Special Article

Is There a Legitimate Role for the Therapeutic Use of Cannabinoids for Symptom Management in Chronic Kidney Disease?

Sara N. Davison, MD, and Joseph S. Davison, PhD

Division of Nephrology and Immunology (S.N.D.), University of Alberta, Edmonton; and Department of Physiology and Biophysics (J.S.D.), University of Calgary, Calgary, Alberta, Canada

Abstract

Chronic pain is a common and debilitating symptom experienced in the context of numerous other physical and emotional symptoms by many patients with chronic kidney disease (CKD). Management of pain with opioids in CKD can be problematic given the prominence of adverse effects of opioids in CKD, which may exacerbate symptoms, such as nausea, anorexia, pruritus, and insomnia, all of which affect negatively patients' health-related quality of life. Novel therapeutic approaches for pain and symptom management in CKD are required. Recent research in the area of cannabinoids (CBs) is legitimizing the use of cannabis-based medicine. In this review, we describe the symptom burden borne by patients with CKD and review some of the key basic science and clinical literature to evaluate the potential use of CBs for the management of overall symptom burden in CKD. J Pain Symptom Manage 2011;■:■—■. *© 2011 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.*

Key Words

End-stage renal disease, pain, symptom management, cannabinoids, marijuana

Introduction

Despite the use of current first-line agents for symptom management, patients suffering from chronic nonmalignant illnesses continue to experience substantial symptom burden related to both disease and side effects from treatments. In advanced chronic kidney disease (CKD), the symptom burden and health-related quality of life (HRQL) is so adversely impacted that, increasingly, patients are being managed conservatively (without the use of dialysis) or are choosing to withdraw from dialysis. Novel therapeutic approaches for pain and symptom management are required. Cannabis has been used both recreationally and therapeutically for more than 5000 years, yet there remains significant social, legal, and medical debate over its therapeutic use, primarily because of its psychotropic effects and its potential for abuse. However, recent research in the area of cannabinoids (CBs) is legitimizing the use of cannabis-based medicine. In this review, we describe the symptom burden borne by patients with CKD

Address correspondence to: Sara N. Davison, MD, Division of Nephrology and Immunology, University of Alberta, 11-107 Clinical Sciences Building, Edmonton, Alberta T6G 2G3, Canada. E-mail: sara.davison@ualberta.ca

Accepted for publication: June 27, 2010.

0885-3924/$ - see front matter
doi:10.1016/j.jpainsymman.2010.06.016

and then review some of the key basic science and clinical literature to evaluate the potential use of CBs for the management of overall symptom burden in CKD.

Prevalence and Affect of Chronic Pain in CKD

Pain is one of the most commonly experienced and debilitating symptoms of patients with CKD. Approximately 50% of dialysis patients and those with advanced CKD who choose to be managed conservatively (i.e., without chronic dialysis) experience chronic pain, with 82% reporting this pain as moderate to severe in intensity.[1–3] Causes of chronic pain in CKD are diverse and often multifactorial (Table 1). Although pain is one of the principal factors in determining HRQL in CKD, it is neither the only one nor indeed the most common. Pain is experienced in the context of numerous other physical and emotional symptoms (Fig. 1), all of which impact negatively on HRQL. Symptom burden has been shown to account for 39% of the impairment in mental HRQL and 29% of the impairment in physical HRQL. More importantly, change in symptom burden has been shown to account for 46% and 34% of the changes in mental and physical HRQL, respectively.[4,5] The overall symptom burden of patients with advanced CKD is similar to that of many cancer patients admitted to palliative care settings.[4,6] Despite improvements in dialysis technology, pain and overall symptom burden may not improve after the initiation of dialysis.[7] Effective clinical approaches to symptom management, and in particular chronic pain, are clearly essential if efforts to improve HRQL for CKD patients are to be successful.

Table 1
Examples of Causes of Chronic or Recurrent Pain in CKD[1]

Causes of Chronic or Recurrent Pain in CKD
Comorbid illnesses
Diabetic peripheral neuropathy
Peripheral vascular disease
Cause of kidney failure
Polycystic kidney disease
Syndromes unique to CKD
Renal bone disease
Dialysis-related amyloidosis
Uremic peripheral neuropathy
Calcific uremic arteriolopathy (calciphylaxis)
Nephrogenic systemic fibrosis
Syndromes common in or exacerbated by CKD
Inflammatory arthritis
Osteoarthritis
Osteoporosis
Complications of the dialysis procedure
Recurrent pain while on dialysis: cramps, headaches, and needling of arteriovenous fistula
Discitis/osteomyelitis from central venous catheters (dialysis access)
Vascular steal from arteriovenous fistulae (dialysis access)
Lower back strain from abdominal distension with peritoneal dialysis

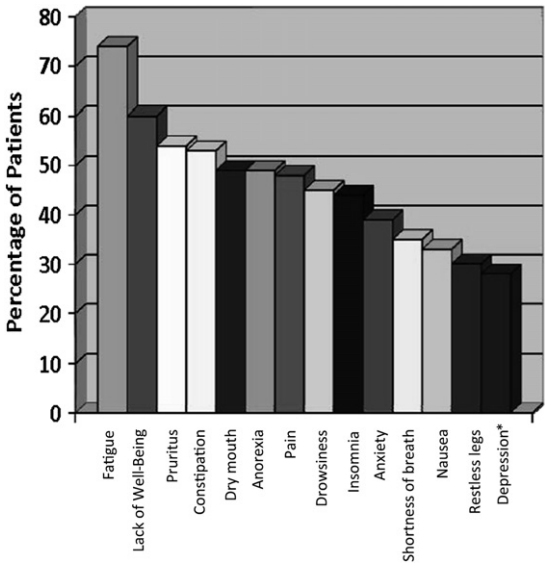

Fig. 1. Symptom burden in CKD. *Although no large-scale, well-designed, epidemiologic studies of depression in end-stage renal disease have been conducted, the prevalence appears to be 5%–50% in dialysis patients.

Current Analgesic Use in Patients with CKD

Despite what appears to be an increasing prevalence of chronic pain, analgesic use in 142 U.S. dialysis facilities[8] has decreased (Fig. 2). These findings are consistent with other reports where 35% of hemodialysis patients with chronic pain were not prescribed analgesics, despite the vast majority experiencing moderate or severe pain, and less than 10% were prescribed opioids.[1] The active metabolites of opioids are excreted renally

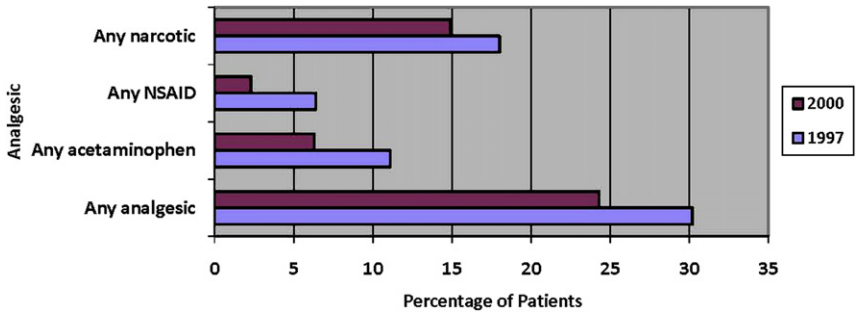

Fig. 2. Point prevalence of analgesic use in the Dialysis Outcomes and Practice Patterns Study. Seventy-four percent of patients with pain that interfered with work had no analgesic prescription. NSAID = nonsteroidal anti-inflammatory drug.

and may accumulate rapidly. As a result, adverse effects of opioids, such as constipation, nausea, gastroparesis, reflux, dry mouth, pruritus, decreased libido, restlessness, agitation, insomnia, central nervous system depression, hypotension, and opioid toxicity are more common in patients with CKD.

Theoretical Reasons Why Cannabis-Based Medicine May Be Particularly Beneficial in CKD

Despite pain relief, opioid adverse effects may exacerbate numerous symptoms already commonly experienced in CKD, thus increasing total symptom burden and failing to improve HRQL. Currently, there are no data on the overall impact of opioid therapy for chronic pain in CKD. The rationale for considering cannabis-based medicine for these patients is based on the encouraging results of CB agonists in treating not only intractable pain (neuropathic, inflammatory, and visceral) in a range of medical conditions but also in the treatment of other debilitating symptoms problematic in CKD, such as nausea, emesis, anorexia, pruritus, insomnia, and an overall lack of well-being (Table 2).[9]

The Biology of Marijuana-Derived CBs and Their Receptors

Marijuana is a crude drug derived from the plant *Cannabis sativa*. It contains more than 400 compounds, of which 66 are defined as CBs[10] based on their typical 21-carbon structure and their interaction with two CB receptors,

Table 2
Additional Benefits of CBs

Indication	Comments
Anorexia/cachexia	AIDS patients have experienced a substantial improvement in appetite with dronabinol that was sustained for more than 12 months and associated with a modest (2 kg) increase in lean body mass.[45]
Pruritus	Topical CBs were effective in 21 hemodialysis patients with uremic pruritus.[46] Dronabinol was effective in three patients with intractable pruritus secondary to cholestatic liver disease.[47]
Insomnia	It remains unclear how, if at all, CBs alter sleep patterns. THC has been found to be sedative, whereas CBD appears to have alerting properties. Numerous clinical studies report significantly improved sleep quality in patients taking CBs for symptomatic treatment of multiple sclerosis, chronic pain, or intractable pruritus. Beneficial effects may be, in large part, a result of improved symptom control.
Anxiety/depression	CB_{2R} agonists are thought to have anxiolytic and antidepressant properties but good data are currently lacking.
Cardiovascular stability	CB_{1R} and especially CB_{2R} agonists limit cardiac infarct size induced by ischemia-reperfusion injury, and CB_{2R} agonists inhibit the progression of established atherosclerotic lesions in animal models. Pretreatment with $CB_{1/2R}$ agonists improves endothelial cell dysfunction and survival in both cardiogenic and endotoxic shock.[25,26]

AIDS = acquired immunodeficiency syndrome.

CB_{1R} and CB_{2R}, through which many of their biological effects are mediated.[11,12] Two of these CBs, Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Fig. 3), are the most extensively studied. The principal pharmacological effects of THC and CBD are shown in Table 3. THC not only acts as an analgesic but also appears to have antiemetic, antinausea, muscle relaxant, and appetite stimulant properties.[13,14] THC is the principal psychoactive constituent of cannabis.[11,12] It is a nonspecific CB receptor agonist as well as a partial agonist.[11] CBD also acts as an analgesic and muscle relaxant. In addition, it appears to have anticonvulsant, anxiolytic, neuroprotective, and antioxidant properties. The evidence is summarized in several excellent reviews.[15,16] Most importantly, although it has effects on the central nervous system, CBD is virtually without psychotropic actions and indeed may be an antipsychotic.[15–17]

Both CB_{1R} and CB_{2R} are G-protein-coupled receptors. The CB_{1R} is distributed widely in the brain and spinal cord[18] and in the enteric nervous system, where it regulates gastrointestinal motility.[19] It also is found in several other organs, such as the uterus, prostate, adrenals, urinary bladder, liver, heart, and blood vessels.[18] The CB_{2R} is closely associated with the immune system, being prevalent in peripheral immune cells, such as white blood cells. Also, CB_{2R} mRNA has been localized in the spleen, tonsil, and thymus, organs that are important sites of immune cell production and regulation.[18] Recently, however, the CB_{2R} has been found in the brain where it has been implicated in nausea and emesis,[20] in sensory neurons and peripheral nerves where agonists produce antinociceptive effects in models of inflammatory and nociceptive pain,[21] and in the enteric nervous system where it is involved in inflammation-induced changes in gastrointestinal motility.[22] There is also evidence that CB_{2R} agonists

Table 3
Physiological Actions of THC and CBD

Δ9-Tetrahydrocannabinol	Cannabidiol
• $CB_{1R/2R}$ agonist	• Analgesia
• Analgesia	• Muscle relaxation
• Muscle relaxation	• Anticonvulsant effects
• Antiemetic actions	• Anxiolytic effects
• Appetite stimulation	• Antipsychotic effects
• Psychotropic effects	• Neuroprotection
	• Anti-inflammatory effects (e.g., antioxidant)

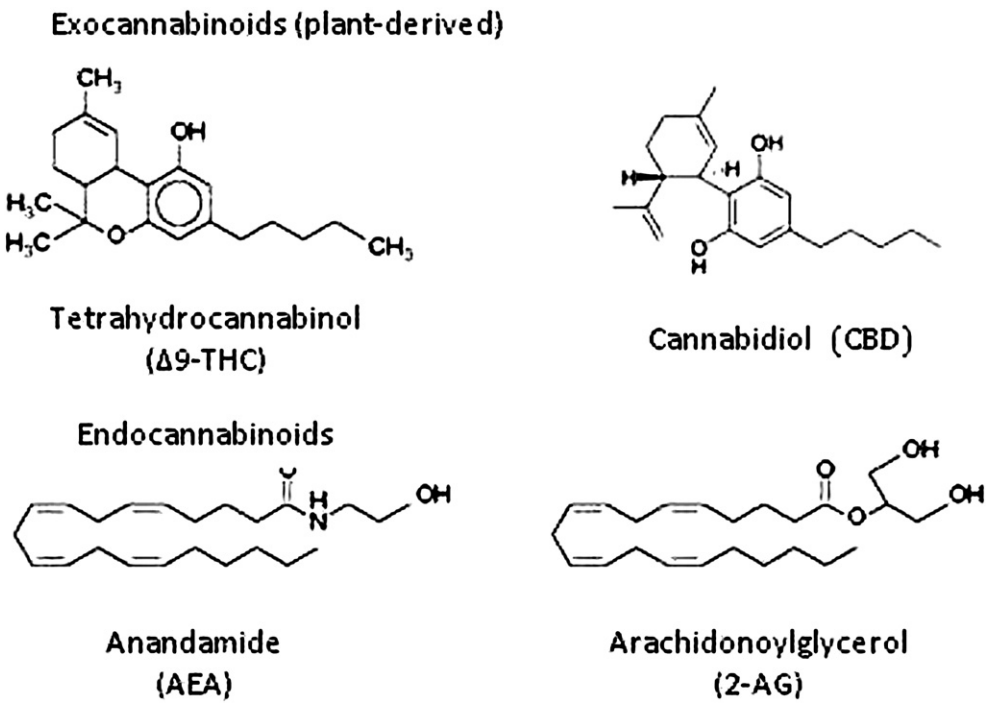

Fig. 3. Cannabinoid structure.

enhance the effect of μ-opioid receptor agonists, suggesting that opioids and CB_{2R} agonists may produce synergistic effects.[21]

The mode of action of CBD remains enigmatic. It has little affinity for the CB_{1R} or the CB_{2R}, but it does have potent antioxidant actions and can inhibit uptake and hydrolysis of anandamide, an endogenous CB, at both CB_{1R} and CB_{2R}, which could account for its beneficial therapeutic actions.[17] As detailed below, this action would enhance the efficacy of the endo-CB system activated in states, such as pain, inflammation, nausea, and emesis, leading to an amelioration of symptoms.

In addition, a family comprising at least five ionotropic CB receptors (ICRs) has recently been identified.[23] These ICRs are all members of the family of transient receptor potential (TRP) channels, which are located on peripheral sensory neurons. Activation of ICRs by CBs can desensitize certain TRP channel activities (e.g., TRPA1 and TRPV1 channels), leading to inhibition of peripheral nociceptors with a resulting allodynia and antihyperalgesia. Hence, CBs can potentially produce analgesia through peripheral and central mechanisms.

Endo-CB System

The discovery of CB_{1R} and the CB_{2R} and their subsequent cloning led to the identification of the endogenous ligands, anandamide and 2-arachidonoylglycerol (2-AG) (Fig. 3), and to the development of the concept of an endo-CB signaling system regulating a number of physiological functions, in particular neuronal and immune cell activity.[18,24] In the brain and enteric nervous system, the endo-CB system provides negative feedback within neuronal circuits by suppressing neurotransmitter release[16] (Fig. 4). Within the immune system, it has been shown that endo-CBs are upregulated in conditions of inflammation, that they downregulate the functionality of several types of human and rodent immunocytes, and that this anti-infection/anti-inflammatory action is largely mediated through CB_{2R} activation.[18,24] Activation of the CB_{2R} attenuates proliferation of T cells, activation of macrophages, and cytokine production; enhances proliferation of B cells, retaining immature precursor cells in the bone marrow; and limits leukocyte recruitment.[24] Because of these and other anti-inflammatory actions, CB_{2R} agonists have considerable therapeutic potential in several inflammatory conditions and have been shown to protect against ischemia-reperfusion injury and to slow the progression of atherosclerosis and restenosis in animal models.[25,26]

Studies on the role of the endo-CB system in the brain and elsewhere have indicated a potential therapeutic approach that could avoid the use of exogenous administration of CBs with the attendant risks of psychotropic effects and dependence. In the brain, endo-CBs are only synthesized and released "on demand," that is, when a neural pathway or network is activated. Blockage of endo-CB uptake or enzymatic degradation should result in localized accumulation of endo-CBs and enhancement of the negative feedback within the activated areas only, thereby limiting unwanted side effects because of generalized activation of CB (in particular CB_{1R}) receptors. For example, in the ferret, blockage of the processes that reduce synaptic uptake and the subsequent degradation of anandamide by fatty acid amide hydrolase (FAAH) has been shown to increase the accumulation of endo-CBs in the brainstem and to alleviate nausea and emesis, with no signs of unwanted psychotropic effects.[20]

In a recent review, Schlosburg et al.[27] summarized the evidence from recent investigations of the functional consequences of blocking FAAH in a variety of models of inflammatory and neuropathic pain. FAAH deficiency or blockade produced attenuation of inflammatory and nociceptive responses with a similar efficacy as exogenous CB treatment. The effects were mediated by CB_{1R} and/or CB_{2R} activation, although non-CB mechanisms also might play a primary or at least a contributory role. Significantly, despite the role of the CB_{1R}, no psychotropic effects were observed in any of the studies. Another recent study by Long et al.[28] showed that a selective inhibitor of monoacylglycerol lipase, which degrades the endo-CB 2-AG, produced an eightfold increase in brain concentrations of 2-AG with no measurable increase in anandamide. The treated animals exhibited a number of CB_{1R}-mediated behaviors and responses, including analgesia.

Thus, for the treatment of certain symptoms, including visceral and somatic pain,

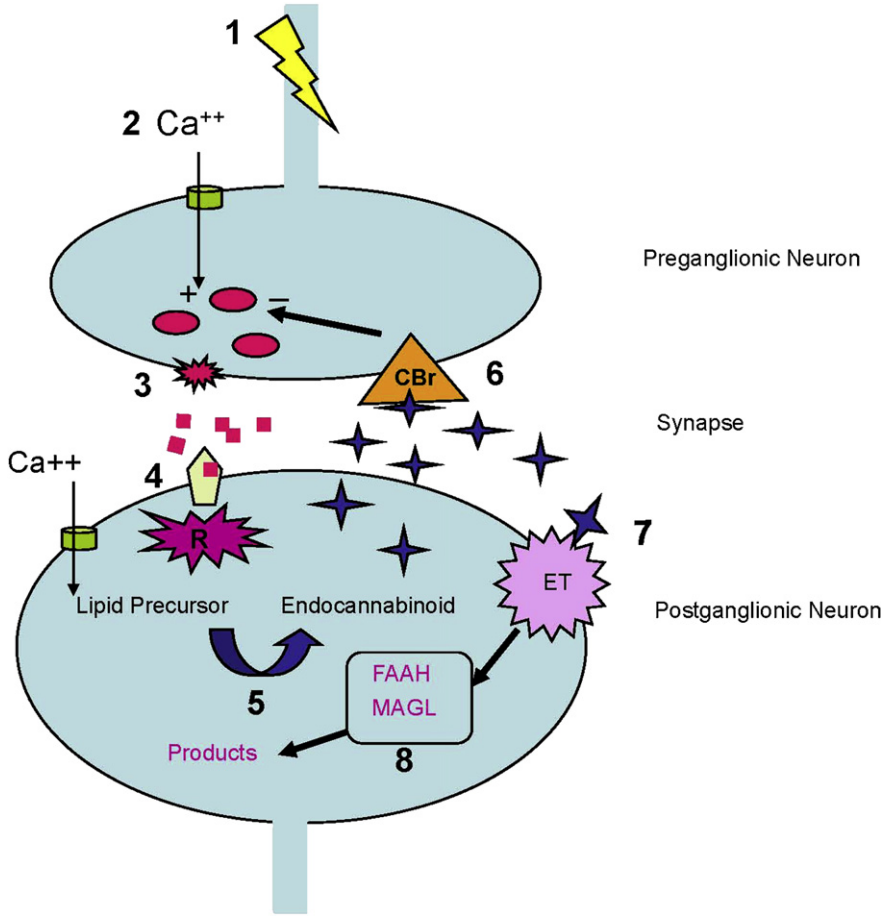

Fig. 4. Endo-CB signaling. Activation of the presynaptic neuron axon (1) leads to depolarization of the nerve terminal resulting in calcium influx (2), which stimulates (+) transmitter release (3) from presynaptic vesicles into the synaptic space. The transmitter binds to its receptors on the postsynaptic neuron (4) resulting in a neuronal response (R). This can initiate calcium influx or activation of other second messengers, which then stimulate endo-CB production from lipid precursors (5). The endo-CBs thus produced "on demand" then diffuse across the postsynaptic membrane and bind to the CBr on the presynaptic membrane (6) resulting in suppression of transmitter release from the presynaptic nerve terminal (−). The endo-CBs are prevented from accumulating in the synaptic space by rapid uptake into neurons and/or glia after binding (7) to an ET and subsequent degradation (8) by enzymes, such as FAAH or MAGL. CBr = cannabinoid receptors; ET = endo-CB transporter; FAAH = fatty acid amide hydrolase; MAGL = monoacylglycerol lipase.

nausea, and emesis, this approach of enhancing the localized concentrations of endo-CBs by blocking uptake and degradation would appear to have certain advantages. However, the drugs used in the above animal studies are not yet licensed for human use. Furthermore, when dealing with a complex cluster of symptoms, such as those experienced by CKD patients, there may be some value in using exogenous CBs despite the well-identified potential problems[13,29] and the need for further elucidation of the mechanism of action of CB agonists.[14]

Exogenous CBs Available for Clinical Use

In the United Kingdom, doctors were able to prescribe marijuana (cannabis) as recently as 1971; and in a 1994 survey, 74% of U.K. doctors wanted cannabis to continue to be available by prescription. The illicit use of cannabis by patients with high symptom burdens is widespread, and there are an estimated three million frequent users in the United Kingdom alone.[30] In Canada and the United States, the use of medicinal marijuana is

regulated under federal law. In 1996, California passed the Compassionate Use Act, which decriminalized medical marijuana. Currently, 14 states make some allowance for medical marijuana. However, these state laws do not supersede federal laws that continue to criminalize the use of medicinal marijuana, so federal prosecution is still possible. In 2001, Health Canada allowed people suffering from grave and debilitating illnesses access to marijuana. However, access is limited, and authorization to use marijuana is governed by regulations annexed to Canada's Controlled Drugs and Substance Act.

Three exogenous CBs are available for clinical use (Table 4). Levonantradol, a fourth CB, is a synthetic analog of dronabinol, but it is not used clinically because dronabinol and nabilone are believed to be more useful for most conditions. However, it has been used in research.

The adverse effects of CBs (Table 5) are not dissimilar to those of other systemically administered therapies for pain and symptom management. However, it is the psychotropic effects because of the activation of central CB_{1R} that most limits the use of THC. However, the antipsychotic actions of CBD, as with the THC:CBD spray discussed below, represent an approach to circumvent, or at least attenuate, the psychotropic effects of THC.

Clinical Evidence to Support the Use of CBs for Symptom Management

A qualitative systematic review of randomized controlled trials of CBs from 1975 to 1997 in patients with acute and chronic nonmalignant and cancer pain identified nine studies and concluded that THC is about as effective as codeine 50−120 mg. Adverse effects, most often psychotropic, were common.[30] However, in the past decade, the use of CBs in pain has been studied more systematically and the THC:CBD buccal spray (Sativex®, GW Pharmaceuticals, London, UK) has become available for clinical use. A meta-analysis of seven double-blind, placebo-controlled trials of CB-based treatments for multiple sclerosis-related neuropathic pain demonstrated that THC:CBD buccal spray, dronabinol, and CBD alone were all superior to placebo in controlling neuropathic pain;

Table 4
Indications and Properties of Exogenous CBs

Indications and Properties	Dronabinol	Nabilone	THC:CBD Buccal Spray
Proprietary name	Marinol®	Cesamet®	Sativex®
Active agents	Synthetic THC	Synthetic cannabinoid similar to (analog of) THC	*Cannabis* extract of THC and CBD
Indications	• Anorexia/wasting in HIV patients (United States and Canada) • Nausea and vomiting induced by chemotherapy (United States and Canada)	• Nausea and vomiting induced by chemotherapy (United States, Canada, and United Kingdom)	• Adjunctive for neuropathic pain (in multiple sclerosis) (United States and Canada) • Adjunctive for cancer pain (Canada) • General license on a named patient basis (United Kingdom)
Route of administration	Oral	Oral	Buccal mucosa
Onset of action (minutes)	30–60	60–90	30–150
T_{max} (hours)	1–4	2	1.5–4.0
Duration of action (hours)	4–6	8–12	6–8
Plasma $T_{1/2}$ (hours)	19–56	2	1.5
Urine THC testing	Yes	No	Yes

HIV = human immunodeficiency virus.

Table 5
Common Adverse Effects of CBs[a]

Central nervous system	Dizziness
	Feeling intoxicated
	Cognitive impairment
	Anxiety/panic attacks
	Psychosis/paranoia
Cardiovascular[b]	Palpitations
	Transient tachycardia and a small pressor effect with acute administration
	Bradycardia and postural hypotension with chronic administration (more than one to two days)
Upper gastrointestinal	Upper abdominal pain
	Angular cheilitis, aphthous stomatitis
	Gastroesophageal reflux disease
Nausea/vomiting	
Dry mouth	
Blurred vision	

[a]Most adverse effects are reported as mild or moderate in severity, and patients often appear to develop tolerance to them.
[b]During the two-year follow-up study with the THC:CBD buccal spray, there were no changes in electrocardiogram, heart rate, systolic or diastolic blood pressure.

the THC:CBD buccal spray was the most effective.[31] Recently, a randomized, double-blind, placebo-controlled study of CBs as adjunctive treatment for refractory cancer-related pain in 177 patients demonstrated that the THC:CBD buccal spray was effective when compared with both THC and placebo. THC alone was not significantly different from placebo.[32]

CBs are thought to act centrally through activation of CB_{1R} to inhibit emesis.[33–35] Recent evidence has shown that CB_{2R} also plays a role.[12] Systematic reviews and a meta-analysis have evaluated 30 randomized controlled trials of dronabinol, nabilone, and levonantradol for the control of chemotherapy-induced nausea and vomiting.[36,37] When these three THC analogs were analyzed separately (using intention to treat), only dronabinol was found to have statistically significant greater antiemetic efficacy than neuroleptics (number needed to treat [NNT] 3.4).[36] Although nabilone and levonantradol showed clinical superiority, statistical significance was not reached because of the small number of studies and the small sample size of each study. When all THC analogs were analyzed as a single group, CBs were superior to active controls (prochlorperazine, metoclopramide, chlorpromazine, domperidone, haloperidol, and alizapride) in reducing the frequency and severity of chemotherapy-induced nausea and vomiting, with an NNT of six for complete control of nausea and an NNT of eight for complete control of vomiting.[37] For chemotherapy regimens with nausea and vomiting rates of 25%–75%, complete relief of nausea was 70% and complete relief of vomiting was 72% in patients receiving CBs, compared with 41% and 57%, respectively, for patients receiving conventional therapies.[37] Although adverse effects were more common with CBs, patient satisfaction was also significantly greater compared with conventional antiemetic therapies (NNT 1.8).[36] It should be noted that these studies did not examine CBs vs. 5-hydroxytryptamine Type 3 (5-HT3) receptor antagonists; they were all earlier generation antiemetics. However, 5-HT3 receptor antagonists appear to have limited impact on delayed and anticipatory chemotherapy-induced nausea and vomiting. A comparative study between dronabinol and the 5-HT3 receptor antagonist ondansetron found CBs to be more effective in resolving delayed chemotherapy-induced nausea and vomiting,[38] and animal models would suggest that CBs are more effective than 5-HT3 receptor antagonists for the treatment of anticipatory chemotherapy-induced nausea and vomiting.[39] Within the endo-CB system, coactivation of CB_{1R} and CB_{2R} is necessary for the antiemetic action of endo-CBs.[25]

There is a growing body of evidence that cannabis-based medicine may be beneficial for many of the symptoms experienced by CKD patients, some of which opioids may exacerbate. These include anorexia, nausea, emesis, pruritus, insomnia, anxiety, depression, and cardiovascular stability (Table 2).

The Impact of Renal Failure on the Metabolism of CBs

CBs are metabolized rapidly in the liver by the cytochrome P450 enzyme system. Although the

risk of clinically significant reactions is believed to be low, there is the possibility for potential drug interactions with analgesics, such as fentanyl; adjuvant therapies, such as amitriptyline; and immunosuppressive therapy with cyclosporine or tacrolimus. THC is metabolized to 11-hydroxy-tetrahydrocannabinol (11-OH-THC), a psychoactive metabolite. 11-OH-THC is excreted renally (~13%) and in the feces (~53%). CBD is extensively metabolized in the liver, and more than 33 metabolites have been identified in the urine, although their clinical activity remains unknown. All CBs have a large volume of distribution, as they are highly lipid soluble and accumulate in fatty tissue. They are also highly protein bound. As a result, they will unlikely be removed effectively by hemodialysis.[40]

Although there are no data for oral cannabis-based medicine in CKD, tolerability and safety data in other patient populations with chronic illness, such as rheumatoid arthritis, multiple sclerosis, and cancer, are encouraging and, in fact, show that cannabis-based therapy may be better tolerated than conventional therapies for many symptoms. Mean (standard deviation) daily doses of Sativex®, ranging from 5.4 (0.84) to 9.6 (6.1) sprays, have been given for up to two years with very few, if any, serious adverse effects (0%–7%), and withdrawals ranging from 0% to 26%.[41–43] Dizziness appears to be the most common symptom, ranging in prevalence from 9% to 59%[31,41,42,44] (Table 5). Even in the two-year study, there were no clinically significant changes in electrocardiogram, pulse rate, or systolic or diastolic blood pressure from baseline.[43] In this study, most adverse effects appeared to be mild to moderate and many resolved with chronic use. There is also no evidence to suggest tolerance to therapeutic effects, unlike with chronic opioid use.[43]

Summary

We are only just beginning to appreciate the therapeutic potential of CBs. To realize the therapeutic potential suggested by preclinical data, it is likely that, in managing the symptom burden in CKD, both CB_{1R} and CB_{2R} agonists, alone or in combination with each other and/or with CBD, and ultimately, the endo-CB system, will have to be targeted to achieve effective symptom control without dose-limiting adverse effects. Unfortunately, the paucity of long-term therapeutic efficacy data does not permit us to advocate for the routine use of CBs in the management of the chronic symptom burden in CKD. In fact, at this time, it seems prudent to limit the long-term use of CB_{1R} agonists, such as THC. However, CB_{2R} agonists and unconventional CBs, such as CBD may circumvent or attenuate the difficulties associated with THC use. Even small improvements in symptoms with the use of THC:CBD in patients with difficult-to-treat symptoms may be clinically meaningful. This is particularly relevant for CKD patients where the second leading cause of death is withdrawal from dialysis, with most of these decisions reflecting poor HRQL. Moreover, given the prominence of adverse effects of opioids in CKD, which may exacerbate an already high symptom burden, CBs may present a reasonable alternative to pain and symptom management.

References

1. Davison SN. Pain in hemodialysis patients: prevalence, cause, severity, and management. Am J Kidney Dis 2003;42:1239–1247.

2. Weisbord SD, Fried LF, Arnold RM, et al. Prevalence, severity, and importance of physical and emotional symptoms in chronic hemodialysis patients. J Am Soc Nephrol 2005;16:2487–2494.

3. Murtagh FE, Addington-Hall J, Higginson IJ. The prevalence of symptoms in end-stage renal disease: a systematic review. Adv Chronic Kidney Dis 2007;14:82–99.

4. Davison SN, Jhangri GS, Johnson JA. Longitudinal validation of a modified Edmonton Symptom Assessment System (ESAS) in haemodialysis patients. Nephrol Dial Transplant 2006;21:3189–3195.

5. Davison SN, Jhangri GS, Johnson JA. Cross-sectional validity of a modified Edmonton Symptom Assessment System in dialysis patients: a simple assessment of symptom burden. Kidney Int 2006; 69:1621–1625.

6. Saini T, Murtagh FE, Dupont PJ, et al. Comparative pilot study of symptoms and quality of life in cancer patients and patients with end stage renal disease. Palliat Med 2006;20:631–636.

7. Abdel-Kader K, Unruh ML, Weisbord SD. Symptom burden, depression, and quality of life in chronic and end-stage kidney disease. Clin J Am Soc Nephrol 2009;4:1057–1064.

8. Patel SS, Shah VS, Peterson RA, Kimmel PL. Psychosocial variables, quality of life, and religious beliefs in ESRD patients treated with hemodialysis. Am J Kidney Dis 2002;40:1013–1022.

9. Maida V. Cannabinoid-based therapies in supportive oncology: growing evidence for a broad role in symptom management. Oncol Exch 2007;6: 22–28.

10. El Sohly M. Chemical constituents of cannabis. In: Grotenhermen F, Russo E, eds. Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential. Binghamton, NY: The Haworth Press, Inc, 2002: 27–36.

11. Pertwee RG. Cannabinoid pharmacology: the first 66 years. Br J Pharmacol 2006;147(Suppl 1): S163–S171.

12. Pertwee RG. Ligands that target cannabinoid receptors in the brain: from THC to anandamide and beyond. Addict Biol 2008;13:147–159.

13. Grant I, Cahn BR. Cannabis and endocannabinoid modulators: therapeutic promises and challenges. Clin Neurosci Res 2005;5:185–199.

14. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. Br J Pharmacol 2008;153: 199–215.

15. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol—recent advances. Chem Biodivers 2007;4:1678–1692.

16. Zuardi AW, Crippa JAS, Hallak JEC, Moreira FA, Guimaraes FS. Cannabidiol, a *Cannabis sativa* constituent, as an antipsychotic drug. Braz J Med Biol Res 2006;39:421–429.

17. Mechoulam R, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. J Clin Pharmacol 2002;42:11S–19S.

18. Basavarajappa BS. Neuropharmacology of the endocannabinoid signaling system-molecular mechanisms, biological actions and synaptic plasticity. Curr Neuropharmacol 2007;5:81–97.

19. Duncan M, Davison JS, Sharkey KA. Review article: endocannabinoids and their receptors in the enteric nervous system. Aliment Pharmacol Ther 2005;22:667–683.

20. Van S, Duncan M, Kingsley PJ, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 2005;310: 329–332.

21. Anand P, Whiteside G, Fowler CJ, Hohmann AG. Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. Brain Res Rev 2009;60:255–266.

22. Duncan M, Mouihate A, Mackie K, et al. Cannabinoid CB_2 receptors in the enteric nervous system modulate gastrointestinal contractility in lipopolysaccharide-treated rats. Am J Physiol Gastrointest Liver Physiol 2008;295:978–987.

23. Akopian AN, Ruparel NB, Jeske NA, Patwardhan A, Hargreaves KM. Role of ionotropic cannabinoid receptors in peripheral antinociception and antihyperalgesia. Trends Pharmacol Sci 2009;30:79–84.

24. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev 2006;58:389–462.

25. Patel KD, Davison JS, Pittman QJ, Sharkey KA. Cannabinoid CB2 receptors in health and disease. Curr Med Chem 2010;17:1393–1410.

26. Mendizabal VE, Adler-Graschinsky E. Cannabinoids as therapeutic agents in cardiovascular disease: a tale of passions and illusions. Br J Pharmacol 2007; 151:427–440.

27. Schlosburg JE, Kinsey SG, Lichtman AH. Targeting fatty acid amide hydrolase (FAAH) to treat pain and inflammation. AAPS J 2009;11:39–44.

28. Long JZ, Li W, Booker L, et al. Selective blockade of 2-anachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat Chem Biol 2009;5:37–44.

29. Rice AS. Should cannabinoids be used as analgesics for neuropathic pain? Nat Clin Pract Neurol 2008;4:654–655.

30. Campbell FA, Tramer MR, Carroll D, et al. Are cannabinoids an effective and safe treatment option in the management of pain? A qualitative systematic review. BMJ 2001;323:13–16.

31. Iskedjian M, Bereza B, Gordon A, Piwko C, Einarson TR. Meta-analysis of cannabis based treatments for neuropathic and multiple sclerosis-related pain. Curr Med Res Opin 2007;23:17–24.

32. Johnson JR, Burnell-Nugent M, Lossignol D, et al. Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain. J Pain Symptom Manage 2010; 39:167–179.

33. Sharkey KA, Cristino L, Oland LD, et al. Arvanil, anandamide and N-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB1 and vanilloid TRPV1 receptors in the ferret. Eur J Neurosci 2007;25:2773–2782.

34. Van S, Oland LD, Mackie K, Davison JS, Sharkey KA. Delta9-tetrahydrocannabinol selectively acts on CB1 receptors in specific regions of dorsal vagal complex to inhibit emesis in ferrets. Am J Physiol Gastrointest Liver Physiol 2003;285: G566–G576.

35. Van S, Oland LD, Ho W, et al. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology 2001;121: 767–774.

36. Rocha M, Stefano S, Cassia Haiek R, Oliveira R, Da Silveira D. Therapeutic use of *Cannabis sativa* on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care 2008;17:431–443.

37. Tramer M, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ 2009;323:2–3.

38. Meiri E, Jhangiani H, Vredenburgh J, et al. Dronabinol treatment of delayed chemotherapy-induced nausea and vomiting. J Clin Oncol 2005; 23:8018.

39. Parker LA, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in *Suncus murinus*: an animal model of anticipatory nausea and vomiting. Physiol Behav 2006;87:66–71.

40. GW Pharma Ltd. Product monograph—Sativex, 2008.

41. Blake DR, Robson P, Ho M, Jubb RW, McCabe CS. Preliminary assessment of the efficacy, tolerability and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis. Rheumatology (Oxford) 2006;45: 50–52.

42. Rog DJ, Nurmikko TJ, Friede T, Young CA. Randomized, controlled trial of cannabis-based medicine in central pain in multiple sclerosis. Neurology 2005;65:812–819.

43. Rog DJ, Nurmikko TJ, Young CA. Oromucosal delta9-tetrahydrocannabinol/cannabidiol for neuropathic pain associated with multiple sclerosis: an uncontrolled, open-label, 2-year extension trial. Clin Ther 2007;29:2068–2079.

44. Berman JS, Symonds C, Birch R. Efficacy of two cannabis based medicinal extracts for relief of central neuropathic pain from brachial plexus avulsion: results of a randomised controlled trial. Pain 2004; 112:299–306.

45. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage 1997;14:7–14.

46. Szepietowski JC, Szepietowski T, Reich A. Efficacy and tolerance of the cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. Acta Dermatovenerol Croat 2005;13:97–103.

47. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. Am J Gastroenterol 2002;97:2117–2119.