Drugs on the Horizon for Chronic Pruritus

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KEYWORDS

• Chronic pruritus • Chronic itch • Atopic dermatitis • Psoriasis • Uremic pruritus • Cholestatic pruritus • Novel therapies

KEY POINTS

- The elucidation of itch signaling pathways has led to the development of novel therapeutic agents.
- Emerging systemic therapies include neurokinin 1 antagonists, drugs acting on the k- and μ-opioid receptors, interleukin antagonists, janus kinase inhibitors, histamine antagonists, leukotriene receptor antagonists, and bile acid transporter inhibitors.
- Emerging topical and local therapies include drugs acting on transient receptor potential vanilloid 1, tropomyosin-receptor-kinase A inhibitors, phosphodiesterase-4 inhibitors, analgesics, cannabinoids, and botulinum toxin type A.

INTRODUCTION

Chronic pruritus, which is defined as a greater than 6-month duration of sensations that lead to the desire to scratch,[1,2] is a common condition with an estimated point prevalence of 8.4% to 13.5%.[3,4] Diseases associated with chronic pruritus can be divided into 4 broad categories: dermatologic (eg, atopic dermatitis [AD], psoriasis, chronic urticaria, lichen planus, scabies), systemic (eg, chronic renal disease, cholestatic disease, hyperthyroidism, myeloproliferative disorders), neuropathic (eg, notalgia paresthetica, brachioradial pruritus, post-herpetic neuralgia), and psychogenic (eg, depression, obsessive-compulsive disorder).[5] Chronic pruritus is known to have a detrimental impact on quality of life and is associated with depressive symptoms, sleep impairment, agitation, impaired concentration, and sexual dysfunction.[6–8]

Itch is primarily mediated by unmyelinated, slow-conducting C-fibers, which are found at the dermal–epidermal junction with free nerve endings extending into the epidermis.[9] When a pruritogen is encountered, G-protein coupled receptors or ion channels initiate itch signaling. G-protein coupled receptor signaling may be induced by proteases such as tryptase, cathepsin S, and kallikreins, neuropeptides such as substance P, prostaglandins, and histamines.[9,10] Ion channels in the transient receptor potential (TRP) family play a role in itch signaling and include TRP vanilloid 1(TRPV1), which is a receptor for capsaicin, and TRPA1.[9,11] Several

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cytokines can induce itch including interleukin (IL)-31, which is highly associated with pruritus in AD, prurigo nodularis, lichen amyloidosis, and cutaneous T-cell lymphoma.[12–15] Tropomyosin receptor kinase A, which responds to nerve growth factor by stimulating the growth of small diameter nerves expressing tropomyosin receptor kinase A and TRPV1, is also implicated in itch signaling.[16] Finally, opioid receptors are thought to play a role in itch pathogenesis, with μ-opioid receptors having an excitatory effect on itch signaling and κ-opioid receptors having an inhibitory effect.[10,17] Decreased numbers of κ-opioid receptors are observed in patients with AD[18] and psoriasis patients suffering from pruritus,[19] suggesting a role for κ-opioid receptors in the normal suppression of pruritus.

Current therapies for chronic pruritus include topical glucocorticoids, topical calcineurin inhibitors, topical capsaicin, antidepressants, antihistamines, gabapentin, cyclosporine, methotrexate, naloxone, naltrexone, and phototherapy.[20] As the molecular pathogenesis of itch continues to be elucidated, novel therapies are being developed to disrupt itch pathways. Herein, we review the drugs that have been recently approved or are under investigation for the treatment of chronic pruritus (**Table 1**).

SYSTEMIC THERAPIES

Drugs Targeting the Neural System

Neurokinin antagonists

Neurokinin 1, which is the receptor for substance P, plays a significant role in chronic itch.[21] Aprepitant is an oral neurokinin-1 receptor antagonist that is reported to be effective in reducing pruritus of various etiologies including cutaneous T-cell lymphoma,[22] biological therapies for solid tumor

Table 1
Emerging therapies for chronic pruritus listed by class

Drug Class	Drug Name	Route
Neurokinin antagonists	Aprepitant	Oral
	Serlopitant	Oral
	Tradipitant	Oral
κ-Opioid receptor agonists	Nalfurafine hydrochloride	Oral
	Difelikefalin (CR845)	Intravenous
	Asimadoline	Oral
Mixed κ-opioid receptor agonist/μ-opioid receptor antagonists	Nalbuphine hydrochloride	Oral
Interleukin antagonists	Nemolizumab	Subcutaneous
	Dupilumab	Subcutaneous
	Secukinumab	Subcutaneous
	Ixekizumab	Subcutaneous
Janus kinase inhibitors	Tofacitinib	Oral
	Upadacitinib	Oral
Histamine antagonists	Bilastine	Oral
	JNJ-39758979	Oral
	ZPL-389	Oral
Leukotriene receptor antagonists	Montelukast	Oral
Bile acid transporter inhibitors	GSK2330672	Oral
	A4250	Oral
Drugs acting on TRPV1	PAC-14028	Topical
	Capsaicin	Topical
TrkA inhibitors	Pegcantratinib (CT327)	Topical
PDE-4 inhibitors	Crisaborole	Topical
	OPA-15406/MM36	Topical
Analgesics	Ketamine-amitriptyline-lidocaine	Topical
Cannabinoids	PEA	Topical
	AEA	Topical
Botulinum toxin	Botulinum toxin type A	Intradermal

Abbreviations: AEA, *N*-acetylethanolamine; PDE-4, phosphodiesterase-4; PEA, *N*-palmitoylethanolamine; TrkA, tropomyosin-receptor-kinase A; TRPV1, transient receptor potential vanilloid 1.