Humans have used cannabis for centuries and the systematic study of its health impact has only recently begun in earnest. The endocannabinoid system is an ancient chemical signaling system affecting emotion, sensory function and behavior. Understanding how exogenous cannabinoids affect this system has been limited by decades of regulatory prohibitions in the United States. Despite its federal status as a Schedule I drug, cannabis was first approved for medicinal use in California in 1996; and now all but 7 states allow some form of medicinal cannabinoid use. A naturalistic experiment is occurring in states like Colorado and Washington where recreational cannabis has been available for years. Along with California, Illinois, Michigan and New York, almost half of the United States population now lives in a state where cannabis is legal for recreational use without a prescription. Nevertheless, we have comparatively little evidence for cannabis’ direct effects on liver disease patient outcomes before and after liver
transplantation (LT) despite cannabinoids’ broad implications in the field of organ transplantation.¹

Data on cannabis use in LT is difficult to recover for various reasons. Cannabinoid products are often inconsistent in their dose and content² which, along with myriad strains, preparations, and routes of administration, obscures effects, benefits, and harms. Plant-form cannabis contains numerous cannabinoids, not just tetrahydrocannabinol (THC) and cannabidiol (CBD), whose precise effects in liver disease and LT are unclear. The focus on THC effects on brain and behavior often overshadows efforts to study CBD which has different psychotropic properties. Cannabis’ Schedule I status makes it difficult to fund drug trials. With regard to liver disease and LT, transplant centers may not be gathering and publishing routine, prospective, and standardized cannabinoid data and may lack the initiative or incentive to do so. Patients likely under-report use due to bias, stigma, and concerns about transplant access. Overall, we simply do not know enough about how many of LT recipients use cannabinoids, for what purpose, and any effects of their quality of life. Along with a general cannabis use rate in Colorado that is approximately double the national average, this was the backdrop to Yan’s and Forman’s efforts to more thoroughly address cannabinoids in LT.³

The authors hypothesized that a LT patient sample from Colorado (72% of their sample originates from the state), would have prevalent cannabinoid use which they sought to characterize using anonymous surveys separately querying THC and CBD use. Their sample is the largest to date (n=538, 44% response rate) with regards to granular cannabinoid use in LT and the first to characterize CBD product use alongside cannabis. There are several findings that are not only empirically informative on their own but also invite further discussion and investigation on a variety of topics related to cannabinoid use in LT.

Cannabinoids use is likely relatively frequent and may be impacting thousands of new and existing LT recipients yearly in ways we do not yet understand and are not prepared to address. Yan and Forman found that almost 24% of their survey respondents reported current cannabis
use and an additional 25% reported former use. Current and former CBD use was less common (21%, 6%). We do not know how much cannabis use in LT recipients (current users reported a 20-year average length of use and 47% use daily) meets substance use disorder (SUD) criteria with the inherent implications for health outcomes, treatment need, and access to re-transplant. We do not know how cannabis’ myriad potential medical and psychiatric benefits and adverse effects might indirectly affect key transplant outcomes and quality of life. There are no commensurate consensus guidelines for the assessment of cannabinoid use and transplant-related decision-making is heterogenous among centers. There are also no proposed or accepted cannabinoid-related research outcomes or clinical procedures comparable to those emerging for other substance-using LT populations. But given likely frequent and increasing usage, cannabinoids simply must be more thoroughly addressed by our field.

More studies are needed about how cannabinoids intersect with the psychosocial complexity regularly encountered in LT. Extant reports suggest that while cannabis may not associate with “hard” outcomes like pre-LT delisting or mortality or post-LT survival, there is substantial psychosocial complexity associated with cannabinoid use given published links with patterns of other substance use and diagnoses of hepatitis C (HCV) and alcohol-related liver disease (ALD), both diagnostic subpopulations heavily impacted by potent psychosocial variables. Should patients with a history of disorders of mood, anxiety, alcohol, or opioids be using cannabis before or after LT? Yan and Forman found elevated OR for HCV and ALD (1.8 for both) in multivariable analysis predicting cannabis use (but not for CBD products). They also found that current and former tobacco use was a strong predictor of cannabis and CBD use, respectively. There are “softer” substance-related outcomes proposed elsewhere in LT, which may also be important to consider in the future study of cannabinoids’ effects in LT and how policies should be developed and ethically applied.

While perceptions of physical health were comparable among study populations, there were significant mental health (MH) differences among groups. 28% of current users reported
“excellent” MH which was lower than never and former users (48%, 37%). “Good” MH was higher (58%) in current users than never and former users (44%, 48%). Does this mean that cannabinoids are adversely affecting LT recipients? As anxiety (55%), pain (53%), nausea (25%), and insomnia (22%) were among the top reasons for current use, are cannabinoids instead helping a population already burdened with MH challenges? The top reason reported for current cannabinoid use was recreational (57%) which will require teams to decide whether, as a health behavior relevant to LT, it should be tracked (i.e. toxicology, clinical interviews) alongside weight, exercise, medication adherence, alcohol use, and diet. More prospective and standardized assessment of LT recipient functional status, MH, cognition, and social interactions may illuminate reasons for new or resumed cannabinoid use and any derived benefits (i.e. pain relief, anxiolysis) and harms (i.e. hyperemesis, impaired memory).

A majority of current users are using the traditional plant form of cannabis (75%) by smoking it (73%), a highly variable delivery method in terms of drug dose received, while 55% ingest it and 32% vaporize it. The variability in product content and patient usage coupled with known drug interactions mean that all LT clinicians must remain pharmacologically interested in patient cannabinoid use regardless of a LT team’s cannabinoid policies or attitudes. As laws and regulations continue to evolve, there may be more eventual standardization in content and dose which could reduce uncertainty and clinical concern.

Clinical and policy decisions among LT clinicians, teams, centers, and across the field will undoubtedly be subject to a wide range of opinions and strong emotions which are common in cannabinoid-related discussions throughout society. Additional data, like those found in Yan and Forman, are essential stabilizing anchors to guide ongoing efforts to assess cannabinoids and make LT-related clinical decisions. We can count on the persistence and importance of the cannabinoid issue within LT and that the Colorado experience will likely quickly translate to the rest of the country. We should be prepared.

REFERENCES


4. The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research, an expert, ad hoc committee of the National Academies of Sciences, Engineering, and Medicine, 2017


