Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Clin Pharmacol Ther. Author manuscript; available in PMC 2022 April 21.

Published in final edited form as:

Clin Pharmacol Ther. 2022 April ; 111(4): 732–735. doi:10.1002/cpt.2470.

Cannabis for Medical Use: Clinical Pharmacology Perspectives on Scientific and Regulatory Challenges

Zhu Zhou[1,*], **Mary F. Paine**[2], **Tory R. Spindle**[3], **Shiew-Mei Huang**[4], **Lei Zhang**[5,*]

[1]Department of Chemistry, York College, City University of New York, Jamaica, New York, USA;

[2]Department of Pharmaceutical Sciences, Washington State University, Spokane, Washington, USA;

[3]Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA;

[4]Office of Clinical Pharmacology, Office of Translational Sciences, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA;

[5]Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland, USA.

Abstract

There has been growing interest in developing therapeutic agents and other consumer products derived from cannabis and its components. To date, the US Food and Drug Administration (FDA) has not approved cannabis as a safe and effective drug for any indication. With the progressive state legalization of cannabis for medical use, healthcare providers and consumers must understand what is known about the safety and efficacy linked to cannabis.

Cannabis (*Cannabis sativa*) contains more than 500 chemicals, including more than 100 cannabinoids. The most well-known cannabinoids are nonpsychoactive cannabidiol (CBD) and psychoactive Δ-9-tetrahydrocannabinol (THC) (The terms "cannabis" and "marijuana" are often used interchangeably, but they are not the same. "Cannabis" refers to all products derived from the plant *Cannabis sativa*, whereas "marijuana" refers to parts of or products from the plant *Cannabis sativa* that contain > 0.3% THC (from https://www.nccih.nih.gov/health/cannabis-marijuana-and-cannabinoids-what-you-need-to-know).). As cannabis remains federally illegal in the United States and elsewhere, a comprehensive understanding of the safety and efficacy of cannabis remains lacking due largely to the many legal and regulatory approvals needed to conduct research studies with cannabis (Figure 1). This perspective provides an overview and update on both scientific and regulatory

*Correspondence: Zhu Zhou (zzhou1@york.cuny.edu); Lei Zhang (leik.zhang@fda.hhs.gov).

CONFLICTS OF INTEREST

T.R.S. has served as a paid consultant for Canopy Health Innovations Inc. All other authors declared no competing interests for this work.

Publisher's Disclaimer: DISCLAIMER

Publisher's Disclaimer: The opinions expressed in this perspective are those of the authors and should not be construed to represent FDA's views or policies.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

approaches and challenges to study pharmacokinetic (PK) cannabis-drug interactions and the pharmacodynamics (PDs) of cannabis, with the goal of fostering research in the community to develop appropriate cannabis and cannabis-derived products that are safe and effective to meet unmet medical needs.

PHARMACOKINETIC CANNABIS-DRUG INTERACTIONS

Scant clinical PK studies have suggested marijuana-containing cigarettes and oral CBD modulate some cytochromes P450 (CYPs).[1] For example, the area under the plasma concentration vs. time curve (AUC) of the CYP1A2 substrate theophylline was 30% lower in habitual marijuana (and tobacco) smokers compared with nonsmokers, suggesting marijuana induces CYP1A2. In addition, oral CBD was shown to increase the AUC or average plasma concentration of hexobarbital, clobazam, and the *N*-desmethyl metabolite of clobazam (norclobazam) by at least 50% compared with baseline (absence of CBD), suggesting inhibition of CYP2C9, CYP2C19, and/or CYP3A by CBD.

Compared with clinical studies, myriad *in vitro* studies have evaluated the modulatory effects of cannabinoids, particularly THC and CBD, on various drug metabolizing enzymes and transporters. For example, both cannabinoids were shown to inhibit multiple CYPs and carboxylesterase 1, and CBD was shown to inhibit UDP-glucuronosyltransferase (UGT) 1A9 and 2B7.[1,2] Both cannabinoids were also shown to inhibit the efflux transporters P-gp, MRP1, and BCRP.[1] CBD had no inhibitory effect on the efflux transporters BSEP and MATE1/2-K and the uptake transporters OATP1B1/3, OAT1/3, and OCT1/2.[2]

Although THC and CBD inhibit multiple drug metabolizing enzymes and transporters, the low aqueous solubility and extensive nonspecific binding to human liver microsomes and/or labware of these highly lipophilic compounds were not considered.[1] Thus, the true inhibitory potencies and potential to precipitate PK drug interactions may have been underestimated. This hypothesis was recently tested by applying experimentally determined solubility, binding, and CYP inhibition data to a mechanistic static model to predict the likelihood of each cannabinoid to precipitate drug interactions at oral doses used for recreational or medicinal purposes.[3] Using the FDA-recommended substrate drug AUC ratio (AUC in absence to presence of cannabinoid) cutoff of 1.25, THC (20 mg) was predicted to be a moderate inhibitor of CYP2C9 and CYP3A (AUC ratio, 1.25–2), whereas CBD (700 mg) was predicted to be a moderate to strong inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A (AUC ratio, 2–5). Based on model predictions, the logical research question arose: What is the drug interaction potential of the complex mixture (cannabis) when co-administered as an edible with oral CYP probe drugs? With legal and regulatory approvals in place, a clinical PK study was launched to address the research question. In brief, 18 healthy adult intermittent cannabis users will participate in each of three arms involving an oral CYP probe cocktail consisting of caffeine (CYP1A2), losartan (CYP2C9), omeprazole (CYP2C19), dextromethorphan (CYP2D6), and midazolam (CYP3A):

- Oral CYP cocktail + placebo brownie
- Oral CYP cocktail + brownie containing a cannabis extract high in THC (20 mg + trace CBD)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

- Oral CYP cocktail + brownie containing a cannabis extract high in CBD (640 mg + 20 mg THC)

The sample size was based on 80% power to detect a 20% change in the primary end point (log transformed AUC ratio of losartan in the presence of a THC- or CBD-rich brownie to the presence of the placebo brownie) with a type 1 error of 0.05. Losartan AUC was selected because a CYP2C9-mediated interaction was predicted for both cannabinoids. More details are provided in the ClinicalTrials.gov registry (NCT04201197). Results from this study will advance the mechanistic understanding of clinical PK cannabis-drug interactions.

PHARMACODYNAMICS OF CANNABIS

The PDs of THC and THC-dominant cannabis have been well-characterized in controlled clinical studies. THC exposure reliably produces myriad effects, including subjective effects that are positive (e.g., feelings of euphoria and improved mood) or negative in nature (e.g., paranoia and anxiety), physiological effects (e.g., tachycardia), and impairments to cognitive and/or psychomotor functioning (e.g., working memory, reaction time, tracking ability, and attention).

Historically, individuals have used cannabis predominantly by smoking dried cannabis flowers using instruments, such as joints, blunts, pipes, or bongs. Although smoked cannabis remains the most popular route of administration, many novel cannabis products have emerged in recent years that are intended to be administered through nonsmoked routes. For example, cannabis flowers or concentrated cannabis extracts can be inhaled using vaporizers, consumed via various oral formulations (e.g., foods and drinks), and administered through other means (e.g., topical/transdermal products). In addition to novel routes of administration, there are different “strains” (or chemotypes) of cannabis beyond those that are THC-dominant (e.g., CBD-dominant).

Various clinical laboratory studies have demonstrated that the magnitude and time course of cannabis effects are impacted by route of administration, cannabis type, and other individual-level factors. For example, peak clinical effects after oral ingestion of cannabis occur much later compared with smoked cannabis (smoked: 10–30 minutes post-inhalation; oral: ~ 2–5 hours post-ingestion); effects also persist much longer after orally consumed compared to smoked cannabis. Despite differences in the onset of effects, the magnitude of acute effects between oral and smoked cannabis is often similar.[4] For vaporized cannabis, the time course of effects is generally similar to that of smoked cannabis; however, cannabis vaporizers deliver more THC to users, thus causing stronger effects, relative to the same dose of smoked cannabis.[4] The type of cannabis used (e.g., THC-dominant vs. CBD-dominant) is another important predictor of the effects produced. In some studies, CBD-dominant cannabis (or CBD administered in isolation) produced discriminable subjective drug effects, although products high in CBD generally are not associated with impaired cognitive/psychomotor functioning and other adverse effects synonymous with THC-dominant cannabis (e.g., acute paranoia).[5] Finally, sex and user experience are critical factors that contribute to interindividual differences in clinical effects. In general, women are more sensitive to acute effects from cannabis relative to men, meaning the same cannabis

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

dose may elicit stronger effects in women than men.[6] Beyond sex, user experience with cannabis is another critical factor to consider. Individuals who are regular cannabis users, and who are thus tolerant to its effects, experience less pronounced effects from a given dose of cannabis relative to an inexperienced/nontolerant user.[7] Last, more work is needed to understand how cannabis constituents, including those beyond THC and CBD (e.g., minor cannabinoids and terpenes) interact and how these interactions may complicate the assessment of PKs or PDs of cannabis.

CLINICAL PHARMACOLOGY PERSPECTIVES ON DEVELOPMENT OF CANNABIS AND CANNABIS-DERIVED DRUGS

To date, the FDA has approved a cannabis-derived drug, Epidiolex (CBD); two drugs containing a synthetic version of THC (dronabinol), Marinol and Syndros; and one drug, Cesamet, containing a synthetic analog of THC (nabilone). These drug products are not botanical drug products. The development of drugs from botanicals such as cannabis poses numerous clinical pharmacology challenges. Development of these drugs and the related clinical pharmacology reviews followed the regular drug product evaluation process as detailed below.

The general goal of clinical pharmacology evaluation of drug products is to improve public health by building and translating knowledge of drug response into patient centered regulatory decisions of highest quality. To determine if a drug or drug dose is suitable for a given patient, *in vitro*, *in vivo*, and/or *in silico* methods can be used to evaluate the effects of individual and combined critical intrinsic (e.g., age, race, sex, organ function, and genetics) or extrinsic (e.g., concomitantly administered drugs, foods, and alcohol) factors on the PKs and/or PDs of the drug and thereby drug response (both efficacy and safety). The Prescription Drug User Fee Act VI contains provisions to support drug development and review, including a range of model-informed drug development tools (e.g., exposure-response relationships, physiologically-based PK, PK/PD, population PK, quantitative systems pharmacology, quantitative structure activity relationship, and quantitative structure-property relationship) to enhance regulatory decisions.[8]

The FDA has approved two botanical drug products to date, sinecatechins (2006) and crofelemer (2012), and has received more than 800 botanical Investigational New Drug (IND) applications during the past 3 decades. Of these submissions, 9% were related to cannabis or cannabis-related products.[9] Approval of botanical drug products requires the "totality of evidence" approach because botanicals are variable and complex mixtures with multiple plant combinations, with many marketed as dietary supplements in the United States. The FDA has published two guidance documents related to the development of botanical drug products: a final guidance, "Guidance for Industry – Botanical Drug Development" (2016) and a draft guidance, "Draft Guidance for Industry – Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research" (2020).

The FDA will continue to facilitate the work of all stakeholders interested to bring safe, effective, and quality products to the market appropriately, including science-based research regarding the medical uses of cannabis. The FDA recognizes the potential

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

opportunities that cannabis or cannabis-derived compounds may offer and acknowledges the significant interest in these possibilities (https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd).

CONCLUSION

As of June 15, 2021, 36 states and 4 territories in the United States have legalized cannabis for medical use. The increasing state legalization, widespread use, and increasing availability of cannabis products raise concerns for potential adverse pharmacokinetic cannabis-drug interactions and high interindividual variability in pharmacodynamics. Additionally, development of drugs from botanicals, including cannabis, poses numerous challenges. Some knowledge gaps that exist regarding the safety and efficacy of cannabis are identified and potential research directions are offered (Table 1). More research is needed to address scientific and regulatory challenges to help the community understand PK cannabis-drug interactions and elucidate factors that impact cannabis PDs, including safety considerations. Importantly, to accomplish these goals, investigators need a streamlined regulatory pathway to facilitate research on the vast array of commercially available cannabis products, which are currently challenging to obtain/study given the illegality of cannabis at the federal level.

ACKNOWLEDGMENTS

Content of this perspective has been presented at the 2021 ASCPT Annual Meeting.

FUNDING

M.F.P. was supported by the National Institutes of Health National Center for Complementary and Integrative Health and Office of Dietary Supplements (grant no. U54 AT008909).

References

1. Cox EJ et al. A marijuana-drug interaction primer: precipitants, pharmacology, and pharmacokinetics. Pharmacol. Ther 201, 25–38 (2019). [PubMed: 31071346]
2. Greenwich Biosciences. EPIDIOLEX (cannabidiol) [package insert]. U.S. Food and Drug Administration website. Revised Oct 2020. Accessed Sep 19 2021.
3. Bansal S, Maharao N, Paine MF & Unadkat JD Predicting the potential for cannabinoids to precipitate pharmacokinetic drug interactions via reversible inhibition or inactivation of major cytochromes P450. Drug Metab. Dispos 48, 1008–1017 (2020). [PubMed: 32587099]
4. Spindle TR, Bonn-Miller MO & Vandrey R Changing landscape of cannabis: novel products, formulations, and methods of administration. Curr. Opin. Psychol 30, 98–102 (2019). [PubMed: 31071592]
5. Spindle TR et al. Pharmacodynamic effects of vaporized and oral cannabidiol (CBD) and vaporized CBD-dominant cannabis in infrequent cannabis users. Drug Alcohol Depend. 211, 107937 (2020). [PubMed: 32247649]
6. Cooper ZD & Craft RM Sex-dependent effects of cannabis and cannabinoids: a translational perspective. Neuropsychopharmacology 43, 34–51 (2018). [PubMed: 28811670]
7. Ramaekers JG, Mason NL & Theunissen EL Blunted highs: pharmacodynamic and behavioral models of cannabis tolerance. Eur. Neuropsychopharmacol 36, 191–205 (2020). [PubMed: 32014378]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

8. Liu Q, Ahadpour M, Rocca M & Huang SM Clinical pharmacology regulatory sciences in drug development and precision medicine: current status and emerging trends. AAPS J. 23, 54 (2021). [PubMed: 33846878]

9. Wu C et al. Scientific and regulatory approach to botanical drug development: a U.S. FDA perspective. J. Nat. Prod 83, 552–562 (2020). [PubMed: 31977211]

10. Watkins PB, Church RJ, Li J & Knappertz V Cannabidiol and abnormal liver chemistries in healthy adults: results of a Phase I clinical trial. Clin. Pharmacol. Ther 109, 1224–1231 (2021). [PubMed: 33022751]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

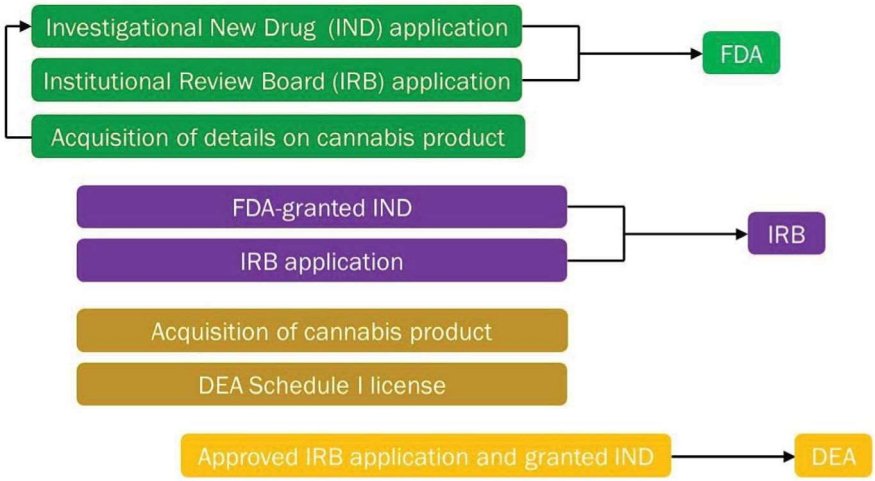

Figure 1.

Legal and regulatory requirements for cannabis clinical studies. IND status is needed from the FDA, which requires a clinical study protocol and details about the cannabis product (e.g., certificates of analysis providing cannabinoid profile/purity and testing for contaminants; stability testing; and manufacturing procedures). The timeline for initial IND submission review is 30 days. However, for IND amendments, there is no specific timeline. Once the IND is granted (safe to proceed), the clinical protocol, along with the IND can be submitted to the IRB. During this time, acquisition of the cannabis product can begin, which requires a DEA schedule I license (if the product contains > 0.3% THC (https://www.deadiversion.usdoj.gov/fed_regs/rules/2020/fr0821.htm)), which can take up to a year to obtain. Once the clinical protocol is approved and the IND is granted, the DEA provides final approval. The entire approval process can take up to a year. DEA, Drug Enforcement Administration; FDA, US Food and Drug Administration.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1

Knowledge gaps, research questions, and directions for studying cannabis for medical use

Knowledge gaps and research questions	Proposed research directions
What is the risk of pharmacokinetic interactions between cannabis products and comedications?	• Determine the kinetics of enzyme- or transporter-mediated drug interactions using established *in vitro* assays • Use or develop mechanistic static and/or PBPK models to predict pharmacokinetic interactions • Conduct well-designed clinical studies to evaluate model predictions and help manage potential interactions
How do non-THC cannabis constituents contribute to the pharmacodynamics of cannabis? What individual-level factors impact the pharmacodynamics of cannabis?	• Characterize the pharmacodynamics of minor cannabinoids, terpenes, and other cannabis components (including possible interactions with THC) through well-designed clinical studies • Use controlled clinical studies to determine how individual-level factors, such as age, race/ethnicity, genetics, etc., contribute to differences in the pharmacodynamics of cannabis
What are the regulatory and legal requirements for cannabis clinical studies?	• Obtain approvals from multiple authorities, including the researcher's Institutional Review Board, FDA, and DEA, for cannabis research. Note that a DEA schedule I license is not needed for hemp products (i.e., products containing < 0.3% THC). • Plan the study referring to the suggested timeline for these approvals based on the authors' experience (Figure 1)
What are the adverse events and toxicity of CBD in humans?	• Conduct comprehensive toxicological studies and clinical trials to understand the association between adverse events and toxicities and therapeutic doses of CBD intake. For example, results from a phase I, open-label, drug-drug interaction trial between caffeine and CBD indicated that therapeutic doses of CBD could lead to serum alanine aminotransferase elevations consistent with drug-induced liver injury in healthy adults[10]

CBD, cannabidiol; DEA, Drug Enforcement Agency; FDA, US Food and Drug Administration; PBPK, physiologically-based pharmacokinetic; THC, Δ-9-tetrahydrocannabinol.

Clin Pharmacol Ther. Author manuscript; available in PMC 2022 April 21.