Review Article

Clinical Evidence and Pharmacologic Considerations for Cannabinoid Use in Multiple Sclerosis

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Abstract

Objective: To review the clinical evidence supporting the use of cannabinoids in Multiple Sclerosis (MS), and summarize clinically meaningful pharmacokinetic and pharmacodynamic characteristics and drug-drug interactions.

Summary: Patients with MS frequently experience potentially debilitating symptoms which can affect quality of life. Current symptomatic management can be associated with adverse effects and do not always provide adequate relief, causing some to seek alternative therapies such as cannabinoids. Given the widespread availability of various formulations that are available without a prescription, patients, as well as healthcare professionals, may be unaware of potential drug interactions and adverse effects. This article explores cannabinoid pharmacology, pharmacokinetics, clinical evidence, and possible CYP-mediated interactions between cannabidiol (CBD) and tetrahydrocannabinol (THC) and common medications used in patients with MS such as analgesics, antidepressants, and carbamazepine.

Conclusions: With increasing access to cannabis derived products, there is a need for close examination of each patient's medication regimen prior to use. Some medications that are used by patients with MS pose an interaction risk with cannabinoids and dose adjustments may be necessary. There is limited research in the medical use of cannabinoids, specifically in humans, leaving many of these interactions up to clinical judgement. Nonetheless, pharmacists can play an active role in protecting patient safety by being aware of such interactions, level of evidence for clinical efficacy, and evaluate product quality and variability. Pharmacists, particularly in the easily accessible retail setting, are in the ideal role to complete such tasks due to their frequent touchpoints with patients and extensive medication knowledge.

Since the November 5th, 1996 California Proposition 215 statute was approved legalizing medical cannabis, recreational and medical cannabis has exploded, compelling states to develop policies surrounding its use. Cannabis is a genus consisting of the species *Cannabis indica, Cannabis sativa*, and *Cannabis ruderalis*.[1] A cannabinoid is any compound in Cannabis that acts on the cannabinoid receptor. Over 120 cannabinoids are present in the Cannabis plant, but the two most well-known cannabinoids include cannabidiol (CBD) and tetrahydrocannabinol (THC). THC is responsible for the psychoactive effects of cannabis. Conversely, CBD has no intoxicating properties. Cannabis that is smoked is typically referred to as marijuana, which contains both THC and CBD and the user will experience a range of effects depending on the concentrations of THC, CBD, and other cannabinoids. Alternatively, hemp is defined as having less than 0.3% THC and typically contains higher levels of CBD; therefore, the user will not experience intoxicating effects.

Currently, 11 states have legalized recreational marijuana and 33 states have approved medical cannabis programs.[2] In Wisconsin, cannabis-derived CBD for medical uses is legal, while CBD, and all other cannabinoids, for recreational use is illegal. The 2018 Farm Bill removed hemp as a Scheduled 1 Controlled Substance and Wisconsin initiated an industrial hemp pilot program that requires the hemp grower to obtain a license and destroy the hemp that tests higher than the allowed THC limit (>0.3%). Of note, neighboring states such as Michigan and Illinois have legalized medical and recreational use of marijuana in 2018 and 2020, respectively. For pharmacists working in a Veterans Affair system, marijuana is federally illegal regardless of state legislation.

In addition to the products available through recreational or medical cannabis programs, the FDA has approved one cannabis-derived and three cannabis-related compounds available by prescription only and are indicated for specific seizure disorders, nausea, and pain syndromes: Epidiolex® (CBD), Marinol (dronabinol), Syndros (dronabinol), and Cesamet (nabilone).[3-6] Nabixamols (Sativex), a sublingual spray formulation in a 1:1 mixture of THC and CBD, is approved in 30 countries as an add-on agent to

conventional anti-spastic therapies but is not yet approved in the US.[7]

Multiple sclerosis (MS) is one of many conditions for which cannabinoids have a proposed role in symptom management, such as spasticity. The typical treatment of MS includes a disease modifying therapy (DMT) and symptom management specific to each patient (e.g. pain, spasticity, tremors, depression, etc.).[8] However, some patients may find themselves needing additional options to complement their conventional treatment regimen and turn to cannabis for relief. In fact, approximately 20% - 60% of patients with MS use cannabis.[9] Due to increased access and widespread use, there is a need for drug utilization review and subsequent medication adjustment to ensure safe and appropriate use and to screen for potential interactions. Pharmacists, with their advanced understanding of pharmacology, interactions, disease state management, and accessibility, are the ideal health care professionals to provide guidance to both the patient and the provider on appropriate use. The purpose of this article is to summarize our understanding of potentially clinically meaningful pharmacokinetic and pharmacodynamic characteristics, review the clinical evidence supporting the use of cannabinoids in MS, and outline potential drug-drug interactions between cannabinoids and medications used in MS.

Pharmacology

Two of the most abundant cannabinoids, THC and CBD, have been a popular topic of discussion due to therapeutic potentials they both possess (e.g. pain, spasticity, loss of appetite management, etc.).[10] Such pharmacologic properties rely on modulation of the endocannabinoid system (ECS): an endogenous signaling system responsible for responding to pain, reward, mood, and memory.[11] The ECS is influenced by diet, stress, sleep, and exogenous compounds, including cannabinoids, via their binding to CB_1 and CB_2 receptors.

The CB1 receptor is highly concentrated in the central nervous system where it mediates neurotransmitter release. A CB_1 neuronal agonist inhibits electrically-evoked contractile transmitter release, terminating the resulting contraction.[12] Due to this inhibition, the CB_1 receptor is primarily responsible for the psychoactive, analgesic, and antispasmodic effects of cannabis.[13] The CB_2 receptor is predominantly found in the periphery, residing in immune cells where it modulates cytokine release.[12] Therefore, this receptor likely elicits the anti-inflammatory and immunomodulating properties associated with cannabis.

THC, the compound responsible for the intoxicating effects of cannabis, acts as a partial agonist to CB_1 and CB_2, resulting in a plethora of effects including sleepiness, relaxation, impaired learning and memory, and reduced reaction time.[14,15]

CBD also has biological effects of therapeutic interest, including analgesic, anti-inflammatory, and anticonvulsant properties.[15] Although CBD's mechanism of action is not fully understood, low affinity for the CB_1 receptor due to steric hindrance between the receptor and CBD explains why CBD lacks intoxicating effects.[16] Additionally, CBD may partially modulate the psychoactive effects of THC. CBD antagonizes or acts as a negative allosteric modulator of CB_1 receptors, causing a pharmacodynamic interaction between CBD and THC. Therefore, the user may experience fewer psychoactive effects when THC and CBD are used combination than with THC alone.[9]

THC and CBD are very lipophilic molecules, have low bioavailability, and are subject to extensive first pass metabolism. THC is predominantly metabolized in the liver to its inactive metabolite by CYP2C9 and possibly CYP3A4, and inhibits CYP1A2 and CYP2C9.[10,17] CBD is extensively metabolized in the liver by cytochrome P450 enzyme CYP2C19 into 7-hydroxy-cannabidiol, an active metabolite, which is further metabolized to the inactive metabolite, 7-carboxy-cannabidiol, by CYP3A4. Additional conjugations via UDP-glucuronosyltransferase (UGT) isoforms UGT1A9, UGT2B7, and UGT2B17 may also occur.[18] Given extensive hepatic biotransformation, CYP2C19 inhibitors or inducers may alter active CBD concentrations. CBD is a potent inhibitor of CYP3A4 and CYP2C19 and a weak inhibitor of CYP2D6, UGT1A9, and UGT2B7.[18,19]

Moderate and severe hepatic impairment as defined by the Child-Pugh score has been shown to increase CBD exposure, likely due to a decrease in CBD biotransformation.[20] Therefore, hepatic impairment should be taken into account when dosing CBD. Specifically, moderate to severe hepatic impairment justifies a dose reduction by either 2- or 5-fold, respectively.[21]

TABLE 1. Average Dose-Normalized Maximum Concentration and Time to Maximum Concentration for Cannabinoid Products by Route of Administration[22,23]

Route of Administration	Dose-Normalized Maximum Concentration (nM/mg)*	Time to Maximum Concentration (hr)
Inhaled	9.9 (7.0 – 14.1)	0.75 – 6
Sublingual	1.47 (0.63 – 3.39)	1.64 – 4.2
Oral	1.50 (1.32 – 1.71)	0.99 – 4

Values listed as geometric mean (95% confidence interval)

Pharmacokinetic Considerations

Cannabinoids are available by many routes of administration, including inhaled, intravenous, sublingual, oral, and topical. An oral solution formulation is available by prescription (CBD; Epidiolex®), whereas other routes of administration can be found through non-prescription routes. Each method of administration impacts the compound's pharmacokinetic profile, particularly the peak plasma concentration (Cmax) and time to peak plasma concentration (Tmax) (Table 1). Sublingual administration, such as oromucosal sprays and sublingual drops, have similar Tmax and Cmax to oral administration, which

takes approximately 1 to 4 hours.[22] At low doses of orally administered CBD and THC, Cmax and total exposure appear to be dose-dependent, however, at high doses, Cmax does not differ greatly, suggesting a saturation effect.[23] Although topical administration is available, there is limited evidence on the pharmacokinetic profile of this route. With this information in mind, pharmacists can provide advice to questioning patients regarding timing of administration and when their symptoms are the worst for maximum symptom relief. Due to limited evidence, recommending topical products may not be justifiable.

Detailed understanding of the impact of route of administration on cannabinoid pharmacokinetics is important when considering what formulation to recommend. For example, if a patient needs rapid symptom relief an inhaled route of administration may be most appropriate, alternatively, if the patient requires sustained symptom control, oral administration would be preferred.

Clinical Evidence

Current evidence best supports the use of cannabis in MS symptom management for spasticity and pain. Approximately 80% of patients with MS suffer from spasticity and conventional anti-spastic therapies, such as baclofen or tizanidine, do not always adequately manage spasticity.[7] It is at this point when nontraditional therapies could be explored for treatment refractory spasticity. Sublingual administration allows for a rapid onset and relief of symptoms. Since 2003, numerous clinical trials have evaluated the safety and efficacy of nabixamols for moderate to severe spasticity in patients with MS.[7,24,25] Results from these trials demonstrated low incidence of adverse events, although dizziness along with sublingual administration side effects such as dry mouth and impaired taste were reported.[24,25] Additionally, a reduction in Visual Analog Scale, a 0 to 10 scale used to measure symptom intensity, by 31.3 points in the nabixamols group versus 8.4 in the placebo group (P = 0.001) was identified demonstrating greater perceived reduction in spasticity by the patients in the nabixamols group.[26] Overall, nabixamols is a safe and effective add-on therapy for symptom management patients with MS.[7]

Studies of both chronic pain and pain as a secondary outcome in patients with MS have demonstrated reduction in pain with cannabinoids compared to placebo. One study of 66 patients with MS related pain found a 41% decrease in pain intensity in the nabiximols group compared to 22% decrease in the placebo control.[27]

Dose selection is guided by cannabinoid, targeted symptom relief, and individual variability. On average, the daily dose of nabiximols required to appropriately managed spasticity and pain for patients with MS were 40 and 26 mg, respectively.[27,28] The doses of CBD for approved seizure disorders range from an initial 2.5 mg/kg to a maximum of 10 mg/kg. For non-approved conditions, you will see a wide variety of dosing options, from 1 mg to 1500 mg, making it difficult to recommend a safe and effective dose. Single daily doses administered orally up to 6000 mg CBD have been generally well tolerated.[18] The most common side effects observed include nausea, diarrhea, headache, and dizziness. Additionally, ingesting high-fat meals at the time of dosing CBD results in an increased bioavailability of CBD, increasing the likelihood of these side effects.[18] This highlights the importance of consistent medication administration.

Lack of national standardization and quality control introduces concerns regarding labeling accuracy and potential contamination of cannabinoid products. In 2015, less than 30% of cannabidiol products surveyed were within 10% of the claimed cannabidiol concentration.[29] However, many states are increasing regulation and quality control which may translate into the general consumer marketplace. If commercial, non-FDA approved products are used, they should be accompanied by a certificate of analysis or one should be provided following a request. This documentation illustrates the contents of the product's specific lot to demonstrate that contents agree with the product claim.

Potential Drug-Drug Interactions

Considering MS therapy and potential concomitant therapies used for disease and symptomatic management, primary literature, systematic reviews, and established metabolism of approved products, probable interactions were extrapolated that may impact patients with MS. Treatment agents for MS begin a with first- or second-generation oral, injectable, or infused disease modifying therapy (DMT).[30] Common DMTs used in MS are beta interferons, glatiramer acetate, alemtuzumab, fingolimod, and ocrelizumab. There are no known P450 enzyme driven interactions between DMTs and THC or CBD.

Despite a lack of DDIs between cannabis and DMTs, there are numerous symptomatic therapies where interactions may occur within MS therapy. Up to 50% of patients with MS suffer from depression.[31] Therefore, use of antidepressants is not uncommon. Selective serotonin reuptake inhibitors (SSRIs), a first-line treatment class for depression, are CYP2D6 inhibitors in addition to providing varying degrees of CYP3A4 inhibition.[32] Use of SSRIs could potentially increase the concentration of active CBD. Treating depression with over-the-counter supplements such as Saint John's Wort, a CYP3A4 inducer, could decrease plasma concentrations of THC and CBD.

All of the DMTs, except glatiramer acetate and beta-interferons, have been associated with infections ranging from community-acquired to opportunistic infections, most notably alemtuzumab.[33] Therefore, there is a risk for interactions between CBD, THC, and infectious disease treatments. Ketoconazole inhibition and rifampin's induction of CYP3A4 have been shown to increase and decrease plasma concentrations of THC and CBD, respectively.[10,21] Bactrim, a CYP2C9 inhibitor, may increase THC concentrations. Other CYP3A4 inhibitors that pose a potential DDI risk with THC and CBD include macrolides and other azole antifungals. Reviewing which antibiotic or antifungal a patient is prescribed will help to guide decision-making on how to adjust or hold the cannabinoid therapies.

Sensory and pain symptoms, such as trigeminal neuralgia, are common and often treated with carbamazepine, a strong inducer of CYP3A4. Concurrent use of carbamazepine with THC or CBD could

TABLE 2. CBD and THC Drug Interactions

Drug	*Interaction*	*Pharmacokinetic Impact*	*Management*
SSRIs	SSRIs have varying degrees of CYP3A4 inhibition	Possible increased concentration of CBD	Decrease cannabinoid dose
St. John's Wort	SJW is a CYP3A4 inducer	Possible decreased concentration of CBD	Consider an increase in cannabinoid dose
Azole antifungals	Azoles are CYP3A4 and 2C19 inhibitors	Possible increased concentration of CBD and THC	Consider a decrease in cannabinoid dose
Sulfamethoxazole/ Trimethoprim	SMX/TMP is a CYP2C9 inhibitor	Possible increased concentration of THC	Consider a decrease in cannabinoid dose
Rifampin	Rifampin is a CYP3A4 inducer	Possible decreased concentration of CBD	Consider an increase in cannabinoid dose
Codeine	Codeine, hydrocodone, and dihydrocodeine are CYP2D6 substrates	Possible decreased analgesia due to weak CBD inhibition of CYP2D6 and subsequent loss of active metabolite	Consider stopping cannabinoid
Hydrocodone			
Dihydrocodeine			
Fentanyl	Fentanyl, oxycodone, tramadol, and methadone are CYP3A4 substrates	Possible increased analgesia due to potent CBD inhibition of CYP3A4	Consider stopping cannabinoid
Oxycodone			
Tramadol			
Methadone			
Carbamazepine	Carbamazepine is a CYP3A4 inducer	Possible decreased concentration of CBD	Consider an increase in cannabinoid dose
Clobazam	Clobazam is a CYP2C19 substrate	Possible increased concentration of clobazam due to CBD inhibition of CYP2C19	Consider a decrease in cannabinoid dose or stop cannabinoid
Stiripentol	Stiripentol is a CYP2C19 substrate	Possible increased concentration of stiripentol due to CBD inhibition of CYP2C19	Consider a decrease in cannabinoid dose or stop cannabinoid
Warfarin	Warfarin is a CYP2C9 substrate	Possible increased concentration of warfarin due to THC inhibition of CYP2C9	Consider stopping cannabinoid
PDE5 inhibitors	PDE5 inhibitors are CYP3A4, CYP2C19, CYP2C9, and CYP2D6 substrates	Possible increased concentration of PDE5 inhibitors due to CBD inhibition of CYP2C19, CYP2D6, and CYP3A4	Consider a decrease in cannabinoid dose or stop cannabinoid

CBD - cannabidiol; PDE5 - phosphodiesterase type 5 inhibitor; THC - Tetrahydrocannabinol; SMX/TMP - Sulfamethoxazole/Trimethoprim; SWJ - St. John's Wort

decrease plasma concentrations of THC and CBD, possibly leading to a decrease in efficacy. Alternatively, gabapentin was shown to have a synergistic relationship with THC, where it improved THC's therapeutic window and enhanced its analgesic activity.[10]

There is a higher incidence of sexual dysfunction (SD) in both males and females with MS compared to the general population.[34] The most common form of SD in the MS population is erectile dysfunction in men (50-75%) and reduced libido in females (31.4%).[34] Common treatment options include phosphodiesterase-5 (PDE5) inhibitors, which are substrates for CYP3A4, CYP2C19, CYP2C9, and CYP2D6. Therefore, concomitant use of a PDE5 inhibitor with CBD could lead to increased plasma concentrations of PDE5 inhibitors through CBD's inhibition of CYP2C19, CYP2D6, and CYP3A4.

To treat pain, opioids and over the counter pain medications, such as acetaminophen or nonsteroidal anti-inflammatory drugs, are commonly used. The CYP2D6 pathway contributes to the metabolism of codeine and hydrocodone into their active metabolites, whereas CYP3A4 is the major player when it comes to metabolizing fentanyl, oxycodone, tramadol, and methadone.[35] Concurrent use of CBD with codeine or hydrocodone could decrease their analgesic effects as CBD weakly inhibits the active metabolite from being formed. Conversely, the concurrent use of CBD with fentanyl, oxycodone, tramadol, or methadone could prolong the analgesic and adverse effects of these opioids due to CYP3A4 inhibition.

CBD (Epidiolex®), approved for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS), has shown to be effective in reducing the frequency of seizures in patients with refractory LGS or DS.[36] To date, most well-constructed drug-drug interaction (DDI) studies have focused on CBD and antiseizure medications. Clinical examples

of CBD mediated DDIs include clobazam and midazolam. Clobazam is metabolized by CYP3A4 to an active metabolite, n-desmethylclobazam, which is further metabolized to an inactive species via CYP2C19. While changes in the parent molecule are not seen, an over 3-fold increase in the n-desmethyl metabolite is consistently noted.[19] Increases in plasma concentration may be associated with increased risk of clobazam adverse effects (lethargy, sedation, and ataxia), therefore, dose reduction may be considered. The product information for CBD (Epidiolex®) suggests that no significant interaction with the CYP3A substrate midazolam exists.[3] Taken together, these observations suggest minimal risk of pharmacokinetic interactions with CYP3A substrates. However, in vitro data suggest that CBD may have potent inhibitory potential on some isoforms of CYP3A4 and/or CYP3A5.[24,37] In addition, a recent case report noted significant elevations in tacrolimus, also a substrate of both CYP3A4 and the efflux pump, P-glycoprotein. This would suggest that until further formal studies are conducted, clinicians should be mindful of at least the potential for other unrecognized CYP3A interactions.

It is important to explore the DDIs between CBD and other anti-seizure drugs used to manage LGS and DS including stiripentol and valproate. Co-administration of stiripentol and CBD result in a slight increase in stiripentol exposure, possibly related to CBD mediated CYP2C19 inhibition.[19] However, this interaction is likely not clinically significant. Finally, there was no relevant effect of CBD on valproate, however, this conclusion was based off of total valproate levels rather than free valproate. It is the free valproate that would be available for CBD interaction and therefore would be a better measure for CBD effect.[19]

In addition to effects on CYP2C19, both CBD and THC have also demonstrated in vitro inhibitory activity on CYP2C9, suggesting a possible DDI between warfarin and THC.[38] In vitro and case studies demonstrate THC's inhibition of warfarin metabolism, leading to an increase in INR and bleed risk requiring warfarin dose reductions in patients co-medicated with CBD.[39] The limited data suggests against the use of these compounds while on warfarin.[17]

Clinical human data is lacking in regard CBD and THC DDIs. Therefore, it is important for there to be an open discussion between provider and patient on potential advantages and disadvantages of cannabis use. If cannabis is used, there may be additional monitoring needed to ensure safety and efficacy of their treatment. These findings and detailed knowledge of the cannabinoid metabolism aid in the prediction of future DDIs (Table 2).

Conclusion

Patients with MS experience numerous symptoms which can affect daily activities and quality of life.[40] MS symptomatic therapies can be associated with adverse effects and do not always adequately manage these symptoms. Some patients seek out alternative therapies such as THC or CBD. However, there is a need for close examination of each patient's medication regimen prior to use. Despite limited rigorous research in the medical use of cannabinoids, specifically in humans, many interactions can be predicted. Medications that are commonly used by patients with MS pose interaction risks with THC or CBD and dose adjustments may be necessary and recommended by a pharmacist depending on clinical judgement and strength of CYP interaction. In addition, pharmacists can offer advice such as to use the same manufacturer to decrease the risk of varying potencies, timing of administration for maximum benefit when symptoms are worst, and reviewing of potential side effects. Frequent touchpoints with patients and extensive medication knowledge make pharmacists an ideal provider for such services to protect patients' health and safety.[16] To improve patient care, cannabinoid therapeutics should be incorporated into pharmacy curriculums and offered as continuing education for practicing pharmacists.

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