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Article

Pharmacological Evaluation of Signals of Disproportionality Reporting Related to Adverse Reactions to Antiepileptic Cannabidiol in VigiBase

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Abstract: Cannabidiol, is the first cannabis-derived drug approved for the treatment of Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and Tuberous Sclerosis Complex (TSC). The current study performed a descriptive analysis followed by a disproportionality analysis of potential adverse events caused by CBD extracted from the database VigiBase®. Further, biological plausibility of the association between CBD and the serotonin 5-HT$_{1A}$ receptor, as possible cause of adverse events was analyzed and discussed. Data were extracted from VigiBase® database using VigiLyze® signal detection and signal management tool. Adverse events in VigiBase® reports were coded using MedDRA, version 19 of Preferred Terms (PTs). Data were uploaded into SPSS software and analyzed via disproportionality analysis. Statistically significant disproportionality signals for CBD were found for "weight decreased" 5.19 (95% CI: 4.54 - 5.70), "hypophagia" 3.68 (95% CI: 3.22 - 5.27), and "insomnia" 1.6 (95% CI: 1.40 - 1.83). Positive IC025 values were found for "weight decreased" (2.2), "hypophagia" (1.3), and "insomnia" (0.5), indicating a surplus of reported cases. CBD's interactions with 5-HT$_{1A}$ serotonin receptors may offer a potential biological explanation for the occurrence of insomnia in patients. It is noteworthy that the risk profiles mentioned in the prescribing information for CBD as antiepileptic agent by regulatory agencies showed disparities specifically related to the adverse event "insomnia".

Keywords: cannabidiol; cannabis; adverse reaction; adverse event; pharmacovigilance; serotonin; 5-HT$_{1A}$ receptor

1. Introduction

Cannabis sativa is a plant containing greater than 100 active cannabinoids, and several of them have been identified and isolated [1]. These cannabinoids have been used for various purposes throughout history, including religious, recreational, and medicinal uses, specifically as anti-inflammatory, antiemetic, anxiolytic, and seizure disorders [2,3]. Among the many cannabinoids present in *Cannabis*, two of the most abundant and well-known ones are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). THC (delta-9-tetrahydrocannabinol) and CBD (cannabidiol) indeed have the same molecular formula, C21H30O2, but their structures differ slightly, resulting in different pharmacological activities. These structural differences result in variations in how THC and CBD interact with brain receptors (e.g., cannabinoid receptors) and other biological targets, leading to distinct pharmacological activities and effects [4].

Cannabis recreational use is known to cause "high" or intoxicating effects primarily due to THC's psychotomimetic properties. CBD does not cause THC-like euphoric and psychotomimetic effects,

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and has garnered increasing attention due to its potential therapeutic benefits. While THC and CBD are both present in *Cannabis*, THC was generally found in higher concentrations compared to CBD [5]. However, the exact ratios of THC to CBD can vary depending on the specific *Cannabis* strain or cultivar. These differences in cannabinoid composition contribute to the varying effects and uses of different *Cannabis* products [6].

Pharmacological activity and therapeutic applications of THC, the active component of *Cannabis*, have been prominently studied over the years [7,8]. While the exact mechanisms of CBD are not yet fully understood, even if significant progress has been made through randomized clinical trials, animal model studies, and real-world data [9,10,11]. CBD showed to have a weak link with cannabinoid receptors 1 (CB1) and cannabinoid receptor 2 (CB2) [12], but binds to the peroxisome proliferator-activated receptor gamma [13] and has a high affinity for orphan receptors GPR55 [14]. Some of the cannabinoid-mediated effects attributed to CBD may be due to its ability to inhibit endocannabinoid degradation due to the FAAH enzyme, thus increasing anandamide level [15]. CBD has been found to be the most potent and efficacious phytocannabinoid activating transient receptor potential vanilloid (TRPV)2 and, at lower values, also TRPV1 [16]. CBD has the capability to inhibit the reuptake of adenosine, prolonging the activity of this endogenous neurotransmitters [17]. The equilibrative nucleoside transporter type (ENT)-1, regulating the concentration of adenosine, is inhibited by CBD causing indirect agonistic activity of adenosine receptor signaling [18]. CBD is an allosteric modulator at mu and delta opioid receptors [19] and has also inhibitory activity on sodium, calcium, and potassium channels, which is partially explaining its anticonvulsant effects [20]. CBD exhibits agonistic activity on serotonin 5-HT$_{1A}$ receptors. In this regard, it is noteworthy the finding that CBD is a full agonist towards serotonergic 5-HT$_{1A}$ receptor. As well as serotonin does, CBD increases [35S] GTPcS binding at this receptor and reduces cAMP concentration at equivalent levels of receptor occupancy [21]. The [35S] GTPgammaS assay measures the level of G protein activation following agonist occupation [22]. Serotonin is believed to be involved in several cannabis effects, such as relief of anxiety and pain [23] and is of great importance also for the hedonic tone, reinforcement processes [24] and sleep-wake cycle [25]. Furthermore, CBD has been proven to directly activate serotonin 5-HT$_{1A}$ receptors, which are associated with mood regulation, anxiety, and stress responses suggesting that can reduce acute autonomic responses to stress and its delayed emotional consequences by facilitating 5-HT$_{1A}$ receptor-mediated neurotransmission [26].

Use of CBD is generally considered safe, however, its safety profile is not completely defined. List of important risks for CBD licensed as antiepileptic agent includes hepatocellular injury, somnolence and sedation, lethargy, pneumonia, rash hypersensitivity reactions [27]. This information is based on available data obtained with clinical studies which supported requirement of medicinal authorization. Poor data are existing from real world data, even though, with a recent previous study analyzing European database EudraVigilance we suggested that precautions should be adopted for appropriate monitoring of CBD potential adverse effects used as antiepileptic, such as awareness of interactions with other drugs, epilepsy aggravation, and drug effectiveness [28]. Starting from this point of view, in the present study the relationship between CBD safety profile and serotonin involvement in potential adverse reactions has been investigated. In particular, the objectives of the study were to perform a descriptive analysis of spontaneous reports of adverse reactions to CBD licensed as antiepileptic agent in the VigiBase® database followed by a disproportionality analysis of selected adverse events potentially associated with activity at the serotonin 5-HT$_{1A}$ receptor level and finally to investigate on the biological plausibility of the interaction between this receptor and CBD.

2.0. Methods

Data were extracted from the Uppsala Monitoring Centre (UMC) database VigiBase®. VigiBase® holds over 30 million anonymised individual case safety report (ICSRs) of suspected adverse effects related to medicines use (as of January 2023). In this database, the information is recorded in a structured form, its purpose is to provide the evidence from which potential medicine safety hazards (signals) may be detected and communicated. Demographic characteristics (age, sex, area of

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residence, notifier's country) and details concerning the reported effect (suspected drugs, concomitant drugs, adverse drug reaction, date of occurrence, and seriousness) are collected in the database [29]. Adverse events in Vigibase® reports are coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 19.0) of Preferred Terms (PTs). PTs of MedDRA are intended to represent a single medical concept, linked with broader Higher-Level Terms (HLT), Higher Level Group Terms, and System Organ Classes (MedDRA Hierarchy, 2023) [30]. All cases linked to CBD administration recorded in Vigibase® up to 15 May 2023 were analyzed.

2.1. Case of interest definition

Hence, we sought a potential pharmacovigilance signal for the use of medical CBD and adverse reactions potentially associated with the serotonin receptor $5HT_{1A}$, using the PT terms: weight decreased, insomnia, dizziness, hypophagia, and palpitations.

2.2. Exposure definition

All reports of the term "Cannabidiol" recorded in Vigibase® up to 15 May 2023 were identified using the Vigibase browser Vigilyse®.

2.3. Statistical Analysis

A descriptive analysis was done for adverse reactions potentially linked to CBD use as antiepileptic agent contained in the database VigiBase® until December 2022.

A disproportionality analysis by using VigiBase®, the World Health Organization Pharmacovigilance Database, was performed based on two different measures, the reporting odds ratio (ROR) and the information component (IC). The ROR, as an approximate of the odds ratio (used in case–control studies), used to assess the strength of disproportionality. Reports linked to CBD were compared with all the other ICSR of VigiBase®. A ROR equal to 1 states the absence of signal, conversely, a ROR greater than 1 indicates a signal and the existence of the association. Higher the ROR, stronger is the association. The precision of the approximate ROR is reflected by a 95% confidence interval (95% CI). Consequently, a ROR is statistically significant when the lower bound of its 95% CI is greater than 1 [31,32]. The IC compares observed and expected values for the combination of a given drug and an ADR to yield associations between them. The positivity of the IC reveals the superiority of the number of observed reports over the number of expected reports. IC is a logarithmic measure of the strength of the association between a drug and a single type of adverse reaction [33].

We followed as guide "The **Re**porting of **A D**isproportionality analysis for dr**U**g **S**afety signal detection using spontaneously reported adverse events in **P**harmaco**v**igilance (READUS-PV)". READUS-PV is an international collaborative which aim at developing the first reporting recommendations for studies using disproportionality analyses in databases of spontaneously reported adverse events (https://readus-statement.org).

3.0. Results

3.1 Characteristics of the reports

The reports examined in this study were sent from various countries, with the USA being the most represented, the other countries whose reports we have analyzed are France, Spain, Italy, Canada, Australia, Uruguay and the United Kingdom. From January 2009 to May 15, 2023, VigiBase® collected 12,702 ICSR related to CBD, of which 5466 (43.0%) corresponding to criteria for serious adverse reactions.

A total of 820 ICSRs (6.5% of whole CBD-related ICSRs) correspond to events potentially related to $5\text{-}HT_{1A}$ activation. They mainly originated from USA (754; 92.0%) and mostly from consumers (463 reports; 56.5%). Gender was frequently not reported (524; 63.9%), while in the remaining part there is a substantial balance between men and women (149 Vs 147, respectively). Stratification for age suggests that the age group most affected is represented by adults aging between 18 and 44 years

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with 57 cases (7%), even if in most of the cases the age of the subject is not reported (685; 83.5%). The most used product was Epidiolex (753 ICSRs, 91.8%), while the other cases were distributed as follows: CBD oil 15 cases (1.8%), unknown CBD formula 47 (5.7%). The most represented diseases for which CBD was employed were Lennox-Gastaut Syndrome (315 reports; 38.4%) and Epilepsy (200 reports; 24.4%; Table 1).

Table 1. Main characteristics of individual case safety reports (ICSRs) related to cannabidiol (CBD) collected in VigiBase®.

Main characteristics	N° cases (820)	%
Patient age		
28 days-23 months	1	0.1%
2 - 11 years	23	2.8%
12 - 17 years	23	2.8%
18 - 44 years	57	7.0%
45 - 64 years	18	2.2%
65 - 74 years	6	0.7%
≥ 75 years	6	0.7%
Unknown	685	83.5%
28 days-23 months	1	0.1%
Sex		
Male	149	18.2%
Female	147	17.9%
Unknown	524	63.9%
Countries		
Usa	754	92.0%
UK	18	2.2%
France	12	1.5%
Germany	8	1.0%
other countries	28	3.4%
Reporter qualification		
Physician	154	18.8%
Pharmacist	22	2.7%
Other Health Professional	179	21.8%
Consumer/Non Health Professional	463	56.5%
Unknown	8	1.0%
Drug/Product		
Epidiolex	753	91.8%
Unknown (Cannabidiol)	47	5.7%
CBD oil	15	1.8%
Convupidiol (Argentina)	3	0.4%
Xannadiol (Uruguay)	2	0.2%
Indication		
Epilepsy NOS	200	24.4%
Lennox Gastaut Syndrome	315	38.4%
Seizures	40	4.9%
Parzial seizure	41	5%
Idiopatic epilepsy	34	4.1%
Tuberous Sclerosis Complex	11	1.3%
Product use for unknown indication	79	9.6%
Other indications	100	12.2%
	Serious/non serious adverse reactions	

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Yes	233	28.4%
No	587	71.6%

3.2. Disproportionality analysis

Among the selected events, "Weight decreased" was related to the highest ROR values with 5.2 (95% CI 4.5; 5.7), followed by "Hypophagia" 3.7 (3.2; 5.3), and "Insomnia" 1.6 (1.4; 1.8). "Dizziness" and "Palpitations" were related with a negative ROR (0.2 [0.2 – 0.3] and 0.1 [0.1; 0.2], respectively).

IC component results confirmed the ROR ones. Data on IC025, extracted by the VigiBase® database was also reported. They show an IC positive for the adverse reactions "Weight decreased", "Hypophagia", and "Insomnia" (**Table 2**).

Table 2. Reporting odds ratio (ROR), information component (IC) and IC025 of individual cases of suspected adverse reactions to cannabidiol (CBD) reported in VigiBase® signaling as suspected adverse reactions "weight decreased", "hypophagya", "insomnia", "dizziness", "palpitations".

Adverse reaction	N. of cases	ROR (95% CI)	IC (IC025)
Weight decreased	456	5.19° (4.54 - 5.70)	2.4* (2.2)
Hypophagia	30	3.68° (3.22 - 5.27)	1.8* (1.3)
Insomnia	221	1.60° (1.40 - 1.83)	0.7* (0.5)
Dizziness	118	0.23 (0.20 - 0.27)	- 2.1 (-2.4)
Palpitations	16	0.12 (0.10 - 0.19)	- 3.1 (-3.9)

° = statistically significant when the lower bound of 95% CI is greater than 1. * = positivity of the IC reveals the superiority of the number of observed reports over the number of expected reports.

3.3. Characteristics of insomnia reports

Among signals of adverse reactions analyzed, only "Insomnia" is not mentioned in other studies nor within the summary of product characteristics (SmPC) of Epidiolex, a medicinal product regularly licensed and based on CBD [34]. Thus, we performed a post hoc analysis only on its related ICSRs (n=221). As already seen for the general data, here too there are not many ICSRs that report the data on age (25; 11.3%), but among those in which it is present, the most represented age group is from 2 to 11 years (8; 3.6%). As for sex, we also find in this case a slightly more representative number for the male than the female (28 vs 25; 12.7% and 11.3%). Regarding the drugs used, the use of Epidiolex (206; 93.2%) stands out (**Table 3**).

Table 3. Main characteristics of individual case safety reports (ICSRs) of insomnia related to cannabidiol (CBD) collected in VigiBase®.

Main characteristics	N° cases (221)	%
Patient age		
2 - 11 years	8	3.6%
12 - 17 years	5	2.3%
18 - 44 years	4	1.8%
45 - 64 years	4	1.8%
65 - 74 years	2	0.9%
≥ 75 years	2	0.9%
Unknown	196	88.7%
Sex		
Male	28	12.7%

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Female	25	11.3%
Unknown	168	76.0%
Drug/Product		
Epidiolex	206	93.2%
Unknown Cannabidiol	11	5.0%
CBD oil	2	0.9%
Convupidiol (Argentina)	2	0.9%

We have reported the indications of use extrapolated from reports on insomnia: the most represented therapeutic indications are Lennox-Gastaut and epilepsy respectively with 73 (33.0%) and 59 (26.7%) reports (**Figure 1**). In the cases of insomnia found in individual reports, serious cases reported are 48 (21.7%).

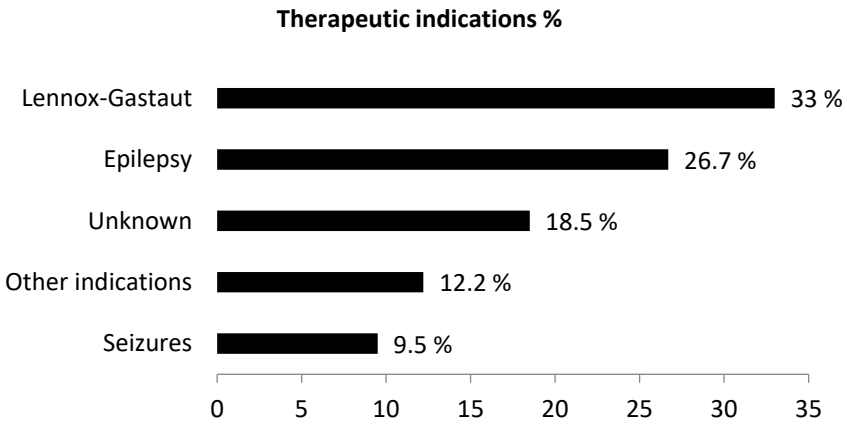

Figure 1. Therapeutic indications of individual cases of insomnia (N = 221) as suspected adverse reaction to cannabidiol.

4. Discussion

Quantitative analysis of spontaneous adverse drug reaction signaling is a routinary activity in research defining drug safety and reporting odds ratio (ROR) and information component (IC) are among the most common methods used. Results of the present study show that adverse reactions to CBD traceable in the database VigiBase® are mostly reported when people take the licensed drug Epidiolex generally use as antiepileptic agent, while adverse reactions linked to unlicensed CBD oil are reported in a minor percentage. Application of statistical methods reveals that among all adverse events to CBD potentially associated with the serotonin receptor $5HT_{1A}$, ROR is increased for "Weight decreased", "Hypophagia", "Insomnia". Both "Weight decreased" and "Hypophagia" are adverse reactions included in the risk management published for CBD used as drug, however, the adverse reactions "Insomnia" has not ever signaled by data available from clinical studies.

ROR indicates the odds of an adverse reaction occurring with a substance or a drug, in comparison to the odds of the same adverse reaction when occurring with all the other substances or drugs in the database [35]. Information component (IC) indicates if a particular association between a substance or a drug and an adverse reaction is signaled more often than it can be expected in the remaining whole adverse reactions in the database. In this case, the value of IC is positive and means that the association event/drug is not expected. When the substance (or drug) and the particular adverse reactions are not dependent, the value of IC is zero [36]. In the present study calculation of ROR for the adverse reaction "Insomnia" reveals that risk linked to its occurrence is moderately higher (1.60; C.I. 1.40-1.83) and IC analysis indicates that it is signaled more often than expected. Insomnia is a sleep disorder defined as chronic dissatisfaction with sleep quantity and/or quality. It is associated with difficulty initiating and/or maintaining sleep, early morning awakening, and unrefreshing sleep [37].

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Despite increased use of medicinal cannabis to treat insomnia and other sleep disorders, the evidence supporting therapeutic utility of cannabinoid therapies in sleep disorders is not strong [38]. Positive effects of CBD against insomnia were observed in an old small clinical study, however, more recent clinical research showed that sleep architecture polysomnography was not changed by acute daily administration of 300 mg of CBD [39]. CBD is generally considered a substance causing somnolence instead than insomnia, however, effects of CBD on sleep are not yet fully understood. In clinical studies in which 25/mg/kg CBD in children affected by epilepsy, somnolence and sedation was detected. However, CBD reduces metabolism of concomitant anticonvulsants used, thus sedation observed in these trials could be indirectly caused by its inhibitory effect [40]. Drowsiness was also reported as one of the most common side effects in a Phase 1 trial of CBD in carried out in healthy volunteers, but without any difference compared to placebo and the highest frequency of the effect with the too much higher dose of 6000 mg, while the unit dose as antiepileptic is 100 mg [41]. Furthermore, insomnia related to CBD use could be due to the known CBD activity as a negative allosteric modulator of the CB1 receptor [42], so the possibility exists that CBD could exhibit stimulating or inhibiting properties at different doses.

Biological plausibility of the link between CBD and insomnia has to be found in the mechanism of action of the cannabinoid. As above yet exposed CBD can influence serotonergic system activity, in particular acting on the 5-HT$_{1A}$ receptor. Serotonergic neurons in the brain stem Raphe nuclei are responsible for the initiation and maintenance of slow wave sleep and for the 'priming' of rapid eye movement sleep [43]. 5-HT$_{1A}$ autoreceptors play a role in controlling serotonergic tone through a negative feedback inhibition in response to increases in serotonin; thus, the growing autoreceptor desensitization may be the cause for the delayed onset of action of the antidepressants selective serotonin reuptake inhibitors (SSRIs) [44]. The 5-HT$_{1A}$ receptor subtype is a heptahelical G protein coupled receptor associated with inhibitory G proteins (Gi/Go) [45] and widely distributed throughout the CNS in both pre- and postsynaptic sites. It is one of the most abundant and widely expressed in the brain as autoreceptor or heteroreceptor [46], 5-HT$_{1A}$ autoreceptors play a role in controlling serotonergic tone through a negative feedback inhibition in response to increases in serotonin; thus, growing autoreceptor desensitization may be the cause for the delayed onset of action of SSRIs. The expression of 5-HT$_{1A}$ receptor in the limbic system and brain stem nuclei raphe support its role in regulating functions like mood and memory [47,48]. At this regard, it has been hypothesized that 5-HT$_{1A}$ receptor activation modulates anxiety [49] and the response to antidepressant drugs [50].

It has been shown that systemic administration of 8-hydroxy-2-(di-*n*-propilamino)tetralin (8-OH-DPAT), selective 5-HT$_{1A}$ receptor agonist [51], in doses ranging from 0.010-0.375 mg/kg consistently increases waking, and reduces slow wave sleep and rapid eye movement sleep [52]. Finally, the role played by of serotonin, and in particular by the 5-HT$_{1A}$ receptor, in the regulation of cycle sleep/wakefulness is controversial. It is thought that agonistic activity towards the 5-HT$_{1A}$ receptors could increase waking or sleep depending on the route of administration and the brain region involved [53].

In conclusion, analysis of real-world data from VigiBase® suggests that, in order of risks linked to CBD utilization, insomnia could emerge as potential adverse reaction not signaled by clinical trials and in risk management of licensed drugs containing it. Biological plausibility of causal relationship between between CBD and insomnia can be explained through the knowledge of the mechanism of action of the cannabinoid and its potential influence on serotonergic system activity, by acting on the 5-HT$_{1A}$ receptor. In order to reach definitive or more stable conclusions, better quality of data is needed. It will provide clearer results to be communicated to physicians and consumers using or prescribing CBD for treatment or for well-being. Furthermore, as people who suffer from insomnia with the use of cannabidiol are mostly patients with epilepsy, it is important to verify the external validity of these results to establish the extent to which it is possible to generalize the findings of this study to the general population.

Supplementary Materials: Not applicable.

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Conflicts of Interest: "The authors declare no conflict of interest."

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