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Factors that Impact the Pharmacokinetic and Pharmacodynamic Effects of Cannabis: a Review of Human Laboratory Studies

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Abstract

Purpose of Review With cannabis legalization expanding throughout the world, an unprecedented number of people now have access to legal cannabis. This expanded legalization has also created an extensive retail market that includes a litany of cannabis products, which vary on factors such as chemical profile (i.e., chemotype), formulation, and intended route of administration. Despite increases in cannabis access and product variety, research on the effects of product and user characteristics on drug effect profiles is limited.

Recent Findings Controlled laboratory studies are important because they can reveal what factors influence the pharmacokinetic (PK) and pharmacodynamic (PD; e.g., subjective, cognitive, psychological) effects of cannabis and its principal constituents D-9-tetrahydrocannbinol (D-9-THC) and cannabidiol (CBD). In this review, we describe the various product (e.g., chemotype, route of administration) and user factors (e.g., frequency of use, sex, and age) that influence the PK and PD effects of cannabis.

Summary Understanding the factors that impact the PK/PD profile of cannabis could be used to promote more consistency in drug effects, as well as cannabinoid delivery for medical purposes. Furthermore, such knowledge is key to informing eventual regulatory actions and dosing guidelines for cannabis products.

Keywords Cannabis · Pharmacokinetics · Pharmacodynamics · Route of administration · Cannabinoids

Introduction

The regulation of cannabis is experiencing a rapid and large-scale shift throughout the developed world, with widespread policy reforms aimed toward the legalization of cannabis access for medicinal and/or non-medicinal purposes. Coincident with such policy reforms, the perceived risks associated with cannabis have decreased while overall use and availability have increased, at least for adults [1, 2]. Expanded cannabis legalization has given rise to a booming retail industry of cannabis products that vary with respect to chemical composition (or "chemotype"), product formulation (e.g., plant material vs. concentrated extracts), and intended routes of administration. Despite the increased diversity of cannabis products and growing diversity of cannabis users, relatively few controlled laboratory studies have been conducted to elucidate the impact of specific product or user characteristics on the pharmacokinetic (PK) and/or pharmacodynamic (PD) effects of cannabis.

Controlled human laboratory studies are a valuable method for developing a comprehensive understanding of the PK and PD profile of cannabis. In this review, we discuss results from controlled cannabis administration studies in humans and summarize the various product and user factors, including the cannabis chemotype and dose, route of administration, and user factors (e.g., age, sex), that have been shown to impact PK/PD outcomes.

This article is part of the Topical Collection on *Cannabis*

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Cannabis Chemotype and Dose

The composition of cannabis products can be broadly categorized into four distinct groups based on chemical composition: (1) delta-9-tetrahydrocannbinol (D-9-THC)-dominant, (2) cannabidiol (CBD)-dominant, (3) balanced D-9-THC and CBD (approximately equal D-9-THC and CBD concentrations), and (4) minor cannabinoid-dominant [3, 4]. The cannabis plant has over 120 unique phytocannabinoids that have been identified [5–7]. The two principal phytocannabinoids present in cannabis are D-9-THC and CBD; these two compounds have also been the primary focus of cannabis research to date. D-9-THC is a partial agonist at both the type 1 and type 2 cannabinoid (CB) receptors [8, 9] and is believed to be the primary driver of most behavioral effects associated with acute cannabis administration (e.g., euphoria, "high," increased appetite, memory impairment; [10]). CBD has increased in popularity in recent years due to its purported therapeutic effects for myriad health conditions (e.g., autism, anxiety, posttraumatic stress disorder; pain; [8, 11, 12]). CBD has multiple mechanisms of action, with evidence that CBD interacts with GPR55, TRPV1, and 5-HT1A receptors [8, 9]. Moreover, though CBD has low binding affinity for the CB_1 and CB_2 receptors, there is evidence that it can act as a negative allosteric modulator at CB_1 and can increase endogenous cannabinoid tone via inhibition of fatty acid amide hydrolase (FAAH) [13]. Beyond D-9-THC and CBD, cannabis also contains many so-called minor cannabinoids such as tetrahydrocannabivarin (THCV; [14]), cannabinol (CBN; [15]), cannabigerol (CBG; [15]), as well as non-cannabinoid compounds including terpenes (e.g., limonene, pinene, myrcene; [16]). The cannabis "entourage effect" theory asserts that these additional constituents contribute to the effects of cannabis by interacting synergistically with D-9-THC, and/or by producing pharmacological effects of their own. However, the overwhelming majority of clinical research on cannabis to date has focused on D-9-THC and CBD and the pharmacological effects of other cannabis constituents remains understudied. Therefore, more research is needed to understand the contribution of each constituent to the diverse pharmacological outcomes produced by botanically derived cannabis products.

Many controlled clinical laboratory studies have focused on PD outcomes following D-9-THC administration. For example, D-9-THC alone (e.g., dronabinol) administration increases ratings of subjective "high," "drug liking," "hunger," and "anxiety and nervousness" among many others [17–24], increases ratings of objective intoxication (as assessed by the Clinician Administered Dissociative States Scale; [25]), impairs cognitive and psychomotor function (e.g., working memory; [19, 20, 26, 27]), and reliably increases heart rate (e.g., [24, 28, 29]).

Only a few controlled laboratory studies have examined PD outcomes following CBD, balanced D-9-THC and CBD, or minor cannabinoid administration. CBD does not produce D-9-THC-like increases in subjective drug effects or objective intoxication [25], cognitive and psychomotor impairment, or changes in cardiovascular function [30–34]. Furthermore, CBD has been shown to produce anxiolytic effects [35] and reduce the frequency of convulsive seizures [36, 37]. Equal proportions of D-9-THC and CBD produce increases in subjective drug ratings [38, 39], impairment of cognitive and psychomotor function, and increases in cardiovascular effects similar to D-9-THC and D-9-THC-dominant chemotypes [40, 41]. Of the few studies investigating minor cannabinoids, neither THCV [42] nor CBN [43] produced alterations in subjective drug effects, cognitive performance, or cardiovascular function, though THCV acutely reduced D-9-THC-induced memory impairment and increased heart rate. Another study compared D-8-tetrahydrocannbinol (D-8-THC) to D-9-THC following oral ingestion and intravenous infusion in six healthy adults and found that D-8-THC had a lower potency to produce the intoxicating effects associated with D-9-THC, including dizziness, incoordination, muscle tremor, distortions of vision and time perception, and impaired cognition, but this could be overcome by increasing the administered dose of D-8-THC [19].

Several controlled studies have shown that the magnitude of drug impairment is dose related [44, 45, 46•, 47]. For example, in one illustrative study, oral administration 10 mg of D-9-THC produced subjective effects of drug liking without producing cognitive/psychomotor impairment, while 25 mg D-9-THC increased positive and negative subjective effects and produced marked impairment of cognitive/psychomotor skills [41].

Other product factors may also influence PK and PD outcomes following cannabis use but have yet to be examined systematically in controlled laboratory studies. For example, differences in the manufacturing of cannabis products could conceivably impact PK/PD effects. Environmental factors, cultivation, and processing of whole plant cannabis can substantially impact the chemical composition of cannabis product formulations [48]. Cannabis extraction methods can vary across a range of variables (e.g., extraction time, oil vehicle), which can also alter the chemical composition of the end-product (e.g., increasing concentrations of one constituent such as D-9-THC while reducing the concentration of other cannabinoids; [49]). Likewise, trends have emerged among manufacturers to either grow cannabis with targeted terpene profiles (or to add terpenes to the end-product) as a means of purportedly producing tailored PD effects. However, there is essentially no published research to elucidate whether, and to what extent, minor cannabinoids or terpenes contribute to

overall cannabis effects, either through direct pharmacological actions of their own or via interactions with D-9-THC.

Routes of Administration

The route of administration can have considerable influence on both the PK and the PD effects of cannabis. Additionally, within a given route of administration, there can be key differences in product formulation that may also impact PK and PD effects.

Smoked Cannabis

Smoking is one of the primary and most popular routes of administration for cannabis use [50, 51]. Smoked cannabis is consumed by combusting dried cannabis flowers using instruments like joints, blunts, pipes, or bongs [52]. Most previous human laboratory studies have focused on the effects of smoked D-9-THC-dominant cannabis. Smoking provides rapid and efficient delivery of D-9-THC and other cannabinoids to organs like the brain, lungs, and liver [53], and produces peak plasma D-9-THC concentrations within within the first 15-30 min of administration [54–56].

Subjective drug effects typically peak within the first 15–30 min of smoked cannabis administration and persist for about 4–5 h. In prior laboratory studies, lower doses of smoked D-9-THC-dominant products (between 8.4 and 13.5 mg D-9-THC) increased subjective drug effect ratings of drug liking and pleasantness, but adverse subjective drug effects such as nausea, anxiety, and paranoia were rare and tended to be of mild severity [46•, 55, 57–61]. Laboratory studies in which moderate-to-high doses of smoked D-9-THC (between 15 and 69 mg D-9-THC) were administered resulted in higher subjective drug effect ratings overall, but the frequency and magnitude of adverse drug effects were increased as dose increased [46•, 55, 57–61].

Similarly, impairment of cognitive performance has been shown to be more pronounced at moderate to higher doses compared with lower doses. For example, impairment of performance on the Buschke selective reminding task (7.5 mg vs. 15 mg D-9-THC; [44]), rapid visual information processing task (7.5 mg vs. 15 mg D-9-THC; [44]), divided attention task (DAT; 54 mg D-9-THC; [62•]; 10 mg vs. 25 mg D-9-THC; [46•]) and paced serial addition task (PASAT; 10 mg vs. 25 mg D-9-THC; [46•]) have been shown to be more pronounced as dose was increased. Furthermore, performance on the digit symbol substitution test (DSST; 8.4 mg vs. 16.9 mg D-9-THC; [61]; 10 mg vs. 25 mg D-9-THC; [46•]) and the critical tracking task (CCT; 54 mg D-9-THC; [62•]; 35 mg D-9-THC; [63]), two measures of psychomotor activity, were reduced following smoked cannabis administration in a dose-orderly fashion. In these studies, cognitive and psychomotor impairment generally peaked between 30 and 60 min after cannabis smoking and persisted for 4–5 h relative to placebo and baseline conditions.

Smoked D-9-THC dominant cannabis also has marked effects on cardiovascular function. Specifically, heart rate is significantly increased in a dose-dependent manner by D-9-THC, with increased changes of up to 30 beats per minute (BPM) at peak effect. These effects peak shortly after drug administration and gradually decrease over 2–3 h [47, 57, 60, 62•, 64]. Increased heart rate has been detected at doses as low as 8.4 mg D-9-THC [61]. The acute impact of cannabis on resting blood pressure has been mixed across studies. In some studies, neither systolic nor diastolic blood pressures are altered following D-9-THC administration of lower (e.g., 10 mg D-9-THC) and higher (e.g., 25 mg D-9-THC) doses [46•, 64, 65], while some studies demonstrated only an increase in systolic blood pressure [66], and other studies indicated that D-9-THC decreased diastolic blood pressure [55].

Aside from cannabis joints, which only contain cannabis, cannabis is often smoked in combination with nicotine/tobacco [67]. Tobacco, which contains varying concentrations of the addictive chemical nicotine, has been shown to increase D-9-THC in smoke condensate (i.e., the solid material that remains after the smoke) from cannabis, which would expose users to higher levels of D-9-THC [68]. Cannabis blunts are another popular method for smoking cannabis and are made by rolling dried cannabis flowers in hollowed-out cigar paper [69]. Depending on the blunt wrapper used, the nicotine concentrations can vary from 1.2 to 6 mg [70]. Blunts decreased blood plasma concentrations of D-9-THC and subjective cannabis intoxication in a dose-orderly fashion, without altering D-9-THC-induced cardiovascular effects, relative to joints [71]. A "spliff" is the common term used to refer to a cannabis cigarette that contains a combination of cannabis and tobacco; this is a popular way of consuming cannabis in European countries [72, 73]. Although they are quite popular, little is known about whether or how spliffs alter the PK and PD effects of smoked D-9-THC.

Only one controlled laboratory study has examined the effects of smoked CBD. In a study of patients with obsessive–compulsive disorder (OCD), 41.6 mg of smoked CBD did not produce subjective intoxication or changes in cardiovascular function relative to placebo, though 28 mg D-9-THC significantly increased all reported PD outcomes in the same study [74]. There are a few naturalistic observational studies that have examined PK and PD outcomes following smoked CBD-dominant and balanced D-9-THC and CBD cannabis products. CBD-dominant products displayed decreased peak plasma concentrations of D-9-THC and 11-OH-THC with increased CBD concentrations, as well as increased positive mood affects (e.g., relaxation)

with reduced subjective intoxication, anxiety, and paranoia relative to D-9-THC-dominant products [75, 76]. Smoked cannabis with equal proportions of D-9-THC and CBD exhibited decreased peak plasma concentrations of D-9-THC and D-9-THC metabolites [76], with similar positive subjective effects, reduced desire to smoke, lower subjective ratings of physically and mentally "stoned," lower anxiety and paranoia, and had no effect on cognitive impairment relative to D-9-THC-dominant cannabis [76, 77]. These studies should be considered in the context of study limitations, including the lack of control over participant dosing, lack of placebo controls, the timing of the dose versus the study assessments, and lack of participant blinding. Despite these limitations, naturalistic administration studies provide unique opportunities to examine the PK and PD effects of commercially available products under natural conditions. Future controlled laboratory studies will be needed to corroborate these findings under controlled dosing procedures.

Vaporized Cannabis

Vaporization is another form of cannabis administration that involves inhalation. Unlike smoking, which exposes the user to toxic combustion by-products (e.g., carbon monoxide, tar; [78]), vaporizers heat dried cannabis or cannabis extracts to temperatures high enough to produce an aerosol (i.e., vapor), but below the temperatures associated with combustion [52]. Vaporizers can generally be used more discreetly (e.g., due to less aerosol emission and less odor) compared to smoked cannabis [79, 80], which further increases their appeal. As such, vaporization of cannabis has increased in popularity among cannabis users over the past decade [51, 81, 82]. Cannabis vaporizers come in a variety of forms, with some pen-style devices resembling e-cigarettes while others can be categorized as larger "desktop" devices (e.g., Volcano vaporizers [52, 83, 84]). Some vaporizers contain concentrated extracts, often suspended in a liquid vehicle while others allow the user to inhale vaporized dried cannabis flower [84]. Oftentimes, these extracts contain higher concentrations of cannabinoids (e.g., D-9-THC, CBD) relative to dried cannabis flowers [85].

Like smoked cannabis, vaporized cannabis produces peak whole blood [46•, 56] and plasma [25, 41, 86] D-9-THC concentrations within the first 30 min of use, but D-9-THC concentrations generally return to baseline within 4 h. Studies comparing the PK and PD effects of vaporized vs. smoked D-9-dominant cannabis are mixed. For example, in one study, vaporized D-9-THC-dominant cannabis produced greater blood D-9-THC concentrations, subjective drug effects, and impairment of cognitive/psychomotor performance relative to the same doses of smoked cannabis (i.e., 10 mg and 25 mg D-9-THC) [46•]. Conversely, another study did not find differences in PK or PD effects between smoked and vaporized cannabis at a 50.6 mg D-9-THC dose [87, 88]. In both studies, D-9-THC administration was delivered using a Volcanic Medic vaporizer (Storz & Bickel, Oakland, California) that heats and aerosolizes cannabis before trapping the resulting vapor in a balloon for administration. The former study [46•] administered three separate balloons of aerosolized D-9-THC-dominant cannabis as it was required to exhaust and administer the highest dose (i.e., 25 mg D-9-THC), while the latter study [87, 88] only used one balloon, which may have been insufficient for delivering the full study vaporized dose (i.e., 50 mg D-9-THC). It is likely that vaporized cannabis is more efficient at delivering D-9-THC when compared to smoking due to degradation of D-9-THC during combustion and/or loss of D-9-THC through side stream smoke when it is burned [89]. Finally, like smoked cannabis, heart rate increases following cannabis vaporization in the first 15–30 min following D-9-THC-dominant cannabis administration and returns to baseline within a 1–1 ½ h [90].

There have been several studies investigating PK and PD outcomes of CBD-dominant and balanced D-9-THC and CBD vaporized cannabis. Peak blood concentrations typically occur within 15–30 min following administration of vaporized CBD-dominant cannabis and subside after 3–4 h [34]. At low doses (16 mg CBD; [91]), pure CBD does not produce any subjective drug effects. However, at moderate (100 mg CBD; [34]) and higher (400 mg CBD; [25]) concentrations, CBD increases subjective ratings of positive drug effects and drug liking; further, at higher doses (i.e., 400 mg CBD), participants report subjective feelings of intoxication (e.g., "feeling stoned"). Vaporized CBD has not impaired cognitive or psychomotor functioning ([34]), nor has it produced changes in cardiovascular function in any of the aforementioned studies [25, 34, 91]. However, CBD-dominant cannabis with low concentrations of D-9-THC (100 mg CBD/3.7 mg D-9-THC) produced greater subjective effects, including ratings of heart racing, relaxed, and sleepiness [34], as well as increased heart rate [25, 34] relative to vaporized CBD administered alone and placebo. Additionally, a high dose of CBD (400 mg CBD) reduced experimenter-observed objective intoxication relative to D-9-THC alone or when mixed with low amounts of CBD (4 mg CBD; [25]). Finally, low amounts of D-9-THC combined with CBD did not affect cognitive or psychomotor function [34].

Relative to D-9-THC-dominant cannabis (13.75 mg D-9-THC), balanced D-9-THC and CBD (13.75 mg of both D-9-THC and CBD) produced similar levels of D-9-THC and D-9-THC metabolites in plasma, subjective intoxication, cognitive and psychomotor impairment, impairment of simulated driving outcomes, and physiological changes in heart rate [40, 41]. Although no differences were noted between the two chemotypes, there was only a single, moderate dose

of D-9-THC and low dose of CBD used (i.e., both 13.75 mg) in this study. Future studies should assess the generality of these findings using higher doses of D-9-THC:CBD across various PK and PD outcomes.

Oral Cannabis

Oral cannabis products (aka "edibles") are ingested rather than inhaled to produce their drug effects. Large-scale national surveys show that edibles are now the second most commonly used form of cannabis (next to smoked cannabis) and that at least 25% of cannabis users have taken edibles [81, 82]. Like vaporized cannabis, edibles are perceived to have reduced health risks compared to smoking [92]. Moreover, edibles allow for discreet cannabis use, which contributes to their overall appeal [93]. Edibles come in a variety of formulations, including baked goods, gummies, hard candies, ethanol-based tinctures, oromucosal sprays, capsules, and beverages. Additionally, oral cannabis products can be absorbed via sublingual (e.g., sprays), buccal (i.e., hard candies, sprays), and gastric mechanisms, and some initial research suggests that variation in formulation can alter the PK outcomes across oral cannabis product types [94, 95]. For example, 10 mg of D-9-THC and CBD had similar peak concentrations under a sublingual, buccal, and oral formulations, but varied in time to peak concentrations, with oral (gastric) being the fastest and buccal being the slowest [94]. However, despite the growing popularity of cannabis edibles and formulations, controlled research on these products is extremely limited and, thus, should be a focus for future research.

Drug effects following oral cannabis ingestion are associated with a later onset period and longer duration of action compared with inhalation methods. Absorption of D-9-THC is slower and more erratic when taken orally. Oral ingestion of cannabis is often associated with increased risk for accidental acute overdose due to the delayed onset of effects [96]. Factors that contribute to slow/variable absorption of D-9-THC include slow gastric absorption, degradation of D-9-THC in the stomach (which is also affected by its contents), significant first-pass metabolism of D-9-THC in the liver into its psychoactive metabolite 11-OH-THC and inactive metabolites, and the frequency and magnitude of use [97]. These factors also contribute to low bioavailability of D-9-THC (approximately 4–20%) following oral administration [97].

Concentrations of D-9-THC and its metabolites in blood/plasma peak between 1 and 5 h [44, 47, 98, 99] after dosing. Prior studies have shown that D-9-THC concentrations after oral administration are dose dependent [45], and also impacted by biological sex; women had greater maximum concentrations (Cmax) and longer time to maximum concentrations (Tmax) compared with men [100]. Also, in studies that included multiple routes of administration, peak whole blood [47, 101] and plasma [88, 102] D-9-THC concentrations were significantly lower, but the active metabolite 11-OH-THC and inactive metabolite D-9-THC-COOH concentrations were significantly higher [88] following oral administration compared with inhaled cannabis.

Despite producing lower peak D-9-THC blood concentrations and having a different time course of effects, oral cannabis produced subjective, cognitive, and psychomotor effects that were comparable in peak magnitude to inhaled methods [44, 47]. For example, a low dose of D-9-THC-dominant cannabis (5–10 mg D-9-THC) produced an increase in reported drug effects, including good drug effect, and relaxation that were comparable to vaporized [47] and smoked cannabis [61]. Similarly, at higher doses (e.g., 25 mg D-9-THC), cannabis ingestion produced subjective ratings of negative affect in conjunction with the positive subjective drug ratings that are comparable to vaporized [46•] and smoked cannabis [61]. Ingestion of edibles at higher doses (25 mg D-9-THC), but not lower doses (10 mg D-9-THC) also produced impairment of performance on tasks of divided attention, and psychomotor performance [47, 101], as well as motor coordination and attention [103]. Finally, ingestion of D-9-THC dominant cannabis also increased physiological measures like heart rate and diastolic blood pressure [30, 47, 101] and reliably induced orthostatic hypotension [104]. In general, PD effects from cannabis edibles peak 1–5 h after ingestion and persist for about 8 h, though considerable variability across individuals has been observed.

Pure CBD and CBD-dominant cannabis products are commonly administered orally, often as tinctures or infused in food and beverage products [105]. Like D-9-THC, orally administered CBD exhibited low bioavailability (approximately 13–19%) in controlled studies, likely due to first-pass metabolism in the liver [106]. Plasma CBD and CBD metabolites peaked 1–6 h after administration [31, 94, 107] and was dose dependent up to doses of 400 mg CBD, but not greater [31, 33]. One explanation is that CBD is metabolized by cytochrome p450 enzymes, and that these enzymes become saturated at higher doses (i.e., CBD cannot be metabolized at higher rates due to insufficient enzyme activity).

With respect to PD outcomes, oral CBD administration produced no difference from placebo on subjective, cognitive and psychomotor function, and cardiovascular effects at doses ranging from 100 to 900 mg [30, 31, 34, 108, 109]. However, one study demonstrated that oral CBD at doses of 1500 mg and 4500 mg produced discriminable subjective drug effects, increasing ratings of drug liking compared to placebo [33]. Together, these studies indicate that oral CBD is well-tolerated and does not produce psychoactive or cardiovascular effects generally associated with D-9-THC.

Sativex, a formulated oromucosal spray consisting of roughly equal proportions of D-9-THC and CBD, is currently approved for the treatment of moderate to severe spasticity associated with multiple sclerosis in 29 countries, including Canada and the UK, and is under clinical investigation in the USA [53]. Peak plasma concentrations of D-9-THC and 11-OH-THC at low (5.4 mg D-9-THC, 5.0 mg CBD) and medium (16.2 mg D-9-THC, 15.0 mg CBD) doses of Sativex were comparable to low (5 mg D-9-THC) and medium (15 mg D-9-THC) doses of oral pure D-9-THC [38, 110]. Low dose (5.4 mg D-9-THC, 5.0 mg CBD) Sativex produced significantly higher subjective ratings of good drug effect relative to low dose (5 mg) D-9-THC, but not at the medium dose [110]. Interestingly, neither dose of Sativex was associated with increased subjective ratings of "high," though ratings of "high" were increased by D-9-THC [38]. Sativex and oral D-9-THC did not differ on any other subjective drug effects, and the medium doses of Sativex and D-9-THC significantly increased heart rate compared with placebo [38].

Topical Cannabis

Topical products are another emerging product category in the cannabis market. These products come in various forms such as cannabis-infused lotions, creams, and gels [52]. Despite the increase in popularity and availability of these products, there have been no published results of laboratory studies on the PK or PD effects following controlled administration of topical cannabis products. One case report evaluated the topical application of a high CBD/low D-9-THC lotion on PK outcomes; neither D-9-THC or any D-9-THC metabolites (e.g., D-9-THC-COOH) were detected in blood or urine [111]. An open-label study reported significant improvement of anxiety and behavioral symptoms in a small sample of children with Fragile X Syndrome after 12 weeks of using a topical CBD product in development (up to 250 mg CBD/day), but no PD data were reported in this study [112].

User Factors

User Frequency and Tolerance

A number of individual characteristics have been shown to significantly impact PK and PD effects of cannabis. For example, chronic cannabis users exhibited greater cannabinoid levels circulating in biological matrices (e.g., urine; [113]) due to accumulation of cannabinoids with repeated exposure. Furthermore, frequent cannabis users have increased concentrations of D-9-THC and its metabolites compared to infrequent users after inhaling cannabis using the same administration methodology, presumably by altering their puff topography [88, 114].

Frequent users generally experience less pronounced PD effects after D-9-THC-dominant cannabis administration compared with infrequent users, likely due to developed tolerance to D-9-THC effects. For example, frequent D-9-THC dominant cannabis users reported decreased magnitude of subjective drug effects (e.g., "good drug effect," "stimulated," and "anxiety") and a shorter duration of acute drug effects compared to infrequent cannabis users across several studies [62•, 115–118]. Moreover, infrequent users experienced greater impairment of cognitive functioning following D-9-THC-dominant cannabis administration, relative to frequent users, on assessments of divided attention [63, 119–122], perceptual alterations [123, 124], immediate recall [20, 26], and time perception [125]. Tolerance to cannabis-induced impairment of psychomotor functioning has also been observed across several studies [126, 127]. Acute tolerance to increased heart rate following repeated administration of D-9-THC dominant cannabis has been observed in frequent [128] versus infrequent users [62•, 116]. However, other cognitive function measures, like impulse control or working memory [127], have not exhibited differences between frequent/infrequent users after acute cannabis administration, suggesting that D-9-THC tolerance may not mitigate impairment for all aspects of cognitive performance.

The Influence of Sex

In recent years, there has been a notable increase in women using cannabis for both medicinal [129] and non-medicinal (aka "recreational") purposes [2]. Despite this increase, research on sex differences associated with cannabis use is limited and few controlled laboratory studies have directly compared the acute PK and PD effects of cannabis in men vs. women. There is some evidence that women metabolize D-9-THC differently than men, though evidence in this area is mixed. For example, in one study, women displayed greater D-9-THC and D-9-THC metabolites (e.g., 11-OH-THC), and shorter time to reach peak concentrations in whole blood following oral D-9-THC-dominant cannabis administration when compared to men [100]. In another study, following both vaporized and smoked cannabis administration at 10 mg and 25 mg D-9-THC, women displayed qualitatively higher concentrations of D-9-THC and the D-9-THC metabolite 11-OH-THC relative to men, although there were no differences in time to peak concentrations [56]. In a third study, when D-9-THC-dominant cannabis cigarettes were freely self-administered, no differences in D-9-THC PK were observed between men and women, but in this study, women generally smoked less cannabis than men [130].

In laboratory studies evaluating PD effects of D-9-THC-dominant cannabis, women have reported greater subjective drug effects, more abuse liability (e.g., increased ratings of drug liking), increased ratings of anxious/nervous, and increased subjective experience of heart racing compared to men [90, 131, 132]. Despite the trend towards increased magnitude of subjective drug effects, men and women did not differ across multiple cognitive and psychomotor tasks [90, 132], cardiovascular effects [90, 131, 132], or physiological effects [132] following controlled acute D-9-THC-dominant cannabis administration.

One potential mechanism for the observed sex differences in these laboratory studies is differential expression of the CB_1 receptor in females versus males. In a recent PET imaging study, CB_1 receptor availability was significantly higher in non-cannabis using women compared with non-cannabis using men [133]. Though sex differences were observed in many of the listed studies, it should be noted that none directly assessed the role of menstrual cycle on any of the outcomes. Hormonal fluctuations at various stages of the menstrual cycle may introduce variability on many outcomes [134]. Sex hormones may also mediate differences in D-9-THC metabolism observed in some studies, which, in turn, could account for some of the sex differences observed on subjective drug effects [135]. Future studies are clearly warranted to evaluate the impact of CB receptor expression, menstrual cycle, and hormone levels on subjective, cognitive, psychomotor, and physiological outcomes following acute cannabis administration.

Age

With increased access due to legalization, older adults have shown the greatest increase in both medicinal and non-medicinal cannabis use [136, 137]. A limited number of controlled laboratory studies have been conducted in which oral D-9-THC has been administered to older adults (e.g., [138]), but none have directly compared the PK or PD of older and younger adults. In an observational study, younger adults (aged 21–25) and older adults (aged 55–70) were assessed over 5 days of ad-libitum use of D-9-THC-dominant, CBD-dominant, or balanced D-9-THC and CBD smoked cannabis [139]. During the study, no significant differences in PK were observed. The older adults reported greater anxiety following CBD-dominant cannabis administration and reduced craving for all chemotypes compared with the younger adults. Cognitive impairment was greater in the younger adults after administration of the D-9-THC-dominant chemotype [139].

Though this study suggests minimal differences between younger and older adults, it is important to note that it was conducted in participants who frequently used cannabis (i.e., > 4 times per month) and used only one route of administration (i.e., smoked cannabis). It has been reported that older populations prefer non-smoked routes of administration (e.g., edibles; [140]). Furthermore, as people age, the metabolism and clearance of drugs, including psychotropic drugs like D-9-THC, decreases, which may significantly affect PD outcomes [141]. Age-related changes also alter receptor and signal transduction, as well as homeostatic mechanisms, which could lead to differing PD outcomes [141]. As such, future work should test the generality of these findings across multiple routes of administration, in adults who do or do not use cannabis regularly, and across more measures of potential risks (i.e., motor function and driving impairment).

Conclusions and Future Directions

Recent policy changes have resulted in increased medicinal and non-medicinal cannabis use and decreased perceptions of harm related to cannabis use [1, 2]. In this review, we highlighted findings from controlled human laboratory studies in which cannabis was acutely administered, specifically focusing on factors that influenced the PK and PD outcomes associated with cannabis exposure (Table 1). These studies clearly demonstrate that multiple factors (e.g., chemotype, dose, route of administration, frequency of use, sex, age) can significantly influence drug absorption and elimination, as well as the phenomenology, time course, and magnitude of drug effects after acute exposure to a given cannabis product. This highlights the importance of using more explicit language when referring to cannabis use moving forward as the term "cannabis" now encompasses too broad a product category for meaningful interpretation. Specifically, there is a need to differentiate cannabis product chemotypes and routes of administration in all forms of data collection and dissemination. More precise measures of dosing are needed for product labels, population surveys, and research instruments.

Moreover, though a substantial number of human laboratory studies of cannabis have been conducted, dating back several decades, most extant research was focused on the PK and PD of smoked D-9-THC-dominant cannabis. Major gaps in knowledge were identified and include the need for research on the acute effects of cannabis products in which minor cannabinoids are the dominant chemical constituent, controlled dosing of topically applied cannabis products or other under-studied routes of administration, increased evaluation of sex differences in laboratory experiments and the need to study the impact of hormones on acute cannabis metabolism and PD outcomes and the need for controlled research on PK and/or PD changes as a function of age. With increased cannabis access and increased use being broadly observed, research to close these knowledge gaps is critical.

Table 1 Summary of factors that influence cannabis pharmacokinetics and pharmacodynamics

Factor	Description	Example references
Cannabis chemotype and constituents	Cannabis chemotypes are defined by their cannabinoid (primarily D-9-THC and CBD) and terpene composition. Cannabinoid constituents such as D-9-THC and CBD produce unique pharmacological effects, and the combination of multiple constituents may produce interactive pharmacokinetic and behavioral effects	3, 17–24, 30–34, 42, 43
Dose	The concentrations of cannabinoids detected in blood and the magnitude of pharmacodynamic effects are generally increased in a dose-orderly fashion	41, 44–47
Route of administration		
Smoking	Most commonly used route of administration. Rapid delivery of cannabinoid constituents to major body organs. Whole blood and plasma concentrations of D9-THC and D-9-THC metabolites peak within the first 15 to 30 min of administration. During this time, peak subjective drug effects, impairment of cognitive ability, and effects on cardiovascular function are observed. These pharmacodynamic effects typically subside 4 to 5 h after administration	53–64
Vaporization	Cannabis or cannabis extracts can be vaporized to produce an aerosol (or "vapor") for users to inhale. Rapid and efficient delivery of D-9-THC and CBD can be achieved and can produce greater concentrations of D-9-THC and D-9-THC metabolites in whole blood and plasma relative to smoked and oral cannabis. Subjective drug effects, impairment of cognitive ability, and effects on cardiovascular function are greater when compared to smoked and oral cannabis. These effects peak in the first 30 min and subside within 4 h following administration	25, 41, 46, 56, 86–88, 90
Oral	Slow absorption of cannabinoids, susceptible to first-pass metabolism. Later onset of effects and longer duration of action. Concentrations of cannabinoids in whole blood and plasma peak between 1 to 5 h, and concentrations of D-9-THC are lower than inhaled routes of administration. Subjective drug effects, impairment of cognitive ability and increases in cardiovascular function are comparable to smoked cannabis, but peak much later, generally between 1.5 to 3 h, and usually persist for about 6 h, but can last longer, especially after high doses	30, 44, 47, 96–102
User factors		
User frequency and tolerance	Greater frequency of use is associated with increased concentrations of D-9-THC and its metabolites in blood and urine. Additionally, daily or near daily use of D-9-THC is associated with CB1 receptor downregulation and tolerance to the subjective drug effects, impairment of cognitive ability, and cardiovascular effects of acute cannabis exposure	62, 113, 115–128
Sex	Sex differences have been observed in some studies. When observed, females typically have different pharmacokinetics, especially greater blood/plasma concentrations of 11-OH-THC, compared with males. In addition, females have reported greater subjective drug effects with no differences in cognitive impairment or cardiovascular effects compared with males	56, 90, 100, 130–133
Age	Observational studies reveal that older adults report greater subjective drug effects, with reduced impairment of cognitive ability relative to younger adults. However, controlled laboratory studies are needed to confirm these effects across varying laboratory conditions (e.g., route of administration, frequency of use) between the two populations	139

Data from controlled laboratory studies can be applied in many different settings. For example, human laboratory research can be used to inform cannabis policy related to appropriate unit doses of retail cannabis goods, differential product regulation based on chemotype or intended route of administration, or assessment of policies related to safety (e.g., cannabis and the workplace, detection of driving impairment, age restrictions). Human laboratory studies can also inform risk–benefit decision making for health care providers and patients considering the medicinal use of cannabis. Though these laboratory studies are not intended to demonstrate clinical efficacy for therapeutic purposes, they can serve as a guide with respect to understanding differences in chemotype, route of administration and dose that could help inform initial product selection given that most medicinal cannabis use neither involves a product or health condition for which traditional clinical development has been completed to establish a standard dosing regimen.

In addition, as cannabis legalization continues to unfold, human laboratory studies will be an important research methodology for the characterization of novel retail products as they emerge as well as the identification of sub-populations vulnerable to increased risk of harm. Last, although this review focused solely on the acute effects of a variety of cannabis products, in real-world use, cannabis products are often combined with other medications and/or other non-medicinal drug use. An urgent area of research need is the application of controlled laboratory studies to evaluate the impact of concomitant use of various cannabis product types in combination with other drugs on PK and PD outcomes, especially those related to metabolic interactions and driving and workplace safety. This information will be critical for informing and guiding public health policies as cannabis use becomes more assimilated into mainstream culture.

Declarations

Competing Interests Dr. Vandrey has been paid as a consultant or scientific advisory board member for Canopy Health Innovations Inc., Jazz Pharmaceuticals, MyMD Pharmaceuticals, Syqe Medical Ltd., and Radicle Science LLC. outside the submitted work. Dr. Spindle has been a paid consultant for Canopy Health Innovations Inc.

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