Marijuana Use In The Liver Transplant Recipient: "Highs & Lows With Mary-j"

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DISCLOSURE

I have no financial interest to disclose

LEARNING OBJECTIVES

State risks associated with continued use post transplantation

Identify the affect of marijuana use on immunosuppression

Discuss patient outcomes with marijuana use

MARIJUANA

- the most common drug of abuse in the U.S.
- the most likely illicit substance to be identified by transplant programs on toxicology screening

Psychosomatics 2011:52;190-193

Δ^9-TETRAHYDRACANNIBINOL (THC)

- chief psychoactive compound in marijuana
- is quickly absorbed
- widely distributed after consumption (especially into adipose tissue)
- slowly redistributed throughout the body
- oxidized by the liver into the carboxy compound 11-nor-9-carboxy-Δ^9-THC (THC-COOH).

Psychosomatics 2011:52;190-193

THC-COOH

THC-COOH is the major metabolite of THC found in the urine (as its glucuronide).

Urine immunoassays are used for preliminary screening for THC use with positive results confirmed by the "gold standard" gas chromatography with mass spectrometry (GM/MS).

Psychosomatics 2011:52;190-193

THC DETECTION

The duration of detection of THC by GC/MS is determined by

- frequency
- amount of use
- timing of last use.

A single use of THC can result in positive results from hours to several days

Infrequent use may be detected for 5 to 15 days and heavy

Chronic use from several weeks to a month.

Psychosomatics 2011:52;190-193

MARIJUANA EXPOSURE

Passive exposure to marijuana smoke has been shown to produce detectable urine levels in marijuana-naïve subjects, although the level of exposure required to produce this effect is likely above that which would be routinely tolerated

Psychosomatics 2011:52;190-193

Some drugs may create false positives on initial immunoassay (e.g. ibuprofen, naproxen, ketoprofen, promethazine, pantoprazole, riboflavin) confirmation by GC/MS should clarify the actual substance.

Medicinal uses of THC such as dronabinol (marinol) cannot be distinguished from other sources of THC.

Psychosomatics 2011:52;190-193

CREATINE-CORRECTED URINE THC-COOH

used as a test for resumption of marijuana use, and a $\geq$ 50% increase between two seral samples has been proposed as a forensic indicator of return to use.

Psychosomatics 2011:52;190-193

NATIONAL SURVEY OF PROVIDER OPINIONS ON CONTROVERSIAL CHARACTERISTICS OF LIVER TRANSPLANT

PATIENT CHARACTERISTICS BY POLICY AVAILABILITY AND CONTROVERSY RANKING

	Total Respondents (n)	Ranked as Most Controversial Issue [n (%)]	Ranked as 1 of 3 Most Controversial Issues [n (%)]	Policy Available by Issue [n (%)]*
Incarceration	218	54 (24.8)	121 (55.5)	63 (28.9)
Psychiatric diagnoses	222	21 (9.5)	106 (47.7)	102 (45.9)
Marijuana use	229	38 (16.6)	107 (46.7)	163 (71.2)
Obesity	224	26 (11.6)	102 (45.5)	141 (62.9)
Citizenship/residency	216	40 (18.5)	96 (44.4)	64 (29.6)
Advanced age	219	30 (13.7)	61 (27.9)	83 (37.9)
Cognitive disability	217	9 (4.1)	58 (26.7)	29 (13.4)
HIV seropositivity	225	17 (7.6)	52 (23.1)	178 (79.1)

*The percentages do not add up to 100% because the respondents could select multiple responses.

Provider Opinions on Contraindications to Liver Transplantation

Patient Characteristic	Total Respondents (n)	Contraindication [n (%)] Not	Relative	Absolute
Advanced age				
65–69 years	249	214 (85.9)	35 (14.1)	0 (0.0)
70–74 years	248	82 (33.1)	160 (64.5)	6 (2.4)
75–79 years	250	23 (9.2)	149 (59.6)	78 (31.2)
≥80 years	249	9 (3.6)	84 (33.7)	156 (62.7)
HIV seropositivity	249	94 (37.8)	136 (54.6)	19 (7.6)
Obesity by BMI				
35–39 kg/m^2	249	143 (57.4)	103 (41.4)	3 (1.2)
40–44 kg/m^2	249	37 (14.9)	152 (61.0)	60 (24.1)
≥45 kg/m^2	249	14 (5.6)	94 (37.8)	141 (56.6)
Psychiatric diagnosis in acute liver failure				
First suicide attempt	246	113 (45.9)	131 (53.3)	2 (0.8)
Two or more suicide attempts	245	10 (4.1)	127 (51.8)	108 (44.1)
Major psychiatric illness, stable	245	141 (57.6)	101 (41.2)	3 (1.2)
Major psychiatric illness, unstable	244	18 (7.4)	129 (52.9)	97 (39.8)
Psychiatric diagnosis in chronic liver failure				
History of suicide attempt	244	103 (42.2)	141 (57.8)	0 (0.0)
Major psychiatric illness, stable	244	157 (64.3)	85 (34.8)	2 (0.8)
Major psychiatric illness, unstable	243	5 (2.1)	128 (52.7)	110 (45.3)
Incarceration				
Current, not lifetime sentence	243	60 (24.7)	129 (53.1)	54 (22.2)
Current, lifetime sentence	243	32 (13.2)	78 (32.1)	133 (54.7)
Marijuana use				
Daily, nonmedical	244	25 (10.2)	105 (43.0)	114 (46.7)
Occasional, nonmedical	244	76 (31.1)	118 (48.4)	50 (20.5)
Medical	243	130 (53.5)	86 (35.4)	27 (11.1)
Cognitive disability				
Mild	244	200 (82.0)	41 (16.8)	3 (1.2)
Moderate	244	104 (42.6)	120 (49.2)	20 (8.2)
Severe	244	27 (11.1)	96 (39.3)	121 (49.6)
Citizenship and residency status				
Documented immigrant	241	218 (90.5)	21 (8.7)	2 (0.8)
Undocumented immigrant	241	70 (29.0)	101 (41.9)	70 (29.0)
Noncitizen temporarily in the United States	241	124 (51.5)	93 (38.6)	24 (10.0)

ABSOLUTE CONTRAINDICATIONS TO LIVER TRANSPLANT

- More than 50% of the providers identified an age ≥80 years (62.7%)
- BMI > 45 kg/m2 (56.6%)
- current incarceration with a lifetime sentence (54.7%) as absolute contraindications.

Provider/Center Characteristics Associated with Most Frequently Identified Absolute Contraindications

Variable*	Age ≥ 80 years (n = 230)	BMI ≥ 45 kg/m^2 (n = 230)	Lifetime incarceration (n = 225)
Male (female)	0.57 (0.26–1.23)	0.84 (0.39–1.82)	0.33 (0.15–0.75)†
Age > 50 years (age ≤ 50 years)	1.18 (0.61–2.30)	0.81 (0.41–1.58)	1.47 (0.73–2.98)
White race (other)	0.83 (0.42–1.64)	1.46 (0.75–2.85)	0.64 (0.32–1.30)
Provider type (hepatologists)			
Surgeons	0.44 (0.23–0.87)	0.42 (0.22–0.81)†	0.35 (0.18–0.71)†
Psychosocial provider	0.51 (0.23–1.14)	1.48 (0.66–3.30)	0.48 (0.21–1.13)
Liver recipient volume (<50)			
50–100	0.58 (0.29–1.13)	0.95 (0.49–1.86)	0.87 (0.43–1.73)
≥101	0.49 (0.23–1.04)	0.45 (0.21–0.96)	1.13 (0.52–2.49)
Region (Northeast)			
Midwest	0.90 (0.41–2.00)	0.42 (0.19–0.94)	3.17 (1.42–7.11)†
South	0.75 (0.35–1.58)	0.71 (0.33–1.51)	5.49 (2.45–12.27)†
West	0.95 (0.39–2.34)	0.81 (0.33–2.01)	2.17 (0.88–5.38)
Unknown	0.84 (0.12–5.86)	1.40 (0.13–14.56)	—‡
≥20 years in service (<20 years)	0.95 (0.402–2.26)	0.73 (0.31–1.72)	0.67 (0.28–1.63)

CONCEPTUAL MODEL

		Written Policy Available	
		Yes	No
Consensus on absolute contraindications	Yes	Most Optimal • Obesity	Suboptimal • Advanced age • Incarceration
	No	Suboptimal • HIV • Marijuana use	Least optimal • Psychiatric diagnosis • Citizenship • Cognitive disability

NOTE: A consensus was identified for a patient characteristic if 1 of its subcategories (eg, age ≥ 80 years) was identified as an absolute contraindication by 50% or more of the respondents. A written policy was identified as available if 50% or more of the respondents answered that their center had a written policy on a patient characteristic.

Although a high proportion of centers have a strict policy for marijuana use, few outcome data are available except for 1 study that did not show a difference in post-transplant survival between marijuana users and marijuana nonusers

The providers were divided about whether daily nonmedical marijuana use and medical marijuana use were absolute contraindications.

Marijuana Use in Potential Liver Transplant Candidates

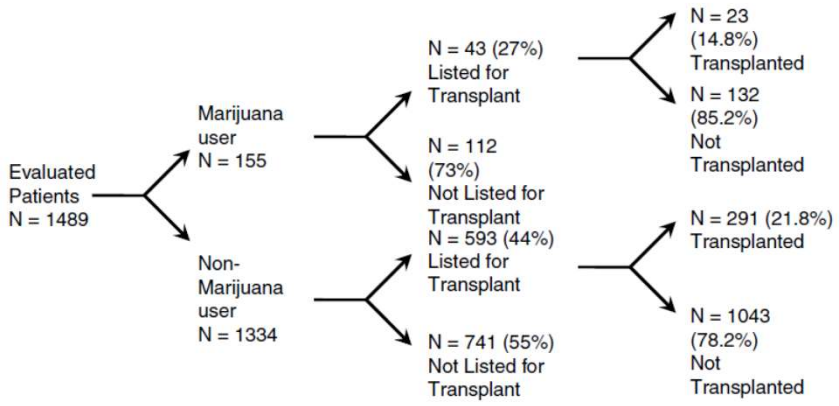
SUBSTANCE ABUSE POLICIES

- Help ensure potential liver transplant recipients will be reliable recipients
- May have inappropriate and disproportionate impact on marijuana users

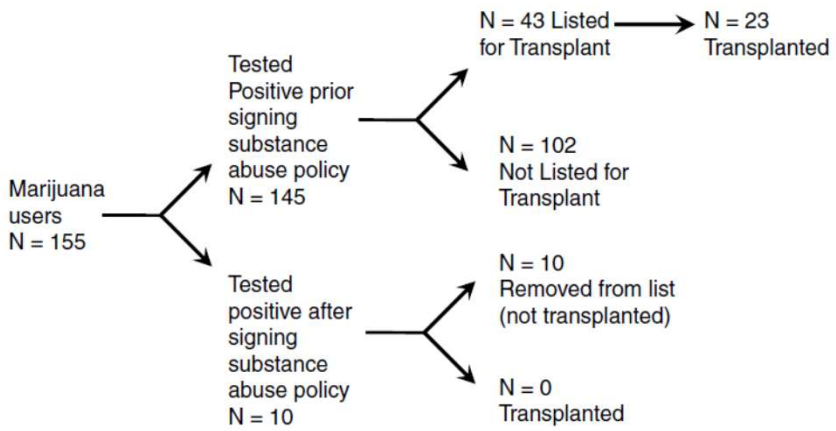
ARGUMENTS OF MARIJUANA USE

- Marijuana users should not have limited access to transplantation, particularly within the context of medical marijuana
- Currently toxicology screening methods produce a positive toxicology screen for cannabinoids up to two months after the patient's last use which makes it more difficult for chronic marijuana users to show abstinence prior to life-ending decompensation of their liver disease
- Patients with chronic liver disease who are marijuana users will have inferior survival

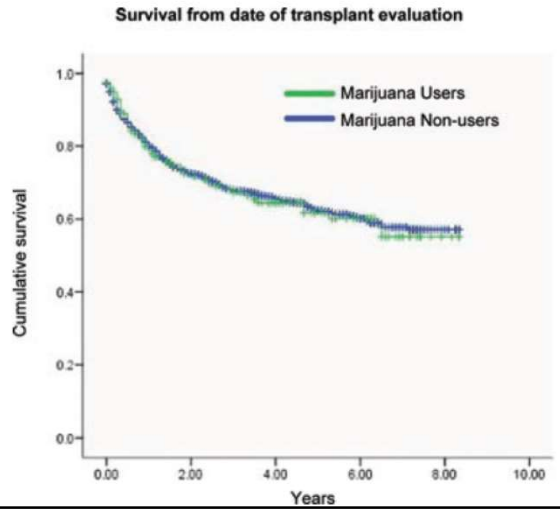
LISTING/TRANSPLANT STATUS OF PATIENTS WITH CHRONIC LIVER DISEASE (*N*=1489)



LISTING/ STATUS OF LIVER TRANSPLANT PATIENTS (MARIJUANA USERS) (*N*=155)



SURVIVAL FROM DATE OF TRANSPLANT EVALUATION



MARIJUANA HEALTH RISKS

Dose-dependent respiratory symptoms

Long-term abuse is associated with cognitive deficits and cerebrovascular disorders (strokes)

Severe aspergillosis fumigatus (contaminated marijuana)

Contributes to the pathogenesis of various liver diseases

Recreational Marijuana Use Is Not Associated With Worse Outcomes After Renal Transplantation

No data exist on the effect of Mary J (MJ) on kidney allograft outcomes, and there is No consensus on whether MJ use should be a contraindication to transplantation.

Retrospective study- 1225 kidney recipients from 2008 to 2013

Marijuana used defined by positive urine toxicology screen

Marijuana was not associated with wores outcomes

Isolated recreational MJ use is not associated with poorer patient or kidney allograft outcomes at 1 year therefore, MJ use should not be considered a contraindication to kidney transplantation

Primary and Secondary Outcomes

	MJ non-users (n=1169)	MJ users (n=56)	*P*-value
Patient survival (%)	97.7	100	.62
Graft failure[a] (%)	17.4	19.7	.62
Mean creatinine of functioning grafts at 1 y, 95% CI	1.42 mg/dL, 1.42–1.49	1.52 mg/dL, 1.39–1.69	.38
Mean GFR of functioning grafts at 1 y, 95% CI	49.5 mL/min^2, 48.3–50.7	50.7 mL/min^2, 45.6–56.5	.65

[a]Defined as GFR<20 mL/min/1.73 m^2 at 1 year. Percentages calculated only among those with 1-year follow-up data. When those lost to follow-up were included in functioning grafts, 1-year graft failure rates are <10% in both groups.

Denial Of Hepatic Transplantation On The Basis Of Smoking: Is It Ethical?

FINDINGS

There is a disagreement and inconsistency between liver transplant programs regarding the acceptance or rejection of smokers as candidates for transplantation

Recently published articles continue to demonstrate an increased risk of noncutaneous malignancies, higher rates of graft arterial thrombosis and a higher mortality rate in liver transplant patients who smoke as compared with nonsmokers

CANNABIS USE VERSUS CIGARETTE SMOKING

Active cannabis use is a frequent, if not universal, U.S. transplant center criterion for transplant denial

Cannabis use prohibits transplantation but cigarette smoking does not, despite the adverse outcomes in tobacco smokers undergoing transplantation

Evidence demonstrates an increased risk of adverse outcomes in transplanted smokers as compared to non smokers

An expectation of ongoing abstinence from smoking is a reasonable exclusion criterion for transplantation because of this

It is medically and ethically reasonable to use active smoking as an exclusion criterion for organ transplantation

Do Cannabinoids Have A Therapeutic Role In Transplantation?

CANNABINOIDS

- Have emerged as powerful drug candidates for the treatment of inflammatory and autoimmune diseases due to their immunosuppressive properties
- No studies have been performed on their potential role in transplant rejection
- CB2 agonists may offer a new avenue to selectively target immune cells involved in allograft rejection
- Development of mixed CB1/CB2 agonists that cannot cross the blood-brain barrier may help prevent their undesired psychotropic properties
- Manipulation of endocannabinoids may offer yet another pathway to regulate immune response during allograft rejection