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ORIGINAL RESEARCH ARTICLE

Cannabis and Cannabinoid-Related Suspected Adverse Drug Reactions: Global Patterns and Cross-National Analysis Based on VigiBase® Data

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Abstract

Background and Objectives Despite increasing global use of cannabis and cannabinoids, comprehensive data on their safety profile remain limited. This study aimed to examine global patterns in pharmacovigilance reports associated with cannabis and cannabinoids, irrespective of regulatory status or context of use.

Methods VigiBase®, the World Health Organisation's global database of individual case safety reports (ICSRs), was analysed in a retrospective cross-sectional study from 1 January 2020 to 31 December 2024 (data extraction: 19 February 2025). "Cannabis ICSRs" included at least one mention of *Cannabis sativa* or cannabinoids. Temporal and geographical distributions, reported substances, and suspected adverse drug reactions (ADRs) were assessed. A single ICSR may include multiple substance mentions and several suspected ADRs.

Results Among 7,007,689 records, 9983 cannabis ICSRs were identified across 44 countries, comprising 12,538 cannabis or cannabinoid mentions and 27,593 suspected ADRs. The median age was 29 years, with 62.7% males. Most cases were serious (68.5%), including hospitalisation (45.9%) and death (28.6%). The highest reporting rates relative to national ICSR numbers were observed in France, Greece, and the USA. The most frequently reported substances were *Cannabis sativa* (n = 5951) and cannabidiol (n = 2967). Suspected ADRs were predominantly psychiatric (29.2%) and nervous system disorders (16.8%), with gastrointestinal, respiratory, and cardiac disorders less common (6.4%, 3.6%, and 2.8%).

Conclusions This study provides the first comprehensive global overview of suspected ADRs associated with cannabis and cannabinoids. The predominance of serious cases, particularly psychiatric and nervous system reactions, highlights important safety considerations, offering key insights to inform clinical practice and risk assessment worldwide.

1 Introduction

Cannabis is the most widely used psychoactive substance worldwide, with an estimated 244 million people reporting past-year use in 2023 [1]. In 2026, it remains an illicit drug scheduled under the 1961 United Nations (UN) single convention on narcotic drugs [2]. However, its legal status has evolved significantly, particularly since the late 2010s, with the marketing of cannabinoid-based medicines and the expansion of authorised medical cannabis use [1, 3–6]. Canada, like Uruguay before, has fully legalised both medical

Key Points

Global pharmacovigilance data identified a substantial proportion of serious suspected adverse drug reactions (ADRs) associated with cannabis and cannabinoids, including cases resulting in hospitalisation and death.

Psychiatric and nervous system disorders were the most frequently reported suspected ADRs, with *Cannabis sativa* most commonly involved and distinct patterns observed across substances.

These findings should be interpreted with caution due to cross-national variability in reporting practices, heterogeneity in causality assessment, and the inherent limitations of spontaneous pharmacovigilance data.

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and recreational cannabis, whereas other countries, including those in Europe, such as Germany, have implemented varying degrees of regulated access.

The effects of cannabis and cannabinoids are mediated through activation of the endocannabinoid system, a complex regulatory network involving specific cannabinoid G-protein-coupled receptors known as CB1 and CB2 and interactions with multiple neurotransmission systems [7]. The primary active components of *Cannabis sativa* are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Both are present in various cannabis products, in varying concentrations and ratios, which can be used for different purposes in different contexts. One such context is the pursuit of psychoactive effects through recreational use of THC products. However, THC also has therapeutic properties and is used in certain medical treatments. Another context involves the use of CBD products, notably for wellness and therapeutic purposes. The CBD market has expanded rapidly in recent years, alongside increasing approvals of medical cannabis across countries. Both THC and CBD are used as active ingredients in medicinal products approved for several indications [8]. Nabiximols, an equimolar mixture of THC and CBD (marketed as Sativex®), is approved for the treatment of muscle spasticity associated with multiple sclerosis in many countries, notably in Europe but also in America, Canada and Brazil. In the European Union (EU), North America, the UK and other countries including Australia, CBD (Epidiolex®/Epidyolex®) is approved for use in seizures associated with Lennox-Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex. Dronabinol (Marinol®, Syndros®), a synthetic form of THC, and nabilone (Cesamet®, Canemes®), a synthetic analogue of THC, are approved for anorexia associated with weight loss in patients with AIDS, as well as for nausea and vomiting related to cancer chemotherapy [3, 9]. While anecdotal reports and lived experiences suggest that cannabis may help manage various symptoms, its use continues to expand, yet robust evidence supporting efficacy for many therapeutic indications remains limited [10].

The main safety concerns associated with cannabis have been described in the literature and include neuropsychological disorders (e.g., psychosis, affective disorders, anxiety, sleep disorders, cognitive impairment), as well as other clinical disorders (e.g., respiratory issues, cardiovascular diseases, gastrointestinal disorders) [11]. However, comprehensive knowledge of the overall safety profile of cannabis and cannabinoid-based products, regardless of regulatory status, remains limited, particularly in real-world settings, given their increasing market availability and evolving patterns and contexts of use [12]. To address this gap, this study aimed to examine global patterns and trends in spontaneous reports of suspected adverse drug reactions (ADRs) associated with cannabis and its derivatives, irrespective of their regulatory status or context of use, based on individual case safety reports (ICSRs) recorded in the international pharmacovigilance database VigiBase® between 2020 and 2024.

2 Methods

This study was carried out in accordance with international standards, following the STROBE statement for observational studies [13].

2.1 Data Source

Suspected ADRs related to the use of cannabis and cannabinoids were identified from VigiBase®, the World Health Organisation (WHO) global database of ICSRs, managed and maintained by the Uppsala Monitoring Center (UMC) [14]. Since its inception in 1968, VigiBase® has recorded ICSRs submitted by national pharmacovigilance systems from the 182 countries participating in the WHO Programme for International Drug Monitoring (PIDM) [15].

Given the concomitant pandemic situation worldwide during the study period and the associated increase in reporting rates, COVID-19 vaccine-related cases were excluded from the total number of ICSRs to avoid distorting the estimates. Individual case safety reports include patient characteristics (age and sex), administrative details (e.g., country of origin, reporter qualification, reporting dates), and any suspect or concomitant drugs coded using the WHO Drug Global terminology, along with all related suspected ADRs. The latter are classified according to the Medical Dictionary for Regulatory Activities (MedDRA), which comprises several hierarchical levels, including lowest-level term (LLT) and preferred term (PT) to high-level group term (HLGT) and system organ classes (SOCs) [16].

Access to ICSRs was provided through VigiLyze™, following contributions from the Toulouse Pharmacovigilance and Addictovigilance Centres to VigiBase®, as part of their regulatory vigilance activities [17]. Numerous studies have used VigiBase® data, particularly on psychoactive substances [18–21].

2.2 Inclusion Process of Cannabis ICSRs

Eligible ICSRs were those recorded in VigiBase® between January 1, 2020, and December 31, 2024, and associated with at least one mention of cannabis or cannabinoid recorded as "suspect" or "interacting" from the following list of active ingredients: 8-tetrahydrocannabinol (8-THC), cannabidiol, cannabidiol;dronabinol, cannabinol, *Cannabis sativa*, delta-9-tetrahydrocannabinolic acid, dronabinol

(synonym in VigiBase® for 9-tetrahydrocannabinol, THC), nabilone. In this article, "cannabidiol;dronabinol" and "THC:CBD" are used as synonymous.

Individual case safety reports were included for analysis only if information on age, sex, seriousness, reporter qualification, and country of origin was available; consequently, no missing data were present for these variables. No restrictions were applied regarding the type of adverse reactions, and all MedDRA terms across all SOCs were considered. Reports related to subjects aged < 2 years were excluded, as cases involving young children (in particular, accidental paediatric exposures) were outside the scope of this study.

Data extraction was conducted on February 19, 2025, and duplicate reports were automatically identified. All ICSRs included in the present analysis are referred to as "Cannabis ICSRs".

2.3 Statistical Analysis

A descriptive analysis was conducted on the complete dataset, with drug-specific analyses. Patterns of suspected ADRs associated with each studied drug were established based on their categorisations by SOC and further detailed using PTs.

Quantitative variables were described using the median, first and third quartiles (Q1 and Q3), and total range. Qualitative variables were described using frequencies.

Additionally, to account for the background reporting in VigiBase®, rates were calculated by dividing the crude counts of cannabis ICSRs in a given year or country by the total number of ICSRs reported in VigiBase® for the same year or country.

Mekko charts were drawn to represent the distribution of each studied drug across countries having over 100 ICSRs, based on frequencies calculated as the proportion of ICSRs for a given drug relative to the total ICSRs in that country. These charts encode qualitative variables separately, with mark width and height representing relative frequencies. Results were contextualised by comparison with data from 2015–2019, as previously analysed [22].

To minimise the risk of overestimation, ICSRs were selected as the statistical unit of analysis, as a single report can contain several references of the same cannabinoid substance. A sensitivity analysis was conducted on ICSRs reporting only cannabis or cannabinoids, excluding any concomitant exposures.

All analyses were performed using R version 4.5.0 (R Core Team, 2025; https://cran.r-project.org).

3 Results

3.1 Characteristics of ICSRs

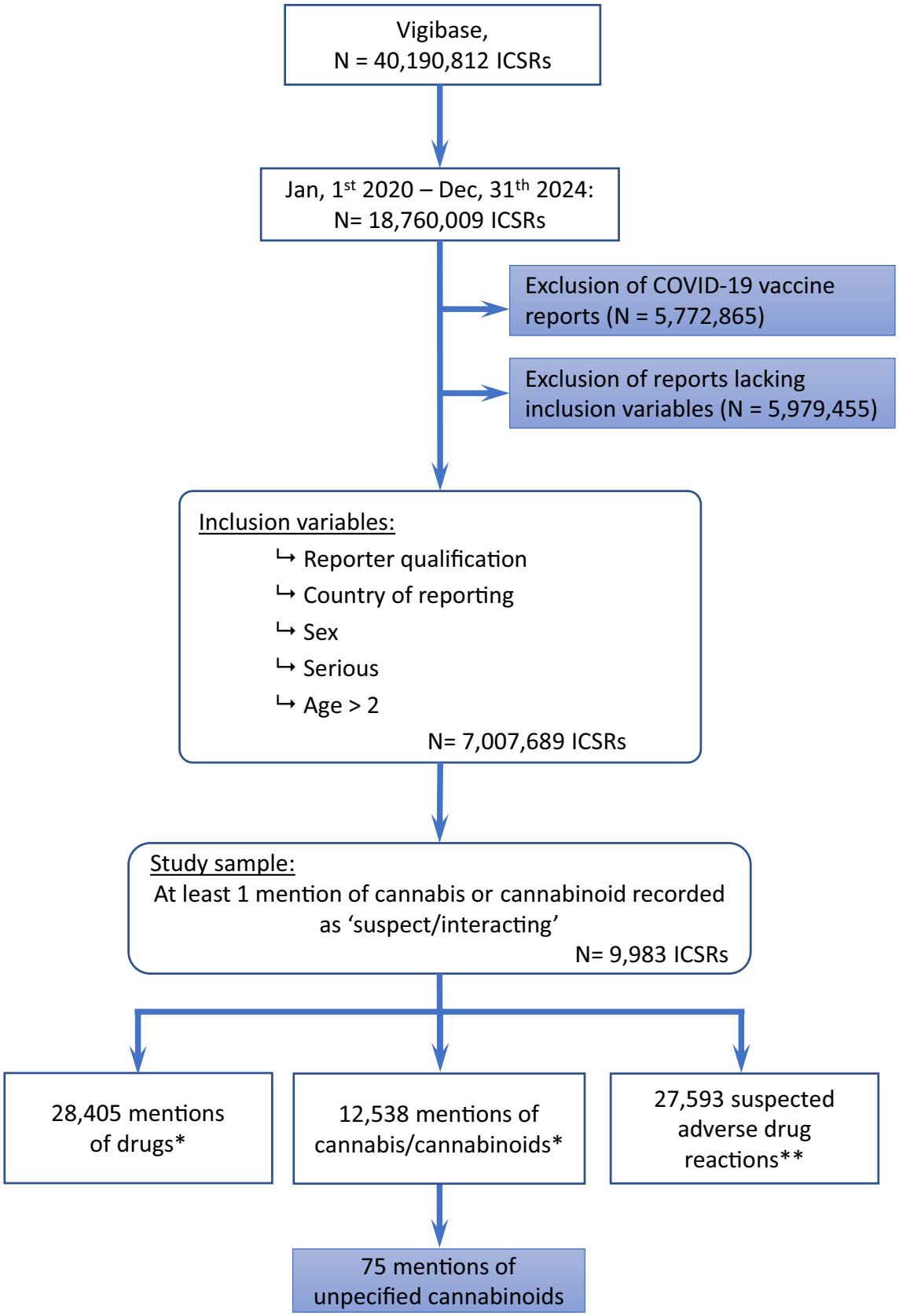
Of the 40,190,812 ICSRs recorded in VigiBase®, including 18,760,009 between 2020 and 2024, 7,007,689 contained complete data for all inclusion variables (Fig. 1). Among these, 9983 ICSRs contained at least one mention of cannabis or its derivatives recorded as "suspect" or "interacting", including 2251 reports in 2024. Details of the ICSRs included in this study are summarised in Table 1. The concerned subjects had a median age of 29 years and were more frequently male (6261 ICSRs; 62.7%). Most ICSRs were classified as serious (6839; 68.5%), including 45.9% (n = 3197) and 28.6% (n = 1953) meeting the seriousness criteria of "hospitalisation" and "death", respectively. Regarding serious cases, hospitalisation was most frequently reported with CBD (33.5%) and *Cannabis sativa* (33.1%), whereas deaths were most often associated with *Cannabis sativa* and dronabinol (23.4%), followed by CBD (14.7%).

Annual rates during the study period ranged from 7.6 per 10,000 total ICSRs in 2020 to 12.3 per 10,000 in 2024, with peak values observed in 2022 (21.7) and 2023 (18.4) (Fig. 2). France reported the highest crude number of included ICSRs, with 4692 records (Fig. 3) and the highest rate of cannabis ICSRs relative to total national ICSRs (148.4 per 10,000), followed by Greece (105.9 per 10,000) and the USA (17.1 per 10,000).

Individual case safety reports involving cannabis or cannabinoids without concomitant exposures accounted for 45.1% of the dataset. These cases had a higher proportion of females and individuals aged < 18 years, more frequent reporting of CBD by consumers/non-health professionals, and a larger share of cases originating from the USA (Supplementary Table 1).

3.2 Drug Reports

The included ICSRs were associated with 28,405 mentions of suspect/interacting drugs including 12,538 mentions of cannabinoids, with an average of 2.4 individual drugs and 1.0 individual cannabinoid per ICSR (SD: 2.5, and 1, respectively) (Fig. 1 and Table 1). The primary drug was *Cannabis sativa* (n = 6217; 5951 ICSRs), followed by CBD (n = 4741; 2967 ICSRs), THC:CBD (n = 715; 530 ICSRs), dronabinol (n = 401; 304 ICSRs), and 8-THC (n = 359; 313 ICSRs). The dataset also included 18 mentions of delta-9-tetrahydrocannabinolic acid (17 ICSRs), 11 mentions of cannabinol (11 ICSRs) and 2 mentions of nabilone (2 ICSRs). Notably, 62 ICSRs reported both a specific cannabinoid and, concurrently, not otherwise specified cannabinoids (e.g., "cannabinoids NOS"), totalling 75 mentions.


Vigibase,
N = 40,190,812 ICSRs
Jan, 1st 2020 – Dec, 31th 2024:
N= 18,760,009 ICSRs
Exclusion of COVID-19 vaccine reports (N = 5,772,865)
Exclusion of reports lacking inclusion variables (N = 5,979,455)
Inclusion variables:
↳ Reporter qualification
↳ Country of reporting
↳ Sex
↳ Serious
↳ Age > 2
N= 7,007,689 ICSRs
Study sample:
At least 1 mention of cannabis or cannabinoid recorded as 'suspect/interacting'
N= 9,983 ICSRs
28,405 mentions of drugs*
12,538 mentions of cannabis/cannabinoids*
27,593 suspected adverse drug reactions**
75 mentions of unpecified cannabinoids

◂**Fig. 1** Flow-chart. *An individual case safety report (ICSR) may include multiple suspected drugs; therefore, the total number of cannabis/cannabinoid and drug mentions exceeds the total number of ICSRs. **An ICSR may include multiple suspected adverse drug reactions (ADRs); therefore, the total number of ADR mentions exceeds the total number of ICSRs

The Mekko chart highlights the predominance of *Cannabis sativa* in France (88.4%), CBD in Italy (60.9%) and THC:CBD in Greece (97.5%) (Fig. 4a). In contrast, the distribution of drugs was more balanced between CBD and *Cannabis sativa* in the USA (53.3% and 36.2%, respectively) and the UK (54.5% and 31.6%, respectively), with THC:CBD negligible in the USA and representing 9.1% in the UK. In Germany, THC:CBD (45.1%) was followed by CBD (36.3%) reflecting a relatively balanced distribution. This distribution of cannabinoids remained relatively stable compared with the 2015–2019 period in Germany and the UK, unlike in other countries (Fig. 4b). For instance, the proportion of THC:CBD in Italy decreased in favour of CBD.

3.3 Suspected Adverse Drug Reactions (ADRs) Reported

All ICSRs included were associated with 27,593 suspected ADRs (Fig. 1 and Table 2). The most frequent SOC was psychiatric disorders (n = 8069; 29.2%), predominantly comprising PTs related to substance use disorders (including drug abuse, drug dependence, substance use disorder, substance abuse) (4810/8069; 17.4%). Overall, 43.4% of suspected ADRs related to *Cannabis sativa* belonged to this SOC (n = 6800); compared with 24.6% for 8-THC (n = 349) and 18.9% for dronabinol (n = 186) (Fig. 5). Within this SOC, substance use disorders were the most frequent PTs for all cannabinoids except THC:CBD (Fig. 6a). For the latter, the main reported PTs were not in the top ten PTs of the psychiatric SOC and included insomnia, confusional state and euphoria (data not shown).

Nervous system disorders were the second most frequent SOC overall (4628 reactions, 16.8%; Table 2). They were the primary SOC for ADRs reported with CBD (22.0% among ADRs with this drug) and THC:CBD (19.3%; Fig. 5). Cannabidiol was most frequently associated with seizure, accounting for 46.2% of CNS disorders related to this product (Fig. 6b). In contrast, THC:CBD was mainly associated with dizziness (33.3% of CNS disorders within this product), and 8-THC with somnolence (17.9%).

Injury, poisoning and procedural complications accounted for 11.4% of total suspected ADRs (n = 3145). For *Cannabis sativa*, the most frequent PTs were toxicity/poisoning (27.2%), misuse (12.6%), and overdose (5.6%), whereas for CBD they were primarily off-label use (28.5%), administration interrupted (15.3%), and product dose omission issue (12.5%) (Fig. 6c).

Then, general disorders and administration site conditions represented 10.4% of total suspected ADRs (n = 2869), largely represented by death (n = 560; 2.0% of total suspected ADRs) and drug ineffective (n = 298; 1.1%). In proportion by product, death represented 0.2%, 1.2%, 0.1% of CBD, dronabinol and *Cannabis sativa*-related suspected reactions overall, respectively; and 30.0%, 16.2% and 14.0% of the same cannabinoids within this SOC (Fig. 6d). Gastrointestinal disorders represented 6.4% of total suspected ADRs (n = 1769), with vomiting/nausea being the major reactions. These reactions were mainly related to 8-THC (totalising 64.3% of gastrointestinal disorders among this product), dronabinol (46.0%) and *Cannabis sativa* (41.8%) (Fig. 6e). Among CBD-related gastrointestinal suspected ADRs, diarrhea predominated (29.2%). Hyperemesis syndrome accounted for 8.1% of *Cannabis sativa*-related gastrointestinal disorders (3.3% of all suspected ADRs in this SOC) and was rarely reported with other cannabinoids.

Finally, cardiac and vascular disorders represented 2.8% and 1.1%, respectively, including 77 suspected ADRs of acute coronary syndrome (including terms such as coronary artery spasm, vasoconstriction, acute myocardial infarction). Overall, 61 cases of stroke were also reported in the nervous system disorders SOC, giving a total of 138 cases of major acute cardiovascular events (MACE), representing 0.5% of total suspected ADRs.

4 Discussion

In this study using VigiBase® records, nearly 10,000 safety reports related to cannabis and cannabinoids were included over five years, originating from 44 countries worldwide. The trend in cannabis- or cannabinoid-related ICSRs observed in VigiBase® between 2020 and 2024 cannot be solely explained by overall VigiBase® reporting patterns. Indeed, the proportion of cannabis ICSRs relative to total ICSRs increased from 2020 to 2022 before declining in 2023–2024, indicating a substance-specific pattern. The observed rise in reports may partly mirror global trends in cannabis use, which moved from an estimated 228 million users in 2002 (the highest estimate to that date) to 244 million users in 2023 [1, 23]. These observations reflect post-COVID market recovery and policy changes in many countries [1, 24]. Increasing popularity of cannabinoids and particularly CBD products, including for wellbeing purposes, may also contribute to the enhanced acceptability of recreational cannabis with impacts on global reported suspected ADRs [25].

The majority of ICSRs included in this study originated from France (47.0%) and the USA (37.8%), with smaller

Table 1 Characteristics of cannabis ICSRs recorded in VigiBase® between 2020 and 2024 and the related subjects: overall results and details by drug

	Total	*Cannabis sativa*	Cannabidiol	Cannabidiol-Dronabinol	8-THC	Dronabinol	Other cannabinoids
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Subjects (*n*)	9983 (100)	5951 (59.6)	2967 (29.7)	530 (5.3)	313 (3.1)	304 (3.0)	30 (0.3)
Sex							
Male	6261 (62.7)	4212 (70.8)	1611 (54.3)	199 (37.5)	143 (45.7)	164 (53.9)	17 (56.7)
Female	3722 (37.3)	1739 (29.2)	1356 (45.7)	331 (62.5)	170 (54.3)	140 (46.1)	13 (43.3)
Age (y)							
Median (Q1–Q3)	29 (19–43)	31 (22–42)	18 (10–33)	56 (47–64)	36 (26–49)	44 (29–61)	32 (28–48)
Min–Max	2–96	2–91	2–96	14–92	2–83	4–92	14–84
Age class (y)							
< 18	1951 (19.5)	504 (8.5)	1402 (47.3)	2 (0.4)	27 (8.6)	18 (5.9)	1 (3.3)
[18–25]	1932 (19.4)	1379 (23.2)	488 (16.4)	3 (0.6)	42 (13.4)	33 (10.9)	6 (20.0)
[25–35]	2139 (21.4)	1601 (26.9)	392 (13.2)	23 (4.3)	76 (24.3)	60 (19.7)	11 (36.7)
[35–45]	1699 (17.0)	1251 (21.0)	284 (9.6)	74 (14.0)	69 (22.0)	45 (14.8)	4 (13.3)
[45–55]	1091 (10.9)	690 (11.6)	179 (6.0)	148 (27.9)	47 (15.0)	47 (15.5)	3 (10.0)
[55–65]	672 (6.7)	365 (6.1)	104 (3.5)	148 (27.9)	26 (8.3)	35 (11.5)	2 (6.7)
≥ 65	499 (55.0)	161 (2.7)	118 (4.0)	132 (24.9)	26 (8.3)	66 (21.7)	3 (10.0)
ICSR							
Serious case (total)	6839 (68.5)	4331 (72.8)	2005 (67.6)	105 (19.8)	260 (83.1)	177 (58.2)	25 (83.3)
Caused/prolonged hospitalisation	3137 (49.5)	1967 (33.1)	995 (33.5)	57 (10.8)	93 (29.7)	52 (17.1)	6 (20.0)
Death	1953 (28.6)	1393 (23.4)	435 (14.7)	19 (3.6)	28 (8.9)	71 (23.4)	17 (56.7)
Life threatening	247 (3.6)	177 (3.0)	32 (1.1)	1 (0.2)	29 (9.3)	8 (2.6)	2 (6.7)
Disabling/incapacitating	71 (1.0)	22 (0.4)	21 (0.7)	1 (0.2)	22 (7.0)	3 (1.0)	2 (6.7)
Congenital anomaly/birth defect	6 (0.1)	3 (0.1)	2 (0.1)	0 (0)	0 (0)	1 (0.3)	0 (0)
Other medically important condition	3744 (54.7)	2114 (35.5)	1406 (47.4)	47 (8.9)	105 (33.5)	96 (31.6)	11 (36.7)
Year							
2020	934 (9.4)	579 (9.7)	187 (6.3)	132 (24.9)	2 (0.6)	37 (12.2)	2 (6.7)
2021	1373 (13.8)	1047 (17.6)	231 (7.8)	67 (12.6)	23 (7.3)	35 (11.5)	7 (23.3)
2022	2616 (26.2)	1497 (25.2)	899 (30.3)	27 (5.1)	134 (42.8)	88 (28.9)	4 (13.3)
2023	2809 (28.1)	1683 (28.3)	921 (31.0)	34 (6.4)	87 (27.8)	97 (31.9)	11 (36.7)
2024	2251 (22.5)	1148 (19.3)	729 (24.6)	270 (50.9)	67 (21.4)	47 (15.5)	6 (20.0)
Country (having at least 20 ICSRs)							
France	4692 (47.0)	4248 (71.4)	324 (10.9)	0 (0)	41 (13.1)	153 (50.3)	3 (10.0)
USA	3771 (37.8)	1377 (23.1)	2028 (68.4)	0 (0)	252 (80.5)	108 (35.5)	21 (70.0)
Germany	302 (3.0)	22 (0.4)	111 (3.7)	138 (26.0)	11 (3.5)	24 (7.9)	0 (0)

Table 1 (continued)

	Total	*Cannabis sativa*	Cannabidiol	Cannabidiol-Dronabinol	8-THC	Dronabinol	Other cannabinoids
	N (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Greece	204 (2.0)	0 (0)	5 (0.2)	199 (37.5)	0 (0)	0 (0)	0 (0)
UK	195 (2.0)	66 (1.1)	114 (3.8)	19 (3.6)	3 (1.0)	3 (1.0)	3 (10.0)
Italy	137 (1.4)	19 (0.3)	84 (2.8)	29 (5.5)	4 (1.3)	2 (0.7)	0 (0)
Argentina	92 (0.9)	0 (0)	88 (3.0)	0 (0)	0 (0)	0 (0)	0 (0)
Spain	91 (0.9)	3 (0.1)	73 (2.5)	15 (2.8)	0 (0)	0 (0)	0 (0)
Colombia	79 (0.8)	6 (0.1)	25 (0.8)	45 (8.5)	0 (0)	3 (1.0)	0 (0)
Thailand	65 (0.7)	64 (1.1)	0 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)
Peru	51 (0.5)	51 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Brazil	48 (0.5)	10 (0.2)	37 (1.2)	0 (0)	0 (0)	0 (0)	1 (3.3)
Australia	42 (0.4)	26 (0.4)	9 (0.3)	2 (0.4)	1 (0.3)	3 (1.0)	1 (3.3)
Sweden	40 (0.4)	1 (0)	2 (0.1)	36 (6.8)	0 (0)	2 (0.7)	0 (0)
Austria	28 (0.3)	0 (0)	7 (0.2)	18 (3.4)	0 (0)	2 (1.0)	1 (3.3)
Reporter qualification							
Physician	4765 (47.7)	3923 (65.9)	603 (20.3)	136 (25.7)	26 (8.3)	129 (42.4)	6 (20.0)
Consumer/non-health professional	2661 (26.7)	459 (7.8)	1633 (55.0)	309 (58.3)	220 (70.3)	49 (16.1)	8 (26.7)
Other health professionals	1675 (16.8)	669 (11.3)	596 (20.1)	280 (52.8)	52 (16.6)	83 (27.3)	17 (56.7)
Pharmacist	1281 (12.8)	929 (15.6)	248 (8.4)	22 (4.2)	15 (4.8)	82 (27.0)	0 (0)
Lawyer	16 (0.2)	14 (0.2)	1 (0)	0 (0)	0 (0)	1 (0.3)	0 (0)
Completeness score							
Median (Q1–Q3)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.7 (0.5–0.9)	0.4 (0.3–0.5)	0.4 (0.3–0.5)	0.3 (0.3–0.4)
Range	0.2–1	0.2–1	0.2–1	0.2–1	0.2–1	0.2–1	0.2–0.6
Number of different suspect cannabinoids per ICSR							
Median (Q1–Q3)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–1)	1 (1–2)
Range	1–4	1–4	1–4	1–3	1–3	1–4	1–4
Number of different suspect drugs per ICSR							
Median (Q1–Q3)	2 (1–3)	3 (2–4)	1 (1–1)	1 (1–1)	2 (1–4)	1 (1–2)	4 (1–6)
Range	1–28	1–28	1–25	1–8	1–23	1–28	1–14

8-THC 8-tetrahydrocannabinol, *ICSRs* individual case safety reports

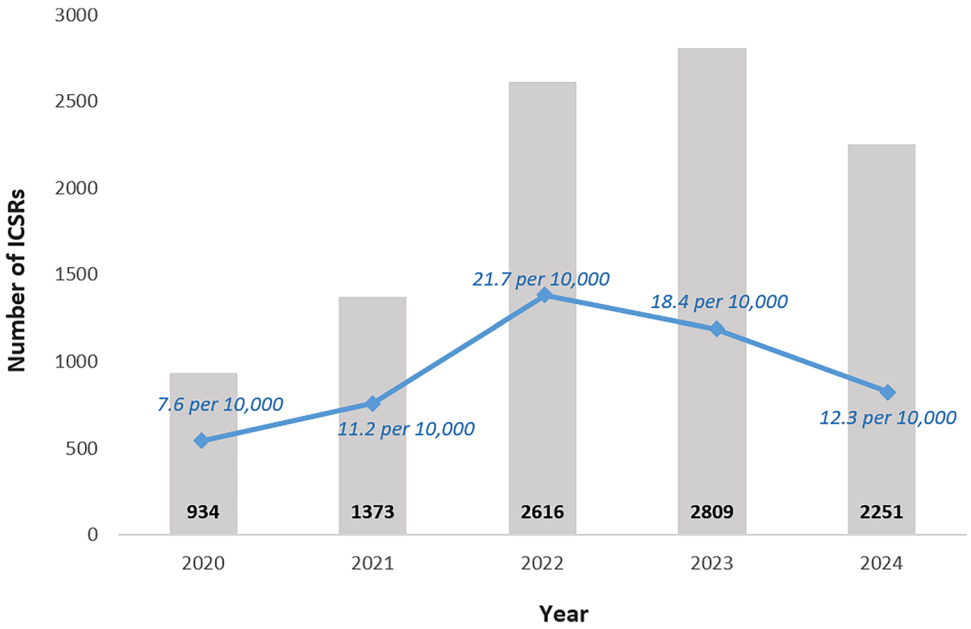


Fig. 2 Annual numbers (histogram, bold values) of cannabis individual case safety reports (ICSRs) recorded in VigiBase® and the corresponding annual rates per 10,000 ICSRs (curve, italic values). Regarding the denominator, ICSRs relative to COVID-19 vaccines were excluded from the total number of ICSRs to prevent from distortion of estimates. Legend: The 2251 ICSRs with at least one mention of suspect cannabis or derivatives included in 2024 relative to the 1,825,983 reports recorded the same year corresponded to a rate of 12.3 "cannabis ICSRs" per 10,000 ICSRs

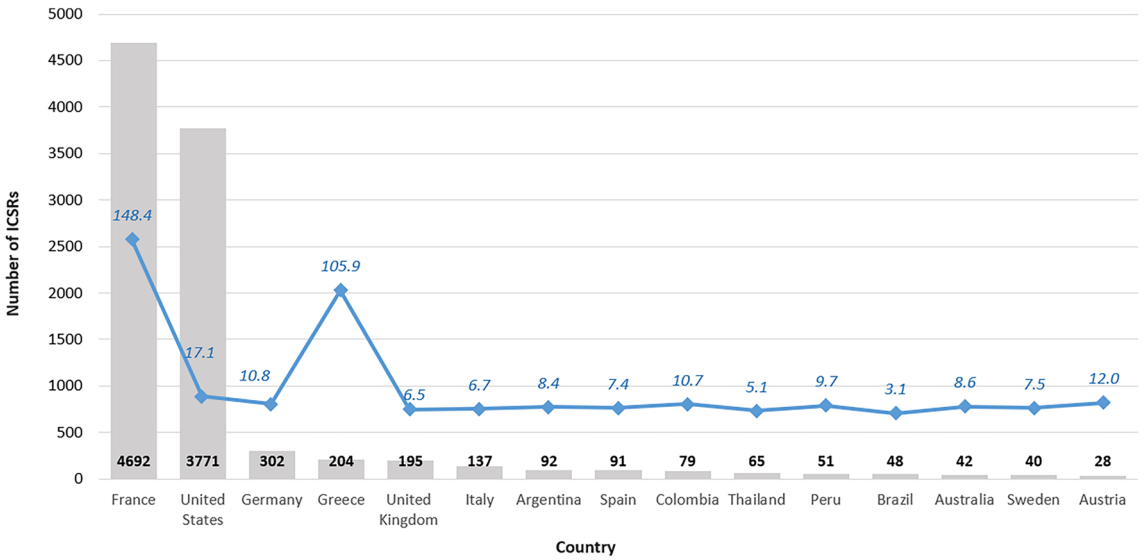


Fig. 3 Crude numbers (histogram, bold values) of cannabis individual case safety reports (ICSRs) reported by country between 2020 and 2024 and the corresponding rates per 10,000 ICSRs in the country considered (curve, italic values). Regarding the denominator, ICSRs relative to COVID-19 vaccines were excluded from the total number of ICSRs to prevent from distortion of estimates. Legend: The 302 ICSRs with at least one mention of interacting/suspect cannabis or cannabinoids recorded in Germany between 2020 and 2024 relative to the 279,515 total reports matching the inclusion criteria recorded by this country during the same period corresponded to a rate of 10.8 cannabis ICSRs per 10,000 national ICSRs

contributions from Germany, Greece, and the UK. France is a small country with some of the strictest cannabis regulations; its prominence as the leading source of cannabis ICSRs worldwide likely reflects its medical cannabis pilot programme and a well-established Addictovigilance system. The latter is based on the systematic recording of suspected ADRs related to substances with an abuse potential and may thus provide insights not captured through conventional pharmacovigilance [26–29]. In the USA, high reporting reflects long-standing pharmacovigilance practices as this country accounted for 36.1% of the total ICSRs recorded between 2020 and 2024, well above the UK, the leading contributor in Europe, which accounted for 5%. These findings underscore that geographic differences are influenced

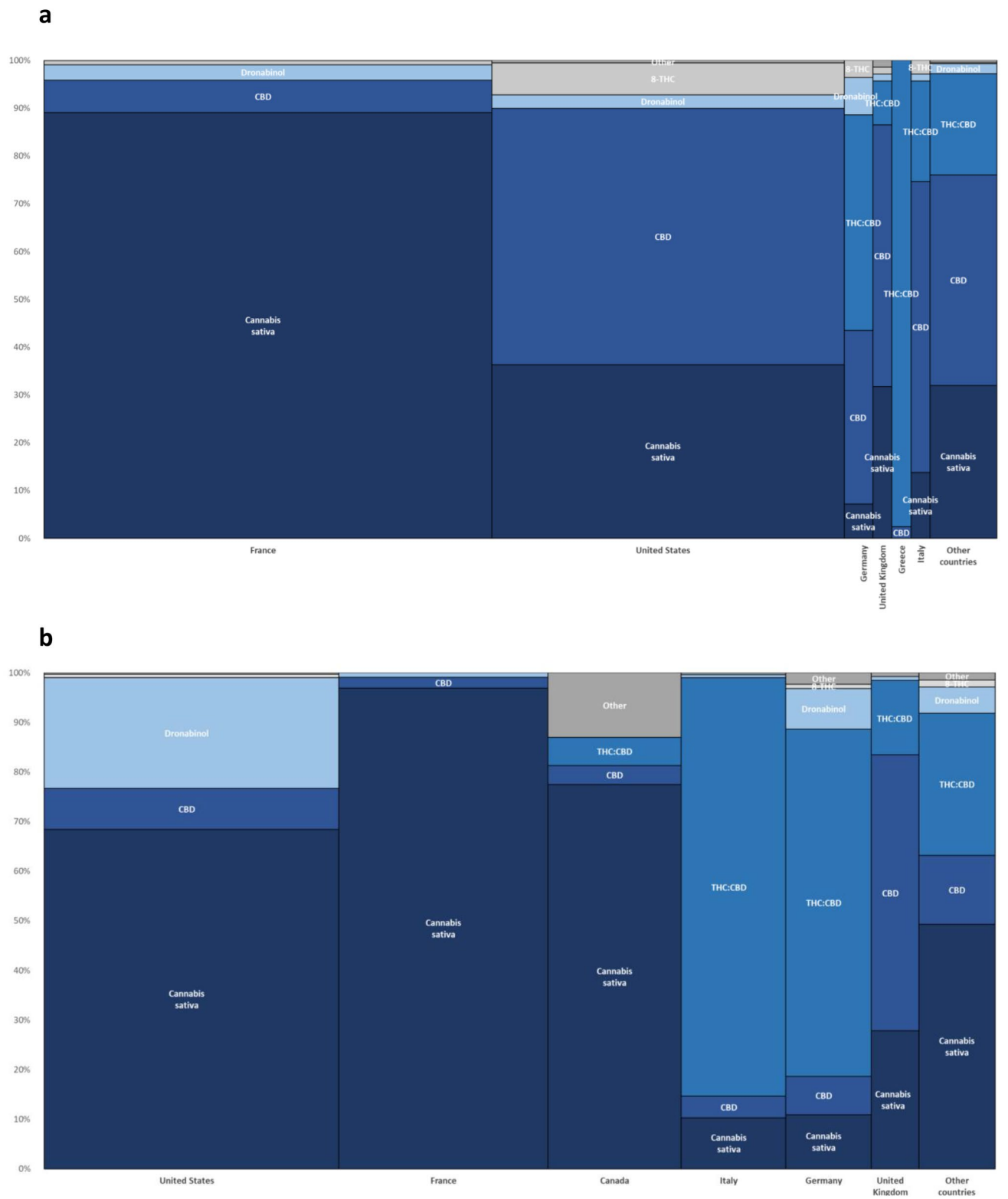


Fig. 4 Mekko chart of cannabinoid products by reporting country (in countries with at least 100 individual case safety reports [ICSRs]), as observed in the 2020–2024 period (a) comparatively to the 2015–2019 period (b)

by national safety monitoring and pharmacovigilance systems, legal frameworks, and healthcare practices. In Europe, reporting is strongly encouraged for healthcare professionals and consumers, or even mandatory for all suspected ADRs in certain Member States.

Differences across countries are also influenced by local regulatory and market changes, along with evolving consumption patterns. In the USA, there was a marked decline in *Cannabis sativa* reports and a concomitant increase in CBD-related reports between 2020 and 2024 compared with 2015–2019. Concurrently, the use of CBD for self-reported health conditions has been increasing in North America [30]. In 2024, the global consumer health CBD market was valued at USD 20.9 billion, with North America leading the market at 61.1%, followed by Europe at 17.5% [31]. In Europe, France showed a relative increase in CBD or dronabinol reports; however, reports associated with *Cannabis sativa* remained predominant. In Greece, all included ICSRs were recorded in 2024, the vast majority of which were associated with THC:CBD. In this country where cannabis is illegal for recreational use, the use of cannabis-based medicines for a defined list of indications has been regulated from March 2018; however, these drugs were scarcely available until 2024 [32]. In Germany, the regulatory status of cannabis has markedly evolved, with the authorisation of cannabis for medical use in 2017, followed by that for recreational use in 2024 [33]. The proportion of ICSRs related to THC:CBD has decreased in Germany compared with 2015–2019, while the proportion of ICSRs related to CBD has increased. An even more pronounced trend was observed in Italy, with a sharp rise in CBD-related reports and a corresponding decline in THC:CBD-related reports. In Italy, non-prison penalties regarding cannabis have initially been increased before being decreased: both strategies were followed by a similar rise in the prevalence of cannabis use among adults aged 15–34 years [4, 34]. Based on these findings, reports of suspected ADRs may serve as indirect indicators of access to and use of cannabis and cannabinoids.

Cannabis sativa remained the most frequently reported substance, followed by CBD and THC:CBD combinations. Importantly, cannabis extracts reported during the French pilot programme were recorded as *Cannabis sativa* in VigiBase®, representing a total of 1477 ICSRs between March 2021 and March 2024 (i.e., 14.8% of total ICSRs and 31.5% of ICSRs from France) [29]. Overall, median age was 29 years, with predominance of males, consistent with known sex and age distributions among cannabis users [1]. Cannabidiol reports were associated with younger ages, and THC:CBD with older ages, likely reflecting the medical use of Epidiolex®/Epidyolex® for refractory epilepsy, and Sativex® for spasticity related to multiple sclerosis [35, 36].

Psychiatric and nervous system disorders were the most frequent suspected ADRs. From a mechanistic perspective, THC acts as a partial agonist at central CB1 receptors, which are widely distributed in brain regions involved in cognition, emotion, and reward processing. This interaction modulates neurotransmitter systems and potentially contributes to psychiatric ADRs [37]. In contrast, CBD has indirect effects on the endocannabinoid system and other neurological targets, which may influence neuronal excitability and help explain the neurological adverse reactions observed [38]. *Cannabis sativa* was primarily associated with psychiatric disorders, including substance use disorders, suicidal ideation and completed suicide. This aligns with the well-known addictive potential of cannabis: indeed, approximately 42% of substance use disorders worldwide have been attributed to cannabis use [1, 37]. The relationship between cannabis use and suicidal behaviours has been recently confirmed in the meta-analysis by Maffre Maviel et al., despite the known implication of depression, established to be a partial confounder [39]. Nervous system disorders were mainly related to *Cannabis sativa* and CBD. *Cannabis sativa*-related reports included coma, amnesia, and altered consciousness, which correspond to the known effects of THC [37]. Seizures and epilepsy were most frequently associated with CBD, which was also frequently associated with the "drug ineffective" PT, inconsistent with previous results suggesting the effectiveness of highly purified CBD extracts across a broad range of epilepsy disorders [40]. Nonetheless, a detailed analysis of the French pharmacovigilance database identified the ineffectiveness of pharmaceutical CBD as the main risk factor for cannabinoid-related seizures [41]. Convulsions have been reported in preclinical studies following the administration of high dose of CBD (150–300 mg/kg/day) [38, 42]. Regarding vascular disorders, the use of cannabis has been associated with MACE, with a dose-dependent relationship [43]. These substance-specific mechanistic considerations complement broader questions regarding the role of the endocannabinoid system in the pathophysiology of neuropsychiatric, vascular, and other disorders, and the corresponding risks among individuals exposed to cannabis and cannabinoids [44].

Substance-specific patterns observed highlight the need for careful risk-benefit assessment prior to cannabis or cannabinoid use. Suspected ADRs reflect both medical and recreational contexts, with effect variability influenced by dose, formulation, and route of administration. In particular, the multifactorial complexity of cannabis use encompassing its various forms and contexts, which themselves depend on legal status and the availability or lack of cannabis-based medications or medical cannabis, as well as the interplay of many individual factors, makes it difficult to accurately assess its relationship with mental health [45]. The high proportion of serious cases, with a significant proportion of the "death" criterion, emphasises the importance of continued clinician awareness and pharmacovigilance follow-up.

Global trends in CBD use, often for self-medication, may drive new patterns of suspected ADRs, particularly neurological disorders.

One of the main strengths of this study is that it provides a comprehensive global overview of suspected ADRs related to cannabis and cannabinoids, using data from VigiBase®, the largest international pharmacovigilance database [46]. This large-scale approach allowed the identification of substance-specific patterns and temporal trends across diverse regions and regulatory contexts. However, several limitations inherent to spontaneous reporting systems must be acknowledged. First, despite the extensive geographic coverage of the WHO PIDM, data from VigiBase® are not representative of the true incidence or distribution of

Table 2 Distribution by system organ class of suspected ADRs reported in the ICSRs with at least one mention of suspect cannabis or one of its derivatives recorded in VigiBase® between 2020 and 2024: overall results and details by substance

	Total	Cannabis sativa	Cannabidiol	Cannabidiol; Dronabinol	8-Tetra hydrocannabinol	Dronabinol	Other cannabinoids
System organ class	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)	*N* (%)
Psychiatric disorders	8069 (29.2)	6800 (43.4)	681 (8.9)	153 (8.2)	349 (24.6)	186 (18.9)	13 (11.2)
Nervous system disorders	4628 (16.8)	1956 (12.5)	1688 (22.0)	360 (19.3)	329 (23.2)	168 (17.1)	11 (9.5)
Injury, poisoning and procedural complications	3145 (11.4)	1504 (9.6)	1121 (14.6)	292 (15.6)	84 (5.9)	136 (13.8)	24 (20.7)
General disorders and administration site conditions	2869 (10.4)	1124 (7.2)	1161 (15.2)	305 (16.3)	150 (10.6)	142 (14.4)	21 (18.1)
Gastrointestinal disorders	1769 (6.4)	718 (4.6)	555 (7.2)	300 (16.1)	101 (7.1)	98 (9.9)	5 (4.3)
Respiratory, thoracic and mediastinal disorders	980 (3.6)	561 (3.6)	213 (2.8)	108 (5.8)	70 (4.9)	48 (4.9)	4 (3.4)
Investigations	950 (3.4)	383 (2.4)	407 (5.3)	54 (2.9)	84 (5.9)	26 (2.6)	4 (3.4)
Cardiac disorders	773 (2.8)	596 (3.8)	88 (1.1)	24 (1.3)	47 (3.3)	33 (3.4)	4 (3.4)
Infections and infestations	672 (2.4)	172 (1.1)	434 (5.7)	43 (2.3)	4 (0.3)	14 (1.4)	0 (0)
Surgical and medical procedures	601 (2.2)	121 (0.8)	418 (5.5)	21 (1.1)	9 (0.6)	5 (0.5)	0 (0)
Eye disorders	418 (1.5)	311 (2.0)	46 (0.6)	30 (1.6)	19 (1.3)	16 (1.6)	2 (1.7)
Metabolism and nutrition disorders	417 (1.5)	191 (1.2)	191 (2.5)	7 (0.4)	11 (0.8)	19 (1.9)	3 (2.6)
Skin and subcutaneous tissue disorders	374 (1.4)	165 (1.1)	162 (2.1)	19 (1.0)	12 (0.8)	18 (1.8)	5 (4.3)
Musculoskeletal and connective tissue disorders	345 (1.3)	190 (1.2)	63 (0.8)	57 (3.1)	23 (1.6)	14 (1.4)	7 (6.0)
Social circumstances	318 (1.2)	238 (1.5)	23 (0.3)	2 (0.1)	50 (3.5)	8 (0.8)	0 (0)
Vascular disorders	301 (1.1)	197 (1.3)	45 (0.6)	24 (1.3)	22 (1.6)	15 (1.5)	1 (0.9)
Product issues	212 (0.8)	29 (0.2)	127 (1.7)	24 (1.3)	26 (1.8)	5 (0.5)	1 (0.9)
Renal and urinary disorders	167 (0.6)	101 (0.6)	49 (0.6)	10 (0.5)	4 (0.3)	4 (0.4)	3 (2.6)
Hepatobiliary disorders	154 (0.6)	92 (0.6)	62 (0.8)	0 (0)	1 (0.1)	3 (0.3)	0 (0)
Ear and labyrinth disorders	145 (0.5)	87 (0.6)	18 (0.2)	15 (0.8)	17 (1.2)	12 (1.2)	1 (0.9)
Blood and lymphatic system disorders	80 (0.3)	43 (0.3)	32 (0.4)	1 (0.1)	0 (0)	2 (0.2)	2 (1.7)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	57 (0.2)	19 (0.1)	24 (0.3)	5 (0.3)	0 (0)	6 (0.6)	3 (2.6)
Immune system disorders	52 (0.2)	13 (0.1)	26 (0.3)	5 (0.3)	3 (0.2)	5 (0.5)	1 (0.9)
Reproductive system and breast disorders	36 (0.1)	19 (0.1)	10 (0.1)	6 (0.3)	1 (0.1)	1 (0.1)	0 (0)
Pregnancy, puerperium and perinatal conditions	35 (0.1)	35 (0.2)	1 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Endocrine disorders	14 (0.1)	4 (0)	8 (0.1)	1 (0.1)	0 (0)	0 (0)	1 (0.9)
Congenital, familial and genetic disorders	12 (0)	6 (0)	6 (0.1)	0 (0)	0 (0)	1 (0.1)	0 (0)
Total	27593 (100)	15675 (100)	7659 (100)	1866 (100)	1416 (100)	985 (100)	116 (100)

ADR adverse drug reaction, *ICSR* individual case safety report

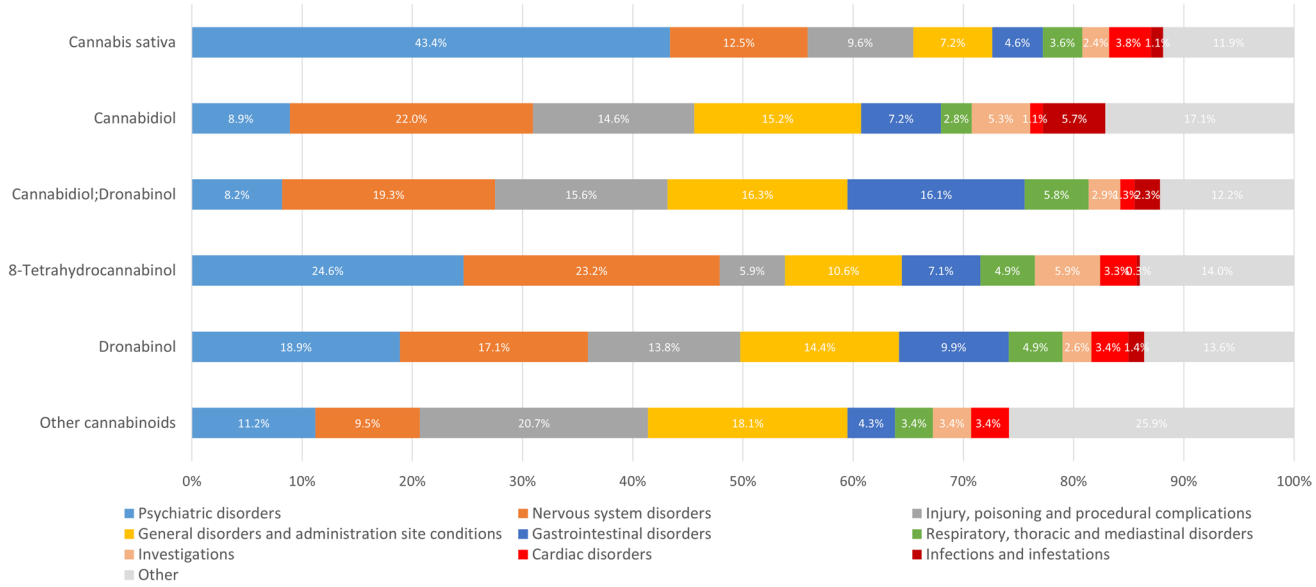


Fig. 5 Percentage distribution of adverse events by system-organ class (SOC) for cannabis and each cannabinoid having at least 50 mentions

ADRs at the population level. Differences in national pharmacovigilance practices, healthcare systems, and reporting behaviours, including underreporting, notoriety bias related to increased attention to cannabis and cannabinoids, and time-related reporting biases following changes in product availability or regulatory status, contribute to heterogeneity in the data's quality, completeness, and consistency. The completeness score of ICSRs included in the present analysis ranged from 0.2 to 1. Furthermore, at the time of data extraction, no cases originating from Canada were identified in VigiBase® in 2020–2024 (whereas it was the third-largest contributing country in 2015–2019), likely reflecting reporting delays rather than an absence of suspected adverse reactions. This may result in an underrepresentation of Canadian cases in the analysed sample. Second, in countries where both medical and recreational cannabis uses coexist, it is not possible to reliably distinguish the context of use in ICSRs [47]. Third, VigiBase® does not capture patient-level information such as sociodemographic characteristics, medical history, comorbidities, concomitant drug use, or contextual details including history of use and the chronological sequence of events. This lack of detailed information limits the possibility of conducting robust pharmacological assessments. Consequently, no causality assessment was systematically performed by the researchers to determine whether cannabis or cannabinoids were responsible for the suspected adverse drug reactions reported, including serious outcomes such as death, and causality cannot be inferred from these data. However, causality is evaluated in certain national pharmacovigilance systems and is therefore incorporated into the corresponding VigiBase® records.

Also, we did not specifically analyse additional suspect and/or interacting drugs that may be co-reported with cannabis or cannabinoids in the included ICSRs. The sensitivity analysis of ICSRs involving cannabis or cannabinoids without co-exposures suggested different use patterns and a likely selection bias (toward therapeutic use). Due to this limitation, results from this complementary analysis are not detailed, but they informed the overall interpretation. Fourth, a single ICSR may include multiple mentions of the same cannabinoid, potentially leading to an overestimation of substance frequency. To address this, we used ICSRs as the unit of analysis to minimise the risk of inflated frequency estimates. Fifth, some products of interest in this study, such as synthetic cannabinoids, were hardly visible in the database. More specifically, the potential presence of unlabelled cannabinoids in cannabinoid products, including in CBD products, remain out of reach. Lastly, while children under 2 years of age were excluded, it is possible that cases of accidental paediatric ingestions in older children were included in the analysed sample, even though these cases were not the primary focus of the study. Notwithstanding these limitations, and particularly the variability in the level of causality assessment, VigiBase® centralises suspected ADRs associated with the use of cannabis-based products from monitoring systems [46]. Taken together, these limitations highlight the need for cautious interpretation of the findings and underline the exploratory nature of pharmacovigilance-based analyses.

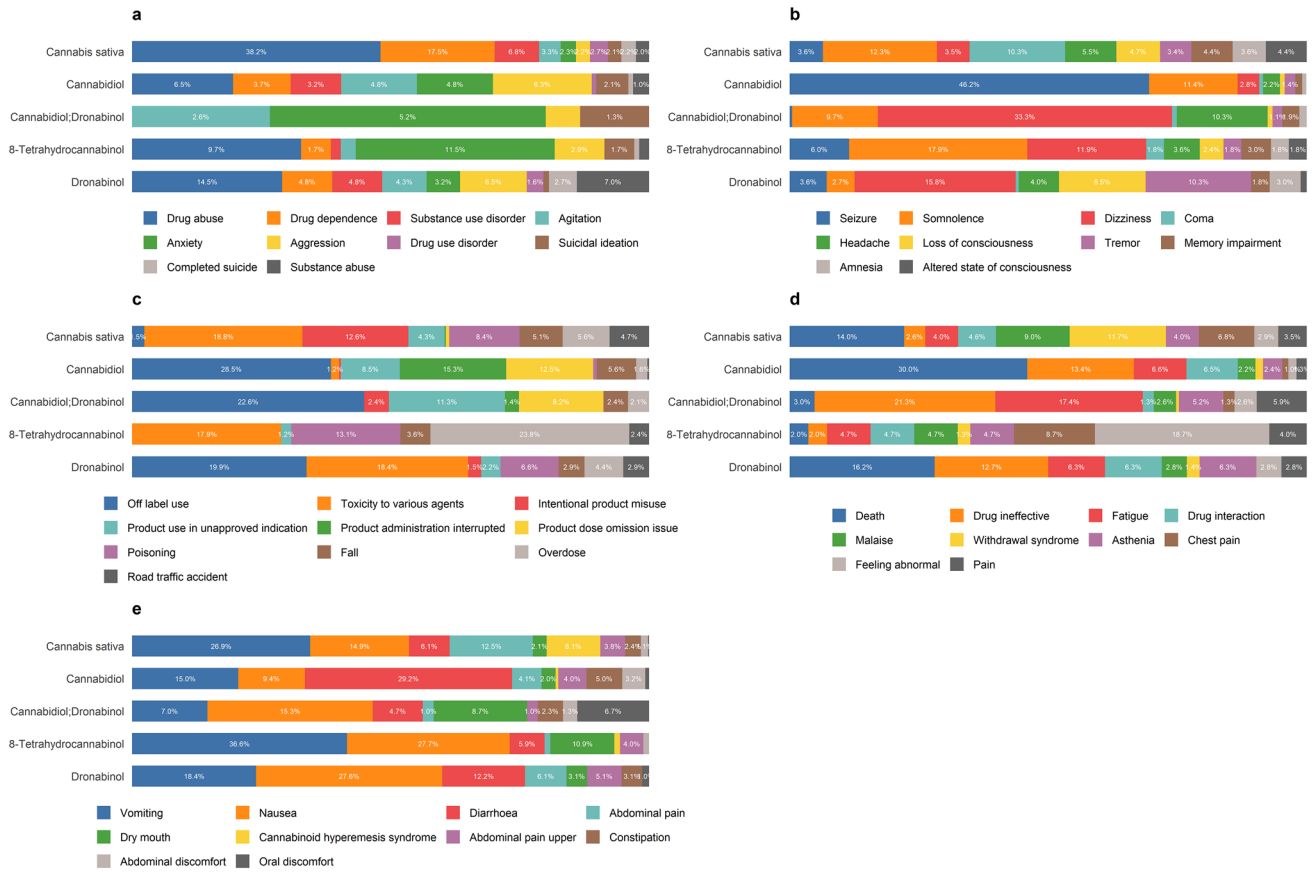


Fig. 6 Top ten preferred terms reported per system organ class (SOC): Psychiatric disorders (a); Nervous system disorders (b); Injury, poisoning and procedural complications (c); General disorders and administration site conditions (d) and Gastrointestinal disorders (e). Legend: Values are expressed as percentages and only percentages greater than 1% are shown. The top ten preferred terms (PTs) for each SOC were identified from the overall dataset and then stratified by cannabinoid. Consequently, for a given cannabinoid, the sum of the percentages shown may be less than 100% when some frequently reported PTs were not included in the SOC-specific top ten. For example, in panel (a), the most frequently reported PTs associated with THC:CBD include insomnia, confusional state, and euphoria; however, these PTs are not among the top ten in the overall dataset and therefore do not appear in the figure

5 Conclusion

This study provides a comprehensive overview of suspected ADRs related to cannabis and cannabinoids reported in Vigibase® between 2020 and 2024, regardless of their intended use or regulatory status, encompassing nearly 10,000 reports from 44 countries. Our analysis highlights substance-specific and geographic patterns, with *Cannabis sativa* remaining the most frequently reported substance, followed by CBD and THC:CBD combinations. Temporal trends suggest a rise in cannabinoid-related reports, particularly for CBD, reflecting evolving patterns of use, regulatory changes, and global market evolutions. Psychiatric and nervous system disorders were the most commonly reported ADRs, with serious cases, including hospitalisations and death, emphasising the need for continued monitoring.

While these findings enhance understanding of the safety profiles of cannabis and cannabinoids, several limitations must be acknowledged. Data from spontaneous reports cannot reliably estimate incidence or causality, and underreporting, reporting biases, and variable completeness of ICSRs may affect representativeness. Distinctions between medical and recreational use were often unavailable, and patient-level information was limited.

This comprehensive overview provides valuable insights for healthcare professionals, policy makers, and researchers, supporting risk assessment and management of cannabis and cannabinoid use in diverse clinical and recreational contexts, while highlighting the need for cautious interpretation and further investigation.

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Declarations

Competing interests The authors have no competing interests to declare that are relevant to the content of this article.

Author contributions Conceptualisation: Emilie Jouanjus, Pauline Schiro, Maryse Lapeyre-Mestre; Data acquisition and curation: Monica Galvez, Emilie Jouanjus, Pauline Schiro; Methodology: Pauline Schiro, Emilie Jouanjus and Maryse Lapeyre-Mestre; Formal analysis and interpretation: Pauline Schiro, Monica Galvez, Adèle Le Guilloux, Amélia Déguilhem, Sonia Merad and Emilie Jouanjus; Data interpretation: Pauline Schiro, Emilie Bouquet, Marine Auffret, Joëlle Micallef, Maryse Lapeyre-Mestre and Emilie Jouanjus; Writing – original draft preparation: Pauline Schiro, Monica Galvez, Emilie Jouanjus; Writing – review and editing: all authors; Final approval: all authors; Funding acquisition: not applicable; Supervision: Emilie Jouanjus. All coauthors have read and approved the final submitted manuscript and agree to be accountable for the work.

Ethical statement This study did not involve the inclusion of human participants nor have access to identifiable information; therefore, ethical approval or consent was not required.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

Data availability statement The data explored in this study have been extracted from a database that is not publicly available, but available to professionals working at a Pharmacovigilance Centre in one of the countries contributing to VigiBase®. The authors will not share the data directly; however, any interested researcher with authorised access may apply the search strategy developed for this analysis and made fully available as an online supplementary content.

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