REVIEW

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The nephrologist's guide to cannabis and cannabinoids

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Purpose of review
Cannabis (marijuana, weed, pot, ganja, Mary Jane) is the most commonly used federally illicit drug in the United States. The present review provides an overview of cannabis and cannabinoids with relevance to the practice of nephrology so that clinicians can best take care of patients.

Recent findings
Cannabis may have medicinal benefits for treating symptoms of advanced chronic kidney disease (CKD) and end-stage renal disease including as a pain adjuvant potentially reducing the need for opioids. Cannabis does not seem to affect kidney function in healthy individuals. However, renal function should be closely monitored in those with CKD, the lowest effective dose should be used, and smoking should be avoided. Cannabis use may delay transplant candidate listing or contribute to ineligibility. Cannabidiol (CBD) has recently exploded in popularity. Although generally well tolerated, safe without significant side effects, and effective for a variety of neurological and psychiatric conditions, consumers have easy access to a wide range of unregulated CBD products, some with inaccurate labeling and false health claims. Importantly, CBD may raise tacrolimus levels.

Summary
Patients and healthcare professionals have little guidance or evidence regarding the impact of cannabis use on people with kidney disease. This knowledge gap will remain as long as federal regulations remain prohibitively restrictive towards prospective research.

Keywords
cannabidiol, kidney, marijuana, nephrology, renal

INTRODUCTION

Cannabis (marijuana, weed, pot, ganja, Mary Jane; Fig. 1) is the most commonly used federally illicit drug in the United States. As of December 2019, 33 states and the District of Columbia have medical cannabis programs. Eleven states and the District of Columbia have legalized recreational use. Several countries worldwide have legalized recreational use whereas many others have medical cannabis and decriminalization laws. The prevalence of cannabis use more than doubled between 2001 and 2013 in the United States [1] particularly among people over the age of 50 and even more so among those over 65 years [2▪,3,4▪,5▪]. These age groups are enriched with chronic illness including chronic kidney disease (CKD) that is associated with excess morbidity and mortality [6].

Cannabis is the dried flower bud of the *Cannabis sativa* and *Cannabis indica* plants, and naturally contains numerous phytocannabinoids. Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are the most abundant and well described phytocannabinoids, with differing activities and affinities for the ubiquitously expressed $G_{i/o}$-protein-coupled cannabinoid receptors CB1 and CB2. THC is the primary psychoactive component of cannabis and is a partial agonist to CB1 and CB2 receptors. In contrast, CBD is nonintoxicating and has little affinity for these receptors but acts as a negative allosteric modulator of CB1 with pharmacological effects on other receptor systems including GPR55, TRPV1,

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KEY POINTS

- Cannabis may have medicinal uses for treating symptoms of advanced CKD and ESRD.
- In the context of the opioid epidemic, cannabis could have a therapeutic role in pain management while decreasing opioid prescriptions among patients with CKD and ESRD.
- Cannabis use may have transplant listing implications and may delay candidate listing or contribute to ineligibility, but evaluation criteria vary by center.
- Research regarding kidney outcomes is limited to a few retrospective cohort studies that nephrologists should be familiar with to best address patient concerns.
- With growing acceptance of both medical and recreational cannabis use, future research is warranted to investigate the renal endocannabinoid system and the impact of cannabis use on kidney disease outcomes.

5-HT_{1A}, adenosine A2A, and nonreceptor mechanisms [7]. Plant breeding has created numerous genetically unique *Cannabis* chemovars, enhancing certain desired effects. For example, chemovars with a higher concentration of THC are selectively produced for recreational use, because THC activation of CB1 mediates the psychotropic effects of cannabis, whereas medical cannabis generally has higher CBD levels than recreational chemovars, often even exceeding the THC content. In fact, symptom relief may be obtained with THC doses lower than what is needed to induce psychotropic effects. Endogenous cannabinoids are eicosanoids derived from cell membrane phospholipids. The two primary endocannabinoids are anandamide/N-arachidonoylethanolamine and 2-arachidonoylglycerol, which are the natural ligands for the cannabinoid receptors. The endocannabinoid system is present in many tissues including the kidney where it has been shown to influence renal blood flow [8,9], glomerular filtration rate [10], fibrosis [11–13], proteinuria [14–21], and tubular function [22–27]. The endocannabinoid system has been comprehensively reviewed elsewhere [28,29▪,30] including specific interactions with the kidney [31,32,33▪,34▪,35–38]. Whole cannabis contains numerous cannabinoid compounds with different affinities, making the predicted cumulative effect on cannabis receptors, and potential renal effects difficult to predict.

Physicians remain poorly educated with respect to cannabis and the endocannabinoid system [39,40▪]. The federal stigma against cannabis in the United States, leading up to the Marihuana Tax Act of 1937 and the Controlled Substances Act of 1970, have strongly limited research and prevented teaching about the drug in medical education. State legalized consumption of cannabis is in conflict with federal law where it remains a Schedule I controlled substance without accepted medical use and a high potential for abuse. Despite this, the World Health Organization classifies CBD as having no potential for abuse [41] and several oral cannabinoid-based pharmaceuticals are U.S. Food and Drug Administration (FDA) approved, having demonstrated efficacy in treating certain medical conditions. Cannabis derived CBD (Epidiolex) is an FDA approved medication for pediatric epilepsy whereas synthetic THC is FDA approved as dronabinol (Marinol, Syndros), and a synthetic THC analogue as nabilone (Cesamet). The cannabis extract nabiximols (Sativex, THC/CBD 1:1) is approved for medical use outside of the United States.

CANNABIS AND CANNABINOIDS

Cannabis can be home grown or purchased from retail and medical dispensaries, dependent on the jurisdiction. Cannabis contains over 200 phytocannabinoids, terpenoids, and flavonoids that may act in concert, described as the 'entourage effect', so that the combination of plant components act synergistically to be more efficacious than the individual isolated compounds [42,43]. Cannabis can be consumed as dried flower bud through smoking burned plant material or heated in a vaporizer to the vaporizing points for the various cannabinoids (311°F–428°F) without burning the plant and generating smoke. Recently, electronic cigarettes and vape pens have become a popular means to inhale heated aerosol from a concentrated oil containing cannabinoids and/or nicotine. Unfortunately, some THC oil concentrates from illicit manufacturers/underground vape-makers have been associated with fatal lung injury attributed to inhalation of chemical irritants [44▪,45], including vitamin E acetate, used as an oil diluent [46].

Cannabis and isolated cannabinoids can also be processed into foods or 'edibles'. Over 90% of current users consume cannabis through inhalation whereas oral consumption accounts for less than 10% of cannabis use [47]. Inhalation provides an onset of action within minutes and allows for real-time dose titration. Peak effects are seen within 15–30 min with a half-life of 1–2 h. After oral consumption, the onset of action may be delayed up to 1–2 h, with peak effects at 2–3 h and half-life of 3–6 h. Inexperienced users who do not feel an effect right away may be tempted to overconsume innocuous appearing edible preparations that can lead to drug

FIGURE 1. *Cannabis sativa* W.O.Müll. (A) flowering male and (B) seed-bearing female plant, actual size; (1) male flower, enlarged detail; (2) and (3) pollen sac of same from various angles; (4) pollen grain of same; (5) female flower with cover petal; (6) female flower, cover petal removed; (7) female fruit cluster, longitudinal section; (8) fruit with cover petal; (9) same without cover petal; (10) same; (11) same in cross-section; (12) same in longitudinal section; (13) seed without hull. From Franz Eugen Köhler's Medizinal-Pflantzen. Published and copyrighted by Gera-Untermhaus, FE Köhler in 1887 (1883–1914). Original figure is now in the public domain. https://commons.wikimedia.org/wiki/File:Cannabis_sativa_Koehler_drawing.jpg.

accumulation and prolonged adverse side effects. For this reason, edibles have been associated with higher rates of emergency room visits, primarily for acute psychiatric symptoms, intoxication, and cardiovascular symptoms [48▪]. Cannabinoids are highly lipophilic and bioavailability is increased with high fat intake compared to consumption on an empty stomach [49]. THC and CBD may interact with the metabolism of prescription medications [50]. CBD is metabolized by CYP3A4 and CYP2C19 with a growing body of evidence suggesting it is also a potent inhibitor of these pathways [51,52] including CYP2C9 [53] and CYP2D6 [54]. The clinical relevance of these interactions is largely unknown. THC has a large volume of distribution (V_d) with slow elimination from the body. Cannabinoids are primarily cleared by the liver and the minority of inactive metabolites are excreted in the urine, accounting for 20% of metabolite elimination. Terminal half-life varies based on frequency of use: several days in infrequent users to over 1 month in heavy chronic users. Cannabinoid pharmacokinetics have been comprehensively reviewed [55,56▪,57]. Evidence regarding the pharmacokinetics of cannabinoids in people with impaired kidney function is scarce. The only published study evaluated 200mg of oral CBD and found no statistically significant differences in maximum measured plasma concentration (Cmax), time to Cmax, area under the plasma concentration–time curve (AUC) from time zero to last measurable concentration, or AUC from time zero to infinity values between participants with severe renal impairment (mean eGFR ~22 ml/min/1.73 m2) and normal renal function [58▪]. Given the primary hepatic metabolism, dose adjustments are unlikely to be needed. The large V_d for THC and high protein binding [57] suggest limited clearance with hemodialysis.

Dosing recommendations for cannabis and cannabinoid preparations have been previously published [59▪]. Almost 90% of current adult cannabis use is in part or entirely for recreational reasons and slightly less than half is in part or entirely for medicinal purposes [47]. CBD-infused oils, tinctures, creams, food items, and drinks, along with a host of other products, have exploded in popularity since the passage of the Agriculture Improvement Act of 2018 (2018 Farm Bill), which removed hemp (*Cannabis sativa* with <0.3% THC) from the Controlled Substances Act and legalized its domestic agricultural production as a commodity. CBD is sold in health food stores, retail shops, dispensaries, pharmacies, convenience stores, and on the internet. Already, 14% of Americans use CBD, primarily for pain, anxiety, insomnia, and arthritis [60]. CBD is well tolerated, safe, and effective for a variety of neurological and psychiatric conditions [61–63, 64▪], although at high doses, CBD may increase liver enzymes and interact with some prescription medications [65▪]. Consumers have easy access to a wide range of unregulated CBD products with inaccurate labeling and false health claims. A clinical guide on the therapeutic actions and safety of CBD and hemp oils has been recently published [66▪]. In addition to CBD isolate, hemp extract may be marketed as 'full spectrum', which contains whole plant extract and a variety of compounds. Hemp seed oils are also sold but do not contain any phytocannabinoid compounds.

There is no evidence to suggest that CBD has any adverse effect on kidney function. In fact, CBD prevented cisplatin induced nephrotoxicity in a mouse model by reducing oxidative stress [67]. However, some products may contain toxic contaminants such as heavy metals, pesticides, and solvents. A study of 84 CBD products sold online found that 42% of products contained more CBD than stated on the label, 26% were overlabeled, whereas only 31% contained the stated amount [68]. Additionally, 20% of these products were contaminated with THC that could potentially be detected on a urine toxicology screen. Some products do not contain a sufficient quantity of CBD to achieve pharmacological activity.

Consumers should scrutinize labels, ensure that the product has been made with good manufacturing practice, ensure cannabinoid extraction using carbon dioxide, ensure organic certification by the U.S. Department of Agriculture, and purchase from a certified medical dispensary or company that has a certificate of analysis. If CBD is regularly consumed, careful monitoring of clinical parameters and drug interactions is warranted.

SYMPTOMS ASSOCIATED WITH CHRONIC KIDNEY DISEASE AND END-STAGE RENAL DISEASE

Over 1.5 million people with advanced CKD and about 750 000 people with end-stage renal disease (ESRD) live in the United States [6]. One-quarter to one-half of patients with CKD experience chronic symptoms such as pain, nausea, anorexia, sleep disturbance, anxiety, and depression [69], several of which are approved indications for medical cannabis. In addition, anxiety, depression, and insomnia are the most common psychiatric conditions that people self-treat with cannabis [70]. Evidence supports the use of cannabis in patient populations without CKD for treating several of these symptoms including chronic pain, nausea, and loss of appetite. The rationale for its use in patients with CKD and

ESRD has been previously reviewed by myself and others [71,72,73▪].

Pain prevalence among patients with CKD and ESRD is as high as 50% [74]. Pain attributed to kidney disease occurs from polycystic kidney disease, renal colic from nephrolithiasis, renal osteodystrophy, or uremic neuropathy. Historically, cannabis has been recommended for a wide range of ailments including as a spasmolytic for cases of renal colic and to facilitate the excretion of small kidney stones [75].

Over 60% of dialysis patients receive at least one opioid prescription annually and approximately 20% of them take prescription opioids chronically [76]. Both short-term and chronic use of prescription opioids are associated with increased morbidity and mortality [76,77]. Cannabis could have a therapeutic role in pain management that deserves clinical consideration and further clinical trial investigation. Access to medical cannabis has been associated with decreased opioid prescriptions and dose reductions [78–82,83▪]. The National Academies concluded that substantial evidence exists for the use of cannabis and cannabinoids to treat chronic pain [84] while meta-analyses and systematic reviews of cannabis use, including prescription cannabinoids, have given mixed results for treating chronic pain [85–87].

IMPAIRED KIDNEY FUNCTION

Recreational cannabis is most often smoked (>90%) [47,88] and generally contains higher THC content whereas medical cannabis is vaporized or consumed orally and often has a higher CBD content. Medical cannabis programs in several states only allow for edibles and vaporizers and do not allow smoking. Existing research regarding cannabis is biased towards recreational cannabis consumed by smoking prior to or early into state legalization programs.

Among participants with an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2) in the multicenter Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) study self-reported chronic cannabis usage was associated with more rapid eGFR decline compared to those with an eGFR more than 60 ml/min/1.73 m^2 over a median 4.1 years [89]. Cannabis usage was not associated with changes in albuminuria over time. Conversely, sicker patients who may already have progressive CKD may be more inclined to use medical cannabis for symptom management. An analysis of the Chronic Renal Insufficiency Cohort (CRIC) Study from 2003 to 2008 among 3939 adults with baseline eGFR between 20 and 70 ml/min/1.73 m^2 did not demonstrate an association between cannabis use and CKD progression over 5.5 years of follow-up [90▪].

Among healthy individuals, analysis of the Coronary Artery Risk Development in Young Adults (CARDIA) Study did not demonstrate a longitudinal association between cannabis use and eGFR change, rapid eGFR decline, or prevalent albuminuria after 15 years of follow-up in 3765 participants [91]. Past or current cannabis use was reported by 83% of participants. The CARDIA study began in 1988 and at that time, cannabis had lower THC content and a lower THC/CBD ratio than current levels. Similar findings were revealed in a cross-sectional analysis of 13 995 adults aged 18–59 years in the nationally representative National Health and Nutrition Examination Survey (NHANES) from 2007 to 2014 that did not find a clinically significant effect of self-reported past or current cannabis use on serum creatinine, eGFR, microalbuminuria, or stage 2 or higher CKD [92].

Renal function in cannabis users with CKD should be closely monitored, the lowest effective dose should be used, and smoking should be avoided. It is currently unknown if other routes of administration attenuate kidney risk but they at least avoid potential pulmonary complications.

ACUTE KIDNEY INJURY

Synthetic cannabinoids are potent CB1 agonists originally developed as research compounds but have emerged on the marketplace as popular and potentially dangerous recreational drugs referred to as ‘spice’ or ‘K2’. Numerous cases during 2012 have linked synthetic cannabinoids to acute kidney injury (AKI) [93–95]. Specifically, the synthetic cannabinoid XLR-11 has been identified as a nephrotoxic compound [95] possibly related to effects on proximal tubule mitochondrial function [96]. Synthetic cannabinoids may be nephrotoxic, but a non-cannabinoid contaminant has been proposed as an alternative explanation [97,98]. Nausea, vomiting, and flank pain are common in the majority of cases. Kidney biopsy most often demonstrates acute tubular necrosis with some cases of acute interstitial nephritis [99]. Synthetic cannabinoids are not detected on standard blood and urine toxicology screens. Therefore, nephrologists should have a high index of suspicion when diagnosing unexplained AKI.

Cannabinoid hyperemesis syndrome (CHS) [100] is a rare complication of heavy and frequent cannabis use over many years characterized by intractable vomiting that is relieved with hot showers. CHS is occasionally associated with prerenal AKI [101–106], treated with intravenous fluids and

antiemetics. Interestingly, hypophosphatemia was observed in a case series of 6 men with CHS [107].

KIDNEY TRANSPLANTATION

CB2 is widely expressed on immune cells and cannabinoids have immunomodulatory effects in animal models of allogeneic transplantation and autoimmune diseases [108–111]. As such, cannabis and cannabinoids may have immunomodulatory effects among kidney transplant recipients. Interestingly, a study of routine kidney transplant biopsies revealed significant upregulation of glomerular and tubular CB1 expression in those with chronic allograft dysfunction compared to low levels in normal kidney allografts, suggesting a role for CB1 in allograft fibrosis [112].

Cannabis use in potential transplant recipients may have implications for pretransplant screening, such as delayed candidate listing or contributing to ineligibility [113▪], with implications for posttransplant outcomes. There is concern regarding adherence to immunosuppressive medications, the ability to follow instructions, and attendance of follow-up appointments. An American Society of Transplantation survey revealed that about half of transplant centers vary in their policy according to the organ, whereas slightly more than one-quarter of centers rejected all candidates regardless of organ [114▪]. Drug screening of potential transplant donors and recipients should consider the prolonged excretion of THC metabolites which may range from a few days in casual users to several weeks to over 1 month with chronic heavy use.

A retrospective single center study of kidney transplant candidates revealed that cannabis abuse and dependence were associated with a high prevalence of other substance use disorders, psychiatric comorbidities, and strong family histories of addictions, resembling other substance use populations that generally adversely affect kidney graft outcomes [115]. A study of a national kidney transplant database demonstrated that cannabis dependence or abuse (CDOA) in the year before transplant was not associated with death or graft failure in the year after transplant, but was associated with posttransplant psychosocial problems such as alcohol abuse, other drug abuse, noncompliance, schizophrenia, and depression [116▪]. CDOA after kidney transplantation was associated with cardiovascular, pulmonary, psychosocial complications, accidents, and fractures. Accordingly, CDOA was associated with an approximately two-fold increased risk of death-censored graft failure, all-cause graft loss, and death in the subsequent 2 years. Although associations likely, in part, reflect comorbid conditions or behaviors, CDOA after kidney transplantation appears to have consequences for allograft and patient outcomes. Additionally, patients who carry a formal diagnosis of CDOA likely reflect 'extreme' users who were not able to hide their use and raised suspicion. Data from patients with CDOA cannot be generalized to all as cannabis does not have adverse effects on life in everyone [117▪]. A single center study of 56 cannabis users out of 1225 kidney recipients from 2008 to 2013 demonstrated that recreational cannabis use, defined by positive urine toxicology screen and/or self-reported recent use, did not affect mortality, graft loss, or graft function 1-year posttransplant [118]. Finally, a single center study of 919 kidney transplant recipients from 2001 to 2015 revealed that smoking status was not significantly associated with acute rejection, eGFR, or pneumonia within 1-year posttransplant. Patients with isolated cannabis use had similar overall graft survival compared to nonusers [119▪].

With regards to kidney donation, a retrospective single center study of 294 living kidney donors and 230 recipients between 2000 and 2016 showed that donor cannabis use did not demonstrate any deleterious effects on donor or recipient posttransplantation eGFR over a mean follow up of 2.1 years for donors and 5.2 years for recipients [120▪]. Among recipients of a kidney from a cannabis user, the rates of acute rejection, graft, and patient survival of the kidney allografts were similar to those from nonusers.

Although rare, fungal contamination of cannabis and pulmonary complications have been reported among kidney transplant recipients, including pulmonary aspergillosis associated with smoking cannabis [121,122] and exogenous lipid pneumonia secondary to smoking weed oil [123]. These cases have occurred prior to current cannabis legalization where microbial testing has become a regulatory requirement in the medical and recreational cannabis markets. Although sterilization of cannabis buds can eliminate fungi and may eliminate the risk of fatal opportunistic infections among immunosuppressed individuals [121,124], several toxigenic fungi and bacteria have been detected in cannabis samples [125,126]. Based on existing evidence, cannabis usage alone should not be the sole deciding factor for declining a patient for kidney transplant listing.

Several case reports demonstrate increased tacrolimus levels associated with CBD in a patient with interstitial nephritis and in non-kidney transplant recipients [127▪,128,129], whereas one small case series of low dose CBD for chronic pain among kidney transplant recipients did not reveal any change in tacrolimus levels [130]. Inaccurate

product labeling and batch to batch variability of CBD products [68] may lead to unpredictable CNI levels, potential toxicity, or underdosing, especially with intermittent use of different cannabinoid products. Furthermore, CBD inhibits hepatic cyclosporine metabolism *in vitro* and in mice [131].

MEDICAL RISKS AND COMPLICATIONS

The public health impact of state legalization of cannabis remains unclear and these policies may have contributed to the increasing perception that cannabis is harmless. In fact, more than one-third of U.S. adults strongly or somewhat strongly agree that edible cannabis prevents health problems and more than a quarter strongly or somewhat strongly agree that smoking or vaping cannabis prevents health problems [132▪▪]. Medical cannabis as an option for those with CKD or ESRD, will include people who are older, frailer, and have more comorbid conditions and co-medications, potentially increasing susceptibility to adverse effects. The most common side effects are dizziness and dry mouth.

Smoking is associated with increased mortality among people with CKD and ESRD [133]. Although smoked cannabis is a source of oxidative stress to the respiratory tract [134] and associated with bronchial irritation and chronic bronchitis [135], regular heavy use is associated with lower risk for pulmonary complications compared to tobacco use [136,137]. A systematic review and meta-analysis demonstrated low-strength evidence that smoking cannabis more than once per week for at least 1 year was associated with cough, sputum production, and wheezing while evidence regarding cannabis use and obstructive lung disease and pulmonary function was insufficient [138▪▪].

CKD and ESRD are associated with increased cardiovascular morbidity and mortality [139]. Endocannabinoids are involved in various functions of the cardiovascular system including blood pressure regulation [140–142]. Some observational studies suggest a higher incidence of cardiovascular events with cannabis exposure, [143–145] while other studies do not [146,147]. Low strength evidence suggests that cannabis use is associated with tachycardia [148▪]. Acutely, cannabis may cause orthostatic hypotension whereas long-term cannabis use may be associated with a modest increase in systolic blood pressure [149]. Systematic reviews do not reveal any hemodynamic effects of either CBD [150] or THC [151].

Cognitive impairment is common among people with CKD and ESRD [152–154]. Acute cannabis usage may cause sedation and impair spatial-visual distortion while acute and long-term cannabis use can impair verbal learning, memory, and attention [155]. However, a comprehensive review of recreational cannabis and cognitive function revealed inconsistent findings across studies [156▪].

CONCLUSION

Given the rapidly expanding market for cannabis, large-scale longitudinal studies are needed to explore the long-term effects of chronic and frequent cannabis use. Consistent with recommendations regarding the use of tobacco and other smoked substances among patients with CKD and ESRD, smoked cannabis should be avoided among people with cardiovascular or pulmonary disease. Other routes of administration such as oral consumption may avoid these risks.

With growing acceptance of both medical and recreational cannabis and cannabinoids, further research is required to determine the efficacy, safety, and acceptability of medical and recreational cannabis use among people with CKD and ESRD. As clinicians, we should be informed and able to provide guidance with the most up to date information for our patients.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
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