Cannabinoids for the treatment of chronic pruritus: A review

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Medical marijuana is becoming widely available to patients in the United States, and with recreational marijuana now legalized in many states, patient interest is on the rise. The endocannabinoid system plays an important role in skin homeostasis in addition to broader effects on neurogenic responses such as pruritus and nociception, inflammation, and immune reactions. Numerous studies of in vitro and animal models have provided insight into the possible mechanisms of cannabinoid modulation on pruritus, with the most evidence behind neuronal modulation of peripheral itch fibers and centrally acting cannabinoid receptors. In addition, human studies, although limited due to differences in the cannabinoids used, disease models, and delivery method, have consistently shown significant reductions in both scratching and symptoms in chronic pruritus. Clinical studies have shown a reduction in pruritus in several dermatologic (atopic dermatitis, psoriasis, asteatotic eczema, prurigo nodularis, and allergic contact dermatitis) and systemic (uremic pruritus and cholestatic pruritus) diseases. These preliminary human studies warrant controlled trials to confirm the benefit of cannabinoids for treatment of pruritus and to standardize treatment regimens and indications. In patients who have refractory chronic pruritus after standard therapies, cannabinoid formulations may be considered as an adjuvant therapy where it is legal. (J Am Acad Dermatol 2020;82:1205-12.)

Key words: atopic dermatitis; cannabinoids; eczema; endocannabinoid system; itch; medical marijuana; pruritus.

Pruritus is one of the most common complaints from patients who come to the dermatologist. Chronic pruritus, defined as pruritus lasting longer than 6 weeks, reduces quality of life and can be as debilitating as chronic pain.[1] Pruritus has been reported in 30.9% to 36.2% of dermatology patients, and 16.8% of the general population reports chronic pruritus at some point in their lives.[2-4] Current treatment options include a combination of emollients, topical anesthetics, menthol, oral and topical glucocorticoids, oral antihistamines, and neuroactive medications; however, none can claim consistent or complete efficacy.[5,6] Cannabinoids, which modulate the endogenous endocannabinoid system (ECS), have shown promise for treatment of itch in the clinical literature to date, which encompasses clinical studies in multiple diseases including for the management of refractory pruritus.[7-10]

THE ENDOCANNABINOID SYSTEM

Cannabinoids represent a broad class of endogenous and exogenous arachidonic acid-derivative compounds with activity at the cannabinoid receptors, CB1 and CB2. These exist as phytocannabinoids derived from the *Cannabis sativa* plant (eg, Δ(9)-tetrahydrocannabinol [THC], cannabidiol [CBD]), endogenous endocannabinoids (eg, anandamide and 2-arachidonoylglycerol [2-AG]), and synthetic cannabinoids.[11,12]

The ECS refers to the lipid-signaling system that includes the endocannabinoids, their receptors, and degradative or inactivating enzymes and is involved in physiologic and pathologic mechanisms throughout the human body, such as cognition, nociception, and inflammation.[13,14] The ECS plays an important role in skin health. The ECS maintains epidermal homeostasis, regulates hair follicles and

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Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
Accepted for publication January 18, 2020.

Reprints not available from the authors.
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Published online January 25, 2020.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2020.01.036

sebaceous glands, and is involved in nociception and inflammation. ECS dysregulation has been linked to several skin diseases, including atopic dermatitis, psoriasis, scleroderma, and skin cancer.[15-17] Cannabinoids are ligands to the canonical cannabinoid receptors CB1 and CB2 and the transient receptor potential (TRP) ion channels with individual differences in affinity and activity (Table I).[18-29] These receptors have near ubiquitous expression in the skin and are present on terminal nerve endings of cutaneous fibers that extend to the dermis and epidermis.[22]

CAPSULE SUMMARY

- The endocannabinoid system plays an active role in the skin, and cannabinoid products are an emerging consideration for skin therapy, particularly for itch.
- Physicians should be knowledgeable about the mechanistic justification for the use of cannabinoids for refractory pruritus that fails standard therapies when it is a legal option.

THE ROLE OF CANNABINOIDS FOR PRURITUS

The evidence in the literature suggests the antipruritic effects of cannabinoids are due to a combination of effects on neuronal activation, transmission along the afferent pathway, and local modulation of keratinocyte and mast cells (Fig 1).[30-33] The antipruritic effect of cannabinoid receptor ligation on peripheral and central nervous tissue may be a result of actions at multiple receptors, as experiments in various models of skin diseases show individual CB1, CB2, or TRP channel modulation exhibit reduced pruritus.[18,23,24,34]

Similar to the role of cannabinoids in pain, increased activity at both CB1 and CB2 have been shown to alleviate pruritus.[23,25,26,35] These analgesic and antipruritic effects occur at the central and peripheral level. In the central nervous system, the analgesic and antipruritic effects are predominately mediated through CB1 receptors, congruent with their activity as the main centrally acting cannabinoid receptor.[25,26,35,36] In the periphery, activity at both CB1 and CB2 are thought to induce analgesia.[26,35]

These effects have been shown in both inflammatory and neurogenic pain and itch and are due to activity on both local inflammation and neuronal activation. Increased endocannabinoids in neural tissue specifically decreases histaminergic itch, and direct effects of cannabinoids on neuronal receptors increase the nociceptive threshold.[10,27,37] Alterations of CB1 and CB2 expression occur in states of chronic pain, and this modulation of activity at these receptors is thought to be responsible for the effects of cannabinoids on sensation.[38] Together this suggests that the ECS regulates neuronal transmission in the itch sensory pathway through direct binding of receptors on the nerves. Topical cannabinoid agonists can also decrease mast cell recruitment to the skin; however, the antipruritic effect can be independent of local histamine release.[19]

The TRP ion channels are a group of membrane proteins widely expressed in the skin and nervous system that mediate sensory responses such as nociception and pruritus.[39] These channels play a critical role in cutaneous nerve fiber activation and respond to various stimuli such as inflammatory mediators, temperature, pH, and mechanical stimuli.[40] Six TRP channels from 3 subfamilies—TRP vanilloid (TRPV1, TRPV2, TRPV3, TRPV4), TRP ankyrin (TRPA1), and TRP melastatin (TRPM1)—all of which play roles in itch sensation, have been reported to interact with endogenous and exogenous cannabinoids.[40,41]

TRPV1, widely known as the capsaicin receptor, has been the most studied TRP channel with regards to cannabinoid-mediated modulation of pruritus.[39,42] TRPV1 and TRPA1 have been shown separately to play key roles in itch pathways, with blockade or absence showing consistent reductions in itch.[24,43-47] TRPV1 has a paradoxical effect upon activation because it is rapidly desensitized, which leaves it refractory to additional stimulation.[41] In the case of TRPV1, cannabinoids disrupt neurogenic inflammation through antagonism or stabilization of the ion channel in the closed confirmation, which prevents neuronal activation by pruritic mediators.[41]

Many of the clinical trials performed on cannabinoids for treatment of pruritus have used palmitoylethanolamine (PEA), which is a ligand at TRPV1 channels and has no direct interaction with CB1 and CB2.[48,49] Capsaicin cream, a current option for refractory neuropathic pain, works in part through activation/desensitization of the TRPV1 channels.[50] The antipruritic effects of cannabinoids through the TRPV1 ion channel would support the use of CBD, which has a similar effect on TRPV1 and no direct activity at the canonical CB1/CB2 receptors.

Inflammation in the skin is a major contributor to the pathogenesis of pruritus, with local inflammatory factors, such as histamine, cytokines, and neuropeptides, serving as pruritogens. CB2 is widely expressed in peripheral immune cells, and most studies have found CB2 binding decreases inflammation, including in models of dermatitis.[51] CB1 activation may have anti-inflammatory properties in

Abbreviations used:

2-AG: 2-arachidonoylglycerol
AE: asteatotic eczema
CB1: cannabinoid receptor 1
CB2: cannabinoid receptor 2
CBD: cannabidiol
ECS: endocannabinoid system
GPCR: G-protein–coupled receptor
THC: Δ(9)-tetrahydrocannabinol
TRP: transient receptor potential
TRPA1: TRP ankyrin 1
TRPM1: TRP melastatin 1
TRPV1: TRP vanilloid 1
TRPV2: TRP vanilloid 2
TRPV3: TRP vanilloid 3
TRPV4: TRP vanilloid 4
PEA: palmitoylethanolamine

skin diseases as well, and CB1 binding in a murine model of atopic dermatitis decreased T-helper cell type 2 cytokine production.[18] Mast cells, which coexpress CB1 and CB2, have inhibited activation, proliferation, and degranulation by CB1 binding, and tonic suppression of mast cell function is thought to occur specifically through CB1 agonism.[19,52,53]

CLINICAL TRIALS OF CANNABINOIDS FOR PRURITIC DISEASES

Topical application and oral administration of cannabinoids have shown promise for treatment of itch specifically in several diseases, which include pruriceptive itch, such as dermatitis, neurogenic itch in metabolic derangements, and chronic intractable itch in prurigo (Table II).[8-10,52,54-58] Atopic dermatitis is one of the most common forms of chronic itch and has been one of the most studied pruritic conditions in preclinical and clinical studies for cannabinoids.[49] Topical treatments of PEA and adelmidrol (a PEA analog) significantly reduced inflammation and pruritus in a large observational study and in a small open-label study after patients with atopic dermatitis applied the cannabinoid-containing cream for 4 weeks.[56,58] Topical cannabinoids have also shown promise for treatment in asteatotic eczema; however, differences between the vehicles in that specific study confound the study findings.[8]

Although most itch can be attributed to etiologies in the skin, pruritus can be a herald of underlying systemic diseases and metabolic abnormalities. One of the most common systemic causes of itch is uremic pruritus, which affects more than one-half of patients who require long-term dialysis.[59] Topical application of a derma-membrane system–based lotion combined with anandamide and PEA for 3 weeks decreased pruritus in patients on hemodialysis, and by the end of the study, itch was completely eliminated in nearly one-half of the patients.[7,54] Cholestatic disease causes pruritus in a large number of patients with primary biliary cirrhosis or hepatitis C infections, and dronabinol, a synthetic THC, was incidentally reported to provide short-term relief in 3 patients with intractable pruritus secondary to chronic liver disease.[55,60]

Randomized controlled trials of cannabinoids for treatment of itch with topicals containing PEA have been reported in recent years in asteatotic eczema (n = 60) and chronic pruritus (n = 100) specifically, and although both showed reduction of itch, the difference was only significant in the case of asteatotic eczema.[7,8] This finding, along with the fact that most reported studies have been open label or observational, shows the need for additional controlled trials to delineate whether there is a true benefit to cannabinoid-containing topicals.

FORMULATIONS

The delivery method of cannabinoids, which are highly lipophilic, determines efficacy due to different bioavailability and distribution dependent on the route of administration.[61] Although the most common method of recreational marijuana use is inhalation, oral ingestion and topical transdermal applications hold promise for treatment of skin

Table I. Select cannabinoids and their receptors*

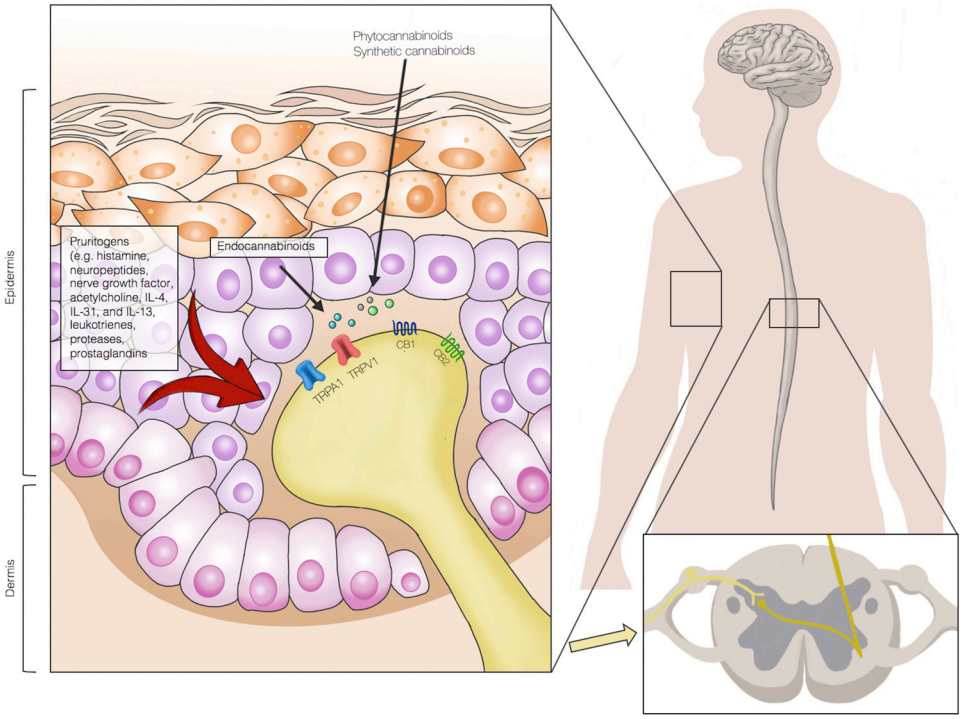
Receptor	Type	Pruritus	Pain
CB1	GPCR	↑ activity, ↓ pruritus	↑ activity, ↓ pain
CB2	GPCR	↑ activity, ↓ pruritus	↑ activity, ↓ pain
TRPV1	Ion channel	↓ activity, ↓ pruritus	↓ activity, ↓ pain

Cannabinoid	Type	Receptor interactions
2-AG	Endocannabinoid	CB1, CB2, TRPV1
AEA	Endocannabinoid	CB1, CB2, TRPV1
THC	Phytocannabinoid	CB1, CB2, TRPV1
CBD	Phytocannabinoid	TRPV1†
PEA	Synthetic cannabinoid	TRPV1†

2-AG, 2-arachidonoylglycerol; *AEA*, anandamide; *CB1*, cannabinoid receptor 1; *CB2*, cannabinoid receptor 2; *CBD*, cannabidiol; *GPCR*, G-protein–coupled receptor; *THC*, Δ(9)-tetrahydrocannabinol; *TRPV1*, transient receptor potential vanilloid 1; *PEA*, palmitoylethanolamine.

*The cannabinoids have different affinities for both cannabinoid-specific and -nonspecific receptors. In general, increased activity at the CB1 and CB2 receptors has been reported to alleviate pruritus, whereas decreased activity of the TRPV1 ion channels alleviates pruritus.

†CBD and PEA may both have indirect effects on CB-specific receptors because both have been shown to increase AEA levels.[22-29]



Abbreviations: CB1 = cannabinoid receptor 1, CB2 = cannabinoid receptor 2, CBD = cannabidiol, TRPA1 = TRP ankyrin 1, TRPV1 = TRP vanilloid 1

Fig 1. The itch pathway and intersection with the endocannabinoid system. Cannabinoids as a class are an enticing treatment option for neurogenic diseases because of the ability to modulate the endocannabinoid system in the central and peripheral nervous systems. This level of modulation is responsible for the efficacy of cannabinoids found for treatment of chronic pain, neuropathic pain, spasticity due to multiple sclerosis, and refractory pediatric seizures.[30,31] The antipruritic effect of treatment with topical or systemic cannabinoids is most likely due to a similar mechanism of action. Most itch occurs in response to local inflammation and skin disease. Unmyelinated C fibers that extend to the epidermis and dermis detect pruritogens from exogenous (eg, mechanical stimulation) and endogenous sources, such as histamine, and secreted products from nearby keratinocytes and mast cells. Activation of pruritogenic receptors, usually a G protein–coupled receptor, initiates a cascade of intracellular signaling processes and ultimately neuronal stimulation.[32] After the interaction with local pruritogens, the impulse passes the dorsal root ganglion to the synapse in the dorsal horn of the spinal cord before ascension up the contralateral spinothalamic tract to the thalamus and ultimately the cortex to process the information.[33] Pruritus can occur due to pathology at any point along this pathway, from peripheral skin diseases and distal neuropathies to central causes such as an underlying psychologic condition. The canonical cannabinoid receptors 1 (CB1) and 2 (CB2) and the nonspecific transient receptor potential (*TRP*) channels are both present on cutaneous nerve fibers, and agonism and antagonism/desensitization, respectively, have reported antipruritic effects. *CBD*, Cannabidiol; *TRPA1*, TRP ankyrin 1; *TRPV1*, TRP vanilloid 1.

diseases with regards to efficacy and safety profile, and most studies to date use these delivery methods. Oral delivery of cannabinoids has the advantage of standard concentrations and doses; however, there are individual differences in bioavailability due to absorption and first-pass metabolism in the liver.[61] The onset of action and maximal plasma concentrations occur 1 to 2 hours after ingestion (up to 6 hours), with effects reported for up to 20 hours increasing the risk of overdose when individuals self-administer oral cannabinoids.[61]

Owing to the studies that show that the antipruritic effect of cannabinoid agonists is partly due to cannabinoid receptors in the central nervous system, systemic cannabinoids may be optimal for severe itch whereas topicals would only address peripheral mechanisms. The effects of inhaled marijuana on chronic itch have not been reported to date;

Table II. Changes in pruritus after modulation of the endocannabinoid system in human studies*

Study	Study type	No.	Disease	Treatment	Control	Route	Outcome
Dvorak,[10] 2003	Experimental	12, 6	Histamine-induced itch	HU-210 (cannabinoid receptor agonist) 24 hours, once	Vehicle control	Skin patch, dermal microdialysis	Reduction in itch measured by VAS for 1.5 minutes ($P < .05$); reduced normalized itch rating ($P < .04$)
Neff,[55] 2002	Observation	3	Intractable cholestatic-related pruritus	Dronabinol 5 mg in the evening indefinitely	N/A	Oral	Resolution of pruritus in 3/3 patients for 2-6 hours after the dose
Eberlein,[56] 2008	Observation	2456	Atopic dermatitis	0.3% PEA cream BID 4-6 weeks	N/A	Topical	58.6% improvement in pruritus, excoriation, erythema, scaling, and lichenification Reductions of VAS scores for pruritus at day 6 (45.6%) and after 6 weeks (60%) of treatment 79.3% physician-reported complete resolution or clinical improvement after 5-6 weeks of treatment
Ständer,[57] 2006	Open-label	22	Prurigo, lichen simplex, and pruritus	PEA-containing cream	N/A	Topical	14/22 had documented antipruritic effect from cream
Szepietowski,[54] 2005	Open-label	21	Uremic pruritus	AEA, PEA-containing cream BID 3 weeks	N/A	Topical	38.1% patients had eliminated pruritus at 3 weeks based on VAS and patient questionnaire
Pulvirenti,[58] 2007	Open-label	20	Atopic dermatitis	2% Adelmidrol BID 4 weeks	Untreated lesions	Topical	Improvement in erythema and pruritus in 12 patients (60%)10-15 days after initiation Clinical resolution in 16 patients (80%) within 4 weeks treatment
Yuan,[8] 2014	Randomized double-blind	60	Asteatotic eczema	0.3% PEA, 0.21% AEA emollient BID 4 weeks	Vehicle	Topical	Eczema Area and Severity Index reduction in itch (baseline: 1.3 $\pm$ 1.0; 28 days: 0.1$\pm$ 0.3)
Visse,[9] 2017	Randomized	100	Isolated pruritus	PEA-containing lotion BID 3 weeks	Vehicle	Topical	30.1% $\pm$ 29.8% of the patients who used the PEA cream vs 24.2% $\pm$ 29.3% who used placebo had pruritus improvement based on verbal rating scale, but this was not significant ($P = .378$)

AEA, Anandamide; *BID*, twice daily; *N/A*, not available; *No.*, number; *PEA*, palmitoylethanolamine; *VAS*, visual analog scale.
*The studies listed include human and clinical studies to date that used pruritus as a measurement after treatment with a cannabinoid-containing compound. There were documented antipruritic effects in studies that used compounds that favored cannabinoid receptor 1 (CB1) and CB2 (AEA, dronabinol) and also those that favored the non-specific transient receptor potential channels (PEA).

however, smoked marijuana has been shown effective for management of neuropathic pain, which suggests it has promise for treating pruritus.[62] In addition to smoking the plant product, marijuana can be inhaled through aerosolization (vaping), which has risen in popularity due to the false perceptions about its safety. In truth, both methods pose significant health risks to the user, with vaping specifically linked to recent cases of acute severe pulmonary disease, likely due to the numerous chemicals in the products.[63,64]

Topical cannabinoids are of particular interest in skin disease because of the high safety profile and direct, local application to involved areas, and recent years have brought an assortment of cannabinoid-containing topicals specifically advertised for use on the skin, such as oils, lotions, emollients, creams, and patches. Cannabinoids are lipophilic and are readily absorbed through the skin, with only aqueous layers of the skin to limit diffusion. To date, systemic effects have not been reported after topical application of cannabinoids, and furthermore, many of the antipruritic effects of cannabinoids were shown using non-THC cannabinoids (CBD, PEA), eliminating the concern for undesired psychoactive effects.

Although most studies showed reductions in pruritus, increased pruritus was reported as an adverse effect in a small number of patients.[56] Allergic reactions to cannabis are rare but possible and range from life-threatening to more mild reactions. Direct contact with plants was reported to cause urticaria and contact dermatitis in a small number of patients.[65]

LIMITATIONS

Given the complexity of the ECS and the heterogeneity of cannabinoid structure and function, cannabinoids may have different effects depending on the origin of the pruritus, and future research will hopefully provide more mechanistic precision.[66] Preclinical studies have shown that cannabinoids alleviate itch after both topical and systemic administration and shed light on the possible underlying mechanism. Interpretation of clinical studies, however, is limited by the lack of double-blinded controlled clinical trials and by the variation in cannabinoid products, delivery methods, and formulations.

CONCLUSION

An estimated 1% of individuals who live in states with medical marijuana programs use physician-recommended cannabis, and although pruritus is not a qualified condition for recommendation, topical cannabinoids are sold by dispensaries and advertised as antipruritic, analgesic, and anti-inflammatory.[67,68] Despite the limited number of published studies, trials done at present have shown consistent improvement in pruritus in the setting of multiple diseases. In the future, patient interest and use of cannabinoid products, whether it is the botanical product, derivative, or targeted compound, will continue to rise. The literature warrants further investigation as an antipruritic agent, and physicians should be knowledgeable to use of cannabinoids for chronic pruritus that fails standard therapies in states where it is a legal option.

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