5-2020

An Analysis of the Incidence and Severity of Drug-Drug Interactions Between Prescribed Pharmaceuticals and Cannabinoids

Jennifer Lee McRae
University of North Dakota, jennifer.mcrae@und.edu

An Analysis of the Incidence and Severity of Drug-Drug Interactions Between Prescribed Pharmaceuticals and Cannabinoids

by

Jennifer Lee McRae, PA-S

Master of Science, Oklahoma State University, 2006

Contributing Author:

Daryl Sieg, MSPAed, PA-C

A Scholarly Project

Submitted to the Graduate Faculty of the University of North Dakota

in partial fulfillment of the requirements for the degree of

Master of Physician Assistant Studies

Grand Forks, North Dakota

May 2020

Table of Contents

Acknowledgements

First and foremost, I would like to express my deep and sincere gratitude to my advisor, Daryl Sieg, MSPAed, PA-C, for his patience, guidance, and expertise throughout the entire process of this research work.

Additionally, I must offer my genuine thanks to Tona Hetzler, EdD, Sports Medicine, and Athletic Training Director and Department Head, Missouri State University, for her willingness to review, critique, and guide me in the interpretation and analysis of the statistics included in this research work.

I am genuinely indebted to Charith Scott, RN. When the individual who agreed to serve as an interdisciplinary reviewer was unable to assist me, Charith joyfully stepped up to the plate to offer her beneficial suggestions.

I wish to thank my classmate Brenton Green for his assistance in the editing of this work; his time and attention to detail are very appreciated.

Finally, I would like to recognize and express my thanks to my fellow UND PA 2020 classmates for always being available to discuss ideas, answer questions, and offer guidance during this project.

Abstract

The purpose of this research and systematic literature review is to identify the incidence and severity of drug-drug interactions between commonly prescribed medications and cannabinoids. In this review, four databases were searched including PubMed, CINAHL, and Embase from October 1 to January 5, 2019. A variety of key terms were used when searching. Works chosen for review were published after the year 2014, were peer reviewed, and included randomized control trials (RCTs), systematic literature reviews, and meta-analyses. For this review, 9 resources were selected. Much of the research presented shows evidence that medications that are substrates for CYP2C19, CYP2C9 and CYP1A2 are at the greatest risk of interaction with concomitant use of phytocannabinoids or synthetic cannabinoids. Furthermore, caution is recommended with medications metabolized via UGT or CES1, however information is currently limited and further research is necessary. The lack of universal standards for laboratory testing of cannabinoid products call into question the legitimacy of reported results in currently reported research as the contents of many cannabinoid products are inaccurately labeled.

Introduction

The cannabis plant contains over 100 distinct phytocannabinoids; however, the concentration varies amongst the different strains (Lewis et al., 2017). Phytocannabinoids can elicit both psychotropic and non-psychotropic effects; Δ9-tetrahydrocannabinol (THC) is responsible for psychotropic, and the non-psychotropic effect via cannabidiol (CBD). Historically, wild cannabis plants contained equal concentrations of THC and CBD, but the breeding of hybrid strains via commercial and home cultivation has led to plants with higher concentrations of THC in order to focus on the psychotropic effect (Russo, 2007).

The medicinal use of cannabis is not proprietary to the United States. Ancient civilizations of Egypt, China, Indian Hindus, Greeks, Persians, and Romans utilized the medicinal properties of the plant thousands of years ago (Russo, 2007). Cannabis was introduced to the United States Pharmacopeia in the 1850s with pharmaceuticals manufactured and prescribed by physicians until the 1970s when cannabis was designated a Schedule 1 drug after the passage of the Controlled Substances Act (Takakuwa & Schears, 2019). This designation equated cannabis to LSD and heroin and defining drugs in this category to have "no currently accepted medical use and a high potential for abuse" (*Drug Scheduling*, 2006). In 1996, California became the first state to legalize medical cannabis with the passage of Proposition 215 "Compassionate Use Act" (HSC, 1996). According to the National Conference of State Legislatures, 33 states have decriminalized the use of cannabis for medicinal purposes and operate a "comprehensive, publicly available medical marijuana/cannabis" program. Fourteen states have entirely decriminalized the use of cannabis in the adult population (Medical & Laws, 2018). Medicinal and recreational use of cannabis remains illegal at the federal level. The Agriculture Improvement Act of 2018 (2018 Farm Bill, PL 115-334) removed "hemp, defined as cannabis (Cannabis sativa L.) and derivatives of cannabis with low concentrations of the

psychoactive compound delta-9-tetrahydrocannabinol (THC)...from the definition of marijuana in the Controlled Substances Act (CSA)" (FDA, 2019). Hemp containing products, i.e., foodstuffs, human and veterinary drugs, and cosmetics, would continue to fall under the purview of the FDA ensuring the safety and accuracy in labeling products on the consumer market (FDA, 2019). Epidiolex, with CBD as an active ingredient, gained FDA approval in June 2018 (FDA, 2019) to treat two specific and rare forms of pediatric seizure disorder. Establishing CBD as an active drug ingredient creates critical regulatory implications. Per the Federal Food, Drug, and Cosmetics ACT (FD&C), it is unlawful to add an active drug to food, human or animal, without significant clinical trial and approval. Therefore, CBD is a legal substance per the 2018 Farm Bill as it does not contain high levels of THC, and it is an FDA approved active drug. Thus, CBD is mostly unregulated; the FDA only exercises regulatory oversight for marketed products that list CBD as a dietary supplement or food containing CBD.

Statement of the Problem

According to The United States Food and Drug Administration (FDA, 2019), three cannabis-derived products: Marinol, Syndros, and Cesamet, and one cannabis-related drug product, Epidiolex, have been approved for prescription by a licensed healthcare provider. Products containing cannabinoids marketed in states that have legalized the recreational and medicinal use of cannabis and cannabinoids do not undergo FDA (2019) examination to determine the safety or efficacy. Furthermore, cannabinoids do not fall under the FDA's Over the Counter (OTC) Drug review, nor do they meet the definition of a dietary supplement and are thus excluded from section 201(ff)(3)(B) of the FD&C Act (FDA, 2019) leaving them largely unregulated and a potential risk to consumers.

As a schedule 1 drug, research on a human subject regarding the safety and efficacy of cannabinoids pales in comparison to that of therapeutic agents falling under the regulatory

oversight umbrella of the FDA. Research studies examining the phytochemistry, pharmacodynamics, and pharmacokinetics of cannabis and cannabinoids identified the target receptors, CB1 and CB2, and the metabolism of the compounds via the cytochrome P-450 system. Therefore, drug-drug interactions have been identified, and warnings issued; however, no oversight regarding cannabinoid concentration or truthfulness in labeling exists in products currently on the market. Which begs the question, what product are consumers purchasing? How are cannabinoids regulated since no FDA oversight exists?

Research Questions

Are adults who consume cannabinoids in various forms compared to nonusers at an increased risk of experiencing a significant morbidity or mortality event secondary to a drug-drug interaction?

Does a lack of regulatory oversight regarding the manufacturing and marketing of products containing cannabinoids increase the risk of experiencing a significant morbidity or mortality event in adults who utilize cannabinoid products in various forms?

Research Methods

This comprehensive literature review utilized PubMed, CINAHL, and Embase databases. The searches were filtered so that only peer-reviewed articles, meta-analyses, and systematic reviews published between 2014 and 2019 were retrieved. Keywords used to conduct searches included: *cannabinoid, medical marijuana, pharmacology, pharmacokinetics, pharmacodynamics, therapeutic effects, drug-drug interactions, adverse effects, safety, efficacy, and variability*. The database searches utilized an advanced search builder using AND or OR for each theme. The inclusion of additional publications determines the legal status, oversight, and verification of cannabinoids.

Cannabinoids

A review of current literature demonstrates the need for further testing on human subjects to determine appropriate therapeutic dosing. Furthermore, it is imperative for consumer safety that the cultivation, extraction, and titration of cannabis and cannabinoid products is standardized and certified to mitigate unintended adverse effects and significant morbidity incidents due to the variability in concentration and dosing of products currently available to consumers.

Pharmacology of cannabinoids

Amin et al. (2019) sought to conduct a review of the current literature focusing on the use of cannabis in the treatment of pain, epilepsy, and neurodegenerative diseases while identifying the origins of the cannabis plant, receptors activated, pharmacokinetics and the medicinal applications.

The most researched cannabinoids include Δ9-tetrahydrocannabivarin (Δ9-THC), predominant in C. Sativa, and cannabidiol (CBD), predominant in C. Indica. A review of the cannabinoid pharmacology reveals that phytocannabinoids and endocannabinoids and synthetic cannabinoids bind to the CB1 and CB2 receptors with different affinity producing agonist and antagonistic effects. The CB1 receptor is predominantly located in the brain and the central nervous system (CNS), while CB2 is found in the peripheral nervous and immune system; both receptors negatively coupled to adenylate cyclase with activation resulting in a reduction or stimulation of cAMP production. The effects are determined by the adenylate cyclase isoform that is downstream from the activated CB receptor. CB receptors that are co-expressed with adenylate cyclase isoforms 1, 3, 5, 6, or 8 results in inhibition of cAMP while co-expression with adenylate cyclase isoforms 2, 4, or 7 lead to stimulation of cAMP; most of the activity is inhibitory. Potential for a third cannabinoid receptor exists with the orphan receptor GRP55. Activation of GRP55 results in increased release of stored Ca2+ and possibly potentiating the increased activity of the hippocampus. Amin and Ali reported that studies characterizing the

GPR55 receptor utilized the ligand [3H]CP55940, a synthetic cannabinoid that mimics Δ9-THC. The cannabinoid [3H]CP55940 is a full agonist at the CB1 (K_i = 0.58 nM) and CB2 (K_i = 0.68 nM). Interestingly, [3H]CP55940 binds to the GPR55 receptor with a high specificity and serves as an antagonist and partial agonist of GPR55 (Kapur et al., 2009). Furthermore, the studies reviewed by Amin and Ali demonstrated that the phytocannabinoid Δ9-THC and the endocannabinoids 2-arachidonoylglycerol (2-AG) and 2-arachidonyl glyceryl ether (noladin) that all bound to GRP55 receptor. The endocannabinoid 2-AG functions as a CB1 agonist and CB2 ligand. Interestingly, 2-AG showed a 200-fold greater potency on the GPR55 receptor in comparison CB1 and CB2(Amin & Ali, 2019). Δ9-THC demonstrated a greater efficacy at GRP55 in comparison to THC's efficacy on CB1 and CB2 (Amin & Ali, 2019).

Cannabinoids directly interact with transient receptor potential channels of vanilloid type 1 and 2 (TRPV1 and TRPV2) and transient receptor potential of ankyrin type 1 (TRPA1) (Amin & Ali, 2019). TRPV1 receptors are found in the cerebellum, basal ganglia, hippocampus, diencephalon, and dorsal root ganglion (DRG) neurons; TPRA receptors are co-located with TRPV1 in sensory neurons. While TRPV2 receptors are found in the sensory neurons of DRG, spinal cord, and trigeminal ganglia, but are also found in the cerebellum. Activation of the receptors influences the passage of cation channels, Na+, K+, and Ca2+, leading to membrane depolarization (Amin & Ali, 2019). In addition to activation by cannabinoids, TRPV1 is activated by capsaicin or heat, while TRPA1 is activated by menthol and cold. TRPV1 and TRPA1 exhibit functional desensitization, followed by sensitization and, subsequently, inhibition because further activation by ligands, heat, or cold is muted as the channels are in a desensitized state (Amin & Ali, 2019).

While Amin and Ali presented observations and conclusions from over one hundred references, they failed to include a section describing the methods employed to conduct the systematic

review. This absence of methodology lends to skepticism regarding the lack of bias or reliability of the information presented. Amin and Ali (2019) recognized that current research is limited by a lack of well-constructed, adequately controlled, randomized, and double-blind clinical trials on human subjects.

In addition to the above systematic review, authors Brown and Winterstein (2019) focused their review on two federally approved substances containing CBD. Sativex, a combination of THC and CBD, and Epidiolex, containing CBD. The review excluded products that contained only THC. The methods employed to conduct the review included extraction of prescribing information such as adverse events, clinical pharmacology, drug-drug interaction (DDI) studies, and contraindications, focusing specifically on adverse reactions attributed to DDI, potentiation interactions, and adverse drug events (ADE). A focused literature review provided information regarding the pharmacokinetics and pharmacodynamics of cannabis, as well as the utilization of *DrugBank* for consistency in the description of interactions, enzyme substrates, and pharmacodynamics.

The results presented reveal that the complex pharmacokinetic and pharmacodynamic profile of CBD shows that it is not a biologically inert compound and should be viewed in the same light as any other medication with the potential to interact with other medications and elicit adverse drug events. Cannabinoids target specific cannabinoid receptors within the endocannabinoid system. THC binds to the CB1 receptor, eliciting psychotropic effects on mood, memory, and anxiety. CBD is a negative allosteric modulator of anandamide, an endogenous endocannabinoid, leading to CBD serving as an inverse agonist at the CB2 receptor. CBD has agonist at 5-HT1A/2A/3A and TRPV-1 receptors, antagonist activity on the a-1 adrenergic and m-opioid receptor, inhibition of synaptic uptake of noradrenaline, dopamine,

serotonin, and gamma-aminobutyric acid, inhibition of anandamide uptake, effects on ion channels, and activation of the peroxisome proliferator-activity receptor (PPAR)-g. CBD influences several CYP450 enzymes leading to increased bioavailability of CBD when co-administered with substrate inhibitors and decreased availability when co-administered enzymatic inducers, both of which have the potential to elicit undesirable effects and potential adverse drug events.

Additionally, the ingestion of CBD impacts phase II metabolism pathways by causing dose-dependent inhibition of UGT1A9 and UGTB7. UGT1A9/2B7 substrates include some of the most commonly utilized over-the-counter medications such as acetaminophen and ibuprofen, as well as, commonly prescribed medications in medically complex patients leading to the potential for toxicity and significant side effects. The inactive, hydroxylated, 7-COOH-CBD, a P-glycoprotein substrate, has the potential to cause adverse effects and toxicity by inhibiting the actions of the breast cancer resistance proteins (BCRP) in the bile salt export pump (BSEP) at clinically relevant concentrations. This enzymatic inhibition results in decreased substrate transportation from tissue and excretion. Observation of increased adverse drug events in clinical trial participants provided insight regarding the synergistic pharmacodynamic effects of the co-administration of CBD, precisely Epidiolex 10 mg/kg/day and 20 mg/kg/day. The use of Epidiolex in conjunction with other medications with similar ADEs potentiated or increased the frequency in which participants experienced the adverse drug effect.

The authors failed to present a focused description of the methodology utilized to collect the referenced articles instead, alluding only to the supplementation of information regarding the pharmacokinetics and pharmacodynamics of synthetic cannabidiol. Brown and Winterstein (2019) breakdown the beneficial utilization of cannabidiol (CBD) to treat specific conditions

exploring the impact of CBD on already known adverse drug events inherent to the medications already utilized in current treatment protocols. While this information proves beneficial, generalization to patients without complex medical conditions included in the cohort is difficult.

The goal of the literature review authored by Cox et al. (2019)was to present the current issues surrounding marijuana terminology, taxonomy, and dosing; summarizes cannabinoid pharmacology and pharmacokinetics; assess the drug interaction risks associated with co-consuming marijuana with conventional medications. The article does not describe the methodology utilized by the authors in the preparation of the literature review.

In part, the term cannabinoids can interchangeably be applied to three distinct types: phytocannabinoids produced by the cannabis plant, endocannabinoids synthesized on demand by the body, and synthetic cannabinoids. In their review, Cox et al. (2019) examined the most commonly researched phytocannabinoids including tetrahydrocannabinol (THC) and cannabidiol (CBD), as well as, the major endocannabinoids in humans: N-arachidonoylethanolamide (anandamide), 2-arachidonylglycerol, 2-arachidonylglycerol ether (noladin ether) and N-arachidonoyl-dopamine.

While synthetic cannabinoids include those utilized as prescription medications, dronabinol and nabilone, they are also drugs of abuse: "K2" and "Spice." Pharmacologically, cannabinoids universally act on two G-protein coupled cannabinoid receptors, CB1 and CB2; however, cannabinoid affinity and efficacy vary at each receptor. The following evidence presented by Cox et al. (2019) supports the findings presented in the above systematic review published by Amin and Ali (2019). CB1 is primarily located in the central and peripheral nervous system, and CB2 is expressed predominantly in the peripheral nervous system and organs of the immune system. However, in unlike the previous two articles the authors stated

that phytocannabinoids have a higher affinity for CB1 and CB2 receptors as compared to endocannabinoids (Cox et al., 2019). Research shows the THC has both agonist and antagonistic effects at CB1 and CB2 receptors. Additionally, the authors indicate that CBD binds weakly to CB1 and CB2 with Ki of 17 nM and 211 nM, respectively, eliciting minimal pharmacological effect at these receptors instead of producing its most significant pharmacological effect at 5-HT receptors (Cox et al., 2019).

The results of the literature as they pertain to the pharmacokinetics of phytocannabinoids indicate that absorption varies based upon the route of administration. Phytocannabinoids undergo substantial first-pass metabolism or incomplete absorption. The bioavailability of THC after inhalation, oral administration, or oral mucosal spray is low, 5-7%. After accounting for the amount of THC lost via pyrolysis, 23-30%, and non-inhaled smoked, 40-50%, only 20-37% of the initial THC is available for absorption. CBD follows a similar pattern; the absolute bioavailability of CBD with inhalation is approximately 30%, after oral administration 7-13%, and after oral mucosal spray, only 4% is available. Cannabinoids are highly lipophilic, accumulating to a high degree in adipose, liver, and lung tissue. THC is highly protein-bound, primarily to lipoproteins, with a fraction unbound in plasma of <5%. THC is enzymatically oxidized via CYP2C9 to the psychoactive metabolite, 11-OH-THC, and further oxidation produces the inactive metabolite COOH-THC. CYP3A4 catalyzes THC producing a second primary, but inactive metabolite 8β-OH-THC. Oxidation of CBD produces many hydroxylated metabolites; most notably, CYP2C19 catalyzes the formation of 7-OH-CBD. The half-life of inhaled cannabis ranges from 1.4-12.8 minutes with a terminal half-life estimated at 20-30 hours. THC and CBD inhibit CYP1A/1B1, CYP2D6, 2C9, and 3A4/5. CBD inhibits ethanol glucuronidation via UGT1A9 and UGT2B7, leading to supraphysiological levels of CBD in the

body. Clinical studies indicated a pharmacological interaction between CBD and clobazam secondary to the CBD-mediated inhibition of CYP2C19; in this instance, oral administration of CBD led to a 300% increase in mean plasma concentration of the active metabolite N-desmethylclobazam leading to increased reports of sedation (Cox et al., 2019). One referenced case report indicated a pharmacological interaction between inhaled cannabis and warfarin; this interaction was most likely due to inhibition of CYP2C9-mediated warfarin metabolism and, to a lesser extent, and the displacement of warfarin from plasma protein binding sites by marijuana constituents leading to a supratherapeutic INR of 10.4 (Cox et al., 2019).

The review offered by Cox et al. (2019) presents a well-researched article that sufficiently acknowledges the difficulties in dosing, specifically via different routes, secondary to the variability in the concentration of commercially cultivated phytocannabinoids. However, the authors do not outline the methodology utilized in collecting the referenced material leading to a lack of confidence in the reliability of the information. Furthermore, this study was limited by a lack of well-designed, randomized, controlled human studies.

Therapeutic effects of cannabinoids

In addition to providing the pharmacokinetics and pharmacodynamics of cannabinoids, Amin and Ali (2019) presented the therapeutic effects of the most commonly researched cannabinoids: THC and CBD. THC is a partial agonist at CB1 and CB2 receptors. Due to its lipophilic nature, THC accumulates and is stored for long periods in adipose tissue, the heart, liver, and spleen.

Bioavailability of THC is highest when delivered via smoking, with 37% delivered to the body while 30% is lost to pyrolysis. THC rapidly enters the bloodstream with increasing levels detected within 1-2 minutes of inhalation, readily crossing the blood-brain barrier; however, bioavailability depends on individual weight, gender, age, health, and physiologic background

(Amin & Ali, 2019). Data regarding the therapeutic use of THC for short-term neuropathic pain is inconsistent and problematic secondary to increasing side effects as a psychoactive agent. Studies show increased efficacy of THC when used in combination with other psychoactive medications (Amin & Ali, 2019). In comparison, synthetic cannabinoids are full agonists at CB1 and CB2 and have more potential to treat pain therapeutically.

Amin and Ali (2019) reported that cannabidiol (CBD) does not activate CB1 receptors; instead, CBD is a negative allosteric modulator of the CB1 receptor lacking in psychoactive side effects. CBD activates CB2 receptors in the peripheral nervous system; study results hold promise for therapeutic use as an anti-inflammatory agent to treat acute/chronic pain and osteoarthritis pain (Amin & Ali, 2019). Currently, this research is lacking in adequately controlled, double-blind, randomized clinical trials. THC/CBD has anecdotal evidence as an anticonvulsant agent to treat epilepsy via activity on the CB1 receptor. CB1 regulates neuronal excitability by reducing presynaptic neurotransmitter release. Therefore, increased activation of CB1 shows promise in reducing neuronal excitation. Oral-mucosal use of a 1:1 ratio of THC:CBD produces analgesic effects and reduction in the spasticity of muscles; CBD is especially useful in the treatment of neuropathic pain associated with multiple sclerosis. Two studies presented by Amin and Ali (2019) stated that the use of THC/CBD combination products improved or alleviated symptoms of spasticity, spasms, tremor, pain, and bladder control despite the lacking statistical significance. Evidence suggests that THC may prove beneficial in the treatment of Alzheimer's disease by actively inhibiting Aβ aggregation by competitively inhibiting acetylcholinesterase activity.

The authors failed to present a focused description of the methodology utilized to collect the referenced articles instead, alluding only to the supplementation of information regarding the pharmacokinetics and pharmacodynamics of synthetic cannabidiol.

MacCallum and Russo (2018), propose an initial guide to Good Clinical Practice in respect to cannabis utilizing their clinical experience in internal medicine and review of the literature. They opine that no matter the intended use of the cannabis, medicinal, recreational or over the counter, it should be organically cultivated, free from genetic modification and processed in accordance with Good Manufacturing Practice. Furthermore, consumers should be supplied with the full cannabinoid and terpenoid profiles, as well as, certification that the material is free of contamination.

In a review of the pharmacology, MacCallum and Russo (2018) support the finding s of the previously presented articles; cannabis produces the phytocannabinoids tetrahydrocannabinolic acid-A (THCA-A) and cannabidiolic acid (CBDA), decarboxylation via heating of the acids produces tetrahydrocannabinol (THC) in cannabidiol (CBD). THC is responsible for the psychoactive properties of cannabis and is a weak partial agonist on CB1 and CB2 receptors. THC has been found to beneficially treat pain, nausea, spasticity/spasms, appetite stimulation, anxiety, depression, post-traumatic stress disorder (PTSD) and insomnia. Adverse events occur secondary to the psychoactive component of THC. CBD is a negative allosteric modulator of CB-1, with pharmacological effects on receptors TRPV1, 5-HT1a, adenosine a2a. Therapeutically, CBD Is used as an anticonvulsant, antipsychotic, neuroprotectant and an anti-inflammatory. The pharmacokinetics of cannabinoids vary secondary to their lipophilicity; when delivered via topical or oral routes are best absorbed in the presence of other lipids or polar solvents.

In regard to dosing, it is best if patients begin with lower doses and titrate up to treat symptoms and better tolerate side effects; specifically, THC mediated adverse reactions such as fatigue, tachycardia and dizziness. Patient should be aware of the cannabinoid concentration as higher concentrations require lower dosing amounts to achieve intended effects. Onset of action is dependent upon delivery method; smoking/vaporization has the quickest onset, 5-10 minutes, and the shortest duration of action, 2-4 hours, and is therefore beneficial in the treatment of acute or episodic signs and symptoms such as nausea or pain. The oral mucosal route has an onset of action of 15 to 45 minutes and a duration of 6 to 8 hours. Ingestion via the oral route has an onset of 60 to 180 minutes and a duration of 6 to 8 hours; titration is challenging due to the delayed onset. In patients wishing to treat localized areas the topical route is often the most beneficial however onset of action and duration are variable.

A majority of reported adverse events are related to the THC-mediated psychoactive effects and can be avoided utilizing a proper titration protocol or combining with CBD. Most patients quickly develop a tolerance to the psychoactive adverse effects over a period of days. The most commonly reported adverse events include drowsiness/fatigue, dizziness, dry mouth, smoking related cough, phlegm and bronchitis, anxiety, nausea and cognitive effects. Blurred vision, headache, and euphoria are commonly reported adverse events, followed by rare events such as orthostatic hypotension, toxic psychosis paranoia, depression, ataxia/discoordination, tachycardia, hyperemesis, and diarrhea. According to the authors, pertinent drug interaction studies are few. Existing studies have not demonstrated toxicity or loss of effect when administered with medications; however, interactions are theoretically possible (MacCallum & Russo, 2018). One exception is a combination of high-dose CBD co-administered with

clobazam; a dose reduction is necessary secondary to high levels of the sedating metabolite N-desmethyl clobazam.

Therapeutically, cannabis has been utilized to treat seizures. THC has been found to cause convulsions at high doses in rodent studies, but CBD has been proven safe and effective in the treatment of intractable epilepsies in both observational settings and Phase 3 clinical trials. THC utilization during cancer chemotherapy positively serves as an antiemetic; Phase II clinical trials show that THC is a beneficial palliative sleep aid in opioid-resistant cancer pain, but these effects were not proven in Phase III clinical trials. Cannabis has not been found beneficial in the treatment of acute pain, however RCTs have proven THC and CBD safe and effect in the treatment of chronic non-cancer pain, whether somatic or neuropathic, peripheral or central. THC has been utilized to treat agitation in elderly dementia patients. Cannabis use in the treatment of Parkinson's disease has shown variable efficacy in clinical studies, anecdotal surveys have concluded that acid cannabinoids may be beneficial when slowly titrated over a prolonged period of time.

MacCallum et al. (2018), provides readers with an experience-based guide to dosing cannabinoids based upon route and condition. The authors support their recommendations by supplying the audience with the levels of evidence for treatment of specific conditions with cannabinoids. However, this information is based in part upon the observations of the authors highlighting the need for a lack of well-designed, randomized, controlled human studies to further support their findings.

The goal of the study authored by Millar et al. (2018) was to review and analyze all available pharmacokinetic data on CBD in humans. Two independent researchers conducted a systematic review, in accordance with PRISMA (Preferred Reporting Items for Systematic

Reviews and Meta-Analyses) guidelines. The PubMed and EMBASE (including Medline) databases were utilized to retrieve all articles reporting pharmacokinetic data of CBD utilizing the following search terms: CBD, cannabidiol, Epidiolex, pharmacokinetics, C_{max}, plasma concentrations, plasma levels, half-life, peak concentrations, absorption, bioavailability, AUC, T_{max}, C_{min}, and apparent volume of distribution. The search was not restricted by the type of study, publication year or language, however only articles retrieved by March 14, 2018 were included in the review. In order for an article to be included in the review it had to be an original, peer-reviewed paper that involved the administration of CBD in humans and included at least one pharmacokinetic measurement. The authors extracted data such as, sample size, gender, administration route of CBD, source of CBD, dose of CBD, and any pharmacokinetic details. Where available, plasma mean or median C_{max} (ng/mL) were plotted against CBD dose (mg). Mean or median T_{max} and range and mean or median are under the curve and SD were plotted against CBD dose (mg).

The search resulted in a total of 792 articles retrieved, but only 24 met eligibility criteria. The articles reviewed discussed various routes of administration including intravenous (n=1), oromucosal spray (n=21), oral capsules (n = 13), oral drops (n = 2), oral solutions (n = 1), nebulizer (n = 1), aerosol (n = 1), vaporization (n = 1), and smoking (n = 8). Nine of the articles utilized only CBD with the remaining sixteen utilizing a combination of CBD and THC or within a cannabis extract. Only one study was conducted on children with Dravet syndrome, the remaining twenty-three were conducted on healthy adults. The studies included in the search were deemed good quality but had small samples sizes and not all studies included both men and women. Many studies were limited by the use of chronic cannabis smokers as subjects therefore potentially skewing the interpretation and extrapolation of the results.

The results of the systematic review concluded that eight articles discussed the pharmacokinetic parameters utilizing only CBD, the remaining sixteen utilized a combination of THC/cannabis. The authors observed that the peak plasma concentration and area under the curve are dose-dependent with minimal accumulation; C_{max} is reached faster after administration via IV and inhalation. Furthermore, administration in a fed state achieves increased C_{max} as well as reaching C_{max} faster. T_{max} of CBD is not dose-dependent, but half-life is dependent upon dose and route of administration. Area under the curve, dose dependent C_{max} and T_{max} occurred between one and four hours. Bioavailability of CBD was increased, by 3-fold, when CBD was co-administered with lipids while co-administration with pro-nanlipospheres increased bioavailability by 6-fold. Animal studies exploring the topical use of CBD via gels and creams elicited successful results, but there was a lack of data in human subjects. The authors were not able to conclusively determine the extent of plasma and tissue accumulation secondary to a lack of date utilizing human subjects, however animal studies showed higher concentrations of CBD, after intraperitoneal injection. Only one study explored the use of CBD in children (n=34) with results concluding that area under the curve increased dose-dependently, however there is a lack of data exploring the pharmacokinetic differences in children vs. adults. The authors noted that many of the studies took into account the patient's weight, but they failed to fully explore the alterations in metabolism accounting for the amount of adipose tissue versus lean muscle tissue. Research has concluded that CBD is lipophilic and stored in adipose tissue for gradual release therefore studies not accounting for percentage of body fat vs lean tissue potentially skew the results of the studies. Millar et al. (2018) concluded that overall the use of CBD in combination with other medications is well-tolerated, but caution should be employed with other drugs

utilizing the CYP3A4 pathway, substrates of UGT1A9 and UGT2B7, and other drugs metabolized via CYP2C19.

Millar et al. (2018) acknowledged the following limitations of their review. The studies did not differentiate between healthy/diseased patient population, nor cannabis naïve/chronic users; instead these populations were all grouped together potentially interfering with the ability to generalize results. The studies did not utilize equal proportions of men and women. Lack of standardization in dosing and alterations in polymeric forms, and purity alterations can impact the pharmacokinetics of CBD. Furthermore, the study was limited by the utilization of only two search data bases, inclusion of other databases could have resulted in improved reliability and validity of the data. The systematic review performed by Millar et al. (2018) highlights a lack of research regarding CBD.

Drug-Drug Interactions between pharmaceutical agents and cannabinoids

In addition to the previously mentioned drug-drug interactions outlined in the above article reviews; the systematic review performed by Qian et al. (2019) identified the potential for drug-drug interactions between prescribed medications and cannabis by identifying crossover in drug-metabolizing enzymes and drug transporters and the potential for alterations in exposure to one or more of the three major cannabinoids, Δ9-Tetrahydrocannabinol (THC), cannabidiol (CBD) and cannabinol (CBN).

The materials and methods performed by Qian et al., conducted in March 2019, searched the electronic databases of Google Scholar ad MEDLINE (PubMed) limiting results to those published in English and pharmacokinetic (PK) interactions utilizing the terms ‘cannabis,’ ‘marijuana,’ ‘cannabinoids,’ ‘THC,’ ‘cannabinol,’ ‘interactions,’ and ‘drug interactions’ in combination with ‘cytochrome P450,’ ‘CYP,’ or ‘uridine 5’-diphospho glucuronosyltransferase,’ ‘UGT,’ ‘drug transporter,’ ‘esterase,’ ‘inhibition,’ and ‘induction.’ Studies utilizing animal

models were excluded due to interspecies differences in metabolism and the utilization of intraperitoneal dosing routes. Qian et al. divided the assessment of drug interactions into two categories, iv vitro studies and clinical studies. A total of 25 studies, 15 in vitro studies and 10 clinical drug interaction studies, involving cannabis or 1 or more of its components were retrieved and reviewed, as well as, 3 case reports describing changed drug efficacies due to the use of cannabis.

The systematic review concluded that due to the pharmacokinetics of cannabinoids or their metabolites concluded that there is potential for significant drug-drug interactions with conventional medications. Cannabidiol has the most potential for interactions due to the greater inhibitory effects of isoforms CYP3A4/5/7, CYP3A, 2B6, 2J2, 2D6, 2C9, 2C19, 2B6, CYP1A1/2, and CYP1. Clinical drug interactions secondary to the inhibitory effects of THC are likely at isoforms CYP3A, 2B6, 2J2, 2D6, 2C19, 2B6, CYP1A1/2, and CYP1, but to a lesser extent when compared to CBD. Low concentrations of THC were responsible for activation of CYP2C9 and induced the expression of CYP1A1. Uridine 5'-diphospho-Glucuronosyltransferase enzymes catalyze the conjugation of glucuronic acid to smaller molecules studies exploring the effects of cannabinoids on the UGT enzymes are limited, however, available studies revealed that CBD inhibited glucuronidation by UGY1A9 by 49% and UGT2B7 by 70%. A minor phytocannabinoid, cannabinol (CBN), was shown to inhibit UGT1A9 by 34% but activated UGT2B7 by 429%. THC, CBD and CBN were found to have inhibitory effects of the esterase CES1 with K_i = 0.541, 0.974, and 0.263 μM respectively. When THC, CBD and CBN are combined in a common route, i.e. smoking, the inhibition of CES1 occurs to a greater extent. This inhibition potentially impacts phase 1 enzymatic drug metabolism, deactivation of medications or inhibits the activation of prodrugs.

Enzyme	Assay System	Substrate	Cannabis Preparation/Component			Reference
			THC	CBD	CBN	
CYP3A4	rEnzyme	Diltiazem	↓*	↓↓↓	↓*	Yamaori et al, 2011[20]
CYP3A5			↓*	↓↓↓	↓*	
CYP3A7			↓*	↓↓	↓*	
CYP3A	HLM		↓*	↓↓	↓*	
CYP2D6	rEnzyme HLM	AMMC and DXM	↓↓*	↓↓↓	↓*	Yamaori et al, 2011[21]
CYP2C9	rEnzyme HLM	Phenytoin	↑	—	—	Bland et al, 2005[22]
	rEnzyme	S-warfarin and diclofenac	↓↓	↓↓↓	↓↓	Yamaori et al, 2012[23]
	HLM		↓↓	↓↓	↓↓	
CYP2C19	rEnzyme	S-mephenytoin	↓↓	↓↓↓	—	Jiang et al, 2013[24]
CYP2A6	rEnzyme	Coumarin	↓†	↓†	↓†	Yamaori et al, 2011[25]
CYP2B6		7-Benzoxyresorufin	↓↓	↓↓↓	↓	
CYP1A1	Hepa-1 cell	7-Ethoxyresorufin	↑mRNA	—	—	Roth et al, 2001[26]
	rEnzyme		↓‡	—	—	
			↓↓†	↓↓↓†	↓↓†	Yamaori et al, 2010[27]
CYP1A2	rEnzyme		↓↓	↓↓↓†	↓↓↓	
CYP1B1			↓↓	↓↓†	↓↓↓	
CYP1	HLM		↓↓	↓↓↓†	↓↓↓	
CYP2J2	rEnzyme	Anandamide	↓↓	↓↓	↓	Arnold et al, 2018[28]
UGT1A9	rEnzyme	Ethanol	—	↓‡	↓‡	Al Saabi et al, 2013[29]
UGT2B7			—	↓‡	↑	
CES1	rEnzyme	Oseltamivir	↓↓↓	↓↓↓	↓↓	Qian et al, 2019[30]

The inhibition potency of CBs was evaluated by the ratio of $C_{max,u}/(K_i$ or $IC_{50})$. In accordance with the current FDA guidance, a ratio value of higher than 0.02 indicates potential systemic drug interactions. C_{max} values were obtained from reported PK studies (0.515 μM for THC after smoking a cannabis cigarette[31]; 1.05 μM for CBD after 750 mg twice-daily doses[32]; and 0.0387 μM for CBN after smoking a cannabis cigarette[33]). The C_{max} values were further corrected by plasma protein binding (97.2% for THC,[34] 94% for CBD [from Epidiolex FDA review], and 90% for CBN [empirical]), and the resulted $C_{max,u}$ were 14.4 nM for THC, 63 nM for CBD, and 3.87 nM for CBN. Because nonspecific binding of CBs to assay materials was unknown, boundary K_i/IC_{50} values assuming either no or same nonspecific binding as that in the plasma were calculated in our assessment. Clinical drug interactions are considered very likely if the observed K_i/IC_{50} is lower than the boundary one with no nonspecific binding (THC, 0.721 μM; CBD, 3.15 μM; CBN, 0.194 μM), not likely if the observed K_i/IC_{50} is higher than the boundary one with the same nonspecific binding as that in the plasma (THC, 25.8 μM; CBD, 52.5 μM; CBN, 1.94 μM) and likely if the observed K_i/IC_{50} is in between. K_i values were used if both K_i and IC_{50} values were available.

*Only IC_{50} value was available.

†Inhibition was time dependent.

‡K_i or IC_{50} was not calculated.

↑ indicates induction; ↓, inhibition with K_i or IC_{50} suggesting clinical drug interactions not likely; ↓↓, inhibition with K_i or IC_{50} suggesting clinical drug interactions likely; ↓↓↓, inhibition with K_i or IC_{50} suggesting clinical drug interactions very likely; AMMC, 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin; DXM, dextromethorphan; rEnzyme, recombinant enzyme.

Figure 1. From "The Potential for Pharmacokinetic Interactions Between Cannabis Products and Conventional Medications," by Y. Qian, B. J. Gurley, and J. S. Markowitz, 2019, *Journal of Clinical Pharmacology*, Volume 39, p. 466. Copyright 2019 by Wolters Kluwer Health, Inc.

Safety and Efficacy of marketed cannabinoids: THC and Cannabidiol.

The study and research letter by Bonn-Miller et al. (2017) examined the accuracy in labeling of CBD products available for purchase in the online marketplace. The methods, conducted between September 12, 2016, and October 15, 2016, included a keyword search of 'CBD,' 'cannabidiol,' 'oil,' 'tincture,' and 'vape.' Study participation required products to display CBD content on the label; excluded products included those sold under the same brand with identical formulations. The original labels were replaced by blind study identifiers before

shipment to a lab for cannabidiol content analysis by high-performance liquid chromatography in triplicate, and results were averaged and reported by weight. The study employed a 10-point method validation procedure, triplicate test results were averaged, reported by weight, and analyzed using SPSS Statistics utilizing descriptive analyses and a 2-tailed x^2 ($a < .05$) and allowed ± 10% variance.

In total 84 products containing CBD were analyzed; the average labeled CBD concentration was 15.00 mg/mL (range 1.33-800.00) however the observed CBD concentration ranged from 0.10 mg/mL to 655.27 mg/mL (median, 9.45 mg/mL). Thirty-six or 42.85% (95% CI, 32.82%-53.53%) of CBD products were underlabled, 22 or 26.19% (95% CI, 17.98%-36.48%) of CBD products were overlabeled and 26 or 30.95% (95% CI, 22.08%-41.49%) were accurately labeled. The study further delineated accuracy in labeling by analyzing CBD products by extract type. Furthermore, Bonn-Miller et al. (2017) compared labeling accuracy between product types [$x^2(1) = 16.75$; $p = .002$] and determined that CBD vaporization liquid was the most frequently mislabeled product at 87.50% [n=21, (95% CI, 69.00%-95.66%)] and CBD oil was accurately labeled the most frequently at 45.00% [n=18, (95% CI 30.71%-60.71%)]. The liquid chromatography reported substances contained in the products in addition to the expected CBD; 21.43% (n=18 [95% CI, 14.01%-31.55%]) of samples contained THC, 15.48% (n=13 [95% CI, 9.28%-24.70%]) contained cannabidiolic acid and 2.38% (n=2, [95% CI, 0.65%-8.27%]) contained cannabigerol.

Bonn-miller et al. (2017) identified a major consumer safety issue. Patients ingesting product improperly labeled could potentially lead to harm via accidental ingestion of unwanted compounds or via adverse drug interactions. However, this study is limited to a small sample of products available on the consumer market within a thirty day period.

The number of producers and sellers of cannabidiol products has increased rapidly. Hazecamp (2018) explored the uncertainties around the legality of CBD oils, the quality of the product, and safety. He outlines the risks and issues related to CBD product composition and discusses the lack of regulation regarding accuracy in labeling and whether or not the health claims are backed by science.

CBD oil is a concentrated solvent extracted from cannabis flowers or leaves and then combined with an oil such as sunflower, hemp or olive oil. Oil has increased in popularity as the dosage of the concentrated extracts can be increased in any easily digestible form while avoiding the risk of intoxication, as well as, avoiding the odor that accompanies administration via smoking or vaporization. Hazekamp (2018), identifies a wide range of beneficial therapeutic uses of CBD such as Dravet syndrome, a severe form of epilepsy in children, Parkinson's disease, schizophrenia, and anxiety disorder via its function as an indirect antagonist of CB1 and CB2 receptors, decreasing receptor activation therefore protecting the nervous and immune system. Preclinical evidence for the use of cannabinoids inducing apoptosis, inhibition of angiogenesis and arresting of the cell cycle in cancer cells. However, no solid clinical evidence exists to support this claim, in some instances cannabinoids can accelerate certain types of cancer (Hazekamp, 2018). To date, the use of CBD oil in adults is gaining acceptance, but data regarding the long-term effects of high-dose CBD on the brain function and development of children is lacking.

The legal status of CBD in the USA is a bit convoluted; currently cannabis is illegal federally, but states have passed their own medicinal or recreational cannabis laws. The legality of CBD products is dependent upon how it was produced, the contents of the final product and location of consumers as some CBD products still contain amounts of the psychoactive

cannabinoid THC. While current literature based on human studies indicates that CBD is well tolerated in doses up to 1,500 mg per day there is limited knowledge regarding the long-term effects of chronic use and drug-drug interactions between CBD and other medications. One of the potential issues regarding the production of CBD is the presence of contaminants to increase yield, weight or potency or unintended contaminants such as heavy metals, molds, or bacteria. The author describes several instances where pesticides were found in medicinal cannabis and the residual presence of toxic solvents from the extraction process. Currently, there is no standard procedure for analyzing and quantifying the content of cannabinoids in products and analysis can vary significantly between labs. Producers and consumers are at risk as it is difficult to accurately determine the quality of the product or quantity of specific cannabinoids. Hazekamp (2018) references a study performed in the Netherlands analyzing the accuracy in labeling on the contents of 46 cannabis oil samples collected from patients. Twenty-nine of the samples were homemade or purchased from web sources with 46% of the samples labeled with CBD/THC content. The analysis revealed inaccuracies between cannabinoid content and claimed content; seven samples had no cannabinoid content at all. Fifty-seven percent of samples contained >1% THC, with one containing 57.5% THC; 39% of the sample only contained THC with less than <0.1% CBD. Researchers were unable to determine if consumers were always aware of the high THC content and the exposure to the adverse effects of the psychotropic compound. The study also noted increased amounts of non-decarboxylated cannabinoids in multiple samples. CBD-acid and THC-acid are the carboxylic acids that serve as precursors to the CBD and THC cannabinoids. These carboxylic acids are converted into CBD and THC via the decarboxylation process. Fifteen percent of samples tested contained >25% of its cannabinoids in the form of acidic cannabinoid indicating poor control of the decarboxylation

process. Regulation regarding the production and accuracy in labeling products is necessary for consumer safety.

According to Hazecamp (2018), the lack of oversight regarding the growing, harvesting and inaccuracies regarding concentration of cannabinoids potentiates an unnecessary risk to consumers. Legalization of cannabinoids at the federal level will lead to increased funding for properly constructed clinical trails to assess the benefits, risks and ensure the exact composition of products prior to availability on the consumer market. This investigation is limited to only cannabidiol products, however the concerns presented by the author can be applied to all cannabinoid products.

This study authored by Nick Jikomes, a research scientist with *Leafly*, and Michael Zoorob, Department of Government at Harvard University, underlines the need for standardized laboratory methodologies for the analysis of cannabis and cannabinoid products (Jikomes & Zoorob, 2018). The current lack of standardized methodology brings to question the legitimacy of all reported results regarding the cannabinoid content of products on the consumer market today. This study documents that variation in reporting of cannabinoid content by different laboratories in the state of Washington, despite controlling for factors related to differences in producers, product type, and the strain name of the samples. Jikomes and Zoorob (2018), utilized the *Washington I-502 Cannabis Test Data*, a large dataset from Washington state's seed-to-sale traceability system. The dataset comprises hundreds of thousands of measurements of the principal cannabinoids on the commercial market, including tetrahydrocannabinol (THC) and cannabidiol (CBD), allowing the authors to analyze the cannabinoid composition of products between various laboratories statewide. Differences between labs were apparent across all three identified cannabis chemotypes (THC-dominant vs. balanced vs. CBD-dominant) in both flower,

and concentrated form. One of the most problematic aspects of the report is the propensity of labs to report THC-dominant strains with low total CBD levels inaccurately. The median total THC in chemotype 1 or THC-dominant flower products ranged from 17% to 23% between labs. A two-sided t-test for pairwise comparison revealed this to be a statistically significant difference with a p-value of < 0.001, but this result does not an intuitive assessment of the differences between the two labs. In order quantify the magnitude of the differences the authors applied two different metrics: Cohen's d, which standardizes the difference between two means, and a "Common Language" (CL) effect size, which determines the probability that a random value from one sample will be higher than a random value from the other. THC levels in THC-dominant flower products analyzed by Lab B and Lab A were 18.4% and 17.7%, respectively. The effect size or Cohen's d was small, $d=0.13$ and the CL was 0.54 meaning that there is a 54% chance that a random THC value from Lab B will be larger than a random value for Lab A. When comparing Lab F and Lab A, labs that reported the highest and lowest total mean THC, the effect size was more substantial, $d=1.28$ and $CL = 0.82$. Labs consistently reported variation when comparing CBD measurements in chemotype II (balanced) and chemotype III (CBD-dominant) samples. Labs that reported the highest levels of THC also reported the highest levels of CBD, indicating a systematic tendency to report higher labs across chemotypes and product categories. The accurate and precise ratio of THC to CBD is imperative in the correct dosing of cannabinoid products in order to avoid unnecessary adverse events.

The inter-lab variations described above persisted even after controlling for strain name, the producer-processor submitting the samples, and the time of measurement. Estimating four separate regression models: (1) THC levels in chemotype I flower products ($n = 161,933$); (2) THC levels in chemotype I concentrate products ($n = 33,888$); (3) CBD levels in chemotype II

and III flower products (n = 4,661); and (4) CBD levels in chemotype II and III concentrate products (n = 2,156). The authors applied a fixed-effect transformation for each grower-strain combination in order to absorb heterogenicity in cannabinoid content attributed to the above factors using the Least Squares Dummy Variable formulation in order to compare the categorical data as quantitative data. The results depicted large inter-lab variability in reported THC and CBD levels that persisted despite controlling for the above variables. Differences were observed for both flowers and concentrate. Interestingly, Lab F consistently reported higher average totals in all of the analyzed variables. For instance, in chemotype 1 flowers, the average adjusted total THC level for Lab F (~23%) was significantly higher than all other labs ($p<0.01$). In chemotype 1 concentrates, Lab F's average reported THC, ~75%, exceeded that of all the other labs. For CBD levels in chemotype II and chemotype II flowers, Labs F reported significantly higher mean quantities at 13%, $p<0.01$. While analyzing THC:CBD content amongst chemotypes with less than 0.1% dry weight CBD content, substantial variations in reporting chemotype I (THC-dominant) with low levels of CBD became apparent. Due to the volume of data, small differences between labs produced statistically significant results ($p<0.001$) in pairwise comparisons, Mann-Whitney U tests, therefore the authors computed Cohen's h for all pairwise comparisons. The results showed that the inter-lab differences were considerable in effect size ($|h|>0.08$), confirming a lack of sensitivity in the detection of low levels of CBD in chemotype I flowers.

Anecdotally, THC content is attributed to the chemovars with "sativa" containing the greatest amount of THC and eliciting more psychoactive effects. The "hybrid" chemovar is said to be a balance of THC and CBD, while "indica" is thought to consist of the CBD phytocannabinoids predominantly. In order to investigate the accuracy of these claims, the

authors analyzed the distribution of THC content amongst indica, sativa, and hybrid categories. The authors matched test results to the producer-given strain name to categorize the samples yielding 166,594 flowers for analysis: 42,711 indica (25.6%), 31,822 sativa (19.1%), and 92,061 hybrid (55.3%). Analysis results of THC levels across consumer categories showed an overlap (~19 %) in chemotype 1 flower with hybrid products having slightly more THC than the other categories (20.2%). The authors then estimated a bivariate regression model of THC on strain category across all labs. The model concluded that hybrid chemovars contain modestly greater THC content, than either indica (hybrid vs. indica: 1.22%, $p<0.001$) or sativa (hybrid vs. sativa: 0.89%, $p<0.01$). Furthermore, the variability in CBD content across the strain categories for chemotype 2 and chemotype 3 elicited similar results, hybrid vs indica: 2.17%, $p < 0.01$; hybrid vs sativa: 0.90%, $p = 0.261$; sativa vs indica: 1.26%, $p < 0.05$). Therefore, it can be concluded that THC or CBD content cannot be inferred based solely upon the indica, sativa, or hybrid labels.

Jikomes and Zoorob (2018) published a very through and well written article highlighting the need for standardized laboratory protocols in the testing of cannabinoids. Without uniform standards the inaccuracies in labeling and potential for consumer harm cannot be fully addressed. This study is limited to the results that producers reported to the *Washington I-502 Cannabis Test Data* and thus the accuracy or inaccuracy of testing by labs. The dataset did not include measurements of other phytocannabinoids or terpenes, compounds produced by Cannabis that modulate the effects of phytocannabinoids. Thus, the differences in the profiles of sativa and indica could not be wholly analyzed for differences. The study is also limited to the analysis of only two product categories, flowers, and concentrates.

Discussion

Well-funded and rigorous academic research on cannabis and cannabinoid derivatives is lacking secondary to its classification as a Schedule 1 drug. The legalization of products containing derivatives of cannabis with low concentrations of THC contributed to an increase in studies exploring the phytocannabinoids, cannabidiol and cannabinol. The robust availability of cannabinoid products wildly outpaces the much needed regulatory oversight, standardization in manufacturing and testing of cannabinoids compounded by a lack of research. Current data indicates that cannabinoids are safe for consumption and show promise in the therapeutic management of neurological conditions and inflammatory processes without significantly increased risk of morbidity and/or mortality events secondary to drug-drug interactions.

Are Adults Who Consume Cannabinoids in Various Forms Compared to Nonusers at an Increased Risk of Experiencing a Significant Morbidity of Mortality Event Secondary to a Drug-drug Interaction?

A review of the current literature demonstrates that the phytocannabinoids THC, CBD, and CBN bind to G-protein coupled cannabinoid receptors: CB1, found in the central and peripheral nervous system, and CB2, expressed predominantly in the peripheral nervous system, spleen, and thymus. Once activated, cannabinoid receptors elicit a downstream inhibitory effect on adenylate cyclase production, thus modulating calcium and potassium channels (Cox et al., 2019). Furthermore, in comparison to competitive binding assays, cannabinoid receptors showed expressed a higher affinity for phytocannabinoids displacing naturally occurring endocannabinoids; however, these receptors expressed an even higher affinity for synthetic (pharmaceutical) cannabinoids (Cox et al., 2019). However, Amin et al. (2019) present evidence that the orphan receptor GRP55 exhibits similar characteristics to CB1 and CB2 and, therefore, a type 3 cannabinoid receptor, CB3. THC is primarily a weak partial agonist on CB1 and CB2 receptors. Once bound, THC elicits a psychoactive effect modulating pain, appetite, digestion, emotions, and thought processes (MacCallum et al., 2018 and Brown et al., 2019). Although

Amin et al. (2019), intimated that current research has not conclusively determined the full effect of THC on CB1 and CB2 receptors. In contrast, literature supports CBD as a negative allosteric modulator of CB1, with further effects on a variety of other receptor systems including TRPV1 (MacCallum et al., 2018 and Amin et al. 2019), TRPV2, TRPA1 and serotonin 5-HT2 (Amin et al.) capable of eliciting analgesic, anti-inflammatory, anti-anxiety, and anti-psychotic effects (MacCallum et al. 2019).

The potential for drug-drug interactions and cannabinoids lies mostly in the inhibition and induction effects of THC, CBD, and CBN, the cytochrome P450 system. According to the reviewed literature, THC, CBD, and CBN, all inhibit CYP2C9, CYP1A1/2, and CYP1B1. THC and CBD both inhibit CYP2D6, CYP2C19, CYP2B6, and CYP212. CBD alone inhibits CYP2A6, CYP2B6, and CYP3A4/5. Specific drug-drug interactions occurred between co-administration of Sativex, synthetic CBD, and ketoconazole, a potent CYP3A4 inhibitor leading to an 89% increase in CBD bioavailability. In the same in-vitro study presented by Brown et al. (2019), 100% of healthy patients co-administered THC with ketoconazole reported adverse events related to the central nervous system. Rifampin, a strong CYP3A4, and CYP2C19 inducer decreased the bioavailability of CBD by 52% (Brown et al., 2018. The most significant potential drug-drug interaction occurred with the co-administration of CBD and clobazam. Clobazam, metabolized by CYP3A4, CYP2C19, and CYP2B6, elicited a 73% increase in CBD. Furthermore, clobazam concentrations increased by 60% with a 3-5 fold increase in the active metabolite norclobazam (Brown et al., 2019) One case report indicated at potential interaction between smoked cannabis and warfarin via inhibition of CYP2C9-mediated warfarin metabolizing leading to supratherapeutic INR levels of 10.4 (Cox et al., 2019).

Cannabinoid interaction with phase II metabolism via UDP-glucuronosyltransferases (UGT), specifically UGT1A9 and UGT2B7, and via activity as both substrates and inhibitors of drug transportation however the magnitude of influence and involvement of the individual isoforms requires further study (Qian et al., 2019 and Cox et al., 2019).

Current research indicates few significant drug-drug interactions between commonly prescribed medications and cannabinoids.

Does a Lack of Regulatory Oversight Regarding the Manufacturing and Marketing of Products Containing Cannabinoids Increase the Risk of Experiencing a Significant Morbidity or Mortality Event in Adults Who Utilize Cannabinoid Products in Various Forms?

CBD products for purchase online benefit from loose regulatory oversight. Bonn-Miller et al. (2017) discovered labeling inaccuracies in products available in the online marketplace. Eighty-four products, including oils, tinctures, and vaporization liquid, with identical formulation, underwent analysis via high-performance liquid chromatography to determine the exact cannabinoid content. Only 30.95% of the products tested had accurately identified the concentration of CBD on the label. The study concluded that 60.94% of CBD products were either over labeled, 26.19%, or under labeled, 42.85%. Vaporization liquid was most inaccurately labeled, 87.50% (n=21), and oils were most accurately labeled, 45% (n=18). A product containing less than the indicated concentration appears harmless. However, products containing more than the indicated concentration have the potential for unintended adverse drug events or drug-drug interactions.

Additionally, a review by Hazekamp (2018) identified concerns regarding the quality and safety of manufactured CBD oil. A potential safety issue regarding the production of CBD products is the presence of contaminants utilized to increase yield, weight or potency as well as unintended contaminants including heavy metals, molds, or bacteria.

Perhaps the most problematic aspect regarding the safety and efficacy of cannabinoid products is the lack of standardized laboratory methodology to accurately analyze cannabinoid products as described in studies published by Jikomes et al. (2018) and Hazekamp (2018). The labs studied by Jikomes et al. (2018) frequently reported variation in identical samples of cannabinoid products across all labs. This inconsistency in analysis regarding the concentration of cannabinoid products potentially increases the incidence of drug-drug interactions between commonly prescribed medications and cannabinoids, specifically related to interactions that are dose dependent.

There is a lack of well-constructed, adequately controlled, randomized and double-blind clinical trials exploring the co-administration of cannabinoids and commonly prescribed medications. Further research is necessary to support the therapeutic claims that cannabinoids have a positive impact on complicated disease states as long-terms studies are lacking in current literature. A lack of standardization in the production, cultivation, and harvesting of cannabis along with variability in laboratory analysis secondary to a lack of standard analysis parameters. At this time studies utilizing cannabinoid products available for consumers are unable to control for the cannabinoid content of samples. Future research should be designed in such a way to account for differences in the pharmacokinetics of women and men and with considerations regarding adiposity, genetic factors influencing metabolism and absorption and the effects of disease states.

Conclusion

The potential limitations regarding the methodology of this review should be discussed. The use of specific search engines and broad keywords in no way guarantees that the results are comprehensive. While the information related to pharmacokinetics, pharmacodynamics, and ultimately the fate of exogenous cannabinoids has increased over the years, specifically the last

five years, significant gaps in the data remain. The paucity of quality human studies focuses on the major metabolic pathways of THC and CBD, leaving hundreds of phytocannabinoids unstudied, resulting in an unclear risk to individuals regarding metabolic drug interactions. First and foremost, the laboratory process regarding the testing of cannabinoids must be standardized to ensure the accuracy and validity of the results generated in future research. The focus of future research should include investigation, isolation, and full characterizations of specific cannabinoids rather than compounds containing many cannabinoids.

Furthermore, future studies must be well designed controlling for age, gender, body composition, co-morbidities, administration, and route before applying generalized conclusions. Currently, drug-drug interactions involving cannabinoids vary dramatically in their clinical significance secondary to the extreme variability in the cultivation, harvesting, products, doses, routes of administration, and populations utilizing cannabinoid substances. In order to produce quality clinical research examining the effects of exogenous cannabinoids, including terpenes, thoroughly, the current regulatory barriers must be addressed. Until the federal government addresses the legal status of cannabis or adjusts the restrictive policies and regulations currently in place regarding the research into health harms or benefits of cannabis and cannabis metabolites, the lack of evidence-based information will continue to perpetuate a potential public health risk.

Applicability to Clinical Practice

The information gleaned from the literature review provides medical providers with the data necessary to participate in the shared decision-making model of patient care. While the current literature does not endorse many drug-drug interactions with the co-administration of cannabinoids and commonly prescribed medications the topic requires further research. Cannabinoids continue to gain popularity amongst the patient population. It is imperative that

clinicians understand the potential for interactions based upon route and dose in order to participate in the shared decision making process with patients.

References

Amin, M. R., & Ali, D. W. (2019). Pharmacology of medical cannabis. *Advances in Experimental Medicine and Biology*, *1162*, 151–165. https://doi.org/10.1007/978-3-030-21737-2_8

Bonn-Miller, M. O., Loflin, M. J. E., Thomas, B. F., Marcu, J. P., Hyke, T., & Vandrey, R. (2017). Labeling accuracy of cannabidiol extracts sold online. *JAMA - Journal of the American Medical Association*, *318*(17), 1708–1709. https://doi.org/10.1001/jama.2017.11909

Brown, J. D., & Winterstein, A. G. (2019). Potential adverse drug events and drug–drug interactions with medical and consumer cannabidiol (CBD) use. *Journal of Clinical Medicine*, *8*(7), 989. https://doi.org/10.3390/jcm8070989

Cox, E. J., Maharao, N., Patilea-Vrana, G., Unadkat, J. D., Rettie, A. E., McCune, J. S., & Paine, M. F. (2019). A marijuana-drug interaction primer: Precipitants, pharmacology, and pharmacokinetics. *Pharmacology and Therapeutics*, *201*, 25–38. https://doi.org/10.1016/j.pharmthera.2019.05.001

Drug Scheduling. (2006). https://doi.org/10.1201/9781420009835.ax1

FDA. (2019). *FDA Regulation of Cannabis and Cannabis-Derived Products, Including Cannabidiol (CBD)*. U.S Food & Drug Administration. https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd

Hazekamp, A. (2018). The trouble with CBD oil. *Medical Cannabis and Cannabinoids*, *1*(1), 65–72. https://doi.org/10.1159/000489287

HSC. (1996). *Compassionate use act of 1996*. State of California Health and Safety Code. https://leginfo.legislature.ca.gov/faces/codes_displaySection.xhtml?sectionNum=11362.5.&

lawCode=HSC

Jikomes, N., & Zoorob, M. (2018). The cannabinoid content of legal cannabis in Washington state varies systematically across testing facilities and popular consumer products. *Scientific Reports*, *8*(1), 1–15. https://doi.org/10.1038/s41598-018-22755-2

Kapur, A., Zhao, P., Sharir, H., Bai, Y., Caron, M. G., Barak, L. S., & Abood, M. E. (2009). Atypical responsiveness of the orphan receptor GPR55 to cannabinoid ligands. *Journal of Biological Chemistry*, *284*(43), 29817–29827. https://doi.org/10.1074/jbc.M109.050187

Lewis, M., Yang, Y., Wasilewski, E., Clarke, H., & Kotra, L. (2017). Chemical profiling of medical cannabis extracts. *ACS Omega*, *2*(9), 6091–6103. https://doi.org/http://dx.doi.org/10.1021/aceomega.7b00996

MacCallum, C. A., & Russo, E. B. (2018). Practical considerations in medical cannabis administration and dosing. *European Journal of Internal Medicine*, *49*(January), 12–19. https://doi.org/10.1016/j.ejim.2018.01.004

Medical, S., & Laws, M. (2018). *State Medical Marijuana Laws 1/22/2018*. National Conference of State Legislatures. http://www.ncsl.org/research/health/state-medical-marijuana-laws.aspx

Millar, S. A., Stone, N. L., Yates, A. S., & O'Sullivan, S. E. (2018). A systematic review on the pharmacokinetics of cannabidiol in humans. *Frontiers in Pharmacology*, *9*(NOV). https://doi.org/10.3389/fphar.2018.01365

Qian, Y., Gurley, B. J., & Markowitz, J. S. (2019). The potential for pharmacokinetic interactions between cannabis products and conventional medications. *Journal of Clinical Psychopharmacology*, *39*(5), 462–471. https://doi.org/10.1097/JCP.0000000000001089

Russo, E. B. (2007). History of cannabis and its preparations in saga, science, and sobriquet.

Chemistry and Biodiversity, *4*(8), 1614–1648. https://doi.org/10.1002/cbdv.200790144

Takakuwa, K., & Schears, R. (2019). A history of the US medical cannabis movement and its importance to pediatricians: Science versus politics in medicine's greatest catch-22. *Clnical Pediatrics*. https://doi.org/http://dx.doi.org/10.1177/0009922819875550