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A Review of Cannabis in Chronic Kidney Disease Symptom Management

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Abstract

Purpose of Review: Physical and psychological symptom burden in patients with advanced chronic kidney disease (CKD) is significantly debilitating; yet, it is often inadequately treated. Legalization of cannabis in Canada may attract increasing interest from patients for its medical use in refractory symptom management, but its indications and long-term adverse health impacts are poorly established, creating a challenge for clinicians to support its use. In this review, we summarize key clinical studies and the level of evidence for nonsynthetic cannabinoids in the treatment of common symptoms encountered in advanced stages of CKD, including chronic pain, nausea and vomiting, anorexia, pruritus, and insomnia.

Sources of Information: Medline and Embase

Methods: A search was conducted in MEDLINE and EMBASE (inception to March 1, 2018) on cannabis and CKD symptoms of interest, complemented with a manual review of bibliographies. Studies that examined synthetic cannabinoids that are manufactured to mimic the effects of Δ9-tetrahydrocannabinol such as dronabinol, levonantradol, nabilone, and ajulemic acid were excluded. We focused on studies with higher level of evidence where available, and quality of studies was graded based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (1a to 5).

Findings: Based on studies conducted in patients without renal impairment, those treated with nonsynthetic cannabinoids were 43% to 300% more likely to report a ≥30% reduction in chronic neuropathic pain compared with placebo. However, there is currently insufficient evidence to recommend nonsynthetic cannabinoids for other medical indications, although preliminary investigation into topical endocannabinoids for uremia-induced pruritus in end-stage renal disease is promising. Finally, any benefits of cannabis may be offset by potential harms in the form of cognitive impairment, increased risk of mortality post-myocardial infarction, orthostatic hypotension, respiratory irritation, and malignancies (with smoked cannabis).

Limitations: Nonsynthetic cannabinoid preparations were highly variable between studies, sample sizes were small, and study durations were short. Due to an absence of studies conducted in CKD, recommendations were primarily extrapolated from the general population.

Implications: Until further studies are conducted, the role of nonsynthetic cannabinoids for symptom management in patients with CKD should be limited to the treatment of chronic neuropathic pain. Clinicians need to be cognizant that nonsynthetic cannabinoid preparations, particularly smoked cannabis, can pose significant health risks and these must be cautiously weighed against the limited substantiated therapeutic benefits of cannabis in patients with CKD.

Abrégé

Justification: Les symptômes physiques et psychologiques ressentis par les patients souffrant d'insuffisance rénale chronique (IRC) sont particulièrement débilitants, et souvent traités inadéquatement. La légalisation du cannabis au Canada pourrait susciter un intérêt croissant chez ces patients avec l'emploi médical de cette substance pour le traitement de ces symptômes. Cependant, les indications thérapeutiques du cannabis et ses effets nocifs sur la santé à long terme sont mal connus, rendant difficile son soutien par les cliniciens. L'article présente l'état des preuves et une synthèse des principales études cliniques portant sur l'usage des cannabinoïdes non synthétiques dans le traitement des symptômes fréquemment observés aux stades avancés de l'IRC, soit la douleur chronique, les nausées, les vomissements, l'anorexie, le prurit et l'insomnie.

Sources: Medline et Embase

Méthodologie: On a procédé à une recherche dans MEDLINE et EMBASE (de leur création jusqu'au 1er mars 2018) sur le cannabis et les symptômes d'intérêt en contexte d'IRC, puis à un examen manuel des biographies. Ont été exclues les études portant sur le dronabinol, le levonantradol, le nabilone et l'acide ajulémique, des cannabinoïdes synthétiques fabriqués pour reproduire les effets du Δ9-tétrahydrocannabinol. Nous nous sommes intéressés aux études pour lesquelles le niveau de preuve était le plus élevé, et leur qualité a été établie avec le tableau de l'*Oxford Centre for Evidence-based Medicine Levels of Evidence* (niveaux 1a à 5).

Observations: Des études menées chez des patients non atteints d'insuffisance rénale montraient que les sujets recevant des cannabinoïdes non synthétiques étaient 43 à 300 % plus susceptibles de rapporter une réduction d'au moins 30 % de la douleur neuropathique chronique comparativement aux sujets recevant un placebo. Mais pour l'heure, les preuves permettant de recommander les cannabinoïdes non synthétiques à d'autres fins médicales sont insuffisantes; quoique des résultats préliminaires soient prometteurs avec les endocannabinoïdes topiques dans le traitement du prurit provoqué par l'urémie en contexte d'IRC. Cependant, tout bienfait du cannabis pourrait se voir neutralisé par de potentiels effets nocifs tels que troubles cognitifs, risque accru de mortalité après un infarctus du myocarde, hypotension orthostatique, irritation des voies respiratoires ou tumeurs malignes (dues à l'inhalation).
Limites: Les préparations de cannabinoïdes non synthétiques employées dans les études retenues étaient très variables, les échantillons étaient faibles et les études de courte durée. En absence d'études menées en contexte d'IRC, les résultats présentés sont principalement extrapolés d'une population générale.
Constatations: Jusqu'à ce que d'autres études soient menées, l'utilisation des cannabinoïdes non synthétiques chez les patients atteints d'IRC devrait se limiter au soulagement des douleurs neuropathiques chroniques. Les cliniciens doivent comprendre que les cannabinoïdes non synthétiques, particulièrement lorsqu'ils sont inhalés, comportent des risques significatifs pour la santé et que ceux-ci doivent être examinés avec prudence en regard des bienfaits thérapeutiques limités du cannabis chez les patients atteints d'IRC.

Keywords
medical marijuana, cannabis, chronic kidney disease, chronic pain, neuropathic pain, nausea, vomiting, anorexia, pruritus, and insomnia

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What was known before

Synthetic cannabinoids such as dronabinol and nabilone have been approved for a wide range of indications such as HIV/AIDS-induced anorexia, chemotherapy-induced nausea and vomiting, and neuropathic pain. Although nonsynthetic cannabinoids have been used for a plethora of therapeutic claims, the evidence to support these indications has not been well reviewed, particularly with respect to chronic kidney disease.

What this adds

This review summarizes the evidence for the use of nonsynthetic cannabinoids in common symptoms encountered in chronic kidney disease and potential risks in relevance to renal impairment.

Introduction

Patients with chronic kidney disease (CKD) have limited life expectancy: the estimated residual life span is approximately 8 to 4.5 years after dialysis initiation for those aged 40 to 64 years, respectively.[1] Consequently, optimizing quality of life (QOL) is of high priority. Unfortunately, patients are often afflicted with numerous symptoms, with one cross-sectional study reporting an average of 13 symptoms experienced by patients with stage 4 CKD and above.[2] Symptom burden and QOL of end-stage renal disease (ESRD) have also been compared with that of terminal malignancy[3] and commonly experienced symptoms such as pain, nausea, anxiety, and insomnia remain significantly undertreated, with only 20% to 60% of patients with CKD receiving treatment.[4,5] Conventional pharmacological agents exist, but adverse effects, intolerances, refractory conditions, and heavy pill burden can limit their use. In stage 5 CKD, poorly controlled uremic symptoms are managed with the initiation of dialysis. Nonetheless, compared with late dialysis initiation, early dialysis initiation in progressive CKD has been associated with higher dialysis costs without improving survival or overall QOL.[6-8]

Following legalization in Canada, softening of social attitudes and reduced stigmatism toward cannabis use is expected to garner increased interest in medical cannabis,

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especially for chronic refractory symptoms and palliative conditions such as those observed in patients with CKD. With expanded cannabis access through licensed retailers and self-grown plants, self-medicating of cannabis will also become inevitable among some patients with suboptimal symptom control. To minimize the risk of adverse drug effects and potential for substance abuse, it is paramount that clinicians are able to provide evidence-based guidance and education to patients to make well-informed decisions. However, our understanding of the effects of cannabis on patients with CKD and its role in symptom management remains limited. In this article, we aim to review the benefits and risks of cannabis use in this population and, where available, establish evidence-based indications of cannabis for CKD-related symptom management.

Properties of Cannabinoids

Cannabis is derived from the dried flowering tops and leaves of the hemp plant *Cannabis Sativa* and its subspecies, *Cannabis sativa, Cannabis indica, and Cannabis ruderalis*, which are comprised of more than 400 compounds with at least 66 phytocannabinoids identified.[9] Cannabinoids refer to all ligands of the cannabinoid receptors, CB_1 and CB_2, and encompass phytocannabinoids, synthetic cannabinoid analogues, and endogenous ligands, such as anandamide and 2-arachidonoylglycerol.[10] CB_1 receptors are present in peripheral organs such as the gastrointestinal tract, where CB_1 activation influences gut motility, promotes energy storage, and impairs glucose and lipid metabolism.[11,12] High densities of CB_1 receptors in the forebrain and cerebellum contribute to cannabinoid effects on cognitive impairment and depressed motor function; contrastingly, minimal presence in the lower brainstem explains the lack of lethal respiratory and cardiovascular depressive effects with high doses such as those observed in opioid overdoses.[13] CB_2 receptors, on the contrary, are predominantly distributed on leukocytes, macrophages, lymphocytes, spleen, and thymus, resulting in immunosuppressive and anti-inflammatory responses via inhibition of neutrophil migration, suppression of pro-inflammatory factor proliferation, and reduction of signaling to T cells.[14-18] The varying affinity of cannabinoids to each of these receptors accounts for differences in a range of physiological effects.

Despite the numerous phytocannabinoids found in marijuana, studies have primarily focused on the most abundant and major active components, cannabidiol (CBD), a nonpsychoactive phytocannabinoid that activates the body's endocannabinoid system (ECS) during pain, nausea, or inflammation, and Δ9-tetrahydrocannabinol (THC), the principal psychoactive ingredient in marijuana.[19] Effects of THC include muscle relaxation, analgesia, antiemesis, and sedation, but psychosis, anxiety, and psychoactive effects limit its potential therapeutic benefits.[20,21] While THC is a partial agonist of both CB_1 and CB_2 receptors, CBD is an antagonist with low affinity for both receptors that indirectly inhibits the reuptake and hydrolysis of the endogenous ligand anandamide.[22] Because CBD inhibits the metabolism of THC into its psychoactive metabolite 11-hydroxyTHC, it mitigates THC-induced paranoia and anxiety and potentiates the non-psychoactive effects of THC through its indirect mechanism.[17] CBD has less analgesic and antiemetic effects than THC; however, its anxiolytic, antipsychotic, anticonvulsant, and neuroprotective properties have raised great interest in its potential therapeutic role.[23-26]

The administration routes of marijuana are diverse, with inhalation via smoking or vaporization and oral ingestion being the most common methods. Studies have shown comparable THC plasma concentration changes and onset of psychotropic effects between inhalation by smoking and intravenous injection.[27] Following inhalation, maximum plasma concentrations of THC occur within 3 to 10 minutes while psychotropic effects present within seconds to minutes, peaking at 15 to 30 minutes and lasting for up to 3 hours.[6] In contrast, oral absorption is slower and more erratic; psychotropic effects occur at 30 to 90 minutes with peak concentrations at 2 hours and lasting for 4 to 12 hours depending on product potency.[6]

With respect to metabolism, cannabinoids are mainly dependent on the liver and, to a lesser extent, on the heart and lungs.[28-30] Specifically, hepatic cytochrome 450 (CYP450) isoenzymes 2C9 and 3A4 are involved in the metabolism of THC, while CBD is metabolized by 3A4, but inhibits 2C9, 2D6, and 2C19.[31-33] Data on drug interactions between marijuana use and other medications are scarce, but similar to the effects of polycyclic aromatic hydrocarbons in cigarette smoking, inhalation of marijuana results in CYP1A1 and CYP1A2 induction.[34] As a result, marijuana can not only increase the clearance of drugs that are CYP1A2 substrates, such as chlorpromazine, clozapine, olanzapine, and theophylline, but the combined use of tobacco and marijuana can also have additive clearance on these drugs.[30,35,36] Moreover, the effect on drug clearance is dependent on the frequency of marijuana use: increased clearance of theophylline was only observed with the use of $\geq$2 marijuana joints per week, but not with occasional use or $<$1 joint per week.[37] As a CYP3A4 substrate, THC serum concentration is reduced by strong CYP3A4 inducers such as rifampin and ketoconazole, which have been documented to alter the metabolism of Δ9-THC/CBD oral mucosal spray (Sativex®).[38] Other CYP3A4 and CYP2C9 inhibitors such as clarithromycin, cyclosporine, voriconazole, fluconazole, verapamil, amiodarone, cotrimoxazole, metronidazole, and fluoxetine would also be expected to inhibit THC elimination. For CBD, inhibition of CYP2D6 can reduce the metabolism of warfarin and diclofenac, thereby raising serum levels.[39] By inhibiting CYP2C19, CBD can also increase the plasma concentration of clobazam and its active metabolite *N*-desmethylclobazam.[40] The product monograph of Sativex® also warns of increased effects of amitriptyline and fentanyl due to CYP2C19 and CYP3A4

Table 1. Physiological Effects of Δ9-THC and CBD.[9,10]

Δ9-THC	CBD
• Euphoria • Hallucinations • Sedation • Aggravation of psychotic states • Memory disturbance • Deterioration or amelioration of motor coordination • Analgesia • Orthostatic hypotension • Increase in oxygen demand • Tachycardia • Appetite stimulation • Delayed gastric emptying • Antiemetic	• Sedation • Antidystonic • Antiepileptic • Antiemetic • Anti-inflammatory • Anxiolytic • Antipsychotic

Note. THC = tetrahydrocannabinol; CBD = cannabidiol.

interactions.[41] As a result, during both initiation and discontinuation of marijuana use, consideration should be given to possible altered drug response from such interactions.

Finally, excretion of THC, mostly as acidic metabolites, occurs predominantly via feces (65%-80%) over days to weeks as a result of significant enterohepatic recirculation and high protein binding.[6] Only 20% to 35% of THC is excreted through the urine; its high lipophilicity leads to high tubular reabsorption and low renal excretion of the unchanged drug.[6,42] The pharmacokinetics of other cannabinoids resemble THC in that there is a large volume of distribution and high protein binding; as a result, they are unlikely to be effectively removed by conventional hemodialysis or peritoneal dialysis.[43] As THC and CBD elimination is primarily achieved through the fecal route with minimal renal excretion, renal dose adjustment is unnecessary for the 2 most abundant cannabinoids in cannabis. Furthermore, in spite of the paucity of pharmacokinetic data of other cannabinoids and their metabolites, the clinical significance of potential accumulation in renal impairment is low given their relative trace amounts in nonsynthetic cannabis. It is unclear whether other compounds, chemical contaminants, or adulterants, particularly in recreational cannabis, may pose nephrotoxic risks. Until clinical trials of cannabis are conducted in severe renal impairment, close monitoring is still highly warranted in CKD.

Cannabinoid Effects on the Kidney

While both CB_1 and CB_2 receptors are expressed in the kidneys, the effects of the endocannabinoid system (ECS) in the kidneys are not well understood. Endocannabinoids, such as anandamide, have been shown to influence renal hemodynamics and tubular sodium reabsorption via CB_1 receptor activation.[44] Several animal models of kidney diseases have also demonstrated that an imbalance of cannabinoid receptor signaling with dominant CB_1 receptor activation over CB_2 receptor activation can lead to deleterious effects such as oxidative stress, inflammation, cell dysfunction, apoptosis, and fibrosis.[45] More importantly, restoration of the imbalance in the ECS via CB_1 blockade and CB_2 agonism may be renoprotective and counter the effects of metabolic syndrome. In obese insulin-resistant rats, CB_1 receptor blockade prevented proteinuria, renal function decline, and reduced both glomerular and tubule interstitial fibrosis in conjunction with improving body weight, fasting glucose, and lipids.[46] Without influencing body weight, CB1 receptor deletion, specifically in the renal proximal tubules, has also been shown to reduce renal lipotoxicity and nephropathy in obese rats, suggesting direct endocannabinoid effects in the kidneys.[47] Similarly, in nondiabetic animal models, excessive CB_1 receptor activity resulted in podocyte damage, nephron loss, and proteinuria, and correction of systemic and peripheral imbalance of CB_1 and CB_2 receptor activation reduced albuminuria and podocin loss in diabetic animals for secondary prevention.[48,49] The association between endocannabinoid imbalance and diabetic nephropathy has yet to be replicated in human studies; nonetheless, these preliminary findings suggest that CB_1 receptor blockade and CB_2 receptor agonism may be possible therapeutic targets for the management of diabetic nephropathy. The impact of recreational marijuana on these processes in the kidney, however, is less clear given that concentrations of cannabinoids vary with each strain and the affinity of each cannabinoid can fall along a wide spectrum between agonism and antagonism to each receptor.

Methods

A search was conducted in MEDLINE and EMBASE (inception to March 1, 2018) on cannabis and CKD symptoms of interest, complemented with a manual review of bibliographies. We examined the role of medical marijuana in the treatment of the following common CKD symptoms: chronic pain, nausea, anorexia, pruritus, and insomnia. Due to the paucity of studies conducted with cannabinoids in CKD, we reviewed and extrapolated findings from populations with normal renal function in absence of data in renal impairment. Studies that examined synthetic cannabinoids that are manufactured to mimic the effects of Δ9-THC such as dronabinol, levonantradol, nabilone, and ajulemic acid were excluded. We focused on studies with higher level of evidence where available, and quality of studies was graded based on the Oxford Centre for Evidence-based Medicine Levels of Evidence (1a to 5).

Chronic Pain

Approximately two thirds of predialysis patients with CKD stages 3 to 5 are afflicted with chronic pain, and among them, 48% report their pain as severe.[50] Although opioids are

frequently prescribed in patients with CKD, concerns for increased risk of adverse drug effects, physical dependency, and addiction have been raised. Moreover, neuropathic pain in patients with diabetic CKD is often less responsive to opioids than visceral and somatic pain, and treatment options with anticonvulsant and antidepressant agents can be limited. In marijuana-legalized states in the United States, observational studies have not only shown a significant decline in annual opioid doses prescribed per physician through Medicare, but also a 24.8% reduction in annual opioid overdose mortality rate.[51,52] Amid a surge in opioid-related deaths in Canada and the United States, patients afflicted with chronic pain are anticipated to increasingly pursue cannabinoids as a means of curbing opioid use and opioid-related morbidity and mortality.

Due to a lack of studies conducted in patients with CKD, we identified 3 systematic reviews that examined nonsynthetic cannabinoids in patients without renal impairment for a variety of pain conditions. In a large meta-analysis (n = 1370) of nonsynthetic cannabinoids by Whiting et al,[53] 7 trials on nabiximols as Sativex® oromucosal spray (natural extract of 27 mg THC and 25 mg CBD per mL, maximum dose of 8 sprays/3 h or 48 sprays/24 h) and 1 trial on smoked cannabis (3.56% THC inhaled thrice a day for 5 days) were pooled together and included diabetic neuropathy, central neuropathic pain from multiple sclerosis, HIV-associated sensory neuropathy, fibromyalgia, rheumatoid arthritis, and cancer pain. Although a greater proportion of patients in the cannabinoid group achieved a minimum of 30% pain reduction compared with placebo, which is considered moderately clinically meaningful,[54] statistical significance was not achieved (odds ratio [OR] = 1.4 [95% confidence interval (CI) = 0.99-2.00], I^2 = 47.6%). The greatest benefit was driven by the single randomized controlled trial (RCT) with smoked cannabis (OR = 3.43 [95% CI = 1.03-11.48]),[55] which was similar to the effect size seen in a pooled analysis of inhaled cannabinoids by Andreae et al that did achieve statistical significance. Nabiximols demonstrated greater pain reduction on several pain scales, but findings were not consistent across trials and there was no difference in average quality-of-life scores according to the EQ-5D health status index (weighted mean difference= −0.01 [95% CI = −0.05 to 0.02]; 3 trials). Moderate heterogeneity was introduced to the meta-analysis due to the wide assortment of pain conditions that were pooled together. Other limitations of individual studies included short duration of follow-up, ineffective participant blinding secondary to the psychoactive effects of THC, incomplete outcome reporting, and unclear blinding of outcome observer, leading to possible high risk of detection and performance bias. Whiting et al concluded that based on GRADE methodology, there was overall moderate quality evidence to support the use of cannabinoids in the treatment of chronic pain, which indicates that further research is likely to have an impact on the confidence of estimated effects and potentially change the estimate.

Andreae et al[56] conducted a Bayesian meta-analysis of 5 RCTs using individual patient data (n = 178) that investigated the effect of inhaled cannabis (vaporizer, pre-rolled cigarettes, and gelatin capsules smoked through pipe) compared with placebo on neuropathic pain. Two of these RCTs were included in a review by Whiting et al. Doses of cannabis ranged from THC 1% to 9.4% inhaled 3 to 4 times a day via cigarette and pipe and 1.29% to 3.53% for 8 to 12 puffs per day via vaporizer. Inhaled cannabis achieved more than 30% clinical reduction in chronic neuropathic pain on the visual analog scale (VAS) for 1 in every 6 patients (number needed to treat [NNT] = 5.6 [95% Bayesian credible interval (CRI) = 3.35-13.7]) with an OR of 3.2 (95% CRI = 1.59-7.24; Bayes factor of 332 corresponding to a posterior probability of effect of 99.7%) in a dose-dependent manner. The use of individual patient data enhanced the power of the study, as evidenced by the high posterior probability of effect, and permitted exploration of heterogeneity at the patient level, which was highly homogeneous (Bayesian I^2 analogue = 0%). Studies were mostly of good quality in the different domains of the Cochrane Risk of Bias tool with the exception of blinding of participants and outcome observers due to the psychotropic effects of the intervention. Other shortcomings of the studies included brief treatment duration (3 to 5 days) of individual studies and a lack of power to adequately assess publication bias through funnel plot due to the synthesis of less than 10 studies.

Finally, a systematic review commissioned by the Veterans Health Administration by Nugent et al[57] included all RCTs from the previous 2 reviews with 3 additional RCTs and 3 observational studies of nonsynthetic cannabinoids (inhaled, oils, extracts) in neuropathic pain, multiple sclerosis, cancer pain, and other mixed pain conditions. Although studies did not identify any difference between placebo and cannabis on continuous pain scales for neuropathic pain, a greater proportion of patients receiving cannabis achieved clinically significant pain relief (defined as ≥30% reduction, 2-point reduction on numerical rating scale [NRS], or 20-mm reduction on VAS) up to several months later. Moreover, a study-level meta-analysis of 9 RCTs found that patients receiving cannabis were more likely to report a minimum of 30% clinical improvement in neuropathic pain (OR = 1.43 [95% CI = 1.16-1.88], I^2 = 38.6%, P = .111). However, most of the RCTs were limited to 2 to 3 weeks in duration and studies with low risk of bias had few patients enrolled. Findings were also inconsistent and there was high variability in dosing and delivery mechanism. As such, Nugent et al concluded that there was low-strength evidence to support the use of cannabis for neuropathic pain based on the consistency, coherence, and applicability of the body of evidence, in addition to the internal validity of individual studies. For multiple

sclerosis, cancer pain, and mixed pains, the strength of evidence was insufficient to support a conclusion.

The majority of evidence in pain was derived from patients with neuropathic pain associated with peripheral neuropathy, post-herpetic neuralgia, nerve or spinal cord injury, complex regional pain syndrome, HIV, and diabetes. Despite the exclusion of patients with renal impairment from studies, treatment of neuropathic pain is highly relevant in patients with CKD due to its common occurrence as a diabetic complication in this population. Based on systematic reviews of low to moderate heterogeneity, there is sufficient evidence that, compared with placebo, nonsynthetic cannabinoids can achieve a moderate reduction of chronic neuropathic pain, defined as a minimum of 30% pain reduction[57] (level of evidence 1a). As estimated in the meta-analysis by Andreae et al, the NNT is 5.6 with nonsynthetic cannabinoids.[56] In contrast, a more recent Cochrane systematic review that was published beyond our search date reported the NNT to achieve ≥30% and 50% pain reduction to be 11 (risk difference [RD] = 0.09 [95% CI = 0.03-0.15], $P = .004$, $I^2 = 34\%$) and 20 (61% vs 29%; RD = 0.38 [95% CI = 0.18-0.58]), respectively.[60] While the study pooled data from both synthetic and nonsynthetic cannabinoids and would have been excluded from our review, the results were primarily driven by nabiximols in the form of the oromucosal spray. These benefits were outweighed, however, by an increase in adverse effects of the nervous system (number needed to harm [NNH] of 3) and associated with higher treatment withdrawal due to adverse events (NNT = 25). With respect to the lower NNT observed in a review by Andreae et al, the authors of the Cochrane review attributed the difference to the inclusion of unpublished studies with negative reviews and the exclusion of studies of short duration (less than 12-week duration) and vague definitions of neuropathic pain in their analysis. When compared with other pharmacological treatments, the NNT to achieve at least moderate pain benefit as defined by Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) for gabapentin in diabetic neuropathy is 6.6 (95% CI = 4.9-9.9) at doses ≥900 mg daily in patients without renal impairment, suggesting nonsynthetic cannabinoids have lower to comparable efficacy at best.[61] Currently, there is inconclusive evidence to comment on the effects of cannabis on other specific types of pain such as cancer pain and multiple sclerosis.

Nausea and Vomiting

Incidences of nausea and vomiting in patients receiving hemodialysis are estimated to be as high as 18.2% to 28.3% and 9.8% to 11.7%, respectively.[58,59] In CKD stages 4 and 5, changes in salivary composition likely related to uremia, such as higher salivary sodium levels and greater sodium to potassium ratio, have been linked to nausea.[62] Although acidosis and uremia-induced nausea and vomiting typically resolve with initiation of dialysis, disequilibrium syndrome, aggressive fluid removal, dialyzer reactions, and intravenous iron administration during dialysis can also precipitate these symptoms. Moreover, other comorbidities such as diabetic gastroparesis and adverse effects of medications can further obscure the underlying cause. The multifactorial nature of nausea and vomiting in patients with renal impairment renders it a complex condition to explore. Although there are a few case reports, a small crossover study, and expert opinion to support the use of metoclopramide, ondansetron, and haloperidol for uremia-induced nausea and vomiting,[63-65] the effects of cannabis in uremia-induced nausea and vomiting have not been examined.

Evidence to support cannabinoid use in the treatment of nausea and vomiting has primarily been in the setting of severe or refractory chemotherapy-induced nausea and vomiting (CINV) with synthetic cannabinoids, which exclude the CKD population. Nabilone and dronabinol, for instance, have comparable efficacy with prochlorperazine and metoclopramide for treatment of nausea and vomiting in moderate to highly emetogenic chemotherapy regimens, but with higher incidences of patient withdrawal due to adverse effects such as dizziness and sedation[66] (level of evidence 1a).

Evidence to support the use of nonsynthetic cannabinoids for CINV is less established: nonsynthetic cannabinoids in CINV were studied in only 3 small RCTs ($n < 20$) in the form of Sativex® oromucosal spray and inhaled marijuana[67-69] (level of evidence 2b). Compared with placebo, Sativex® oromucosal spray achieved greater complete antiemetic response in 16 patients refractory to standard antiemetic prophylaxis (corticosteroids, 5-HT_3 receptor antagonists, metoclopramide) while receiving moderate emetogenic chemotherapy regimens (OR = 3.22, 95% CI = 0.01-0.75).[70] Two older, small RCTs combined preparations of nonsynthetic oral THC followed by inhaled THC if vomiting persisted and found that THC was effective as an antiemetic for low emetogenic chemotherapy regimens, but not for chemotherapy of high emetogenic potential[68,69] (level of evidence 2b). In the study with high emetogenic chemotherapy, THC plasma concentrations achieved were low and the authors attributed this to inadequate inhalation of THC by inexperienced patients. Studies also demonstrated that inhaled cannabis achieved better therapeutic plasma concentrations of THC than the oral route and a linear relationship existed between increasing THC plasma concentration and antiemetic effect. Incidences of nausea and vomiting were 44%, 21%, and 6% with concentrations of <5.0 ng/mL, 5.0 to 10.0 ng/mL, and >10 ng/mL, respectively. Similar to previous studies, the rate of adverse drug reaction (ADR) was high: 80% of patients experienced sedation in the study with low emetogenic chemotherapy. Evidence to support the use of nonsynthetic cannabinoids in CINV is significantly limited by small study sizes and low doses of THC used (1.95%).

Aside from CINV, a small study (n = 13) found a modest effect of smoked marijuana (2.11% THC) in reducing

ipecac-induced emesis, which is caused by activation of emetic sensory receptors at the proximal small intestines and central stimulation of the medullary chemotherapy trigger zone.[70,71] However, the study also found that ondansetron was a more effective antiemetic as it completely eliminated emetic effects of ipecac, which, again, suggests that cannabinoids may not offer an advantage over conventional antiemetics. Further studies are still necessary to determine whether cannabinoids are effective for causes of nausea and vomiting beyond CINV and to advise on the optimal THC and CBD ratio to mitigate cannabinoid adverse effects.

Anorexia

As a manifestation of uremic syndrome, anorexia progressively leads to malnutrition, cachexia, and poor QOL toward later stages of CKD. The cause of uremic anorexia is multifaceted and arises from a combination of increased anorexigenic compounds and cytokines such as TNF-alpha, pro-inflammatory substances, and disturbances in amino acid concentrations in the central nervous system, which triggers the synthesis of serotonin, an appetite suppressant.[72] THC induces appetite by activating CB_1 receptors centrally in the hypothalamic region responsible for homeostatic regulation of feeding and peripherally to signal the nutritional state of the gut and lipogenesis.[73,74]

The use of cannabinoids for anorexia has only been studied in the context of AIDS and HIV wasting syndrome, cancer, and anorexia nervosa, but has not been explored in uremic anorexia.

In adults with cancer-related anorexia-cachexia syndrome, a double-blinded RCT (n = 243) demonstrated no differences in appetite or QOL between a natural cannabis extract of 2.5 mg THC and 1 mg CBD, 2.5 mg THC, and placebo administered orally twice a day for 6 weeks[75] (level of evidence 1b). Due to insufficient differences between study arms, patient recruitment was terminated early on the recommendation of an independent data review committee.

In HIV-associated wasting syndrome, 2 small within-subjects studies (total n = 40) demonstrated a significant dose-dependent effect on increasing caloric intake and body weight with smoked marijuana (up to 3.9% THC) and oral dronabinol (up to 40 mg daily) through increased frequency of daily food intake and proportion of daily calories from fat intake (level of evidence 2b).[76,77] Significant weight gain for nonsynthetic cannabinoids in HIV- and AIDS-associated wasting syndrome was also observed as a secondary outcome in a 3-week RCT (n = 67) that compared smoked marijuana (3.95% THC, up to 3 cigarettes per day) (3.0 kg, $P = .021$), dronabinol 2.5 mg orally 3 times daily (3.2 kg, $P = .004$), and oral placebo (1.1 kg).[78] While synthetic cannabinoids such as dronabinol have been Food and Drug Administration (FDA) approved for this indication, the primary study behind the approval was a 6-week RCT (n = 139) with a mean weight gain of only 0.1 kg in the dronabinol group compared with a weight loss of 0.4 kg in the placebo group over 6 weeks (95% CI = 0.72-6.06) (level of evidence 2b).[79] The high risk for attrition bias from protocol violations in the placebo group (presence of cannabinoids in urine in placebo group) and the brevity of the study duration warrant cautious interpretation of the benefits shown in the study.

Studies evaluating nonsynthetic cannabinoids in anorexia nervosa were not identified, but a small double-blinded crossover RCT found benefit with a synthetic cannabinoid. Dronabinol 2.5 mg PO bid for 4 weeks resulted in significant weight gain of 1 kg compared with placebo.[80]

Although increased appetite is a known effect, there is currently inadequate evidence to support or disprove the use of nonsynthetic cannabinoids as appetite stimulants in uremia-induced anorexia and cachexia in patients with CKD due to a lack of studies in this population. There is some literature to support the short-term use of cannabis and oral cannabinoids in improving appetite and weight gain in patients with HIV- and AIDS-associated wasting syndrome, but the pathophysiology of this condition is significantly different from uremic anorexia. As well, these benefits have not been replicated in other types of anorexia including cancer-associated anorexia and anorexia nervosa.

Uremic Pruritus

Systemic inflammation, imbalance in opioid receptor expression, poorly controlled mineral bone disease, and mast cell release of histamine and other pruritogens have all been implicated in uremic pruritus, but treatment remains nonspecific and limited. Moreover, uremic pruritus impacts 40% of patients with ESRD to a moderate to severe degree.[81] Cannabinoids have been identified as neuronal modulators of pruritus and a single observational study appears promising for uremic pruritus. In the absence of antihistamine effects, peripheral transdermal administration of cannabinoid receptor agonists can attenuate histamine-induced itch by decreasing nerve fiber activation and subsequent neuropeptide and inflammatory mediator release.[82,83] In a small study of patients receiving hemodialysis experiencing uremic pruritus (n = 21), endocannabinoids containing N-acetylethanolamine and N-palmitoylethanolamine with structured physiological lipids (Derma Membrane Structure) in the form of a topical cream (Physiogel AI cream®) applied twice daily for 3 weeks effectively reduced both pruritus and xerosis.[84] Pruritus and xerosis were completely eliminated in 38.1% and 81% of patients, respectively (level of evidence 2b). Due to the brevity of the study duration, minute sample size, and absence of adjustment for potential confounders of this observation study, there is currently insufficient evidence to recommend the use of nonsynthetic cannabinoids for uremic pruritus. Nonetheless, the advantage of topical endocannabinoids to minimize systemic adverse drug effects compared with oral and inhaled routes and their potential

role in managing uremic pruritus certainly warrant further investigation.

Insomnia

The incidence of sleep disorders is greater in patients with ESRD compared with the general population, with insomnia, restless leg syndrome, sleep-disordered breathing, and excessive daytime sleepiness being the most frequently reported.[85] Research in cannabinoid for treatment of insomnia began in the 1970s, but has excluded patients with renal impairment.

Literature on cannabinoids for insomnia has predominantly been in the context of concomitant neuropathic pain, rather than in primary insomnia. Whiting et al identified 17 RCTs in a systematic review with placebo comparators that assessed nonsynthetic cannabinoids for neuropathic pain and spasticity in patients with multiple sclerosis and included insomnia as a secondary outcome.[56] There were 2 pooled analyses of very low GRADE rating, mostly of nabiximols, which demonstrated a higher average improvement in sleep quality (weighted mean difference of −0.58 on NRS of 0 to 10 [95% CI = −0.87 to −0.29]; 8 trials) and sleep disturbance (weighted mean difference of −0.26 on NRS [95% CI = −0.52 to 0.00]; 3 trials) compared with placebo. However, the minor difference of −0.58 observed over a 10-point scale is unlikely to be clinically significant. Moreover, as a secondary outcome, these findings are not only hypothesis generating, but also confounded by concomitant improvement in neuropathic pain and multiple sclerosis-related spasticity. As cannabinoids are effective in the treatment of neuropathic pain, studies in primary insomnia are needed to definitively establish cannabinoid effects on sleep without the interference of confounders.

Current evidence is insufficient to provide guidance on the use of cannabinoids for primary insomnia or in association with chronic pain, but provokes further studies. Preliminary studies in healthy volunteers and animal models have also suggested that a ratio of high-dose CBD and low-dose THC may be therapeutically favorable for sleep,[86] but this remains to be validated through adequately powered clinical trials in the general population and in CKD patients with insomnia.

Adverse Effects of Marijuana

The adverse effect of marijuana can be described in 3 general themes: behavioral, respiratory, and effects in other body systems. With respect to adverse effects in patients with ESRD, cognitive impairment is of concern for home dialysis patients and those driving to a dialysis center. Also concerning is the association of an increased mortality post-myocardial infarction (MI), and respiratory complications, as described below.

A recent paper described the effects on cognition, motivation, and psychosis noting that adolescents may be particularly vulnerable to longer term neuropsychological impairment.[88] Young adults with long-term cannabis use may underachieve in education and have impaired motivation.[89] More troubling is the finding that cannabis may trigger a long-term psychiatric illness in those with a genetic vulnerability.[90] Given the evidence, it is now accepted that use be limited to the adult population older than the age of 25 years. In the short term, THC can induce dose-dependent positive and negative symptoms such as panic attacks, paranoid thoughts, and hallucinations.[91] In addition, cannabis use impairment increases the risk of being involved in a motor vehicle accident—a recent systematic review determined that THC in body fluids was associated with a 20% to 30% higher odds, described as a low to moderate risk.[92] Vehicle accident studies do have a number of confounders but overall the evidence is considered substantial.[93] Finally, cannabis dependence is estimated to occur in approximately 1 in 10 users who smoke cannabis.[94]

With regard to the respiratory system, cannabis can be an irritant, leading to chronic bronchitis.[95] When combined with tobacco use, dyspnea, hoarseness, chronic obstructive pulmonary disease (COPD), or pharyngitis have been noted.[96,97] When smoked, cannabis has been associated with tumors of the upper respiratory tract, gastrointestinal tract, lungs, bladder, and nasopharyngeal area. It is not associated with head and neck tumors (level of evidence 2b).[98] All-cause mortality is affected by motor vehicle accidents and tumors attributed to cannabis but the data are from systematic reviews of case reports (level of evidence 3a).[99] Evidence of other effects on the respiratory system, skin, mucosa and on the immune system are rated at a level 4.

In the cardiovascular system, there is a dose-dependent relationship between cannabis consumption and mortality after a MI with a hazard ratio of 4.2 for weekly consumption (level of evidence 1b).[100] Metabolically, chronic cannabis users have a higher proportion of abdominal fat and demonstrated higher adipocyte resistance to insulin and lower oral glucose tolerance (level of evidence 2b).[99] Given the burden of cardiovascular disease and diabetes in the renal failure population, these effects may be magnified although this has not been determined. The THC in cannabis has been associated with dose-dependent transient rises in heart rate and a modest rise in supine blood pressure,[101,102] but a clear association with hypertension has not been established. Episodes of orthostatic hypotension and syncopal episodes have also been reported with smoked cannabis particularly with high doses (level of evidence 2b-),[103] which may preclude its use in CKD patients with symptomatic orthostatic hypotension secondary to diabetic autonomic neuropathy. However, following 1 to 2 days of repeated exposure, tolerance develops and chronic cannabis use has been associated with reduced heart rate and resolution of orthostatic hypotension.[103]

Unapproved for human consumption, synthetic cannabinoids in the form of designer drugs such as "K2" and "Spice" are analogs of THC, but with greater potency and binding affinity to CB_1 receptors. Although the term *synthetic*

Table 2. Adverse Effects and Precautions With Cannabis Use.

	Adverse effects	Precautions with cannabis use
Central nervous system	Impaired cognition, drowsiness, dizziness, euphoria[9,10]	• Driving under the influence of cannabis increases the risk of motor vehicle accidents. All patients should be advised not to drive for a minimum of 3 to 4 h after smoking, 6 h after oral consumption, and 8 h if euphoria occurs.[87] Patients who drive to hemodialysis centers may need to consider an alternative mode of transportation if the above administrative precautions cannot be adhered to. • Avoid in late-stage predialysis CKD patients who may be at risk for uremic encephalopathy. • Avoid in patients with heavy alcohol consumption or receiving high-dose opioids, benzodiazepines, or sedatives due to potential for additive effects on cognitive impairment.
	Cannabis use disorder[94]	• Avoid in patients with active substance abuse.
	Anxiety and panic attacks[91]	• Avoid in patients with mood or anxiety disorder.
	Psychosis, hallucinations[9,10]	• Avoid in patients with a history or strong family history of psychosis. • Avoid in patients aged 25 years or younger due to increase risk of long-term neuropsychological impairment and psychiatric illness in those with genetic vulnerabilities.[88-90]
Cardiovascular	Increased mortality post-myocardial infarction[100]	• Avoid smoked cannabis in patients with cardiovascular disease.
	Orthostatic hypotension[103]	• Consider initiating at a low dose with gradual titration. Tolerance may develop with repeated administration in 1 to 2 days.[103]
Respiratory	Chronic bronchitis, COPD, lung cancer[95-97]	• Avoid smoked cannabis in patients with respiratory disease.
Gastrointestinal	Cannabinoid hyperemesis syndrome[115]	• Associated with chronic cannabinoid use and has been associated with prerenal acute kidney injury.[108-114]

Note. CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

cannabinoids is frequently used to refer to these designer drugs, they are unregulated drugs of abuse and are distinctively different from pharmaceutical synthetic cannabinoids such as dronabinol and nabilone. These designer drugs are frequently dissolved in a solvent, sprayed onto dried plant material, and either smoked or vaped and have been linked to acute kidney injury. In a case series of 9 men, one required dialysis with all surviving.[105] A similar cluster has been also reported with 5 of 16 previously young healthy patients requiring hemodialysis, and in most cases, renal biopsies have demonstrated acute tubular necrosis.[104] It is unclear whether reports of AKI associated with smoked synthetic cannabinoids is due to a prior unrecognized toxicity, the effects of contaminants or known nephrotoxin, or a specific synthetic cannabinoid compound in the market. It should be emphasized that cannabis itself has not been shown to be associated with a loss of kidney function. In a large observational study of US veterans (n = 6788) with advanced CKD and progression to dialysis, those who tested positive for cannabis use within the year of dialysis initiation did not experience a more rapid loss in kidney function compared with those who did not use cannabis.[106]

Finally, it is worth noting that for heavy cannabis users, cannabis withdrawal syndrome has been noted to occur during conventional hemodialysis. Nervousness, irritability, restlessness, twitch, nausea, stomach pain, increased appetite, and muscle pain occurred in one case report at hour 3 of dialysis as THC may be more dialyzed than previously thought.[107] In addition, there are at least 7 case reports of cannabinoid hyperemesis syndrome–associated prerenal acute kidney injury and dehydration from intractable vomiting and, in a few cases, concomitant compulsive hot showering.[108-114] Cannabinoid hyperemesis syndrome is associated with chronic cannabinoid use and is characterized by recurrent nausea, vomiting, abdominal pain, and frequent hot bathing, a learned behavior that temporarily alleviates the syndrome. Clinicians should be aware that cannabinoid hyperemesis syndrome may initially be viewed as uremic symptoms so a routine inquiry into cannabis use is prudent.[115]

Discussion

The focus of this article has been on nonsynthetic cannabis as opposed to synthetic cannabinoids such as dronabinol and nabilone, as the effects of isolated cannabinoids can be different from that produced by the whole plant. However, there are significant methodological challenges of studying nonsynthetic cannabis: standardization of drug delivery and exposure is poor due to the diversity of cannabis strains and their administration routes. Aside from nabiximols, which is available as a fixed dose of THC:CBD as an oromucosal spray, there is high variability in cannabis preparations in literature, which is further complicated by a lack of reporting of cannabis strains used. For studies that examine

Table 3. Summary of Evidence of Nonsynthetic Cannabinoids for Symptom Management in CKD.

Indication	Level of evidence[a]	Conclusion
Chronic pain	1a	• Based on extrapolated evidence from patients without renal impairment, nonsynthetic cannabinoids have a moderate effect on the reduction of chronic neuropathic pain, which is a minimum of 30% pain reduction.[53,56,57,60]
Nausea and vomiting	—	• There is a lack of evidence to support or disprove the use of nonsynthetic cannabinoids for uremia-induced nausea and vomiting, as cannabinoids have not been studied for this indication.
	2b	• Based on limited evidence extrapolated from patients without renal impairment, nonsynthetic cannabinoids may possibly be effective in the treatment of chemotherapy-induced nausea and vomiting secondary to low-to-moderate emetogenic chemotherapy regimens.[67-69]
	1a	• Based on extrapolated evidence from patients without renal impairment and receiving moderate to highly emetogenic chemotherapy regimens, synthetic cannabinoids, nabilone, and dronabinol[b] have comparable efficacy with prochlorperazine and metoclopramide for the treatment of chemotherapy-induced nausea and vomiting, but with higher incidences of adverse effects.[66]
Anorexia	—	• There is a lack of evidence to support or disprove the use of nonsynthetic cannabinoids as appetite stimulants in uremia-induced anorexia and cachexia due to an absence of studies for this indication.
	2b	• In extrapolated data from patients without renal impairment with HIV-associated wasting syndrome, there is limited evidence that nonsynthetic cannabinoids are effective in increasing caloric intake and body weight in the short term.[76-78]
	1b	• In extrapolated data from patients without renal impairment, nonsynthetic cannabinoids are ineffective for increasing appetite or improving quality of life in cancer-related anorexia-cachexia syndrome.[75]
	—	• There is a lack of evidence to support or disprove the use of nonsynthetic cannabinoids as appetite stimulants in patients with anorexia nervosa, as they have not been studied for this indication.
Uremic pruritus	2b	• Topical endocannabinoids may possibly be effective for uremic pruritus in patients receiving hemodialysis based on limited evidence from a small observational study.[84]
Insomnia	—	• There is currently a lack of evidence to support or disprove the use of nonsynthetic cannabinoids for insomnia, as studies have not been conducted in patients with primary insomnia.

Note. CKD = chronic kidney disease.
[a]Based on the Oxford Centre for Evidence-based Medicine Grading.
[b]Dronabinol has been discontinued in Canada, but is approved for use in the United States.

whole plant cannabis, dosage is frequently reported only based on proportion of THC, which limits guidance to the different effects of cannabis strains and hybridized breeds available. Variation in smoking techniques, such as depth and frequency of inhalation, can also lead to inconsistent drug delivery to study participants. Moreover, it is unclear whether administration methods such as vaporization, which spares the production of toxic combustion compounds by heating cannabinoids at a lower temperature, produce comparable efficacy and bioavailability of cannabinoids as smoking. Implementation of an effective placebo is also a significant barrier to conducting quality cannabis trials. Despite of double blinding of RCTs, psychotropic effects of THC are difficult to mask, particularly among experienced cannabis users; hence, risk for detection and performance bias is often high. The significant increase in THC potency from 3% to 12% since 1980s to 2012 in confiscated marijuana suggests that relevance of earlier studies with low potency cannabis may be limited, particularly with respect to long-term adverse effects.[116]

It is crucial that clinicians justify the degree of therapeutic benefit of nonsynthetic cannabinoids for CKD symptom management against its harms, particularly with inhaled cannabis, which has a similar carcinogenic chemical profile as tobacco smoke.[117-119] If treatment with cannabis were pursued, it would be prudent to engage a clinical pharmacist to assess for potential drug interactions involving cytochrome P450 isoenzymes and to consider implications on the risk for adverse effects in patients with hepatic impairment. With current studied doses, the neuropathic analgesia and antiemetic effects in CINV of cannabinoids have demonstrated only modest improvement and may be less efficacious or, at best, comparable with conventional pharmacological treatments. Nonetheless, with the risk for dependency, cognitive impairment, and mortality post-MI, the adverse effect profile can potentially be more harmful than conventional treatments in patients with CKD. Considering this, cannabinoids should be reserved for patients with intolerances or refractory conditions where conventional therapies have failed and benefits may outweigh the risks. As well, their role may be most impactful in patients with ESRD, where life span is often limited particularly with advanced age, and transition to palliative care is most frequent.

Conclusion

Due to limited treatment options, symptom management in patients with CKD can be challenging, and therefore

Oxford Centre for Evidence-based Medicine Levels of Evidence (March 2009).[120]

1a	Systematic reviews (with homogeneity) of randomized controlled trials
1a-	Systematic reviews of randomized controlled trials displaying worrisome heterogeneity
1b	Individual randomized controlled trials (with narrow confidence interval)
1b-	Individual randomized controlled trials (with a wide confidence interval)
1c	All or none randomized controlled trials
2a	Systematic reviews (with homogeneity) of cohort studies
2a-	Systematic reviews of cohort studies displaying worrisome heterogeneity
2b	Individual cohort study or low-quality randomized controlled trials (eg, <80% follow-up)
2b-	Individual cohort study or low-quality randomized controlled trials (eg, <80% follow-up/wide confidence interval)
2c	"Outcomes" research; ecological studies
3a	Systematic review (with homogeneity) of case-control studies
3a-	Systematic review of case-control studies with worrisome heterogeneity
3b	Individual case-control study
4	Case-series (and poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal or based on physiology bench research or "first principles"

therapeutic alternatives are in high demand. In recent years, medical marijuana has emerged as an attractive therapeutic option, but continues to be used for a variety of unsubstantiated indications with minimal guidance on known risks, particularly with respect to the altered physiological state of patients with CKD. At this time, the supportive evidence for using nonsynthetic cannabinoids for symptom management is limited to the treatment of chronic neuropathic pain, with promising potential when used topically for the treatment of uremic pruritus. Clinicians need to be cognizant that nonsynthetic cannabinoids, particularly smoked cannabis, pose significant health risks which must be cautiously weighed against the limited substantiated therapeutic benefits of cannabis.

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