










## ARTICLE OPEN ACCESS

# Genotype-Specific Safety and Pharmacokinetics of Cannabidiol in Healthy Volunteers

Jumar Etkins<sup>1</sup>  | Gerald C. So<sup>1</sup>  | Jessica Bo Li Lu<sup>1</sup> | Sachiko Koyama<sup>2</sup>  | Debora L. Gisch<sup>1</sup>  | Ricardo Melo Ferreira<sup>2</sup>  | Ying-Hua Cheng<sup>2</sup>  | Kelsey McClara<sup>1</sup> | Joshua Jun<sup>1</sup> | Matthew Miller<sup>1</sup>  | Zeruesenay Desta<sup>1</sup>  | Michael T. Eadon<sup>1,2</sup> 

<sup>1</sup>Division of Clinical Pharmacology, Indiana University School of Medicine, Indianapolis, Indiana, USA | <sup>2</sup>Division of Nephrology, Indiana University School of Medicine, Indianapolis, Indiana, USA

**Correspondence:** Michael T. Eadon ([meadon@iu.edu](mailto:meadon@iu.edu))

**Received:** 1 October 2025 | **Revised:** 30 November 2025 | **Accepted:** 9 December 2025

**Keywords:** 7OH-cannabidiol | adverse drug event | CYP2C19 | CYP2C9 | CYP3A4/5 | drug-drug interaction | pharmacogenomics

## ABSTRACT

Cannabidiol (CBD) use has increased in America due to its widespread availability. Cannabidiol is metabolized by multiple polymorphic enzymes including CYP3A, CYP2C9, and CYP2C19. We sought to evaluate the genotype-specific adverse events and pharmacokinetic profiles of cannabidiol, 7-OH cannabidiol (an active metabolite), and 7-COOH cannabidiol. We completed a secondary analysis of an open-label, fixed-sequence, single-center study of cannabidiol in 33 healthy subjects. Patients first received a single dose of cannabidiol 5 mg/kg orally with serial plasma concentrations measured. Later, patients were titrated to 5 mg/kg twice daily for 14 days to reach steady state with serial plasma concentrations measured. CYP3A, CYP2C9, and CYP2C19 genotypes were assessed. Pharmacokinetic parameters were calculated by noncompartmental analysis. Diarrhea was observed more frequently in individuals with both CYP3A5 poor metabolism and CYP2C19 intermediate/normal metabolism (39%) compared to individuals with other genotypes (7%,  $p=0.0463$ ). Individuals with both CYP3A5 poor metabolism and CYP2C19 intermediate/normal metabolism had increased 7-OH cannabidiol and 7-COOH cannabidiol exposure at steady state. Cannabidiol parent drug exposure varied by CYP2C19 metabolizer status, with lower cannabidiol exposure and parent to metabolite ratios in intermediate metabolizers after single dose ( $p=0.014$ ) and at steady state ( $p=0.0033$ ). Similar CYP2C19 genotype-specific exposure was observed in an external validation cohort. Minor differences in exposure of cannabidiol and its metabolites were observed between CYP3A5 and CYP2C9 genotype groups. Significant changes in pharmacokinetics were observed between CYP2C9, CYP2C19, and CYP3A5 genotype groups. Future studies should assess whether pharmacogenomics can predict intestinal concentrations of CBD, its metabolites, and diarrhea.

## 1 | Introduction

Cannabidiol (CBD) is the major non-psychotic cannabinoid derived from *Cannabis sativa L* and is commonly available in the United States without a prescription. US sales of CBD were estimated to reach upwards of \$20 billion in 2024, marking a steady increase in usage [1, 2]. CBD has many side effects including somnolence, decreased appetite, diarrhea, pyrexia, fatigue, drowsiness, rash, and ataxia [3]. CBD is subject to wide

interindividual pharmacokinetic variability from differences in both absorption and metabolism [4]. With unrestricted access and minimal dosing guidance, consumers may be exposed to unforeseen risks.

CBD has a complex metabolic pathway, with parent drug and metabolites involved in drug-drug interactions (DDI) as a substrate, inhibitor, or inducer of drug metabolizing enzymes [5–8]. These DDIs occur due to the extensive first-pass

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) 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.

© 2025 The Author(s). *Clinical and Translational Science* published by Wiley Periodicals LLC on behalf of American Society for Clinical Pharmacology and Therapeutics.

## Study Highlights

- What is the current knowledge on the topic?
  - Cannabidiol (CBD) use has increased across America due to its widespread availability over the counter and via prescription. Cannabidiol is metabolized by multiple polymorphic enzymes, including CYP3A, CYP2C9, and CYP2C19. The relationship between genotype and adverse events is not known.
- What question did this study address?
  - This study evaluated the genotype-specific adverse events and pharmacokinetics of cannabidiol, 7-OH cannabidiol and 7-COOH cannabidiol.
- What does this study add to our knowledge?
  - This study demonstrates that pharmacogenomic variants lead to mild drug–gene interactions, with changes in pharmacokinetics and incidence of diarrhea associated with CBD and metabolite exposure.
- How might this change clinical pharmacology or translational science?
  - The results of this study show changes in CBD parent drug and metabolite pharmacokinetics based on CYP2C9, CYP2C19, and CYP3A5 genotypes. Future investigations should assess whether pharmacogenomics may predict intestinal concentrations of CBD metabolites and related diarrhea.

metabolism of CBD and its ability to modulate multiple cytochrome P450 (CYP450) enzymes [6, 9]. Phase 1 metabolic enzymes such as CYP2C19 and CYP2C9 are responsible for the conversion of CBD to 7-hydroxy-CBD (7-OH-CBD), the primary active metabolite [5, 10]. CBD may also form minor metabolites via CYP3A4/5 or other major inactive metabolites by UDP-glucuronosyltransferases (UGT) enzymes [11]. In contrast, 7-OH-CBD is metabolized into the inactive 7-carboxy-CBD (7-COOH-CBD), the most abundant circulating metabolite in plasma, by aldehyde dehydrogenase (ALDH) enzymes with minor phase 1 involvement [12].

Several human studies have evaluated CBD's role as a perpetrator of DDIs; however, fewer have investigated CBD as a victim of drug–drug or drug–gene interactions [3, 13]. Pharmacogenomic polymorphisms in phase 1 metabolic enzymes increase tetrahydrocannabinol (THC) exposure in humans and alter metabolism in vitro [14, 15]. Pharmacogenomic variation may also impact CBD exposure. One human study suggested CYP2C9 and CYP2C19 predicted enzyme function may affect CBD exposure [16], while a sub-study demonstrated CYP2C19 polymorphisms affected CBD exposure to a greater extent in females than males [17]. The impact of polymorphisms has also been evaluated in vitro and in silico [10]. The objective of this study is to evaluate the significance of CYP3A5, CYP2C19, and CYP2C9 genotypes on the pharmacokinetics (PK) and safety of CBD and its metabolites, 7-OH and 7-COOH CBD, in healthy adults.

## 2 | Methods

### 2.1 | Study Design

This is a secondary analysis of a phase 1, open label, fixed three period, genotype stratified single-center study in 33 healthy volunteers designed primarily to test the effect of CBD on tacrolimus pharmacokinetics and pharmacodynamics (PD). The trial was conducted in accordance with the ethical standards of the Declaration of Helsinki. The study is registered with [Clini caltrials.gov](https://clinicaltrials.gov) (NCT05490511), was approved by the Institutional Review Board of Indiana University (IRB #12763) and has an Investigational New Drug application (IND #158474) filed with the Food and Drug Administration (FDA). Written informed consent was obtained from all study participants at the screening visit. All study visits were conducted at the Indiana Clinical Research Center (ICRC). This study represents a secondary analysis of CBD PK in a larger DDI study [18].

### 2.2 | Participants

Recruitment was initiated on October 18, 2022, and was completed on October 31, 2024. This analysis included a cohort of 33 healthy participants with known CYP2C19, CYP3A5, and CYP2C9 genotype status who received at least one dose of CBD. Adults aged 18–75 were recruited and were stratified according to metabolizer status for the CYP enzymes of interest. The major exclusion criteria include liver impairment, kidney impairment, recent smoking history, having a known CYP3A4 \*22/22 genotype, and use of cannabis or marijuana as determined by a urine drug screen. Participants were required to hold or substitute any medications or supplements known to impact drug protein binding or inhibit or induce CYP3A4/5, CYP2C9, or CYP2C19 as determined by the study pharmacist.

### 2.3 | Study Procedures

In the single dose phase, participants received one dose of cannabidiol (EPIDIOLEX; Greenwich Biosciences, Carlsbad, CA) at 5 mg/kg orally with serial blood draws to determine pharmacokinetics. Samples were drawn prior to dosing, and at 20 m, 40 m, 60 m, 2 h, 4 h, 6 h, 12 h, 24 h and 48 h (for steady state) or 72 h after administration of CBD (for single dose). Samples were collected in ethylenediaminetetraacetic acid (EDTA)-containing tubes at each timepoint for quantification of CBD, 7-OH CBD and 7-COOH CBD. Participants received a standardized high-fat meal during pharmacokinetic sampling.

In the steady state phase, participants were administered CBD at 2.5 mg/kg for 3 days and then 5 mg/kg for 11 days to reach steady state. Samples were drawn at identical time points starting at day 12 to quantify CBD and its metabolites. Participants continued to take CBD twice daily during steady state pharmacokinetic sampling. Participants were asked to keep a journal and self-report ADEs during the trial.

Plasma samples were separated via centrifugation and stored at –80°C until analysis.

## 2.4 | Genotyping

Genotyping was performed at Indiana University Genomics Testing Laboratory using polymerase chain reaction (PCR) and TaqMan allele discrimination in a custom designed microarray as previously described [19]. Each subject's CYP2C19, CYP3A and CYP2C9 metabolizer status was classified according to CPIC guidelines [20] as ultrarapid metabolizer (UM), rapid metabolizer (RM), normal metabolizer (NM), intermediate metabolizer (IM) and poor metabolizer (PM) (Table S1). Given the unique CYP2C19 metabolism profile of CBD illustrated within the Epidiolex FDA drug label [2], we classified the one individual with a \*2/\*17 genotype as a NM. Unlike typical CYP2C19 substrates, CBD undergoes extensive metabolism via multiple pathways (CYP2C19, CYP3A4, and UGT enzymes), and the FDA label does not indicate a clinically significant reduction in clearance for \*2/\*17 carriers. This classification was intended to reflect potential CBD-specific pharmacogenetic behavior rather than general CPIC recommendations. CYP3A5 participants with \*1/\*1, \*1/\*3, \*1/\*6 or \*1/\*7 genotypes were classified as Expressors (Exp), and those with two nonfunctional alleles were classified as Non Expressors (NE).

## 2.5 | Quantification of CBD and Its Metabolites

The quantification method for CBD and its metabolites has been previously published [18], the procedures are briefly described. CBD, 7-OH CBD, and 7-COOH CBD were quantified with Ultra-High Performance Liquid Chromatography (UHPLC) paired with QTRAP 6500+ mass spectrometer equipped with an electrospray ionization source (ESI). The MultiQuant software 3.0.2 (ABSciex, Framingham, MA) was used for data acquisition and processing.

Briefly, plasma (200  $\mu$ L) was mixed with 300  $\mu$ L of internal standard (nevirapine, 25 ng/mL in methanol), vortexed, and extracted with methyl tertiary butyl ether (MTBE). The supernatant was evaporated, reconstituted in methanol, and 5  $\mu$ L was injected for LC-MS/MS analysis. Samples exceeding 1000 ng/mL were diluted 10-fold prior to injection. Calibration curves for cannabidiol ranged from 0.3 to 1000 ng/mL (methanol diluent), with a lower limit of quantification (LLOQ) of 0.3 ng/mL. Quality controls were prepared at 1, 80, and 800 ng/mL for cannabidiol. Acceptable intra- and inter-day variability was < 10% and < 20%, respectively.

## 2.6 | Pharmacokinetic Analysis

Pharmacokinetic parameters were determined in 30 of 33 participants due to study withdrawal ( $N=2$ ) or incomplete sampling ( $N=1$ ). Additionally, the steady state 7-OH CBD measurements of one participant failed quality control and were excluded from analyses. Pharmacokinetic parameters were estimated by non-compartmental analysis using Phoenix WinNonlin version 8.5.2 (Certara L.P, Princeton, NJ). Pharmacokinetic parameters were reported as arithmetic means with standard deviation (SD) except  $T_{max}$ , which was reported as median and range. The geometric mean was used to evaluate the magnitude of the interaction between each of the phenotypes.

The maximum plasma concentration ( $C_{max}$ ), last measured concentration ( $C_{last}$ ), and the time to  $C_{max}$  ( $T_{max}$ ) were recovered

directly from the concentration-versus-time data. Area under the plasma concentration time curve (AUC) was estimated via the linear up-log down trapezoidal method for  $AUC_{0-t}$ .  $AUC_{t-\infty}$  (extrapolated) was obtained from the ratio of  $C_{last}$  to terminal elimination rate constant ( $\lambda_z$ ).  $AUC_{0-\infty}$  was calculated as the sum of  $AUC_{0-t} + AUC_{t-\infty}$ .  $\lambda_z$  was estimated using the slope of the regression line fitted to the log plasma concentrations by the method of linear least squares. Clearance (CL/F) was calculated by dose/AUC ( $AUC_{0-\infty}$  for single dose and  $AUC_{0-t}$  for steady state), and volume of distribution ( $V_z/F$ ) was calculated by dividing CL/F by  $\lambda_z$ . The  $C_{max}$  and AUC parent to metabolite ratios (CBD/7-OH CBD) for each CYP2C19 phenotype group were also calculated.

For the primary endpoint, geometric mean ratios (GMRs) of  $C_{max}$  and  $AUC_{0-t}$  for CBD and its metabolites at steady state in CYP2C19 IM/NM were compared to RM/UM. Analogously, CYP3A5 groups were compared between Exp and NE. CYP2C9 NMs were also compared to IM/PM to quantify the magnitude of change in drug exposure.

## 2.7 | Validation Dataset

The pharmacokinetic data used in our validation analysis were accessed and analyzed from pharmacology review of GWEP 1543 approval [2]. The datapoints were determined using Webplotdigitizer [21] software and were replotted and used as a visual check.

## 2.8 | Safety

Adverse events (ADE) were reported by the participants in diaries, and the severity and relatedness to cannabidiol were assessed using National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 (NCI CTCAE v5.0) [22]. Adverse events were then graded on a scale of 1 to 5, with Grade 1 being no ADE and Grade 5 being a death related to ADE. No serious ADEs occurred.

## 2.9 | Statistical Analysis

Pharmacokinetic parameters were calculated as described above. For graphical depiction, we used GraphPad Prism 10.4.1 (GraphPad software, Boston, MA). The difference between the genotype groups was assessed using the Student's/Welch's  $T$  test after testing for equal variance. When assessing the difference among the different CYP2C19 genotypes, a one-way ANOVA was used. A  $p$  value < 0.05 was considered significant.

## 3 | Results

### 3.1 | Baseline Characteristics

Thirty-three participants were included in the intention-to-treat secondary analysis after receiving at least one dose of CBD. All 33 subjects completed journals recording adverse events. Of the 33 subjects, 30 individuals completed PK sampling in both the single dose and steady-state phases. Demographic and baseline characteristics are summarized in (Table S2).

Most participants were female (69.7%) with 54.5% white and 36.4% African American. The average eGFR was  $95.4 \pm 18.2$  mg/mL/1.73 m<sup>2</sup>. Several phase 1 enzymes are involved in CBD metabolism (Figure 1). We evaluated the genotype-defined metabolism status of these key enzymes in our population. Most subjects were CYP3A5 NE (69.7%). For CYP 2C19, subjects were frequently NM (48.5%) or IM (24.2%). For CYP2C9, 75.8% of the population were NM with only 1 PM.

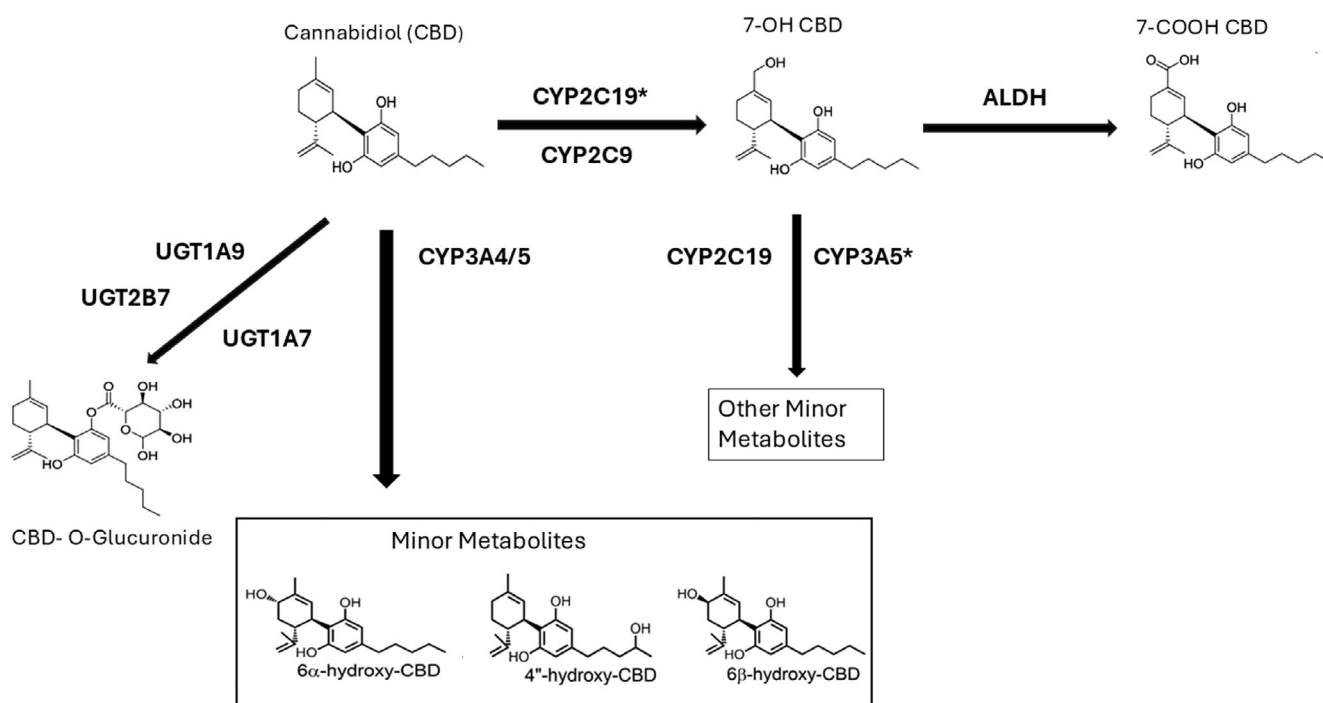
### 3.2 | Cannabidiol Pharmacokinetics in All Subjects

We calculated the plasma concentration versus time profiles in individuals ( $N=30$ ) for CBD, 7-OH CBD, 7-COOH CBD in the single dose and steady-state phases (Figure 2, Table S3).

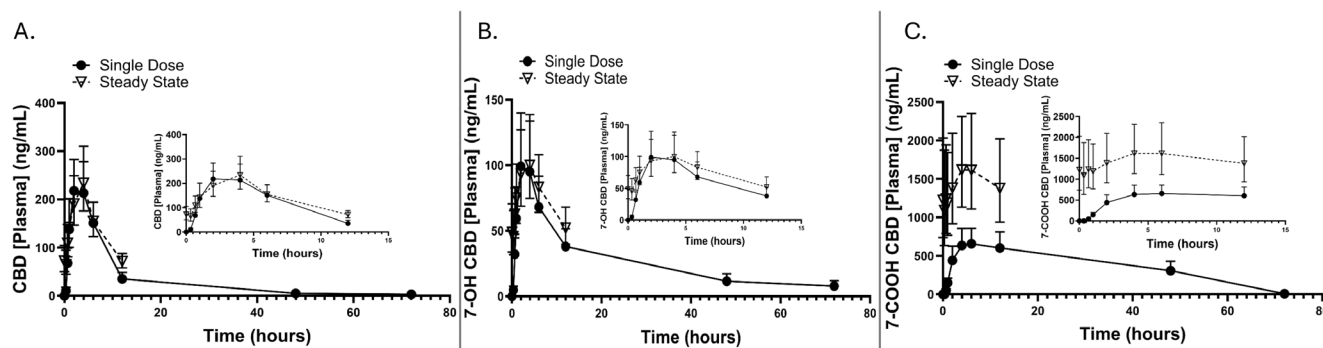
### 3.3 | CYP2C19 And CBD Exposure

The Epidiolex FDA pharmacology review reported an unexpected trend in increasing CBD concentrations from CYP2C19 IMs (lowest exposure)  $\leq$  NMs  $\leq$  RMs (highest exposure) [2]. We sought to assess this observation in our own cohort.

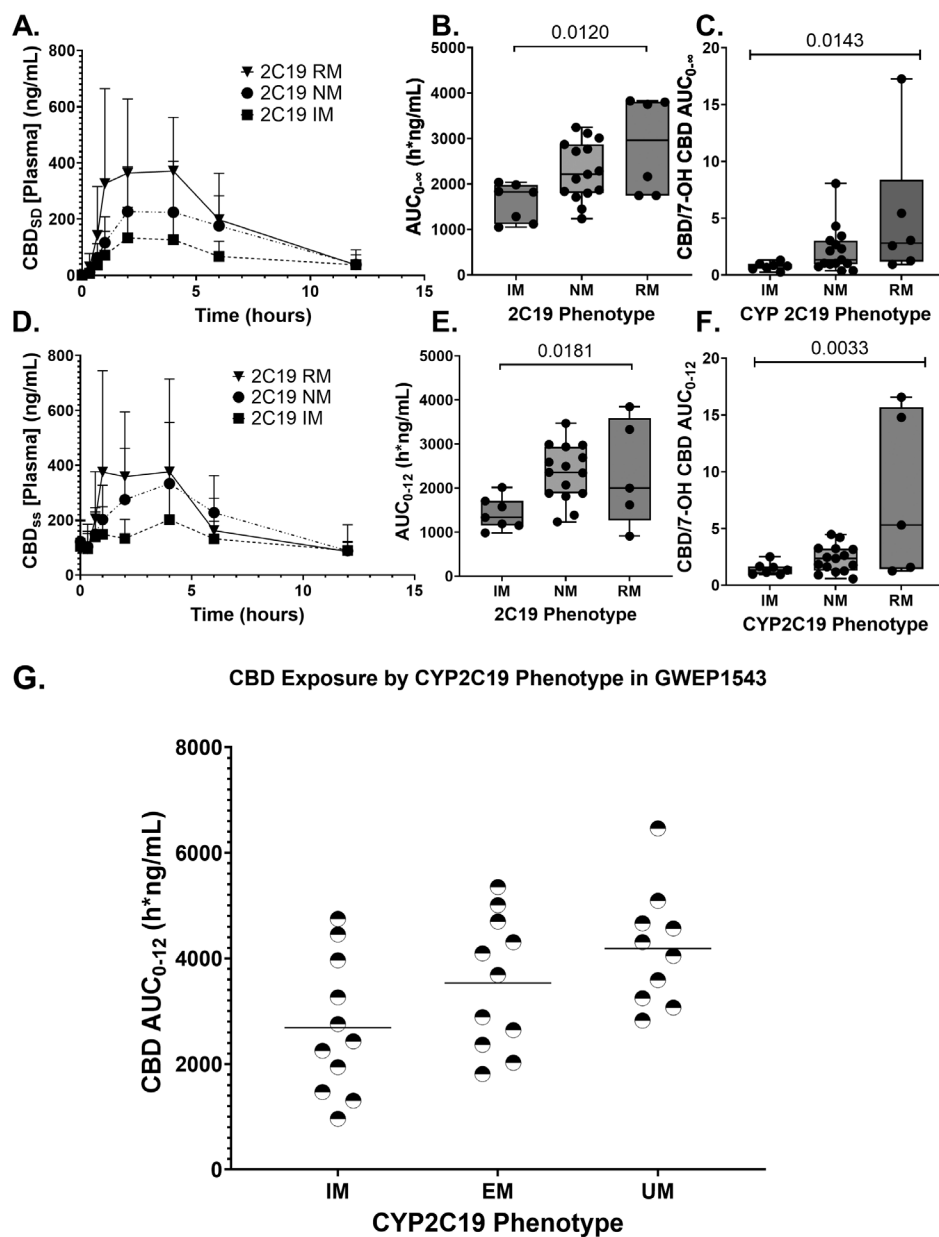
We similarly observed a significant difference in single dose and steady state CBD exposure associated with variable CYP2C19 genotype (Figure 3). The  $C_{max}$  and  $AUC_{0-\infty}$  or  $AUC_{0-12}$  increased with increasing CYP2C19 metabolizer status (Table 1). After a single dose of CBD, the  $AUC_{0-\infty}$  and  $C_{max}$  were lower in IM when compared to NM and RM. At steady state, the CBD  $AUC_{0-12}$  was significantly lower in IM compared to NM but not RM; the  $C_{max}$  followed a similar direction of effect. To understand the impact CYP2C19 phenotype has on metabolite formation, the parent to metabolite ratios (P/M) for cannabidiol and



**FIGURE 1** | The putative metabolic pathway of cannabidiol (CBD) and its metabolites 7-OH CBD and 7-COOH CBD, as supported by the work of Mazur [23] et al., Jiang [10] et al., and Beers [24] et al. \* indicates the major in vitro enzyme responsible for metabolism or clearance within that stage of the pathway.



**FIGURE 2** | Pharmacokinetic profiles of (A) CBD, (B) 7-OH CBD, and (C) 7-COOH CBD in 30 healthy volunteers. The mean plasma concentration-time plots after a single dose (solid circles) and steady state (open triangle) are provided on a linear scale. The inset magnifies the absorption phase from time 0 to 12h. Data points were plotted with geometric mean and 95% confidence interval.



**FIGURE 3** | CBD mean plasma concentration versus time plots, summaries, and parent to metabolite ratios after a single dose (A–C) and at steady state (D–F) with corresponding AUC<sub>0-∞</sub> or AUC<sub>0-12</sub> (respectively) with participants grouped according to their CYP2C19 phenotype ( $N=30$ ). There is a significant difference in exposure between genotype groups, with increased exposure associated with increased CYP2C19 activity (IM<NM<RM) after single dose. At steady state, the lowest exposure was again seen in the IM group. Parent to metabolite ratios (Cannabidiol to 7-OH cannabidiol) held significant trends after both single dose (C) and steady state (F). These results align with the direction of effect observed in the Epidiolex FDA pharmacology review (G) [2]. Data points were plotted with mean and standard deviation. Significance was tested via ordinary one-way ANOVA.

7-OH cannabidiol were also assessed (Table 1). The relative concentrations of CBD and 7-OH CBD were significantly different depending on CYP2C19 phenotype. After a single dose, the  $P/M_{AUC_{0-\infty}}$  was lowest in IM (0.69) compared to NM (1.54) and RM (3.08) with a significant intergroup difference ( $p=0.0143$ ). At steady state, the  $P/M_{AUC_{0-12}}$  values for IM (1.38) were also lower compared to NM (2.02) and RM (4.2) with a significant difference between the groups ( $p=0.0033$ , Figure 3C,F).

We reassessed publicly available Epidiolex exposure data by CYP2C19 genotype group from the FDA pharmacology review. The CBD exposure ( $AUC_{0-12}$ ) increased with increasing CYP2C19 metabolizer status, aligning with our dataset (Figure 3G).

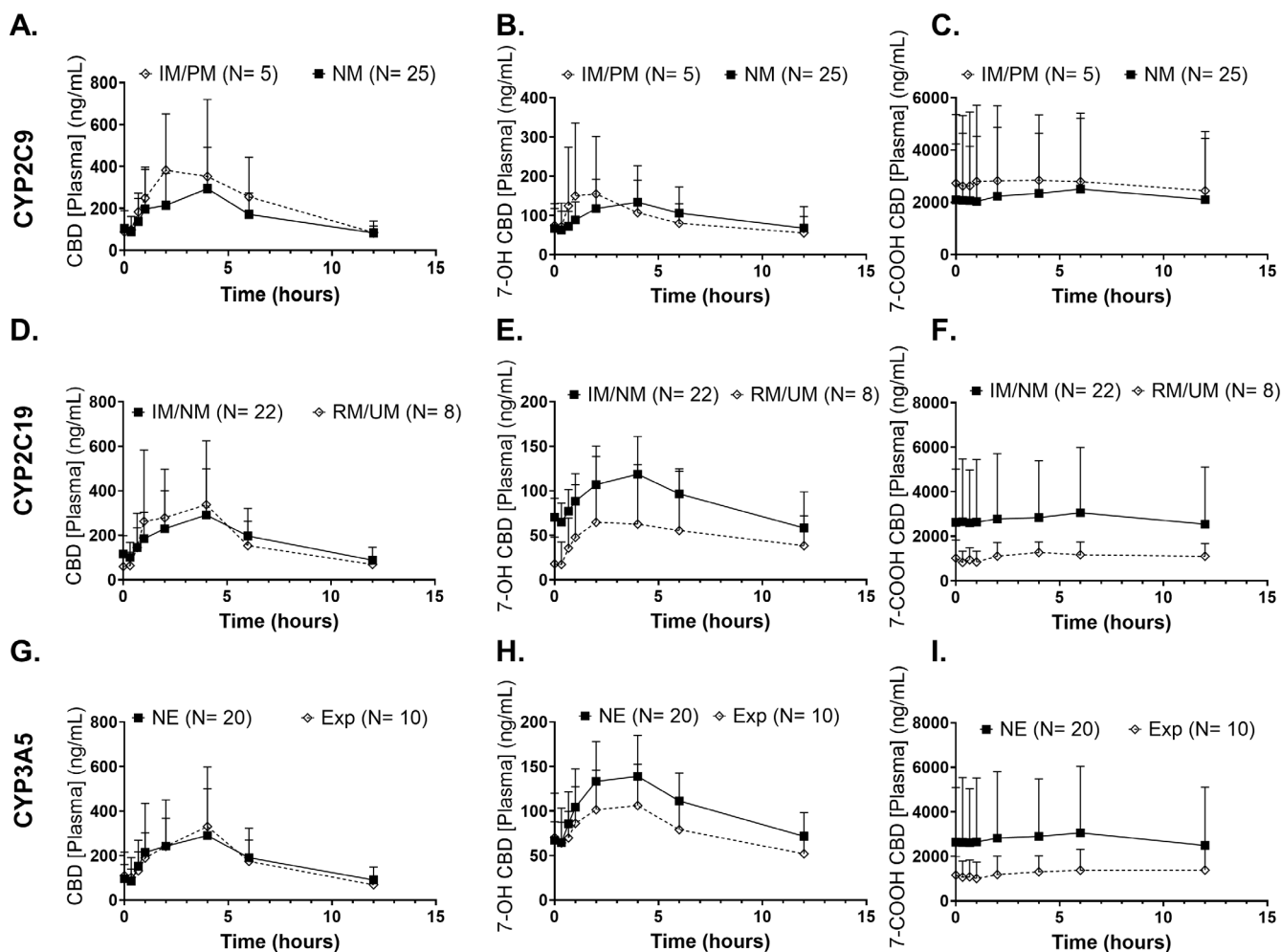
### 3.4 | Genotype—Specific Pharmacokinetics After Single Dose CBD

The single dose PK parameters for CBD and its metabolites were next evaluated in Table S4 for associations with CYP2C9, CYP2C19, and CYP3A5 genotype (Figure 4). CBD's single dose pharmacokinetics were minimally impacted by CYP2C9 and CYP3A5 genotype, and there was no significant change in clearance between the different genotype groups. For example, no significant difference was observed for the  $C_{max}$  based on CYP2C9 phenotype. For symmetry, we grouped CYP2C19 individuals into IM/NM genotypes and RM/UM genotypes (Figure 4D) and identified similar trends

**TABLE 1** |  $AUC_{0-\infty}$ , area under the curve from time zero to infinity;  $AUC_{0-12}$ , area under the curve from time zero to 12h, CBD, cannabidiol; 7-OH CBD, 7 Hydroxy cannabidiol; 7-COOH CBD, 7 Carboxy cannabidiol;  $C_{max}$ , maximal blood concentration; (P/M); parent to metabolite ratios for cannabidiol and 7-OH cannabidiol. Statistical significance between groups was tested via ordinary one-way ANOVA.

Single dose	IM (N = 7)	NM (N = 15)	RM (N = 6)	GMR (IM/NM)	P	GMR (IM/RM)	P	GMR (NM/RM)	P
<b>CBD</b>									
$C_{max}$	190 ± 84.1	353.1 ± 148.5	433.6 ± 282.2	0.51 (0.28–0.92)	0.023*	0.48 (0.23–0.98)	0.043*	0.938 (0.50–1.74)	0.96
$AUC_{0-\infty}$	1591 ± 423	2283 ± 636.8	2839 ± 1057	0.70 (0.49–1.0)	0.052	0.57 (0.37–0.89)	0.011*	0.82 (0.56–1.2)	0.42
<b>7-OH CBD</b>									
$C_{max}$	107.2 ± 42.7	141.4 ± 118.5	86.9 ± 56.2	0.91 (0.4–2.1)	0.96	1.5 (0.55–4.2)	0.55	1.7 (0.69–3.9)	0.33
P/M (CBD/7OH) $C_{max}$	1.69 ± 0.87	3.0 ± 2.2	5.4 ± 25.9	0.55 (0.21–1.4)	0.29	0.31 (0.09–1.0)	0.051	0.56 (0.2–1.5)	0.35
$AUC_{0-\infty}$	2644 ± 2099	1545 ± 957.4	1146 ± 712	1.56 (0.61–3.9)	0.47	2.57 (0.82–7.9)	0.12	1.6 (0.64–4.4)	0.43
P/M (CBD/7OH) $AUC_{0-\infty}$	0.69 ± 0.33	1.5 ± 2.0	3.1 ± 6.2	0.44 (0.17–1.1)	0.11	0.22 (0.06–0.73)	0.011*	0.50 (0.18–1.4)	0.22
<b>7-COOH CBD</b>									
$C_{max}$	730.8 ± 588.5	507 ± 712.9	581.3 ± 230.6	1.4 (0.46–4.5)	0.7	1.3 (0.3–5.0)	0.91	0.87 (0.26–2.9)	0.95
$AUC_{0-\infty}$	29,118 ± 15,968	23,583 ± 47,687	17,604 ± 9899	1.2 (0.36–4.2)	0.9	1.7 (0.37–7.4)	0.68	1.3 (0.36–4.9)	0.84
<b>Steady state</b>									
<b>CBD</b>									
$C_{max}$	302.5 ± 62	428.1 ± 187	435.9 ± 360	0.71 (0.43–1.17)	0.21	0.62 (0.33–1.18)	0.18	0.88 (0.49–1.5)	0.85
$AUC_{0-12}$	1384 ± 361.7	2255.7 ± 630	1897.9 ± 1179	0.61 (0.41–0.91)	0.01*	0.67 (0.40–1.1)	0.14	1.0 (0.69–1.7)	0.88
<b>7-OH CBD</b>									
$C_{max}$	156 ± 47.3	171.3 ± 124.4	68.1 ± 53	0.91 (0.43–1.9)	0.94	2.4 (0.93–6.2)	0.07	2.63 (1.1–6.0)	0.021*
P/M (CBD/7OH) $C_{max}$	1.94 ± 0.88	2.5 ± 1.7	7.5 ± 13.2	0.77 (0.34–1.7)	0.72	0.26 (0.09–0.73)	0.0098*	0.33 (0.13–0.83)	0.017*
$AUC_{0-12}$	1003.5 ± 254	1114.7 ± 720.9	554.8 ± 546.4	0.90 (0.44–1.8)	0.92	2.2 (0.9–5.3)	0.08	2.4 (1.1–5.3)	0.023*
P/M (CBD/7OH) $AUC_{0-12}$	1.38 ± 0.54	2.0 ± 1.2	4.2 ± 7.3	0.68 (0.31–1.5)	0.45	0.28 (0.10–0.78)	0.01*	0.42 (0.17–1.0)	0.055
<b>7-COOH CBD</b>									
$C_{max}$	2367 ± 1443	2131 ± 3556	351.9 ± 360.8	1.1 (0.36–3.3)	0.96	1.47 (0.3–5.6)	0.75	1.3 (0.4–4.2)	0.82
$AUC_{0-12}$	1539.4 ± 361.7	2196.2 ± 630.6	2667.3 ± 1179.2	1.1 (0.33–3.5)	0.98	1.54 (0.36–6.4)	0.73	1.4 (0.4–4.9)	0.75

\*p < 0.05.



**FIGURE 4** | Mean (and standard deviation) plasma concentration versus time graphs are depicted for (A, D, G) CBD, (B, E, H) 7-OH CBD, and (C, F, I) 7-COOH CBD after a single dose of CBD was administered. Groups are compared according to metabolic enzyme genotype for (A–C) CYP2C9, (D–F) CYP2C19, and (G–I) CYP3A5. Significance was tested by Student's *T* test.

in CBD  $C_{max}$  and  $AUC_{0-\infty}$  in the same direction of effect as in Figure 1.

For 7-OH CBD and 7-COOH CBD, no statistically significant difference in  $C_{max}$  or  $AUC_{0-\infty}$  was observed between CYP2C9 genotypes. However, a mild drug-metabolite-gene interaction was appreciated for 7-OH CBD and 7-COOH CBD based on CYP3A5 genotype. The 7-OH CBD  $C_{max}$  was 58% higher in CYP3A5 NE compared to Exp. The 7-COOH CBD  $AUC_{0-\infty}$  and  $C_{max}$  were 32% and 53% higher in CYP3A5 NE respectively when compared to CYP3A5 Exp. For CYP2C19, no significant difference in 7-OH CBD was observed between CYP2C19 metabolizer groups. However, the direction of effect of the metabolite inversely correlated with the parent drug. For 7-COOH CBD, the  $AUC_{0-\infty}$  was 66% higher in CYP2C19 IM/NM compared to RM/UM and the  $C_{max}$  trended higher in CYP2C19 IM/NM compared to RM/UM.

### 3.5 | Genotype—Specific Pharmacokinetics at Steady-State CBD

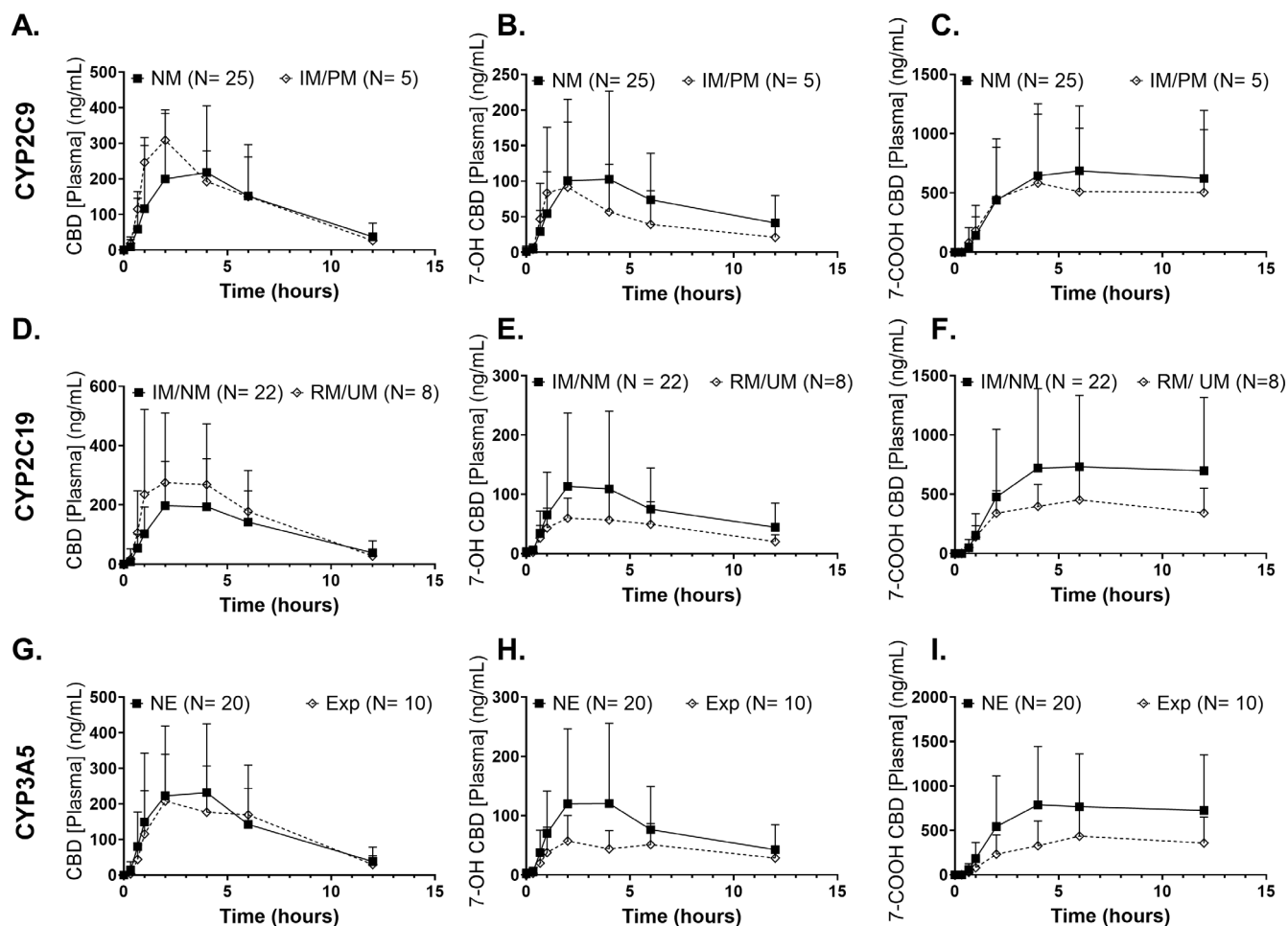
We next evaluated the genotype-specific differences in CBD, 7-OH CBD, and 7-COOH CBD at steady state (Table S4). At steady state, no significant difference was seen between CYP2C19 and

CYP3A5 genotype groups. However, a mild drug-gene interaction was appreciated for CBD and CYP2C9 as the CBD  $C_{max}$  was 73% higher for CYP2C9 IM/PM compared to 2C9 NM (Figure 5).

For CYP2C9, no difference was observed in 7-OH CBD or 7-COOH metabolite exposure. Mild differences were observed in 7-OH CBD metabolite exposure for CYP2C19 IM/NM who had a 78% higher  $AUC_{0-\tau}$  and 96% higher  $C_{max}$  compared to CYP2C19 RM/UM. For 7-COOH CBD, the  $AUC_{0-\tau}$  was 71% higher and  $C_{max}$  was 60% greater in CYP2C19 IM/NM compared to RM/UM. For CYP3A5, no significant increase in 7-OH CBD  $AUC_{0-\tau}$  was observed in CYP3A5 NE compared to Exp. For 7-COOH CBD, CYP3A5 NE had a 61% higher  $AUC_{0-\tau}$  vs. Exp and a 69% higher  $C_{max}$  as well.

### 3.6 | Safety

No severe or life-threatening ADEs were reported within the cohort. A total of 20 of 33 (60.1%) subjects experienced at least one related ADE (Tables S5–S8). In the entire cohort, 24.2% of participants had diarrhea reported during the single-dose, titration, or steady-state phases (Figure 6). A greater incidence of diarrhea was appreciated in individuals with both CYP3A5 NE and CYP2C19 IM/NM genotypes (7 of 18, 39%), compared



**FIGURE 5** | Mean (and standard deviation) plasma concentration versus time graphs are depicted for (A, D, G) CBD, (B, E, H) 7-OH CBD, and (C, F, I) 7-COOH CBD at steady state after 11 days of CBD 5 mg/kg twice daily was taken. Groups are compared according to metabolic enzyme genotype for (A–C) CYP2C9, (D–F) CYP2C19, and (G–I) CYP3A5. Significance was tested by Student's *T* test.

to those with either CYP3A5 Exp or CYP2C19 RM/UM (1 of 15, 7%,  $p=0.04$ ). CYP2C19 IM/NM subjects accounted for (7 of 8, 87.5%) of all diarrhea cases; however, these participants could not be analyzed separately due to substantial overlap with CYP3A5 NE.

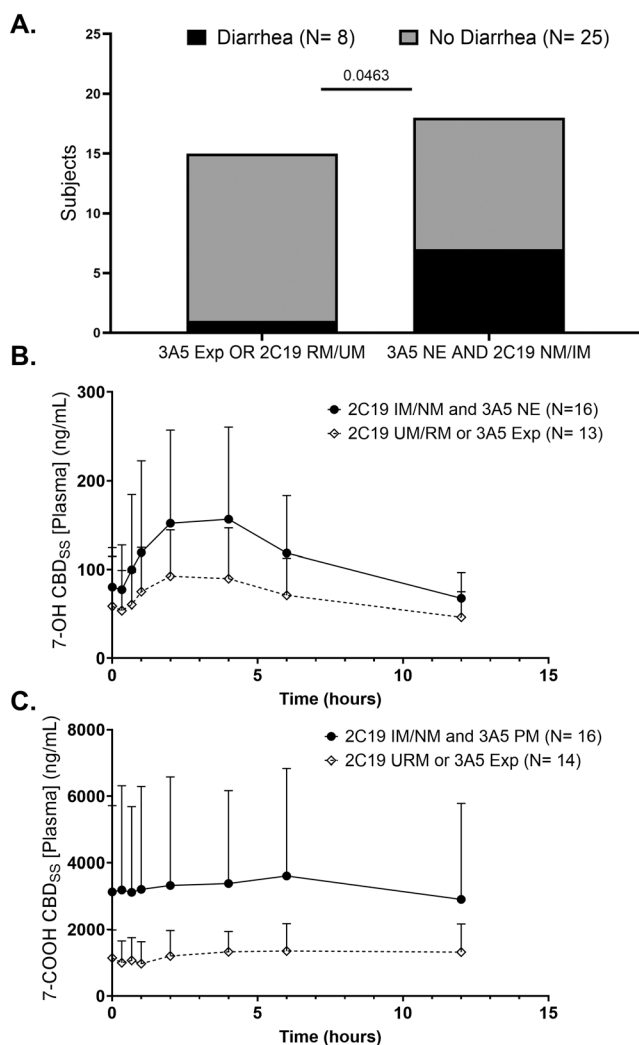
Based on this ADE observation, we next assessed the pharmacokinetics in individuals with both CYP3A5 NE and CYP2C19 IM/NM genotypes. These individuals had higher 7-OH-CBD exposure compared to the rest of the cohort with a 73% higher  $AUC_{0-\tau}$  and 87% higher  $C_{max}$  when compared to patients who were either CYP3A5 Exp or CYP2C19 RM/UM ( $AUC_{0-\tau}$ :  $1153 \pm 680.5$  hour\*ng/mL versus  $667.4 \pm 382.8$  hour\*ng/mL,  $p=0.023$  and  $C_{max}$ :  $179.1 \pm 116.7$  versus  $95.9 \pm 67.1$  ng/mL,  $p=0.017$ ). For steady state 7-COOH CBD, the CYP3A5 NE and CYP2C19 IM/NM group had 83% higher  $AUC_{0-\tau}$  and 89% higher  $C_{max}$  when compared to other participants ( $AUC_{0-\tau}$ :  $37747 \pm 33,325$  hour\*ng/mL versus  $14497 \pm 8500$  hour\*ng/mL,  $p=0.015$ , and  $C_{max}$ :  $3994 \pm 3341$  versus  $1601 \pm 798$  ng/mL,  $p=0.013$ ).

Although diarrhea was mostly observed in the CYP2C19 IM/NM genotype, we assessed the combined effects of CYP2C19 RM/UM with CYP3A5 NE as a sensitivity analysis because of their overlapping direction of effect in parent CBD exposure.

Only 4 individuals were both CYP2C19 RM/UM and CYP3A5 NE. The direction of  $C_{max}$  and AUC of 7-OH CBD reversed, suggesting that CYP2C19 is a larger contributor to the exposure of 7-OH CBD, albeit in only 4 subjects.

## 4 | Discussion

The popularity of cannabidiol has increased due to its utilization as an over-the-counter substance with anti-inflammatory, anti-anxiolytic, and antiepileptic therapeutic properties [25, 26]. There exists significant interindividual variability in CBD exposure which may contribute to a wide array of ADEs [27, 28]. Dosing guidance for CBD may help to reduce future ADEs. There are multiple factors which affect CBD exposure, including liver function, the post-prandial or fed state, adipose tissue proportion, high fat consumption, and sex [2, 4, 17, 28, 29]. The impact of genotype on CBD's wide variability of exposure has been infrequently explored, especially in diverse populations. In this study, we assessed the association of genotype with adverse events and pharmacokinetic exposure of CBD, 7-OH CBD, and 7-COOH CBD in healthy adults. Our results demonstrated that polymorphisms in CYP2C9, CYP2C19, and CYP3A5 were associated with modest changes in pharmacokinetic exposure to cannabidiol after a single dose or at steady state. Most



**FIGURE 6** | Diarrhea adverse events in genotype groups. (A) Diarrhea was more frequently observed in individuals with both CYP3A5 NE and CYP2C19 IM/NM genotypes (7 of 18, 39%), compared to those with either CYP3A5 Exp or CYP2C19 RM/UM (1 of 15, 7%,  $p=0.04$ ). Concentration versus time curves reveal differences in (B) 7-OH CBD and (C) 7-COOH exposure as individuals with both CYP3A5 NE and CYP2C19 IM/NM genotypes had higher exposure of both compared to the rest of the cohort. Data points were plotted with mean and standard deviation. Significance was assessed by chi-square analysis (A) or Student's *T* test (B–C).

PGx-associated changes in AUC were commensurate with the magnitude of a mild drug–drug interaction (25% to 100% increase in AUC). We also identified a signal that CYP2C19 and CYP3A5 genotypes were associated with pharmacokinetics of CBD metabolites and the incidence of diarrhea in this cohort.

Previous studies have demonstrated that the CYP2C9, CYP2C19, and CYP3A enzymes are responsible for the metabolism of CBD, with CYP2C9 and CYP2C19 predominantly responsible for 7-OH CBD formation [5, 10]. 7-OH CBD is a pharmacologically active metabolite that is further metabolized (inactivated) into 7-COOH CBD mainly by aldehyde dehydrogenase, and to some extent through CYP2C19 and CYP3A5 [5, 12]. Importantly, CBD and 7-OH CBD both undergo glucuronidation by UGT enzymes, which is purported to be the dominant clearance pathway

[11]. This study focused on phase 1 metabolism and identified changes in AUC and  $C_{max}$  which were partially consistent with the metabolic pathway of CBD. For example, we identified increased  $C_{max,ss}$  of CBD in individuals with CYP2C9 IM and PM genotypes, which have been previously reported [16] and align with the known CYP2C9 drug–drug interaction [5, 6, 9, 30–32].

Although somewhat counterintuitive, our results also demonstrated that CBD concentrations increased with CYP2C19 activity. This unexpected direction of effect was also seen in the FDA Epidiolex Clinical Pharmacology Review [2]. The underlying mechanism for this paradoxical *in vivo* finding is unknown. *In vitro* studies have not demonstrated an association between CYP2C19 genotype and CBD or 7-OH CBD clearance [5, 33]; however, 7-OH CBD formation was positively correlated with CYP2C19 activity [5, 10]. It is possible that phase 2 metabolism [11], other alternative pathways, or changes in absorption [4] contribute to the results we observed.

Our participants took high dose Epidiolex at 5 mg/kg twice daily. One hypothesis proposed by Beers et al. is that the relative contribution of CYP2C9 to 7-OH CBD formation is dependent on both CBD concentration and the CYP2C19 activity level within that individual [5]. CBD inhibits CYP2C9 and CYP2C19 metabolism at steady state. In the Beers study, inhibition of CYP2C9 was more impactful than CYP2C19 inhibition in reducing 7-OH CBD formation in individuals with high CYP2C19 activity [5]. This phenomenon has also been observed for tetrahydrocannabinol (THC), as the formation of its CYP2C9 dependent metabolite 11-OH THC has increased metabolic contribution from CYP2C19 when CYP2C9 functionality is impaired [34]. 7-OH CBD inhibits CYP2C9 in a concentration dependent manner, but inhibits CYP2C9 and CYP3A time-dependently with less potency than CBD [5]. An additional contributor to CYP2C19-specific inhibition may be the location of CBD hydroxylation, wherein a free phenolic hydroxyl group and the pentyl side chain is an important requisite for CYP2C19 inhibition [35]. Thus, the possibility that concentration dependent metabolism of CBD by CYP2C9 occurs cannot be ruled out.

Two additional *in vivo* studies demonstrated different mechanisms for CYP2C19 and CYP3A inhibition of CBD metabolism. Bansal et al. determined that time-dependent inhibition (TDI) was present for both CYP2C19 and CYP3A [6, 9, 30] while Nasrin et al. observed a mixed-type inhibition for CYP2C19 with competitive reversible inhibition for CYP3A4 [7]. The CYP2C9  $K_i$  value ( $5.6\mu\text{M}$ ) is 5 times higher than that of CYP3A4 ( $1.0\mu\text{M}$ ), CYP2C19 ( $0.79\mu\text{M}$ ), or 17 CYP3A5 ( $0.19\mu\text{M}$ ), suggesting that at lower concentrations, CYP2C9 is minimally inhibited while CYP2C19 and CYP3A4/5 will be inhibited at lower concentrations, based on the single dose  $K_i$  values [36, 37]. The CYP2C9  $f_m$  is the rate limiting step, supporting a paradigm of rapid reversible inhibition. The parent to metabolite (P/M) ratios for CYP2C19 IM and RM were 0.69 and 3.08 respectively after a single dose, supporting the reduced contribution of 7-OH CBD to CYP2C19 inhibition.

The adverse event profile of CBD is well characterized. Many studies demonstrate that somnolence, decreased appetite, diarrhea, pyrexia, fatigue, drowsiness, and ataxia are among the most prevalent ADEs [3, 27]. Diarrhea was the most prevalent likely-related ADE in our study. Further analysis showed that

subjects that were both CYP3A5 NE and CYP2C19 IM/NM were disproportionately affected by diarrhea. Individuals with both CYP3A5 NE and CYP2C19 IM/NM genotypes also had higher 7-OH CBD and 7-COOH CBD  $AUC_{0-\tau}$  than the rest of the cohort. We do not suggest a cause-and-effect relationship between plasma 7-OH CBD or 7-COOH CBD concentrations and diarrhea. However, plasma metabolite concentrations may serve as a marker of intestinal metabolism because both CYP2C19 and CYP3A5 enzymes are expressed locally [38]. Prior studies have predicted that 7-OH intestinal formation may exceed plasma concentrations [9]. Future studies should measure fecal concentrations of CBD and its metabolites to correlate with genotype.

This study has limitations. First, we only examined phase 1 metabolism. Multiple publications have demonstrated the importance of phase 2 enzymes in CBD metabolism [11, 23]. A second limitation is that this study is a secondary analysis with a small sample size, which precluded evaluation of sex and age in multivariable enzyme modeling. Third, grouping metabolizer phenotypes for analysis can increase the risk of type I or type II error and complicate the interpretation of pharmacogenomic associations [39]. Finally, our study did not collect urine or fecal concentrations of metabolites.

The results of this secondary analysis show modest but significant changes in PK based on CYP2C9, CYP2C19, and CYP3A5 genotypes. Due to the wide therapeutic window and range of CBD doses, pharmacogenomic testing may hold questionable utility to predict ADEs related to plasma concentrations. Future investigations should assess whether pharmacogenomics may predict intestinal concentrations of CBD metabolites and related diarrhea. Such studies require larger populations with fecal metabolite concentrations to confirm the results of this study.

---

### Author Contributions

J.E., S.K., D.L.G., Z.D., and M.T.E. wrote the manuscript. G.C.S., Z.D., and M.T.E. designed the research. J.E., G.C.S., J.B.L.L., S.K., M.M., K.M., J.J., Z.D., Y.-H.C., and M.T.E. performed the research. J.E., Z.D., R.M.F., and M.T.E. analyzed the data. M.T.E. contributed new reagents/analytical tools.

### Funding

This research was supported in part by the Intramural Research Program of the National Institutes of Health. Jumar Etkins was supported by the National Institutes of Health, National Institute of General Medical Sciences [grant T32GM008425 (J.E.)]. This work was supported by the National Center for Complementary and Integrative Health [grant R01AT011463 (M.T.E.)] and the NIH/National Institute of General Medical Sciences National (NIH/NIGMS) [grant R35GM145383 (Z.D.)].

### Conflicts of Interest

The authors declare no conflicts of interest.

### References

1. P. Newswire, "Market for CBD Infused Products Could Surpass \$20 Billion by 2024," (2025).
2. Evaluation, C.f.D. & Research, "Epidiolex (Cannabidiol) Clinical Pharmacology and Biopharmaceutics Review," (2018).

3. L. Taylor, B. Gidal, G. Blakey, B. Tayo, and G. Morrison, "A Phase I, Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose, Multiple Dose, and Food Effect Trial of the Safety, Tolerability and Pharmacokinetics of Highly Purified Cannabidiol in Healthy Subjects," *CNS Drugs* 32 (2018): 1053–1067.
4. H. B. Schultz, A. Hosseini, A. J. McLachlan, and S. E. Reuter, "Population Pharmacokinetics of Oral-Based Administration of Cannabidiol in Healthy Adults: Implications for Drug Development," *Cannabis and Cannabinoid Research* 8 (2023): 877–886.
5. 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 (2021): 882–891.
6. 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 (2020): 1008–1017.
7. 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 (2021): 1070–1080.
8. G. C. So, J. B. L. Lu, Y. H. Cheng, et al., "Inhibition of Tacrolimus Metabolism by Cannabidiol and Its Metabolites In Vitro," *Clinical and Translational Science* 18 (2025): e70152.
9. 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 (2022): 351–360.
10. R. Jiang, S. Yamaori, S. Takeda, I. Yamamoto, and K. Watanabe, "Identification of Cytochrome P450 Enzymes Responsible for Metabolism of Cannabidiol by Human Liver Microsomes," *Life Sciences* 89 (2011): 165–170.
11. S. Bansal, M. F. Paine, and J. D. Unadkat, "Predicting In Vivo Cannabinoid-Drug Interactions Mediated via Inhibition of UDP-Glucuronosyltransferases Using In Vitro Studies and PBPK Modeling and Simulations," *Drug Metabolism and Disposition* 53 (2025): 100096.
12. J. L. Beers, A. K. Authement, N. Isoherranen, and K. D. Jackson, "Cytosolic Enzymes Generate Cannabinoid Metabolites 7-Carboxycannabidiol and 11-Nor-9-Carboxytetrahydrocannabinol," *ACS Medicinal Chemistry Letters* 14 (2023): 614–620.
13. E. Ben-Menachem, B. Gunning, C. M. Arenas Cabrera, et al., "A Phase II Randomized Trial to Explore the Potential for Pharmacokinetic Drug-Drug Interactions With Stiripentol or Valproate When Combined With Cannabidiol in Patients With Epilepsy," *CNS Drugs* 34 (2020): 661–672.
14. C. Sachse-Seeboth, J. Pfeil, D. Sehart, et al., "Interindividual Variation in the Pharmacokinetics of Delta9-Tetrahydrocannabinol as Related to Genetic Polymorphisms in CYP2C9," *Clinical Pharmacology and Therapeutics* 85 (2009): 273–276.
15. J. A. Wright, L. Huang, B. E. Katamesh, S. Yadav, A. Singla, and A. Vincent, "Hypothesized Pharmacogenomic and Medication Influences on Tetrahydrocannabinol and Cannabidiol Metabolism in a Cohort of Unselected Oral Cannabis Users," *Journal of Cannabis Research* 7 (2025): 1.
16. A. Batinic, D. Sutlović, S. Kuret, et al., "Trial of a Novel Oral Cannabinoid Formulation in Patients With Hypertension: A Double-Blind, Placebo-Controlled Pharmacogenetic Study," *Pharmaceuticals (Basel)* 16 (2023): 645.
17. A. Batinic, D. Sutlovic, S. Kuret, et al., "Differences in Plasma Cannabidiol Concentrations in Women and Men: A Randomized,

- Placebo-Controlled, Crossover Study,” *International Journal of Molecular Sciences* 24 (2023): 10273.
18. G. C. So, J. B. L. Lu, S. Koyama, et al., “A Phase I Trial of the Pharmacokinetic Interaction Between Cannabidiol and Tacrolimus,” *Clinical Pharmacology and Therapeutics* 117 (2024): 716–723.
  19. K. S. Collins, V. M. Pratt, W. M. Stansberry, et al., “Analytical Validity of a Genotyping Assay for Use With Personalized Antihypertensive and Chronic Kidney Disease Therapy,” *Pharmacogenetics and Genomics* 29 (2019): 18–22.
  20. K. E. Caudle, H. M. Dunnenberger, R. R. Freimuth, et al., “Standardizing Terms for Clinical Pharmacogenetic Test Results: Consensus Terms From the Clinical Pharmacogenetics Implementation Consortium (CPIC),” *Genetics in Medicine* 19 (2017): 215–223.
  21. A. Rohatgi, “WebPlotDigitizer,” (2023).
  22. A. Freites-Martinez, N. Santana, S. Arias-Santiago, and A. Viera, “Using the Common Terminology Criteria for Adverse Events (CTCAE—Version 5.0) to Evaluate the Severity of Adverse Events of Anticancer Therapies,” *Actas Dermo-Sifiliográficas* 112 (2021): 90–92.
  23. A. Mazur, C. F. Lichti, P. L. Prather, et al., “Characterization of Human Hepatic and Extrahepatic UDP-Glucuronosyltransferase Enzymes Involved in the Metabolism of Classic Cannabinoids,” *Drug Metabolism and Disposition* 37 (2009): 1496–1504.
  24. J. Beers, D. Fu, and K. Jackson, “Understanding the Cytochrome P450-Catalyzed Metabolism of Cannabidiol and the Implications for Hepatotoxicity,” *FASEB Journal* 35 (2021): 121.
  25. S. Koyama, J. Etkins, J. Jun, et al., “Utilization of Cannabidiol in Post-Organ-Transplant Care,” *International Journal of Molecular Sciences* 26 (2025): 699.
  26. K. Singh, B. Bhushan, D. K. Chanchal, et al., “Emerging Therapeutic Potential of Cannabidiol (CBD) in Neurological Disorders: A Comprehensive Review,” *Behavioural Neurology* 2023 (2023): 8825358.
  27. M. A. Huestis, R. Solimini, S. Pichini, R. Pacifici, J. Carlier, and F. P. Busardò, “Cannabidiol Adverse Effects and Toxicity,” *Current Neuropharmacology* 17 (2019): 974–989.
  28. Q. Zhang, P. W. Melchert, and J. S. Markowitz, “Pharmacokinetic Variability of Oral Cannabidiol and Its Major Metabolites After Short-Term High-Dose Exposure in Healthy Subjects,” *Medical Cannabis and Cannabinoids* 7 (2024): 1–9.
  29. L. MacNair, J. Kulpa, M. L. Hill, et al., “Sex Differences in the Pharmacokinetics of Cannabidiol and Metabolites Following Oral Administration of a Cannabidiol-Dominant Cannabis Oil in Healthy Adults,” *Cannabis and Cannabinoid Research* 9 (2024): e1170–e1178.
  30. 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 (2023): 693–703.
  31. S. Yamaori, K. Koeda, M. Kushihara, Y. Hada, I. Yamamoto, and K. Watanabe, “Comparison in the In Vitro Inhibitory Effects of Major Phytocannabinoids and Polycyclic Aromatic Hydrocarbons Contained in Marijuana Smoke on Cytochrome P450 2C9 Activity,” *Drug Metabolism and Pharmacokinetics* 27 (2012): 294–300.
  32. J. Havlasek, J. Vrba, M. Zatloukalova, et al., “Hepatic Biotransformation of Non-Psychotropic Phytocannabinoids and Activity Screening on Cytochromes P450 and UDP-Glucuronosyltransferases,” *Toxicology and Applied Pharmacology* 476 (2023): 116654.
  33. N. Jaisupa, M. Ashton, and S. Birgersson, “Cannabidiol Metabolism In Vitro: The Role of Antiseizure Medications and CYP2C19 Genotypes,” *Xenobiotica* 55 (2025): 1–10.
  34. K. C. B. Yabut, Y. Winnie Wen, K. T. Simon, and N. Isoherranen, “CYP2C9, CYP3A and CYP2C19 Metabolize  $\Delta^9$ -Tetrahydrocannabinol to Multiple Metabolites but Metabolism Is Affected by Human Liver Fatty Acid Binding Protein (FABP1),” *Biochemical Pharmacology* 228 (2024): 116191.
  35. R. Jiang, S. Yamaori, Y. Okamoto, I. Yamamoto, and K. Watanabe, “Cannabidiol Is a Potent Inhibitor of the Catalytic Activity of Cytochrome P450 2C19,” *Drug Metabolism and Pharmacokinetics* 28 (2013): 332–338.
  36. K. M. Nelson, J. Bisson, G. Singh, et al., “The Essential Medicinal Chemistry of Cannabidiol (CBD),” *Journal of Medicinal Chemistry* 63 (2020): 12137–12155.
  37. O. Zendulka, G. Dovrtělová, K. Nosková, et al., “Cannabinoids and Cytochrome P450 Interactions,” *Current Drug Metabolism* 17 (2016): 206–226.
  38. K. Thelen and J. B. Dressman, “Cytochrome P450-Mediated Metabolism in the Human Gut Wall,” *Journal of Pharmacy and Pharmacology* 61 (2009): 541–558.
  39. J. C. Stingl and R. Viviani, “Pharmacogenetic Guided Drug Therapy—How to Deal With Phenoconversion in Polypharmacy,” *Expert Opinion on Drug Metabolism & Toxicology* 21 (2025): 399–407.

### Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** cts70455-sup-0001-Tables.docx.