REVIEW

Gabapentin and pregabalin for the treatment of chronic pruritus

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Chronic pruritus is a distressing symptom that is often refractory to treatment. Patients frequently fail topical therapies and oral over-the-counter antihistamines, prompting the clinician to consider alternative therapies such as neuroactive agents. Herein, the use of gabapentin and pregabalin, 2 medications well known for treating neuropathic pain and epilepsy that are occasionally used for relieving chronic pruritus is explored. The findings from original sources published to date to evaluate the use of gabapentin and pregabalin as antipruritic agents are explored. They are found to be promising alternative treatments for the relief of several forms of chronic pruritus, particularly uremic pruritus and neuropathic or neurogenic itch, in patients who fail conservative therapies. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.02.1237.)

Key words: gabapentin; itch; neurogenic itch; neuropathic itch; pregabalin; pruritus; uremic pruritus.

Chronic pruritus is defined as itch lasting longer than 6 weeks.[1] It is associated with both primary dermatologic and systemic illness, and patients frequently experience psychological sequelae.[2]

Topical treatments, such as topical corticosteroids, menthol, capsaicin, and topical anesthetics, are typically tried first. In the case that these are ineffective, an antihistamine may be considered next as it is an inexpensive and easily obtained over-the-counter treatment indicated for managing pruritus. However, current evidence suggests that its usefulness is limited to relief of urticaria-associated pruritus and its sedative effects.[3] Indeed, antihistamines are often ineffective for treating other pruritic conditions such as uremic pruritus or pruritus of cholestasis.[4,5] These observations led to the discovery of the neural pathway that mediates histamine-independent itch.[6-9]

Itch and pain have shared signaling pathways on an anatomical level. Both pruritic and painful stimuli are detected by the nerve terminals of primary afferent fibers, then transmitted to the thalamus via the spinal cord dorsal horn and the spinothalamic tract.[10] In the past decade, however, researchers discovered itch-specific molecular pathways distinct from pathways of pain transmission, including signaling through gastrin-releasing peptide receptors and Mas-related G protein-coupled receptors.[11,12] These receptors have emerged as new therapeutic targets for antihistamine-resistant itch,[13,14] but unfortunately no such corresponding therapeutic agents have been evaluated in clinical trials to date.

Recently neuroactive agents have been increasingly used for intractable chronic pain.[15] Given the relevance of the nervous system in the pathophysiology of itch, treatment for chronic refractory pruritus has also increasingly involved neuroactive medications.[16] Herein we focus on 2 systemic neuroactive agents, gabapentin and pregabalin, which have been shown to be effective for relieving multiple forms of pruritus.

Abbreviations used:

HD:	hemodialysis
IL:	interleukin
OLT:	open-label trial
RCT:	randomized controlled trial
VAS:	Visual Analog Scale

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Gabapentin and pregabalin were initially developed as antiepileptics, but are now also used for treating neuropathic pain such as that caused by diabetic neuropathy and postherpetic neuralgia.[17,18] Among the array of agents that can be used for these indications, gabapentin is favored because of its low adverse-effect profile, broad therapeutic index, absence of drug-drug interactions, safety in case of overdose, lack of active metabolites, and renal clearance without significant plasma protein binding such that monitoring of blood levels is not required.[19] Pregabalin is a relatively new drug, which has a stronger pharmacologic effect and more rapid absorption than gabapentin.[20,21]

CAPSULE SUMMARY

- Chronic pruritus is a distressing condition that is often difficult to manage.
- Multiple studies have demonstrated that gabapentin and pregabalin are effective for several forms of pruritus, in particular uremic pruritus and that of neural origin.
- Gabapentin and pregabalin are promising therapeutic options for pruritus refractory to conventional treatment.

The structure of gabapentin and pregabalin, and their mechanisms of action, are quite similar; they are both analogs of γ-aminobutyric acid, but do not interact with γ-aminobutyric acid receptors.[22,23] Their exact mechanism of action is unclear, but it is thought that they inhibit the $\alpha 2\delta$ subunit of voltage-dependent calcium channels in the dorsal root ganglion and the spinal cord dorsal horn, thereby increasing the threshold for neuronal excitation by pruritic stimuli.[23-25]

Our study is a review of published articles that explore treatment of chronic pruritus using gabapentin or pregabalin. We will summarize their results and discuss how these findings can be implemented in clinical practice, the limitations of these reports, and any areas requiring further investigation. Our goal is to provide a concise resource for clinicians to use when conventional modalities of treating itch have been exhausted.

METHODS

We searched the PubMed database, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews for English-language articles using the key words "gabapentin," pregabalin," "pruritus," and "itch." Only primary sources published before October 2015 were included in the study. We have focused only on chronic itch, so we excluded studies concerning acute pruritus. One article[26] was not included, because it was unable to be accessed. Here we define randomized controlled trials (RCTs) as randomized, placebo-controlled, and double-blinded studies, and define open-label trials (OLTs) as all other prospective experimental studies. The level of evidence and the strength of recommendation were determined using Strength of Recommendation Taxonomy system.[27]

RESULTS

We identified 22 studies that used gabapentin (Supplemental Table I; available at http://www.jaad.org), 12 studies that used pregabalin (Supplemental Table II; available at http://www.jaad.org), and 3 studies that used both gabapentin and pregabalin (Supplemental Table III; available at http://www.jaad.org).

Gabapentin

Uremic pruritus. Uremic pruritus is itch associated with renal insufficiency, especially with dialysis-dependent end-stage renal disease. Uremic pruritus is a common condition among dialysis-dependent patients, affects patient's quality of life, and is associated with shorter survival time.[28,29] The cause of uremic pruritus has been attributed to multiple factors including sensitization to itch by uremic neuropathy.[30] Therefore, clinicians hypothesized that neuroactive agents may relieve this condition through depressive action on the itch-sensitive neural pathways.

In patients with hemodialysis (HD), 2 RCTs (n = 25 and 34) showed statistically significant improvement of itch refractory to oral antihistamines or topical moisturizers in Visual Analog Scale (VAS) scores after gabapentin (300-400 mg/HD session).[31,32] Two OLTs (n = 5 and 34) indicated that gabapentin works at a lower dose (100 mg/HD session).[33,34] In 1 retrospective cohort study (n = 30), gabapentin also proved to be effective in HD-independent patients.[35] On the other hand, in 1 OLT (n = 19)[36] gabapentin (300 mg/d, thrice a week) failed to show any significant difference in effectiveness compared with an antihistamine.

Brachioradial pruritus. Brachioradial pruritus is characterized by itch localized to the dorsolateral aspect of the arms.[37-39] This condition has also recently been associated with a generalization of pruritus.[40] In these reports the authors propose the use of neuroactive medications, including gabapentin and pregabalin, in the treatment of this condition given its neurogenic cause.