The Impact of Medical Marijuana on Pharmacy Practice

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Abstract  Objective: As health care providers, it is important to recognize the potential health issues associated with marijuana use and to educate patients appropriately. As with other types of medication, marijuana has drug interactions, side effects, and the potential for toxicity. In addition, as with other substances that are abused, marijuana has the potential for dependence and addiction. The expanding use of marijuana will increase the pharmacist’s involvement with marijuana as part of a patient’s regimen. The objective of this paper is to educate health care providers on potential counseling points for patients in regards to side effects, drug interactions and other potential adverse effects from marijuana use. Summary: Currently in the United States, 29 states (plus Washington D.C.) have passed laws allowing for the use of medical marijuana. It is imperative that pharmacists understand the laws in their state and the overall effects of marijuana. Conclusion: The increased legalization will continue to expand marijuana’s use among patients, necessitating health care providers to be well informed regarding marijuana’s side effects, drug interactions, and addiction potential.

Keywords  Marijuana, Cannabinoids, Dependence, Counseling

1. Introduction

Medical marijuana refers to the use of unprocessed marijuana plant or plant extracts in the treatment of a disease or a symptom of a disease.[1] The plant family Cannabaceae contains the genus Cannabis, which is further divided into the species C. sativa, C. indica, and C. ruderalis.[2] Cannabis containing high levels of the psychoactive cannabinoid, Δ9-tetrahydrocannabinol (THC), and low levels of the non-psychoactive cannabinoid, cannabidiol, is typically referred to as “marijuana.”[2] The Food and Drug Administration (FDA) has not approved marijuana as a medicine and in 2016 the Drug Enforcement Agency reviewed data once more and determined marijuana would remain a Schedule I drug meaning it has a high potential for abuse and currently does not have a medical use in treatment in the United States. Despite the lack of approval or change in schedule, 29 states (plus Washington D.C.), have legalized the use of marijuana for medical purposes.

Marijuana’s principal psychoactive ingredient, THC, is a partial agonist at pre-synaptic CB1 receptors. These G-protein coupled receptors are the primary endocannabinoid receptors in the brain that modulate appetite, mood, and motivation. In the central nervous system, CB1 activation inhibits neurotransmitter release of GABA, glutamate, serotonin, dopamine, acetylcholine, norepinephrine, and D-aspartate at both inhibitory and excitatory synapses.[2] Clinical effects of marijuana vary according to dose, strain, frequency of use, route of administration, and the vulnerability of the user to the psychoactive effects.[3] Marijuana’s actions on CB1 receptors produce varying effects that range from mild euphoria, sedation, relaxation, and hunger to impaired attention, balance, cognition, judgment, memory, and lost sense of time.[4]

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2. Review of Literature

Efficacy

Marijuana has been studied in a multitude of disease states, including nausea/vomiting, epilepsy, and both acute and chronic pain disorders. Pain treatment has been a focus of many studies as alternatives to opioids are more frequently being sought. Studies have been conducted involving neuropathic pain, post-operative pain, and pain...
related to various conditions such as fibromyalgia, cancer and multiple sclerosis. Several studies have focused on the treatment of spasticity in multiple sclerosis patients. A full review is beyond the scope of this article, but statistically significant improvements in pain were seen in several studies [4]. However, it is difficult to draw a definitive conclusion on marijuana’s efficacy in regards to treating pain due to a variety of factors. Most studies consisted of small numbers of patients; doses, dosage forms, and route of administration all varied. Additionally, the subjective nature of pain and lack of validated assessment criteria limits their usefulness until further comparative studies can be conducted.

**Adverse Effects**

When reviewing the literature, there have been several studies analyzing the effects of marijuana in both acute and chronic use. Acute use of marijuana has been found to impair short-term memory and motor coordination, alter judgment, increase or cause paranoia, and precipitate psychosis.[5] It is important to counsel patients on the possible motor coordination impairment and altered judgement when operating a motor vehicle. Studies have linked the potential increased risk of motor-vehicle accidents associated with significant driving impairment with acute marijuana use. Specifically, individuals tended to drive more slowly after smoking marijuana, with decreased control as the complexity of the task increased.[6] Epidemiological data has shown a 2 fold increased involvement in motor-vehicle accidents after smoking marijuana.[7]

Marijuana has also been shown to have significant long-term effects on individuals who use it chronically. The development of the brain appears to be altered in chronic users of marijuana. Adolescents and young adults are those most likely to have an increased risk of impaired neuronal connectivity due to chronic marijuana use. This impaired neuronal connectivity can affect alertness, self-awareness, and inhibitory control. Chronic use has also been associated with increased risk of anxiety, depression, and suicidal thoughts.[8] Finally, poor educational outcomes, diminished life satisfaction, and overall cognitive impairments have been observed in chronic marijuana users. These effects occur more often in individuals who begin marijuana use early in life.[5]

Recently, research has shown that both chronic and acute marijuana use has been associated with several cardiac abnormalities including an increased risk for stroke, heart failure, coronary artery disease, arrhythmias, and sudden cardiac arrest. These cardiovascular effects were observed in young individuals as well as older individuals. Of particular note is that these effects were exaggerated in individuals who also smoked cigarettes or during strenuous exercise. The association with these cardiac complications may be attributed to the effects that cannabinoids have on central and peripheral circulation. Ongoing studies will hopefully provide greater insight into the overall picture of marijuana use and cardiovascular risks. However, in light of new information in this area, educating patients on these risks, particularly if they have a history of cardiac disease, should be considered.[9] Chronic marijuana use and addiction has also been studied. Studies have shown that addiction occurs in approximately 10% of chronic users and the risk of addiction increases when marijuana use is started early in adolescence.[10,11] Although highly debated, some studies suggest that marijuana may act as a “gateway drug” and has been linked to enhancing the response to other drugs, such as nicotine.[12]

**Drug Interactions**

Specific drug interaction studies with marijuana are lacking, however, research has been completed with the enzymes responsible for metabolizing exogenous cannabinoids, including those found in the herb (marijuana) or resin forms of cannabis as well as those found in the synthetic cannabis products (dronabinol and nabilone). Stout et al. summarized the data, drawing conclusions about the potential for cannabinoids to act as substrates, inhibitors, and inducers of various enzymes, and attempted to assign significance to these findings. The authors concluded that in vivo, the primary metabolism of THC occurred via cytochrome P450 pathways, mainly 2C9 and 3A4, and the secondary metabolism of THC metabolites may also occur through the CYP450 pathways (also primarily 3A4 and 2C9), UDP-glucuronosyltransferase (UGT) pathways, and by epoxide hydrolase. In addition to glucuronidation by several UGT isoforms, cannabinol and cannabidiol (other cannabinoid compounds) also undergo metabolism via CYP2C9 and 3A4, and by CYP2C19 and 3A4, respectively.[13]

The question ultimately, however, is whether these interactions have clinical significance. One clinical study found an interaction between ketoconazole, a known CYP3A4 inhibitor, and oromucosal cannabis extract (Sativex®), in which co-administration increased the maximum concentration and AUC of THC by 1.2 and 1.8-fold, respectively, as well as increased the maximum concentration and AUC of the THC metabolite (11-OH-THC) and cannabidiol. The role between concurrent cannabinoid and clopidogrel administration is undetermined. However, clopidogrel is a weak inhibitor of CYP2C9 and may increase serum concentration of THC. The UK Summary of Product Characteristics (SPC) for Sativex® also describes a study in which marijuana was administered with rifampin, a CYP3A4 inducer. Co-administration with rifampin decreased the maximum concentration of THC by 40% and the AUC by 20%. The maximum concentration of 11-OH-THC was reduced by
85% and the AUC of 11-OH-THC was reduced by 87%. Additionally, the maximum concentration of cannabidiol was reduced by 50% and the AUC reduced by 60%.[14] Furthermore, case report data identified a possible link between tacrolimus toxicity in a post allogenic hematopoietic stem cell transplant patient using concomitant oral marijuana. This represents a possible pharmacokinetic link between CYP3A isoform inhibition with marijuana and the effects on medications with a narrow therapeutic index. The current literature suggests that products which act on CYP3A4 could potentially either increase the concentration of cannabinoids to a supratherapeutic concentration, leading to an increase in adverse effects, or decrease the concentration to a subtherapeutic level. Marijuana may also act as a substrate for CYP3A isoenzymes and increase concentrations of other concurrently administered medications.[15]

In addition to pharmacokinetic interactions, as discussed previously, marijuana use in patients with cardiovascular conditions is linked to various cardiovascular risk including increases in heart rate and decreases in heart rate variability, a known cardiovascular parameter associated with reduced autonomic response and increased morbidity and mortality.[4] These effects may be potentiated by other medications or medication classes that induce tachycardia: anticholinergics, α-agonists, theophylline, tricyclic antidepressants, amphetamines, and β-agonists.[16] Furthermore, concomitant opioid, benzodiazepine, or tricyclic antidepressant use can exacerbate alertness levels, motor coordination, and cognition.[4] Due to the lack of specific in vivo data on drug interactions, it is difficult to postulate definitive interactions of which health care providers need to be aware of. (Table 1)

Adherence

One of the roles of a pharmacist is to improve patient outcomes by improving patient adherence to his or her medications. Non-adherence of certain medications can greatly impact patient health. One disease state where adherence is critical is HIV. Non-adherence to HIV antiretrovirals can lead to antiretroviral resistance and virological failure, and is the second strongest predictor (after CD4 count) of progression to AIDS and death.[17,18] Marijuana use is prevalent among HIV patients; with some patients using marijuana to counter side effects from HIV medications. Surprisingly, one study showed that occasional marijuana use has been associated with increased adherence to antiretroviral therapy.[19] However, in a study of 180 HIV patients by Bonn-Miller et al, chronic marijuana use was associated with low antiretroviral adherence as well as negative psychological symptoms.[20] Additionally, patients experienced an increase in HIV symptoms and side effects from antiretrovirals. The authors also noted no difference in symptom relief between patients with moderate marijuana use (more than once weekly but less than daily) and non-users. Other studies suggest no association between marijuana use and adherence to antiretrovirals.[21]

Several studies in patients taking antipsychotics also have shown an association with nonadherence and marijuana use.[22,23] A prospective study by Schoeler et al. suggests that not only is medication adherence affected, but that nonadherence can lead to an increased risk of psychosis relapse.[23]

Until further research is conducted adherence should be assessed, to the degree that it is possible, by clinicians to identify patients who are daily cannabis users with disease states where nonadherence.

3. Summary and Conclusions

Each year in the United States, approximately 6500 individuals begin to use marijuana daily, of whom as many as 10% or more will develop cannabis dependence.[4] With 29 states (plus Washington D.C.) currently having approved legalization for medical use, the use of marijuana among patients will continue to increase. Healthcare providers will therefore need to be informed on the adverse effects of marijuana and understand the potential drug interactions. In vitro research by Zhu et al. demonstrated various cannabinoids inhibited the effects of P-glycoprotein-mediated drug transport.[23] Therefore, in addition to the aforementioned CYP interactions, clinical data evaluating the relationship between medical or recreational marijuana use on plasma concentration or therapeutic endpoints in medications mediated via P-glycoprotein are lacking.[24] We should also keep in mind that cannabis comes in different strains, varies in THC and CBD concentrations, and possesses multiple other compounds (e.g., cannabinoids) which have not been clinically tested clinically. Additionally, counseling on the addiction and dependence potential, adherence, as well as the increased risk of psychotic-induced disorders, will need to remain at the forefront of patient education by healthcare professionals.[25]

The use of marijuana medically is a highly politically charged topic. As healthcare professionals, we must take a step back and examine not only the potential benefits of its use as more studies emerge, but also the risks such as adverse effects and drug interactions that inevitably accompany any chemical patients may be using. Education and the overall health of our patients should be first and foremost as we move forward and the use of marijuana expands.
Table 1. Drug interactions

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Study design</th>
<th>Concomitant agent(s)</th>
<th>Cannabinoids Studied</th>
<th>Results</th>
<th>Enzymes Involved</th>
<th>Summary of Interaction</th>
<th>PK impact of THC</th>
<th>PK impact of CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gaston TE, et al. 2017</td>
<td>N = 81; adult and pediatric patients with treatment-resistant epilepsy</td>
<td>Prospective, open-label safety study</td>
<td>Topiramate Rufinamide Clobazam Zonisamide ELC</td>
<td>CBD [5-50 mg/kg/day]</td>
<td>Concomitant CBD administration significantly increased serum levels of topiramate (p &lt; 0.001), rufinamide (p = 0.004), N-desmethyleclomazob (p &lt; 0.001), zonisamide* (p = 0.017) and ELC* (p = 0.039).</td>
<td>CYP3A4 CYP2C9 CYP2C19</td>
<td>CBD-mediated inhibition of CYP450 enzymes was associated with increased serum levels of several antiepileptic drugs.</td>
<td>topiramate rufinamide N-desmethyleclomazob Zonisamide ELC</td>
<td></td>
</tr>
<tr>
<td>Geffrey AL, et al. 2015</td>
<td>N = 13; pediatric patients with refractory epilepsy</td>
<td>Prospective, open-label safety study</td>
<td>Clobazam</td>
<td>CBD [5-25 mg/kg/day]</td>
<td>Nonsignificant increase in mean plasma clobazam levels after 4 and 8 weeks of CBD therapy Significant increase in mean plasma norclobazam levels after 4 (1.9 fold) and 8 (2.17 fold) weeks of CBD therapy</td>
<td>CYP3A4 CYP2C19</td>
<td>CBD inhibits CYP2C19 and CYP3A4, resulting in higher plasma concentrations of norclobazam.</td>
<td>norclobazam</td>
<td></td>
</tr>
<tr>
<td>Dalton WS, et al. 1976</td>
<td>N = 6; adult male volunteers, non-opioid naive</td>
<td>Double-blind, pharmacokinetic analysis</td>
<td>Secobarbital</td>
<td>CBD [0-500 mcg/kg]</td>
<td>CBD administration did not significantly effect secobarbital PK parameters (t1/2, Cmax, and AUC)</td>
<td>CYP3A4 CYP2C19</td>
<td>THC/CBD PK parameters (Cmax and AUC) were associated with rifampicin and ketoconazole use, but not omeprazole. The impact of CBD/THC on omeprazole disposition was not investigated.</td>
<td>secobarbital</td>
<td>CBD Fentanyl - unknown</td>
</tr>
<tr>
<td>Manini AF, et al. 2015</td>
<td>N = 17; healthy adult volunteers, non-opioid naive</td>
<td>Double-blind, placebo-controlled, cross-over study</td>
<td>Fentanyl (0.5 mcg/kg – 1 mcg/kg)</td>
<td>CBD (400-800mg)</td>
<td>Mean plasma CBD concentration vs. time profiles (hr) were not significantly affected by fentanyl dose None of the subjects in either CBD or placebo group showed detectable plasma fentanyl concentrations</td>
<td>CYP3A4</td>
<td>THC Ketocozalone: THC Omeprazole: CBD</td>
<td>CBD Fentanyl - unknown</td>
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<tr>
<td>Stott C, et al. 2013</td>
<td>N = 36; healthy adult subjects</td>
<td>Phase I, open-label, randomized, crossover study</td>
<td>Rifampicin (600mg) Ketoconazole (400mg) Omeprazole (40mg)</td>
<td>THC (10.8mg) CBD (10mg)</td>
<td>Rifampicin coadministration significantly reduced mean Cmax and AUC values for THC, 11-OH-THC, and CBD. Ketoconazole coadministration significantly increased mean Cmax and AUC values for THC, 11-OH-THC, and CBD. Omeprazole coadministration did not significantly effect THC, 11-OH-THC, or CBD PK parameters.</td>
<td>CYP3A4 CYP2C9 CYP2C19</td>
<td>THC/CBD PK parameters (Cmax and AUC) were associated with rifampicin and ketoconazole use, but not omeprazole. The impact of CBD/THC on omeprazole disposition was not investigated.</td>
<td>Rifampicin: THC Ketocozalone: THC Omeprazole: THC</td>
<td>Rifampicin: CBD Ketoconazole: CBD Omeprazole: CBD</td>
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<tr>
<td>Yameudee Wong W, et al. 2009</td>
<td>N = 1; 56 yo m on chronic warfarin therapy after MVR</td>
<td>Case report</td>
<td>Warfarin (therapeutic INR: 2.5-3.5)</td>
<td>Baseline MJ use: 0.5-1g every 2 weeks MJ use prior to event: 2-2.5g every week</td>
<td>Patient experienced upper gastrointestinal bleed and supratherapeutic INR (10.4); INR at last visit prior to increased MJ use was 3.25</td>
<td>CYP3A4 CYP2C9 CYP2C19</td>
<td>The S- and R-enantiomers of warfarin are primarily metabolized through the CYP450 enzyme system. THC and CBD may have decreased the metabolism of warfarin, resulting in a clinically significant increase in INR.</td>
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<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Type</th>
<th>Compound</th>
<th>Concentration</th>
<th>Reaction Description</th>
<th>Enzyme Involved</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watanabe K, et al.</td>
<td>2007</td>
<td>In vitro</td>
<td>Ketoconazole</td>
<td>10μM</td>
<td>Δ9-THC and Δ9-THC were inhibited formation of 7α-OH-Δ9-THC, 8β-OH-Δ9-THC, and 8-OH-CBN from the corresponding cannabinoids by 96, 91, and 64%, respectively</td>
<td>CYP3A4</td>
<td>Ketoconazole is a potent inhibitor of CYP3A4.</td>
</tr>
<tr>
<td>Watanabe K, et al.</td>
<td>2007</td>
<td>In vitro</td>
<td>Sulfaphenazole</td>
<td>50μM</td>
<td>Δ9-THC and Δ9-THC were inhibited formation of 11-OH-Δ9-THC, 11-OH-Δ9-THC, and 11-OH-CBN from the corresponding cannabinoids by 62, 87, and 89%, respectively</td>
<td>CYP2C</td>
<td>Sulfaphenazole is a selective inhibitor of the CYP2C subfamily.</td>
</tr>
<tr>
<td>Yamaori S, et al.</td>
<td>2011</td>
<td>In vitro</td>
<td>AMMC</td>
<td>Dextromethorphan</td>
<td>Of the cannabinoids studied, CBD was the most potent inhibitor of CYP2D6. All reactions displayed Michaelis-Menten kinetics.</td>
<td>CYP2D6</td>
<td>CBD is a potent, competitive inhibitor of CYP2D6.</td>
</tr>
</tbody>
</table>

*adult patients only; no pediatric patients were prescribed eslicarbazepine in this analysis
MVR – Mechanical valve replacement
MJ – Marijuana
CBD – Cannabidiol
ELC – Eslicarbazepine
THC – Tetrahydrocannabinol
CBN – Cannabinol

**MJ Drug-drug Interactions Table**

REFERENCES


