INFORMATION FOR PHYSICIANS

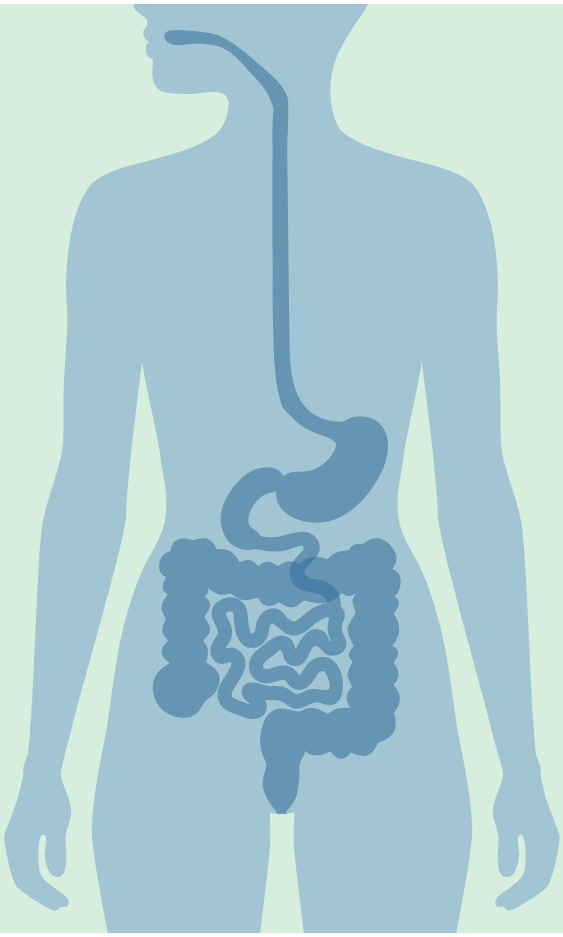
MEDICAL MARIJUANA IN PATIENT'S WITH CROHN'S DISEASE

HOW TO USE THIS RESOURCE

This resource is designed to provide physicians with a summary of current information from the medical and scientific literature on medical marijuana use in patients with Crohn's disease, focusing on clinical applications, and safety considerations. This resource is not intended to guide treatment recommendations nor to be used in determining patient eligibility for certification in the medical marijuana program. From here forward, we use the terms "medical marijuana" and "cannabis" as they appear in the cited references.

CROHN'S DISEASE

Crohn's disease is a chronic inflammatory condition affecting the gastrointestinal tract. It can involve any segment from the mouth to the anus, though it most commonly impacts the terminal ileum and the beginning of the colon.[1]



DEFINING MEDICAL MARIJUANA: *In Florida statute, "medical marijuana" encompasses the entire plant of the Cannabis genus, in any growth stage, as well as its seeds and the resin obtained from any section of the plant. This definition extends to all forms, including every substance, product, salt, derivative, combination, or concoction made from the plant, its seeds, or resin, for which the concentration of delta-0-tetrahydrocannabinol (THC) is above the 0.3% threshold (<0.3% THC is the federal definition of hemp). Medical marijuana is dispensed from certified medical marijuana treatment centers (MMTCs, colloquially called "dispensaries") to patients with a physician certification.*[2]

EFFECT OF MEDICAL MARIJUANA IN CROHN'S DISEASE

The following table outlines clinical outcomes that have been evaluated in at least one randomized controlled trial (RCT) since 1999 that specifically evaluated the effect of formulations of cannabis products containing >0.3% THC on Crohn's Disease symptoms and treatment outcomes.

OUTCOME ASSESSED	MEASUREMENT VARIABLE OR SPECIFIC MEASUREMENT	EFFECT ESTIMATE (95% CI OR OTHER MEASURE OF PRECISION)	FINDINGS
Clinical disease activity indexes[3,4]	Crohn's disease activity index	I: 330±105 to 152±109 C: 373±94 to 306±143 *	Two studies assessing oral and smoked cannabis effect on disease activity indexes reported mixed findings.
	Crohn's disease activity index	I: visit one 282[243–342] visit three 166[82–226] C: 264[234–320] 237 [121–271]	
Indicator for disease remission[3,4]	Crohn's disease activity index score ≤ 150 after 8 weeks of treatment	I: 5/11 (45%) C: 1/10 (10 %)	Two studies assessing oral and smoked cannabis effects on indicator of disease remission reported no change in the outcome.
	Simple Endoscopic Activity Score in Crohn's Disease (0-56)	I: 10 [7–14] to 7 [4–14] C: 11 [7–14] to 8 [4–12]	
	C-reactive protein [mg/dl])	I: 1.4 [0.4–2.7] to 1.7 [0.4–3.8] C: 1.3 [0.2–2.2] to 1.5 [0.5–3]	
	Calprotectin [ug/g])	I: 139 [64–300] to 112 [65–300] C: 112 [50–185] to 117 [50–300]	
Pain[3]	Pain (1-7 Likert scale (1=great improvement, 7=severe deterioration))	I: 2.0±0.91// C: 3.38±1.35*	One study assessing oral cannabis effect on pain reported mixed findings.
	Abdominal pain (0-3; 0=none, 3=severe)	I: 2 [1.25–2] to 1 [0–2] C: 2 [1.75–2] to 2 [0–2]	
Body weight[3]	Change in kilogram body weight	I: 62 [56–77] to 62 [55–74] C: 63 [52–78] to 64 [51–78]	One study assessing oral cannabis effect on body weight reported no change in the outcome.
Quality of life[3,4]	SF-36 (score 0-100)	I: 68 to 86 C: 71 to 79 *	Two studies assessing oral, and smoked cannabis effect on quality of life reported mixed findings.
	SF-36 (score 0-100)	I: 74 [65–87] to 91 [85–102] C: 74 [57–82] to 75 [69–88]	

*Difference between intervention and control group was statistically significant (p-value <0.05).
Abbreviations: I=Intervention group; C=Control group.

To date, there is no conclusive evidence that medical marijuana is effective in alleviating symptoms in patients with Crohn's disease.

SAFETY OF MEDICAL MARIJUANA IN CROHN'S DISEASE

As the safety profile of medical marijuana continues to evolve, it is important to recognize that much of the current research on safety is based on observational studies conducted on cannabis use for non-medical purposes. However, when medical marijuana is considered or monitored in a treatment plan, there are safety considerations to bear in mind. The table below summarizes current known safety considerations and potential risk mitigation strategies.[5] Risk mitigation strategies include links to further resources, such as clinical guidelines and advisory statements, from relevant physician and public health organizations.

CONDITIONS FOR WHICH THERE ARE KNOWN SAFETY CONCERNS WITH MEDICAL MARIJUANA		
CONDITION	**ASSOCIATED RISK OR SAFETY CONCERN**	**POTENTIAL RISK MITIGATION STRATEGY**
Unstable cardiovascular disease	· THC may induce immediate cardiovascular responses like increased heart rate and lowered blood pressure.[6,7]	· Avoid in patients with unstable heart conditions, including recent heart failure or coronary artery disease.[8]
Respiratory disease	· Inhalation of cannabis can exacerbate pulmonary issues (e.g., chest constriction), and lead to repeated bouts of chronic bronchitis.[6] · The relationship between cannabis usage and the development of COPD or asthma is not fully established.[6,9]	· Avoid in patients with pulmonary diseases and use caution even in those without such conditions.[10]
Psychosis and bipolar disorder	· Daily consumption of THC can exacerbate symptoms in individuals with bipolar disorder or existing psychosis, and may trigger these conditions in predisposed individuals.[11,12]	· Avoid in patients with psychotic and bipolar disorders.[13] · Exercise additional caution in patients with personal or familial history of these disorders.[13]
Pregnancy and breastfeeding	· Use of cannabis in the first trimester is linked to adverse pregnancy outcomes.[14] · There is a risk of neonatal morbidity.[14-16]	· MMJ should not be used during pregnancy or lactation.[17]
OTHER CIRCUMSTANCES TO CONSIDER		
CONDITION	**ASSOCIATED RISK OR SAFETY CONCERN**	**POTENTIAL RISK MITIGATION STRATEGY**
Individuals under the age of 25 years	· Regular or high-dose usage is linked to lasting cognitive effects, social issues, anxiety, depression, and dependency on cannabis.[18-20] · Early initiation is associated with earlier and more severe outcomes in schizophrenia and bipolar disorder.[21]	· Weigh benefits against risks carefully. · Considering the limited evidence for medical marijuana in Crohn's disease, risks may surpass benefits.
Cannabis use disorder	· Cannabis use, specifically over a prolonged period and with a high amount of THC is associated with cannabis use disorder.[5,6]	· Weigh benefits against risks carefully. · Considering the limited evidence for medical marijuana in Crohn's disease, risks may surpass benefits.
Substance use disorder or patients at risk for problematic cannabis use	· Cannabis use is associated with the development of substance dependence or substance abuse disorder, and could worsen pre-existing substance abuse disorders.[5]	· Weigh benefits against risks carefully. · Given the limited evidence for medical marijuana in Crohn's disease, risks may surpass benefits.

SAFETY OF MEDICAL MARIJUANA IN CROHN'S DISEASE CONTINUED

CONDITIONS THAT REQUIRE ADDITIONAL CONSIDERATIONS		
CONDITION	**ASSOCIATED RISK OR SAFETY CONCERN**	**POTENTIAL RISK MITIGATION STRATEGY**
Active mood or anxiety disorder	· Cannabis usage could be related to mental health disorders.[22] · Early initiation and high doses of THC might amplify negative effect.[23]	· Exercise caution in dosing.
Risk factor for CV disease	· THC may induce immediate cardiovascular responses like increased heart rate and lowered blood pressure.[7]	· Monitor for signs of unstable cardiovascular disease, and exercise caution.
Tobacco use	· Might lead to further elevation of cardiovascular disease and respiratory disorder risk.[6]	· For tobacco users, non-inhaled forms of cannabis may be considered safer.
Electronic cigarette use	· Use of nicotine and cannabis vape pens has been linked to severe respiratory illness.[24]	· Verify that vaping products are not obtained from illicit sources.
Severe liver dysfunction	· Severe liver dysfunction can alter the pharmacokinetics and pharmacodynamics of cannabis.[5]	· Exercise caution in dosing.
Driving or safety sensitive occupations	· Cannabis use is associated with neurocognitive impairment and an increased risk of motor vehicle crashes.[6,25,26] · THC is primarily responsible for this effect.[26]	· Advise against driving or performing safety-sensitive tasks for at least 4 hours after inhalation, 6 hours following oral ingestion, or 8 hours if experiencing euphoria.

DRUG-DRUG INTERACTIONS WITH MEDICAL MARIJUANA

Cannabis is not known to interact with many medications; however, there are certain potential drug-drug interactions (DDIs) that could potentially have a significant impact on drug therapy safety and we describe these in the table below.[27-29] We do not describe interactions in detail with other substances, such as alcohol, but there are known interactions with other substances that could be considered when engaging in risk communications with patients.

DDI CONSIDERATION	DESCRIPTION OF DDI AND/OR RISK MITIGATION STRATEGIES
Interaction with CNS depressants	· Potential pharmacodynamic interactions, leading to enhanced sedative or cognitive effects.[30] · Commonly used CNS depressants to monitor with cannabis use: Alcohol, opioids, antipsychotics, benzodiazepines, tricyclic antidepressants, antiepileptics (may exacerbate sedation and cognitive impairment).[30-31]
Metabolism and CYP450 Isoenzymes	· THC metabolized mainly by CYP2C9, CYP2C19, CYP3A4. Cannabidiol (CBD) metabolized primarily by CYP2C19, CYP3A4. CYP inhibitors or inducers can alter serum cannabinoid levels.[5] · CBD's inhibition of CYP3A4, CYP2B6, CYP2D6, CYP2E1, UGT1A9, and UGT2B7 might lead to interactions with certain medications.[8,32] · THC's competitive inhibition of CYP1A2, CYP2B6, CYP2C9, CYP2D6 might lead to interactions.[32] · Many interactions noted in cell/animal studies not yet confirmed in humans.[5]
Drug-Drug-Interactions with clinical evidence	· As of June 2021, DDIs reported from at least one observational study or three case reports / clinical trials exist for the following drugs with Cannabis:[33] o Warfarin (4 Case reports described an increase in international normalized ratio from 2-3 up to 11.6, concurrent with gastrointestinal bleeding)[34-37] o Buprenorphine (A retrospective study described 170% higher concentrations of buprenorphine among cannabis user; A case report described a 95 % drop in serum levels of buprenorphine when stopping the use of cannabis)[38] o Tacrolimus (2 case reports, one clinical trials described plasma concentration increases up to 358 % in patients who used cannabidiol)[39-41] o Clobazam (3 clinical trials; Clobazam concentration increased up to 60% in patients that concomitantly used it with cannabidiol)[42-44] o Theophylline (2 clinical trials, one retrospective study, reported reduction of clearance up to 48% with concomitant cannabis use)[45-48] · As of June 2021, DDIs that were reported from less than three case reports / clinical trials, included:[33] o Clozapine[49], Methadone[50], Chlorpromazine[51], Eslicarbazepine[42,52], Hexobarbital[53], Indinavir[54-56], Ketoconazole[57,58], Rifampicin[57,58], Stiripentol[59-61], Valproate[42,62]
High-Risk Scenarios	· Patients at high risk, using high doses of cannabinoids, or on medications with known or potential interactions, or on medications with a Narrow Therapeutic Index and metabolized via similar pathways, should be closely monitored.[5,63] For further information see: Kocis et al.[63]
Management of Drug Interactions	· If interaction is possible, assess the necessity of both therapies. · Increased monitoring for adverse events or drug levels might be needed. · Consider starting at low doses, tapering other medications, adjusting THC/CBD dose, switching chemovars, or discontinuing cannabis.[27]

DRUG-DRUG-INTERACTIONS BETWEEN MEDICAL MARIJUANA AND MEDICATIONS COMMONLY USED IN PATIENTS WITH CROHN'S DISEASE

Despite general considerations for DDIs with medical marijuana, clinical data specific to DDIs in the treatment of Crohn's disease is limited.[64] However, the potential for DDIs when treating a patient with Crohn's disease must be carefully evaluated due to significant interactions between cannabis, and metabolizing enzymes, specifically cytochrome P450 and UDP-glucoronosyl transferase (UGT).

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