Editorial

The use of marijuana by liver transplant candidates and recipients: is the smoke starting to clear?

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Introduction

Has the time come to reconsider the significance of marijuana use by candidates for or recipients of liver transplantation? This question is relevant and timely in light of the recent widespread legalization of "medical marijuana" by 39 states and Washington, DC in the United States and of "recreational marijuana" by 10 states and Washington, DC (1). In this review, we will consider the current state of the data in general, and focus particularly on the study of Wu *et al.* entitled *Clinical Impact of Marijuana Usage in Liver Transplant* published in the December 2020 edition of *Digestive Medicine Research*. We will start by addressing some general questions that bedevil considerations of the use of marijuana in society.

Is marijuana a safe substance for regular use?

In July 2020, the National Institute of Drug Abuse (NIDA) of the U.S. National Institutes of Health (NIH) published the Marijuana Research Report. This comprehensive review provides a thorough and balanced summary of the current science concerning marijuana use (2). In it, Nora Volkow, MD, NIDA's Director, asserts (I) that marijuana impairs short-term memory and judgment, (II) distorts perceptions, (III) impairs performance at school and work and (IV) can make it unsafe to operate a vehicle.

Is marijuana addictive?

In the Marijuana Research Report referred to above, Dr. Volkow concludes that despite popular beliefs, marijuana can be addictive. Additionally, the study noted epidemiological data indicates that up to 30% of current marijuana users will suffer from some form of a Cannabis Use Disorder, including addiction and dependence.

Is marijuana therapeutic?

Dr. Volkow acknowledges that science has not yet resolved whether the putative therapeutic benefits of marijuana outweigh its health risks. It is worth noting that "medical marijuana" has not been approved by the U.S. Food and Drug Administration, despite various marijuana products having been legalized by participating states for a host of indications, some as disparate as amyotrophic lateral sclerosis and autism. Answers to the question of efficacy are confounded by the different and largely uncontrolled formulations and potencies of marijuana products available to the public. Once a prescriber signs off on an approved indication, patients may buy a medical marijuana card and purchase marijuana in a variety of forms from dispensaries such as edibles, flower, oils, or baked goods. The concentration of THC is quite potent in some of these formulations (>15%), raising the risk of side effects and

can even increase pain (3), however, pain is the foremost reason most people go to dispensaries (4). The Marijuana Research Report cites data showing that in the 1990s, the potency of THC, the psychoactive ingredient in marijuana, was approximately 4%, whereas the current "medical and recreational marijuana" products contain at least 15% THC.

What about dronabinol and cannabidiol (CBD)?

Physicians working with liver transplant patients may be familiar with the use of dronabinol, a longstanding legally prescribed synthetic form of THC used to treat nausea, anorexia and intractable pruritis from cholestasis (5). However, unlike "medical or recreational marijuana", dronabinol is FDA approved for use in other populations. Furthermore, dronabinol is prescribed as a capsule or solution with standardized dosing, but without the presence of any of the over 400 chemical constituents found in the products being sold to the general public as "medical" and "recreational" marijuana.

In their paper, Wu *et al.* explain that CBD is a non-psychoactive component of "medical and recreational marijuana" products typically included with THC. There is some evidence that CBD can mitigate some side effects of THC such as psychosis, anxiety, and memory impairment (6,7), but as noted in Wu *et al.*, CBD (at least in theory) might be detrimental to transplant patients through inhibition of the metabolism of tacrolimus resulting in elevated tacrolimus blood levels, thereby increasing the risk of nephrotoxicity and neurotoxicity (8,9).

Wu *et al.*: study design and findings

Wu *et al.* report a retrospective descriptive study of 22 adult liver transplant recipients in whom urine toxicology screens were positive for marijuana. The subjects were transplanted during a 34-year period, with alcohol-related cirrhosis or chronic HCV infection the most frequent underlying disorders. The majority had received toxicology screens if there was a work up of elevated transaminases, non-specific gastrointestinal symptoms or mental health complaints. The most common reasons given by the subjects to account for marijuana use were depression, chronic pain, nausea, and appetite enhancement. Despite positive toxicology screens, three patients denied using marijuana. A total of 9 patients (40.9%) also used concomitant alcohol or drugs; 5/22 (22.7%) used alcohol, 5/22 (22.7%) used opioids, 4/22 (18.2%) used tobacco, 2/22 (9.1%) vaped, 2/22 (9.1%) used amphetamines and 1/22 (4.5%) used cocaine and 1/22 (4.5%) used benzodiazepines. There were 14 patients (63.6%) with elevated liver chemistries which was often linked to non-adherence to immunosuppressants. One patient presented with post-transplant alcohol-related hepatitis. Interestingly, in the patients with elevated liver chemistries, there were no statistically significant differences in how many patients smoked THC as opposed to ingesting it in other ways compared to the 36% who did not have elevated liver enzymes. None of the 14 patients who used CBD products had elevated liver chemistries *vs.* 1 CBD user out of 8 in the group that did not have elevated liver enzymes. There were also no significant differences in concomitant drug use and elevated liver enzymes.

Key caveats and limitations

The authors rightly state that due to the small number of subjects from only one transplant center, their study must be considered descriptive. However, the most important limitation, which was not mentioned, is that they did not use a control group, which ideally should be matched with study patients on variables such as demographics, the etiology of each patient's liver disease, a shared time frame for when they were transplanted, and importantly, the quantity and frequency of marijuana use. In the absence of a control group, while tempting, it cannot be assumed that the presence of one marijuana positive toxicology screen is associated with non-adherence with immunosuppressants, for example. There are many other reasons for non-adherence that were not controlled for such as loss of income affecting patients' ability to afford immunosuppressants or the presence of severe psychiatric illness such as a major depressive episode that could interfere with a patient's ability to care for themselves or memory loss due to a prior traumatic brain injury.

The absence of data describing the quantity and frequency of marijuana use is also an important omission of this study's design. Because of the small sample size, it would not take many patients to bias their study if they used small amounts of marijuana only a few times a year, therefore it is not reasonable to conclude that marijuana was the only variable leading to abnormal liver chemistries or non-adherence.

Comparison with recently published papers

It is notable that Wu's study cohort comprised only 22

patients, accrued over 34 years. This suggests under-recognition of the prevalence of marijuana use. By comparison, the largest study of marijuana and CBD use in liver transplant recipients to date was recently published by Yan *et al.* (10). The authors sent an anonymous survey to 1,714 liver transplant recipients in their center and received 538 responses (44.8%). Of that group, 124 patients (23.0%) reported current marijuana use, of whom 46.8% reported daily use over an average of 20.6 years. Among current marijuana users, 51.6% reported concurrent CBD use, of whom 23.4% used CBD daily. The authors set out to describe the prevalence, habits and predictors of marijuana use in their center, however, their study did not report on post-transplant health related complications associated with regular marijuana use.

Marijuana and adverse health effects in liver transplant patients

In an editorial by Neuberger (11), a brief review of 3 other studies (12-14) was provided on the health effects of marijuana use in liver transplant patients and Neuberger concluded that although these studies consisted of a small number of highly selected patients, they showed "neither current nor past marijuana use was associated with adverse outcomes".

A more recent paper by Guorgui *et al.* (15) provided data from their retrospective study of 184 pre-transplant marijuana users, 42 of whom were recent users (less than 6 months since transplant) and 142 were former chronic users (more than 6 months from liver transplant). The median follow-up was 30.3 months. The authors reported that compared to non-users, recent users were sicker at the time of transplant with higher MELD scores and were more likely to require an ICU stay, but overall, there were no significant differences in rates of post-operative complications or 1-year survival among non-users, former users, and recent users.

Clinical implications and next steps in research

As stated in a commentary by Naugler and Orloff called "*Ganja, no barrier for transplantation?*" (16), attitudes toward accepting people for transplant with addictive substance use are in evolution, especially for marijuana use. They explain how more permissive attitudes toward liver transplantation in marijuana users in the U.S. mirrors the more recent softening of the "6-month rule" of alcohol abstinence in that neither is well-supported by the evidence and requiring a 6-month or more period of abstinence for alcohol or marijuana can prove fatal to patients. In their paper, the authors provide a useful detailed algorithm they developed in their program that is meant to guide a strategy and acceptance criteria for patients with substance use disorders. The goal of the algorithm is to ascertain the existence and severity of substance use disorders that could affect good outcomes, and unless deemed inappropriate for transplant for other reasons, to recommend treatment and ongoing monitoring for patients with substance use disorders. Their approach is flexible and encourages performing transplant evaluations on an individual basis instead of adhering to a blanket inclusion/exclusion policy to determine candidacy. However, their algorithm exempts patients from further monitoring if they do not have a substance abuse problem, are deemed appropriate for listing and use "recreational or medical marijuana". This may be too lenient because marijuana use is not a static process, and patient's lives can change and affect the severity of their substance use. The absence of ongoing monitoring does a disservice to patients who might lose control of their substance use and cannot or will not ask for help.

Encouraging future research has been suggested by every paper reviewed in this piece, and this editorial is no exception. Critical to good science is good research methodology. What is needed is a prospective randomized, controlled design using a consistent marijuana product. Clearly thought out end-points, plausible estimates of the effect of the marijuana product on those end-points, a conservative estimate of power, concomitant objective ongoing substance monitoring for both the treated and control subjects while maintaining the study data confidential from the transplant team are crucial design aspects. A retrospective study with an adequate number of research subjects would be easier to accomplish and would be informative provided the subjects are randomly selected and matched on relevant variables.

A word about treatment

If a patient has an active marijuana use disorder, there is a good chance they also suffer from another psychiatric or substance use disorder. Effective treatments exist and should be recommended. Although there are no FDA approved medications for marijuana use disorder, gabapentin, Buspar and Ambien can be helpful, and studies are ongoing for N-acetylcysteine and allosteric modulators

that interact with endogenous cannabinoid receptors to inhibit the rewarding effects of THC. Psychotherapies such as cognitive behavioral therapy, contingency management and motivational enhancement therapy have all been shown to be helpful and are more thoroughly explained in the July 2020 Marijuana Research Report (2). A useful list of resources is also provided for physicians (NIDAMED: drugabuse.gov/nidamed) and patients.

Conclusions

In conclusion, a significant proportion of liver transplant patients have a psychiatric and/or substance use disorder. This places them at risk for developing a cannabis use disorder given the widespread availability of potent, legal "medical and recreational cannabis". Risks of regular cannabis use include, but are not limited to marijuana addiction or dependence, worsening depression or anxiety, psychosis, impaired cognition, and the Cannabis Emesis Syndrome. The bulk of available data on the health effects of marijuana in liver transplant recipients is derived from underpowered studies using insufficiently rigorous methodology, yet the available data suggests that mortality is not affected, and the risks of medical morbidity are not large. Although effective treatments for Cannabis Use Disorders and co-morbid Psychiatric illness exist, they are very difficult to obtain for most of our patients, and regular use of marijuana is clearly not without risk in this vulnerable group of patients. Furthermore, the admittedly uncontrolled suggestion in Wu's study that regular marijuana users might jeopardize their allografts through non-adherence to immunosuppression warrants urgent evaluation. Until better data is available, to err on the side of caution and keep the door open to transplant patients using "medical and recreational" marijuana seems like the most humanistic and ethical response. We can counsel our patients to procure marijuana and CBD only from approved dispensaries rather than friends or the local convenience store because the former has some degree of quality control and if something goes awry, the source of the marijuana is traceable. Furthermore, we should advise patients to use the lowest potency of THC and CBD available, provide ongoing monitoring of the effects of the marijuana on their condition (a requirement for prescribers of "medical marijuana" in some states), and teach patients and their families what red flags to look for that would necessitate seeking medical attention as soon as possible. Finally, if we accept and transplant liver patients who use marijuana than we should be obligated to provide adequate resources for drug counseling and education if needed.

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