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Abstract

Introduction: This systematic review evaluates the extent to which the effect of anticoagulants may be altered in the presence of cannabinoids.

Methods: The following databases were searched: EMBASE, PubMed, Web of Science, Scopus, PscycINFO, and CINAHL from database inception through May 2023. Search terms included cannabis AND anticoagulant AND drug interactions, and related key words. The major outcome was hemorrhage or thrombosis and if available, the relative change in quantitative intensity of anticoagulation after cannabinoid exposure.

Results: The search generated 959 citations. After removal of 440 duplicates, 519 citations were screened. Overall, with the exception of warfarin, evidence supporting an interaction between cannabinoids and anticoagulants is non-existent. Seven case reports evaluating an interaction with warfarin were reported. Cannabis doses involved were either extremely high (e.g., > 260 mg/day of delta-9-tetrahydrocannabidiol [THC] or > 600 mg/day of cannabidiol [CBD]) or were not known. Hemorrhage was identified in 14.2% (1/7) of reports and thrombosis in 0%. Quantitative anticoagulation levels were increased in patients on warfarin (elevated International Normalized Ratio [INR]) in 6 of 7 cases. A maximum INR change was available in 5 of 7 reports, ranging from +0.4 to +9.61. One report found no change in INR after 4 days of medical cannabis exposure. Another report outlined two separate episodes of INR elevation associated with bleeding requiring hospitalization and reversal after marijuana smoking. Four cases involved reduction in weekly warfarin dose ranging from 22% to 31%. The Drug Information Probability Score was calculated in 6 cases, with a score of probable for 5 cases and possible for one.

Conclusions: Very low-quality data support a potential drug-drug interaction with warfarin and both THC and CBD. Clinician recognition of this potential interaction is important. Available evidence supports the need to conduct a drug interaction study between cannabinoids and warfarin to clarify the existence of an interaction.

Introduction

Medicinal and recreational cannabis use is on the rise as many states have recently legalized the use of cannabis.[1,2] The 2019 Hemp Farming Act removed hemp (*Cannabis sativa*) from being categorized as a schedule I controlled substance in the United States. Thus, products containing less than 0.3% of delta-9-tetrahydrocannabidiol (THC) can legally be sold and consumed.[2] Despite this regulatory status change, there is limited evidence and guidance on the safety, dosing, and formulation of cannabis products.

While cannabis is a broad term generally describing organic products derived from the cannabis plant, marijuana is the mixture of dried leaves and flowers from the *Cannabis sativa* plant. Marijuana is largely sought for the intoxicating effects of the cannabinoid, THC, which can be found in the resin produced in the leaves and flowers of the female plant.[3] The *Cannabis sativa* plant contains over 500 chemical substances including more than 100 of the distinct group of active compounds related to THC known as cannabinoids.[4] The three most abundant and well-known cannabinoids include the phytocannabinoid components: THC, which produces psychoactive effects; and the non-psychoactive constituents cannabidiol (CBD) and cannabinol (CBN), which yield analgesic, anti-seizure, anxiolytic, relaxation, and sleep effects.[5,6] Data are emerging regarding the drug-drug interaction properties of cannabis and cannabinoid products. These data, in combination with increased public access and use may pose a concern for interactions with other prescription therapies.[7]

In vitro studies have proposed that THC may be metabolized by cytochrome P450 CYP3A4, CYP2C9, and CYP2C19, and act as a moderate inhibitor of CYP2C9 and an inhibitor of CYP3A4, enzymes also known to play an important role in the metabolism of the anticoagulant warfarin, among other drugs.[6,8,9] Delta-9-THC has been found to inhibit the formation of warfarin metabolites, and various isomers of THC have been shown to inhibit warfarin metabolism.[10] In vitro findings for CYP-mediated drug interactions for CBD and CBN are mixed. Some suggest that both CBD and CBN are metabolized by and inhibit CYP2C9 activity and CYP3A4 activity, and other in vitro accounts suggest no significant influence of CBD and CBN on either enzyme.[6,9,11,12] In vitro, CBD and THC have been shown to inhibit CYP2C19 enzymes.[9,13] Smoking cannabis has been associated with induction of CYP1A2, which may increase drug clearance above that obtained with tobacco smoking.[8,12,14]

Historically, warfarin has been a mainstay oral anticoagulant and currently, it remains the only anticoagulant used for patients with mechanical heart valve replacement.[15] Warfarin is subject to numerous drug-drug and drug-food interactions. Warfarin is composed of a racemic mixture of R- and S-warfarin, with both isomers involved in the inhibition of the vitamin K epoxide reductase complex, producing warfarin's anticoagulant effect. S-warfarin, predominately metabolized by CYP2C9, is approximately five-fold more potent than R-warfarin, which is metabolized by CYP3A4, CYP1A2, and CYP2C19.[16,17] In vitro findings suggest the CYP2C9-mediated 7-hydroxylation of S-warfarin is inhibited by various cannabinoids.[6,18] Such inhibition of S-warfarin could result in increased levels of circulating warfarin, elevation in the International Normalized Ratio (INR), and the potential for increased risk of bleeding. As CBD, CBN, and THC have been reported to be metabolized via CYP3A4, competition with the metabolism of R-warfarin is possible resulting in potentiation of warfarin's effect.[9,13] Protein binding displacement is another potential mechanism for a drug-drug interaction. THC is 95% protein bound, which may displace highly protein bound warfarin from protein binding sites resulting in increased free-circulating warfarin.[5,16] In consideration of the serious potential for harm related to a warfarin drug-drug

interaction, some have labelled warfarin and marijuana a "red flag" interaction.[14] With the introduction of direct oral anticoagulants (DOACs) to the market, there are increasing numbers of patients receiving anticoagulation therapy. DOACs are preferred over warfarin in patients with non-valvular atrial fibrillation and venous thromboembolism. DOACs are administered in fixed doses and have fewer drug-drug interactions compared with warfarin, yet they are still subject to significant interactions. While none of the DOACs are metabolized by CYP2C9, they are substrates of the efflux transport system permeability-glycoprotein (P-gp).[19] All DOACs have P-gp mediated absorption from the intestinal lumen, and to a lesser extent, P-gp mediated hepatobiliary and renal efflux.[20] Of the DOACs, rivaroxaban and apixaban have partial hepatic metabolism through CYP3A4. Drugs that induce CYP3A4 and/or P-gp may reduce plasma concentrations of DOAC, whereas drugs that inhibit either CYP3A4 and/or P-gp could increase plasma concentration of the anticoagulant and potentiate bleeding risk.[19] In vitro studies have suggested that THC, CBD, and especially CBN and THC-COOH (delta-9-tratradyrocannabinol-carboxylic acid, a non-psychoactive metabolite of THC) are potential P-pg substrates.[11] Furthermore, CBD has been shown to significantly inhibit P-gp-mediated drug transport in vitro.[11] An in vitro study found that THC and CBD decreased P-gp expression after 72 hours of exposure.[21] Thus, it is possible that all of the main cannabinoids, and particularly CBD, could raise DOAC concentrations through inhibition or decreased expression of P-gp.[11,22]

Oral anticoagulant drug interactions that result in increased risk of bleeding or thrombosis are well recognized. Cannabinoids have been implicated in altering the metabolic pathways of both warfarin and DOACs through numerous potential mechanisms (Table 1).[5,6,8,9,11,13,21-25] The objective of this systematic review is to evaluate the extent to which the anticoagulant effect in humans may be altered in the presence of cannabinoids.

Methods

Information Sources and Search Strategy

Following the guidelines for systematic reviews, a protocol was developed and registered with the International Prospective Register of Systematic Reviews (PROSPERO). Literature searches were conducted in EMBASE, PubMed, Web of Science, Scopus, PsycINFO, and CINAHL from inception of these databases to May 2023 to identify English clinical trials, observational studies, case reports, or series on potential drug interactions between cannabis and anticoagulant medications. Grey literature was searched using key words in the Turning Evidence into Practice (TRIP) database, Google Scholar, PROSPERO, the Canadian Agency for Drugs and Technologies in Health (CADTH), the Medical Cannabis Declaration, the International Association of Cannabis Medicines (IACM), the Society of Cannabis Clinicians, the National Institutes of Health (NIH) Clinicaltrials.gov, the Cochrane central register of controlled trials (CENTRAL), and the World Health Organization (WHO) International Clinical Trials Register Portfolio (ICTRP). Search algorithms had the format: cannabis AND anticoagulant AND drug interactions. Keywords, their associated medical subject headings (MeSH), Emtree terms, and CINAHL complete subject headings, were used for the specific database to identify relevant articles. The search query was constructed to search the title, abstract, and subject headings/keyword fields, and excluded certain article types in the protocol using database build-in filters. Editorials, guidelines, commentaries, review articles, systematic reviews, abstracts without full papers, conference proceedings, book chapters, dissertations, animal data, and in vitro data were excluded for the review. A complete search strategy for PubMed is given as an example in the Appendix. Reference lists of relevant studies were manually reviewed to locate additional articles not captured by our database or grey literature searches.

Article Screening, Selection, and Data Extraction

Search results were imported into COVIDENCE systematic review software (Veritas Health Innovation, Melbourne, Australia) and underwent two rounds of screening based on their: (1) title and abstract, and (2) full text. Each round of screening, eligibility assessment, and data extraction were performed by two independent investigators (CLG and MAS), with any discrepancies resolved through

discussion and consensus. Both rounds of screening were conducted using COVIDENCE, whereas data extraction was conducted using Microsoft Excel.

Data were extracted from each case report or case series report in the following areas:

- Exposure: cannabinoids(s) administered including dose, dosage form, route of administration, objective measurement of cannabinoid level, time-frame of cannabinoid ingestion, and anticoagulant administered including dose, dosing history, and history of anticoagulation control
- Laboratory: highest INR, change in INR, other anticoagulant drug levels, hemoglobin
- Clinical: Drug Information Probability Score (DIPS)[26] if reported, evidence of bleeding or thrombosis, confounding factors for outcome
- Management: diagnostic tests and interventions required for bleeding or thrombosis management, cessation or interruption in anticoagulant therapy, change in anticoagulant therapy.

For observational studies, the study population, comparator group (if applicable), design, methods, cannabinoid and anticoagulant exposure, relevant laboratory data, and bleeding andthrombosis outcomes were extracted. The major outcome of interest was hemorrhage or thrombosis and if available, the relative change in quantitative intensity of anticoagulation after exposure to cannabinoid. Data extraction was performed using a standardized data collection instrument in Microsoft Excel which was piloted on two articles prior to continuation for use with all reports. Discrepancies were reconciled through discussion.

Data Synthesis and Risk of Bias Assessment

For case reports or case series, the authors calculated the DIPS.[26] Data from case reports and studies (if available) were synthesized using evidence tables along with a descriptive summary. With expected heterogeneity quantitative synthesis of data was not performed. The quality of case reports was assessed using the instrument recommended by Murad and colleagues with the ascertainment and

causality sections identified as the most relevant.[27] Study quality was to be evaluated using the Newcastle Ottawa scale.[28] DIPS scores and quality assessment were performed independently by the same two investigators with discrepancies resolved through discussion.

Results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram outlining search results, screening, and the selection process is shown in Figure 1. The literature search generated 959 citations. After removal of 440 duplicates, 519 citations were screened with 6 included for data extraction. One additional citation was identified from manual review of the reference lists. No human studies were identified. Ultimately, 7 case reports all involving warfarin were included. No articles were identified with DOACs or other parenteral anticoagulants.

Patient characteristics are presented in Table 2.[7,29-34] All patients were male, with an age range of 27 to 85 years of age. The goal INR was 2-3 in five cases and 2.5 to 3.5 in two cases. Four patients were assessed by the investigators as being stable on warfarin therapy prior to the interaction report with a baseline INR ranging from 1.94 to 3.6. In five cases, the patient appeared adherent to warfarin therapy as noted by the author's description or by report of stable warfarin dosing/INR readings.

An overview of cannabis exposure with the corresponding impact on INR and warfarin management is provided in Table 3. Two reports were with medical cannabis,[31, 32] two were with cannabidiol (Epidiolex®, Jazz Pharmaceuticals, Palo Alto CA),[30, 34] and three with cannabis/marijuana.[7, 29, 33] Administration routes included oral, oromucosal, sublingual, and inhalation. Cannabinoid exposure included THC only in an estimated dose of 286-357 mg/day in one case,[29] CBD only in 2 cases in doses of 20-40 mg/kg/day,[30, 34] and exposure to both THC and CBD in 4 cases (medical cannabis[31, 32] and cannabis in 2 cases each[7, 33]). Quantitative exposure to both THC and CBD were lower with medical cannabis as compared with marijuana.

The main outcome of hemorrhage was identified in 14.2% (1/7) of reports[29] while the outcome of thrombosis was identified in 0% of reports. The relative change in the quantitative anticoagulation level was an increase in anticoagulation in patients on warfarin presenting as an elevated INR in 6 of 7 cases.[7, 29, 30, 32, 33, 34] In 3 of these cases, concurrent medications associated with an INR elevation were administered, however no recent dose changes occurred in the interacting medication(s).[29, 32, 34] The maximum reported INR was 11.55.[29] A maximum INR change was available in 4 of 7 reports and ranged from +0.4 to +9.61.[29, 30, 33, 34] One case report found no change in the INR after 4 days of exposure to medical cannabis providing 0.3-0.925 mg/day of THC and .064-.072 mg/kg/day of CBD.[31] This patient continued to be followed for approximately 9.5 months without a need to modify his warfarin regimen. Interruption in warfarin therapy as a result of an elevated INR occurred in 3 cases. One case report outlined two separate episodes of an elevated INR associated with bleeding requiring reversal after marijuana smoking.[29] Four cases involved a reduction in the weekly warfarin dose ranging from 22% to 31%.[29, 30, 33, 34]

A single case report that described bleeding encompassed two separate bleeding episodes, each requiring hospitalization approximately 3 weeks apart.[29] The case involved a 56 year-old male stable on warfarin for 11 years for a mechanical aortic valve with a target INR range of 2.5 to 3.5. In response to an INR of 2.28, the patient's warfarin regimen was increased by his provider from 4 mg to 5 mg daily four weeks prior to his first hospitalization. During this time, the patient reported an increase in the intensity and frequency of marijuana smoking. In the first episode, the patient presented with a large melenic bowel movement, an INR of 10.41, and a hemoglobin of 6.6 g/dl. The patient was given 4 units of fresh frozen plasma and a single dose of vitamin K 10 mg orally. An esophagogastroduodenoscopy revealed the presence of linear antral ulcers without active bleeding. Warfarin was restarted on hospital day 3, and the patient was discharged after 7 days on a reduced dose. Fifteen days post discharge, after again increasing the intensity and frequency of smoking marijuana, the patient presented with a

persistent nosebleed, increased bruising, and a syncopal episode with an INR of 11.55 and a hemoglobin of 13.9 g/dl. Vitamin K 5 mg orally was given along with nasal packing. Oral vitamin K was repeated at a dose of 10 mg and 2.5 mg on the following two days. Warfarin was restarted on hospital day 4 at a reduced dose, and the patient was discharged on day 5 on a reduced dose. At the time of presentation for both hospitalizations, the patient was receiving several medications with the potential to impact warfarin pharmacokinetics and pharmacodynamics including valproic acid, carbamazepine, omeprazole, sertraline, tramadol, and dual antiplatelet therapy with aspirin and clopidogrel. With the exception of clopidogrel, the patient received these concurrent medications without a change in dose for more than six months prior to his first hospitalization. Clopidogrel was added one month prior to hospitalization for coronary artery stent placement. A patient interview revealed adherence to warfarin and other medications without use of over-the-counter medications. The patient discontinued marijuana after the second hospital discharge. Over a subsequent 9-month period, the patient's INR values remained therapeutic approximately 70% of the time.

Two additional case reports involved rechallenge. A 27 year-old male was found to have an elevated INR of 4.2 after a 24-hour hospital leave during which he smoked cannabis.[7] After a second hospital leave which also involved cannabis smoking, the patient's INR was not elevated. The quantity of cannabis smoked during the first and second leave was not provided. In another case, a 67 year-old male continued to use two medical cannabis products for chronic pain following an episode of an elevated INR with a subsequent reduction in his warfarin dosing regimen.[32] Upon follow-up, the patient reported continued elevations in INR above 3 and below 5, which typically followed an increase in use of his 50:1 THC:CBD product for pain. The patient self- tests and manages his warfarin with an in-home caregiver. The elevated INRs were not associated with bleeding and typically resolved after holding 1-2 doses of warfarin.

The DIPS scale was calculated by the authors in 3 published reports.[29,33,34] The investigators calculated the DIPS in 6 of the 7 cases, which reported an elevated INR post-cannabinoid exposure. A score of probable was found for 5 cases and possible for one case (Table 3).[7,29-34] The authors score varied from the investigators score in a single report, possible versus probable.[34] The quality of case reports is summarized in Table 4.[7,27,29-34] The ascertainment component of the Murad score indicated that the exposure and outcome were adequately assessed in the majority of reports. With respect to causality, greater heterogeneity across subdomains was found.

Discussion

Cannabinoids are becoming increasingly recognized for their drug interaction potential.[35] As anticoagulants are high risk medications with many having a narrow therapeutic index, this systematic review evaluated potential drug interactions with cannabinoids and anticoagulant medications. Although prior reviews of cannabis anticoagulant drug interactions have been published, this review encompasses additional case reports and provides greater patient-level detail.[7,22,24,36,37] Our review was limited to human case reports, case series, and studies to focus on the practice implications of identified interactions. Seven case reports evaluating a potential interaction between warfarin and various cannabinoids were identified. No reports involving other anticoagulant medications were found.

Exposure to warfarin may be increased through cannabinoid pharmacokinetic drug interactions primarily mediated through the cytochrome P450 system. THC is a moderate inhibitor of CYP2C9, the enzyme responsible for the metabolism of the more potent S isomer.[6] CBD and CBN may also inhibit CYP2C9.[6,9] The Epidiolex product label indicates that concurrent use with CYP2C9 substrates is expected to result in clinically significant interactions.[38] Two of the seven warfarin drug interactions cases were with Epidiolex, one with an INR elevation of 6.86 (Table 3).[30,34] In both cases, the weekly warfarin dosing regimen was progressively reduced as the CBD dose was titrated up. Although inhibition of CYP2C9 is

the most commonly cited mechanism of a potential cannabinoid-warfarin drug interaction, several others have been proposed (Table 1).

An elevated INR was reported in six of the seven cases reported.[7, 29, 30, 32-34] In three of these cases, the patient's warfarin regimen was considered stable prior to cannabinoid exposure.[30, 33, 34] The stability of the warfarin regimen was not addressed in two cases,[7, 32] and one case involved a recent 25% increase in the weekly warfarin dose[29] (Table 2). In three cases, interruption in warfarin therapy was necessary including one case in which bleeding required reversal on two separate hospital admissions.[29, 32, 33] Four cases involved a reduction in the weekly warfarin regimen by approximately 20-30%.[29, 30, 33, 34]

The most clinically significant report involved a patient who was hospitalized twice with elevated INRs and bleeding requiring reversal after increasing the intensity and frequency of marijuana smoking.[29] The dried marijuana plant is comprised of approximately 4.5% THC, 0.4% CBD and 0.3% CBN.[6] In a study in chronic cannabis users, the median THC concentration within 24 hours was 1.9 mcg/L (approximately 6.04 µmol/L), with a range 0.5 to 9 mcg/L.[39] The THC concentration remained detectable in 16 of 18 subjects after seven days without smoking, with a median THC 1.1 mcg/L (approximately 3.5 µmol/L). In vitro studies have found that the CYP2C9-mediated 7-hydroxylation of S-warfarin by various cannabinoids occurs with IC50 (half maximal inhibitory concentration) values between 2.29 and 4.81 µmol/L.[6,18] The patient's increased frequency and intensity of marijuana smoking prior to each hospitalization suggests a possible dose response effect.[29] Increased smoking may have resulted in THC concentrations within this inhibitory range. After cessation of marijuana, this patient's INR remained within range 70% of the time. A possible dose response effect with increasing THC was reported in one other case in which a patient using medical cannabis mistakenly increased the dose of a product with a 50:1 content of THC:CBD.[32]

Overall, of the six cases with an elevated INR, there was insufficient information to rule out alternative causes for the elevated INR in three of those cases[7, 30, 34] (Table 4). The DIPS score we

determined was probable in five cases and possible in one. Thomas and colleagues described no interaction between medical cannabis and warfarin in an 85-year old patient.[31] The estimated cannabinoid levels were below those proposed to be needed for CYP inhibition. Age related decline in CYP activity may also have contributed to the absence of an interaction. The likelihood of a potential interaction between cannabinoids and warfarin is likely multifactorial. Route of cannabinoid administration, THC and CBD dose, frequency, cannabinoid levels, and the presence of underlying genetic polymorphisms may all play a role.

Overall, the quality of the available evidence to support a pharmacokinetic interaction between cannabinoids and warfarin using the GRADE criteria is very low.[40] Despite the weak quality of evidence, this potential interaction is becoming increasingly recognized. A recent systematic review of all cannabis drug interactions characterized the cannabis-warfarin interaction as a high risk interaction that was probable, with a severity assessment of severe.[37] Lexicomp and Micromedex, two databases frequently consulted by pharmacists, both address this interaction.[41,42] Micromedex characterizes the supporting documentation for the interaction as fair, while Lexicomp indicates the interaction has a good reliability rating. The interaction severity is classified as major in Micromedex and moderate in Lexicomp. In support of a growing awareness of a potential interaction, an ongoing clinical trial evaluating cannabis for migraine is excluding patients taking warfarin for concerns of a potential drug-drug interaction.[43]

Clinician recognition of a potential drug-drug interaction between cannabinoids and warfarin is important. Structured patient interviewing for patients on warfarin with specific questions regarding cannabinoid use is recommended. Patients should be advised against using recreational marijuana or other non-prescribed cannabinoids. For those receiving medical cannabis or prescribed cannabinoid products, patient education about the potential interaction is warranted. The concurrent use of warfarin with cannabinoids requires that an INR monitoring plan be developed. Although the timeframe of the

interaction is not well described, increased anticoagulant effect within 24 hours have been reported. Persistent concurrent use may require a reduction in the cumulative weekly dose of warfarin.

With respect to DOACs, reports of adverse events with concurrent use of THC and/or CBD have not been published. This could suggest the absence of a clinically significant interaction. Given the predominant use of DOACs and a plausible drug-drug interaction mechanism, clinicians should however be aware of the potential for an increased DOAC effect.

This review is limited by the inclusion of only a small number of case reports as clinical trials were not available. Available reports varied widely with respect to patient specific information included and the type, amount, and route of cannabinoid ingestion. Although data extraction occurred independently by two separate authors using standardized evidence tables, investigator bias is a possible limitation. With respect to causality, alternative causes were not adequately ruled out in all cases. The information extracted from cases often involved patient self-report which might not be reliable. Publication bias is likely with only reports describing an interaction being published. When applying the DIPS score, no cases were scored as highly probable.

Conclusion

In summary, very low quality data support a potential drug-drug interaction with warfarin and both THC and CBD leading to an elevated INR. Clinicians should recognize the potential for a warfarin-cannabis interaction and inquire about recreational cannabinoid use at the time of warfarin initiation and during follow-up appointments. Rarely significant bleeding leading to hospitalization was reported. The available evidence supports the need to conduct a drug interaction study between cannabinoids and warfarin to clarify the existence of an interaction with THC, CBD, and CBN.

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Table 1. Possible Mechanisms of a Pharmacokinetic Drug Interaction of Oral Anticoagulants with Cannabinoids

Proposed Mechanism	Impact
Warfarin	
Inhibition of CYP2C9 by THC, CBN, CBD[6,9,25]	Reduced metabolism of more active S isomer of warfarin, increase in INR
Inhibition of CYP3A4 by CBD, CBN, THC[8,9,13,25]	Reduced metabolism of less active R isomer of warfarin, increase in INR
Inhibition of CYP 2C19 by CBD, THC[8,9,13,25]	Reduced metabolism for S and R isomers of warfarin, increase in INR
Inhibition of CYP1A2 by CBD, THC, CBN[9,25]	Reduced metabolism for S and R isomers of warfarin, increase in INR
Induction of CYP1A2 via activation of the aromatic hydrocarbon receptor from cannabis smoking[8,12,14]	Increased metabolism of less active R isomer of warfarin, decreased INR
Competitive metabolism with warfarin for CYP3A4 by THC, CBD, CBN[9,23]	Reduced metabolism of less active R isomer of warfarin, increase in INR
Competitive metabolism with warfarin for CYP2C9 by THC, CBN[9,23]	Reduced metabolism of less active R isomer of warfarin, increase in INR
Competitive metabolism with warfarin for CYP2C19 by THC,CBD[9,13]	Reduced metabolism of less active R isomer of warfarin, increase in INR
Reduction in warfarin protein binding by THC[5,13,24,25]	Transient increase in warfarin effect
DOACs	
Competitive substrates TCH, CBD, CBN, and TCH-COOH for P-gp mediated transport of DOAC[11,22]	Increase in DOAC effect
Decrease of P-gp expression by THC and CBD[21,22]	Increase in DOAC effect over days

CBD = cannabidiol; CBN = cannabinol; CYP = cytochrome P450; DOAC = direct oral anticoagulant; INR = international normalized ratio; P-gp = P-glycoprotein; THC = delta-9-tetrahydrocannabinol; TCH-COOH = delta-9-tratradyrocannabinol-carboxylic acid.;

Table 2. Patient Characteristics

Reference	Age (years) & Gender	Warfarin Indication	Target INR	Warfarin regimen (mg week)	Baseline INR	Timeframe of Baseline INR	Stable on Warfarin	Duration of Stability	Comments on Warfarin Stability and Baseline INR	Adherent
Yamreudeewong[29]	56, male	Mechanical aortic valve	2.5-3.5	*First Hospitalization*						
				5 mg/day (35 mg)	3.25	• 5 days prior to presenting with high INR	No	Not applicable	• Stable on 4 mg daily for 11 years prior to INR 3.25 • Provider dose adjustment from 4 to 5 mg/day (25% weekly dose adjustment) 4 weeks prior for INR of 2.28 • Pharmacist-managed warfarin began with INR of 3.25	Yes
				Second Hospitalization						
				3.25 mg daily (22.75 mg)	1.94	• 6 days prior to presenting with high INR	No	Not applicable	• Baseline of 1.94 was on 21 mg/week which led to weekly dose increase to 22.75 mg/week	Yes
Grayson[30]	44, male	Mechanical mitral valve	2-3	7.5 mg/day (52.5 mg)	2.22	• 25 days prior to high INR • 14 days prior to cannabinoid exposure	Yes	6 months	• INR range 2- 2.6	Not assessed
Thomas[31]	85, male	Atrial Fibrillation	2-3	2.5 mg daily except 5 mg Sunday & Wednesday (22.5 mg)	3.28 (lab) 3.6 (point of care)	• 12 days prior to highest INR • 8 days prior to cannabinoid exposure	Yes	2 years & 5 months	• Single INR out of range by 0.3 eight days prior resulting in dose decrease to 20 mg/week (9.1% weekly dose adjustment)	Not assessed

Brown[32]	67, male	Secondary Prevention VTE	2-3	6 mg alternating with 7.5 mg daily (46.5-48 mg)	Not available	Not available	Not addressed	Not applicable	• Patient home tests	Not assessed
Damkier[7]	27, male	Mechanical aortic valve	2.5-3.5	Not available	Not available	Not available	Not addressed	Not applicable	• Patient managed in hospital; no dosing information provided	Presumed
Hsu[33]	35, male	VTE Treatment	2-3	Warfarin 10 mg daily with 15 mg T and Th (80 mg)	2.5	• ~ 18 weeks prior to high INR • ~ 14 weeks prior to cannabinoid exposure	Yes	5 weeks	• INR within range for 5 weeks (2 values) then a period of ~ 18 weeks without INR monitoring • Authors report stability for 6 months	Presumed "patient denies extra doses"
Cortopassi[34]	46, male	VTE Treatment	2-3	(80)	3.1 (point of care)	• 3 weeks prior to highest INR • 7 days prior to cannabinoid exposure	Yes	4.5 months	• INR range of 1.7-3.3 during 4.5 months prior to cannabis	Yes

INR = international normalized ratio; mg = milligrams; T = Tuesday; Th = Thursday; VTE = venous thromboembolism.

Table 3. Cannabis Exposure, Impact on Warfarin Anticoagulation, and Interaction Assessment

Reference	Cannabis Product	THC Content (mg/day)	CBD Content (mg/day)	Cannabis Route	Timeframe of Cannabinoid Exposure Prior To Maximum INR	Maximum INR	Maximum INR Change	Interruption in Anticoagulation	Change in Anticoagulation Regimen	Total Duration of Concurrent Warfarin Cannabinoid Exposure	DIPS Category
							First Hospitalization				
Yamreudeewong[29]	Marijuana	~286-357 mg/day[†]	0	Inhalation	Increase quantity and frequency of use ~ 4 weeks prior to each hospitalization	10.41	+ 7.16	Yes, anticoagulation reversed	Warfarin held for 2 days, weekly dose reduced by 30% at discharge, hospital day 7	Not specified	Probable
							Second Hospitalization				
						11.55	+9.61	Yes, anticoagulation reversed	Warfarin held for 2 days, weekly dose reduced ~ 22% at discharge, hospital day 5[‡]	Not specified	Probable
Grayson[30]	Epidiolex	0 mg	5 mg/kg/day starting, titrated up to 40mg/kg/day	Oral	11 days	6.86	+4.64	Not available	Warfarin dose reduced as CBD dose increased from 5 mg/kg/day to 25 mg/kg/day, with a 30% reduction in daily warfarin dose over 7.5 months[§]	Approximately 16 months	Probable
Thomas[31]	Medical cannabis oil products; 1 scheduled & 1 as needed once daily	0.3 mg daily & 0.625 mg as needed (0.3-0.925 mg/day)	5.3 mg daily & 0.625 mg as needed; (range .064 - 0.072 mg/kg)	Oromucosal	4 days	2.5	No supra-therapeutic INR	No	None required	Approximately 9.5 months	Not Applicable

Brown[32]	Medical cannabis (Sativa) in medium chain TG oil, 2 products	Product 1: 0 mg, Product 2: 2.45 mg TID titrated up to 4.9 mg TID; (14.7mg/day¶)	Product 1: 5 mg BID, Product 2, .05 mg TID, titrated up to .1 mg TID (10.3 mg/day¶)	Sublingual	After 7 doses of increased dose of Product 2	5.2	Not available	Yes	Warfarin held x2 days, then resumed, dose at resumption not stated††	Approximately 6 weeks	Probable
Damkier[7]	Cannabis	Not available	Not available	Inhalation	Within 24 hours	4.2 after smoking a lot more	Not available	Not available	Not available	Months	Possible
Hsu[33]	Cannabis	Not available	Not available	Oral & inhalation	Daily cannabis for past month primarily edibles, occasional smoking	7.2‡‡	+4.7	Yes	Warfarin held for 2 days, 31% decrease in weekly dose§§	One month	Probable
Cortopassi[34]	Epidiolex	0 mg	5 mg/kg/day, increase by 5 mg/kg/day every week; over 4 weeks titrated to 20 mg/kg/day	Oral	On day 14, CBD dose 15 mg/kg/day	3.5	+0.4	No	Weekly warfarin dose reduced by ~19% over 3 weeks (80 mg/week to 65 mg/week)	170 days	Probable¶¶

BID = twice daily; CBD = cannabidiol; DIPS = Drug Interaction Probability Scale; INR = international normalized ratio; kg = kilograms; mg = milligrams; TID = three times daily; TG = triglyceride; THC = delta-9-tetrahydrocannabinol.

†Report indicated patient ingested 2-2.5 gram THC/week.
‡During a 9-month period post discharge from hospitalization 2, without marijuana smoking INR ranged from 1.08-4.04 with a warfarin dose of 2-4 mg daily.
§After obtaining a CBD dose of 25 mg/kg/day, no further reductions in warfarin dose was required as CBD dose was further increased.
¶Dose increase for Product 2 arose from patient misunderstanding of dose titration instructions.
††Follow up denotes continued elevated INRs < 5 once per month after increased use of product 2; resolves with holding 1-2 doses; not associated with bleeding.
‡‡Denied using cannabis prior to INR of 7.2.
§§ INRs ranged between 3 and 4 within the 3.5 months following cannabis discontinuation; dose adjustments were made during this timeframe.
¶¶DIPS score reported by authors as possible.

Table 4. Murad Quality of Case Reports, Focus on Ascertainment, and Causality[27]

Reference	Ascertainment		Causality			
	Exposure adequately assessed	Outcome adequately assessed	Alternative causes ruled out	Challenge/ Re- challenge	Dose response effect	Adequate follow up
Yamreudeewong[29]	yes	yes	yes	yes	yes	yes
Grayson[30]	yes	yes	no	no	yes	yes
Thomas[31]	yes	yes	yes	no	no	yes
Brown[32]	yes	yes	yes	yes	yes	yes
Damiker[7]	yes	yes	no	Yes	no	no
Hsu[33]	yes	yes	yes	no	no	yes
Cortopassi[34]	yes	yes	no	no	yes	yes

Figure 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers, and other sources. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.