Gabapentin and pregabalin in dermatology

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Introduction
The anticonvulsants gabapentin and pregabalin are of interest to dermatologists. The drugs have found uses in conditions that are frequently of interest to dermatologists and often primarily present to a dermatologist. These drugs are likely to find greater use in dermatology practice in future. This review is intended to familiarize dermatologists with these drugs.

History
Pregabalin was synthesized in 1990 as an anticonvulsant. It was invented by Richard Bruce Silverman at Northwestern University in Chicago, Illinois. The drug was approved in the European Union in 2004. The US received Food and Drug Administration approval for use in treating epilepsy, diabetic neuropathic pain and postherpetic neuralgia in December 2004. Gabapentin was originally approved by the U.S. Food and Drug Administration in December 1993 for use as an adjuvant medication to control partial seizures in adults; that indication was extended to children in 2000. In 2004, its use for treating postherpetic neuralgia (neuropathic pain following shingles) was approved.

Mechanism of Action
Gabapentin consists of a gamma amino butyric acid molecule covalently bound to a lipophilic cyclohexane ring (C$_9$H$_{17}$NO$_2$) [Figure 1]. It is a centrally active gamma amino butyric acid agonist, with its high lipid solubility aimed at facilitating its transfer across the blood–brain barrier. Despite their design as gamma amino butyric acid agonists, neither gabapentin nor pregabalin mimics gamma amino butyric acid when iontophoretically applied to neurons in primary culture. These compounds bind with a high affinity to a protein in cortical membrane with aminooicid sequence identical to that of calcium channel subunit α2δ-1. It has been speculated that the anticonvulsant effect of gabapentin is mediated by α2δ-1 protein, but whether and how binding of gabapentin to this protein regulate neuronal activity remains unclear. Pregabalin binding is reduced but not eliminated in mice carrying a mutation in α2δ-1 protein. It is unclear whether the anticonvulsant and analgesic effect of gabapentin and pregabalin are mediated by affecting calcium currents, and if so how.

Pharmacokinetics
Gabapentin is not metabolized. It is eliminated via renal mechanism and is excreted unchanged. It does not induce hepatic enzymes. Absorption is nonlinear and dose-dependent at very high doses, but the elimination kinetics is linear. The drug is not bound to plasma protein. Drug–drug interactions are negligible. The half-life is relatively short ranging from 5.0 to 8.0 hours, hence, it is administered two or three times per day. It requires gradual adjustment of the dose. In contrast to gabapentin, pregabalin has linear and dose proportion absorption in therapeutic dose range (150 to 600 mg/d). It also has rapid onset of action and more limited dose range. Similar to gabapentin, it is also not metabolized and is almost entirely excreted unchanged in the urine. It is not bound to plasma proteins and has virtually no drug–drug interaction, again resembling the characteristics of gabapentin. Similarly, other drugs do not affect the pharmacokinetics of pregabalin. The half-life of pregabalin ranges from approximately 4.5 hour to 7.0 hours, thus, requiring more than once daily dosing in most patients.

Dosing
The initial dosage of gabapentin is 300 mg/d and can be increased up to 1200 mg three times a day. It can be started

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at its effective dose rather than gradually titrated upwards in dosage.\textsuperscript{7} It should not be discontinued abruptly, but rather tapered gradually, because it can lead to withdrawal-related side-effects.\textsuperscript{8} It has a high toxicity ratio, minimizing the chance of adverse effects with even very high overdoses,\textsuperscript{9} hence, routine monitoring of clinical laboratory parameters is not required.\textsuperscript{5} Pregabalin is started at an initial dose of 150 mg/d and can be increased up to 600 mg/d.\textsuperscript{10}

**Clinical Uses**

**Postherpetic neuralgia and other similar neuropathies**

Approximately 10–15\% of herpes zoster patients will develop postherpetic neuralgia, which can persist for many years. Dermatologists are often the primary care providers for postherpetic neuralgia patients. Several trials conducted previously reported statistically significant reduction in average daily pain after gabapentin and pregabalin.\textsuperscript{11‑17} Gabapentin is the first oral medication approved in the USA for this condition.\textsuperscript{5} Reviews of controlled studies showed that patients suffering from postherpetic neuralgia experienced a statistically significant reduction in average daily pain after treatment with gabapentin. The study also showed that those receiving gabapentin experienced improvement in sleep and overall quality of life.\textsuperscript{18} Gabapentin is useful in the treatment of neuralgia in all areas of the body [Table 1]. Its positive effect on neuralgia includes trigeminal neuralgia,\textsuperscript{18} glossopharyngeal neuralgia refractory to the usual medical treatments\textsuperscript{19} and facial neuritis.\textsuperscript{20} It is also useful in treating inflammatory pain.\textsuperscript{21} Gabapentin is also effective in the treatment of human immunodeficiency virus (HIV) neuropathy,\textsuperscript{22} painful diabetic neuropathy\textsuperscript{23} and diabetic neuropathic pain.\textsuperscript{24} Of particular interest to dermatologist is the probable usefulness of this drug in decreasing the trophic ulcerations that results from neuropathy in diseases such as HIV, leprosy and diabetes that are prone to such ulcers.\textsuperscript{3} Pregabalin is found to be efficacious in treating Red scrotum syndrome (poorly understood, chronic dysesthetic erythema primarily involving the anterior scrotum).\textsuperscript{25}

**Pruritus**

Generalized pruritus is a distressing symptom that can occur in several dermatologic and systemic disorders. Strong similarities exist between neural induction, transmission and processing of pruritus and pain. While itch is transmitted by a functionally distinct subset of neurons, overlap exists between the mediators and receptors involved in the pathogenesis of these sensations.\textsuperscript{26} In addition, it is now clear that chronic itch is influenced by a phenomenon of neural hypersensitization in a process that parallels what has been observed in chronic pain.\textsuperscript{27} In the wake of these discoveries, agents that target the neural system have emerged as effective antipruritic therapies.\textsuperscript{28} Gabapentin has been reported to be an effective antipruritic agent in uremic pruritus,\textsuperscript{29‑36} brachioradial pruritus,\textsuperscript{37‑40} pruritus associated with wound healing in burns\textsuperscript{41} and notalgia paresthetica\textsuperscript{42} and pruritus of unknown origin.\textsuperscript{6,43} Its effect in pruritus can be central and peripheral. It inhibits voltage-dependent calcium ion channels located in the spinal cord (with particular high density in the superficial laminae of the dorsal horn), inhibiting the release of excitatory

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**Table 1: Various uses of gabapentin in dermatology**

| Neuropathic pain |
|------------------|
| Postherpetic neuralgia |
| HIV neuropathy |
| Diabetic neuropathic pain |
| Neuralgia |
| Glossopharyngeal neuralgia |
| Trigeminal neuralgia |
| Facial neuritis |
| Skin hypersensitivity |
| Allodynia |
| Buccofacial allodynia |
| Mechanical allodynia |
| Reflex sympathetic dystrophy |
| Dynia |
| Glossodynia |
| Carotidina |
| Vulvodynia |
| Orchidynia |
| Prostatodynia |
| Coccycodynia |
| Protodynia |
| Scalp dysesthesia |
| Hot flashes |
| Temperature-sensitive dermatosis |
| Dysesthetic pain after reconstruction surgery |
| Pruritus |
| Brachoradial pruritus |
| Uremic pruritus |
| Pruritus of unknown origin |
| Seizure due to AIP |
| Self-injurious behavior in Lesh-Nyhan syndrome |
| Steroid induced mania |
| Piloleiomyoma-related pain |
| Pain of vasolabile conditions |

**Erythromelalgia**

\( HIV: \) Human immunodeficiency virus, \( AIP: \) Acute intermittent porphyria
neurotransmitters. Other mechanisms involved are increase in the synthesis of γ-aminobutyric acid from glutamate by altering the activity of glutamic acid decarboxylase in neurological tissue, inhibition of the release of calcitonin gene-related peptide, a neuropeptide, described as an itch mediator. Gabapentin also increases the threshold to experience nociception. Related drug Pregabalin, a gamma amino butyric acid analogue of gabapentin, has been used in the treatment of uremic pruritus, brachioradial pruritus, pruritus in prurigo nodularis and polycythemia vera-associated aquagenic pruritus. It was hypothesized that the beneficial effect of Pregabalin in chronic pruritus may result from counteracting the effects on the central sensitizing processes involved in the generation of chronic itch. It has also been reported to improve interleukin 2 and cetuximab-related pruritus in cancer patients. However, at present there are insufficient data to conclude that these anticonvulsants can be an effective therapeutic alternative in the management of pruritus.

### Gabapentin in various dyinas

The “dyinas” are a group of chronic, focal pain syndromes with a predilection for the orocervical and urogenital regions. They include glossodynia, carotidynia, scalp dysesthesia, vulvodynia, orchidynia, prostatodynia, coccygodynia and proctodynia [Table 1]. In some cases, the dynia occur secondarily, but more often, despite an exhaustive evaluation, no etiology is found, and in these cases the cause of pain remains enigmatic. Sometimes, these patients initially present to dermatologist. These dyrias are found responsive to gabapentin. Allodynia is a sensation of pain to slight touch. It is another complication of postherpetic neuralgia. It can be effectively treated by gabapentin which can block both the static and dynamic components of mechanical allodynia. It also relieves cutaneous hyperalgesia after skin has been sensitized to pain. Reflex sympathetic dystrophy is a condition involving persistent pain that results from nerve injury. It has a variety of cutaneous manifestations, including atrophy, edema, erythema, bullae, and ulcers. Gabapentin has a role in the control of reflex sympathetic dystrophy-related pain in children and adults.

### Other uses

Gabapentin has shown benefit in pain related to leiomyomas in patients with painful sclerodermatous changes that have affected nerve conduction, pain of the vasculable condition and erythromelalgia. Gabapentin has also shown benefits in various conditions associated with neurologic problems and skin. It is useful in the treatment of dysesthetic pain after reconstructive surgery, seizures due to acute intermittent porphyria, self-injurious behavior in Lesch-Nyhan syndrome and as a prophylaxis against steroid-induced mania. Finally, gabapentin improves pain control during wound dressing of cancer patients, suggesting that it might have a role in toxic epidermal necrolysis patients who complain of “painful skin.”

In a recent article, gabapentin was also found to be effective for...
Table 2: Contd...

| Use                        | Studies                                                                 | Year  | Study design | Level of evidence |
|----------------------------|-------------------------------------------------------------------------|-------|--------------|-------------------|
| Neuralgias                 | Pandey et al. Gabapentin for refractory idiopathic trigeminal neuralgia. J Indian Med Assoc | 2008  | Case report  | Level III         |
|                            | Maretti et al. Gabapentin treatment of glossopharyngeal neuralgia: A follow up of 4 year of a single case. Eur J Pain | 2002  | Case report  | Level III         |
|                            | Carlsten et al. Gabapentin treatment of glossopharyngeal neuralgia with cardiac syncope. Ugeskr Laeger | 2002  | Case report  | Level III         |
|                            | Garcia Callejo et al. Use of gabapentin in glossopharyngeal neuralgia. Acta Otorrinolaringol Exp | 1999  | Case report  | Level III         |
|                            | Sist et al. Gabapentin for idiopathic trigeminal neuralgia: Report of two cases. Neurology | 1997  | Case report  | Level III         |
|                            | Lucier and Franm L. Use of gabapentin in a case of facial neuritis. Anesth Analg | 1997  | Case report  | Level III         |
|                            | Garcia Callejo et al. Clinical response of gabapentin for glossopharyngeal neuralgia. Rev Neurol | 1994  | Case report  | Level III         |
| Uremic pruritus            | Foroutan et al. Comparison of pregabalin with doxepin in the management of uremic pruritus: A randomized, single-blind clinical trial. Hemodial Int | 2017  | RCT          | Level I           |
|                            | Nofal et al. Gabapentin: A promising therapy for uremic pruritus in hemodialysis patients: A randomized-controlled trial and review of literature. J Dermatolog Treat | 2016  | RCT          | Level I           |
|                            | Hassan et al. Efficacy and safety of gabapentin for uremic pruritus and restless leg syndrome in conservatively managed patients with chronic kidney disease. J Pain Symptom Manage | 2015  | Cohort study | Level II          |
|                            | Yong et al. Uremic pruritus is improved by gabapentin. Int J Dermatol | 2014  | Case report  | Level III         |
|                            | Shavit et al. Use of pregabalin in the management of chronic pruritus. J Pain Symptom Manage | 2013  | Clinical trial | Level II         |
|                            | Solak et al. Pregabalin versus gabapentin in the treatment of neuropathic pruritus in maintenance haemodialysis patients: A prospective, crossover study. Nephrology | 2012  | RCT          | Level I           |
|                            | Rayner et al. Uraemic pruritus: Relief of itching by gabapentin and pregabalin. Nephron clin prac | 2012  | Clinical trial | Level II         |
|                            | Marquez et al. Uremic pruritus in hemodialysis patients: Treatment with desloratidine versus gabapentin. J Bras Nefrol | 2012  | Clinical trial | Level II         |
|                            | Razeghi et al. Gabapentin and uremic pruritus in hemodialysis patients. Ren Fail | 2009  | Clinical trial | Level II         |
|                            | Naini et al. Gabapentin: A promising drug for the treatment of uremic pruritus. Saudi J Kidney Dis Transpl | 2007  | RCT          | Level I           |
|                            | Manenti L. et al. Gabapentin in the treatment of uraemic itch: An index case and a pilot evaluation. J Nephrol | 2005  | Clinical trial | Level II         |
|                            | Gunal et al. Gabapentin therapy for pruritus in haemodialysis patients: A randomized, placebo-controlled, double-blind trial. Nephrol Dial Transplant | 2004  | RCT          | Level I           |
| Brachioradial pruritus     | Atas and Bilir Kayan B. Pregabalin treatment of three cases with brachioradial pruritus. Dermatol Ther | 2017  | Case report  | Level III         |
|                            | Vestita et al. Brachioradial pruritus in a 47-year-old woman treated with pregabalin. G Ital Dermatol Venereol | 2016  | Case report  | Level III         |
|                            | Carvalho et al. Brachioradial pruritus in a patient with cervical disc herniation and Parsonage - Turner syndrome. An Bras Dermatol | 2015  | Case report  | Level III         |
|                            | Uldall pallesen et al. Brachioradial pruritus effectively treated with gabapentin. Ugeskr Laeger | 2012  | Case report  | Level III         |
|                            | Yilmaz et al. Brachioradial pruritus successfully treated with gabapentin. J Dermatol | 2010  | Case report  | Level III         |
|                            | Kanitakis. Brachioradial pruritus: Report of a new case responding to gabapentin. Eur J Dermatol | 2006  | Case report  | Level III         |
|                            | Winhoven et al. Brachioradial pruritus: Response to treatment with gabapentin. Br J Dermatol | 2004  | Case report  | Level III         |
| Dynias                     | Dubey et al. Gabapentin therapy for glossodynia due to an unusual case. Anesth Analg | 2008  | Case report  | Level III         |
|                            | Meiss et al. Gabapentin - a promising treatment in glossodynia. Clin Exp Dermatol | 2002  | Case report  | Level III         |
|                            | Ben David et al. Gabapentin therapy for vulvodynia. Anesth Anal | 1994  | Case report  | Level III         |
| Sclerodermatous changes    | Fischoff and Sirois D. Painful trigeminal neuropathy caused by severe mandibular resorption and nerve compression in a patient with systemic sclerosis: Case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod | 2000  | Case report  | Level III         |

Contd...
Table 2: Contd...

| Use                                      | Studies                                                                 | Year | Study design | Level of evidence |
|------------------------------------------|-------------------------------------------------------------------------|------|--------------|-------------------|
| Erythromelalgia                          | McGraw and Kosek P. Erythromelalgia pain managed with gabapentin.        | 1997 | Case report  | Level III         |
|                                          | *Anesthesiology*                                                        |      |              |                   |
|                                          | Ceyhan et al. A case of erythromelalgia: Good response to treatment with gabapentin. | 2010 | Case report  | Level III         |
|                                          | *J Drugs Dermatol* 2010                                                |      |              |                   |
| Dysesthetic pain after reconstructive surgery | Otley. Gabapentin for the treatment of dysesthetic pain after reconstructive surgery. | 1999 | Case report  | Level III         |
|                                          | *Dermatol Surg*                                                        |      |              |                   |
| Acute intermittent porphyria             | Arora and Mahajan V. Gabapentin in seizures due to AIP. *Neurol India*  | 2000 | Case report  | Level III         |
| Lesch-Nyhan syndrome                     | McManaman and Tam DA. Gabapentin for self-injurious behavior in Lesch-Nyhan syndrome. *Pediatr Neurol* | 1999 | Case report  | Level III         |
| Steroid-induced mania                    | Ginsberg and Sussman N. Gabapentin as prophylaxis against steroid-induced mania. *Can J Psychiatr* | 2001 | Case report  | Level III         |
| Wound dressing care                      | Devulder et al. Gabapentin for pain control in cancer patients’ wound dressing care. *J Pain Symptom Manage* | 2001 | Case report  | Level III         |
| Toxic epidermal necrolysis               | Moshfeghi and Mandler HD. Ciprofloxacin-induced toxic epidermal necrolysis. *Ann Pharmacother* | 1993 | Case report  | Level III         |
| Notalgia paresthetica                    | Maciel et al. Efficacy of gabapentin in the improvement of pruritus and quality of life of patients with natalgia paresthetica. *An Bras Dermatol* | 2014 | Clinical trial | Level II          |
|                                          | Loosmore et al. Gabapentin treatment for natalgia paresthetica, a common isolated peripheral sensory neuropathy. *J Eur Acad Dermatol Venereol* | 2007 | Case report  | Level III         |

RCT: Randomized controlled trial. Level I: RCT, Level II: Case series, Level III: Case Report

Table 3: Side effects

| Most common                              | Drowsiness/sedation                                                                 |
|                                          | Malaise/lassitude                                                                |
| Cutaneous                                | Ucers in mouth due to pancytopenia                                                |
|                                          | Easy bruising                                                                      |
|                                          | Fluid retention (leg)                                                             |
| Weight gain                              | Allergic eruptions                                                                |
| Stevens-Johnsons syndrome                |                                                                                   |
| Other side effects                        | Cholestasis                                                                        |
|                                          | Hepatotoxicity                                                                    |
|                                          | Anorgasemia                                                                       |
|                                          | Dyskinesia                                                                        |
|                                          | Reversible acute renal allograft dysfunction                                      |

Vismodegib-induced muscle cramps. Pregabalin was also used for the treatment of painful hand-foot skin reaction associated with darafenib. Studies showing effect of gabapentin and pregabalin in various dermatological conditions have been described briefly in Table 2.

**Adverse Effects**

These drugs are relatively safe with very few serious adverse effects [Table 3]. The most frequently reported adverse event is drowsiness/sedation. This is seen during the first month of treatment. This is also one of the most common cause for discontinuation of the drug. Others causes include dizziness, malaise/lassitude and ataxia.

Rarely, they can cause pancytopenia, causing fever, sore throat and ulcers in the mouth, or unusual bleeding and easy bruising, fluid retention in the legs and weight gain. A few cases of allergic eruptions and Stevens–Johnson’s syndrome have also been reported.

Very rarely gabapentin has induced cholestasis and hepatotoxicity. Studies conducted for its efficacy in pregnancy showed no congenital anomalies among the infants. However, the crude mortality rate was up to five times higher than in the general population. There are a few isolated reports about anorgasmia in women taking gabapentin.

**Conclusion**

Gabapentin and pregabalin are very promising medications in the treatment of painful conditions that often are domain of dermatologists such as postherpetic neuralgia, painful tumors, neuropathic ulcers or pain during dressing changes in conditions such as toxic epidermal necrolysis. Of great interest to a dermatologist is its use in chronic itch unresponsive to other medication. However, at present, there is insufficient data to suggest that these anticonvulsants can be an effective alternative to treat various types of skin sensitivities and pruritus. Future large randomized controlled studies are required that use behavioral methodology rather than subjective methodology. The chances of placebo effects are quite high with subjective methodologies.

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Conflicts of interest
There are no conflicts of interest.

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