American Journal of Transplantation 2009; 9: 280–285
Wiley Periodicals Inc.

© 2009 The Authors
Journal compilation © 2009 The American Society of Transplantation and the American Society of Transplant Surgeons

doi: 10.1111/j.1600-6143.2008.02468.x

Marijuana Use in Potential Liver Transplant Candidates

D. N. Ranney[a], W. B. Acker[a], S. N. Al-Holou[a], L. Ehrlichman[a], D. S. Lee[a], S. A. Lewin[a], C. Nguyen[a], S. F. Peterson[a], K. Sell[a], J. Kubus[a], D. Reid[b] and M. J. Englesbe[a,*]

[a] *Department of Surgery Summer Research Group and*
[b] *Department of Social Work, University of Michigan, Ann Arbor, MI*
* *Corresponding author: Michael J. Englesbe, englesbe@med.umich.edu*

Concern exists that liver transplant center substance abuse policies may have an inappropriate and disproportionate impact on marijuana users. Our hypothesis is that patients with chronic liver disease who were marijuana users will have inferior survival. This is a retrospective (1999–2007) cohort study. The primary outcome measure is time-dependent, adjusted patient survival from the time of liver transplant evaluation. The primary exposure variable is a positive cannabinoid toxicology screen during the liver transplant evaluation period. Overall, 155 patients qualified as marijuana users while 1334 patients were marijuana non-users. Marijuana users were significantly ($p < 0.05$) younger (48.3 vs. 52.1), more likely to be male (78.1% vs. 63.0%), have hepatitis C (63.9% vs. 40.6%) and were less likely to receive a transplant (21.8% vs. 14.8%). Marijuana users were more likely to use tobacco, narcotics, benzodiazepines, amphetamines, cocaine or barbiturates ($p < 0.05$). Unadjusted survival rates were similar between cohorts. Upon multivariate analysis, MELD score, hepatitis C and transplantation were significantly associated with survival, while marijuana use was not (HR 1.09, 95% CI 0.78–1.54). We conclude that patients who did and did not use marijuana had similar survival rates. Current substance abuse policies do not seen to systematically expose marijuana users to additional risk of mortality.

Key words: Liver, policy, survival, transplant

Received 25 July 2008, revised 18 September 2008 and accepted for publication 19 September 2008

Introduction

Marijuana is the most prevalently used illegal substance in the United States (1). Nearly 40% of American teenagers have tried marijuana in their lifetimes and almost 20% indicate they are current users (2). Among adults, estimates stand at just over 38% for one-time users with 3.5% identifying themselves as current users (3). In addition, the legality of marijuana use, both recreational and medicinal, remains controversial. There are significant potential benefits of cannabinoid use, including therapeutic effects on cancer, appetite, pain control, seizure disorder and glaucoma (4–7). In contrast, marijuana has significant detrimental effects on cognitive-motor skills, as well as memory and attention performance, among others (8,9). Perhaps because of these adverse affects on health and performance, marijuana use carries a stigma that can affect the lives of users, including candidates for liver transplantation.

Even though marijuana use (both legal and illegal) remains a controversial issue, in general, the issue is much less controversial within the liver transplant professional community. For example, liver transplant centers in UNOS Region 10 have maintained a policy of marijuana abstinence for any ambulatory patient to be considered a liver transplant candidate (10). In addition, patients are required to abstain from alcohol and all other illicit drugs. Patients frequently test positive for marijuana, and other substances, at the time of their initial liver transplant evaluation. These patients and others who are thought to have significant substance abuse issues are offered resources to facilitate abstinence. The transplant evaluation committee determines requirements for listing which usually entail both a period of abstinence (generally 6 months) and completion of an approved substance abuse counseling program. In addition, before any patient is listed for transplant, all ambulatory candidates are required to sign the Region 10 substance abuse policy. To prove their compliance with this policy, patients are subjected to blood and urine toxicology screening until transplantation. If a patient tests positive for a prohibited substance after signing this substance abuse policy, he or she will no longer be considered a candidate for liver transplantation at any center in Region 10.

Substance abuse policies are necessary to help ensure that potential liver transplant recipients will be reliable stewards of the new organ. Despite this, concern exists that substance abuse policies may have an inappropriate and disproportionate impact on marijuana users. Firstly, many in the general public would argue that marijuana users should not have limited access to transplantation, particularly within the context of medical marijuana (6, 11). As an example, in May 2008, significant press coverage was given to the case of Timothy Garon, who reportedly died after having been refused a liver transplant, in part, because

of his use of medical marijuana (12). Secondly, current toxicology screening methods produce a positive toxicology screen for cannabinoids up to two months after the patient's last use (13). In contrast, other toxicology screening tests such as those for cocaine and alcohol become negative shortly after use. As a result, it may be more difficult for chronic marijuana users to demonstrate abstinence prior to life-ending decompensation of their liver disease.

Within this context, our hypothesis is that patients with chronic liver disease who are marijuana users will have inferior survival. We define marijuana user as anyone who had a positive toxicology screen for cannabinoids from the time of liver transplant evaluation. In order to address this hypothesis, we compared the survival of all patients who were marijuana users to marijuana non-users.

Methods

Patients

Data collection and analysis was approved by the University of Michigan Institutional Review Board for this retrospective cohort study. All data was collected from the University of Michigan electronic medical record and from a prospectively collected transplant database. All adult patients with chronic liver disease evaluated for liver transplant at the University of Michigan between January 1, 1999 and June 1, 2007 were included in the study group. Clinical data was collected on all patients, including: demographic data, Model for End-Stage Liver Disease (MELD) score components (INR, creatinine and bilirubin at the time of evaluation, listing and transplantation), and the etiology of liver disease. In addition, dates were collected for: evaluation, listing, transplantation, death and last follow-up.

Patients with insufficient toxicology data were excluded from analysis. 'users' were documented by the presence of a positive toxicology screen between the date of evaluation for liver transplant and either date of transplantation or most recent follow-up. Moreover, the patient was considered a marijuana user only if they had documented cannabinoids on toxicology screen. If the patient reported marijuana use by history, but there toxicology screen was negative, they were not considered a user. The substances of interest included: cannabinoids, narcotics, benzodiazepines, ethanol, amphetamines, cocaine and barbiturates. Active smoking history at the time of transplant evaluation and the presence of any psychiatric hospitalization over the life span of these patients were also noted.

Statistical analysis

The primary exposure variable for this analysis was marijuana user. Differences in demographics, substance use, hepatitis C and MELD scores were compared between the two study groups using standard univariate analysis. Categorical variables were analyzed using chi-square analysis. Continuous variables were assessed with a two-tailed Students *t*-test.

Unadjusted rates the patient survival between marijuana users and marijuana non-users were calculated by the method of Kaplan and Meier. The independent effects of marijuana use the patient survival were assessed using multivariable Cox proportional hazards model. A single model was created to analyze time to event outcomes (mortality) from the time the liver transplant evaluation to death or end of follow-up. Potential covariates for entry into the multivariate model were determined to be clinically relevant and/or to have a significant level on univariate assessment of $p < 0.10$. All tests used were 2-sided and a p-value of less than 0.05 was considered to be statistically significant. SPSS V15.0 (Chicago, IL) was used for data analysis.

Results

A total of 2292 adult patients with chronic liver disease were evaluated for liver transplantation at the University of Michigan between Jaunary 1, 1999 and June 1, 2007. Some patients did not have complete data regarding toxicology, smoking or psychiatric history (n = 803). Upon exclusion of these patients, 1489 patients remained. (Figure 1) Of these, 155 were marijuana users and 1334 were marijuana non-users. With respect to listing for transplant, 43 (27%) of marijuana users were listed compared to the 593 (44%) of non-users. The 43 marijuana users who were listed for transplant had fulfilled the substance abuse specific requirements of the liver transplant evaluation committee. Of those listed, a significantly larger proportion of marijuana non-users were transplanted compared to marijuana users (21.8% vs. 14.8%, p = 0.048). In addition, of the 155 marijuana users, 145 tested positive prior to signing the substance abuse policy, 43 of these

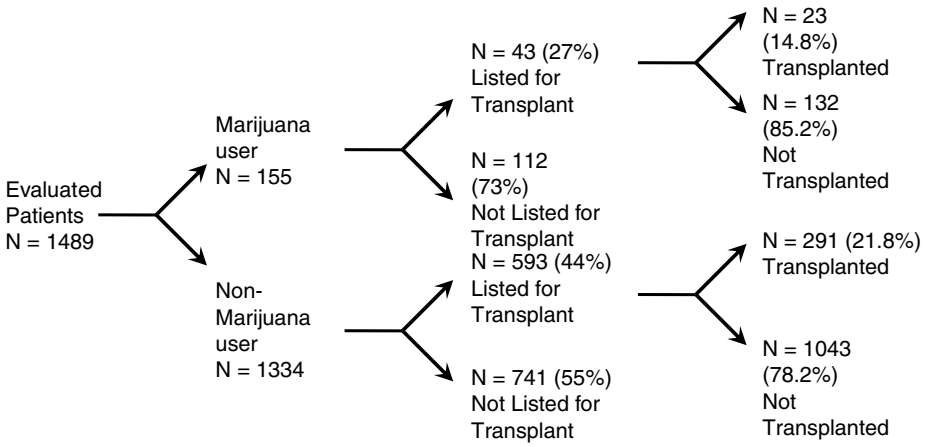

Figure 1: Flow chart detailing the listing and transplant status of 1489 patients with chronic liver disease evaluated for a liver transplant at the University of Michigan, stratified by whether or not the were marijuana users. Marijuana user is defined as any patient with a positive urine toxicology screen for cannabinoids between the date of evaluation for liver transplant and either date of transplantation or most recent follow-up.

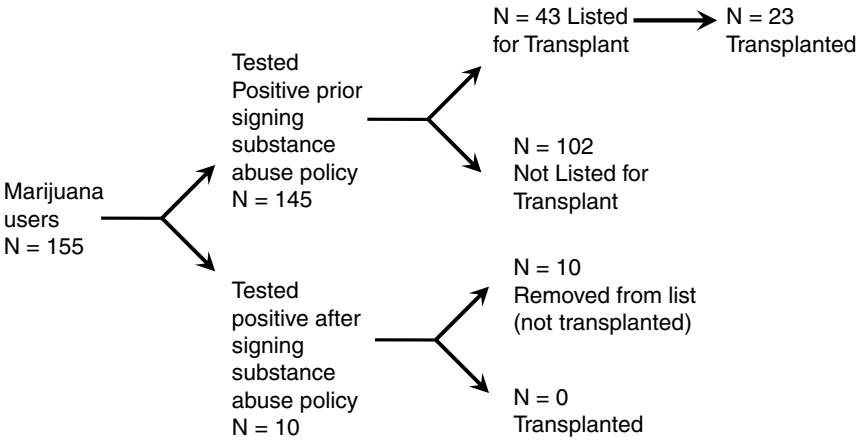

Figure 2: Flow chart detailing the listing and liver transplant status of 155 patients who were marijuana users. Marijuana user is defined as any patient with a positive urine toxicology screen for cannabinoids between the date of evaluation for liver transplant and either date of transplantation or most recent follow-up.

patients were listed and 23 received a transplant (Figure 2). There were 10 patients who tested positive after signing the substance abuse policy and they were removed from the transplant list and did not receive a transplant.

Comparing patient characteristics between marijuana users and non-users (Table 1), revealed that marijuana users were younger (48.3 ± 9.2 vs. 52.1 ± 9.4, p = 0.001) and more likely to be male (78.1% vs. 63.0%, p = 0.001). A significantly higher proportion of the marijuana users had a diagnosis of hepatitis C (63.9% vs. 40.6%, p = 0.001). Interestingly, the marijuana users had lower MELD scores at evaluation than non-users (10.7 ± 5.1 vs. 12.4 ± 6.9, p = 0.004). Racial and psychiatric backgrounds were relatively similar between the two study cohorts.

Between our two groups, the marijuana users and non-users, we compared the presence of other substances noted on toxicology screen. The marijuana users were more likely to have narcotics, benzodiazepines and other substances including barbiturates, amphetamines and cocaine in their system. Marijuana users were not significantly more likely to have a positive serum alcohol level (3.9% vs. 2.2%, p = 0.164). Marijuana users were significantly more likely to be active smokers on the day of the liver transplant evaluation (57.1% vs. 35.6%, p = 0.001).

The unadjusted survival rates from the time of liver transplant evaluation were similar between the two study cohorts (marijuana users and marijuana non-users) (Figure 3). Importantly, patients were censored at death and end of follow-up, but not at transplantation.

We then assessed the independent effects on marijuana detection among patients with chronic liver disease evaluated for a liver transplant. As is demonstrated in Figure 3, marijuana uses did not have a significantly higher hazard of mortality (HR 1.09, 95% CI 0.78–1.54) (Figure 4). Covariates independently associated with hazard of mortality were age at evaluation (HR 1.03, 95%CI 1.02–1.04), meld at evaluation (1.01, 95% CI 1.09–1.12), positive hepatitis C (HR 1.75, 95% CI 1.41–2.17) and transplantation (HR 0.75, 95% CI 0.65–0.86).

Discussion

In the study, we assessed the independent effects of marijuana detection on the survival of patients with chronic

Table 1: Clinical characteristics of patients evaluated for a liver transplant stratified by whether they have a positive toxicology screen for marijuana

	Positive marijuana (n = 155)	Negative marijuana (n = 1334)	p-Value
Age at liver evaluation	48.3 ± 9.2	52. 1 ± 9.4	0.001
Sex (% male)	78.1%	63.0%	0.001
Race (% non-black)	81.3%	82.5%	0.696
Positive hepatitis C status	63.9%	40.6%	0.001
MELD at evaluation	10.7 ± 5.1	12.4 ± 6.9	0.004
Positive transplant status	14.8%	21.8%	0.048
Positive psychiatric hospitalization	3.2%	2.6%	0.600
Positive smoker	57.1%	35.6%	0.001
Positive ethanol	3.9%	2.2%	0.164
Positive narcotics	31.0%	19.9%	0.002
Positive benzodiazepines	21.9%	10.0%	0.001
Positive other substances	7.7%	2.6%	0.002

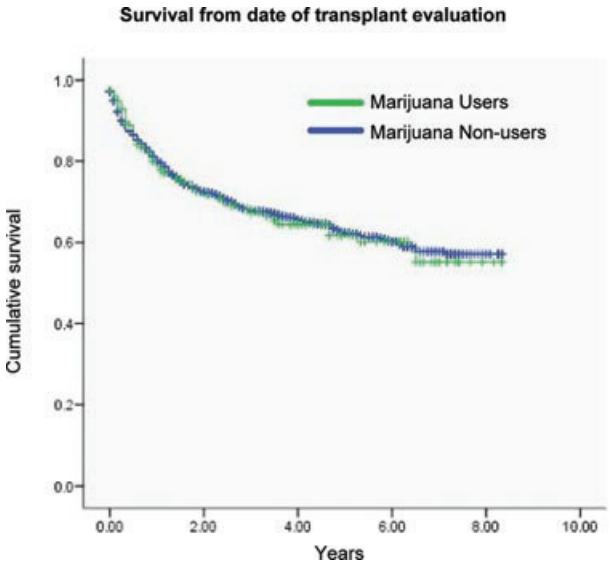

Figure 3: Kaplan–Meier survival curve of 1489 patients with chronic liver disease, evaluated for a liver transplant at the University of Michigan. When marijuana users were compared to marijuana non-users, no significant differences in unadjusted patient survival were noted. Patients were censored at death or end of follow-up, but not at transplant.

liver disease who were evaluated for liver transplantation. We found that patients who tested positive for marijuana had similar survival rates compared to patients that did not test positive. Our group became interested in this topic because of concern that are current substance abuse policies may have a significant and disproportionate impact on marijuana users. Interestingly, our results did not support our hypothesis that marijuana users would have inferior survival.

No previous studies have specifically looked at substance abuse within the context of overall survival (pre- and post-transplant) among patients with chronic liver disease. In fact, little data exists about the implications of substance abuse on transplant outcomes, in general. There are data documenting the deleterious effects of continued use of alcohol on the long-term survival of liver-transplant recipients (14). In contrast, evidence regarding other substances is less compelling. One small study demonstrated similar outcomes for patients who did and did not relapse to poly-substance abuse following transplantation (15). One substance that more clearly seems to be associated with inferior outcomes among transplantation patients is cigarette smoking (16–20). Despite these data, cigarette smoking is not contraindicated by our and presumably other, liver transplant substance abuse policies.

The clinical implications of marijuana use are diverse, and potentially both harmful and beneficial. The health risks of marijuana use are well documented: including dose-dependent respiratory symptoms such as shortness of breath, coughing and increased sputum production (21–24). Long-term marijuana abuse is associated with cognitive deficits, as well as with cerebrovascular disorders such as stroke (25). Isolated incidents of severe *Aspergillosis fumigatus* infection from contaminated marijuana have occurred in transplant recipients (26–28). Interestingly, endocannabinoids, endogenous cannabinoids that bind to the same CB_1 and CB_2 receptors as tetrahydrocannabinol (THC), the active component in marijuana, are highly upregulated in chronic liver disease and may contribute to the pathogenesis of various liver diseases (29,30). This finding suggests that cannabinoids could exacerbate liver disease (29). In contrast to the potential deleterious effects of marijuana, it may provide some therapeutic effects for patients with liver disease. Marijuana use has been shown to positively affect various neurological and psychological phenomena such as mood, appetite, analgesia and nausea control (29,31–33). In addition, cannabinoids have been shown to possess immunomodulatory and antiinflammatory properties in peripheral tissues via CB_2 receptor activation, potentially reducing the risk of rejection (31,34).

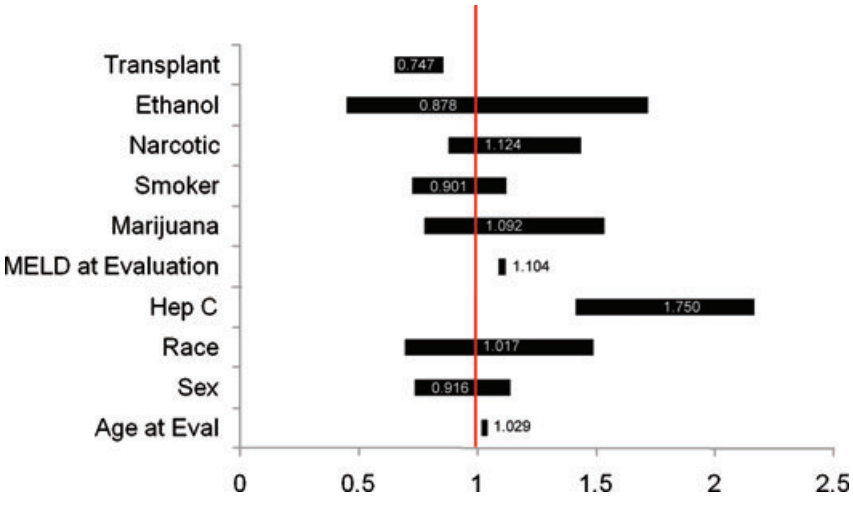

Figure 4: Results of a multivariable Cox proportional hazards model created to analyze time to event outcomes (mortality) from the time the liver transplant evaluation to death or end of follow-up. Marijuana use was not significantly associated with differences in the hazard of mortality.

Though this study is the first to provide a comprehensive assessment of marijuana use among patients with chronic liver disease, it has several important limitations. First, since the data his retrospective in nature, attributing a cause and effect relationship between marijuana use and mortality is not possible. Secondly, this single center study reports upon a relatively small sample size of patients. As a result of the small sample size, we were unable to address the important issue of the implications of posttransplant marijuana use. Thirdly, considering the complexity of the patients studied and how little work has been done describing the relationship between substance abuse and outcomes in liver disease, there are likely confounding factors not considered by our multivariable model. Importantly, toxicology screening data was absent for a significant number of patients. The vast majority of these patients did not undergo a full pretransplantation clinical evaluation, presumably because they were not thought to be transplant candidates. We do not know if these patients were not candidates because there were two well or to sick. In addition, our definition of marijuana use as a positive toxicology screen on or after the date of evaluation does not capture certain details of patients' marijuana habits, particularly frequency and duration. Subsequently, marijuana use was managed as a simple covariate in our survival model, rather than a time-dependent covariate. Other covariates (Age, MELD score, hepatitis C diagnosis, etc.) have previously been shown to affect survival among cirrhotics (35,36). These covariates, in part, controlled for the severity of illness, but did not account for the dynamics of illness severity. Despite these important limitations, our work does represent a timely and comprehensive assessment of a poorly studied the area in liver transplantation.

Overall, the survival of marijuana users, as defined by this manuscript, with chronic liver disease who present for transplant evaluation is not significantly different from marijuana non-users. From these findings, we are able to conclude that marijuana users are not systematically exposed to excess risk of mortality because of the current substance abuse policies used by our center or other centers in UNOS region 10. This is likely in part due to the hard work of our dedicated transplant team members, who educate and rehabilitate the substance abusers who are evaluated by our liver transplant program. Continued study of liver transplant substance abuse policies is necessary to assure that these policies consider the beliefs of patients, transplant professionals, donor families and the public, in general.

Acknowledgments

Dr. Englesbe is supported by a grant from the American Surgical Association Foundation.

References

1. U.S. Department of Health and Human Services Office of Applied Studies. State estimate of substance use. http://www.oas.samhsa.gov/nhsda/2kState/vol1/ch2.htm. Accessed July 23, 2008.
2. Center for Disease Control and Prevention. Trends in the prevalence of marijuana, cocaine, and other illegal drug use national YRBS: 1991–2007. Youth Risk Behavior Survey; 2007.
3. Office of National Drug Control Policy. White house drug policy information clearinghouse fact sheet—drug data summary. www.whitehousedrugpolicy.gov. Accessed July 2008.
4. Doblin RE, Kleiman MA. Marijuana as antiemetic medicine: A survey of oncologists' experiences and attitudes. J Clin Oncol 1991; 9: 1314–1319.
5. Consroe PF, Wood GC, Buchsbaum H. Anticonvulsant nature of marihuana smoking. JAMA 1975; 234: 306–307.
6. Lerner M, Lyvers M. Values and beliefs of psychedelic drug users: A cross-cultural study. J Psychoactive Drugs 2006; 38: 143–147.
7. Frytak S, Moertel CG. Management of nausea and vomiting in the cancer patient. JAMA 1981; 245: 393–396.
8. Weinstein A, Brickner O, Lerman H et al. A study investigating the acute dose—response effects of 13 mg and 17 mg {Delta} 9-tetrahydrocannabinol on cognitive—motor skills, subjective and autonomic measures in regular users of marijuana. J Psychopharmacol 2008; 22: 441–451.
9. Indlekofer F, Piechatzek M, Daamen M et al. Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol. J Psychopharmacol 2008 (in press).
10. University of Michigan Transplant Program. Policy on Substance Abuse and Transplantation. Ann Arbor, MI; 2008.
11. Doblin R, Kleiman MA. Survey research vs. clinical trials in evaluating the medical utility of marijuana. South Med J 1998; 91: 989–991.
12. Medical marijuana and organ transplants don't mix, L. A. Times, May 19, 2008.
13. Bear DM, Paulson RA, Williams RH. Cut-off and toxicity levels for drugs-of-abuse testing. Med Lab Obs 2004; 36: 10–11.
14. Pfitzmann R, Schwenzer J, Rayes N, Seehofer D, Neuhaus R, Nussler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. Liver Transpl 2007; 13: 197–205.
15. Nickels M, Jain A, Sharma R et al. Polysubstance abuse in liver transplant patients and its impact on survival outcome. Exp Clin Transplant 2007; 5: 680–685.
16. Tome S, Said A, Lucey MR. Addictive behavior after solid organ transplantation: What do we know already and what do we need to know? Liver Transpl 2008; 14: 127–129.
17. McConathy K, Turner V, Johnston T et al. Analysis of smoking in patients referred for liver transplantation and its adverse impact of short-term outcomes. J Ky Med Assoc 2007; 105: 261–266.
18. Jimenez C, Manrique A, Marques E et al. Incidence and risk factors for the development of lung tumors after liver transplantation. Transpl Int 2007; 20: 57–63.
19. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. Crit Rev Oncol Hematol 2005; 56: 87–99.
20. Munoz SJ. Tobacco use by liver transplant recipients: Grappling with a smoking gun. Liver Transpl 2005; 11: 606–609.

21. Tanimowo MO, Onaolapo YA. The pattern of tobacco use among non-pulmonary tuberculosis patients attending a chest clinic in south-western Nigeria. Niger J Clin Pract 2007; 10: 314–318.
22. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA. Effects of marijuana smoking on pulmonary function and respiratory complications: A systematic review. Arch Intern Med 2007; 167: 221–228.
23. Patkar AA, Batra V, Mannelli P, Evers-Casey S, Vergare MJ, Leone FT. Medical symptoms associated with tobacco smoking with and without marijuana abuse among crack cocaine-dependent patients. Am J Addict 2005; 14: 43–53.
24. Kalant H. Adverse effects of cannabis on health: An update of the literature since 1996. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 849–863.
25. Jayanthi S, Buie S, Moore S et al. Heavy marijuana users show increased serum apolipoprotein C-III levels: Evidence from proteomic analyses. Mol Psychiatry 2008 (in press).
26. Hamadeh R, Ardehali A, Locksley RM, York MK. Fatal aspergillosis associated with smoking contaminated marijuana, in a marrow transplant recipient. Chest 1988; 94: 432–433.
27. Weinrieb RM, Lucey MR. Treatment of addictive behaviors in liver transplant patients. Liver Transpl 2007; 13(11 Suppl 2): S79–S82.
28. Marks WH, Florence L, Lieberman J et al. Successfully treated invasive pulmonary aspergillosis associated with smoking marijuana in a renal transplant recipient. Transplantation 1996; 61: 1771–1774.
29. Caraceni P, Domenicali M, Bernardi M. The endocannabinoid system and liver diseases. J Neuroendocrinol 2008; 20(Suppl 1): 47–52.
30. Pacher P, Gao B. Endocannabinoids and liver disease. III. Endocannabinoid effects on immune cells: Implications for inflammatory liver diseases. Am J Physiol Gastrointest Liver Physiol 2008; 294: G850–G854.
31. Gabbay E, Avraham Y, Ilan Y, Israeli E, Berry EM. Endocannabinoids and liver disease—review. Liver Int 2005; 25: 921–926.
32. Kirkham T. Endocannabinoids and the neurochemistry of gluttony. J Neuroendocrinol 2008 (in press).
33. Larson AM, Curtis JR. Integrating palliative care for liver transplant candidates: "too well for transplant, too sick for life". JAMA 2006; 295: 2168–2176.
34. Kaminski NE, Koh WS, Yang KH, Lee M, Kessler FK. Suppression of the humoral immune response by cannabinoids is partially mediated through inhibition of adenylate cyclase by a pertussis toxin-sensitive G-protein coupled mechanism. Biochem Pharmacol 1994; 48: 1899–1908.
35. Statistical Model for one year patient survival following liver transplation in the United States. 2007. Available at www.ustransplant.org.
36. Statistical model for liver transplant wait-list mortality. 2007. Available at www.ustransplant.org.