BMJ Open

Overview of global monitoring systems for the side effects and adverse events associated with medicinal cannabis use: a scoping review using a systematic approach

Rebecca Qi Wang ,[1,2] Yvonne Ann Bonomo,[3] Christine Mary Hallinan [2,4]

To cite: Wang RQ, Bonomo YA, Hallinan CM. Overview of global monitoring systems for the side effects and adverse events associated with medicinal cannabis use: a scoping review using a systematic approach. *BMJ Open* 2024;**14**:e085166. doi:10.1136/bmjopen-2024-085166

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-085166).

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-085166).

Received 09 February 2024
Accepted 03 June 2024

For numbered affiliations see end of article.

Correspondence to
Dr Christine Mary Hallinan; hallinan@unimelb.edu.au

ABSTRACT

Objectives The use of cannabis-based medicine (CBM) as a therapeutic has surged in Australia over the past 5 years. Historically, the United Nations Single Convention on Narcotic Drugs (1961) prohibited cannabis use in Europe, the USA, the UK and Australia, leading to legislative resistance and limited preclinical data on CBM. Existing safety monitoring systems for CBM are poorly structured and do not integrate well into the workflows of busy health professionals. As a result, postmarketing surveillance is inconsistent. This review aims to evaluate international systems for monitoring CBM side effects and adverse events.

Design To undertake a scoping review with a systematic approach, we used the Population, Intervention, Comparison, Outcome (PICO) framework to develop keyword elements, and two search queries to maximise search sensitivity and specificity.

Data sources Search queries were entered into Embase and Scopus for peer-reviewed literature, and additional searches for grey literature were conducted on 23 June 2023.

Eligibility criteria We included 54 full-text articles in the review: 39 from peer-reviewed searches, 8 from grey literature and 7 from citations of relevant texts.

Data extraction and synthesis Our search yielded two main forms of monitoring systems: databases and registries. Out of the 24 monitoring systems identified, there were 10 databases and 14 registries, with databases often created by regulatory authorities. Systems differed in methods of causality assessment, level of detail collected, terminology and affiliations.

Results Within the monitoring systems with enough published data for analysis, all except one remain active at the time of this review. VigiBase is the largest centralised monitoring system, receiving international case reports, however data heterogeneity persists.

Conclusions Our study emphasises the need for a centralised, consistent and accessible system for the postmarketing surveillance of side effects and adverse events associated with medicinal cannabis use.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A systematic search, using identical keywords applied to two peer-reviewed databases and grey literature, was used to increase the scope of the search.
⇒ Two combinations of keyword elements were used in the search to maximise both the sensitivity and specificity of the search.
⇒ Data extraction was performed by two individual reviewers, with discrepancies discussed and resolved.
⇒ Given the international scope of our data collection, our paper was limited by the exclusion of papers not published in the English language.

INTRODUCTION

The emergence of *Cannabis sativa* as a therapeutic can be dated back to 2700 BC, with use becoming widely adopted in the USA by the 19th century.[1 2] Since then, both recreational and medicinal cannabis have undergone a series of proscription and later decriminalisation processes globally. As of the 21st century, cannabis for medicinal purposes has been legalised in many countries, including the USA, the UK, Australia, Canada, Israel and the Netherlands.[3]

The *Cannabis* plant contains over 500 different compounds. Of these, 113 are recognised as cannabinoids, where they function as cannabinoid receptors for biological effect.[4] Notably, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) are the two main active constituents of over 100 medicinal cannabis products available worldwide. Cannabis-based medicine (CBM) is the products containing cannabinoids that are used for a clear therapeutic purpose, rather than recreational purposes. CBM may be obtained on prescription or otherwise and is used for symptomatic control of intractable chronic diseases.[2] These include, but are not restricted to, spasticity in multiple sclerosis (MS), epilepsy, neuropathic pain, cancer-related pain, as well as chemotherapy-induced nausea and vomiting.[2] Emerging

evidence is expanding the therapeutic usage of CBM to include psychiatric disorders such as anxiety and post-traumatic stress disorder, sleep disorders, fibromyalgia and Parkinson's disease.[2 5–7]

The growing evidence base and media attention have triggered a shift in public paradigms towards acceptance of cannabis as a medicine.[8] The increasing community demand for CBMs is apparent in the uptrend of prescription approvals. Over the last 7 years in Australia, there were 949,732 patients who were newly prescribed a specific medicinal cannabis product, biannually via the TGA's Authorised Prescriber System.[9] This uptrend in prescribing rates is further reflected by a percentage increase of 402% in new prescriptions in the 6-month period ending January 2022, compared with the 6-month period ending January 2023 (online supplemental material 1).[10]

However, unlike conventional medications, public demand rather than preclinical studies for quality control, have driven increasing clinical uptake.[11 12] Given a history of legislative resistance and restrictions in conducting clinical trials with CBMs, gaps remain in the literature surrounding side effects and adverse reactions. Notably, there is limited safety evidence on CBMs for vulnerable populations commonly excluded from clinical trials, such as pregnant women, children and patients with complex comorbidities.[13–15] Additionally, the illicit drug market, over-the-counter availability and unregulated product commercialisation have created a landscape of products that vary in formulation, strength, route of administration and quality.[16–18] As such, growing use necessitates prescriber and consumer vigilance on side effects and adverse reactions.

The gap between available safety evidence and clinical use warrants rigorous surveillance for postmarketing signal detection of adverse events associated with CBMs. This need has been addressed in various ways by different countries. To our knowledge, no other research has comprehensively described and evaluated the postmarketing surveillance systems which have been established to monitor the adverse effects of CBM. Therefore, the objective of this research is to provide an overview of current methods for real-world monitoring of the side effects and adverse events associated with CBM use. Using a systematic search of peer-reviewed databases and grey literature, this review aims to answer the following question: What are the systems in place internationally to monitor side effects and adverse events of cannabis use as a medicine?

METHODS

Search strategy

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines were used as a methodological framework to inform the approach to a systematic search of literature.[19 20] Five main keyword elements were identified using the Population, Intervention, Comparison, Outcome (PICO) framework, and subsequently used to guide the development of search terms and inclusion/exclusion criteria (online supplemental material 2).

Two separate categories of searches were conducted, each with search terms from a different combination of keyword elements (online supplemental material 3). For the first category, the search query combined terms relating to elements of medical usage, cannabis, monitoring systems and side effects or adverse events. The second category included cannabis-related terms, as well as terms relating to pharmacovigilance, monitoring systems and medical usage. The first category aimed to increase the specificity of our search, whereas the second category focused on search sensitivity, incorporating the more loosely defined concept of pharmacovigilance, without specific mention of side effects and adverse events. Both categories were used to create searches on 23 June 2023, identical across Scopus and Ovid Embase for peer-reviewed publications, with added MESH terms in the latter (online supplemental material 4).

Category 2 search terms were further used for a grey literature search to supplement our literature database search and maximise the scope of our results. The grey literature search composed of extracting the first 1000 titles of a Google Scholar search using Category 2 search terms. An identical search for grey literature was applied to Mednar, a medically focused search engine, to include deep web searches that were not indexed by standard search engines.[21–23] Search terms across different keyword elements were combined with Boolean operator "AND" while terms within a keyword element were combined with the Boolean operator "OR".

Supplementary articles were identified in the references of retrieved papers. All searches were limited to papers published between January 2015 and June 2023; the period in which cannabis legalisation occurred in multiple countries worldwide, triggering the need for widespread monitoring systems.[24–26] The search was manually filtered to papers published in the English language, to yield the results shown in the PRISMA flow chart (online supplemental material 5).

All results from search queries were uploaded into an Excel spreadsheet for duplicate removal. Title and abstract screening were performed, subject to inclusion and exclusion criteria. Records were excluded primarily based on relevance and the a priori decision to exclude records with no mention of pharmacovigilance nor a monitoring system in the title and abstract. Secondary Google searches were performed for primary sources such as reporting forms, where more specific information on databases was required. Small scale surveys were not considered a formal monitoring system and subsequently excluded. All full-text articles identified for inclusion following the screening process were evaluated independently by two reviewers. RQW reviewed all titles, and YAB provided a second review. There was discrepancy between the reviewer assessments in <5% of articles, which were subsequently resolved among the reviewers, thus not

requiring a third reviewer. Any points of contention were discussed in meetings and subsequently resolved for a full list of titles for data extraction.

The PRISMA flow chart (online supplemental material 5) outlines the full search strategy and results.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this review.

RESULTS

Of the 3939 records identified in the initial peer-reviewed database search, 1004 duplicates were removed, with an additional 2889 records excluded following title and abstract screening. The screening process yielded 46 potentially relevant full-texts from the peer-reviewed database search, with 3 unable to retrieved, leaving 43 full texts for inclusion. The grey literature search identified 1127 records. Following duplicate removal and title and abstract screening, 12 full texts were identified. Of these, one record was unable to be retrieved. Subsequently, 11 additional records from the grey literature search were identified for full text review, leaving 54 records for full text review. Of the 54 full texts assessed for eligibility, 5 were excluded on the basis of relevance and 2 were excluded for recreational cannabis use as the study population. Seven additional papers were identified through citations, yielding a total of 54 included records (online supplemental material 6).

Monitoring systems identified by our search were either registries or databases. Although used interchangeably, there are several distinguishing characteristics between the two (online supplemental material 7). There were a total of 7 regulatory authority databases and 17 registries captured within our search (table 1). Of these registries, eight were smaller registries briefly mentioned in articles, without readily available data and were not analysed in depth (table 1).

Table 1 Monitoring systems captured by search with readily available data for analysis*

Databases	Registries
Italian Phytovigilance Database[42 62]	German Pain e-registry[31 34–37]
FDA Adverse Event Reporting System[27 42 91–93]	Quebec Cannabis registry[28–30 42 43]
WHO VigiBase[32 42 50]	The Registry[33 36 94]
Canada Vigilance Adverse Reaction Online Database[27–29 42 43 95]	Australian Emyria Clinical Registry[44]
Eudravigilance European Database of Suspected Adverse Drug Reaction Reports†	UK Medical Cannabis Registry[44 67–85]
Drug Commission of the German Medical Association database[53]	ToxIC registry[38–41]
TGA Database of Adverse Event Notifications[44 46]	SwissCanOn[96]
CB2 Insights' Clinical network database[97]	Italian Medicines Agency (AIFA) Registry‡
NotiFACEDRA database[50]	Project TwentyOne[42 69 85 98 99]
DATACANN: Database for Cannabinoid Consumption and Study[42]	*Israeli Multi-Centre Registry of Medical Cannabis for Chronic Pain*[100]
	Spanish Prospective Registry[94]
	Minnesota Department of Health: Medicinal Cannabis Registry[42]
	Children's Hospital of Philadelphia: Medical Cannabis Registry[42]
	Canadian Paediatric Surveillance Programme[42]

Notably, many registries input data into larger databases. Interactions between registries and databases are captured in online supplemental material 8.[50]
*Monitoring systems in italics were systems captured by search that did not have readily available data for analysis.
†Includes reports from the Yellow Card System in the UK, managed by the Medicines and Healthcare Products Regulatory Agency.
‡Known as a registry but governed by a regulatory authority (AIFA).

Monitoring system characteristics

Primary purpose

There were two distinct purposes for establishment of monitoring systems. Some systems were created as broader forms of postmarketing surveillance to inform safety and regulation. These include all aforementioned databases and all registries with the exception of five. These registries were created as data collection for observational studies, with postmarketing surveillance as a secondary aim of the research. As such, they are categorised as research registries (table 2).

Duration of data collection

Of the sixteen monitoring systems that are included within this review, fifteen are still actively engaging in data collection at the time of review. All systems with postmarketing surveillance as a primary outcome, provide ongoing data collection at the time of our literature search.

Research registries, due to the longitudinal nature of observational studies, are also ongoing forms of monitoring, with two exceptions (table 3). The Quebec Cannabis Registry, established in 2015, ceased data

Table 2 Primary purposes of monitoring systems for side effects and adverse events associated with CBM usage

Postmarketing surveillance for safety and regulation	Data collection for observational studies (research registries)
Italian Phytovigilance Database[42 62]	Quebec Cannabis registry[28–30 42 43]
FDA Adverse Event Reporting System[27 42 91–93]	The Registry[33 36 94]
Canada Vigilance Adverse Reaction Online Database[27–29 42 43 95]	SwissCanOn[96]
WHO VigiBase[32 42 50]	Australian Emyria Clinical Registry[44]
Eudravigilance European Database of Suspected Adverse Drug Reaction Reports[48]	Project TwentyOne[42 69 85 98 99]
Drug Commission of the German Medical Association database[53]	UK Medical Cannabis Registry[44 67–85]
TGA Database of Adverse Event Notifications[44 46]	
Italian Medicines Agency Registry[36 52 101]	
German Pain e-registry[31 34–37]	
ToxIC registry[38–41]	

CBM, cannabis-based medicine.

collection in 2018. Serious adverse events were reported to the Canada Vigilance Database for evaluation.[27–30] The Registry collected data in the UK from 2012 to 2015, however, data collection in Germany and Switzerland remains ongoing.[31–33]

Level of detail assessed

Most systems collect information on formulation and dosage of the CBM, however, this is more common in regulatory databases. Route of administration and concomitant medications are frequently accounted for. Differences in details exist in assessing patient demographics. Age and sex of consumers are commonly collected; however, comorbidities and pregnancy status are not routinely reported (table 3).

Mode of monitoring: spontaneous or mandatory?

Where data sources elect to participate in data collection, the system is considered to adopt a spontaneous reporting protocol. Therefore, all research registries, as well as the ToxiC registry, are spontaneous reporting systems (table 3). The Italian Medicines Agency (AIFA) registry mandates reporting from patients. The German Pain E-registry collects information from 200 pain centres across Germany and fulfils the obligatory requirements of physicians to document patients under treatment for chronic pain.[31 34–37]

Reporter nature

Monitoring systems collect data from combinations of the following subgroups of individuals: patients, healthcare professionals and/or manufacturers. Three registries (table 4) use patient-reported outcomes. Four registries accept reports from healthcare professionals alone. The ToxiC registry,[38–41] collecting data from medical records in participating hospitals, is included in this category. Larger databases encourage reports from patients, healthcare professionals, as well as manufacturers and producers of CBMs.

Specificity to cannabis versus other pharmaceuticals

Six of the sixteen monitoring systems captured by the search are specific to CBM monitoring. Databases offer assessments of adverse events associated with regulated and/or unregulated products within a region, rather than specific CBM monitoring.

Affiliations

Four registries are affiliated with independent ownership (table 5).

Causality assessment

The strength of the causal relationship between CBM usage and the observed adverse event is considered in five monitoring systems (table 5). The Quebec Cannabis Registry conducts causality assessments on reports, however, the mode of assessment is not described in literature captured by our search.[28–30 42 43] The Australian Emyria database does not implement a formal causality assessment, however, possible causal relationships are guided by clinicians' medical judgement.[44]

DISCUSSION

As of June 2023, there remain no robust and rigorous monitoring systems globally for collection of postmarketing safety data to accompany the international expansion in CBM uptake. The existence of several regulatory databases and multiple smaller registries globally, some of which have limited published data, demonstrates heterogeneity in postmarketing surveillance of CBM. The literature included in this review did not identify a quality assessment process for the data collected within the fifteen monitoring systems that remain active at the time of this review.

In some countries, the monitoring of CBM-related adverse events is embedded within the national regulatory framework for pharmaceuticals. The Italian Phytovigilance database, coordinated by the Italian National Institute of Health, collects reports on suspected adverse events associated with plant ingredient preparations and food supplements in Italy.[45] Similarly, Canada Vigilance Adverse Reaction Online Database (CVAR) evaluates reports of suspected adverse reactions related to heath products with marketing authority within Canada.[42] FDA Adverse Event Reporting System (FAERS) in the USA

Table 3 Elements assessed by each monitoring system for side effects and adverse events associated with CBM usage

	Formulation: THC/CBD	Variety of formulations	Dosage	Form/route of administration	Patient demographics mentioned	Indication	Effect	Concomitant medication	Severity of adverse reaction
Italian Phytovigilance Database[42 62]*	Yes	Yes	No	Yes	Age, weight, height, gender, comorbidities, pregnancy status	Yes	No	Yes	Yes
Database of Adverse Event Notifications (DAEN)[44 46]*	Yes	Yes	Yes	Yes	Age, sex, gender, weight, ethnicity	Yes	No	Yes	Yes
WHO VigiBase[32 42 50]*	Yes	Yes	Yes	Yes	All relevant patient demographics as reported in case reports submitted via national regulatory authorities	Yes	No	Yes	Yes
Canada Vigilance Adverse Reaction Online Database[27–29 42 43 95]*	Yes	Yes	Yes	Yes	Age, sex, height, weight	Yes	No	Yes	Yes
Eudravigilance European Database of Suspected Adverse Drug Reaction Reports[48]*	Yes	Yes	Yes	Yes	All relevant patient demographics as reported in case reports submitted via national regulatory authorities	Yes	No	Yes	Yes
Drug Commission of the German Medical Association database[53]†	Not explicitly stated by study	Not explicitly stated by study	Not explicitly stated by study	Not explicitly stated by study	Not explicitly stated by study	Not explicitly stated by study	No	Not explicitly stated by study	Not explicitly stated by study
TGA DAEN[44 46]†	Yes	Yes	Yes	Yes	Age, sex, height, weight, ethnicity, comorbidities maternal/paternal or foetal exposure	Yes	Yes	Yes	Yes
German Pain e-registry[31 34–37]	Not explicitly specified	Yes	Not explicitly stated	Not explicitly specified	Age, comorbidities	Yes	Yes	Yes	No
Quebec Cannabis registry[28–30 42 43]	Yes	Yes	Yes	Yes	Age, sex, occupation, comorbidities, smoking status, alcohol use and recreational drug use (at baseline), pregnancy/breastfeeding status, history of cannabis or substance use disorder	Yes	Yes	Yes	Yes

Continued

Table 3 Continued

	Formulation: THC/CBD	Variety of formulations	Dosage	Form/route of administration	Patient demographics mentioned	Indication	Effect	Concomitant medication	Severity of adverse reaction
The Registry[33 36 94]	Yes (THC:CBD, nabiximols)	No	Yes	Yes	Age, sex	Yes	Yes	Yes	Clinical significance determined by prescriber's professional opinion
Australian Emyria Clinical Registry[44]	Yes	Yes: all TGA approved CBMs	Yes	Oral	Age, comorbidities	Yes	Yes	Yes	Yes
UK Medical Cannabis Registry[44 67–85]	Yes	Yes	Yes	Yes	Demographic, BMI, Comorbidities, drug and alcohol history	Yes	Yes	Yes	Yes
ToxIC registry[38–41]	Yes	Yes, not cannabis-specific	Yes, a part of clinical data	Yes, part of clinical data	Demographics available in hospital patient records	Yes	No	Yes, a part of clinical data	Yes, mortality and whether life support was withdrawn signs and symptoms
SwissCanOn[96]	Not explicitly specified	Yes	Yes	Not explicitly specified	No mention of patient demographics	Yes, oncology	Yes	Not explicitly mentioned	Not explicitly mentioned
Italian Medicines Agency Registry[36 52 101]	Yes (THC: CBD, nabiximols, Sativex)	No, e-registry explicitly set up for Sativex re-imbursement	Yes	Yes	Age, comorbidities	Yes, spasticity in multiple sclerosis	Yes	Yes, other use of antispastic drug	Yes
Project TwentyOne[42 69 85 98 99]	Yes	Yes	Not explicitly stated	Yes	Age, comorbidities	Yes: chronic pain, PTSD, anxiety, MS, Tourette's syndrome, Cannabis use disorder	Yes	Yes	Not explicitly stated

*Where primary reporting forms were accessible.
†Analysis for the purposes of this study was limited by availability of information.
BMI, body mass index; CBD, cannabidiol; CBM, cannabis-based medicine; PTSD, post-traumatic stress disorder; THC, delta-9-tetrahydrocannabinol.

Table 4 Nature of reporters to each monitoring system for the side effects and adverse events associated with CBM usage

Patients only	Clinician/healthcare professionals only	Patients and healthcare professionals	Patients, healthcare professionals and manufacturers
Quebec Cannabis Registry[28–30 42 43]	The Registry[33 36 94]	Italian Phytovigilance Database[42 62]	FDA Adverse Event Reporting System[27 42 91–93]
SwissCanOn[96]	ToxiC Registry[38–41]	German Pain e-registry[31 34–37]	WHO VigiBase[32 42 50]
Project TwentyOne[34 53 70 98 99]	Drug Commission of the German Medical Association database[53]	Australian Emyria Clinical Registry[44]	Canada Vigilance Adverse Reaction Online Database[27–29 42 43 95]
N/A	Italian Medicines Agency Database[36 52 101]	UK Medical Cannabis Registry[44 67–85]	Eudravigilance European Database of Suspected Adverse Drug Reaction Reports[48]
N/A	N/A	N/A	TGA Database of Adverse Event Notifications[44 46]

CBM, cannabis-based medicine; N/A, not available.

Table 5 Features of monitoring systems for monitoring of side effect and adverse events associated with CBM usage*

Monitoring system	Ongoing form of data collection	Mandatory reporting	Specificity to CBM	Affiliations	Formal causality assessment
Italian Phytovigilance					
FAERS					
WHO VigiBase					
Eudravigilance European Database of Suspected Adverse Drug Reaction Reports					
Drug Commission of German Medical Association					
Canada Vigilance Adverse Reaction Online Database					
TGA Database of Adverse Event Notifications					
German Pain E-registry					
Quebec Cannabis Registry					
The Registry					
Australian Emyria Clinic Registry					
UK Medical Cannabis Registry					
ToxiC Registry					
SwissCanOn					
Italian Medicines Agency Database					
Project TwentyOne					

Green=Ongoing form of monitoring; completely mandatory reporting system; system specific to CBM monitoring; system affiliated with private ownership; reports in system accompanied by formal causality assessment tool.
Orange=No ongoing form of monitoring; spontaneous or partially mandatory reporting system, system not specific to CBM monitoring; system not affiliated with private ownership; reports in system not accompanied by formal causality assessment tool.
*The Registry is sponsored by GW Pharmaceuticals[33 36 94] while The UK Medical Cannabis Registry is established by Curaleaf Clinic, previously known as Sapphire Medical Clinics.[44 67–85] Emyria Limited maintains full ownership of the Australian Emyria Clinical e-Registry.[44] The SwissCanOn project is supported by various corporations such as Swiss Alpinopharma, Mobile Health AG and MedCan.[96]
CBM, cannabis-based medicine; FAERS, FDA Adverse Event Reporting System.

and Database of Adverse Event Notifications (DAEN) in Australia follow similar frameworks.[46 47] Eudravigilance European Database of Suspected Adverse Drug Reaction Reports (EDSADR), collecting data on suspected adverse reactions to authorised medicines or products undergoing trials in the European Economic Area, receives reports from National Medicine Regulatory Authorities and Marketing Authorisation Holders that are submitted by patients and healthcare professionals.[48] Prior to Brexit, the UK data collected from the Yellow Card System, managed by Medicines and Healthcare Products Regulatory Agency (MHRA), was integrated into EDSADR, as the centralised database the European Economic Area. Post Brexit, MHRA directly manages data collected via the Yellow Card System, independent of EDSADR.[49] Many of the national databases input individual case reports into Vigibase (online supplemental material 8), the database established by the WHO Programme for International Drug Monitoring, which bears the greatest resemblance to a centralised monitoring system for CBM-related adverse events.[32 42 50 51]

Other countries have established registries, either for observational studies or for regulatory purposes. Although some of these systems provide data targeted to cannabis, many rely on spontaneous reporting and are, therefore, subject to selection bias from affiliations.

Mandatory versus spontaneous reporting systems

The AIFA e-registry, to our knowledge, remains the only completely mandatory reporting system captured by our search, obligating patients to submit any side effects and adverse events experienced. The Italian Medicines Agency, under a reimbursement scheme called the Managed Entry Agreement, established an e-registry for all patients commencing on Sativex, to identify 'non-responders' for subsequent reimbursement and discontinuation of treatment.[52] EDSADR mandates Marketing Authorisation Holders and National Competent Authorities to submit reports of adverse events received from patients and healthcare professionals. However, patients and healthcare professionals are not required to report adverse events.[48] CVAR and TGA follow a similar reporting structure to EDSADR.[42 46] Similarly, German pharmacists are obliged to report encountered suspected adverse reactions to the Drug Commission of the German Medical Association, however, consumers are not required to report side effects and adverse events.[53]

The ad hoc nature of reporting requirements in many databases and registries risks a variety of reporting biases.[54 55] These include under-reporting, notoriety bias and the preference to only report severe, usually rare, adverse events.[54] Spontaneous adverse drug reaction reporting typically peaks following the second year of marketing, then subsequent declines, unaccompanied by changes in drug usage or adverse event incidence.[56 57] Under-reporting can be secondary to complacency, where adverse events are (incorrectly) believed to have been already well documented following marketing. Uncertainty surrounding causal relationships is a further contributing factor to under-reporting in spontaneous systems. Additionally, fear of medicolegal consequences, alongside overall clinician indifference is known to further discourage consistent reporting.[55 58 59]

In November 2017, the change from spontaneous to mandatory submission of suspected ADRs from Marketing Authorisation Holders and National Competent Authorities to the Eudravigilance database, resulted in a significant increase in the number of reports collected.[60] Therefore, mandatory reporting framework appear to mitigate issues of under-reporting. Additional interventions such as financial incentives, training on ADR selection and existing reporting systems, as well as continuous feedback on safety signals identified may lessen other reporting biases intrinsic to spontaneous reporting systems.

Causality assessment

Although postmarketing surveillance is more likely to identify a strong causal relationship between CBMs and adverse events, rather than certain proof of causality, there is variability in the level of causality assessment accepted by each monitoring system.[61] The Italian Phytovigilance database and CVAR both use the WHO-UMC causality classification system, whereas many other registries and databases such as the FAERS and DAEN do not implement a formal causality assessment process. Within these systems, reports are broadly classified as monitoring 'suspected' adverse events. Factors known to help determine the strength of a causal relationship include the temporal relationship between the commencement of CBM and adverse event onset, as well as response to ceasing the CBM and subsequent readministration.[57] The FAERS reporting form provides an opportunity for details on response to dechallenge and rechallenge with the drug agent, however, these fields are not mandatory for report submission. VigiBase, collecting case reports from national pharmacovigilance centres internationally, notes discrepancies between reports and does not validate causality claims.[32 43 50 62] Eudravigilance similarly accepts reports of varying strengths of causality.[48] A standardised method of determining causality across monitoring systems may improve the strength of safety data derived from reports of adverse events.

Diversity in report quality and detail

With no formal assessment of the quality of data collection within the monitoring systems, there are further inconsistencies in the level of detail collected by each monitoring system. Some databases do not specify the dosage or route of administration of the CBM, decreasing the utility of available data in determining accurate safety data. Information collected on patient demographics also varies significantly between systems, especially when considering a patient's comorbidities, pregnancy status and concomitant medications. As potential confounding factors in determining the cause of the adverse reaction,

variations in these demographic details impacts the interpretation of safety data collected.[63 64]

Variability in quality of reports poses an additional problem in centralised databases such as VigiBase, where data are derived from various sources. Between healthcare professionals, consumers and manufacturers from over 150 countries,[43 50 62 65] differences exist in terminology, coding practices and reporting standards across these different regions and healthcare systems. Standard terminology for drug reactions and medicinal products is codified using the Medical Dictionary for Regulatory Activities (MedDRA) and WHODrug classifications respectively.[66] However, data at a national level may be mistranslated and inexact when transferred to the standardised VigiBase terminology. For instance, CBD-dominant cannabis products may be coded as CBD according to the standardised WHODrug system, when their THC content would qualify them to be coded as *C. Sativa* whole extracts. The current MedDRA classification for severity of adverse reactions also provides limited descriptors for cannabis-related adverse events, such as 'cannabis hyperemesis syndrome' or 'cannabis dependence' and 'withdrawal'.[42] Such discrepancies limit data comparability and complicate assessment of adverse events associated with CBM usage.

The diversity of data sources reporting to a centralised system such as VigiBase predisposes to potential duplication reports. Although efforts are made to identify duplicates, slight differences in nomenclature of related reports may allow duplicates to bypass the algorithm employed by VigiBase.[66] As such, the development of one central reporting system with standardised nomenclature and formatting may help with the imprecision in adapting multiple data sources into a standardised framework.

Affiliations

The affiliation of certain registries with independent ownership presents risk of selection bias when evaluating results. The Registry, a multicentre observational research registry collecting data from the UK, Germany and Switzerland, is sponsored by GW Pharmaceuticals, the manufacturers of the THC: CBD oromucosal spray (Nabiximol). Prescribers were identified and invited to participate in data collection by GW Pharmaceuticals, and nominally compensated for completing case report forms.[33] UK Medical Cannabis Registry is maintained by Curaleaf Clinic, inviting patients from a private healthcare setting not representative of the broader population of CBM consumers.[44 67–85] Similarly, the Australian Emyria Clinical e-Registry sources participation from Emerald Clinics, a network of clinics specialising in use of currently unregistered medicines and commercialisation of collected clinical evidence with Spectrum Therapeutics, the medical division of a cannabis company known as Canopy Growth.[44 86] Of note, patients from these registries are a specific subset of CBM consumers, and these registries are aligned with various companies that have interests outside that of the accumulation of real-world safety data.

Accessibility to reporting and safety data

Accessibility to reporting forms, time constraints and awareness of existing reporting schemes have been forwarded as factors limiting participation in monitoring systems.[87–89] Additionally, there exists a delay between onset and recognition of the adverse drug reaction, and another lag between reports being input into national pharmacovigilance centres and successful transfer into a central monitoring system such as VigiBase.[66] Between access issues to reporting forms, as well as access to safety data published by databases, current monitoring systems are difficult to incorporate into the busy workflow of clinical practice. As such, monitoring of CBM adverse events, from reporting to publishing of safety data, requires a streamlined approach to parallel speed of CBM uptake.

Limitations

Information on details collected in smaller registries is limited by the availability of published data, as often the original reporting form was inaccessible via a secondary Google Search. Additionally, the discipline of pharmacovigilance posits a difference between the definition of side effects, adverse events and adverse reactions.[90] However, these terms were used interchangeably in papers, and therefore, adverse events were assumed to encompass side effects.

CONCLUSION

To the best of our knowledge, this is the first scoping review assessing the existing monitoring systems for side effects and adverse events associated with medicinal cannabis usage at an international level. As a novel therapeutic, CBM may be a promising solution for an increasing range of intractable conditions. Our scoping review with a systematic approach has identified various issues with the quality, access, consistency and attitudes towards existing reporting systems for monitoring of adverse events related to CBM usage. Although the ideal international monitoring system has proven difficult among the evolving landscape of cannabis legalisation, there still remains a key need for a centralised and standardised system, that is, accessible and operates in real time. Postmarketing safety data captured in this way, accompanying the growth in clinical use, will support both public and clinical interest in CBMs as a therapeutic in a safe and efficient manner.

Author affiliations
[1]Department of General Practice and Primary Care, The University of Melbourne, Parkville, Victoria, Australia
[2]Melbourne Medical School, The University of Melbourne, Parkville, Victoria, Australia
[3]Addiction Medicine, The University of Melbourne Faculty of Medicine Dentistry and Health Sciences, Parkville, Victoria, Australia
[4]HaBIC R2, Department of General Practice and Primary Care, The University of Melbourne, Parkville, Victoria, Australia

X Christine Mary Hallinan @Cmhallinan

Contributors RQW, YAB and CMH provided substantial contributions to the conception or design of the work and the acquisition, analysis and interpretation of data for the work. RQW, YAB and CMH drafted and reviewed the manuscript for important intellectual content. RQW and CMH reviewed and edited the final manuscript, along with tables and figures. RQW, YAB and CMH provided final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CMH accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This review was supported by the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE), funded by the National Health and Medical Research Council (NHMRC) through the Centre of Research Excellence scheme.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

ORCID iDs
Rebecca Qi Wang http://orcid.org/0009-0004-6955-5108
Christine Mary Hallinan http://orcid.org/0000-0002-0471-4444

REFERENCES

1 Brand EJ, Zhao Z. Cannabis in Chinese medicine: are some traditional indications referenced in ancient literature related to Cannabinoids *Front Pharmacol* 2017;8:108.
2 Bridgeman MB, Abazia DT. Medicinal Cannabis: history, pharmacology, and implications for the acute care setting. *P T* 2017;42:180–8.
3 Shover CL, Humphreys K. Six policy lessons relevant to Cannabis Legalization. *Am J Drug Alcohol Abuse* 2019;45:698–706.
4 Baratta F, Simiele M, Pignata I, *et al*. Cannabis-based oral formulations for medical purposes: preparation, quality and stability. *Pharmaceuticals (Basel)* 2021;14:171.
5 Hazekamp A, Ware MA, Muller-Vahl KR, *et al*. The medicinal use of Cannabis and Cannabinoids—an international cross-sectional survey on administration forms. *J Psychoact Drugs* 2013;45:199–210.
6 National Academies of Sciences E, Medicine, Health. The National academies collection: reports funded by National Institutes of health. In: *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. National Academies Press (US) Copyright 2017 by the National Academy of Sciences, 2017.
7 Arnold JC, Nation T, McGregor IS. Prescribing medicinal Cannabis. *Aust Prescr* 2020;43:152–9.
8 Hallinan CM, Gunn JM, Bonomo YA. Use of electronic medical records to monitor the safe and effective prescribing of medicinal Cannabis: is it feasible? article *Aust J Prim Health* 2022;28:564–72.
9 TGA Medicinal Cannabis Access Data Dashboard. Australian government Department of health. 2023. Available: https://www.tga.gov.au/medicinal-cannabis-access-data-dashboard [Accessed 7 Dec 2023].
10 TGA Medicinal Cannabis Authorised Prescriber Scheme data. Australian government therapeutic goods Administration (TGA) 2023. 2023. Available: https://www.tga.gov.au/products/unapproved-therapeutic-goods/medicinal-cannabis-hub/medicinal-cannabis-access-pathways-and-patient-access-data/medicinal-cannabis-authorised-prescriber-scheme-data [Accessed 7 Sep 2023].
11 Clarke H, Fitzcharles M. The evolving culture of medical Cannabis in Canada for the management of chronic pain. *Front Pharmacol* 2023;14.
12 Sznitman SR, Bretteville-Jensen AL. Public opinion and medical Cannabis policies: examining the role of underlying beliefs and national medical Cannabis policies. *Harm Reduct J* 2015;12:1–10.
13 Wong SS, Wilens TE. Medical uses of Cannabinoids in children and adolescents: a systematic review. *J Am Acad Child Adolesc Psychiatry* 2017;56:S295.
14 National Academies of Sciences E, Medicine. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. 2017.
15 Bonomo Y, Souza JDS, Jackson A, *et al*. Clinical issues in Cannabis use. *Br J Clin Pharmacol* 2018;84:2495–8.
16 Bonn-Miller MO, Loflin MJE, Thomas BF, *et al*. Labeling accuracy of Cannabidiol extracts sold online. *JAMA* 2017;318:1708–9.
17 Hallinan CM, Eden E, Graham M, *et al*. Over the counter low-dose Cannabidiol: a viewpoint from the ACRE capacity building group. *J Psychopharmacol* 2022;36:661–5.
18 Fitzcharles M-A, Shir Y, Häuser W. Medical cannabis: strengthening evidence in the face of Hype and public pressure. *CMAJ* 2019;191:E907–8.
19 Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *PLOS Med* 2021;18:e1003583.
20 Munn Z, Peters MDJ, Stern C, *et al*. Systematic review or Scoping review? guidance for authors when choosing between a systematic or Scoping review approach. *BMC Med Res Methodol* 2018;18.
21 Haddaway NR, Collins AM, Coughlin D, *et al*. The role of Google scholar in evidence reviews and its applicability to grey literature searching. *PLOS ONE* 2015;10:e0138237.
22 Paez A. Gray literature: an important resource in systematic reviews. *J Evid Based Med* 2017;10:233–40.
23 Adams J, Hillier-Brown FC, Moore HJ, *et al*. Searching and Synthesising 'grey literature' and 'grey information' in public health: critical reflections on three case studies. *Syst Rev* 2016;5.
24 Paut Kusturica M, Tomas A, Sabo A, *et al*. Medical Cannabis: knowledge and attitudes of prospective doctors in Serbia. *Saudi Pharm J* 2019;27:320–5.
25 Hallinan CM, Gunn JM, Bonomo YA. Implementation of medicinal Cannabis in Australia: innovation or upheaval? perspectives from physicians as key informants, a qualitative analysis. *BMJ Open* 2021;11:e054044.
26 Lipnik-Štangelj M, Razinger B. A regulatory take on Cannabis and Cannabinoids for medicinal use in the European Union. *Arh Hig Rada Toksikol* 2020;71:12–8.
27 Sharma V, Gelin LFF, Sarkar IN. Identifying Herbal adverse events from spontaneous reporting systems using Taxonomic name resolution approach. *Bioinform Biol Insights* 2020;14.
28 Aprikian S, Kasvis P, Vigano M, *et al*. Medical Cannabis is effective for cancer-related pain: Quebec Cannabis Registry results. *BMJ Support Palliat Care* 2024;13:e1285–91.
29 Moride Y, Hachem Y, Castilloux AM, *et al*. Oral presentation: safety of medical Cannabis: a descriptive study using the Quebec Cannabis Registry. *Drug Saf* 2022;2022:1128–9.
30 Vigano A, Canac-Marquis M, Gamaoun R, *et al*. The Quebec Cannabis Registry: a Pharmacovigilance and effectiveness study on the use of medical Cannabis in cancer patients. *J Clin Oncol* 2020;38:12109.
31 Ueberall MA, Essner U, Vila Silván C, *et al*. Comparison of the effectiveness and tolerability of Nabiximols (THC:CBD) Oromucosal spray versus oral Dronabinol (THC) as add-on treatment for severe neuropathic pain in real-world clinical practice: retrospective analysis of the German pain E-Registry. *J Pain Res* 2022;15:267–86.
32 Pochet S, Lechon A-S, Lescrainier C, *et al*. Herb-anticancer drug interactions in real life based on Vigibase, the WHO global database. *Sci Rep* 2022;12.
33 Etges T, Karolia K, Grint T, *et al*. An observational Postmarketing safety Registry of patients in the UK, Germany, and Switzerland who have been prescribed Sativex(®) (THC:CBD, Nabiximols) Oromucosal spray. *Ther Clin Risk Manag* 2016;12:1667–75.

34 Ueberall MA, Horlemann J, Schuermann N, *et al*. Effectiveness and tolerability of Dronabinol use in patients with chronic pain: A retrospective analysis of 12-week open-label real-world data provided by the German pain E-Registry. *Pain Med* 2022;23:1409–22.
35 Ueberall MA, Essner U, Mueller-Schwefe GH. Effectiveness and tolerability of THC:CBD Oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German pain E-Registry. *J Pain Res* 2019;12:1577–604.
36 Prieto González JM, Vila Silván C. Safety and tolerability of Nabiximols Oromucosal spray: a review of real-world experience in observational studies, registries, and case reports. *Expert Rev Neurother* 2021;21:547–58.
37 Ueberall MA, Vila Silván C, Essner U, *et al*. Effectiveness, safety, and tolerability of Nabiximols Oromucosal spray vs typical oral long-acting opioid Analgesics in patients with severe neuropathic back pain: analysis of 6-month real-world data from the German pain E-Registry. *Pain Med* 2022;23:745–60.
38 Spyres MB, Ruha AM, Wax PM, *et al*. Clinical and demographic factors in marijuana toxicity: the toxic Registry experience since 2010. *Clin Toxicol* 2015;53:677.
39 Spyres MB, Farrugia LA, Kang AM, *et al*. The toxicology investigators consortium case Registry-the 2019 annual report. *J Med Toxicol* 2020;16:361–87.
40 Love JS, Karshenas DL, Spyres MB, *et al*. The toxicology investigators consortium case Registry-the 2021 annual report. *J Med Toxicol* 2022;18:267–96.
41 Farrugia LA, Rhyee SH, Campleman SL, *et al*. The toxicology investigators consortium case Registry—the 2017 annual report. *J Med Toxicol* 2018;14:182–211.
42 Jack S. Pharmacovigilance of Cannabis products for medical and non-medical purposes. In: Barnes J, ed. *Pharmacovigilance for Herbal and Traditional Medicines: Advances, Challenges and International Perspectives*. Springer International Publishing, 2022. Available: https://doi.org/10.1007/978-3-031-07275-8_20
43 Vigano A, Moride Y, Hachem Y, *et al*. The Quebec Cannabis Registry: investigating the safety and effectiveness of medical Cannabis. *Cannabis Cannabinoid Res* 2023;8:1106–16.
44 Vickery AW, Roth S, Ernenwein T, *et al*. A large Australian longitudinal cohort Registry demonstrates sustained safety and efficacy of oral medicinal Cannabis for at least two years. *PLoS One* 2022;17:e0272241.
45 Menniti-Ippolito F, Firenzuoli F. The Italian Phytovigilance spontaneous reporting scheme. In: Barnes J, ed. *Pharmacovigilance for Herbal and Traditional Medicines: Advances, Challenges and International Perspectives*. Springer International Publishing, 2022. Available: https://doi.org/10.1007/978-3-031-07275-8_17
46 TGA. Database of adverse event Notifications (DAEN). 2023. Available: https://www.tga.gov.au/safety/safety/safety-monitoring-daen-database-adverse-event-notifications/database-adverse-event-notifications-daen [Accessed 13 Aug 2023].
47 Pozsgai K, Szűcs G, Kőnig-Péter A, *et al*. Analysis of Pharmacovigilance databases for spontaneous reports of adverse drug reactions related to substandard and falsified medical products: A descriptive study. *Front Pharmacol* 2022;13:964399.
48 Ammendolia I, Mannucci C, Cardia L, *et al*. Pharmacovigilance on Cannabidiol as an antiepileptic agent. *Front Pharmacol* 2023;14:1091978.
49 Hall S. Changes in Pharmacovigilance following the end of the Brexit transition. *Ther Adv Drug Saf* 2021;12.
50 Van HunselFGattepaille LM, Westerberg C, *et al*. Reports for Herbal medicines in the global suspected ADR database Vigibase. *Springer* 2022.
51 WHO Vigibase: who's global database signalling harm and pointing to safer use. n.d. Available: https://who-umc.org/vigibase/vigibase-who-s-global-database/
52 Messina S, Solaro C, Righini I, *et al*. Sativex in resistant multiple sclerosis Spasticity: discontinuation study in a large population of Italian patients (SA.FE. study). *PLoS One* 2017;12:e0180651.
53 Freudewald L, Iliescu O, Robert NP, *et al*. Medicinal Cannabis and related products-analyses of quality defects and adverse drug reactions reported by German community pharmacists. *Drug Saf* 2022;1240–1.
54 Matsuda S, Aoki K, Kawamata T, *et al*. Bias in spontaneous reporting of adverse drug reactions in Japan. *PLOS ONE* 2015;10:e0126413.
55 Palleria C, Leporini C, Chimirri S, *et al*. "Limitations and obstacles of the spontaneous adverse drugs reactions reporting: two "challenging" case reports". *J Pharmacol Pharmacother* 2013;4:S66–72.
56 Weber J. Epidemiology of adverse reactions to nonsteroidal Anti-Inflammatory drugs. *Adv Inflamm Res* 1984.
57 Goldman SA. Limitations and strengths of spontaneous reports data. *Clin Ther* 1998;20 Suppl C:C40–4.
58 Biagi C, Montanaro N, Buccellato E, *et al*. Underreporting in Pharmacovigilance: an intervention for Italian Gps (Emilia–Romagna region). *Eur J Clin Pharmacol* 2013;69:237–44.
59 Costa C, Abeijon P, Rodrigues DA, *et al*. Factors associated with Underreporting of adverse drug reactions by patients: a systematic review. *Int J Clin Pharm* 2023;45:1349–58.
60 Candore G, Monzon S, Slattery J, *et al*. The impact of mandatory reporting of non-serious safety reports to Eudravigilance on the detection of adverse reactions. *Drug Saf* 2022;45:83–95.
61 Hammad TA, Afsar S, McAvoy LB, *et al*. Aspects to consider in causality assessment of safety signals: broadening the thought process. *Front Drug Saf Regul* 2023;3.
62 Crescioli G, Lombardi N, Bettiol A, *et al*. Adverse events following Cannabis for medical use in Tuscany: an analysis of the Italian Phytovigilance database. *Br J Clin Pharmacol* 2020;86:106–20.
63 Gottschling S, Ayonrinde O, Bhaskar A, *et al*. Safety considerations in Cannabinoid-based medicine. *Int J Gen Med* 2020;13:1317–33.
64 Grzeskowiak LE, Grieger JA, Andraweera P, *et al*. The deleterious effects of Cannabis during pregnancy on neonatal outcomes. *Med J Aust* 2020;212:519–24.
65 Lindquist M. The WHO global ICSR database system: basic facts. *Drug Inf J* 2008;42:409–19.
66 WHO. Guideline for using Vigibase data in studies. Uppsula monitoring centre; 2023. Available: https://who-umc.org/media/05kldqpj/guidelineusingvigibaseinstudies.pdf
67 Erridge S, Salazar O, Kawka M, *et al*. An initial analysis of the UK medical Cannabis Registry: outcomes analysis of first 129 patients. *Neuropsychopharmacol Rep* 2021;41:362–70.
68 Olsson F, Erridge S, Tait J, *et al*. An observational study of safety and clinical outcome measures across patient groups in the United Kingdom medical Cannabis Registry. *Expert Rev Clin Pharmacol* 2023;16:257–66.
69 Ergisi M, Erridge S, Harris M, *et al*. An updated analysis of clinical outcome measures across patients from the UK medical Cannabis Registry. *Cannabis Cannabinoid Res* 2023;8:557–66.
70 Wang C, Erridge S, Holvey C, *et al*. Assessment of clinical outcomes in patients with Fibromyalgia: analysis from the UK medical Cannabis Registry. *Brain Behav* 2023;13:e3072.
71 Pillai M, Erridge S, Bapir L, *et al*. Assessment of clinical outcomes in patients with post-traumatic stress disorder: analysis from the UK medical Cannabis Registry. *Expert Rev Neurother* 2022;22:1009–18.
72 Mangoo S, Erridge S, Holvey C, *et al*. Assessment of clinical outcomes of medicinal Cannabis therapy for depression: analysis from the UK medical Cannabis Registry. *Expert Rev Neurother* 2022;22:995–1008.
73 Erridge S, Kerr-Gaffney J, Holvey C, *et al*. Clinical outcome analysis of patients with autism spectrum disorder: analysis from the UK medical Cannabis Registry. *Ther Adv Psychopharmacol* 2022;12.
74 Rifkin-Zybutz R, Erridge S, Holvey C, *et al*. Clinical outcome data of anxiety patients treated with Cannabis-based medicinal products in the United kingdom: a cohort study from the UK medical Cannabis Registry. *Psychopharmacology (Berl)* 2023;240:1735–45.
75 Erridge S, Holvey C, Coomber R, *et al*. Clinical outcome data of children treated with Cannabis-based medicinal products for treatment resistant epilepsy-analysis from the UK medical Cannabis Registry. *Neuropediatrics* 2023;54:174–81.
76 Tait J, Erridge S, Holvey C, *et al*. Clinical outcome data of chronic pain patients treated with Cannabis-based oils and dried flower from the UK medical Cannabis Registry. *Expert Rev Neurother* 2023;23:413–23.
77 Kawka M, Erridge S, Holvey C, *et al*. Clinical outcome data of first cohort of chronic pain patients treated with Cannabis-based Sublingual oils in the United kingdom: analysis from the UK medical Cannabis Registry. *J Clin Pharmacol* 2021;61:1545–54.
78 Dalavaye N, Erridge S, Nicholas M, *et al*. The effect of medical Cannabis in inflammatory bowel disease: analysis from the UK medical Cannabis Registry. *Expert Rev Gastroenterol Hepatol* 2023;17:85–98.
79 Tait J, Erridge S, Sodergren MH. UK medical Cannabis Registry: a patient evaluation. *J Pain Palliat Care Pharmacother* 2023;37:170–7.
80 Ergisi M, Erridge S, Harris M, *et al*. UK medical Cannabis Registry: an analysis of clinical outcomes of medicinal Cannabis therapy for generalized anxiety disorder. *Expert Rev Clin Pharmacol* 2022;15:487–95.
81 Nicholas M, Erridge S, Bapir L, *et al*. UK medical Cannabis Registry: assessment of clinical outcomes in patients with headache disorders. *Expert Rev Neurother* 2023;23:85–96.

82 Erridge S, Holvey C, Coomber R, *et al*. Clinical outcome data of children treated with Cannabis-based medicinal products for treatment resistant epilepsy—analysis from the UK medical Cannabis Registry. *Neuropediatrics* 2023;54:174–81.
83 Harris M, Erridge S, Ergisi M, *et al*. UK medical Cannabis Registry: an analysis of clinical outcomes of medicinal Cannabis therapy for chronic pain conditions. *Expert Rev Clin Pharmacol* 2022;15:473–85.
84 Nimalan D, Kawka M, Erridge S, *et al*. UK medical Cannabis Registry palliative care patients cohort: initial experience and outcomes. *J Cannabis Res* 2022;4:3.
85 Schlag AK, Lynskey M, Fayaz A, *et al*. Characteristics of people seeking prescribed Cannabinoids for the treatment of chronic pain: evidence from project twenty 21. *Front Pain Res (Lausanne)* 2022;3.
86 Tchetvertakov G. Emerald clinics signs Cannabis RWE contract with canopy growth's UK subsidiary spectrum BIOMEDICAL. n.d. Available: https://smallcaps.com.au/emerald-clinics-cannabis-rwe-canopy-growth-uk-subsidiary-spectrum-biomedical/
87 Herdeiro MT, Figueiras A, Pol??nia J, *et al*. Physicians' attitudes and adverse drug reaction reporting. *Drug Saf* 2005;28:825–33.
88 Belton KJ, Lewis SC, Payne S, *et al*. Attitudinal survey of adverse drug reaction reporting by medical practitioners in the United Kingdom British Journal of clinical pharmacology. *Br J Clin Pharmacol* 1995;39:223–6.
89 Bäckström M, Mjörndal T, Dahlqvist R, *et al*. Attitudes to reporting adverse drug reactions in northern Sweden. *Eur J Clin Pharmacol* 2000;56:729–32.
90 World Health Organization. Quality A, Safety of Medicines T. Safety of Medicines: a Guide to Detecting and Reporting Adverse Drug Reactions: Why Health Professionals Need to Take Action. Geneva: World Health Organization, 2002.
91 Lunghi C, Fusaroli M, Giunchi V, *et al*. What is the safety profile of Cannabis-based medications? analysis of the post-marketing signals from the FDA adverse event reporting system. *Drug Saf* 2022;45:1242–3.
92 Simon TA, Simon JH, Heaning EG, *et al*. Delta-8, a Cannabis-derived Tetrahydrocannabinol isomer: evaluating case report data in the food and Drug Administration adverse event reporting system (FAERS) database. *Drug Healthc Patient Saf* 2023;15:25–38.
93 Piracha Z, Ramnarain R. Analyzing Medwatch data in an effort to assess Dronabinol post-marketing safety. *CTBEB* 2017;3:64–5.
94 Guevara CO. Observational safety study of THC: CBD Oromucosal spray (Sativex) in multiple sclerosis patients with Spasticity. *Clin Exp Pharmacol* 2015;05.
95 Jack S, Huff SP, Abramovici H. n.d. Inter-year comparison of adverse reactions associated with legal Cannabis products reported to health Canada, 2018-2019 to 2021. *Drug Saf*2022:1313.
96 Trojan A, Breitkopf S, Pittl S, *et al*. Swisscanon - scientific patient Registry for medicinal Cannabis in oncology including ePROs - trial in progress. In: *Swiss Oncology and Hematology Congress*. Basel Switzerland: EMH Swiss Medical Publishers Ltd, 2022. Available: https://smw.ch/fileadmin/content/supplements/SMW-152-40034.pdf http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emexa&NEWS=N&AN=639854642
97 Mahabir VK, Merchant JJ, Smith C, *et al*. Medical Cannabis use in the United States: a retrospective database study. *J Cannabis Res* 2020;2:32.
98 O'Brien K, Beilby J, Frans M, *et al*. Preliminary findings from project Twenty21 Australia: an observational study of patients prescribed medicinal Cannabis for chronic pain, anxiety, Posttraumatic stress disorder and multiple sclerosis. *Drug Sci Policy Law* 2023;9.
99 Sakal C, Lynskey M, Schlag AK, *et al*. Developing a real-world evidence base for prescribed Cannabis in the United kingdom: preliminary findings from project Twenty21. *Psychopharmacology (Berl)* 2022;239:1147–55.
100 Aviram J, Pud D, Schiff-Keren B, *et al*. The Israeli multi-center Registry of medical Cannabis (MC) for chronic pain: Current findings. *Rambam Maimonides Med J* 2018.
101 Patti F, Messina S, Solaro C, *et al*. Efficacy and safety of Cannabinoid Oromucosal spray for multiple sclerosis Spasticity. *J Neurol Neurosurg Psychiatry* 2016;87:944–51.