Check for updates

Pharmacology Research & Perspectives

SHORT REPORT OPEN ACCESS

Part 1: Evaluation of Pediatric Cannabis–Drug Interaction Reports

Maryann R. Chapin[1] | Sandra L. Kane-Gill[1,2] | Xiaotong Li[1] | Kojo Abanyie[2] | Sanya B. Taneja[3] | Susan Egbert[4] | Mary F. Paine[5] | Richard D. Boyce[1,2,3]

[1]School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, USA | [2]Department of Biomedical Informatics, University of Pittsburgh, Pittsburgh, Pennsylvania, USA | [3]Intelligent Systems Program, University of Pittsburgh, Pittsburgh, Pennsylvania, USA | [4]Department of Chemistry, University of Manitoba, Winnipeg, Manitoba, Canada | [5]Department of Pharmaceutical Sciences, College of Pharmacy and Pharmaceutical Sciences, Washington State University, Spokane, WA, USA

Correspondence: Richard D. Boyce (rdb20@pitt.edu)

Received: 25 July 2024 | **Revised:** 30 October 2024 | **Accepted:** 1 November 2024

Funding: This work was supported by the National Institutes of Health National Center for Complementary and Integrative Health and the Office of Dietary Supplements, specifically the Center of Excellence for Natural Product-Drug Interaction Research (U54 AT008909), and the National Institutes of Health US National Library of Medicine (T15 NLM007059).

Keywords: adolescents | cannabidiol | cannabis | drug interactions | medication safety | natural products | pediatrics

ABSTRACT

Data addressing safety concerns related to potential drug interactions between cannabis-derived products and pharmaceutical medications in the pediatric population are lacking. In this study, we retrieved case reports through a published literature search using PubMed and spontaneous reporting data using the Food and Drug Administration's Adverse Event Reporting System (FAERS) to identify potential cannabis– and cannabinoid–drug interactions in individuals younger than 18 years old. To evaluate the published case reports, we used the Drug Interaction Probability Scale (DIPS), a 10-item questionnaire designed to discern the causal relationship between a potential drug interaction and adverse drug reactions (ADRs). FAERS reports were deduplicated and analyzed to gather information regarding patient demographics, associated drugs, nature of the ADRs, outcomes, professions of the reporters, and reporting timelines. Seven published case reports and 9142 FAERS ADRs reports were included in the final analysis. Based on the findings, caution is warranted when cannabis or cannabinoids are used in combination with prescribed medications, including methadone, everolimus, fluoxetine, and paroxetine. Cannabinoids may inhibit drug-metabolizing enzymes, including several cytochrome P450s, leading to increased drug exposure and potentially, an increased risk for ADRs.

1 | Introduction

Compared with adult cannabis users, children and young adults who use cannabis are at increased risk of neurologic harm, including memory difficulties, psychosis, and cannabis use disorder, due to continued brain development in these age groups [1]. In the United States, medical marijuana is commonly prescribed for pediatric patients with epilepsy, autism spectrum disorder, and spasticity, among other conditions, [2] whereas recreational cannabis is currently illegal for individuals aged less than 21 years due to the potential for neurologic harm. Nonetheless, in 2021, approximately 2.7 million adolescents aged 12–17 years reported using cannabis recreationally [3]. Despite the high cannabis use among adolescents, data regarding potential interactions between cannabis and pharmaceutical drugs and the resulting potential harm remain lacking.

The two most widely studied constituents in cannabis are the cannabinoids cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC). CBD is metabolized primarily

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2024 The Author(s). *Pharmacology Research & Perspectives* published by British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics and John Wiley & Sons Ltd.

by cytochrome P450 (CYP) 2C19, CYP2C9, and CYP3A4, [4] whereas THC is metabolized primarily by CYP2C9 and CYP3A4 [5]. As such, inhibitors of these enzymes can increase cannabinoid systemic exposure and risk of neurologic harm. Both cannabinoids, particularly CBD, have also been reported to inhibit these enzymes in vitro and in vivo [5–8]. Accordingly, using cannabis while taking pharmaceutical drugs can lead to increased systemic exposure to the object drug and potential toxicity. For example, the antiseizure medication, clobazam, is converted to the active metabolite *N*-desmethylclobazam by CYP3A4, which is converted to an inactive metabolite by CYP2C19. When CBD is co-consumed with clobazam, circulating concentrations of both clobazam and *N*-desmethylclobazam increase, leading to increased adverse events compared with the absence of CBD [9]. Ultimately, drug interactions with cannabis or cannabinoids can lead to heightened adverse events, negatively impacting a young person's mental, social, and school performance.

The objective of this study was to increase knowledge and awareness of potential cannabis– or cannabinoid–drug interactions in pediatric individuals due to the high risk of harm. The aims were to (1) conduct a literature search to review potential pediatric cannabis– and cannabinoid–drug interactions discussed in case reports, (2) complete a causality assessment from the case reports, and (3) search the US Food and Drug Administration Adverse Event Reporting System (FAERS) database to identify potential cannabis– and cannabinoid–drug interactions that had been voluntarily reported. Results highlight the need for continued research on this critical public health problem.

2 | Methods

2.1 | Case Reports Analysis

A comprehensive literature search was conducted using PubMed from the start of the database (1966) to July 2023 using an established query (Appendix S1). The following inclusion criteria were applied: (1) case reports only, (2) available in English, (3) person was less than 18 years old, and (4) a potential adverse event from a cannabis– or cannabinoid–drug interaction was discussed. An example search string is shown below. The search strategy consisted of using 'AND' logic with three components: (1) case report, (2) drug interaction, and (3) a comprehensive list of cannabis-related products. The full string can be seen in Appendix S1.

```
Sample Search String:

Case Reports [PT] AND "drug interactions"[All Fields] AND ("Cannabis sativa" [All Fields] OR "CBD" [All Fields] OR "Hemp" [All Fields] OR …).
```

Next, the Drug Interaction Probability Scale (DIPS), a 10-item questionnaire, was used to assess the epistemological probability of a causal relationship between a potential drug interaction and an adverse event for each case report by two pharmacists (Appendix S2) [10]. The DIPS tool evaluates factors such as metabolic pathways, the potential for metabolism and transporter inhibition or induction, standard pharmacokinetic parameters, concentration–response relationships, and indicators of therapeutic response and adverse events. DIPS scores are categorized as follows: <2 (doubtful), 2–4 (possible), 5–8 (probable), and >8 (highly probable). Discrepancies between reviewers were resolved with a third reviewer.

2.2 | FAERS Evaluation

Adverse drug reactions (ADRs) associated with cannabis or a cannabinoid voluntarily reported to FAERS from January 2004 to June 2022 were extracted using both Latin binomials and common names while accommodating character variations (Appendices S3 and S4) [11]. A four-step algorithm was used to remove duplicates from the ADR report: (1) singling out cases with identical identifiers but different versions; (2) identifying cases referencing the same literature citation (because many FAERS reports include a citation), along with the reported drugs, reactions, age, and sex; (3) applying the World Health Organization's likelihood-based vigiMatch algorithm to discern FAERS cases marked as duplicates; [12] and (4) visually inspecting the remaining cases to filter out duplicates. Following deduplication, a descriptive analysis was conducted on the cannabis- or cannabinoid-related cases to elucidate details regarding patient demographics, associated drugs, nature of the ADRs, outcomes, professions of the reporters, and reporting timelines. FAERS reports that specifically declared "drug interaction" as the preferred term were closely analyzed.

3 | Results

3.1 | Case Reports Analysis

The PubMed search revealed seven pediatric case reports that met the inclusion criteria. Tables 1 and 2 describe the case reports analysis for potential cannabis– and cannabinoid–drug interactions and the corresponding DIPS scores. Table 1 provides an overview of the case reports exhibiting a probable or possible DIPS score, whereas Table 2 includes case reports with a doubtful DIPS score. The case reports comprised individuals aged between 6 and 17 years. The included case reports were published between 1997 and 2022. Only two had a previous credible report of the same interaction occurring in humans.

3.2 | FAERS Evaluation

Figure 1 shows the inclusion and exclusion criteria for FAERS reports included in the analysis. The total number of reports extracted from the database for cannabis products (based on a list of product names shown in Appendix S3) and CBD products (shown in Appendix S4) was 8674 and 468, respectively. These two lists also contain names that include THC. We included these products because we could not determine if the names, which seemed to be the result of a standardization process by the FDA, were hierarchical or were combination products. The FDA was contacted regarding this issue of cannabis and CBD strings including THC, but response was not received.

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Case reports that propose possible or probable cannabinoid–drug interactions in pediatric patients, including a postpublication DIPS score analysis.

Object drug	Drug class	Cannabis/ cannabinoid (method of consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS review
Methadone [13]	Opioid analgesic	CBD (oil)	13-year-old female	*CBD is known to inhibit CYP3A4 and CYP2C19. Methadone is metabolized* via *the same CYP pathways, causing increased serum methadone concentrations.*	Increased fatigue, sleepiness, and serum methadone concentrations	6 (Probable)	Pros: • Methadone undergoes *N*-demethylation via multiple CYPs, including CYP3A4, CYP2B6 and CYP2C19 [14]. • Event consistent with known time course, interaction remitted upon de-challenge, object drug detected in blood or other fluids, interaction confirmed by objective evidence, and interaction became greater with increased precipitant dose. • Concomitant use of methadone with CYP inhibitors may result in potentially fatal respiratory depression. Patients should be monitored for sedation, and it was reported this patient experienced increased sleepiness.
Everolimus [15]	Kinase inhibitor	CBD (oily solution)	6.5-year-old female	*Mechanism between everolimus and CBD is unknown; however, an interaction* via *the CYP3A4 pathway is possible.*	Increased everolimus blood trough concentrations	6 (Probable)	Pros: • Use of everolimus with strong CYP3A4 inhibitors should be avoided due to increased exposure to everolimus [16]. • Previous credible reports, event consistent with known time course, interaction remitted upon de-challenge, object drug detected in blood or other fluids, and everolimus blood trough concentrations increased with increasing precipitant dose.

(Continues)

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Object drug	Drug class	Cannabis/ cannabinoid (method of consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS review
Fluoxetine [17]	SSRI	CBD (oil)	17-year-old male	*CBD has been shown to inhibit the CYP2C9-mediated metabolism of fluoxetine.*	Insomnia, increased agitation, hyperactivity, vocal yelling, and worsening OCD	5 (Probable)	Pros: • Event consistent with known time course, interaction remitted upon de-challenge, and interaction confirmed by objective evidence. Cons: • The reporter's suggested mechanism did not identify that fluoxetine is primarily metabolized via CYP2D6 [6]. However, CBD does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • The report mentioned an alternative cause in that the patient had a history of OCD and "had symptoms of repetitive and antisocial behaviors, hyperactivity agitation, insomnia, and panic attacks."
Nortriptyline [18]	TCA	Marijuana (smoked cigarette)	16-year-old male	*THC is metabolized* via *similar hepatic enzymes as TCAs. Combination use of TCAs and THC could result in increased serum and CNS THC concentrations by inhibiting its metabolism.*	Lightheadedness, tachycardia, and confusion	4 (Possible)	Pros: • Previous credible reports, interaction remitted upon de-challenge, interaction confirmed by objective evidence. Cons: • The reporter's suggested mechanism did not identify that nortriptyline is metabolized to hydroxyl metabolites via CYP2D6 [19]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • The reporter's suggested mechanism did not identify that THC may have increased the possibility of CNS adverse reactions of nortriptyline (apart from an interaction), such as dizziness, confusion, and tachycardia.

(Continues)

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Object drug	Drug class	Cannabis/ cannabinoid (method of consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS review
Lithium [20]	Antimanic agent	CBD (oral solution)	13-year-old male	*Mechanism between lithium and CBD remains unknown.*	Hypersomnolence, ataxia, decreased oral intake, and lithium toxicity	4 (Possible)	Pros: • Event consistent with known time course, object drug detected in blood or other fluids, interaction confirmed by objective evidence, and lithium levels increased with increasing precipitant dose. • Patient's lithium concentration reached 2.4 mmol/L, confirming lithium toxicity. Cons: • No previous credible reports found. • No plausible mechanism suggested. Limited evidence that lithium appears to undergo interactions via the CYP pathway.
Brivaracetam [14]	Anticonvulsant	CBD (unknown)	10-year-old male	*CBD inhibits CYP2C19, leading to an increase in brivaracetam concentrations.*	Increased brivaracetam concentrations and diarrhea	2 (Possible)	Pros: • Brivaracetam weakly inhibits CYP2C19 [21]. • Event consistent with known time course and object drug detected in blood or other fluids. Cons: • No previous credible reports found. • Patient reported diarrhea, which is not a known adverse reaction of brivaracetam.

Abbreviations: CBD, cannabidiol; CNS, central nervous system; CYP, cytochrome P450; OCD, obsessive–compulsive disorder; SSRI, selective serotonin reuptake inhibitor; THC, tetrahydrocannabinol; TCAs, tricyclic antidepressants.

[a]The mechanism was rephrased from the case report and does not reflect the proposed mechanism put forth by any of the authors.

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | Case reports that propose a doubtful cannabis–drug interaction in pediatric patients, including a postpublication DIPS score analysis.

Object drug	Drug class	Cannabis/ cannabinoid (method of Consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS Review
Paroxetine [22]	SSRI	Marijuana (smoked)	15-year-old female	*Mechanism between paroxetine and marijuana is unknown.*	Severe hypotension	1 (Doubtful)	Pros: • Event consistent with known time course and interaction confirmed by objective evidence. Cons: • No previous case reports found and reasonable alternative causes. • Paroxetine is metabolized by CYP2D6 and has been shown to be a strong inhibitor [23]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • Use of paroxetine may cause hypotension due to increased serotonin concentrations, causing opposing cardiovascular effects [22].
Amphetamines [22]	CNS stimulant	Marijuana (smoked)	15-year-old female	*Mechanism between amphetamines and marijuana is unknown.*	Severe hypotension	1 (Doubtful)	Pros: • Event consistent with known time course, and interaction confirmed by objective evidence. Cons: • No previous case reports found and reasonable alternative causes. • Metabolism of amphetamine-like psychostimulants is regulated by CYP2D6 [24]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • Acute intoxication of amphetamines may cause severe hypotension via central α_2-adrenoreceptors [22].

(Continues)

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | (Continued)

Object drug	Drug class	Cannabis/ cannabinoid (method of Consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS Review
Sertraline [18]	SSRI	Marijuana (smoked cigarettes)	15-year-old male	*THC is metabolized via similar hepatic enzymes as TCAs. Combination use of TCAs and THC could result in increased serum and CNS THC concentrations by reducing its metabolism.*	Severe confusion, mood lability, irritability, "racing heart"	0 (Doubtful)	Pros: • Interaction remitted upon de-challenge. Cons: • No previous case reports found and reasonable alternative causes. • Sertraline is a potent CYP2D6 in vitro inhibitor [25]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • THC may have increased the possibility of adverse reactions of sertraline, such as confusion, irritability, and tachycardia.
Desipramine [18]	TCA	Marijuana (smoked cigarettes)	15-year-old male	*THC is metabolized via similar hepatic enzymes as TCAs. Combination use of TCAs and THC could result in increased serum and CNS THC concentrations by reducing its metabolism.*	Severe confusion, mood lability, irritability, "racing heart"	0 (Doubtful)	Pros: • Interaction remitted upon de-challenge. Cons: • No previous case reports found and reasonable alternative causes. • Desipramine is a CYP2D6 substrate [26]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • THC may have heightened desipramine adverse reactions (hallucinations, confusion, and tachycardia are common).

(Continues)

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | (Continued)

Object drug	Drug class	Cannabis/ cannabinoid (method of Consumption)	Patient age and sex	Proposed mechanism from case report[a]	Reported adverse event(s)	DIPS score	Notes from DIPS Review
Desipramine [18]	TCA	Marijuana (unknown)	16-year-old male	*THC is metabolized via similar hepatic enzymes as TCAs. Combination use of TCAs and THC could result in increased serum and CNS THC concentrations by reducing its metabolism.*	Hallucinations, depersonalization, confusion, shortness of breath, and tachycardia	−1 (Doubtful)	Cons: • No previous case reports found and reasonable alternative causes. • Desipramine is a CYP2D6 substrate [26]. However, THC does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [8]. • THC may have heightened desipramine adverse reactions (hallucinations, confusion, and tachycardia are common).

Abbreviations: CNS, central nervous system; CYP, cytochrome P450; SSRI, selective serotonin reuptake inhibitor; THC, tetrahydrocannabinol; TCA, tricyclic antidepressant.
[a]The mechanism was rephrased from the case report and does not reflect the proposed mechanism put forth by any of the authors.

After deduplication and filtering for reports of interactions in pediatric patients, seven reports related to cannabis remained. Table 3 describes the FAERS reports for cannabis– and cannabinoid–drug interactions in adolescents. Most of the reports originated from the United States (268/404; 66.3%) and consisted of individuals aged between 13 and 17 years (335; 82.9%). Physicians (165/404; 40.8%) and consumers (102/404; 25.2%) were the most common reporters. The top ten reported ADRs included drug abuse (22.0%), completed suicide (10.4%), toxicity to various agents (9.2%), substance abuse (7.4%), cardiac arrest (6.9%), overdose (6.9%), respiratory arrest (6.7%), somnolence (5.7%), fetal exposure during pregnancy (5.7%), and cardiorespiratory arrest (5.7%). Frequently reported outcomes included serious-important medical event (209/404; 51.7%), hospitalization (164/404; 40.6%), and death (131/404; 32.4%). Seven cannabis FAERS reports mentioned "drug interaction" as the preferred term (Table 3).

Regarding the cannabinoid reports from FAERS, 16/17 (94.1%) originated from the United States and 14/17 (82.4%) and were reported by consumers. Most of these reports involved children aged between 1 and 12 years (11/17; 64.7%), while adolescents 13 to 17 years represented 5/17 (29.4%) reports. The top three ADRs were seizure (23.5%), headache (17.6%), and insomnia (17.6%). Common outcomes included serious-important medical event (8/17; 47.1%), hospitalization (6/17; 35.3%), unknown (5/17; 29.4%), required intervention to prevent permanent impairment/damage (3/17; 17.6%), life-threatening (2/17; 11.8%), death (1/17; 5.9%), and disability (1/17; 5.9%).

4 | Discussion

Our literature review of case reports identified several potential cannabis– or cannabinoid–drug interactions with plausible mechanisms, with three reports having a probable DIPS score suggesting causality. These reports included potential interactions between CBD and methadone, everolimus, and fluoxetine. A brief summary of what is known about each possible interaction is described below. Further scientific investigation is required to obtain a thorough understanding. It is imperative that clinicians provide patients with comprehensive education regarding these interactions while closely monitoring the incorporation of other drugs and natural products, including botanical dietary supplements.

Methadone is an opioid prescribed commonly for opioid use disorder and pain in minors and adults. Accidental methadone poisoning is often a concern in adolescents because ingestion of small doses (0.5–1 mg/kg) could lead to toxicity and death [28]. A case report of a 13-year-old female who was taking methadone for chronic pain due to metastatic cancer suffered from an interaction between methadone and CBD (Table 1). The patient reported increased fatigue and sleepiness. Her serum methadone concentration was 271 ng/mL 2 days following cessation of CBD, then subsequently decreased to 125 ng/mL 14 days postcessation. Methadone is metabolized principally by CYP 2B6, with minimal contribution by CYP3A4 [15, 29]. Given that prior in vitro studies have shown CBD to be potent inhibitor of CYP2B6, this case report raised concern for a potentially severe interaction between CBD and methadone [5, 6, 17].

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

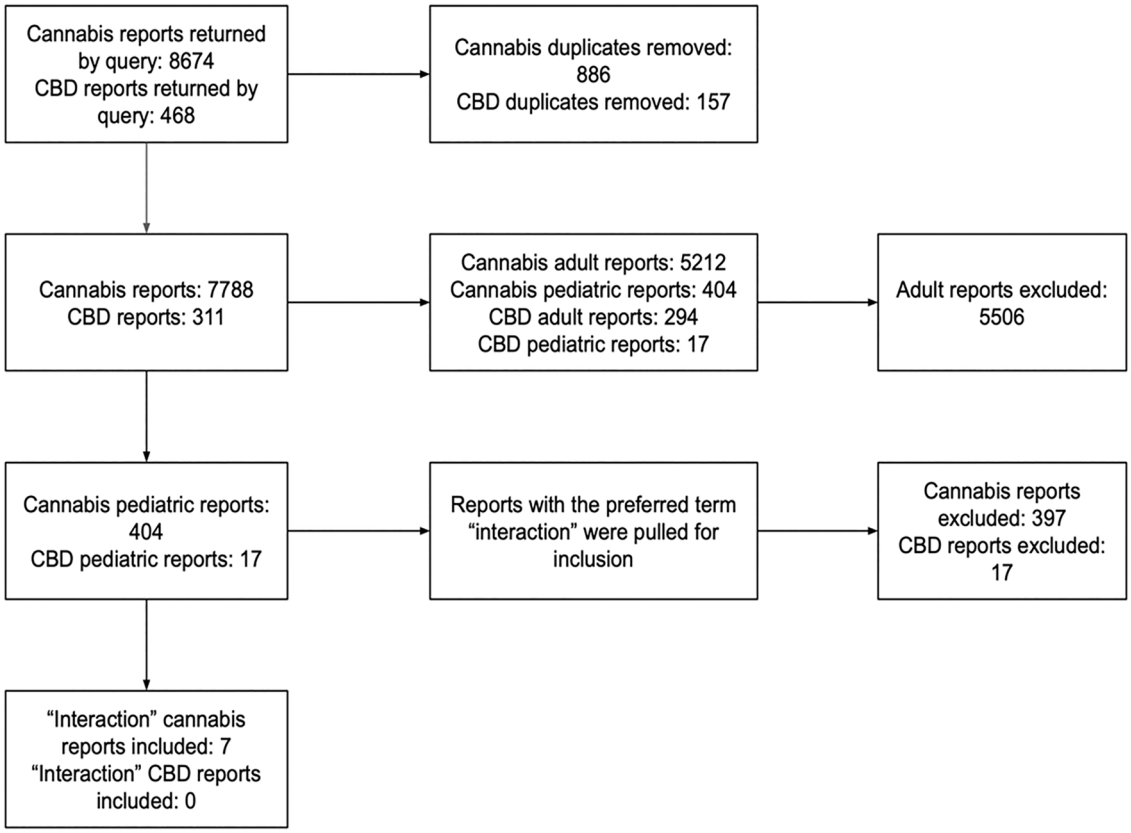


FIGURE 1 | FAERS flow diagram for inclusion of reports of cannabis– or CBD–drug interactions in pediatric patients.

Everolimus, a chemotherapeutic agent, exhibited a DIPS score of 6 (probable). Based on the case report in a 6-year-old female, CBD reportedly increased everolimus blood trough concentrations; however, the exact mechanism for the purported interaction remains unclear [22]. To our knowledge, this case report is the first to mention a potential interaction between CBD and everolimus.

There was one probable case report indicating a potential interaction between the antidepressant fluoxetine and CBD. One report involving fluoxetine and CBD had a DIPS score of 5 (probable), with adverse effects that included insomnia, increased agitation, hyperactivity, vocal yelling, and worsening obsessive–compulsive disorder. A potential mechanism of this interaction is that CBD inhibited the metabolism of fluoxetine by CYP2C9 [30]. Fluoxetine is also a potent inhibitor of CYP2D6 [31]. However, CBD does not inhibit CYP2D6 in vivo, so a plausible mechanism remains unknown [16]. To our knowledge, this case report is the first to describe a CBD-fluoxetine interaction in adolescents.

Potential interactions between cannabis and other antidepressants (desipramine, nortriptyline, paroxetine, and sertraline) were prevalent in seven case reports. These interactions resulted in numerous adverse effects, such as confusion, hallucinations, and irritability, which could cause performance issues during school and social activities. Although the reports had DIPS scores ranging from doubtful to probable, similar adverse effects were noted.

With respect to the FAERS analysis, seven of the cannabis reports contained "drug interaction" as the preferred term. The drugs reported included pain medications, antipsychotics, and antiepileptics. Combinations of these drug classes with cannabis results in psychosis and seizures (Table 3). One report included paroxetine as the primary suspect drug potentially interacting with marijuana that caused hypotension. Another report contained paroxetine as a secondary suspect drug with hypotension as the preferred term. A case report in PubMed also mentioned hypotension when a 15-year-old female co-consumed paroxetine while smoking marijuana [18]. Although the DIPS score was 1 (doubtful), an interaction between paroxetine and marijuana may be cautioned, as concomitant use can be life-threatening and lead to hospitalization according to the FAERS outcome codes. To our knowledge, data suggesting a cannabis–paroxetine interaction in adolescents are nonexistent, warranting further investigation. There were no CBD reports from FAERS that mentioned "drug interaction" as the preferred term.

As alluded above, several in vitro and some clinical studies have demonstrated that both CBD and THC inhibit multiple CYP enzymes; however, CBD appears to precipitate drug interactions more commonly than THC in clinical settings [19]. Factors including route and frequency of administration of a given cannabis product, as well as the dose of CBD and/or THC contained in the product, influence the likelihood of experiencing adverse interactions. Whether one of these cannabinoids alone is less likely to precipitate an interaction compared to a combination thereof is not known.

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 3 | FAERS cannabis–drug interaction results in pediatric patients from Q1 2004 to Q2 2022.

Primary ID	Patient age and sex	Report date	Drugs reported	MedDRA preferred term	Reported outcome
135 277 253	7-year-old female	05/17/2017	clobazam^{PS}; clonazepam^{C}; hemp^{SS}; lamotrigine^{SS}; valproic acid^{SS}	Drug interaction; gait disturbance; seizure; somnolence	Hospitalization
158 207 401	15-year-old female	01/14/2019	marijuana^{SS}; paroxetine^{PS}; sevoflurane^{SS}	Drug interaction; hypotension	Hospitalization
158 867 341	15-year-old female	01/29/2019	amphetamine^{SS}; marijuana^{SS}; oxygen^{C}; paroxetine^{SS}; sevoflurane^{S}	Drug interaction; hypotension	Life-threatening
160 621 561	17-year-old male	03/12/2019	alcohol^{SS}; caffeine^{SS}; marihuana^{SS}; morphine sulfate^{PS}; Opana^{SS}; oxycodone hydrochloride^{SS}	Back pain; brain edema; drug abuse; drug interaction; overdose; pulmonary edema; toxicity to various agents; vomiting	Death
167 993 331	12-year-old male	09/12/2019	acyclovir [aciclovir]^{C}; *Cannabis sativa*^{i}; clobazam^{I}; diazepam^{I}; phenytoin^{PS}; sodium valproate^{C}; stiripentol^{I}	Coma scale abnormal; drug interaction; seizure; somnolence	Hospitalization
5 233 690	15-year-old male	02/08/2007	clonidine^{C}; Klonopin^{SS}; marijuana^{C}; Wellbutrin XL^{PS}; Zyprexa^{C}	Blindness; blindness transient; drug dispensing error; drug ineffective; drug interaction; eye inflammation; eye irritation; eye pain; papilloedema; photophobia; visual disturbance	Other serious-important medical event[a]
6 113 433	17-year-old male	03/12/2009	*Cannabis sativa*^{i}; Depakote^{PS,SS}; olanzapine^{C}; quetiapine fumarate^{C}; risperidone^{C}	Drug interaction; psychotic disorder	N/A

Abbreviations: C, concomitant; I, interacting; N/A, not available; PS, primary suspect drug; SS, secondary suspect drug; XL, extended release.

[a]"Medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent serious outcomes; these events require medical and scientific judgment and fall under the expedited reporting rules (see ICH E2A)." [27].

20521707, 2025, 1, Downloaded from https://bjspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

5 | Limitations

We sought to conduct a comprehensive literature search of PubMed. However, a broader search using other bibliographic databases such as EMBASE might have identified additional case reports. The DIPS score is reflective of the data available in the case report and could change if more data are provided. Reports from FAERS are anecdotal and, while useful for signaling potential issues, do not necessarily imply a causal association. Additionally, we were unable to determine which component of cannabis (e.g., CBD vs. THC) is the main precipitant of a reported interaction, due to the ambiguous and varied descriptions of the cannabis products in the reports.

6 | Conclusions

Cannabis– or cannabinoid–drug interactions can be harmful and life-threatening in the pediatric population, prompting the impetus for this study. Using PubMed and FAERS, potential interactions involving methadone, everolimus, fluoxetine, and paroxetine were identified. Further investigation is needed to help address the lack of knowledge on these interactions, as well as lack of clinical decision support specific to this population.

Author Contributions

Maryann R. Chapin: conceptualization/design, methodology, investigation, data curation, formal analysis, resources, writing and editing. **Sandra L. Kane-Gill:** conceptualization/design, methodology, investigation, supervision/oversight, formal analysis, writing and editing. **Xiaotong Li:** methodology, data curation, formal analysis, writing and editing. **Sanya B. Taneja**, **Susan Egbert:** data curation, formal analysis, writing and editing. **Mary F. Paine:** funding acquisition, writing and editing. **Kojo Abanyie:** formal analysis, resources, writing and editing. **Richard D. Boyce:** conceptualization/design, methodology, investigation, supervision/oversight, data curation, resources, writing and editing.

Ethics Statement

This study was conducted in adherence to the ethical standards outlined by the University of Pittsburgh Institutional Review Board. The research involved analysis of data from PubMed and the Food and Drug Administration's Adverse Event Reporting System (FAERS). The above data sources contain de-identified case reports submitted by healthcare professionals, researchers, consumers, and manufacturers.

Conflicts of Interest

M.R.C.: No COI/disclosures.

S.L.K.-G. receives grant funding from the National Institute of Diabetes and Digestive and Kidney Diseases R01DK121730 and U01DK130010, the National Center for Complementary and Integrative Health and Office of Dietary Supplements (U54AT008909) and the Jewish Healthcare Foundation.

X.L.: No COI/disclosures.

S.B.T.: No COI/disclosures.

S.E.: No COI/disclosures.

M.F.P. receives grant funding from the National Center for Complementary and Integrative Health and Office of Dietary Supplements (U54AT008909), National Institute of Child Health and Human Development (R01HD081299), and National Institute of General Medical Sciences (R16GM146679). M.F.P. is a member of the Scientific Advisory Board for Simcyp, Certara UK Limited.

K.A.: No COI/disclosures.

R.D.B. receives grant funding from the National Center for Complementary and Integrative Health and Office of Dietary Supplements (U54AT008909) and the Jewish Healthcare Foundation. R.D.B. is a board member of the nonprofit CFC International.

Data Availability Statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information.

References

1. The American Academy of Child and Adolescent Psychiatry (AACAP), *Marijuana and Teens* (Washington, DC: The American Academy of Child and Adolescent Psychiatry, 2023), https://www.aacap.org/AACAP/Families_and_Youth/Facts_for_Families/FFF-Guide/Marijuana-and-Teens-106.aspx.

2. A. Aran and D. Cayam-Rand, "Medical Cannabis in Children," *Rambam Maimonides Medical Journal* 11, no. 1 (2020): e0003.

3. Key Substance Use and Mental Health Indicators in the United States: Results from the 2021 National Survey on Drug Use and Health, (2021).

4. J. L. Beers, D. Fu, and K. D. Jackson, "Cytochrome P450-Catalyzed Metabolism of Cannabidiol to the Active Metabolite 7-Hydroxy-Cannabidiol," *Drug Metabolism and Disposition* 49, no. 10 (2021): 882–891.

5. E. J. Cox, N. Maharao, G. Patilea-Vrana, et al., "A Marijuana-Drug Interaction Primer: Precipitants, Pharmacology, and Pharmacokinetics," *Pharmacology & Therapeutics* 201 (2019): 25–38.

6. S. Bansal, M. F. Paine, and J. D. Unadkat, "Comprehensive Predictions of Cytochrome P450 (P450)-Mediated in Vivo Cannabinoid-Drug Interactions Based on Reversible and Time-Dependent P450 Inhibition in Human Liver Microsomes," *Drug Metabolism and Disposition* 50, no. 4 (2022): 351–360.

7. S. Bansal, N. Maharao, M. F. Paine, and J. D. Unadkat, "Predicting the Potential for Cannabinoids to Precipitate Pharmacokinetic Drug Interactions via Reversible Inhibition or Inactivation of Major Cytochromes P450," *Drug Metabolism and Disposition* 48, no. 10 (2020): 1008–1017.

8. S. Bansal, C. A. Zamarripa, T. R. Spindle, et al., "Evaluation of Cytochrome P450-Mediated Cannabinoid-Drug Interactions in Healthy Adult Participants," *Clinical Pharmacology and Therapeutics* 114, no. 3 (2023): 693–703.

9. C. J. Lucas, P. Galettis, and J. Schneider, "The Pharmacokinetics and the Pharmacodynamics of Cannabinoids," *British Journal of Clinical Pharmacology* 84, no. 11 (2018): 2477–2482.

10. J. R. Horn, P. D. Hansten, and L. N. Chan, "Proposal for a New Tool to Evaluate Drug Interaction Cases," *Annals of Pharmacotherapy* 41, no. 4 (2007): 674–680.

11. X. Li, P. Ndungu, S. B. Taneja, et al., "An Evaluation of Adverse Drug Reactions and Outcomes Attributed to Kratom in the US Food and Drug Administration Adverse Event Reporting System From January 2004 Through September 2021," *Clinical and Translational Science* 16, no. 6 (2023): 1002–1011.

12. P. M. Tregunno, D. B. Fink, C. Fernandez-Fernandez, E. Lázaro-Bengoa, and G. N. Norén, "Performance of Probabilistic Method to Detect Duplicate Individual Case Safety Reports," *Drug Safety* 37, no. 4 (2014): 249–258.

13. K. Madden, K. Tanco, and E. Bruera, "Clinically Significant Drug-Drug Interaction Between Methadone and Cannabidiol," *Pediatrics* 145, no. 6 (2020): e20193256.

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

14. D. A. Volpe, Y. Xu, C. G. Sahajwalla, I. R. Younis, and V. Patel, "Methadone Metabolism and Drug-Drug Interactions: In Vitro and in Vivo Literature Review," *Journal of Pharmaceutical Sciences* 107, no. 12 (2018): 2983–2991.

15. K. M. Robinson, S. Eum, Z. Desta, et al., "Clinical Pharmacogenetics Implementation Consortium Guideline for CYP2B6 Genotype and Methadone Therapy," *Clinical Pharmacology and Therapeutics* 116, no. 4 (2024): 932–938, https://doi.org/10.1002/cpt.3338.

16. L. Dean, "Amitriptyline Therapy and CYP2D6 and CYP2C19 Genotype," In *Medical Genetics Summaries [Internet]*, eds. V. M. Pratt, S. A. Scott, M. Pirmohamed, B. Esquivel, B. L. Kattman, and A. J. Malheiro (Bethesda, MD: National Center for Biotechnology Information, 2017), http://www.ncbi.nlm.nih.gov/books/NBK425165/.

17. S. Nasrin, C. J. W. Watson, Y. X. Perez-Paramo, and P. Lazarus, "Cannabinoid Metabolites as Inhibitors of Major Hepatic CYP450 Enzymes, With Implications for Cannabis-Drug Interactions," *Drug Metabolism and Disposition* 49, no. 12 (2021): 1070–1080, https://doi.org/10.1124/dmd.121.000442.

18. A. E. Cossu, L. B. Latham, D. M. Hardacker, and A. H. Jea, "Pharmacologic Chaos: Severe Hypotension From Interactions of Anesthetics, Marijuana, Amphetamines, and Paroxetine," *Journal of Clinical Anesthesia* 55 (2019): 17.

19. S. A. Smith, G. H. Le, K. M. Teopiz, et al., "Effects of Cannabidiol and Δ^9-Tetrahydrocannabinol on Cytochrome P450 Enzymes: A Systematic Review," *Drug Metabolism Reviews* 56, no. 2 (2024): 164–174, https://doi.org/10.1080/03602532.2024.2346767.

20. R. K. Singh, B. Dillon, D. A. Tatum, K. C. Van Poppel, and D. J. Bonthius, "Drug-Drug Interactions Between Cannabidiol and Lithium," *Child Neurology Open* 13, no. 7 (2020): 2329048X20947896.

21. K. A. Klotz, M. Hirsch, M. Heers, A. Schulze-Bonhage, and J. Jacobs, "Effects of Cannabidiol on Brivaracetam Plasma Levels," *Epilepsia* 60, no. 7 (2019): e74–e77.

22. A. Wiemer-Kruel, B. Stiller, and T. Bast, "Cannabidiol Interacts Significantly With Everolimus-Report of a Patient With Tuberous Sclerosis Complex," *Neuropediatrics* 50, no. 6 (2019): 400–403.

23. T. E. Wilens, J. Biederman, and T. J. Spencer, "Case Study: Adverse Effects of Smoking Marijuana While Receiving Tricyclic Antidepressants," *Journal of the American Academy of Child and Adolescent Psychiatry* 36, no. 1 (1997): 45–48.

24. R. de la Torre, S. Yubero-Lahoz, R. Pardo-Lozano, and M. Farré, "MDMA, Methamphetamine, and CYP2D6 Pharmacogenetics: What Is Clinically Relevant?," *Frontiers in Genetics* 3 (2012): 235.

25. C. L. DeVane, H. L. Liston, and J. S. Markowitz, "Clinical Pharmacokinetics of Sertraline," *Clinical Pharmacokinetics* 41, no. 15 (2002): 1247–1266.

26. 205836s009,205837s007,205838s006lbl.pdf [Internet], (2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/205836s009,205837s007,205838s006lbl.pdf.

27. 020031s067,020710s031.pdf [Internet], (2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020031s067,020710s031.pdf.

28. B. Supparamaniam, R. Yunus, J. Y. Fong, and K. L. Tang, "Accidental Methadone Poisoning in a Four-Year-Old Child Reversed With Continuous Intravenous Infusion of Naloxone," *International Journal of Clinical Pediatrics* 10, no. 1 (2021): 18–23.

29. 022334s6lbl.pdf [Internet], (2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022334s6lbl.pdf.

30. L. L. Anderson, J. C. Arnold, I. S. McGregor, and T. R. Nation, "A Potential Drug-Gene-Drug Interaction Between Cannabidiol, CYP2D6*4, and Fluoxetine: A Case Report," *Journal of Clinical Psychopharmacology* 42 (2022): 422–424, https://doi.org/10.1097/JCP.0000000000001568.

31. 018936s108lbl.pdf [Internet], (2023), https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018936s108lbl.pdf.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

20521707, 2025, 1, Downloaded from https://bpspubs.onlinelibrary.wiley.com/doi/10.1002/prp2.70046, Wiley Online Library on [13/12/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License