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A Review of Cannabis and Interactions With Anticoagulant and Antiplatelet Agents

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Abstract

Legalization of medical cannabis has occurred in 33 states and the District of Columbia, and recreational use has increased exponentially since 2013. As a result, it is important to understand how cannabis interacts with other drugs and has potential risks for patients on concomitant medications. Components of medical cannabis can inhibit or compete for several cytochrome P450 (CYP) hepatic isoenzymes, UDP-glucuronosyltransferases, and P-glycoprotein. These enzymes and transporters are involved in the metabolism and absorption of numerous medications, including anticoagulants (ACs) and antiplatelet agents (APs), potentially causing harmful drug-drug interactions. ACs and/or APs are often prescribed to high-risk patients with cardiac conditions, a history of myocardial infarction, or stroke. Cannabis may cause these medications to be less efficacious and put patients at risk for recurrent cardiovascular and cerebrovascular events. Several case reports show cannabis may inhibit the metabolism of warfarin because of CYP2C9 interactions, resulting in increased plasma concentrations, increased international normalized ratio , and risk of bleeding. Cannabidiol inhibits CYP2C19, an isoenzyme responsible for the transformation of clopidogrel to its active thiol metabolite. This interaction could lead to subtherapeutic levels of active metabolite and possibly increased stroke risk. Within this review, a total of 665 articles were screened from PubMed and EMBASE. Four case reports, 1 in vitro study, and 1 pharmacokinetic article were found to be of relevance. This review serves to examine reported and potential cannabis interactions with APs/ACs to help inform patients and health care providers of possible risks and knowledge gaps.

Keywords

anticoagulant, antiplatelet, cannabis, cytochrome P450, drug-drug interactions

Although illegal at the federal level, state restrictions on cannabis and its constituents have become more relaxed, allowing for a diverse array of commercially available products both medicinally and recreationally.[1,2] Similarly, consumer use has increased exponentially with a reported 181.8 million recreational users aged 15 to 64 years in 2013.[3] The ubiquitous presence of cannabis causes concern because of current knowledge gaps regarding its safety, efficacy, composition, and pharmacokinetics (PK). Potential drug-drug interactions with cannabis and its metabolites are of particular interest, as many users are on concomitant medications. These gaps necessitate further research and investigation; however, because of the current legal landscape, interventional research is limited.[1] This review of the current literature serves as a resource for those looking to prescribe anticoagulants or antiplatelet agents along with medical cannabis.

Cannabis is a genus of plants of the Cannabaceae family and contains more than 500 compounds—120 cannabinoids and 80 biologically active chemical compounds.[4,5] It is known to interact with the endocannabinoid system, composed of a network of receptors (CB_1 and CB_2), signaling molecules, and enzymes. Two common compounds found in cannabis are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are available as oral solid and semisolid dosage forms, vaporization, oils, topicals, and transdermal patches. The legalization of products varies from state to state and generally exist as varying ratios from 1:1 to 20:1 (high CBD, low THC).[4,6] However, because medical cannabis is not regulated, exact doses and contents of CBD:THC are unknown. Daily doses of THC and/or CBD are dependent on the patient, provider, and indication but generally should not exceed THC daily dose-equivalent of 30 mg/day.[6]

THC elicits psychoactive effects but also has shown medical benefits, particularly for neurologic disorders.[7,8] In contrast, CBD can help to moderate and subdue the psychosis-inducing effects of THC.[9]

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Although research is ongoing, combinations of THC and CBD have shown benefit for neurodegenerative diseases such as multiple sclerosis, glaucoma, pain management, food intake disorders, involuntary motor disorders, schizophrenia, and sleep conditions.

Although the medical benefits of cannabis are significant, little is known about the PK and pharmacodynamics of specific products and formulations from medical cannabis dispensaries. In general, aspects of the PK profile depend on formulation, route of administration, frequency of use, body size/composition, and pharmacogenetics.[10] Inhalation quickly (3-10 minutes) causes a higher peak plasma concentration relative to oral ingestion, with a bioavailability of 10%-35% for THC and 31% for CBD. Sublingual administration leads to immediate onset. THC and CBD are both highly lipophilic, allowing transport across the placenta, limiting transdermal diffusion, and resulting in low oral bioavailability (6%). When taken orally, THC undergoes extensive first-pass metabolism, taking about 120 minutes to reach peak concentrations similar to CBD. The half-lives of THC and CBD are population estimates predicting a fast initial half-life (~6 minutes) and long terminal half-life (≥22 hours). However, the PK performance of specific medical cannabis products is largely unknown.

THC and CBD are metabolized primarily by the hepatic P450 enzymatic pathway and UDP-glucuronosyltransferase (UGT).[11–14] THC is a substrate of cytochrome P450 (CYP) 2C9 and CYP3A; consequently, plasma concentrations are altered by genetic mutations in these enzymes (Figure 1).[15] THC may be a moderate CYP2C9 inhibitor, increasing concentrations of CYP2C9 substrates including narrow therapeutic drugs such as phenytoin and warfarin.[16] When THC is smoked, it induces CYP1A2, which can decrease levels of chlorpromazine and theophylline.[10,14]

CBD is metabolized mainly in the liver and the gut by CYP2C19, CYP3A, and glucuronidation pathways (Figure 2).[9,11,15] CBD has the potential to inhibit CYP enzymes (CYP2C8, CYP2C9, and CYP2C19) at clinically relevant concentrations as well as UGT1A9 and UGT2B7 isoforms.[11,14,17–19] In vitro, CBD may also bind to P-glycoprotein (P-gp), inhibiting its transport mechanism.[20] These PK characteristics can lead to drug interactions such as increased levels of CYP2C19 substrates including diazepam and decreased concentrations of CYP2C19 prodrugs such as clopidogrel.[18,21]

Research to evaluate cannabis interactions is hindered by federal laws and regulations. Although use of medical cannabis is legal under certain state laws, it is not legal under federal law.[22] Consequently, conducting clinical research involving medical cannabis is limited to observational, noninterventional research. Until the United States legal landscape changes, our understanding of cannabis and its interactions is based on reported observations and in vitro experimentation. This review serves to examine established knowledge and published literature in the field demonstrating interactions, risks, and/or side effects of medical cannabis and anticoagulant or antiplatelet agents in patients.

Methods

A literature search was conducted using 2 comprehensive bibliographic databases, PubMed and EMBASE. The search included material from the inception of each database to September 2019. Databases were searched using combinations of the following terms: ("cannabis" OR "marijuana" OR "cannabidiol" OR "CBD" OR "THC") AND "anticoagulant"/"antiplatelet"/"warfarin"/"clopidogrel"/"heparin"/"fondaparinux"/"apixaban"/"rivaroxaban"/"dabigatran"/"edoxaban." Food and Drug Administration documents were directly sought from the governmental website. Backward citation tracking was also used.

The search yielded 146 articles from PubMed and 519 articles from EMBASE. A total of 204 duplicates were removed, and the remaining articles were examined for relevance. On review, 6 articles were carefully screened and included. The data discussed included 4 case reports, 1 in vitro study, and 1 pharmacokinetic article found to be of relevant importance.

Results

Anticoagulants

Anticoagulants are used by millions of Americans for various indications including heart disease, arrhythmias, artificial heart valves, previous myocardial infarction, or elevated risk of clot formation.[23,24] Medical cannabis has the potential to interfere with the efficacy of these medications.

Warfarin. Warfarin is the most commonly used oral anticoagulant worldwide with a narrow therapeutic window, requiring patients to undergo regular international normalized ratio (INR) testing to ensure adequate anticoagulation.[25] An INR range of 2-3 is generally the therapeutic target for patients on warfarin. Any slight changes to medications or lifestyle can impact warfarin concentrations and coagulation.

Cannabis is metabolized by many of the same cytochrome P450 enzymes as warfarin, including CYP3A4, CYP2C9, and CYP2C19 (Figures 1 and 2).[11,13] CBD has the potential to inhibit CYP2C9, which can impact concentrations of drugs that are substrates of CYP2C9 including warfarin.[21] In vitro studies by Yamaori et al. found that THC, CBD, and

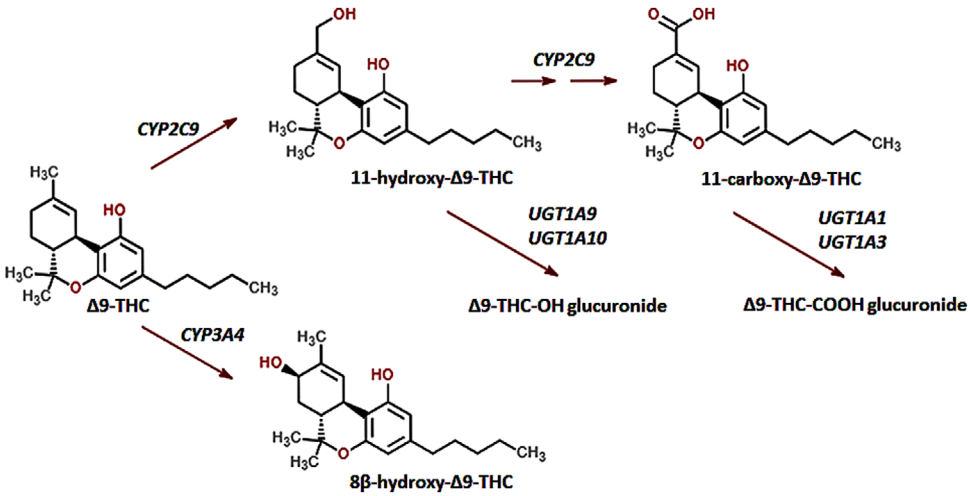

Figure 1. Schematic diagram of Δ-9-tetrahydrocannabinol (THC) metabolism. CYP, cytochrome P450; UGT, uridine 5′-diphosphoglucuronosyltransferase.

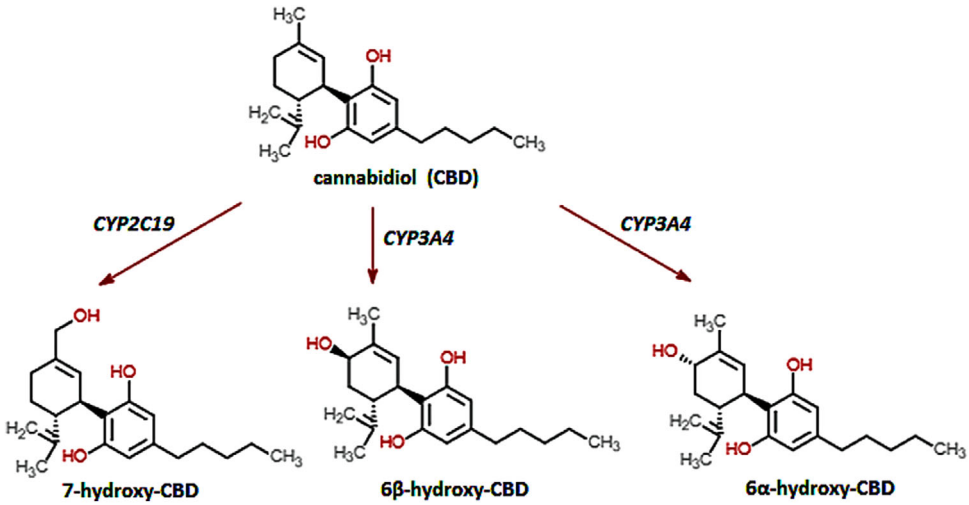

Figure 2. Schematic diagram of cannabidiol (CBD) metabolism. CYP, cytochrome P450.

cannabinol from smoking cannabis directly inhibited CYP2C9-mediated 7-hydroxylation of S-warfarin via mixed and/or competitive mechanisms.[16,26,27]

A case report was released in 2017 describing a 44-year-old white man with Marfan syndrome, poststroke epilepsy, and mechanical mitral valve replacement.[16,28] The patient was diagnosed with a stroke after cardiac surgery at the age of 27, when he was started on warfarin therapy with a goal INR of 2-3. His INR was stable for the preceding 6 months when placed on CBD oil (Epidiolex) at 5 mg/kg/day divided twice daily and titrated up every 2 weeks to a maximum of 40 mg/kg/day for his epilepsy (Figure 3). In response, a nonlinear increase in INR resulted, and warfarin dosing was adjusted accordingly. The authors suggest a correlation between increasing the patient's CBD dose and the resultant rise in INR.[28] At the last reported visit, the patient's warfarin dose was reduced approximately 30% from baseline (7.5 to 5.36 mg).

Damkier et al[16] presented the case of a 27-year-old man who was hospitalized for endocarditis and underwent surgery for mechanical valve placement. Postsurgery, the patient was placed on anticoagulation therapy with warfarin to target an INR of 2.5-3.5. During admission he was allowed a 24-hour leave from the hospital, during which he smoked cannabis recreationally. On returning to the hospital, the patient's INR had increased to 4.6. This rise in INR may be attributed to a drug-drug interaction between cannabis and warfarin.

Similarly, a 56-year-old man was reportedly stable on warfarin therapy for 11 years.[26] The patient had

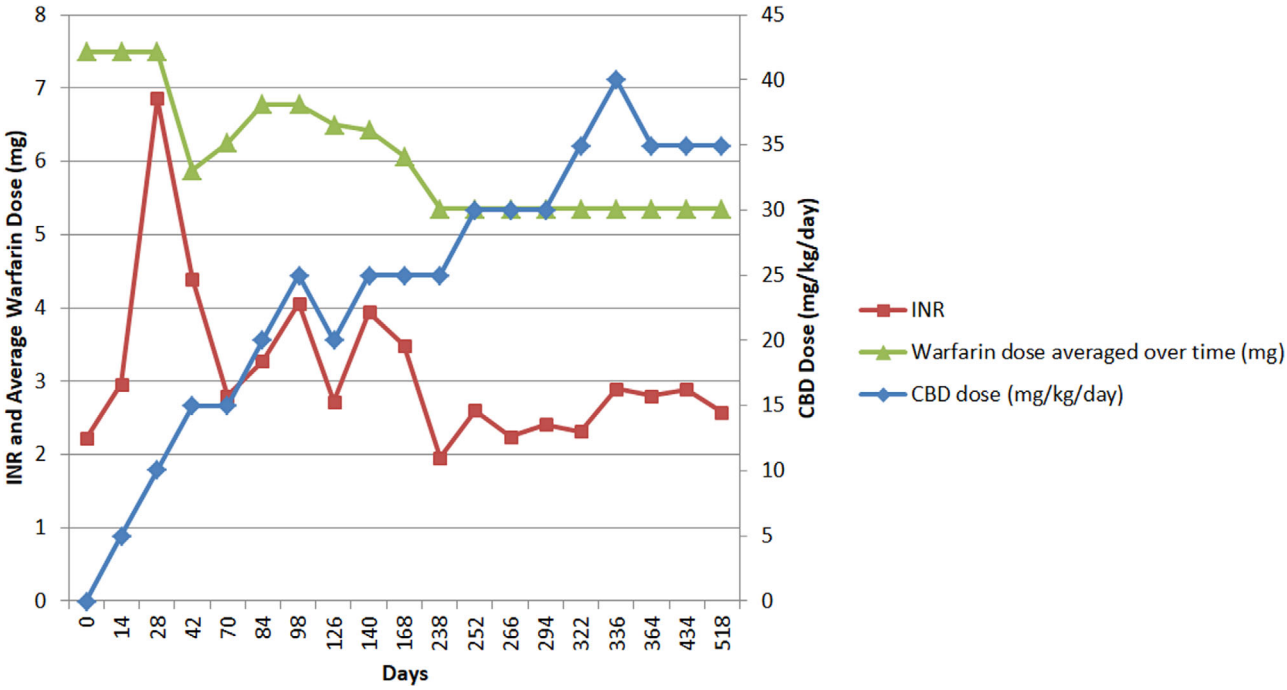

Figure 3. Cannabidiol (CBD) dose, international normalized ratio (INR), and average warfarin dose trends.[28]

an extensive surgical and medical history including mechanical valve replacement, pacemaker placement, coronary artery disease, and recent stent placement. He was admitted to the hospital because of an upper gastrointestinal bleed with an INR of 10.41.[26] He was treated with fresh frozen plasma and oral vitamin K, thus returning his INR to 1.8. The patient reported adherence and no changes in any medications or supplements. Fifteen days later, he was readmitted with complaints of a constant nosebleed and bruising. During this admission, his INR was 11.55. On questioning, the patient reported to smoking an increased amount of cannabis during the past 4 weeks before admission. The patient was counseled by a pharmacist on the potential interaction between warfarin and cannabis. The patient stopped smoking cannabis, and over the following 9 months, his INR remained within the therapeutic window 70% of the time with no significant bleeding episodes.

Most recently, a case report by Hsu and Painter described a 35-year-old man on long-term warfarin therapy with an INR target of 2.0-3.0.[29] The patient had been stable on warfarin 10 mg daily for the past 8 years. However, 1 month after consuming edible cannabis products and smoking cannabis, the patient's INR rose to 7.2. The authors attributed this to a probable interaction between warfarin and cannabis, using the Horn Drug Interaction Probability Scale. They also noted that the interaction may have been because of the inhibition of CYP2C9 by cannabis.

Heparin. Unfractionated heparin and low-molecular-weight heparin are short-acting anticoagulant options given intravenously or subcutaneously. Heparin's metabolism from the bloodstream is dose related via saturable and nonsaturable mechanisms.[23] The saturable pathway involves rapid clearance through endothelial cells, whereas the nonsaturable mechanism relies on renal-mediated excretion. These mechanisms are unaffected by cannabis.[13]

Fondaparinux. Fondaparinux is a synthetic heparin pentasaccharide with activity similar to heparin by inactivating factor Xa and is dosed subcutaneously.[30] However, it has shown superior activity in preventing deep vein thrombosis compared with low-molecular-weight heparin. It has direct renal excretion without any metabolism, and thus would not be expected to display interactions with cannabis.

Direct-Acting Oral Anticoagulants. Direct oral anticoagulants (DOACs) are becoming a favored choice for anticoagulation. The focused update to the 2014 American Heart Association, American College of Cardiology, and Heart Rhythm Society Guideline for the Management of Patients With Atrial Fibrillation recommends DOACs as the preferred treatment for reducing the risk of stroke in those with atrial fibrillation.[31] Current DOACs on the market include rivaroxaban, edoxaban, and apixaban, which directly inhibit factor Xa, and dabigatran, which acts on thrombin (Table 1).[32]

Table 1. Pharmacokinetic Properties and Interactions of Direct Oral Anticoagulants

DOAC	Rivaroxaban	Apixaban	Dabigatran	Edoxaban
Target	Factor Xa	Factor Xa	Factor IIa	Factor Xa
Bioavailability	80%	50%	6.5%	62%
Renal clearance	33% active 33% inactive	50%	25%	80%
Approximate $t_{1/2}$	5-9 hours	5 hours	12-17 hours	10-14 hours
Substrate	BCRP/ABCG2, CYP2J2, CYP3A4, P-gp/ABCB1	BCRP/ABCG2, CYP1A2, CYP2C19, CYP2C8, CYP2C9, CYP3A4, P-gp/ABCB1	P-gp/ABCB1	P-gp/ABCB1
Interactions	CYP3A4, CYP2J2, P-gp	CYP3A4, P-gp	P-gp	P-gp

ABC, ATP-binding cassette; BCRP, breast cancer resistance protein; CYP, cytochrome P450; DOAC, direct oral anticoagulant; P-gp, P-glycoprotein.[32]

All DOACs are substrates of P-gp and are absorbed by the gut through the P-gp efflux transporter, which may be impacted by cannabis.[19,20,23] Cannabinoids may bind to membrane transporters including P-gp, evidence of which has been reported in preclinical studies.[20] CBD inhibition of P-gp, especially in patients with reduced renal function, could lead to accumulation of DOACs including dabigatran etexilate, the prodrug of dabigatran.[33] The product labels for apixaban and rivaroxaban both warn against use with strong CYP3A and P-gp inhibitors, as this could result in drug interactions leading to increased exposure and increased risk of bleeding.[34,35] Drug interaction studies were completed with rivaroxaban and P-gp inhibitors, resulting in increased exposure of rivaroxaban by 30%-160%.[35]

Antiplatelet Agents

Antiplatelet medications are mainstays for the prevention of secondary ischemic strokes, often used lifelong by stroke patients. Cannabis has the potential to interact with the antiplatelet effects of agents such as clopidogrel.[24,36]

$P2Y_{12}$ Inhibitors. $P2Y_{12}$ inhibitors prevent platelet activation and aggregation by irreversibly inhibiting the $P2Y_{12}$ receptor on the surface of platelets.[24,36] This inhibits adenosine diphosphate (ADP) from binding to its receptors and prevents activation of GPIIb/IIIa, decreasing platelet aggregation. These inhibitors are associated with a risk for bleeding, but this is generally less than the risk posed with aspirin.[36]

Clopidogrel is an inactive prodrug that is metabolized by CYP2C19, along with pathways through CYP3A, CYP2C9, CYP1A2, and CYP2B6, into its active thiol metabolite.[37,38] Although the major CYP enzyme responsible for metabolism is controversial, genetic variations of CYP2C19 can lead to varying levels of exposure to active clopidogrel metabolite.[37,39] CBD also impacts CYP2C19 and may prevent metabolism of clopidogrel to its active form.[17] Coadministration of CBD and CYP2C19 substrates has been shown to increase plasma concentrations of these substrates, suggesting CBD inhibits CYP2C19.[14,18] The US Food and Drug Administration warns that CYP2C19 inhibitors such as omeprazole or esomeprazole can affect systemic exposure to the active metabolite of clopidogrel.[38] Jiang and colleagues argue in their pharmacokinetic study that CBD is a potent inhibitor of CYP2C19 and thus could result in decreased metabolism of clopidogrel.[17]

Discussion

Interactions between cannabis and warfarin have resulted in increased warfarin plasma concentrations.[16,26] Warfarin case reports and the in vitro study show that cannabis and specifically CBD may act as a CYP2C9 inhibitor, resulting in increased warfarin plasma concentrations. However, with awareness of this interaction, close monitoring of the patient's INR, and appropriate dosage adjustments of warfarin, this interaction can be managed, and adverse events avoided.

Cannabis may also alter concentrations of DOACs, and as a result, laboratory values such as aPTT could be affected.[32–35] CBD may inhibit P-gp and is a substrate of CYP3A, possibly impacting the metabolism of DOACs and leading to increased concentrations.[20] Although no cases have been reported in the literature, providers should be aware of this potential interaction and monitor patients closely for adverse events.

Clopidogrel may have a drug interaction with cannabis, as it has been shown to inhibit CYP2C19, an enzyme responsible for converting clopidogrel to its active metabolite.[14,17] Laboratory measures of platelet response and aggregation in patients taking clopidogrel should be monitored closely to determine if there is any significant interaction between medical cannabis and clopidogrel.[40]

Conclusions

This review of the current published literature and case reports demonstrating interactions, risks, and/or side

effects of cannabis and anticoagulant or antiplatelet medications serves as a reference for providers to make informed clinical decisions about patient care. Significant knowledge gaps still exist; however, until a change in the current legal status and federal schedule of medical cannabis occurs, conducting interventional clinical research involving medical cannabis and ACs or APs in the United States is not feasible. As health care providers, it is our responsibility to establish appropriate monitoring parameters and close follow-up when adding medical cannabis to patient profiles. By maintaining such vigilance, adverse events may be decreased or avoided.

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Conflicts of Interest

The authors have no conflicts of interest to disclose.

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