Neuropathic itch treated with oral cannabinoids: A case series

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INTRODUCTION

Neuropathic pruritus is defined as an itch arising from diseases of the central or peripheral nervous system, including nerve damage, compression, or irritation. It can be generalized or localized and is encompassed within a broad range of diagnoses, including notalgia paresthetica, brachioradialis pruritus, certain forms of vulvar itch, and small fiber neuropathy, amongst others.[1] Brachioradial pruritus is a well-known type of neuropathic itch that is believed to result from an insult to cervical nerves C5-C8 from degenerative disc disease or trauma.[2] Symptoms include itch, burning, numbness, and tingling affecting the dorsolateral aspects of the upper extremities.

Although most cases of vulvar itch can be attributed to infectious causes or inflammatory dermatoses, such as psoriasis, lichen simplex chronicus, lichen sclerosus, or contact dermatitis, some cases of chronic vulvar itch can be categorized under the umbrella of genitofemoral neuralgia or vulvodynia.[3] Classically regarded as a type of neuropathic pain, itch and burning can accompany vulvodynia in 20% and 70% of cases, respectively,[4] and are similarly addressed in the same way with medications targeting neurogenic pathways.

In many cases of localized neuropathic itch, treatment can be challenging because topical therapies are limited and systemic treatments may provoke many side effects. Treatment options for neuropathic itch typically include topical local anesthesia, capsaicin formulations, calcineurin inhibitors, menthol or camphor, and systemic approaches with gabapentinoids, selective serotonin reuptake inhibitors, and tricyclic antidepressants.[5] We report 3 cases of localized neuropathic itch successfully treated by dronabinol, an oral synthetic formulation of delta-9-tetrahydrocannabinol.

Abbreviations used:

CB: cannabinoid
NRS: numerical rating scale
VAS: visual analog scale

CASE SERIES

Case 1

A 64-year-old woman presented with a 4-year history of debilitating itch localized to her neck, bilateral posterior aspect of the shoulders, lateral aspect of the proximal arms, and radial aspects of her forearms. The patient reported that her itch sometimes reached maximum severity on a visual analog scale (VAS) ranging from 0 (no itch) to 10 (severe itch). On physical examination, she had multiple open and crusted wounds on her arms as well as areas of postinflammatory hyperpigmentation and stellate white scars due to deep excoriation. Primary cutaneous inflammation was not observed. Her presentation was consistent with a diagnosis of brachioradial pruritus. Previous magnetic resonance imaging studies demonstrated degenerative discs at the level of C4 through C6, corresponding to the compromised dermatomes. Prior treatments with emollients, camphor and mentholated creams, moderate-potency topical corticosteroids, antihistamines, selective serotonin reuptake inhibitors, and

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gabapentin failed to alleviate her itch. Oral dronabinol was started at 2.5 mg twice daily and gradually increased to 5.0 to 7.5 mg 3 times daily (for a total of 17.5 to 25 mg daily), depending on her daily itch severity. Upon starting dronabinol, her itch severity decreased to a VAS score of 0 to 1, so that she had only occasional mild flares that were controlled with application of ice. At present, she has been followed for over 4 years without major recurrence of her symptoms.

Case 2

A 71-year-old woman with a history of Crohn's disease and Sjögren's disease presented to our specialized itch clinic complaining of constant and severe vulvar itch for 4 to 5 years. She rated her itch severity at 10 on a numerical rating scale (NRS) for itch ranging from 0 (no itch) to 10 (maximum severity). Multiple treatments had failed, including serial treatment with topical and oral antifungals, potent and ultrapotent topical corticosteroids, estrogen-based creams, pregabalin, and duloxetine. She consulted numerous specialists in gynecology, urology, pain medicine, gastroenterology, dermatology, and rheumatology who diagnosed her with chronic pelvic pain syndrome and interstitial cystitis. She was actively receiving botulinum toxin and transcutaneous electrical nerve stimulation, which partially helped with her cystitis, but she remained symptomatic with pruritus. Physical examination revealed an age-appropriate vulva without erythema, erosion, discharge, signs of genital Crohn's disease, sclerotic plaques, or loss of anatomy. Vaginal cultures repetitively revealed normal bacterial flora, the absence of clue cells or trichomonas, and a negative potassium hydroxide test. The absence of clinical examination findings and negative test results were suggestive of a neuropathic process. A skin biopsy taken from 10 cm above her lateral malleolus showed reduced intraepidermal nerve fiber density, which was consistent with the impression of small fiber polyneuropathy. On the basis of the patient's report of successful self-treatment with medical marijuana, dronabinol 2.5 mg daily was started and slowly titrated up to 2.5 mg 3 times daily. After 2 weeks of therapy, the patient's itch was markedly decreased, achieving a rating between 0 and 1 on the NRS for itch severity. The only side effect of dronabinol was occasional mild drowsiness. At present, she has been taking dronabinol 5 mg 3 times daily for 6 years with complete symptomatic remission, except for periodic, but severe, recurrences of her symptoms whenever she has to discontinue the medication because of a lapse in insurance coverage.

Case 3

A 54-year-old woman has been seen at our clinic for vulvar dysesthesia since the age of 17. In the past, several investigations were conducted, including repeated wet mounts, fungal and bacterial cultures, skin biopsies, and allergic patch testing, all of which failed to show any underlying infectious or inflammatory causes of her symptoms. Over the years, she has been treated unsuccessfully with numerous agents, including topical corticosteroids ranging from medium to high potency, topical estrogen preparations, topical and oral antifungals, topical anesthetics, and a compounded topical combination of amitriptyline, baclofen, and gabapentin. She had partial improvement of her vulvodynia symptoms with oral venlafaxine daily; however, she still experienced what she described as severe episodes of burning and itch. At the time of her presentation to our clinic, she rated her symptoms as 10 or maximal severity on the NRS for itch and reported that her symptoms greatly affected her sleep, sexual life, and overall quality of life on a daily basis. Dronabinol 2.5 mg daily was initiated at that time and gradually increased to 5 mg 3 times daily over the course of 2 months. The sensation of itch and burning quickly improved to nearly complete resolution, rated as a 0 to 1 on the NRS, within weeks, and she has remained on a stable dose for 2.5 years without side effects.

DISCUSSION

In recent years, the role of cannabinoid (CB) signaling and activation of CB receptors 1 (CB1) and 2 (CB2) in the skin has been an area of interest in dermatology and within the itch community. Increased CB1 and CB2 activity in the central and peripheral nervous systems has been shown to have analgesic and antipruritic effects.[6] Pain and itch relief appear to be mediated in part by activation of CB1 in the central nervous system and by activation of CB1 and CB2 in the periphery.[7] Given their wide distribution in the skin, CBs may exert antipruritic effects by influencing local immune or barrier function as well as by modulating neuronal circuits. CB receptors are found on mast cells, macrophages, and keratinocytes, in addition to cutaneous small nerve fibers.[8] Treatment with a CB1 agonist reduced histamine-evoked neurogenic flares.[9] Moreover, direct activity of CBs on neuronal receptors increased the nociceptive threshold.[10] Derangement of endocannabinoid homeostasis has been implicated in several pruritic or painful dermatologic conditions.[9,11] Topical CB formulations have shown benefit in atopic dermatitis and uremic pruritus (Table I).[12,13] Similarly, a small case

Table I. Reports of cannabinoid treatment for pruritus

Study	Study type	Type of itch	Previously attempted therapies	Cannabinoid treatment	Response	Duration of antipruritic effect	Reported side effects
Neff et al,[15] 2002	Case series	Intractable cholestatic-related pruritus	Diphenhydramine, chlorpheniramine, cholestyramine, rifampicin, phenobarbital, doxepin, naltrexone, UV therapy, topical lotions, and plasmapheresis	Dronabinol 5 mg (every 8 h)	Complete resolution of itch in all 3 patients	4-6 h	Lightheadedness in 1 patient
Maghfour et al, 2020	Open-label noncomparative trial	Atopic dermatitis	NA	CBD gel	Reduction in mean POEM from baseline (16 ± 1.35) to 2 wk (8.25 ± 1.80) (P = .0007). Reduction in mean score of the emotional domain on the QOLHEQ from baseline (20.9 ± 2.06) to 2 wk (8.375 ± 1.609) (P = .004). 67% of subjects with decreased itch. 50% perceived eczema improvement	Up to 2 wk	NA
Visse et al, 2017	Randomized comparative study	Xerosis-related pruritus	NA	PEA lotion twice daily for 2 wk	Reduction in pruritus intensity measured by VAS at 2 wk (P < .001)	NA	13.3% of patients reported worsening of skin symptoms, including pruritus, singling, scaling, or reddening

Eberlein et al,[12] 2008	Observational prospective cohort study	Atopic dermatitis-related pruritus	NA	0.3% PEA cream twice daily for 4-6 wk	Significant clinical improvement at day 6. Continued improvement or complete resolution at 5-6 wk of treatment. Reduction of pruritus on VAS from 4.9 $\pm$ 2.6 to 2.0 $\pm$ 2.3 at study end ($P < .001$)	NA	Pruritus, burning, and erythema
Ständer et al,[1] 2007	Open-label noncomparative trial	Patients with prurigo, lichen simplex, and pruritus	Topical steroids, menthol, capsaicin, tacrolimus, pimecrolimus, antihistamines, systemic steroids, naltrexone, serotonin reuptake inhibitors, and UV radiation	N-PEA cream applied for 2 wk to 6 mo	14/22 (63.6%) reported partial or complete resolution of itch. The average reduction in itch was 86.4% as measured by VAS	NA	None reported
Szepietoswki et al, 2005	Open-label noncomparative trial	Uremic pruritus	NA	PEA-containing cream twice daily for 3 wk	Complete resolution of itch in 8 patients (38.1%) on evaluation by VAS and a patient questionnaire ($P < .0001$)	NA	NA
Pulvirenti et al, 2007	Open-label noncomparative trial	Atopic dermatitis-related pruritus	NA	Adelmidrol 2% twice daily for 4 wk	Complete resolution in 16 patients (80%) after 4 wk of treatment	NA	None reported
Yuan et al, 2014	Randomized, double-blind, controlled study	Asteatotic eczema	NA	PEA 0.3% cream, AEA 0.21% cream twice daily for 28 days	73.5% reduction in itch score at day 28 as measured by the Eczema Area and Severity Index ($P < .05$)	NA	None reported

AEA, Anandamide; *CBD*, cannabidiol; *NA*, not available; *PEA*, palmitoylethanolamine; *POEM*, Patient Oriented Eczema Measure; *QOLHEQ*, Quality of Life Hand Eczema Questionnaire; *UV*, ultraviolet; *VAS*, visual analog scale.

series of postherpetic neuralgia demonstrated reduction in mean pain scores by 87.8% in 5 of 8 patients treated with a cream containing N-palmitoylethanolamine, a CB receptor agonist.[14]

Dronabinol, delta-9-tetrahydrocannabinol, is a synthetic form of the cannabinoid found in the plant *Cannabis sativa* and is currently approved in the United States for AIDS-related anorexia and refractory chemotherapy-induced nausea. Its side effects include nausea, vomiting, tachycardia, somnolence, and dizziness. Ingestion will result in positive urine toxicology screening. Dronabinol 5 mg 3 times daily has been reported to reduce itch in cases of refractory cholestatic pruritus (Table I).[15] In this report, patients described rapid-onset (up to 6 to 8 hours after ingestion) but transient relief. Our patients described a similar experience with quick-onset improvement in dysesthesia.

Although cannabinoids have been well established as a therapeutic option for neuropathic pain, very few reports have been published regarding neuropathic itch, a complex and debilitating condition that can be difficult to manage, similar to neuropathic pain. Here, we report 3 cases of severe, treatment-resistant neuropathic itch successfully controlled by dronabinol. All patients have experienced lasting results for several years. One of the advantages of cannabinoid therapy is its rapidity of action. All 3 patients reported improvement within their initial few doses and described a dose-dependent effect. Side effects included lightheadedness, which was mild and transient and resolved with persistent use. We found that initiating therapy at low doses divided throughout the day followed by gradual increases to be helpful in increasing tolerability. Large, placebo-controlled studies are needed to characterize the position of cannabinoids in the treatment of neuropathic pruritus.

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Conflicts of interest

None disclosed.

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