Marijuana and Cannabinoids in ESRD and Earlier Stages of CKD

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Marijuana is the most commonly used recreational drug in the United States, and legal recreational and medicinal use has gained public acceptance during the last decade. Twenty-nine US states have established medical marijuana programs, 8 of which have also legalized recreational marijuana, and Canada is expected to legalize recreational marijuana in 2018. Advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) are chronic conditions with significant associated morbidity and mortality. Patients experience substantial symptom burden that is frequently undertreated due to adverse medication side effects. This article reviews the available evidence for the use of medical marijuana to manage chronic pain, nausea/vomiting, anorexia/cachexia, and pruritus, all of which are frequently reported by patients with advanced CKD or ESRD. Potential adverse health effects of medical and recreational marijuana use are also discussed. Regardless of personal, social, and political beliefs, marijuana use is becoming mainstream, and nephrologists should be aware of the potential impact on our patient population. Further research is warranted to investigate the renal endocannabinoid system, the impact of marijuana use on kidney disease outcomes, and the risks and benefits of medical marijuana use on symptoms of advanced CKD and ESRD.

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Introduction

Marijuana is the most commonly used recreational drug in the United States, and legal recreational and medicinal use of marijuana has increased during the last decade. As of June 2017, twenty-nine US states and the District of Columbia have medical marijuana programs. Eight states and the District of Columbia also allow for recreational use (Fig 1),[1] although marijuana remains illegal under federal law. Legal marijuana sales in the United States are projected to grow to more than $20 billion by 2020. Canada also has a well-established medical marijuana program and is expected to legalize recreational use in 2018. With increasing use and availability of marijuana, it is important to understand the impact of marijuana use on the risk for chronic kidney disease (CKD) and the potential role of medical marijuana in the management of symptoms related to CKD and end-stage renal disease (ESRD).

Marijuana is the dried flower bud from the *Cannabis sativa* and *Cannabis indica* plants and naturally contains numerous phytocannabinoids. The most abundant phytocannabinoids are Δ^9-tetrahydrocannabinol (THC) and cannabidiol, with differing activities and affinities for the G-protein–coupled cannabinoid receptors CB1 and CB2. Plant breeding has created genetically unique *Cannabis* strains with varying concentrations of different phytocannabinoids, enhancing certain desired effects. For example, because THC mediates the psychotropic effects of marijuana, strains with a higher THC concentration are selectively produced for recreational use. The endogenous cannabinoids, or endocannabinoids, anandamide and 2-arachidonoylglycerol are eicosanoids derived from cell membrane phospholipids and are the natural ligands for the cannabinoid receptors. Further detail about cannabinoid receptors and the endocannabinoid system is available in recent reviews.[2,3]

Marijuana can be smoked, vaporized, or consumed as a capsule or in food. Inhalation provides an onset of action within minutes and allows for real-time dose titration. Peak effects are seen within 15 to 30 minutes, and half-life is 1 to 2 hours. After oral consumption, the onset of action may be delayed up to 1 to 2 hours, with peak effects at 2 to 3 hours and half-life of 3 to 6 hours. Urinary excretion accounts for 20% of metabolite elimination.

Cannabinoid-based pharmaceuticals are also available or in development to treat a variety of conditions. Dronabinol (Marinol and Syndros), a synthetic form of THC, and nabilone (Cesamet) are US Food and Drug Administration (FDA)-approved to treat AIDS cachexia and chemotherapy-induced nausea/vomiting. Nabiximols (Sativex) is approved outside the United States for the treatment of multiple sclerosis–related spasticity. In addition to pharmaceutical cannabinoids, more than 170 synthetic cannabinoids have been developed for use in laboratory research, some of which have been adopted as drugs of abuse.

Potential Impact of Marijuana and Cannabinoid Use on the Kidney

It is unknown whether and to what extent marijuana use might affect kidney disease. Both CB1 and CB2 are expressed throughout the body, including in podocytes, mesangial cells, and tubular epithelial cells.[4] In animal models, overactivation of CB1 in podocytes promotes diabetic nephropathy,[5] whereas blocking CB1 decreases albuminuria[6] and renal fibrosis.[7] Activation of CB2, which in general has opposing effects, has been shown to reduce albuminuria and podocyte loss,[8] whereas knockout of CB2 worsens kidney function in a mouse model of diabetic nephropathy.[9] Cannabinoids also have diuretic properties. THC activation of CB1 has been reported to increase urine

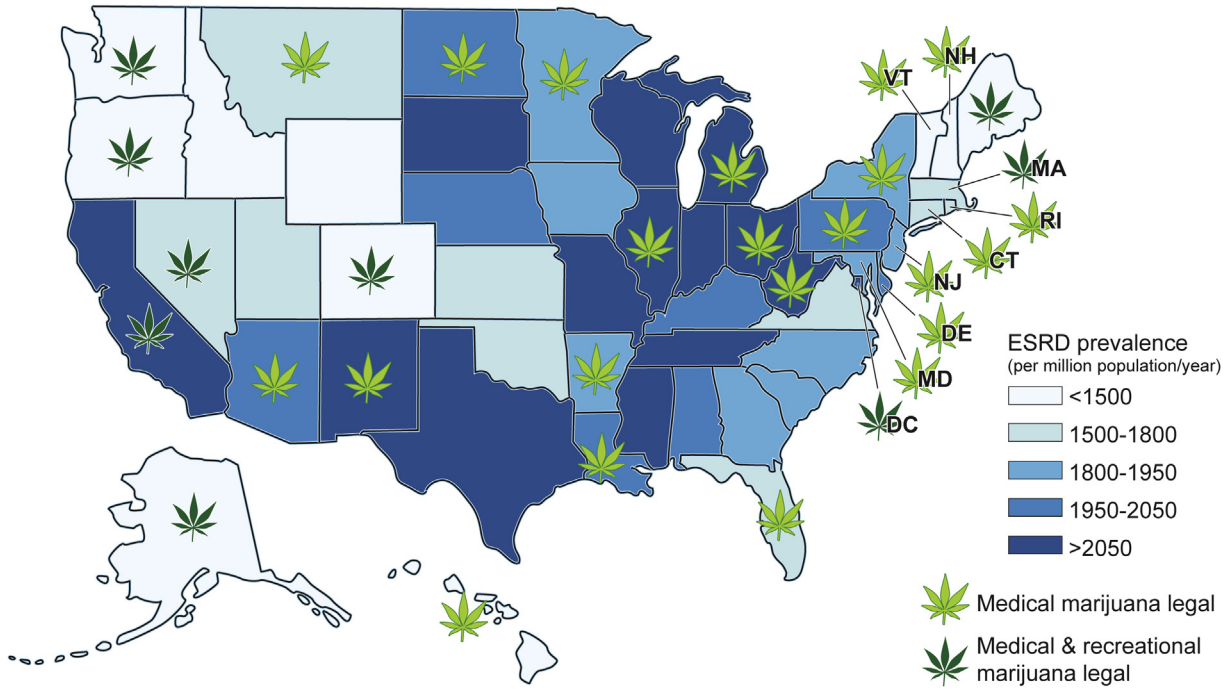

Figure 1. Map of the United States shows states with legalized use of medical or recreational marijuana, superimposed on the prevalence of end-stage renal disease (ESRD) by state. Reproduced with permission from Mount Sinai Health System.

output in rats,[10] possibly by inhibiting the $Na^+/K^+/2Cl^-$ cotransporter NKCC2 and a sodium/hydrogen exchanger in the thick ascending limb.[11]

Data for the relationship between marijuana use and kidney disease in humans are scarce. Cross-sectional studies using nationally representative data have demonstrated lower odds of metabolic syndrome[12,13] and diabetes[14] among marijuana users compared with nonusers; however, renal outcomes were not evaluated. In a prospective cohort of 647 men attending the hypertension clinic at a single Veterans Administration medical center, any self-reported history of recreational drug use was associated with a significant increase in risk for kidney function decline (serum creatinine increase > 0.5 mg/dL) over a median of 7 years. Although marijuana was the most commonly reported drug, marijuana use was not significantly associated with kidney function decline. The nonsignificant trend associated with marijuana use may reflect concomitant use of other drugs, including cocaine or psychedelics, which were independently associated with kidney function decline.[15] Similarly, a small cross-sectional study found elevated β_2-microglobulin concentrations in 2 of 42 cannabinoid users, but not in control patients. Although this could suggest subtle proximal tubular injury with cannabinoid use, the authors did not control for comorbid conditions or concomitant drug or medication use.[16]

Electrolyte concentration abnormalities have been reported with the use of other recreational drugs, but do not appear to be an important complication of isolated marijuana use. Hypophosphatemia was observed in a case series of 6 men with cannabinoid hyperemesis syndrome, an uncommon complication of long-term marijuana overuse.[17] Alkalemia-induced transcellular shift of phosphate from hyperventilation or vomiting was hypothesized as a possible mechanism.

Synthetic Cannabinoid Abuse

Originally developed for laboratory research, synthetic cannabinoids have become popular, and dangerous, drugs of abuse.[18] Synthetic cannabinoids are commonly referred to as "Spice" or "K2" and are sold in smoke shops, convenience stores, and on the internet. Several case series have linked synthetic cannabinoids to acute kidney injury,[19-21] although the mechanism is unknown. Among 21 cases, presenting symptoms included nausea and vomiting in all and flank pain in 15 patients. Kidney biopsy was performed in 13 patients, revealing acute tubular necrosis in 10 and acute interstitial nephritis in 3 cases.[22] Synthetic cannabinoids are not detected on standard blood and urine toxicology screens. Therefore, nephrologists should have a high index of suspicion when diagnosing unexplained acute kidney injury.

Synthetic cannabinoids may be intrinsically nephrotoxic, but a noncannabinoid contaminant has been proposed as an alternative explanation.[23,24] Because plant-based cannabinoids have not been associated with AKI, future investigations comparing marijuana and synthetic cannabinoid users may provide insight into potential mechanisms of kidney injury with synthetic cannabinoid use.