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# Cannabis Use and Heart Transplantation: Disparities and Opportunities to Improve Outcomes

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## Abstract

Heart transplantation remains the optimal therapy for many patients with advanced heart failure (HF). Use of substances of potential abuse has historically been a contraindication to heart transplantation. Decriminalization of cannabis, increasing cannabis use, clinician biases, and lack of consensus for evaluating patients with HF who use cannabis all have the potential to exacerbate racial/ethnic and regional disparities in heart transplant listing and organ allocation. Here we review pertinent pre- and post-heart transplant considerations related to cannabis use. Relative attitudes between opiates and cannabis are offered for context. We conclude with identifying unmet research needs pertaining to the use of cannabis in heart transplantation that can inform a standardized evaluation process.

### Keywords

heart transplantation; cardiac transplantation; heart failure; cannabis; marijuana; cannabis use disorder

## Introduction

Cannabis (also known as marijuana) is a commonly used substance in the United States and worldwide[1] and has been identified as an emerging topic of interest with respect to cardiometabolic health.[2] The prevalence of cannabis use more than doubled between 2001 and 2019, with the greatest increases among people over the age of 25.[1] About 2 million

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adults with cardiovascular disease in the US reported cannabis use in 2015–2016.[3] About 250,000 patients have advanced heart failure (HF) in the US[4] for which heart transplantation (HT) remains the gold standard for the treatment. The number of patients on the HT waiting lists exceeds the number of HT performed, (>4,000 adult patients listed for transplant and ~3,600 heart transplants performed in 2019).[5] Concurrent to the recent legalization and decriminalization of medicinal and recreational cannabis, many US states have passed legislation that prohibits transplant centers from disqualifying candidates based solely on the use of medicinal cannabis.[6]

Transplant societies classify active abuse of drugs—including legalized substances like alcohol or tobacco—as a contraindication to heart transplantation but offer no guidance for cannabis.[7] However, the United Network for Organ Sharing (UNOS) defers to each transplant program for their own policies around recipient eligibility, which are potentially subject to health insurer requirements and state legislation. Cannabis use can lead to limitations on transplant eligibility due to differential rules of health insurers, some who may require a period of negative testing or participation in substance use rehabilitation prior to listing.[8] The lack of guidance creates the potential to widen disparities in heart transplant listing and donor allocation.

This review will explore the relationship of cannabis use to pre-heart transplant and post-heart transplant considerations and conclude with the research priorities to inform standardized evaluations and more equitable heart transplant allocation process for all potential recipients.

## Cannabis: Pharmacology, Pharmacodynamics, and Pharmacokinetics

Cannabis is derived from the *Cannabis sativa, Cannabis indica*, and *Cannabis ruderalis* plants, and contains numerous phytocannabinoids. Delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the two major active components of cannabis, but numerous related cannabinoids have been identified.[9] The physiological effects of cannabis are derived from cannabinoids due to engagement with the endocannabinoid system.[10] Cannabinoids act through G-protein-coupled receptors: cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R) within the endocannabinoid system. CB1R are abundant in the mammalian brain,[10] and it is primarily responsible for the psychotropic effects of cannabis. CB1R is also expressed in the myocardium, vascular endothelial, smooth muscle cells, and vagal afferents. CB2R are predominantly found within the macrophage derived immune cells.[9] THC is the primary psychoactive component of cannabis and a partial agonist to CB1R and CB2R. THC mediates many of the cardiovascular effects of cannabis. CBD acts as a negative allosteric modulator of the CB1R, is associated with antioxidant and anti-inflammatory properties and has limited psychoactive effect.[9, 11, 12] Mechanistically, CB1R stimulation in human atrial myocytes decreases contractility[13] but inhibition of CB1R protects against doxorubicin-mediated cardiotoxicity.[14]

Three synthetic oral cannabinoid-based pharmaceuticals are U.S. Food and Drug Administration (FDA) approved, having demonstrated efficacy in treating certain medical conditions. They include Marinol (dronabinol), Cesamet (nabilone) and Epidiolex (CBD).

Marinol (dronabinol) is a cannabinoid that is chemically similar to THC and binds to CB1R. It is FDA approved for anorexia associated with weight loss in adult patients with acquired immune deficiency syndrome (AIDS) and nausea and vomiting associated with chemotherapy in adults who have failed conventional therapy.[15] Epidiolex® is the brand name for a whole-plant cannabis extract of a high CBD strain of Cannabis sativa and is an oral oil solution product containing > 98% CBD at a concentration of 100 mg/ml. Epidiolex® has received FDA approval (June 2018) for use in patients 2 years and older to treat Dravet syndrome and Lennox-Gastaut syndrome.

## Cannabis Use: Cardiometabolic Effects and Heart Failure

According to the 2020 National Survey on Drug Use and Health, 49.6 million Americans aged >12 had used cannabis (>15% of the population) and 14.2 million Americans (5.1%) had a cannabis use disorder (Persistent cannabis use with significant amount of time spent procuring cannabis leading to social problems and failure to fulfill life obligations).[1] The cardiovascular effects of cannabis are dependent on several factors, including the baseline state of the endocannabinoid system, THC content and the route of administration.[9, 15] The increasing availability and recreational use of synthetic psychoactive compounds (‘designer’ drugs) with potencies 10-times to 200-times greater than that of THC has limited the ability to evaluate the cardiovascular safety of cannabis.[16] Inappropriate marketing, formulation, and packaging practices also contribute to non-standardized dosing across cannabis products and this makes THC and CBD content across samples unpredictable, with unpredictable physiologic effects.[9, 15] This heterogeneity and the inconsistency in cannabis regulation across US states limits standardization of cannabis products.[17]

Despite suggestions of possible cardiovascular events attributable to cannabis,[9] evidence suggesting cardiovascular toxicity of THC including premature atherosclerotic cardiovascular disease,[18] myocarditis,[19] and stress cardiomyopathy[20] is limited to database reviews. A 2018 study of inpatient hospitalizations showed that in patients with a history of recent cannabis use; after controlling for age, sex, comorbidities, tobacco and alcohol use, cannabis use was found to be an independent predictor of HF and stroke.[21]

Advanced HF and end stage solid cell cancers can be marked by symptoms of anorexia, malnutrition, and cachexia.[4] Dosage-controlled capsules of cannabis have been found to increase weights ≥10% in patients with cancer-related cachexia.[22] Given the increasing disease burden of advanced HF, uncertain evidence of harm from cannabis use, and its established role in cancer cachexia, Marinol may be used for symptom control, anorexia and cardiac cachexia associated with advanced HF.

## Cannabis Use and Heart Transplantation

### Pretransplant Considerations

**I. US Federal Cannabis Policy and Disparities in Legislation and Transplant Center Practices—**The World Health Organization classifies CBD as having no potential for abuse, but the US classifies cannabis as a Schedule I drug with a high potential for abuse and little to no medical benefit.[17] Historically, US criminalization and regulation of

substances has targeted substances used more by underserved racial and ethnic minority populations. This legacy of discrimination in cannabis legislation is reflected in the racial disparities in cannabis-related arrests and incarcerations. In 2018, the lifetime prevalence of cannabis use was lower for Black (45.3%) than White (53.6%) adults aged 18 years or older,[23] but Black individuals were 3.64 times more likely to be arrested for cannabis possession.[24] In states with recreational cannabis laws, overall rates of cannabis arrests have decreased but Black and Hispanic individuals are still more likely to be arrested than their White counterparts.[24]

Overall clinicians are poorly prepared to answer questions and prescribe medical cannabis.[25] A survey found that although most transplant centers support listing patients who use medical cannabis after a period of abstinence, much fewer respondents were in favor of transplant listing for legal cannabis users.[26] Members of a transplant society reported variability in pre-transplant screening: 55% of respondents screened all candidates, 20% based screening on the organ to be transplanted, while 20% did not routinely screen or had inconsistency in screening methods (toxicology alone (62%) compared to interview alone).[27] In states with no legal cannabis reform, 34% of respondents declined transplantation to all cannabis users, compared to 25% in states with some form of legal cannabis ($p = 0.15$).[27] There was also dissonance among transplant centers with regards to their perceived risk of cannabis use versus complications routinely seen.[27] Another survey found that many programs do not have a policy related to recreational cannabis use and 31% of programs have a “don’t ask, don’t tell” policy.[28] A study exploring physician decision-making about abstinence from substance use for left ventricular assist device (LVAD) therapy showed that 42.4% of providers required abstinence from both tobacco and THC (cannabis) while 38.4% did not require any abstinence from either substance.[29]

Discordant legislation and inadequate clinician knowledge about cannabis has the potential to worsen disparities in transplant candidacy. Most heart transplant programs will likely pattern their policies towards cannabis use to mirror that of the state legislature. For instance, states with medical cannabis laws are more likely to have policies that permit potential recipients under certain conditions to qualify for heart transplant listing. In response to this ambiguity, some states have passed legislation that transplant candidates cannot be denied transplant candidacy based on solely on medicinal cannabis use.[6] Individual states – including Arizona, California, Delaware, Illinois, Minnesota, New Hampshire, and Washington prohibit transplant centers from denying candidates transplant operations based solely on use of medicinal cannabis.[6]

## II. Cannabis Use by Donors – Are Organs of Cannabis-Using Donors Safe?—

There is inconclusive evidence of the adverse effects of cannabis use on donor hearts.[15] Despite scarcity of donor organs, some HT centers are hesitant to accept organs from cannabis-using donors due to concerns about the cardiovascular impact of cannabis. Nevertheless, the number and percentage of donors with illicit drug use has significantly increased between 2007 and 2017.[30]

A retrospective review of recipients of extended criteria heart donors (55% of donors had history of cannabis use), showed no difference in survival compared to recipients of

non-high-risk donors (without a history of cannabis use).[31] The mean 30-day, 1 year and 5-year survival of recipients of extended criteria donor organs was 95.8%, 92.2% and 84.4% respectively.[31] An analysis of the United Network for Organ Sharing (UNOS) of 23,748 adult heart transplants showed that donors with history of substance use (heavy alcohol use; 15.8%, cocaine use within 6 months; 7.7%, history of other drugs in past 6 months; 31.4%) was not associated with lower survival, regardless of type of substance or use of multiple substances and that history of illicit drug use correlated weakly with illicit drug toxicology.[30] A single center retrospective review of living kidney donor transplants performed showed no statistically significant difference in renal function of recipients of cannabis using and non-cannabis using kidney donors.[32] In summary, the current evidence does not show any differences in outcomes between transplant recipients of cannabis-using donors when compared to recipients of non-users.

**III. Mode of Cannabis Use (Oral vs. Inhaled Cannabis) and Urine Drug Test for Cannabis Use—**Cannabis is consumed through smoking, vaporizing, oral ingestion, or topical application.[33] (Table 1) Smoked THC can be detected in the blood within one minute of circulation.[34] Burning cannabis leads to the release of carcinogens which increase the risk of bronchitis, and pulmonary infections including tuberculosis.[33] Cannabinoid-based oil vapes often contain propylene glycol, vitamin E acetate which causes acute lung injury and severe pneumonitis.[35, 36] Edible cannabis is ingested orally, (Table 1) has a long latency period, delayed effect onset, and peak serum concentration.[37, 38] Given the slower onset of action, people accustomed to an instantaneous effect from inhaled cannabis may ingest excessive doses (“dose stacking”) before peak effects occur thereby increasing the risk of overdosing.[38] Psychiatric and cardiovascular complications are common with edible cannabis. A study of emergency department visits related to cannabis use reported less frequent visits (9% v. 91%), more acute psychiatric visits (18% v. 10.9%), more cardiovascular symptoms (8% v. 3.1%), and higher intoxication (48% v. 28%) from edible cannabis compared to inhaled cannabis users.[39, 40] The American Heart Association Scientific Statement recommends against smoking or vaping cannabis.[15] Smoking/vaped cannabis should be discouraged for potential transplant recipients by transplant centers. Edible cannabis does not appear to have adverse pulmonary manifestations, but its use does not appear to be benign.

Following cannabis consumption, THC is metabolized to a variety of inactive chemicals, one of them being delta-9-tetrahydrocannabinol carboxylic acid (THC-COOH). Urine immunoassays are a screening test for THC-COOH but confirmation by gas chromatography-mass spectrometry is required for employment or medicolegal reasons and to quantify the severity/intensity of cannabis exposure/use. Urinary THC-COOH greater than 15 ng/ml is a strong indicator of cannabis use.[41] THC-COOH has a long half-life and can be detected in urine for more than 7 days after a single use. Urinary THC-COOH greater than 100 ng/mL indicates recent use (within the past 7 days). Levels greater than 500 ng/mL suggest chronic and recent use.[41] Chronic use causes accumulation in adipose tissue and can be excreted into the urine for as long as 30 to 60 days from the time chronic use is halted. Sensitivity of cannabis testing approaches 100% accuracy.[42] In rare circumstances such as

hours immediately after extreme secondhand cannabis smoke exposure, false positive urine tests can occur but this is quite uncommon.[43]

**IV. Psychosocial Considerations: Cannabis Use Disorder (CUD) – Diagnosis and Screening—**Assessment of psychosocial risk is important for patient selection for advanced HF therapies. Calls have been made for transplant centers to de-emphasize mode of cannabis use but rather to focus on the presence or absence of cannabis use disorder (CUD).[44] CUD (Table 2) is a pattern of persistent cannabis use occurring within a 12-month period in which a significant amount of time is spent procuring cannabis and subsequent failure to fulfil school, work or family obligations. It is also manifested by at least two of the following; persistent cravings and recurrent consumption of large amounts of cannabis, continued use despite social/interpersonal problems caused by use, history of withdrawal, and addiction as defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM−5).[45] Risk factors include low socio-economic status, tobacco usage, unstable family, poor academic performance, and household members using cannabis.[15] However, cannabis use is more frequently reported among lower socioeconomic groups and these criteria may be better categorized as markers of low socioeconomic status rather than as markers of CUD. This may be another attempt to criminalize cannabis use among poor people. Treatment options for CUD are fewer than for opiate or alcohol dependence and includes psychological interventions such as cognitive behavioral therapy, supportive-expressive psychotherapy and enrollment in Marijuana Anonymous programs and medications targeted towards symptoms of withdrawal.

The Cannabis Use Disorder Identification Test - Revised (CUDIT-R) (Table 2) is a self-administered questionnaire used to screen for CUD with scores of ≥8 and ≥12 indicating hazardous cannabis use and CUD respectively for which intervention may be required.[46] Screening of HF patients who use cannabis with a validated questionnaire such as CUDIT-R to determine the risk of CUD may be an initial step in transplant evaluations. Additionally, a strategy of toxicologic testing in addition to a history of substance use for all potential HT recipients may lead to more standardized patient assessment. We propose that the presence or absence of CUD be used to further contextualize cannabis use for HF patients being considered for heart transplant. Cannabis use is unlikely to be a binary event such as a Yes or No answer to cannabis use or a positive/negative THC test.

## Post-transplant Outcomes and Considerations

**I. Cannabis Use and Allograft Dysfunction/Failure—**The evidence for the outcomes of solid organ transplant recipients with post-transplant recreational cannabis use has been evaluated in retrospective reviews of kidney/liver transplant—but not in heart transplant recipients—and has not shown clear evidence of allograft dysfunction. A retrospective review of 1225 kidney transplant recipients (N=56, cannabis users; N=1169, non-users) compared cannabis using patients identified by self-reporting or positive urine toxicology and showed no difference in renal function (creatinine; 1.52 versus 1.46 mg/dL, $P$=0.38), death or graft failure at 1 year between cannabis users and cannabis nonusers.[47] Another retrospective review of 316 liver transplant recipients comparing cannabis users, tobacco smokers and nonusers was done. After adjustment, there was no difference in

survival between current/former cannabis users versus never users, but current tobacco users were over 3 times as likely to die within 5 years when compared to never users.[48]

A study linking the Scientific Registry of Transplant Recipients (SRTR) with Medicare claims data evaluated 52,689 kidney transplant recipients with cannabis exposure in 0.5% of the studied patients [n-254; pre-transplant] and [0.3% n=163) posttransplant] demonstrated that a diagnosis of cannabis dependence or abuse in the first-year posttransplant was associated with an approximate 2-fold increase in graft failure, higher all-cause graft loss and death in the subsequent 2 years.[49] Another study of kidney transplant recipients which included 48 cannabis only users showed no difference in graft survival compared to non-cannabis users but showed an increased risk of graft loss with concomitant tobacco use when compared to non-cannabis users.[50] Nevertheless, it remains unclear if this data can be extrapolated to the heart transplant literature.

**II. Cannabis Use and Immunosuppressant Interactions—**THC and CBD affects the cytochrome P450 (CYP) enzymes and drug transporters in in-vitro and in-vivo studies, while CBD also interacts with enzymes in the UDP-glucuronosyltransferase system.[51] Use of calcineurin inhibitors (tacrolimus and cyclosporine) is central to the prevention of graft rejection in heart transplantation. Tacrolimus has a narrow therapeutic window and requires close laboratory monitoring. The P-glycoprotein efflux pump plays a role in tacrolimus absorption from the gut and distribution in other tissues[52] Cyclosporine and tacrolimus are metabolized via the cytochrome P450 system, primarily CYP3A4, and CYP3A5. CBD can raise tacrolimus levels by inhibiting CYP3A4 and P-glycoprotein. Tacrolimus toxicity with cannabinoids consumption has been limited to case reports.[53, 54] Tacrolimus toxicity with altered mental status was reported after edible cannabis use and prophylactic posaconazole in a bone marrow transplant recipient.[53, 55] Therapeutic calcineurin inhibitor levels may have wide variability based on the frequency of use and the concentration of THC and CBD in products used. CBD can also cause elevation of cyclosporine levels by inhibiting CYPA3A4 enzyme activity. Additionally, it is unknown whether inhibition of CYP enzymes and P-gp is dose-related or if it varies based on the chronicity of use or route of administration.

THC and CBD also interact with other medications commonly used in heart transplantation such as antifungals (azoles), diltiazem for hypertension, and warfarin. Azoles can increase THC concentrations by inhibiting cytochrome P2C9 enzyme which is necessary for THC metabolism.[27] THC and CBD inhibit CYP2C9 and can therefore raise international normalized ratio (INR) levels among patients taking warfarin.[51] Table 3 illustrates interactions between cannabis and commonly used transplant medications.

**III. Cannabis Use and Post-transplant Fungal Infection—**Patients who smoked cannabis or have cannabis use disorder may be at increased risk of post-transplant fungal infection. Cannabis harbors mold, mainly aspergillus and penicillium species.[56] A retrospective database review linking national kidney transplant records with Medicare claims showed a higher rate of pneumonia, especially aspiration pneumonia, in cannabis-using kidney transplant recipients compared to non-users.[49] Heart transplant recipients typically require more aggressive immunosuppressive regimens than do recipients of other

solid organs. Intense immunosuppression may play a role in the increased incidence of fungal infections in transplant recipients. Smoked cannabis products used when the initial post-transplant fungal infections were reported may have more impurities than the preparations used today.[56, 57] Given the evidence of possible harm, HT recipients should avoid smoking or vaping cannabis due to the risk of fungal infection. Prospective data from post heart transplant patients of programs that permit cannabis use post-transplant will be helpful to assess for the incidence of fungal infections

## Heart Transplantation: Similarities between Prescription Opiates and Medicinal Cannabis Use

A concern in the transplant community is whether patients with prescription opiates are appropriate for transplant listing. Opiates have an addiction potential and have been linked to reduced cognition, decreased medication adherence, and increased risk of death.[58] A large multi-center study reported increased mortality risk following heart transplantation in association with prescription opiates.[59] Most transplant programs consider prescription opiate use as acceptable prior to transplant listing.[60] Attitudes and legislation towards opioid abuse and related deaths which occur in predominantly White rural and suburban areas[61] has been accompanied by sympathetic responses from community groups and policy-makers. Unfortunately, this type of media and policy attention has not been given to other groups, including Native Americans, who experience similar rates of opioid-related deaths as Whites in the United States while media and policy responses to the rise of cannabis possession or use in black and Latino neighborhoods have been especially harsh[24] while portraying White users as innocent victims and therefore much less likely to be arrested or sentenced.

Cannabis has a safer side effect profile, lower potential risk for overdose, less addiction potential, and fewer associated deaths than opioids.[62] Cannabis may reduce prescription opioid use and improve quality of life in authorized patients. A study (1999–2010) found that states with medical cannabis laws experienced slower increases in opioid analgesic overdose mortality over time.[63] However, another group extended the analysis (2010–2017) and found that these findings did not hold over the longer period, and that the association between state medical cannabis laws and opioid overdose mortality suggested harm from cannabis use after accounting for recreational cannabis laws. There was also no evidence that more restrictive cannabis laws were associated with changes in opioid overdose mortality.[64] It may be reasonable to consider patients who use legal medicinal cannabis use similarly to patients who use prescription opioids when cardiac transplantation is being considered. Table 4 lists a comparison of alcohol, opioids, and cannabis in relation to transplantation.[65]

## Future Research Directions

Transplant listing for HF patients who use cannabis remains an ethical conundrum because of the steward role of transplant centers to ensure allocation of donor organs to patients who will derive the most benefit and preserve the organ longest. Research priorities (Figure 1) to address misconceptions about cannabis use in HF patients are identified. Addressing these priorities will generate the data needed for an evidence-based approach that will identify

patients who may safely undergo heart transplantation. Decriminalization of cannabis at the federal level may free up access to research money to fund these priorities. Table 5 lists the research gaps and proffers solutions to address these gaps towards a more equitable form of evaluation of cannabis-using HF patients. Standardized testing – behavioral (CUDIT-R) and toxicologic screening for all potential recipients and a standardized defined period of abstinence and/or mandated substance abuse counseling as part of transplant evaluation are useful initial steps. Similarities and differences between attitudes towards prescription cannabis and prescription opioids need to be better understood. Establishment of prospective multi-center cohort of post-transplant patients in centers that permit post-transplant cannabis use will be helpful. This will hopefully provide sufficient power to determine the significance of cannabis-immunosuppressant pharmacokinetic interactions, risk of fungal infection, and allograft failure/rejection.

## Conclusion

The rapid legalization of cannabis by US states, impending Federal decriminalization and increasing incidence of HF will worsen the knowledge gaps in evaluation of cannabis use and heart transplantation, but also creates an opportunity to re-examine cannabis use in heart transplantation. To do this, the decision-making processes of HT programs need to be better understood. Heart transplant selection committees may consider not excluding patients from transplant listing based on cannabis use alone but should instead screen patients for cannabis use disorder which may be treatable. Selection teams should evaluate candidates holistically by integrating evidence-based approaches and psychiatric and social factors into the complicated selection process.

There is an urgent need to prospectively research the factors affecting the eligibility of patients who use cannabis for heart transplantation. The data generated will lead to a standardized evaluation process and future guidelines to decrease disparities in heart transplantation for all populations without compromising outcomes. Therefore, access based on assessing cannabis using HF patients most likely to benefit from HT requires a standardized, fair, and ethical process for organ allocation. Further research is urgently needed to establish a data-driven approach to ensure equitable distribution of organs, reduce discrepancies between evaluation of candidates between different HT programs and guide the formulation of transplant guidelines to reduce disparities in allocation of donor organs.

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## Abbreviations:

| | |
|---|---|
| **CBD** | Cannabidiol |
| **THC** | Tetrahydrocannabinol |
| **CUD** | Cannabis use disorder |
| **HT** | Heart transplantation |

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|---|---|
| **CUDIT-R** | Cannabis Use Disorder Identification Test – Revised |
| **DSM-5** | Diagnostic and Statistical Manual of Mental Disorders |

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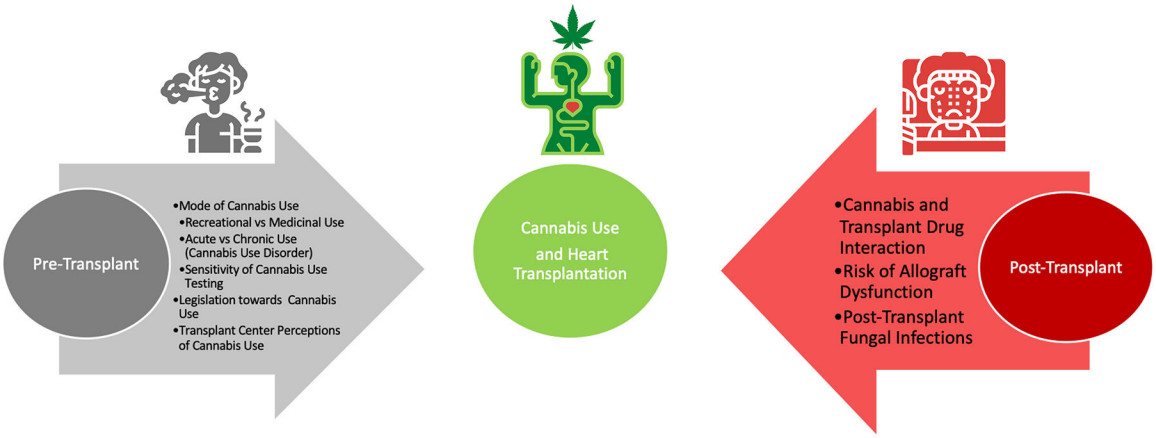


**Figure 1.**

Pre-transplant and Post-transplant Considerations for Cannabis Use and Heart Transplantation

**Table 1.**

Comparison of Characteristics and Risks of the Common Modes of Cannabis Use

| | **Inhaled Cannabis** | **Oral Cannabis** |
|---|---|---|
| **Mode of Use** | Smoked or vaporized | Ingested |
| **Common Forms** | Vapes | Edibles, Beverages |
| **Frequency** | Commonest method of use | Less frequent |
| **Absorption** | Rapid | Slow |
| **Detected within circulation** | 1 minute | 30–60 minutes |
| **Onset** | Fast | Delayed |
| **Effects Peak** | Strong | Drawn Out |
| **Decline in Effects Strength** | Rapid | Gradual |
| **Duration of Experience** | Short | Long |
| **By products - Carcinogens, tar, and carbon monoxide** | Yes | No |
| **Acute lung injury, Severe pneumonitis** - Vaporized cannabis contains propylene glycol, vitamin E acetate | Yes | No |
| **Risk of “Dose Stacking”** | No | Yes |

**Table 2.**

Diagnostic and Statistical Manual 5 Criteria for the diagnosis of Cannabis Use Disorder (CUD)

| **Criteria** | |
|---|---|
| 1. | Use of cannabis for ≥1 year, with a pattern of cannabis use leading to clinically significant impairment or distress |
| 2. | Cannabis usage in larger amounts and over a longer period than intended |
| 3. | Repeated failed efforts to discontinue or reduce the amount of cannabis usage |
| 4. | A lot of time spent acquiring, using, or recovering from the effects of cannabis |
| 5. | Craving or desire to use cannabis |
| 6. | Continued cannabis usage despite adverse consequences |
| 7. | The desire to use cannabis interferes with completing other life responsibilities |
| 8. | Cannabis usage despite potential danger, such as operating a motor vehicle |
| 9. | Cannabis usage despite awareness of drug induced physical or psychological problems |
| 10. | Development of cannabis tolerance |
| 11. | Cannabis withdrawal |

Mild CUD 2–3 criteria; Moderate CUD 4–5 criteria; Severe CUD ≥ 6 criteria

**Table 3.**

Significant Interaction Between Cannabis and Medications Used in Transplant

| Medication | Cannabis Interaction | Metabolic Pathway |
|---|---|---|
| ***CNI*** | | |
| Tacrolimus | ↑ CNI drug level via CYP3A4 inhibition | CYP3A4 |
| Cyclosporine | | CYP3A4, CYP3A5 |
| ***mTORi*** | | |
| Everolimus | ↑ mTORi drug levels via CYP3A4 inhibition | CYP3A4 |
| Sirolimus | | CYP3A4 |
| ***Antiproliferative agents*** | None | None |
| Azathioprine | | |
| MMF[a]/MPA[a] | | |
| ***Antifungal agents*** | | |
| Fluconazole | ↑ THC & CBD drug level via inhibition of CYP2C9 | CYP3A4/CYP2C9 (inhibitor) |
| Ketoconazole | ↑ THC & CBD drug level via inhibition of 3A4 & 2C9 | CYP3A4/2C19/2C8, P-gp (inhibitor) |
| Itraconazole | ↑ THC & CBD drug level via inhibition of CYP2C9 | CYP3A4, P-gp (inhibitor) |
| Posaconazole[a] | ↑ CBD drug level via inhibition of CYP3A4 | CYP3A4 (inhibitor) |
| Voriconazole | ↑ CBD drug level via inhibition of CYP3A4 | CYP3A4/2C9/2C19 (inhibitor) |
| ***Pneumocystis jiroveci prophylaxis*** | | |
| SMX-TMP | ↑ THC & CBD drug level via inhibition of CYP3A4 & 2C9 | CYP2C9 (SMX; substrate) |
| Dapsone[a] | 2C9 | N/A |
| Pentamidine | ↑ SMX level via CY2C9 inhibition | N/A |
| ***CAV prophylaxis*** | | |
| Statins | ↑ Statin exposure through inhibition of CYP3A4 and 2C9 | CYP3A4, CYP2C9 (substrate) |

CNI, calcineurin inhibitors; mTORi, mammalian Target of rapamycin Inhibitors; P-gp, P-glycoprotein; MMF, mycophenolate mofetil; MPA, mycophenolic acid; THC, D9-tetrahydrocannabinol; CBD, cannabidiol; SMX-TMP, sulfamethoxazole-trimethoprim; CYP3A4, cytochromeP3A4; CYP2C9, cytochromeP2C9; CAV, cardiac allograft vasculopathy; N/A, not applicable

[a]Hepatically metabolized via alternative pathways

**Table 4.**

Comparison of Cannabis, Opiates and Alcohol Abuse and Transplantation

| | **Cannabis** | **Alcohol** | **Opiates** |
|---|---|---|---|
| ISHLT guidelines[7] | Transplant eligibility deferred to each center | Contraindication. Class III, Level of evidence C | |
| Addictive Potential[1, 45] | + | + | +++ |
| Drug interaction with Immunosuppressants[55] | + | − | − |
| Altered mental status | + | + | +++ |
| Associated psychiatric disorder[1, 45] | Cannabis Use Disorder | Alcohol Use Disorder | Opioid Use Disorder |
| Associated with cancer | Testicular germ cell tumors | Oral<br>Pharynx + larynx<br>Esophagus + colorectum<br>Breast | − |
| Association with low medication adherence[49] | + | + | − |
| Associated with reduced allograft survival[49, 59, 65] | + | + | ++ |

ISHLT, International Society for Heart and Lung Transplant

**Table 5.**

Research Gaps to be Addressed to Aid Clinical Decision Making for Cannabis Use and Heart Transplantation

| | Research Gap | Potential Solution |
|---|---|---|
| **Pre-transplant** | | |
| | Mechanism of cardiovascular toxicity | Fund basic cannabis cardiovascular research |
| | Accurate labeling of THC/CBD content of cannabis products | Food and Drug Administration (FDA) mandates |
| | Concerns for post-HT medication (immunosuppressant) nonadherences of candidates who use cannabis | Validated measures of medication adherence e.g., Proportion days covered (PDC), medication adherence scales |
| | Non standardized toxicologic evaluation of pre-transplant HF patients | Toxicologic screen for all patients at HT evaluation<br>Exceptions for approved cannabis substances prescribed legally by medical provider |
| | Prevalence of CUD among HF patients | Screen for CUD with validated cannabis questionnaire |
| | Accepted abstinent time prior to consideration for transplant for patients who use cannabis | Accepted period of abstinence with substance abuse treatment (e.g., 6 months) |
| | Bias in decision-making while evaluating cannabis-using HF patients | Establish standardized algorithm for all transplant centers to use for evaluation of all HF patients |
| **Post-transplant** | | |
| | Identify possible cannabis-transplant drug interactions | Determine effect of cannabis on immunosuppressants and implications for frequency of drug monitoring and graft function |
| | Inconsistency in evaluation of recreational versus medicinal cannabis use post-HT | Delineate clear medicinal indications for cannabis use that may be permitted post HT |
| | Post-transplant outcomes of cannabis using HT patients | Multi-center prospective transplant studies with sufficient power to determine risk of infection, cancer, rejection, and graft failure with cannabis use |

THC, Tetrahydrocannabinol; CBD, Cannabidiol; CUD, cannabis use disorder; HF, Heart failure; HT, Heart transplant