Itch: Pathogenesis and treatment

Nishadh Sutaria, BS,[a] Waleed Adawi, MS,[a] Rebecca Goldberg, BS,[a] Youkyung S. Roh, BA,[a] Justin Choi, BA,[a] and Shawn G. Kwatra, MD[a,b]
Baltimore, Maryland

Learning objectives
After completing this continuing medical education activity, learners will be able to discuss the pathophysiology of itch; name the available and emerging treatment options for itch; and choose appropriate treatments tailored to individual patients.

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Itch pathogenesis is broadly characterized into histaminergic and nonhistaminergic pathways and transmitted via 2 main receptor families: G protein—coupled receptors and transient receptor potential channels. In the skin, itch is primarily transmitted by unmyelinated type C and thinly myelinated type Aδ nerve fibers. Crosstalk between the immune and neural systems modulates itch transmission at the skin, spinal cord, and brain. Among the many known pruritogens, Th2 cytokines, such as interleukin-4, interleukin-13, interleukin-31, and thymic stromal lymphopoietin, are particularly important mediators that signal through shared Janus kinase pathways, representing novel targets for novel itch therapeutics. Emerging evidence has also revealed that the opioidergic system is a potent modulator of itch transmission, with increased μ-opioid activity and decreased κ-opioid activity contributing to itch pathogenesis. Optimal management of itch requires that treatment approaches be tailored to specific etiologic itch subtypes. When the etiology is unknown and patients are given a diagnosis of chronic pruritus of unknown origin, treatment should be guided by the presence of Th2 polarization, often reflected by increased blood eosinophils. In the second article of this 2-part series, we outline our current understanding of itch pathogenesis and discuss available and emerging treatments for itch. (J Am Acad Dermatol 2022;86:17-34.)

Key words: itch; management; pathogenesis; pathophysiology; pruritus; therapeutics; treatments.

From the Department of Dermatology[a] and Department of Oncology, Johns Hopkins University School of Medicine, Baltimore.[b]

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Correspondence to: Shawn G. Kwatra, MD, Department of Dermatology, Johns Hopkins University School of Medicine, Cancer Research Building II, Suite 206, 1550 Orleans Street, Baltimore, MD 21231. E-mail: skwatra1@jhmi.edu.

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PATHOGENESIS OF ITCH

Key points

- Itch is classified into histaminergic and nonhistaminergic pathways.
- Itch sensation is primarily transmitted by unmyelinated type C and thinly myelinated type Aδ nerve fibers in the skin.
- The itch signaling cascade involves bidirectional neural circuitry connecting the skin, spinal cord, and brain.
- Crosstalk between the neural and immune systems modulates itch transmission.

Our basic understanding of the mechanisms and pathophysiology of itch has grown in recent years; however, much of this knowledge is limited to mouse models. There is still much to be uncovered relating to the pathogenesis of itch in human itch subtypes. From the skin to the brain, the itch signal consists of multiple pathways, modulated at each level by numerous effector cells, pruritogens, and receptors (Fig 1).

Abbreviations used:

CPUO:	chronic pruritus of unknown differentiation
GRP:	gastrin-releasing peptide
GRPR:	GPR receptor
IL:	interleukin
JAK:	Janus kinase
PAR:	protease-activated receptor
PN:	prurigo nodularis
RCT:	randomized control trial
SP:	substance P
STAT:	signal transducer and activator of transcription
TRP:	transient receptor potential
TRPV1:	TRP vanilloid 1

Itch in the skin

Itch nerve fibers. Itch sensation is primarily transmitted by unmyelinated type C and thinly myelinated type Aδ nerve fibers in the skin (Fig 2).[1] The cell bodies of these nerves reside in dorsal root ganglia (DRG) with axons innervating the skin and dendrites synapsing in the dorsal horn of the spinal cord. There is a complex interplay between these nerve fibers and the skin microenvironment as nerve transmission is modulated by skin pH, temperature, and pain. Itch is initiated when exogenous and endogenous pruritogens bind to their receptors on these sensory nerve endings (Fig 3).

Itch receptors. There are 2 major classes of itch receptors: G protein–coupled receptors and transient receptor potential (TRP) channels (Fig 3). TRP channels include TRP vanilloid 1 (TRPV1) and TRP ankyrin 1, which activate $Na_v1.7$ and $Na_v1.8$ sodium channels, propagating the action potential of the itch signal.[2]

Histaminergic and nonhistaminergic pathways. Histaminergic and nonhistaminergic pathways constitute the 2 major pathways of itch (Fig 4). The histaminergic pathway transmits acute itch and is mediated by histamine secreted primarily by mast cells, basophils, and keratinocytes.[3-5] Once released, histamine binds to H1 and H4 receptors on histaminergic nerves, activating TRPV1.[2] Nonhistaminergic itch is elicited by nerves that express a variety of receptors, activated by pruritogens other than histamine (Fig 3). These pruritogens are released by a variety of effector cells, including mast cells, granulocytes, macrophages, lymphocytes, keratinocytes, and neurons.[4-6] Recent evidence also suggests that basophils can promote itch mediated by immunoglobulin E, independent of mast cells.[5]

Cytokines. The most-studied cytokines in itch pathogenesis are Th2 cytokines, most prominently including interleukin (IL)-4, IL-13, and IL-31 (Fig 3).[7-9] Keratinocytes also release IL-33 and thymic stromal lymphopoietin, which directly induce itch and promote Th2 inflammation.[10,11] Scratching further increases the expression of thymic stromal lymphopoietin, contributing to the "itch-scratch cycle." Other important cytokines are IL-17 in psoriasis itch and IL-22, which induces itch via the gastrin-releasing peptide (GRP) pathway.[9,12,13] Prurigo nodularis (PN), a disease characterized by an intractable itch-scratch cycle, features increased IL-22 in the skin and blood.[14,15] IL-2 and IL-31 have also been implicated in uremic itch.[16,17] Downstream mediators of these inflammatory cytokines involve the intracellular Janus kinase (JAK)/signal transducer and activator of transcription signaling pathways (Fig 3).[11,18] Blockade of those pathways, particularly JAK1, is an attractive therapeutic option due their role in multiple itch pathways.

Neuropeptides and neurotransmitters. Substance P (SP) and calcitonin gene-regulating protein (CGRP) are neuropeptides released by activated sensory neurons that cause neurogenic inflammation and mast cell degranulation.[19] SP binds to receptor neurokinin 1 on sensory nerve endings, keratinocytes, and immune cells (Fig 3).[20] Nerve growth factor, a neuropeptide secreted by eosinophils, binds to tropomyosin receptor kinase A on sensory nerves, sensitizing TRPV1 to SP and calcitonin gene-regulating protein.[21] Finally, opioids are well-established pruritogens, binding to the μ-opioid receptor and κ-opioid receptor on sensory neurons. Itch is induced by μ-opioid

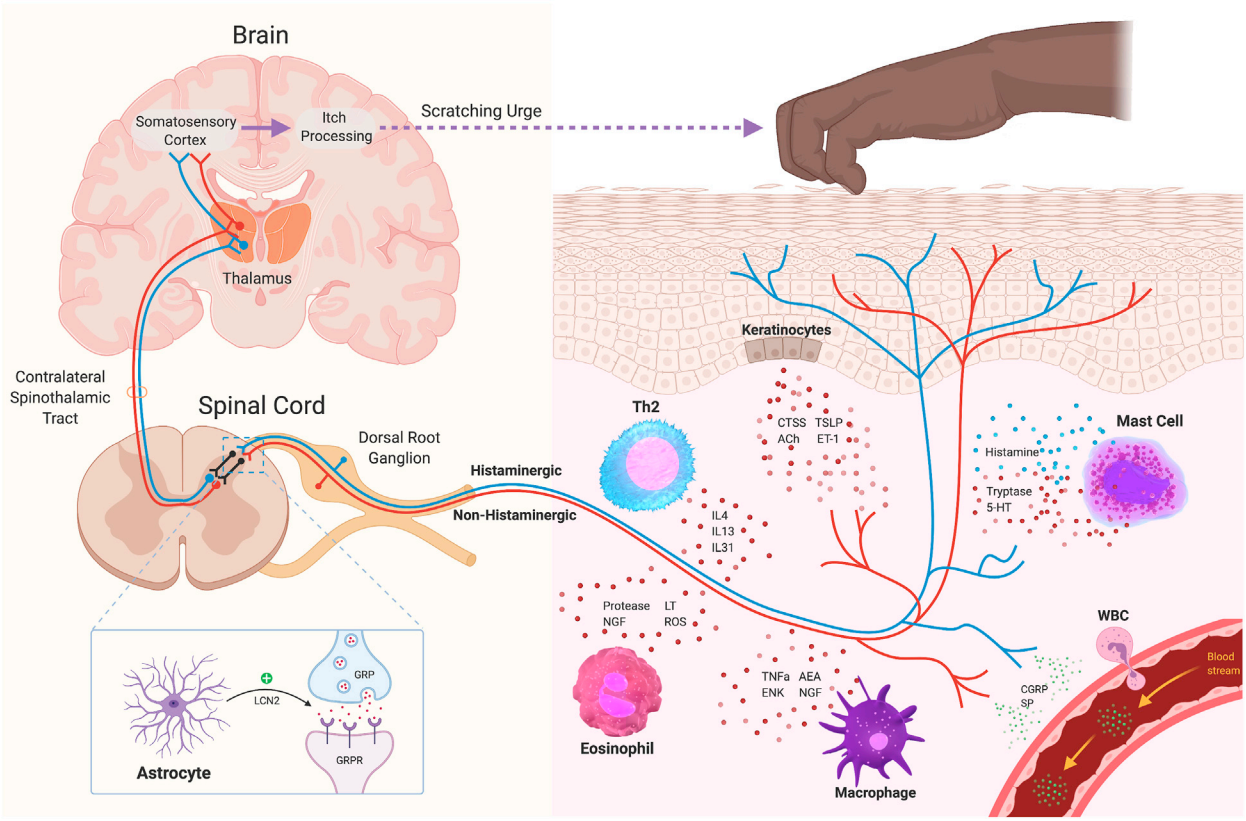

Fig 1. An overview of itch transmission from the skin to the spinal cord and brain. *5-HT*, Serotonin; *Ach*, acetylcholine; *AEA*, anandamide; *CGRP*, calcitonin gene-related peptide; *CTSS*, cathepsin S; *ENK*, enkephalin; *ET-1*, endothelin-1; *GRP*, gastrin-releasing peptide; *GRPR*, gastrin-releasing peptide receptor; *IL4*, interleukin 4; *IL13*, interleukin 13; *IL31*, interleukin 31; *LCN2*, lipocalin-2; *LT*, leukotrienes; *NGF*, nerve growth factor; *ROS*, reactive oxygen species; *SP*, substance P; *Th2*, Type 2 helper T cell; *TNFa*, tumor necrosis factor alpha; *TSLP*, thymic stromal lymphopoietin; *WBC*, white blood cell. All illustrated figures were created with BioRender.com.

activity and suppressed by κ-opioid activity; thus, an imbalance of these 2 receptors contributes to itch (Fig 5).[22]

Proteases and enzymes. Proteases mediate itch by bindings to protease-activated receptors (PARs), which are a type of G protein—coupled receptors.[23] Several proteases bind PAR2/PAR4 to induce itch, including kallikrein, tryptase, trypsin, and cathepsin S (Fig 3).[23-26] Autotaxin, an enzyme important for generating lysophosphatidic acid (LPA), may be involved in cholestatic itch.[27]

Itch in the spinal cord

The itch signal is transmitted through the cell bodies in the DRG to the dorsal horn of the spinal cord (Fig 6). The activated sensory neurons release GRP which binds to GRP receptor (GRPR)-positive neurons in the spinal cord.[28] GRPR-positive neurons are selectively activated for itch but not pain signals, and chemical versus mechanical itch are processed differently as well.[29] The helix-loop-helix family member B5 (Bhlbh5) interneurons, which are modulated by κ-opioid activity, attenuate the itch signal by inhibiting GRPR-positive neurons with dynorphin, glycine, and gamma-aminobutyric acid (Fig 6).[30]

Structural abnormalities of the spinal cord can also modulate the itch signaling pathway, causing localized neuropathic pruritus. Radiculopathy of cervical nerves is a contributor to brachioradial pruritus, notalgia paresthetica, and meralgia paresthetica.[31,32]

Itch in the brain

After passing through the spinal cord, itch signals travel along the spinothalamic tract and reach the thalamus and parabrachial nucleus, followed by the brain (Fig 1).[33] Itch perception involves the primary

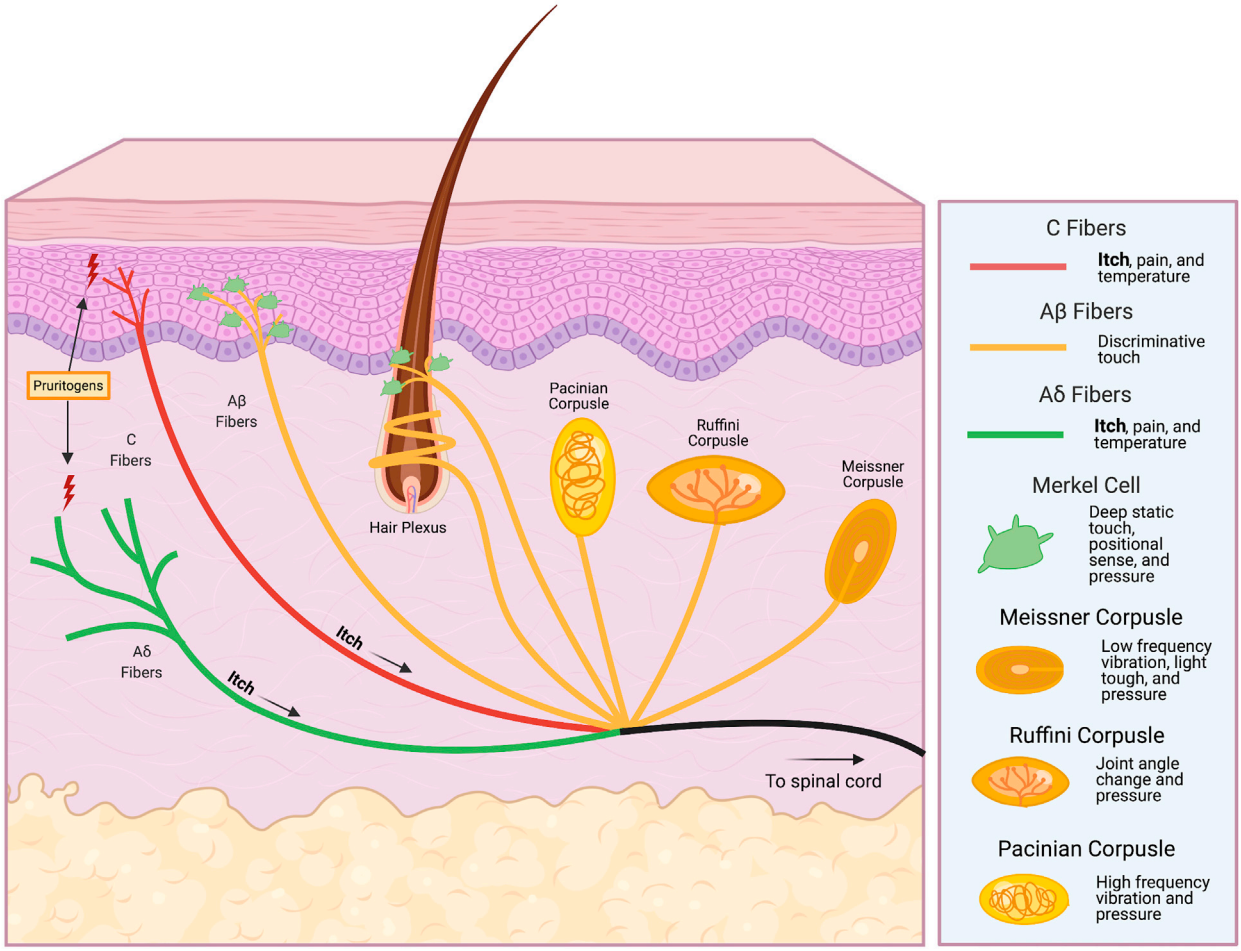

Fig 2. Nerve fibers innervating the skin. Itch is transmitted primarily via Aδ and C fibers.

and secondary somatosensory cortex, insula, and anterior cingulate cortex (Fig 7).[34-36] Histaminergic and nonhistaminergic itch also activate different regions of the brain and can resemble pain perception.[37,38] Scratching inhibits areas related to the unpleasant sensation of itch, including the anterior cingulate cortex and insula (Fig 7).[39,40] Scratching provides pleasure by activating areas of the reward system, including the ventral tegmentum area and striatum.[41] This pleasure can feed into higher-level reward systems involving the midbrain and striatum, potentiating an addictive itch-scratch cycle.

TREATMENT OF ITCH

Key Points

- Itch management requires clinical phenotyping into etiologic subtypes with varying degrees of inflammatory, systemic, neurologic, and psychologic dysfunction.
- Effective itch therapies often modulate both neural and immune components of itch transmission.
- Recalcitrant itch often requires combination multimodal therapy with both topical and systemic agents.

Evidence for many itch therapeutics is largely limited to case reports and series, with few randomized controlled trials (RCTs). Specific dosages and indications for treatments can be found in Tables I and II and suggested treatment ladders can be found in Figs 8 and 9.

Topical and localized therapies

Corticosteroids. Topical corticosteroids, with a range of potencies and concentrations, are the mainstay of treatment for itch associated with inflammatory dermatoses. They improve itch by reducing inflammation and inhibiting pruritic cytokine cascades.[42,43] Intralesional corticosteroids can provide extended relief in localized dermatoses, such as lichen simplex chronicus.[44] Caution should be used due to the risks of skin atrophy and hypopigmentation.

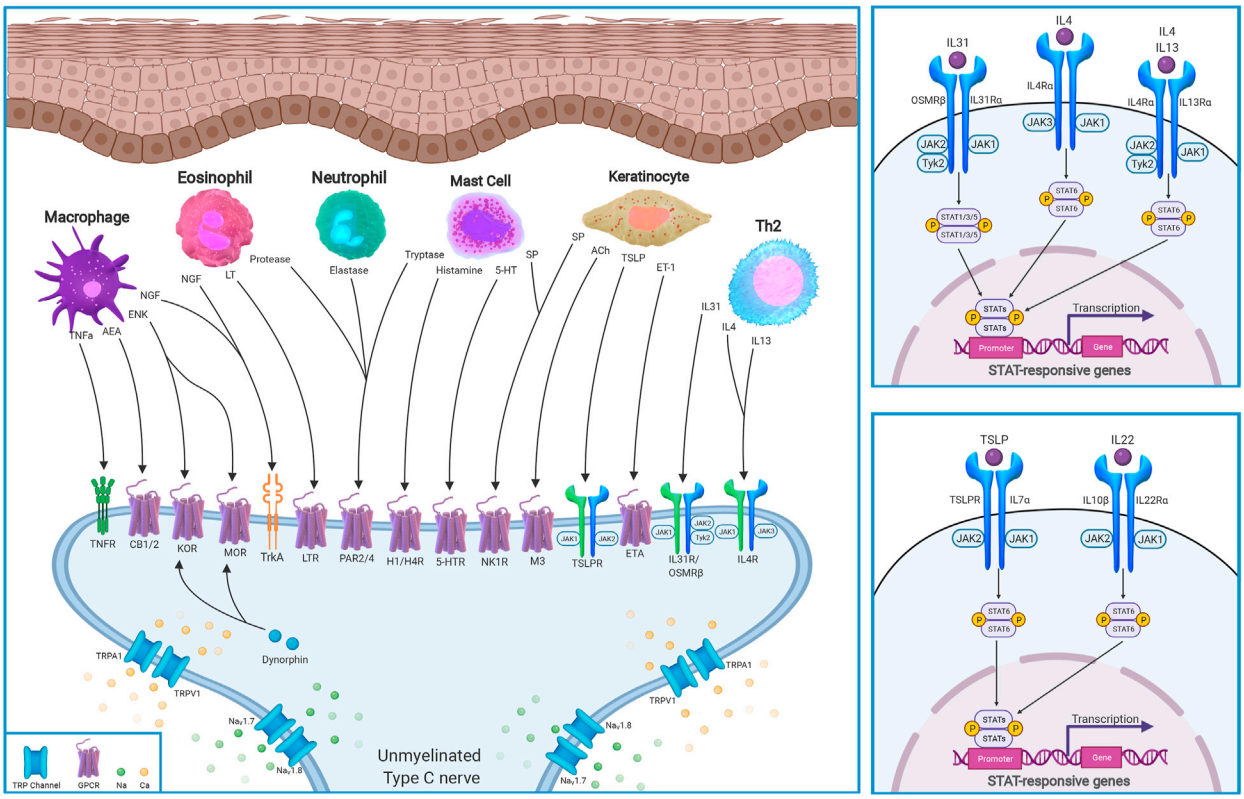

Fig 3. Itch mediators and receptors (left) with downstream JAK/STAT pathways (top and bottom right). *NGF*, Nerve growth factor; *5-HT*, serotonin; *5-HTR*, serotonin receptor; *Ach*, acetylcholine; *AEA*, anandamide; *CB1/2*, cannabinoid receptor type 1 and 2; *ENK*, enkephalin; *ET-1*, endothelin 1; *ETA*, endothelin A receptor; *H1/4R*, histamine receptor type 1 and 4; *IL13*, interleukin 13; *IL22*, interleukin 22; *IL22R*, interleukin 22 receptor; *IL31*, interleukin 31; *IL31R*, interleukin 31 receptor; *IL4*, interleukin 4; *IL4R*, interleukin 4 receptor; *IL7R*, interleukin 7 receptor; *JAK*, Janus kinase; *KOR*, kappa opioid receptor; *LT*, leukotrienes; *LTR*, leukotrienes receptor; *M3*, muscarinic acetylcholine receptor 3; *MOR*, mu opioid receptor; *Na$_v$1.7/1.8*, voltage-gated sodium channel; *NK1R*, neurokinin 1 receptor; *OSMRβ*, oncostatin M receptor beta; *P*, phosphate; *PAR2/4*, protease-activated receptor type 2 and 4; *SP*, substance P; *STAT*, signal transducer and activator of transcription; *TNFa*, tumor necrosis factor alpha; *TNFR*, tumor necrosis factor receptor; *TrkA*, tropomyosin receptor kinase A; *TRPA1*, transient receptor ankyrin 1; *TRPV1*, transient receptor potential vanilloid 1; *TSLP*, thymic stromal lymphopoietin; *TSLPR*, thymic stromal lymphopoietin receptor; *Tyk*, tyrosine kinase; *Th2*, Type 2 helper T cell.

Calcineurin inhibitors. Tacrolimus and pimecrolimus, approved for ages 2 and older, are calcineurin inhibitors that have modest effects on inflammation and desensitization of primary afferent sensory neurons via TRPV1 agonism.[40] The most common side effect is a painful burning sensation, which diminishes with repeated applications.[45] Contraindications include history of hypersensitivity to topical calcineurin inhibitors.[46,47]

Anesthetics. Topical anesthetics such as pramoxine, lidocaine, and prilocaine reduce itch by antagonizing voltage-gated sodium channels. These agents have mild efficacy for uremic and neuropathic itch.[48] Pramoxine 1% lotion formulations can be cooled in the refrigerator to potentiate itch relief in neuropathic itch subtypes that are improved with colder temperatures, via activation of thermoceptive type Aδ and C nerve fibers.[49] For localized relief, the 5% lidocaine patch can be used for up to 12 hours in any 24-hour period. Combined topical ketamine-amitriptyline-lidocaine preparations are available via compound pharmacies with concentrations of each component ranging from 2.5% to 10%. It targets multiple itch mediators and can be effective for refractory itch.[50,51] Topical ketamine-amitriptyline-lidocaine preparations should not be applied to more than 50% total body surface area as systemic absorption leading to toxic encephalopathy has been reported.[52]

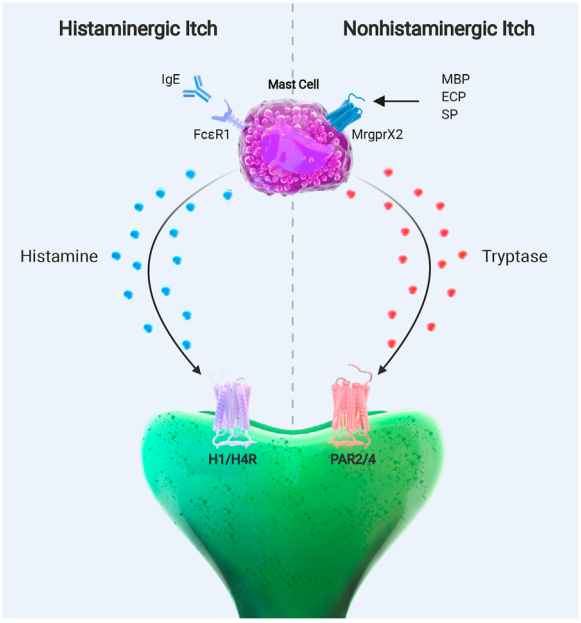

Fig 4. Histaminergic and nonhistaminergic itch pathways. *IgE*, Immunoglobulin E; *FcεR1*, Fc epsilon R1, high affinity IgE receptor; *ECP*, eosinophil cationic protein; *H1/4R*, histamine receptor type 1 and 4 (GPCR); *PAR2/4*, protease-activated receptor type 2 and 4 (GPCR); *MBP*, major basic protein; *MrgprX2*, mas-related G protein—coupled receptor-X2 (GPCR); *SP*, substance P.

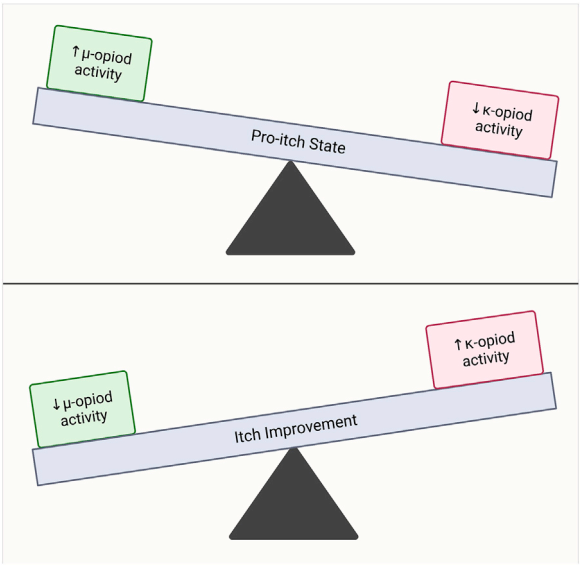

Fig 5. *μ-κ* Opioid imbalance in chronic itch.

Capsaicin. Capsaicin, available as a patch or cream, agonizes and desensitizes TRPV1 channels with chronic use.[53] It also has antipruritic effects via antagonism of histamine, PAR2, and SP.[53] Multiple daily applications and initial burning application may limit patient adherence. The 8% patch can be used to deliver higher concentrations than creams over a localized area.[54] In 1 case series of 7 patients with neuropathic itch, a single application of the patch applied for 60 minutes provided itch relief for all patients within a week, with relief lasting several months and up to 1 year in some patients.[55] Capsaicin should be avoided in visibly inflamed skin, as it can cause extreme pain.

Coolants. Menthol and camphor are organic compounds available over the counter in cream, lotion, and powder formulations. They activate TRP melastatin 8 on afferent nerves, providing a cooling and antipruritic effect, and are utilized especially for neuropathic itch subtypes.[56]

Cannabinoids. N-palmitoylethanolamine is a commercially available topical cannabinoid that relieves itch by enhancing endocannabinoid signaling.[57] Its antipruritic effects have been demonstrated in a RCT of asteatotic eczema patients and in other smaller studies for other itch etioligies.[58,59]

Phosphodiesterase inhibitors. Crisaborole is a phosphodiesterase 4 inhibitor that reduces AD-associated itch.[60] It can be used similarly to calcineurin inhibitors. The most common side effect is transient burning upon application.[61] Other phosphodiesterase 4 inhibitors in development, such as difamilast and roflumilast, have shown promising results as antipruritic agents in trials to date.[62,63]

Doxepin. Topical doxepin 5% reduces itch via H1/H2 receptor antagonism.[64] In 2 RCTs, it reduced itch in inflammatory dermatoses, including AD, contact dermatitis, and lichen simplex chronicus.[64,65] Application to greater than 10% of total body surface area may cause drowsiness, so doxepin should be used with caution in the elderly.[66]

Botulinum neurotoxin. Intralesional botulinum neurotoxin may reduce itch by inhibiting release of pruritogens, such as SP, CGRP, and acetycholine.[67] Small studies have treated itch in lichen simplex chronicus and neuropathic etiologies of itch.[68,69]

Gabapentin. In 1 RCT, short-term use of topical gabapentin 6% reduced uremic itch with no drug-related adverse effects.[70] In a case series, the 10% formulation provided partial relief in subsets of patients with scalp pruritus.[71] Topical gabapentin can be a reasonable option for these itch subtypes in patients who cannot tolerate the oral formulations and is available via compounding pharmacies. Contraindications include history of hypersensitivity to topical gabapentin.[46,47]

Systemic therapies

Antihistamines. Antihistamines reduce itch by blocking histamine receptors. First- and

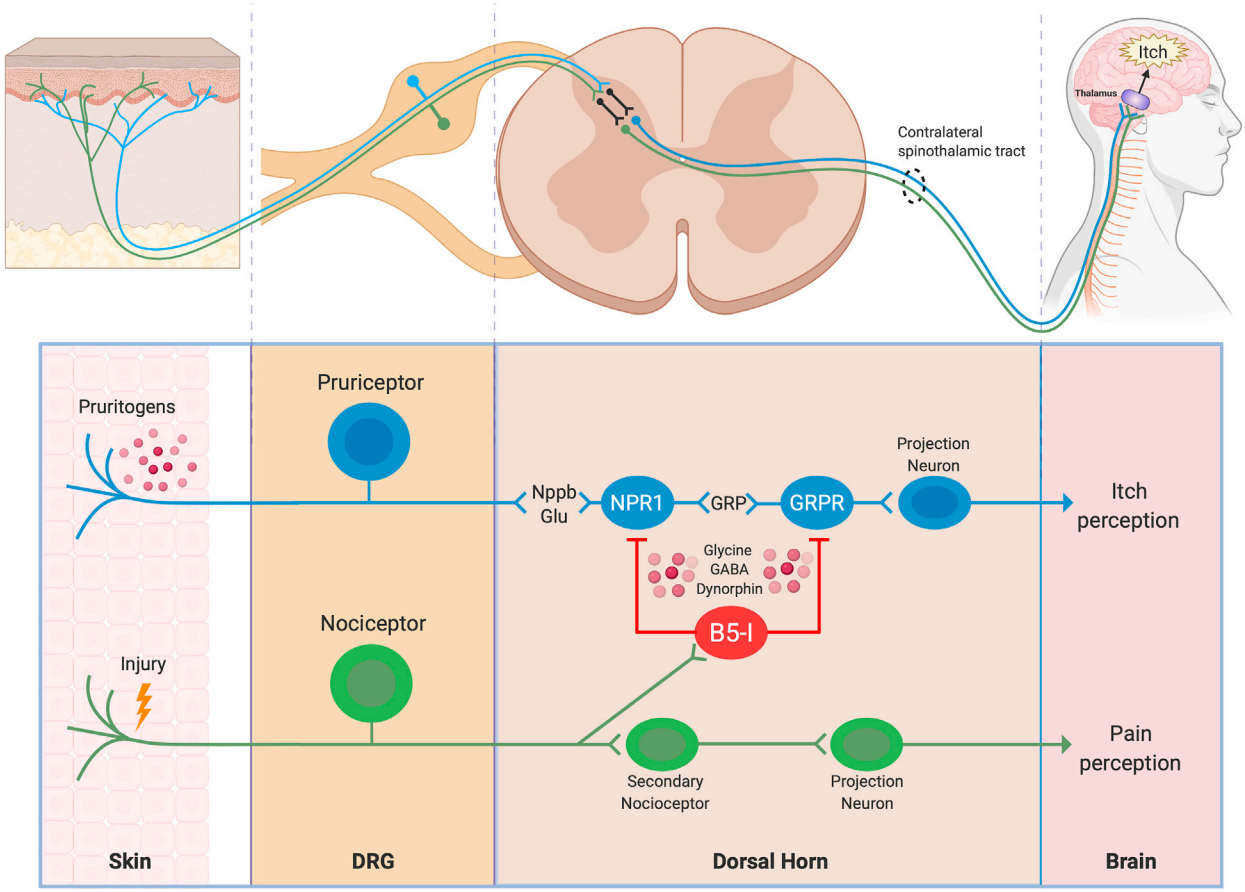

Fig 6. Itch pathways in the spinal cord. *DRG*, Dorsal root ganglion; *Nppb*, natriuretic peptide B; *Glu*, glutamate; *NPR1*, natriuretic peptide receptor 1 positive neurons; *GRP*, gastrin-releasing peptide; *GRPR*, gastrin-releasing peptide receptor positive neurons; *GABA*, gamma-amino butyric acid; *B5-I*, helix-loop-helix family member B5 (bhlhb5) positive inhibitory interneurons.

second-generation antihistamines are best for acute histaminergic itch, such as urticaria, mastocytosis, and insect bites.[72] First-generation antihistamines have the greatest utility in chronic itch, primarily due to their ability to cross the blood-brain barrier and sedating effects.[72,73] Sedating antihistamines also mirror the effects of scratching by deactivating the cingulate cortex and prefrontal area, which are involved in itch perception and scratching motivation.[74] The associated drowsiness makes first-generation antihistamines particularly useful for nocturnal itch; however, they should be used with caution in the elderly. Use of first-generation antihistamines for more than 3 years may increase risk of dementia.[75]

Immunosuppressants. Methotrexate, cyclosporine, mycophenolate, and azathioprine are efficacious for itch associated with cutaneous and systemic inflammation, such as AD, psoriasis, and PN. Oral steroids should be used only as rescue agents for acute itch etiologies due to their long-term effects. Immunosuppressive agents for chronic pruritus of unknown differentiation (CPUO) are most effective in the presence of Th2 differentiation (also referred to as immunosenescence), manifesting as increased blood eosinophils (>4% or >0.30 K/mm^3).[76] Other signs that may be suggestive of Th2 differentiation are spongiosis on histology or elevated serum IgE.[77,78] In this subset of patients with CPUO, methotrexate, dupilumab, or narrow-band UVB phototherapy are reasonable therapeutic options.[76] Azathioprine may also have efficacy for CPUO, shown by a case series of 94 patients.[79] CPUO in the absence of Th2 differentiation is suggestive of neural sensitization, for which immunosuppressants are typically not as effective and neuromodulators like gabapentin or pregabalin are often an initial treatment option.

Biologics and small molecule inhibitors. In addition to their approved indications, some biologics have potent off-label uses as well. Dupilumab has demonstrated efficacy for PN and

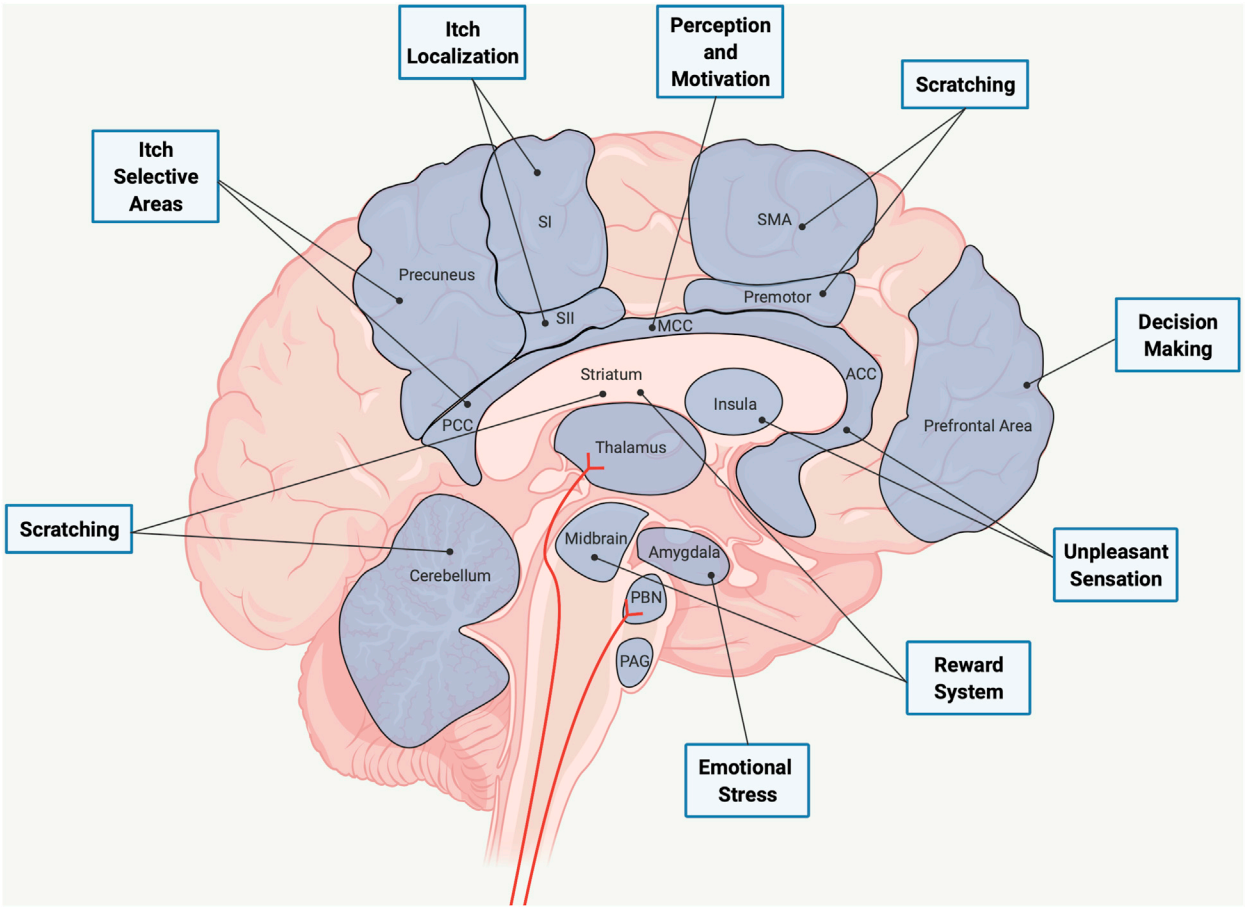

Fig 7. Brain regions associated with itch localization, perception, and motivation. *PAG*, Periaqueductal gray matter; *PBN*, parabrachial nucleus; *PCC*, posterior cingulate cortex; *SI*, primary somatosensory cortex; *SII*, secondary somatosensory cortex; *SMA*, supplementary motor area; *MCC*, midcingulate cortex.

CPUO in multiple studies, which reduces Th2 inflammation in these diseases.[80,81] Unsurprisingly, tofacitinib also reduced itch in recalcitrant AD and CPUO, as JAK1 blockade is a potent modulator of Th2 differentiation.[82,83]

Thalidomide. Thalidomide is a nonspecific immunomodulator that may dysregulate the degeneration of type C unmyelinated nerve fibers. It can be effective for uremic pruritus and PN.[84,85] Notable side effects include sedation and peripheral neuropathy, which is reversible with treatment cessation. Thalidomide is a pregnancy category X drug due to its extreme teratogenicity, requiring adherence to the Risk Evaluation and Mitigation Strategies program.

Antidepressants. Antidepressants can be effective adjunct therapies for chronic itch. Amitriptyline and doxepin are tricyclic antidepressants that are thought to reduce itch via their antihistaminergic effects. They have led to reduced itch in case reports and in 1 RCT.[86-88] High-dose doxepin (280 mg daily) relieved intractable scalp pruritus in 1 case report. These agents should be used with caution in the elderly due to their extensive anticholinergic side effects.[89]

Case series and RCTs have suggested efficacy of selective serotonin reuptake inhibitors, including paroxetine, sertraline, and fluvoxamine for a variety of itch etiologies.[90-93] They reduce itch by modulating descending serotonergic pathways in the spinal cord.[91] Sertraline in particular is a safe option for cholestatic pruritus, as shown in a RCT.[92] Low-dose mirtazapine is particularly useful for nocturnal pruritus given its sedative properties.[94,95]

Anticonvulsants. The gabapentinoids gabapentin and pregabalin inhibit voltage-gated calcium channels at the DRG and dorsal horn, likely reducing central pruritoception and neural excitation by itch stimuli.[96] Controlled trials have shown their effectiveness for uremic pruritus, but their use in neuropathic itch is limited to case reports.[97-99] Gabapentinoids are also a therapeutic option for CPUO without Th2 differentiation (often occurring

Table I. Topical therapies for itch

Class	Treatment	Dosage	Suggested uses	Adverse effects
Corticosteroids	Clobetasol, betamethasone, etc	Variable	Inflammatory itch	Skin atrophy, telangiectasias, hypopigmentation
Calcineurin inhibitors	Tacrolimus	0.03%-0.10%	AD, PN, uremic, cholestatic, and neuropathic itch	Transient burning
	Pimecrolimus	1%		
Anesthetics	Pramoxine	1%	Neuropathic itch, CPUO, uremic pruritus	Local irritation, temporary decreased sensation
	Lidocaine (cream)	2.5%-5%		
	Lidocaine (patch)	5%		
	Prilocaine	2.5%		
	Ketamine-amitriptyline-lidocaine	10%-5%-5%		
Capsaicin	Capsaicin (cream)	0.025%-1%	Neuropathic itch, uremic, and aquagenic itch	Transient pain or burning
	Capsaicin (patch)	8%		
Coolants	Menthol	1%-3%	Neuropathic itch	Skin irritation (high doses)
	Camphor	0.5%		
Cannabinoids	N-palmitoylethanolamine	0.3%	AD, PN, LSC, aquagenic itch	Transient burning
PDE4 inhibitors	Crisaborole	2%	AD	Transient pain or burning
Tricyclic antidepressants	Doxepin	5%	LSC, Neuropathic itch, AD	Transient burning, drowsiness
Gabapentinoids	Gabapentin	6%-10%	Scalp pruritus, uremic itch	
Botulinum neurotoxin	Botulinum neurotoxin	2-10U	LSC, neuropathic itch	Dryness, pain, burning at injection site

AD, Atopic dermatitis; *CPUO*, chronic pruritus of unknown origin; *LSC*, lichen simplex chronicus; *PDE4*, phosphodiesterase 4; *PN*, prurigo nodularis.

in the setting of chronic back pain or spinal cord pathology suggestive of neural sensitization).[76] Compared with gabapentin, pregabalin has a more rapid effect.[100]

Dosages for both drugs should be titrated on initiation and tapered on discontinuation. Gabapentin should be initiated at 300 mg (100 mg in the elderly) at night, and the frequency can be increased every 4 to 5 days, split in dosing 2 to 3 times daily, up to a cumulative 3600 mg/d although patients are rarely able to reach this threshold given gabapentin's sedative properties. Pregabalin can be initiated at 75 mg nightly, then increased to twice daily after 1 week, up to a cumulative 300 mg/d. Dosing can also be adjusted based on the patient's itch diurnal patterns. As gabapentinoids are renally cleared, dosages need to be adjusted in patients with renal dysfunction. Sedation, fatigue, and ataxia are common side effects, so caution must be exercised when prescribing gabapentinoids to the elderly.

Carbamazepine also inhibits voltage-gated sodium channels and was effective for itch due to hematologic malignancy in 1 case series.[101]

Opioid receptor modulators. Opioid modulators are used for intractable itch that is resistant to multiple therapies. Several studies have suggested that naltrexone (μ opioid antagonist) may reduce itch of various etiologies, including cholestatic and uremic itch.[102-104] Low-dose naltrexone administered at 2 mg daily also has antipruritic effects and can be used in patients who cannot tolerate standard doses.[105] Continuous intravenous infusion of 1 μg/mL naloxone (μ opioid antagonist) for 8 hours a day can also reduce itch from various etiologies, particularly in opioid-induced itch.[106] Difelikefalin (κ agonist) was effective for uremic pruritus in 1 trial.[107] Intranasal butorphanol (μ antagonist and κ agonist) has also been studied in case series of intractable pruritus of varying etiologies with promising results.[108,109] Nalfurfarine (κ opioid agonist) demonstrated efficacy for uremic itch; however, its availability is currently limited to Japan.[110]

The most common side effects of opioid modulators include gastrointestinal distress, drowsiness, dizziness, and insomnia. Patients taking opioid agonists should not receive opioid antagonists concurrently, as

Table II. Systemic therapies for itch

Class	Treatment	Dosage	Suggested uses	Adverse effects	Suggested laboratory monitoring
Antihistamines (first generation)	Hydroxyzine	10-25 mg TID	Urticaria, nocturnal itch	Drowsiness	
	Diphenhydramine	10-25 mg BID			
Antihistamines (second and third generations)	Cetirizine	10 mg QD	Urticaria, insect bites, mastocytosis	Drowsiness (with high doses)	
	Loratadine	10 mg QD			
	Fexofenadine	180 mg QD			
Immunosuppressants	Prednisone	40-60 mg QD tapered down over 7-10 d	Acute urticaria, contact dermatitis	Adrenal suppression, hyperglycemia, lymphopenia	CBC, glucose, BP at baseline
	Methotrexate	7.5-20 mg weekly	AD, PN, psoriasis, urticaria, CPUO with immunosenescence representing Th2 differentiation*	GI distress, hepatotoxicity, stomatitis, myelosuppression	CBC, BMP, LFTs, hepatitis panel at baseline, every 1-2 wk when increasing dose, then every 3 mo with stable dose
	Cyclosporine	2.5-5 mg/kg QD		GI distress, hypertension, renal toxicity, hirsutism	BP, BMP at baseline, 2 wk, then monthly. CBC, UA, Mg at baseline, then every mo
	Mycophenolate	1-2 g QD		GI distress, myelosuppression	CBC, BMP, LFTs at baseline, 1 month, then every 3 mo
	Azathioprine	1-3 mg/kg (typically 50-100 mg) QD		GI distress, myelosuppression, hepatotoxicity	CBC, LFTs at baseline, after 1-2 wk, then every 1-3 mo
Thalidomide	Thalidomide	50-200 mg QD	PN, uremic itch, actinic prurigo	Temporary peripheral neuropathy, drowsiness, teratogenicity	REMS, CBC, TSH, LFTs at baseline, monthly
Biologics and small molecule inhibitors (off-label)	Dupilumab	600 mg initial, 300 mg Q2W	CPUO with Th2 differentiation,* PN, uremic itch	Conjunctivitis, injection site reaction	
	Tofacitinib	5-10 mg QD	AD, psoriasis, CPUO with Th2 differentiation*	Upper respiratory and systemic infections	CBC, LFTs, Hgb at baseline, after 4-8 wk, then every 3 mo
Antidepressants	Amitriptyline	25-75 mg QHS	Neuropathic itch, chronic urticaria	Drowsiness, dry mouth, dizziness, blurred vision	EKG at baseline (if cardiac risk factors or other QT-prolonging meds)
	Doxepin	10-50 mg QHS			
	Sertraline	75-100 mg QD	Cholestatic, paraneoplastic, depression-associated itch	GI distress, insomnia, drowsiness	
	Paroxetine	10-40 mg QD		GI distress, insomnia, sexual dysfunction	
	Mirtazapine	7.5-15 mg QHS	AD, nocturnal, and paraneoplastic itch	Drowsiness, weight gain, dry mouth	LFTs, BMP at baseline

Anticonvulsants	Gabapentin Pregabalin	100-1200 mg TID 25-100 mg TID	PN, CPUO without Th2 differentiation,* uremic and neuropathic itch	Drowsiness, weight gain, lower extremity edema, ataxia	
	Carbamazepine	200-1200 mg QD	Paraneoplastic and neuropathic itch	GI distress, drowsiness, dizziness, myelosuppression	CBC, BMP, LFTs at baseline and every 8-12 wk
Opioid modulators	Naltrexone	2-50 mg† QD	Refractory itch of various etiologies	GI distress, headache, insomnia	LFTs at baseline and every 8-12 wk
	Butorphanol	1-4 mg QHS (1 spray in 1 nostril)		Drowsiness, GI distress, dependance	
	Naloxone	1 μg/mL IV infusion for 8 hours QD		Insomnia	
Bile acid resins	Cholestyramine	4-12 mg QD	Cholestatic itch	GI distress	Lipids at baseline, after 4-12 wk, then every 3 mo
Rifampin	Rifampin	300-600 mg QD	Cholestatic itch	Hepatotoxicity, nephrotoxicity, drug interactions	Baseline CBC, BMP, LFTs
Neurokinin-1 inhibitors	Aprepitant	80 mg QD	Sezary syndrome, erlotinib-induced itch	GI distress, drug interactions	INR after 7-10 d if on warfarin
Phototherapy	UVA, UVB, PUVA	Variable	Inflammatory, cholestatic, uremic itch	Skin malignancies, hyperpigmentation	Nonmelanoma skin cancer risk with >250 PUVA sessions

AD, Atopic dermatitis; *BID*, twice daily; *BMP*, basic metabolic panel; *CBC*, complete blood cell count; *CPUO*, chronic pruritus of unknown origin; *EKG*, electrocardiogram; *GI*, gastrointestinal; *Hgb*, hemoglobin; *INR*, international normalized ratio; *LFT*, liver function tests; *Mg*, magnesium; *PN*, prurigo nodularis; *PUVA*, psoralen and ultraviolet A; *Q2W*, every 2 weeks; *QD*, every day; *QHS*, every night; *REMS*, Risk Evaluation and Mitigation Strategies; *Th2*, T-helper type 2; *TID*, 3 times daily; *TSH*, thyroid-stimulating hormone; *UA*, urinalysis; *UVA*, ultraviolet A; *UVB*, ultraviolet B.
*CPUO with Th2 differentiation is represented by increased blood eosinophils (>4% or >0.30 K/mm^3), elevated IgE (>250 IU/mL), or erythema and spongiosis on biopsy.
†Lower doses of naltrexone can be obtained using pill-cutters or compounding pharmacies.

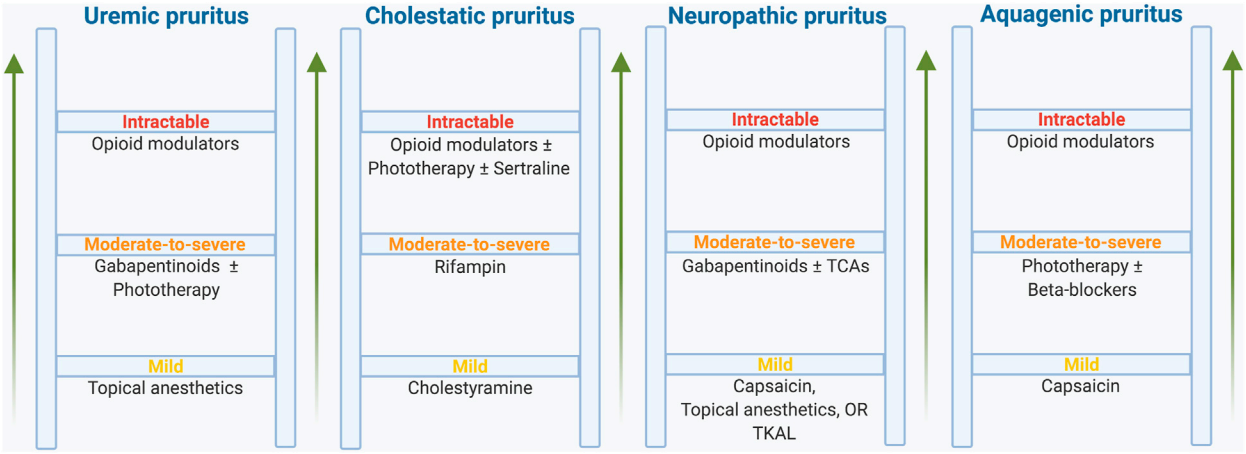

Fig 8. Suggested treatment ladders for select, nonprimary dermatologic itch etiologies. *TCA*, Tricyclic antidepressant; *TKAL*, topical ketamine-amitriptyline-lidocaine.

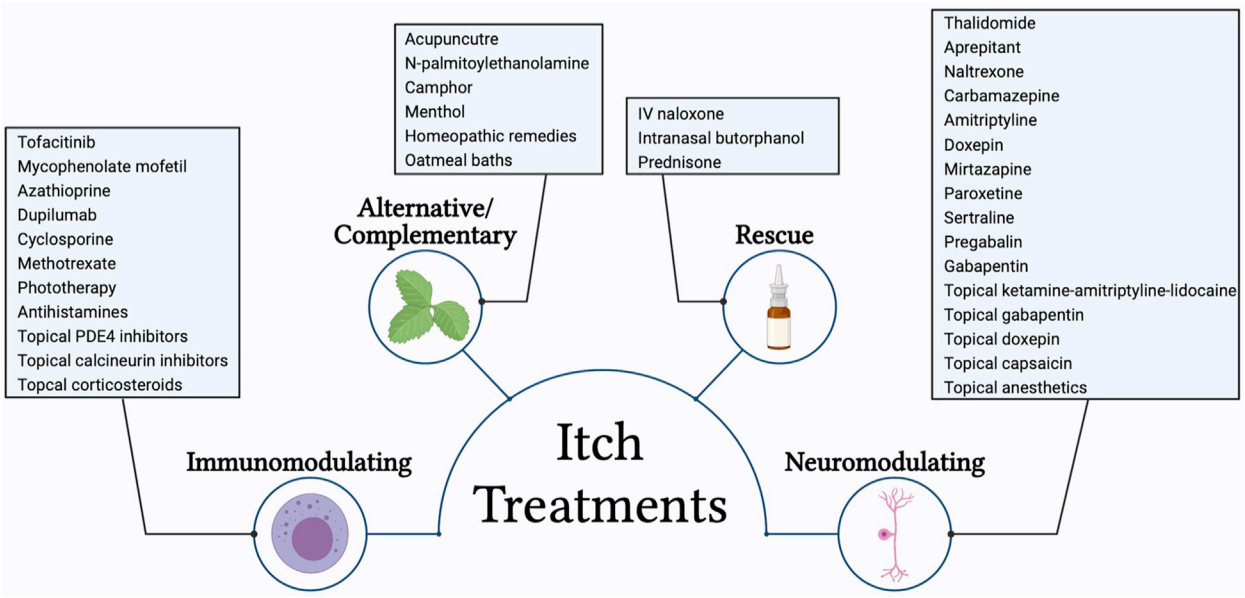

Fig 9. Available treatments of itch grouped by primary mechanism of action. *IV*, Intravenous; *PDE4*, phosphodiesterase 4.

they can precipitate rapid withdrawal. Long-term use of agonists such as butorphanol can also increase risk of dependence.

Bile acid resins and rifampicin. Cholestyramine is a bile acid resin that works by sequestering pruritogenic bile acids. Rifampin is an antibiotic that reduces itch by promoting the conversion of bile acids to less pruritogenic forms, and has demonstrated efficacy in several RCTs.[111,112] The hepatotoxic and nephrotoxic side effects of rifampin preclude long-term therapy, but it can be an effective second-line agent when cholestyramine is ineffective.

Phototherapy. Phototherapy, including ultraviolet (UV) A, psoralen UVA, and narrow-band UVB can reduce itch primarily by reducing local and systemic inflammation.[113] Phototherapy can also decrease nerve fiber density, nerve growth factor, and peripheral nerve fiber activation.[114] All types of phototherapy reduce white blood cell proliferation, however, narrow-band UVB primarily reaches the epidermis and papillary dermis.[115] Narrow-band UVB is preferable to psoralen UVA due to risk of cutaneous carcinogenicity and cataracts with prolonged use of psoralen UVA.

Neurokinin-1 inhibitors. In smaller studies, aprepitant acted as a NK1 inhibitor that reduced itch for recalcitrant pruritus of multiple etiologies.[116,117] In 1 small case series of erlotinib-induced pruritus, aprepitant dramatically reduced itch within 24 hours.[118] Aprepitant was effective for

Table III. Emerging treatments for chronic pruritic diseases with phase 2 or 3 data on itch reduction

Target	Treatment	Indications	Phase status	Itch reduction
JAK1	Abrocitinib (oral)	AD	III	4.0-point decrease in PP-NRS at 12 wk vs 1.7-decrease with placebo
	Upadacitinib (oral)	AD	III	69% decrease in pruritus NRS at 16 wk vs 10% decrease with placebo, $P < .001$
JAK1/JAK2	Baricitinib (oral)	AD	III	47% decrease in pruritus NRS at 16 wk vs 17% decrease with placebo, $P < .001$
		Psoriasis	II	4.7-point decrease in WI-NRS at 12 wk vs 1.1-point decrease with placebo $P < .001$
JAK1/JAK3	Tofacitinib (oral)	Psoriasis	III	4.5-point decrease in ISI at 16 wk (no placebo arm)
JAK1/JAK2	Delgocitinib (topical)	AD	III	27.7% decrease in pruritus NRS through 24 wk vs 17.7% increase with placebo, $P < .001$
	Ruxolitinib (topical)	AD	III	1.8-point decrease in pruritus NRS through 12 wk vs 0.2-point decrease with placebo, $P < .001$
IL-13	Lebrikizumab (subcutaneous)	AD	III	60.6% decrease in pruritus NRS at 16 wk vs 4.3% increase with placebo, $P < .001$
	Tralokinumab (subcutaneous)	AD	III	1.17-point decrease in pruritus NRS at 12 wk, relative to placebo, $P = .002$
IL-31RA	Nemolizumab (subcutaneous)	AD	III	42.8% decrease in pruritus VAS at 12 wk vs 21.4% decrease with placebo, $P < .001$
		PN	III	67.5% decrease in pruritus NRS at 12 wk vs 35.4% decrease with placebo
OSMRβ	Vixarelimab	PN	II	50.6% decrease in WI-NRS at 8 wk vs 29.4% decrease with placebo
TSLP	Tezepelumab (subcutaneous)	AD	II	35.5% decrease in pruritus NRS at 12 wk vs 21.1% decrease with placebo, $P = .050$
KOR agonist	Difelikefalin (intravenous)	Uremic pruritus	III	49.1% of patients with 3 point drop in WI-NRS at 12 wk vs 27.9% with placebo, $P < .001$
KOR agonist and MOR antagonist	Nalbuphine (oral)	Uremic pruritus	III	3.5-point decrease in pruritus NRS at 8 wk vs 2.8-point decrease with placebo, $P = .017$
NK1R	Tradipitant (oral)	AD	III	4.74-point decrease in WI-NRS at 8 wk vs 3.14-point decrease with placebo (only in mild AD, IGA 1 or 2) $P = .015$
			II	44.2% decrease in WI-NRS at 8 wk vs 30.6% with placebo, $P = .019$
TrkA	Pegcantratinib (topical)	Psoriasis	III	37.1 mm decrease in pruritus VAS at 8 wk vs 16.1 mm with placebo, $P = .007$
PDE4	Difamilast (topical)	AD	III	Significant decrease in pruritus VAS through 8 wk compared with placebo, $P = .043$
	Roflumilast (topical)	AD	III	3.05-point decrease in pruritus NRS at 12 wk vs 1.50-decrease with placebo
AHR	Tapinarof (topical)	Psoriasis	III	4-point decrease in pruritus NRS at 12 wk in 59.7% of tapinarof patients vs 31.3% with placebo patients

AD, Atopic dermatitis; *IGA*, Investigator's Global Assessment; *IL*, interleukin; *ISI*, itch severity score; *JAK*, Janus kinase; *KOR*, κ opioid receptor; *MOR*, μ opioid receptor; *NK1R*, neurokinin 1 receptor; *OSMR*, oncostatin M receptor; *PN*, prurigo nodularis; *PP-NRS*, peak pruritus numeric rating score; *TrkA*, tropomyosin receptor kinase A; *TSLP*, thymic stromal lymphopoietin; *VAS*, visual analog scale; *WI-NRS*, worst itch numeric rating score.

PN in an open-label study, however, the phase 2 trial failed to meet primary endpoints.[116] A Phase 2 trial of serlopitant, another NK1 inhibitor, showed promise for PN, although phase 3 trials failed to meet primary endpoints.[119,120] Aprepitant's clinical use is also limited by the prohibitive cost and numerous drug interactions (CYP3A4 inducer).

PSYCHOLOGIC THERAPIES

Most evidence for psychologic therapy is for AD-associated itch, which may respond to cognitive behavioral therapy, psychotherapy, and stress management education.[121-124] These techniques may also be helpful in other forms of itch, as cognitive behavioral therapy helps by teaching patients to stop catastrophizing their itch and use alternative coping strategies.[124]

COMPLIMENTARY AND ALTERNATIVE THERAPIES

Oatmeal baths can be helpful. They are thought to possess antiinflammatory properties and restore skin barrier function.[125] In 1 trial of AD patients, acupuncture reduced itch-evoked activation of the insula, putamen, and prefrontal area on fMRI.[126] Transcutaneous electric nerve stimulation is an over-the-counter tool that delivers localized low voltage to inhibit pruritoceptive type C nerve fibers for neuropathic itch.[127] Cannabinoids and marijuana consumption can also be effective for some patients.[128,129]

EMERGING TREATMENTS

Table III lists novel treatments for chronic pruritic diseases being investigated in phase 2 and phase 3 clinical trials. In particular, IL-31 blockade and the JAK/STAT pathway have emerged as rapid itch modulators. JAK1 blockade is thought to have a rapid and robust effect on itch associated with modulation of multiple itch mediators.[130-135] The most promising agents include lebrikizumab (anti—IL-13), tralokinumab (anti—IL-13), nemolizumab (anti—IL-31), abrocitinib (JAK1), and upadacitinib (JAK1).

Conflicts of interest

Dr Kwatra is an advisory board member or consultant for Abbvie, Celldex Therapeutics, Incyte Corporation, Galderma, Pfizer Inc, Regeneron Pharmaceuticals, and Menlo Therapeutics; is an investigator or has received grant funding from Galderma SA, Kiniksa Pharmaceuticals, Pfizer, and Sanofi; is a recipient of a Dermatology Foundation Medical Dermatology Career Development Award; and has received grant funding from the Skin of Color Society. Authors Sutaria, Adawi, Goldberg, Roh, and Choi have no conflicts of interest to declare.

REFERENCES

1. Ringkamp M, Schepers RJ, Shimada SG, et al. A role for nociceptive, myelinated nerve fibers in itch sensation. *J Neurosci*. 2011;31(42):14841-14849. https://doi.org/10.1523/JNEUROSCI.3005-11.2011
2. Shim WS, Tak MH, Lee MH, et al. TRPV1 mediates histamine-induced itching via the activation of phospholipase A2 and 12-lipoxygenase. *J Neurosci*. 2007;27(9):2331-2337. https://doi.org/10.1523/JNEUROSCI.4643-06.2007
3. Graham HT, Lowry OH, Wahl N, Priebat MK. Mast cells as sources of tissue histamine. *J Exp Med*. 1955;102(3):307-318. https://doi.org/10.1084/jem.102.3.307
4. Shimizu K, Andoh T, Yoshihisa Y, Shimizu T. Histamine released from epidermal keratinocytes plays a role in α-melanocyte—stimulating hormone-induced itching in mice. *Am J Pathol*. 2015;185(11):3003-3010. https://doi.org/10.1016/j.ajpath.2015.07.015
5. Wang F, Trier AM, Li F, et al. A basophil-neuronal axis promotes itch. *Cell*. 2021;184(2):422-440.e17. https://doi.org/10.1016/j.cell.2020.12.033
6. Meixiong J, Anderson M, Limjunyawong N, et al. Activation of mast-cell-expressed Mas-related G-protein-coupled receptors drives non-histaminergic itch. *Immunity*. 2019;50(5):1163-1171.e5. https://doi.org/10.1016/j.immuni.2019.03.013
7. Cevikbas F, Wang X, Akiyama T, et al. A sensory neuron—expressed IL-31 receptor mediates T helper cell—dependent itch: involvement of TRPV1 and TRPA1. *J Allergy Clin Immunol*. 2014;133(2):448-460. https://doi.org/10.1016/j.jaci.2013.10.048
8. Feld M, Garcia R, Buddenkotte J, et al. The pruritus- and TH2-associated cytokine IL-31 promotes growth of sensory nerves. *J Allergy Clin Immunol*. 2016;138(2):500-508.e24. https://doi.org/10.1016/j.jaci.2016.02.020
9. Lou H, Lu J, Choi EB, et al. Expression of IL-22 in the skin causes Th2-biased immunity, epidermal barrier dysfunction, and pruritus via stimulating epithelial Th2 cytokines and the GRP pathway. *J Immunol*. 2017;198(7):2543-2555. https://doi.org/10.4049/jimmunol.1600126
10. Wilson SR, Thé L, Batia LM, et al. The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch. *Cell*. 2013;155(2):285-295. https://doi.org/10.1016/j.cell.2013.08.057
11. Oetjen LK, Mack MR, Feng J, et al. Sensory neurons co-opt classical immune signaling pathways to mediate chronic itch. *Cell*. 2017;171(1):217-228.e13. https://doi.org/10.1016/j.cell.2017.08.006
12. Czarnecka-Operacz M, Polańska A, Klimańska M, et al. Itching sensation in psoriatic patients and its relation to body mass index and IL-17 and IL-31 concentrations. *Postepy Dermatol Alergol*. 2015;32(6):426-430. https://doi.org/10.5114/pdia.2015.56097
13. Wongvibulsin S, Sutaria N, Kannan S, et al. Transcriptomic analysis of atopic dermatitis in African Americans is characterized by Th2/Th17-centered cutaneous immune activation. *Sci Rep*. 2021;11(1):11175. https://doi.org/10.1038/s41598-021-90105-w
14. Belzberg M, Alphonse MP, Brown I, et al. Prurigo Nodularis is characterized by systemic and cutaneous Th22 immune polarization. *J Invest Dermatol*. 2021;141(9):2208-2218. https://doi.org/10.1016/j.jid.2021.02.749
15. Kwatra SG. Breaking the itch—scratch cycle in prurigo nodularis. *N Engl J Med*. 2020;382(8):757-758. https://doi.org/10.1056/NEJMe1916733

16. Fallahzadeh MK, Roozbeh J, Geramizadeh B, Namazi MR. Interleukin-2 serum levels are elevated in patients with uremic pruritus: a novel finding with practical implications. *Nephrol Dial Transplant*. 2011;26(10):3338-3344. https://doi.org/10.1093/ndt/gfr053
17. Ko MJ, Peng YS, Chen HY, et al. Interleukin-31 is associated with uremic pruritus in patients receiving hemodialysis. *J Am Acad Dermatol*. 2014;71(6):1151-1159.e1. https://doi.org/10.1016/j.jaad.2014.08.004
18. Schindler C, Levy DE, Decker T. JAK-STAT signaling: from interferons to cytokines. *J Biol Chem*. 2007;282(28):20059-20063. https://doi.org/10.1074/jbc.R700016200
19. Weidner C, Klede M, Rukwied R, et al. Acute effects of substance P and calcitonin gene-related peptide in human skin—a microdialysis study. *J Invest Dermatol*. 2000;115(6):1015-1020. https://doi.org/10.1046/j.1523-1747.2000.00142.x
20. Azimi E, Reddy VB, Pereira PJS, Talbot S, Woolf CJ, Lerner EA. Substance P activates Mas-related G protein-coupled receptors to induce itch. *J Allergy Clin Immunol*. 2017;140(2):447-453.e3. https://doi.org/10.1016/j.jaci.2016.12.980
21. Skoff AM, Adler JE. Nerve growth factor regulates substance P in adult sensory neurons through both TrkA and p75 receptors. *Exp Neurol*. 2006;197(2):430-436. https://doi.org/10.1016/j.expneurol.2005.10.006
22. Melo H, Basso L, Iftinca M, et al. Itch induced by peripheral mu opioid receptors is dependent on TRPV1-expressing neurons and alleviated by channel activation. *Sci Rep*. 2018;8(1):15551. https://doi.org/10.1038/s41598-018-33620-7
23. Steinhoff M, Neisius U, Ikoma A, et al. Proteinase-activated Receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci*. 2003;23(15):6176-6180. https://doi.org/10.1523/JNEUROSCI.23-15-06176.2003
24. Steinhoff M, Corvera CU, Thoma MS, et al. Proteinase-activated receptor-2 in human skin: tissue distribution and activation of keratinocytes by mast cell tryptase. *Exp Dermatol*. 1999;8(4):282-294. https://doi.org/10.1111/j.1600-0625.1999.tb00383.x
25. Guo CJ, Mack MR, Oetjen LK, et al. Kallikrein 7 promotes atopic dermatitis-associated itch independently of skin inflammation. *J Invest Dermatol*. 2020;140(6):1244-1252.e4. https://doi.org/10.1016/j.jid.2019.10.022
26. Reddy VB, Shimada SG, Sikand P, Lamotte RH, Lerner EA. Cathepsin S elicits itch and signals via protease-activated receptors. *J Invest Dermatol*. 2010;130(5):1468-1470. https://doi.org/10.1038/jid.2009.430
27. Kremer AE, van Dijk R, Leckie P, et al. Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions. *Hepatology*. 2012;56(4):1391-1400. https://doi.org/10.1002/hep.25748
28. Mishra SK, Hoon MA. The cells and circuitry for itch responses in mice. *Science*. 2013;340(6135):968-971. https://doi.org/10.1126/science.1233765
29. Chen XJ, Sun YG. Central circuit mechanisms of itch. *Nat Commun*. 2020;11(1):3052. https://doi.org/10.1038/s41467-020-16859-5
30. Ross SE, Mardinly AR, McCord AE, et al. Loss of inhibitory interneurons in the dorsal spinal cord and elevated itch in Bhlhb5 mutant mice. *Neuron*. 2010;65(6):886-898. https://doi.org/10.1016/j.neuron.2010.02.025
31. Marziniak M, Phan NQ, Raap U, et al. Brachioradial pruritus as a result of cervical spine pathology: the results of a magnetic resonance tomography study. *J Am Acad Dermatol*. 2011;65(4):756-762. https://doi.org/10.1016/j.jaad.2010.07.036
32. Kwatra SG, Stander S, Bernhard JD, Weisshaar E, Yosipovitch G. Brachioradial pruritus: a trigger for generalization of itch. *J Am Acad Dermatol*. 2013;68(5):870-873. https://doi.org/10.1016/j.jaad.2012.11.026
33. Mu D, Deng J, Liu KF, et al. A central neural circuit for itch sensation. *Science*. 2017;357(6352):695-699. https://doi.org/10.1126/science.aaf4918
34. Yosipovitch G, Ishiuji Y, Patel TS, et al. The brain processing of scratching. *J Invest Dermatol*. 2008;128(7):1806-1811. https://doi.org/10.1038/jid.2008.3
35. Mochizuki H, Tashiro M, Kano M, Sakurada Y, Itoh M, Yanai K. Imaging of central itch modulation in the human brain using positron emission tomography. *Pain*. 2003;105(1-2):339-346. https://doi.org/10.1016/S0304-3959(03)00249-5
36. Mochizuki H, Kakigi R. Central mechanisms of itch. *Clin Neurophysiol*. 2015;126(9):1650-1660. https://doi.org/10.1016/j.clinph.2014.11.019
37. Papoiu ADP, Coghill RC, Kraft RA, Wang H, Yosipovitch G. A tale of two itches. Common features and notable differences in brain activation evoked by cowhage and histamine induced itch. *Neuroimage*. 2012;59(4):3611-3623. https://doi.org/10.1016/j.neuroimage.2011.10.099
38. Drzezga A, Darsow U, Treede RD, et al. Central activation by histamine-induced itch: analogies to pain processing: a correlational analysis of O-15 H2O positron emission tomography studies. *Pain*. 2001;92(1-2):295-305. https://doi.org/10.1016/s0304-3959(01)00271-8
39. Papoiu ADP, Nattkemper LA, Sanders KM, et al. Brain's reward circuits mediate itch relief. A functional MRI study of active scratching. *PLoS one*. 2013;8(12):e82389. https://doi.org/10.1371/journal.pone.0082389
40. Ständer S, Schürmeyer-Horst F, Luger TA, Weisshaar E. Treatment of pruritic diseases with topical calcineurin inhibitors. *Ther Clin Risk Manag*. 2006;2(2):213-218. https://doi.org/10.2147/tcrm.2006.2.2.213
41. Setsu T, Hamada Y, Oikawa D, et al. Direct evidence that the brain reward system is involved in the control of scratching behaviors induced by acute and chronic itch. *Biochem Biophys Res Commun*. 2021;534:624-631. https://doi.org/10.1016/j.bbrc.2020.11.030
42. Pavlis J, Yosipovitch G. Management of itch in atopic dermatitis. *Am J Clin Dermatol*. 2018;19(3):319-332. https://doi.org/10.1007/s40257-017-0335-4
43. Elmariah SB, Lerner EA. Topical therapies for pruritus. *Semin Cutan Med Surg*. 2011;30(2):118-126. https://doi.org/10.1016/j.sder.2011.04.008
44. James AP. Intradermal triamcinolone acetonide in localized lesions. *J Invest Dermatol*. 1960;34:175-176. https://doi.org/10.1038/jid.1960.25
45. Pereira U, Boulais N, Lebonvallet N, Pennec JP, Dorange G, Misery L. Mechanisms of the sensory effects of tacrolimus on the skin. *Br J Dermatol*. 2010;163(1):70-77. https://doi.org/10.1111/j.1365-2133.2010.09757.x
46. *Protopic. (Tacrolimus) Package Insert*. Astellas Pharma US, Inc; 2011.
47. *Elidel. (Pimecrolimus) Package Insert*. Valeant Pharmaceuticals North America LLC; 2014.
48. He A, Kwatra SG, Sharma D, Matsuda KM. The role of topical anesthetics in the management of chronic pruritus. *J Dermatolog Treat*. 2017;28(4):338-341. https://doi.org/10.1080/09546634.2016.1243787
49. Bernhard JD, Bordeaux JS. Medical pearl: the ice-pack sign in brachioradial pruritus. *J Am Acad Dermatol*. 2005;52(6):1073. https://doi.org/10.1016/j.jaad.2005.02.056

50. Poterucha TJ, Murphy SL, Davis MDP, et al. Topical amitriptyline-ketamine for the treatment of brachioradial pruritus. *JAMA Dermatol*. 2013;149(2):148-150. https://doi.org/10.1001/2013.jamadermatol.646
51. Poterucha TJ, Murphy SL, Sandroni P, et al. Topical amitriptyline combined with topical ketamine for the management of recalcitrant localized pruritus: a retrospective pilot study. *J Am Acad Dermatol*. 2013;69(2):320-321. https://doi.org/10.1016/j.jaad.2013.03.013
52. Cardis MA, Pasieka HB. Safety of topical neuromodulators for the treatment of pruritus. *JAMA Dermatol*. 2016;152(12):1390-1391. https://doi.org/10.1001/jamadermatol.2016.3118
53. Sekine R, Satoh T, Takaoka A, Saeki K, Yokozeki H. Anti pruritic effects of topical crotamiton, capsaicin, and a corticosteroid on pruritogen-induced scratching behavior. *Exp Dermatol*. 2012;21(3):201-204. https://doi.org/10.1111/j.1600-0625.2011.01433.x
54. Andersen HH, Arendt-Nielsen L, Elberling J. Topical capsaicin 8% for the treatment of neuropathic itch conditions. *Clin Exp Dermatol*. 2017;42(5):596-598. https://doi.org/10.1111/ced.13114
55. Misery L, Erfan N, Castela E, et al. Successful treatment of refractory neuropathic pruritus with capsaicin 8% patch: a bicentric retrospective study with long-term follow-up. *Acta Derm Venereol*. 2015;95(7):864-865. https://doi.org/10.2340/00015555-2085
56. Palkar R, Ongun S, Catich E, et al. Cooling relief of acute and chronic itch requires TRPM8 channels and neurons. *J Invest Dermatol*. 2018;138(6):1391-1399. https://doi.org/10.1016/j.jid.2017.12.025
57. Ständer S, Schmelz M, Metze D, Luger T, Rukwied R. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. *J Dermatol Sci*. 2005;38(3):177-188. https://doi.org/10.1016/j.jdermsci.2005.01.007
58. Yuan C, Wang XM, Guichard A, et al. N-palmitoylethanolamine and N-acetylethanolamine are effective in asteatotic eczema: results of a randomized, double-blind, controlled study in 60 patients. *Clin Interv Aging*. 2014;9:1163-1169. https://doi.org/10.2147/CIA.S65448
59. Avila C, Massick S, Kaffenberger BH, Kwatra SG, Bechtel M. Cannabinoids for the treatment of chronic pruritus: a review. *J Am Acad Dermatol*. 2020;82(5):1205-1212. https://doi.org/10.1016/j.jaad.2020.01.036
60. Yosipovitch G, Gold LF, Lebwohl MG, Silverberg JI, Tallman AM, Zane LT. Early relief of pruritus in atopic dermatitis with Crisaborole ointment, A non-steroidal, phosphodiesterase 4 inhibitor. *Acta Derm Venereol*. 2018;98(5):484-489. https://doi.org/10.2340/00015555-2893
61. Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494-503.e6. https://doi.org/10.1016/j.jaad.2016.05.046
62. Saeki H, Baba N, Oshiden K, Abe Y, Tsubouchi H. Phase 2, randomized, double-blind, placebo-controlled, 4-week study to evaluate the safety and efficacy of OPA- 15406 (difamilast), a new topical selective phosphodiesterase type-4 inhibitor, in Japanese pediatric patients aged 2-14 years with atopic dermatitis. *J Dermatol*. 2020;47(1):17-24. https://doi.org/10.1111/1346-8138.15137
63. Agnihotri G, Lio PA. Revisiting therapies for atopic dermatitis that failed clinical trials. *Clin Drug Investig*. 2020;40(5):421-431. https://doi.org/10.1007/s40261-020-00905-7
64. Drake LA, Fallon JD, Sober A. Relief of pruritus in patients with atopic dermatitis after treatment with topical doxepin cream. The doxepin Study Group. *J Am Acad Dermatol*. 1994;31(4):613-616. https://doi.org/10.1016/S0190-9622(94)70225-X
65. Drake LA, Millikan LE. The antipruritic effect of 5% doxepin cream in patients with eczematous dermatitis. Doxepin Study Group. *Arch Dermatol*. 1995;131(12):1403-1408.
66. *Zonalon Cream (5% Doxepin Hydrochloride). Package insert*. GenDerm Corp; 1995.
67. Gazerani P, Pedersen NS, Drewes AM, Arendt-Nielsen L. Botulinum toxin type A reduces histamine-induced itch and vasomotor responses in human skin. *Br J Dermatol*. 2009;161(4):737-745. https://doi.org/10.1111/j.1365-2133.2009.09305.x
68. Gazerani P. Antipruritic effects of botulinum neurotoxins. *Toxins (Basel)*. 2018;10(4):143. https://doi.org/10.3390/toxins10040143
69. Boozalis E, Sheu M, Selph J, Kwatra SG. Botulinum toxin type A for the treatment of localized recalcitrant chronic pruritus. *J Am Acad Dermatol*. 2018;78(1):192-194. https://doi.org/10.1016/j.jaad.2017.08.001
70. Aquino TMO, Luchangco KAC, Sanchez EV, Verallo-Rowell VM. A randomized controlled study of 6% gabapentin topical formulation for chronic kidney disease-associated pruritus. *Int J Dermatol*. 2020;59(8):955-961. https://doi.org/10.1111/ijd.14953
71. Thornsberry LA, English JC III. Scalp dysesthesia related to cervical spine disease. *JAMA Dermatol*. 2013;149(2):200-203. https://doi.org/10.1001/jamadermatol.2013.914
72. O'Donoghue M, Tharp MD. Antihistamines and their role as antipruritics. *Dermatol Ther*. 2005;18(4):333-340. https://doi.org/10.1111/j.1529-8019.2005.00034.x
73. Dunford PJ, Williams KN, Desai PJ, Karlsson L, McQueen D, Thurmond RL. Histamine H4 receptor antagonists are superior to traditional antihistamines in the attenuation of experimental pruritus. *J Allergy Clin Immunol*. 2007;119(1):176-183. https://doi.org/10.1016/j.jaci.2006.08.034
74. Kim HJ, Park JB, Lee JH, Kim IH. How stress triggers itch: a preliminary study of the mechanism of stress-induced pruritus using fMRI. *Int J Dermatol*. 2016;55(4):434-442. https://doi.org/10.1111/ijd.12864
75. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175(3):401-407. https://doi.org/10.1001/jamainternmed.2014.7663
76. Roh YS, Khanna R, Patel SP, et al. Circulating blood eosinophils as a biomarker for variable clinical presentation and therapeutic response in patients with chronic pruritus of unknown origin. *J Allergy Clin Immunol Pract*. 2021;9(6):2513-2516.e2. https://doi.org/10.1016/j.jaip.2021.01.034
77. Xu AZ, Tripathi SV, Kau AL, Schaffer A, Kim BS. Immune dysregulation underlies a subset of patients with chronic idiopathic pruritus. *J Am Acad Dermatol*. 2016;74(5):1017-1020. https://doi.org/10.1016/j.jaad.2015.11.029
78. Dehner C, Chen L, Kim B, Rosman IS. Chronic itch of unknown origin is associated with an enhanced Th2 skin immune profile. *Am J Dermatopathol*. 2021. https://doi.org/10.1097/DAD.0000000000001902
79. Maley A, Swerlick RA. Azathioprine treatment of intractable pruritus: a retrospective review. *J Am Acad Dermatol*. 2015;73(3):439-443. https://doi.org/10.1016/j.jaad.2015.05.025
80. Chiricozzi A, Maurelli M, Gori N, et al. Dupilumab improves clinical manifestations, symptoms, and quality of life in adult patients with chronic nodular prurigo. *J Am Acad Dermatol*. 2020;83(1):39-45. https://doi.org/10.1016/j.jaad.2020.03.049

81. Jeon J, Wang F, Badic A, Kim BS. Treatment of patients with chronic pruritus of unknown origin with dupilumab. *J Dermatolog Treat*. 2021;2021:1-4. https://doi.org/10.1080/09546634.2021.1880542
82. Levy LL, Urban J, King BA. Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate. *J Am Acad Dermatol*. 2015;73(3):395-399. https://doi.org/10.1016/j.jaad.2015.06.045
83. Wang F, Morris C, Bodet ND, Kim BS. Treatment of refractory chronic pruritus of unknown origin with tofacitinib in patients with rheumatoid arthritis. *JAMA Dermatol*. 2019;155(12):1426-1428. https://doi.org/10.1001/jamadermatol.2019.2804
84. Sharma D, Kwatra SG. Thalidomide for the treatment of chronic refractory pruritus. *J Am Acad Dermatol*. 2016;74(2):363-369. https://doi.org/10.1016/j.jaad.2015.09.039
85. Silva SRB, Viana PCF, Lugon NV, Hoette M, Ruzany F, Lugon JR. Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron*. 1994;67(3):270-273. https://doi.org/10.1159/000187978
86. Yong A, Chong WS, Tey HL. Effective treatment of uremic pruritus and acquired perforating dermatosis with amitriptyline. *Australas J Dermatol*. 2014;55(3):e54-e57. https://doi.org/10.1111/ajd.12026
87. Haber R, Bachour J, Salloum A, et al. Comparison of gabapentin and doxepin in the management of uremic pruritus: a randomized crossover clinical trial. *Dermatol Ther*. 2020;33(6):e14522. https://doi.org/10.1111/dth.14522
88. Boozalis E, Khanna R, Zampella JG, Kwatra SG. Tricyclic antidepressants for the treatment of chronic pruritus. *J Dermatolog Treat*. 2021;32(1):124-126. https://doi.org/10.1080/09546634.2019.1623369
89. Chan S, Reddy V, Myers B, Brownstone N, Thibodeaux Q, Koo J. High-dose doxepin for the treatment of chronic, intractable scalp pruritus. *JAAD Case Rep*. 2021;8:71-73. https://doi.org/10.1016/j.jdcr.2020.12.017
90. Ständer S, Böckenholt B, Schürmeyer-Horst F, et al. Treatment of chronic pruritus with the selective serotonin reuptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol*. 2009;89(1):45-51. https://doi.org/10.2340/00015555-0553
91. Zylicz Z, Krajnik M, van Sorge AA, Costantini M. Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage*. 2003;26(6):1105-1112. https://doi.org/10.1016/j.jpainsymman.2003.05.004
92. Mayo MJ, Handem I, Saldana S, Jacobe H, Getachew Y, Rush AJ. Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology*. 2007;45(3):666-674. https://doi.org/10.1002/hep.21553
93. Boozalis E, Khanna R, Kwatra SG. Selective serotonin reuptake inhibitors for the treatment of chronic pruritus. *J Dermatolog Treat*. 2018;29(8):812-814. https://doi.org/10.1080/09546634.2018.1456639
94. Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. *J Am Acad Dermatol*. 2004;50(6):889-891. https://doi.org/10.1016/j.jaad.2004.01.045
95. Khanna R, Boozalis E, Belzberg M, Zampella JG, Kwatra SG. Mirtazapine for the treatment of chronic pruritus. *Medicines (Basel)*. 2019;6(3):73. https://doi.org/10.3390/medicines6030073
96. Iannetti GD, Zambreanu L, Wise RG, et al. Pharmacological modulation of pain-related brain activity during normal and central sensitization states in humans. *Proc Natl Acad Sci U S A*. 2005;102(50):18195-18200. https://doi.org/10.1073/pnas.0506624102
97. Loosemore MP, Bordeaux JS, Bernhard JD. Gabapentin treatment for notalgia paresthetica, a common isolated peripheral sensory neuropathy. *J Eur Acad Dermatol Venereol*. 2007;21(10):1440-1441. https://doi.org/10.1111/j.1468-3083.2007.02256.x
98. Ehrchen J, Ständer S. Pregabalin in the treatment of chronic pruritus. *J Am Acad Dermatol*. 2008;58(2 suppl):S36-S37. https://doi.org/10.1016/j.jaad.2007.07.017
99. Matsuda KM, Sharma D, Schonfeld AR, Kwatra SG. Gabapentin and pregabalin for the treatment of chronic pruritus. *J Am Acad Dermatol*. 2016;75(3):619-625.e6. https://doi.org/10.1016/j.jaad.2016.02.1237
100. Bockbrader HN, Wesche D, Miller R, Chapel S, Janiczek N, Burger P. A comparison of the pharmacokinetics and pharmacodynamics of pregabalin and gabapentin. *Clin Pharmacokinet*. 2010;49(10):661-669. https://doi.org/10.2165/11536200-000000000-00000
101. Korfitis C, Trafalis DT. Carbamazepine can be effective in alleviating tormenting pruritus in patients with hematologic malignancy. *J Pain Symptom Manage*. 2008;35(6):571-572. https://doi.org/10.1016/j.jpainsymman.2008.01.004
102. Terg R, Coronel E, Sordá J, Muñoz AE, Findor J. Efficacy and safety of oral naltrexone treatment for pruritus of cholestasis, a crossover, double blind, placebo-controlled study. *J Hepatol*. 2002;37(6):717-722. https://doi.org/10.1016/s0168-8278(02)00318-5
103. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet*. 1996;348(9041):1552-1554. https://doi.org/10.1016/s0140-6736(96)04176-1
104. Malekzad F, Arbabi M, Mohtasham N, et al. Efficacy of oral naltrexone on pruritus in atopic eczema: a double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol*. 2009;23(8):948-950. https://doi.org/10.1111/j.1468-3083.2009.03129.x
105. Frech T, Novak K, Revelo MP, et al. Low-dose naltrexone for pruritus in systemic sclerosis. *Int J Rheumatol*. 2011;2011:804296. https://doi.org/10.1155/2011/804296
106. Kwatra SG, Ständer S, Kang H. PD-1 blockade-induced pruritus treated with a mu-opioid receptor antagonist. *N Engl J Med*. 2018;379(16):1578-1579. https://doi.org/10.1056/NEJMc1805637
107. Fishbane S, Jamal A, Munera C, Wen W, Menzaghi F, KALM-1 Trial Investigators. A phase 3 trial of difelikefalin in hemodialysis patients with pruritus. *N Engl J Med*. 2020;382(3):222-232. https://doi.org/10.1056/NEJMoa1912770
108. Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol*. 2006;54(3):527-531. https://doi.org/10.1016/j.jaad.2005.12.010
109. Khanna R, Kwon CD, Patel SP, et al. Intranasal butorphanol rescue therapy for the treatment of intractable pruritus: a case series from the Johns Hopkins Itch Clinic. *J Am Acad Dermatol*. 2020;83(5):1529-1533. https://doi.org/10.1016/j.jaad.2020.07.017
110. Wikström B, Gellert R, Ladefoged SD, et al. Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol*. 2005;16(12):3742-3747. https://doi.org/10.1681/ASN.2005020152
111. Podesta A, Lopez P, Terg R, et al. Treatment of pruritus of primary biliary cirrhosis with rifampin. *Dig Dis Sci*. 1991;36(2):216-220. https://doi.org/10.1007/BF01300759

112. Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin: results of a double-blind, crossover, randomized trial. *Gastroenterology*. 1988;94(2):488-493. https://doi.org/10.1016/0016-5085(88)90442-8
113. Rivard J, Lim HW. Ultraviolet phototherapy for pruritus. *Dermatol Ther*. 2005;18(4):344-354. https://doi.org/10.1111/j.1529-8019.2005.00032.x
114. Kamo A, Tominaga M, Tengara S, Ogawa H, Takamori K. Inhibitory effects of UV-based therapy on dry skin-inducible nerve growth in acetone-treated mice. *J Dermatol Sci*. 2011;62(2):91-97. https://doi.org/10.1016/j.jdermsci.2011.01.004
115. Bulat V, Situm M, Dediol I, Ljubicić I, Bradić L. The mechanisms of action of phototherapy in the treatment of the most common dermatoses. *Coll Antropol*. 2011;35(suppl 2):147-151.
116. Ständer S, Siepmann D, Herrgott I, Sunderkötter C, Luger TA. Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLoS One*. 2010;5(6):e10968. https://doi.org/10.1371/journal.pone.0010968
117. He A, Alhariri JM, Sweren RJ, Kwatra MM, Kwatra SG. Aprepitant for the treatment of chronic refractory pruritus. *BioMed Res Int*. 2017;2017:4790810. https://doi.org/10.1155/2017/4790810
118. Vincenzi B, Tonini G, Santini D. Aprepitant for erlotinib-induced pruritus. *N Engl J Med*. 2010;363(4):397-398. https://doi.org/10.1056/NEJMc1003937
119. Yosipovitch G, Ständer S, Kerby MB, et al. Serlopitant for the treatment of chronic pruritus: results of a randomized, multicenter, placebo-controlled phase 2 clinical trial. *J Am Acad Dermatol*. 2018;78(5):882-891.e10. https://doi.org/10.1016/j.jaad.2018.02.030
120. Ständer S, Kwon P, Hirman J, et al. Serlopitant reduced pruritus in patients with prurigo nodularis in a phase 2, randomized, placebo-controlled trial. *J Am Acad Dermatol*. 2019;80(5):1395-1402. https://doi.org/10.1016/j.jaad.2019.01.052
121. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol*. 1995;63(4):624-635. https://doi.org/10.1037/0022-006x.63.4.624
122. Habib S, Morrissey S. Stress management for atopic dermatitis. *Behav Change*. 1999;16(4):226-236. https://doi.org/10.1375/bech.16.4.226
123. Melin L, Frederiksen T, Noren P, Swebilius BG. Behavioural treatment of scratching in patients with atopic dermatitis. *Br J Dermatol*. 1986;115(4):467-474. https://doi.org/10.1111/j.1365-2133.1986.tb06241.x
124. van Os-Medendorp H, Ros WJG, Eland-de Kok PCM, et al. Effectiveness of the nursing programme "Coping with itch": a randomized controlled study in adults with chronic pruritic skin disease. *Br J Dermatol*. 2007;156(6):1235-1244. https://doi.org/10.1111/j.1365-2133.2007.07919.x
125. Kurtz ES, Wallo W. Colloidal oatmeal: history, chemistry and clinical properties. *J Drugs Dermatol*. 2007;6(2):167-170.
126. Napadow V, Li A, Loggia ML, et al. The brain circuitry mediating antipruritic effects of acupuncture. *Cereb Cortex*. 2014;24(4):873-882. https://doi.org/10.1093/cercor/bhs363
127. Tang WY, Chan LY, Lo KK, Wong TW. Evaluation on the antipruritic role of transcutaneous electrical nerve stimulation in the treatment of pruritic dermatoses. *Dermatology*. 1999;199(3):237-241. https://doi.org/10.1159/000018254
128. Roh YS, Sutaria N, Biles NF, Kwatra SG. Treatment of chronic pruritus with medical marijuana. *JAMA Dermatol*. 2021;157(7):879-880. https://doi.org/10.1001/jamadermatol.2021.1194
129. Neff GW, O'Brien CB, Reddy KR, et al. Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol*. 2002;97(8):2117-2119. https://doi.org/10.1111/j.1572-0241.2002.05852.x
130. Lio P, Boguniewicz M, Alexis A, et al. Depth and rapidity of response with Abrocitinib and dupilumab in patients with moderate-to-severe atopic dermatitis (AD) in JADE COMPARE. *J Allergy Clin Immunol*. 2021;147(2):AB34. https://doi.org/10.1016/j.jaci.2020.12.159
131. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T. Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study. *J Am Acad Dermatol*. 2020;82(4):823-831. https://doi.org/10.1016/j.jaad.2019.12.015
132. Kim BS, Howell MD, Sun K, et al. Treatment of atopic dermatitis with Ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145(2):572-582. https://doi.org/10.1016/j.jaci.2019.08.042
133. Asahina A, Etoh T, Igarashi A, et al. Oral tofacitinib efficacy, safety and tolerability in Japanese patients with moderate to severe plaque psoriasis and psoriatic arthritis: a randomized, double-blind, phase 3 study. *J Dermatol*. 2016;43(8):869-880. https://doi.org/10.1111/1346-8138.13258
134. Simpson EL, Lacour JP, Spelman L, et al. Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. *Br J Dermatol*. 2020;183(2):242-255. https://doi.org/10.1111/bjd.18898
135. Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020;145(3):877-884. https://doi.org/10.1016/j.jaci.2019.11.025