q1 2023

SOC	PT	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (95% CrI)
Nervous system disorders	Seizure cluster	86	219.04 (170.54-281.34)	217.68 (169.66-279.27)	6.36 (6.05-6.68)
Nervous system disorders	Change in seizure presentation	60	204.31 (151.86-274.88)	203.43 (151.35-273.43)	6.07 (5.68-6.45)
Nervous system disorders	Atonic seizures	59	191.44 (142.30-257.55)	190.62 (141.83-256.21)	6.02 (5.64-6.41)
Nervous system disorders	Seizure	4169	68.95 (66.41-71.58)	48.34 (47.06-49.65)	5.47 (5.43-5.51)
Investigations	Weight abnormal	126	72.00 (59.76-86.75)	71.35 (59.3-85.83)	5.67 (5.4-5.93)
Product issues	Product supply issue	298	46.99 (41.70-52.95)	45.99 (40.91-51.7)	5.31 (5.14-5.48)
Investigations	Anticonvulsant drug level increased	48	109.77 (80.49-149.71)	109.39 (80.29-149.05)	5.56 (5.14-5.99)
Surgical and medical procedures	Emergency care	124	55.51 (46.11-66.81)	55.01 (45.77-66.12)	5.39 (5.12-5.65)
Injury, poisoning and procedural complications	Product administration interrupted	205	36.55 (31.70-42.14)	36.02 (31.3-41.45)	4.97 (4.77-5.18)
General disorders and administration site conditions	Sudden unexplained death in epilepsy	20	72.37 (45.39-115.39)	72.27 (45.35-115.16)	4.66 (3.95-5.36)
Nervous system disorders	Drooling	84	21.28 (17.18-26.60)	21.25 (17.1-26.41)	4.2 (3.86-4.54)
Injury, poisoning and procedural complications	Prescribed overdose	196	16.64 (14.42-19.2)	16.42 (14.26-18.91)	3.94 (3.72-4.16)
Product issues	Product distribution issue	84	17.24 (13.87-21.44)	17.14 (13.81-21.29)	3.93 (3.59-4.27)
General disorders and administration site conditions	Therapy responder	13	137.44 (74.83-252.45)	137.31 (74.79-252.09)	4.45 (3.56-5.33)
Nervous system disorders	Generalised tonic-clonic seizure	183	14.77 (12.74-17.12)	14.59 (12.61-16.88)	3.78 (3.55-4.01)
Psychiatric disorders	Aggression	289	12.97 (11.53-14.59)	12.72 (11.33-14.27)	3.61 (3.43-3.79)
Surgical and medical procedures	Brain operation	27	19.84 (13.51-29.13)	19.8 (13.49-29.06)	3.85 (3.24-4.45)
Nervous system disorders	Status epilepticus	87	12.86 (10.39-15.91)	12.78 (10.34-15.8)	3.55 (3.22-3.89)
Nervous system disorders	Tonic convulsion	18	26.75 (16.66-42.95)	26.72 (16.65-42.87)	3.94 (3.19-4.69)
Injury, poisoning and procedural complications	Product administered to patient of inappropriate age	72	12.06 (9.54-15.24)	12 (9.51-15.15)	3.45 (3.09-3.82)
Nervous system disorders	Petit mal epilepsy	37	13.53 (9.76-18.75)	13.49 (9.74-18.69)	3.5 (2.99-4.02)
Surgical and medical procedures	Vagal nerve stimulator implantation	9	117.77 (57.32-241.99)	117.7 (57.3-241.74)	4 (2.92-5.08)
Nervous system disorders	Drug withdrawal convulsions	19	17.47 (11.06-27.6)	17.45 (11.06-27.55)	3.59 (2.86-4.31)
Psychiatric disorders	Head banging	11	38.03 (20.64-70.08)	38 (20.63-69.99)	3.83 (2.86-4.8)
Psychiatric disorders	Inappropriate affect	16	20.46 (12.42-33.71)	20.44 (12.41-33.65)	3.65 (2.86-4.45)
Nervous system disorders	Myoclonic epilepsy	16	18.96 (11.52-31.22)	18.94 (11.51-31.17)	3.59 (2.79-4.38)
Psychiatric disorders	Abnormal behaviour	137	8.45 (7.13-10.01)	8.37 (7.08-9.91)	3.01 (2.74-3.27)
Nervous system disorders	Sedation	118	8.5 (7.08-10.21)	8.44 (7.04-10.11)	3.01 (2.73-3.3)
Injury, poisoning and procedural complications	Product use in unapproved indication	1674	7.84 (7.45-8.26)	7.01 (6.7-7.33)	2.79 (2.72-2.86)
General disorders and administration site conditions	Screaming	31	11.49 (8.05-16.4)	11.47 (8.04-16.36)	3.27 (2.71-3.84)

CI confidence interval, *CrI* credible interval, *IC* information component, *NA* not applicable, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, *SOC* system organ class

Appendix 4.2 The top 30 disproportionality analysis estimates for CBD ranked by IC at the PT and SOC levels from Q2 2018 to Q1 2023

SOC	PT	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (95% CI)
General disorders and administration site conditions	Multiple-drug resistance	65	94.66 (73.66-121.63)	93.04 (72.71-119.06)	5.73 (5.35-6.12)
Investigations	Blood pressure diastolic decreased	64	39.24 (30.58-50.35)	38.59 (30.2-49.32)	4.88 (4.49-5.27)
General disorders and administration site conditions	Device related thrombosis	24	96.1 (63.73-144.91)	95.49 (63.49-143.64)	5 (4.36-5.65)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant cranial nerve neoplasm	17	8561.53 (2879.45-25456.18)	8522.92 (2869.16-25317.61)	5.1 (4.33-5.87)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Retro-orbital neoplasm	17	2140.38 (1080.62-4239.44)	2130.73 (1077.36-4214.01)	5.08 (4.31-5.85)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neuroblastoma recurrent	16	767.21 (430.98-1365.77)	763.96 (429.91-1357.56)	4.96 (4.17-5.76)
Investigations	Blood pressure diastolic abnormal	35	39.46 (28.2-55.22)	39.1 (28.03-54.55)	4.65 (4.12-5.18)
Nervous system disorders	Tonic convulsion	19	103.78 (65.37-164.75)	103.26 (65.19-163.57)	4.81 (4.09-5.54)
Injury, poisoning and procedural complications	Metal poisoning	15	260.35 (151.91-446.2)	259.32 (151.59-443.59)	4.78 (3.96-5.6)
Investigations	Urine leukocyte esterase positive	15	68.95 (41.17-115.47)	68.68 (41.09-114.79)	4.42 (3.6-5.24)
Psychiatric disorders	Behaviour disorder	34	22.41 (15.96-31.47)	22.22 (15.87-31.1)	4.08 (3.54-4.61)
Nervous system disorders	Sinus headache	21	31.2 (20.25-48.07)	31.03 (20.19-47.7)	4.18 (3.49-4.87)
Investigations	Blood pressure systolic abnormal	22	28.21 (18.5-43.01)	28.05 (18.44-42.67)	4.12 (3.45-4.79)
Investigations	Blood pressure systolic increased	68	15.31 (12.04-19.48)	15.05 (11.88-19.07)	3.76 (3.38-4.14)
General disorders and administration site conditions	Post viral fatigue syndrome	11	168.88 (91.2-312.72)	168.39 (91.09-311.29)	4.33 (3.36-5.3)
Gastrointestinal disorders	Large intestine polyp	31	19.92 (13.96-28.41)	19.76 (13.89-28.11)	3.92 (3.36-4.48)
Musculoskeletal and connective tissue disorders	Finger deformity	21	25.02 (16.25-38.53)	24.89 (16.2-38.23)	3.99 (3.3-4.68)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to spine	17	30.82 (19.07-49.81)	30.69 (19.03-49.49)	4.04 (3.27-4.81)
General disorders and administration site conditions	Infusion site pruritus	17	28.32 (17.53-45.76)	28.2 (17.49-45.46)	3.98 (3.21-4.75)
General disorders and administration site conditions	Infusion site scar	10	126.46 (66.69-239.78)	126.13 (66.62-238.76)	4.17 (3.15-5.19)
Skin and subcutaneous tissue disorders	Nail disorder	24	18.17 (12.14-27.19)	18.06 (12.1-26.96)	3.73 (3.09-4.38)
Nervous system disorders	Status epilepticus	30	15.97 (11.14-22.91)	15.85 (11.08-22.67)	3.66 (3.09-4.24)
Nervous system disorders	Psychomotor hyperactivity	34	14.49 (10.32-20.33)	14.37 (10.27-20.1)	3.58 (3.04-4.12)
Product issues	Product formulation issue	20	19.57 (12.58-30.43)	19.47 (12.55-30.21)	3.74 (3.03-4.44)
Investigations	Culture urine positive	10	75.02 (39.87-141.16)	74.83 (39.83-140.56)	4.04 (3.02-5.06)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to liver	41	13.11 (9.63-17.86)	12.98 (9.57-17.62)	3.5 (3.01-3.98)
Investigations	Body temperature decreased	33	13.97 (9.9-19.7)	13.85 (9.85-19.48)	3.53 (2.99-4.08)
Infections and infestations	Microsporidia infection	9	126.51 (64.46-248.31)	126.21 (64.4-247.35)	4.04 (2.97-5.12)
Renal and urinary disorders	Urine abnormality	17	18.9 (11.71-30.5)	18.81 (11.68-30.3)	3.63 (2.86-4.4)
Infections and infestations	Pyelonephritis chronic	8	208.79 (100.74-432.73)	208.35 (100.67-431.21)	3.97 (2.82-5.12)

CI confidence interval, *CrI* credible interval, *IC* information component, *NA* not applicable, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, *SOC* system organ class

Appendix 4.3 The top 30 disproportionality analysis estimates for Rx THC ranked by IC at the PT and SOC levels from 1999 to Q1 2023

SOC	PT	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (95% CI)
Psychiatric disorders	Somatic symptom disorder	63	168.38 (130.09-217.95)	167.16 (129.37-216)	6.13 (5.73-6.52)
Investigations	White blood cell count abnormal	186	74.27 (64.06-86.11)	72.69 (62.89-84.02)	5.89 (5.66-6.11)
Musculoskeletal and connective tissue disorders	Sacroiliitis	64	92.49 (71.92-118.94)	91.81 (71.52-117.85)	5.71 (5.32-6.1)
Psychiatric disorders	Parkinson's disease psychosis	32	661.37 (443.04-987.28)	658.92 (441.9-982.53)	5.85 (5.29-6.4)
Metabolism and nutrition disorders	Failure to thrive	61	26.01 (20.19-33.51)	25.83 (20.08-33.23)	4.41 (4.01-4.81)
Psychiatric disorders	Acute psychosis	31	29.65 (20.78-42.3)	29.55 (20.74-42.1)	4.33 (3.77-4.89)
Investigations	Mean cell haemoglobin concentration abnormal	13	295.82 (165.1-530.04)	295.38 (164.98-528.84)	4.62 (3.73-5.5)
Infections and infestations	Infective pulmonary exacerbation of cystic fibrosis	42	17.61 (12.99-23.87)	17.53 (12.94-23.73)	3.87 (3.38-4.35)
Hepatobiliary disorders	Immune-mediated hepatitis	14	33.6 (19.8-57.01)	33.55 (19.79-56.87)	3.97 (3.12-4.82)
Investigations	Occult blood	12	45.86 (25.86-81.31)	45.79 (25.85-81.13)	4.02 (3.1-4.95)
Psychiatric disorders	Terminal insomnia	15	27.32 (16.41-45.5)	27.28 (16.39-45.39)	3.87 (3.05-4.7)
Respiratory, thoracic and mediastinal disorders	Nocturnal dyspnoea	14	27.02 (15.94-45.8)	26.97 (15.92-45.69)	3.82 (2.97-4.67)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma metastatic	21	16.54 (10.76-25.43)	16.51 (10.75-25.35)	3.59 (2.9-4.28)
Gastrointestinal disorders	Cannabinoid hyperemesis syndrome	8	879.37 (382.26-2022.96)	878.56 (382.11-2020.01)	4.05 (2.9-5.2)
Musculoskeletal and connective tissue disorders	Fibromyalgia	86	9.58 (7.74-11.86)	9.5 (7.69-11.72)	3.17 (2.84-3.51)
Metabolism and nutrition disorders	Malnutrition	48	10.62 (7.99-14.12)	10.57 (7.96-14.02)	3.26 (2.81-3.71)
General disorders and administration site conditions	Hangover	22	14.19 (9.32-21.59)	14.16 (9.31-21.52)	3.45 (2.77-4.12)
Musculoskeletal and connective tissue disorders	Muscle mass	9	51.92 (26.78-100.68)	51.87 (26.77-100.51)	3.81 (2.73-4.89)
Social circumstances	Economic problem	67	9.06 (7.12-11.53)	9 (7.08-11.43)	3.08 (2.7-3.46)
Infections and infestations	Gastric infection	20	13.59 (8.75-21.11)	13.56 (8.74-21.04)	3.37 (2.66-4.08)
Psychiatric disorders	Anhedonia	102	8.09 (6.65-9.83)	8 (6.6-9.71)	2.95 (2.64-3.25)
Blood and lymphatic system disorders	Hyposplenism	7	769.36 (321.26-1842.49)	768.74 (321.16-1840.06)	3.87 (2.63-5.11)
Musculoskeletal and connective tissue disorders	Musculoskeletal stiffness	255	7.4 (6.53-8.38)	7.21 (6.38-8.13)	2.83 (2.63-3.02)
Injury, poisoning and procedural complications	Contraindicated product administered	81	8.15 (6.54-10.15)	8.08 (6.5-10.04)	2.95 (2.6-3.29)
Congenital, familial and genetic disorders	Cystic fibrosis	26	11.02 (7.49-16.21)	10.99 (7.48-16.15)	3.2 (2.59-3.82)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lip and/or oral cavity cancer	12	20.2 (11.43-35.68)	20.17 (11.43-35.61)	3.51 (2.58-4.43)
Investigations	Blood pressure systolic abnormal	14	16.44 (9.71-27.83)	16.41 (9.7-27.76)	3.41 (2.56-4.27)
Blood and lymphatic system disorders	Asplenia	7	192.34 (88.5-418.02)	192.19 (88.48-417.45)	3.8 (2.56-5.03)
Respiratory, thoracic and mediastinal disorders	Bronchial wall thickening	9	34.72 (17.95-67.12)	34.68 (17.95-67.01)	3.64 (2.56-4.71)
Infections and infestations	Vascular device infection	17	13.46 (8.35-21.7)	13.44 (8.34-21.64)	3.3 (2.53-4.07)

CI confidence interval, *CrI* credible interval, *IC* information component, *NA* not applicable, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, *SOC* system organ class

Appendix 4.4 The top 30 disproportionality analysis estimates for THC ranked by IC at the PT and SOC levels from 1999 to Q1 2023

SOC	PT	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (95% CI)
Investigations	Drug screen positive	60	138.29 (106.49-179.6)	130.7 (102.09-167.32)	5.97 (5.57-6.38)
Injury, poisoning and procedural complications	Multiple drug overdose	44	122.47 (90.48-165.77)	117.54 (87.9-157.17)	5.66 (5.19-6.14)
Psychiatric disorders	Polysubstance abuse	28	734.51 (500.55-1077.82)	715.58 (492.29-1040.15)	5.72 (5.13-6.31)
Injury, poisoning and procedural complications	Drug toxicity	51	61.42 (46.34-81.4)	58.58 (44.79-76.62)	5.23 (4.79-5.66)
Injury, poisoning and procedural complications	Toxicity to various agents	260	39.96 (34.76-45.95)	30.63 (27.54-34.06)	4.85 (4.68-5.03)
Psychiatric disorders	Drug abuse	143	38.13 (31.98-45.47)	33.24 (28.53-38.73)	4.9 (4.65-5.14)
Respiratory, thoracic and mediastinal disorders	Respiratory depression	35	51.12 (36.49-71.63)	49.51 (35.72-68.62)	4.88 (4.35-5.4)
Social circumstances	Drug abuser	31	56.79 (39.71-81.22)	55.2 (38.99-78.14)	4.89 (4.33-5.45)
Psychiatric disorders	Substance abuse	27	62.33 (42.51-91.39)	60.8 (41.86-88.31)	4.86 (4.26-5.47)
Nervous system disorders	Brain oedema	33	46.81 (33.09-66.23)	45.42 (32.44-63.58)	4.77 (4.22-5.31)
Respiratory, thoracic and mediastinal disorders	Pulmonary congestion	33	45.14 (31.91-63.87)	43.8 (31.29-61.32)	4.74 (4.19-5.28)
Respiratory, thoracic and mediastinal disorders	Pulmonary oedema	67	27.18 (21.23-34.81)	25.57 (20.27-32.25)	4.43 (4.07-4.79)
Investigations	Toxicologic test abnormal	16	18.51 (11.29-30.33)	138.86 (85.19-226.33)	4.74 (3.95-5.54)
Injury, poisoning and procedural complications	Accidental overdose	48	26.01 (19.47-34.74)	24.9 (18.88-32.84)	4.32 (3.87-4.77)
Respiratory, thoracic and mediastinal disorders	Aspiration	24	42.26 (28.19-63.37)	41.35 (27.82-61.45)	4.5 (3.86-5.14)
Nervous system disorders	Serotonin syndrome	30	32.68 (22.73-47)	31.81 (22.34-45.28)	4.4 (3.83-4.97)
Injury, poisoning and procedural complications	Accidental poisoning	13	275.07 (158.46-477.5)	271.79 (157.59-468.74)	4.62 (3.74-5.51)
Psychiatric disorders	Intentional misuse	13	108.21 (62.51-187.32)	106.93 (62.17-183.89)	4.44 (3.55-5.32)
Cardiac disorders	Sinus tachycardia	23	28.39 (18.77-42.92)	27.81 (18.55-41.68)	4.14 (3.49-4.8)
Psychiatric disorders	Aggression	48	17.15 (12.84-22.91)	16.44 (12.46-21.67)	3.82 (3.37-4.27)
Nervous system disorders	Coma	49	16.97 (12.74-22.6)	16.25 (12.36-21.36)	3.81 (3.37-4.26)
Respiratory, thoracic and mediastinal disorders	Asphyxia	14	33.12 (19.54-56.14)	32.7 (19.42-55.06)	3.96 (3.11-4.82)
Investigations	Blood ph decreased	10	69.44 (37.2-129.6)	68.81 (37.08-127.69)	4.02 (3-5.04)
Nervous system disorders	Depressed level of consciousness	33	14.35 (10.15-20.29)	13.94 (9.96-19.51)	3.55 (3-4.09)
General disorders and administration site conditions	Drug interaction	87	10.57 (8.49-13.16)	9.81 (8.02-12)	3.22 (2.91-3.54)
Nervous system disorders	Unresponsive to stimuli	21	16.37 (10.63-25.22)	16.07 (10.52-24.55)	3.57 (2.88-4.26)
Nervous system disorders	Dysarthria	28	13.48 (9.26-19.62)	13.16 (9.13-18.97)	3.44 (2.84-4.03)
Social circumstances	Substance use	8	151.94 (75.54-305.62)	150.83 (75.37-301.83)	3.94 (2.79-5.09)
Cardiac disorders	Cardiomegaly	16	18.51 (11.29-30.33)	18.25 (11.22-29.69)	3.58 (2.79-4.38)
Injury, poisoning and procedural complications	Overdose	98	9.25 (7.51-11.38)	8.5 (7.04-10.27)	3.03 (2.74-3.33)

CI confidence interval, *CrI* credible interval, *IC* information component, *NA* not applicable, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, *SOC* system organ class

Appendix 4.5 The top 30 disproportionality analysis estimates for Cannabis ranked by IC at the PT and SOC levels from 1999 to Q1 2023

SOC	PT	Case Reports	ROR (95% CI)	PRR (95% CI)	IC (95% CI)
Psychiatric disorders	Substance abuse	823	163.89 (152.1-176.58)	154.74 (144.15-166.11)	6.98 (6.88-7.08)
Psychiatric disorders	Substance dependence	98	257.65 (206.92-320.82)	255.93 (205.79-318.3)	6.67 (6.37-6.97)
Psychiatric disorders	Polysubstance abuse	90	190.38 (152.28-238.03)	189.22 (151.53-236.29)	6.43 (6.12-6.74)
Investigations	Red blood cell sedimentation rate	59	325.46 (243.79-434.5)	324.16 (243.03-432.36)	6.34 (5.96-6.73)
Investigations	C-reactive protein abnormal	214	84.22 (73.24-96.84)	83 (72.32-95.26)	6.04 (5.84-6.24)
Psychiatric disorders	Substance use disorder	77	114.7 (90.72-145.03)	114.11 (90.34-144.11)	5.97 (5.63-6.3)
Social circumstances	Substance use	76	116.01 (91.6-146.93)	115.41 (91.23-146.01)	5.97 (5.63-6.31)
Psychiatric disorders	Drug abuse	2936	65.61 (62.96-68.37)	52.66 (50.94-54.44)	5.64 (5.59-5.7)
Investigations	Alanine aminotransferase abnormal	96	76.3 (62.03-93.86)	75.81 (61.71-93.13)	5.71 (5.39-6.02)
Psychiatric disorders	Alcohol abuse	123	64.06 (53.39-76.87)	63.53 (53.03-76.12)	5.6 (5.32-5.88)
Investigations	Red blood cell sedimentation rate abnormal	94	66.78 (54.21-82.26)	66.36 (53.94-81.63)	5.57 (5.24-5.89)
Social circumstances	Drug abuser	340	47.49 (42.56-53)	46.42 (41.7-51.67)	5.39 (5.22-5.56)
Musculoskeletal and connective tissue disorders	Enthesopathy	70	75.57 (59.31-96.29)	75.22 (59.1-95.73)	5.56 (5.19-5.94)
Infections and infestations	Intestinal sepsis	32	280.85 (190.87-413.27)	280.24 (190.58-412.09)	5.66 (5.11-6.22)
Eye disorders	Miosis	232	44.39 (38.9-50.66)	43.7 (38.37-49.78)	5.28 (5.07-5.48)
Musculoskeletal and connective tissue disorders	Tenosynovitis	104	52.44 (43.06-63.87)	52.08 (42.82-63.34)	5.34 (5.03-5.64)
Investigations	Synovial fluid analysis	26	1123.62 (655.58-1925.81)	1121.62 (654.73-1921.46)	5.6 (4.99-6.22)
Investigations	Blood parathyroid hormone decreased	63	64.76 (50.22-83.5)	64.48 (50.06-83.06)	5.37 (4.98-5.77)
Skin and subcutaneous tissue disorders	Granuloma skin	45	88.96 (65.67-120.51)	88.69 (65.53-120.04)	5.44 (4.98-5.91)
Musculoskeletal and connective tissue disorders	Rheumatoid nodule	92	47.46 (38.5-58.49)	47.16 (38.31-58.06)	5.19 (4.87-5.52)
Psychiatric disorders	Drug use disorder	132	40.74 (34.23-48.5)	40.39 (33.98-48)	5.09 (4.82-5.36)
Musculoskeletal and connective tissue disorders	Joint ankylosis	33	87.35 (61.31-124.47)	87.16 (61.21-124.1)	5.21 (4.66-5.75)
Social circumstances	Victim of chemical submission	27	141.28 (94.73-210.71)	141.03 (94.62-210.19)	5.27 (4.66-5.87)
Skin and subcutaneous tissue disorders	Panniculitis	67	43.5 (34.07-55.54)	43.31 (33.95-55.24)	5 (4.62-5.38)
Respiratory, thoracic and mediastinal disorders	Asphyxia	176	31.54 (27.13-36.66)	31.17 (26.86-36.17)	4.81 (4.58-5.04)
Musculoskeletal and connective tissue disorders	Tenosynovitis stenosans	30	84.78 (58.5-122.86)	84.61 (58.43-122.52)	5.12 (4.54-5.69)
Injury, poisoning and procedural complications	Poisoning deliberate	149	31.32 (26.59-36.88)	31.01 (26.37-36.46)	4.78 (4.53-5.04)
Injury, poisoning and procedural complications	Poisoning	251	28.66 (25.26-32.52)	28.19 (24.9-31.92)	4.71 (4.51-4.91)
Injury, poisoning and procedural complications	Multiple drug overdose accidental	30	80.12 (55.33-116.03)	79.96 (55.26-115.71)	5.08 (4.51-5.65)
Respiratory, thoracic and mediastinal disorders	Rheumatoid lung	39	56.23 (40.76-77.57)	56.08 (40.69-77.3)	5.01 (4.51-5.51)

CI confidence interval, *CrI* credible interval, *IC* information component, *NA* not applicable, *PRR* proportional reporting ratio, *PT* preferred term, *ROR* reporting odds ratio, *SOC* system organ class