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Emilie Fowler, BS, Gil Yosipovitch, MD

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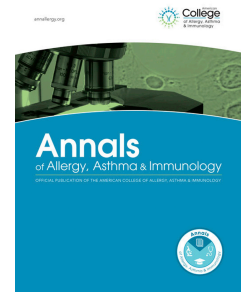
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Title: Chronic Itch Management: Therapies Beyond Those Targeting the Immune System

Authors: Emilie Fowler BS^{1, 2}, Gil Yosipovitch MD^{1, 2}

¹Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine

²Miami Itch Center, University of Miami Miller School of Medicine

Corresponding Author:

Gil Yosipovitch MD

1600 NW 10th Ave, RMSB 2067B

Miami, FL, 33136, USA

Phone: 305-243-6191

Email: gyosipovitch@med.miami.edu

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Abbreviations:

CB, cannabinoid receptor

CBT, cognitive behavioral therapy

EMLA, eutectic mixture of local anesthetic

GABA, gamma-aminobutyric acid

GPCR, G-protein coupled receptor

GRPR, gastrin-related peptide receptor

HRT, habit reversal training

IL, interleukin

IV, intravenous

JAK, janus kinase

MRGPR, mas-related G protein-coupled receptor

Nav, voltage-gated sodium channel

NGF, nerve growth factor

NK, neurokinin receptor

NMDA, N-methyl-D-aspartate

PAR, protease activated receptor

PEA, palmitoylethanolamide

PMR, progressive muscle relaxation

SNRI, serotonin norepinephrine reuptake inhibitor

SSRI, serotonin reuptake inhibitor

TCA, tricyclic antidepressant

TrkA, tropomyosin receptor kinase A

TRP, transient receptor potential channel

TRPA, transient receptor potential ankyrin

TRPM, transient receptor potential melastatin

TRPV, transient receptor potential vanilloid

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Introduction

Itch, a sensation that leads to a desire to scratch, becomes chronic when it persists for more than 6 weeks.¹ Chronic itch can be debilitating and lead to a significantly reduced quality of life. It affects sleep, mood, and can cause symptoms of anxiety and depression.² Pruritus may be perpetuated by inflammatory conditions, as seen in atopic dermatitis and psoriasis. However, chronic pruritus may not always have an inflammatory component, and therefore requires treatments that do not work on the immune system, but instead target the nerves.

There are significant advances in our understanding of inflammatory, immune-mediated itch, which has manifested into the development of targeted treatments such as interleukin-4 (IL-4) and IL-13 inhibitors (eg, dupilumab), IL-31 inhibitors, and Janus kinase (JAK) inhibitors.³ The purpose of this article is to discuss treatments for itch from non-immune-mediated diseases, focusing mainly on the neural system.

Overview of Chronic Itch Mechanisms

Pathophysiology & Neural Sensitization

In brief, the sensation of itch begins in the skin with itch-selective, unmyelinated C nerve fibers (Figure 1). These fibers synapse at the dorsal root ganglion, where a secondary neuron crosses and ascends the spinothalamic tract to the thalamus and parabrachial nucleus in the brain. Signals are further projected and multiple areas are activated in the brain, including the primary and secondary somatosensory cortex, anterior cingulate cortex, insula, striatum, and cerebellum among others.^{1,3}

Additionally, the mechanism of chronic itch includes a component of neural sensitization. Neural sensitization is a phenomenon causing an increase in sensitivity of itch-selective neurons

at the level of the skin, spinal cord, and brain. At the level of the skin, inflammation and abnormal innervation are the main causes of neuronal sensitization. In the spinal cord, dysfunction and attenuation of the inhibitory pathways can lead to a state of neuronal hypersensitivity. In the brain, chronic itch can lead to functional and structural changes which can perpetuate the sensation of itch.^{3,4}

Receptors Involved in Chronic Itch

Pruritus is typically classified as either histaminergic or nonhistaminergic itch. The majority of histaminergic itch is related to acute itch, while chronic itch is nonhistaminergic in nature, and therefore is not responsive to antihistaminic medications. Nonhistaminergic neurons are instead activated by a variety of pruritogens beyond cytokines. Many receptors are involved, which provide various potential targets for therapy. Figure 2 provides a schematic diagram of the major neural receptors involved in itch in the peripheral nerves and spinal cord.

G-protein coupled receptors (GPCRs) make up the majority of receptors on itch-selective unmyelinated C nerve fibers in the skin. Activation of GPCRs triggers the opening of ion channels such as transient receptor potential channels (TRPs) and voltage-gated sodium channels (Nav) such as Nav 1.7, which generate action potentials in the nerves.³ Prominent GPCRs involved in chronic itch include the opioid receptors and cannabinoid receptors. TRPs encompass many subfamilies of receptors such as TRP vanilloid (eg, TRPV1), and TRP ankyrin (eg, TRPA1). In addition to their activation downstream of GPCRs, TRPs can also be activated by external stimuli such as temperature, pH, and capsaicin.^{3,5}

Other receptors implicated in the pathway of chronic itch include opioid receptors, protease-activated receptors (PARs), and neurokinin receptors (NK). Opioid receptors involved

in the itch pathway include the mu-opioid receptors and kappa-opioid receptors. Imbalance in mu-opioid and kappa-opioid receptor activation can result in neural sensitization leading to chronic itch.³

PARs are a type of GPCR that are activated by proteolytic cleavage of an extracellular domain. Cowhage, a well-known nonhistaminergic itch mediator, activates PAR-2 and PAR-4. Proteases such as trypsin, kallikrein, and many others can also activate PAR-2 and PAR-4 causing nonhistaminergic itch.³

Lastly, NK receptors are abundant throughout the central nervous system and skin. NK-1 is activated by substance P, which causes a downstream release of additional molecules causing pruritus.³ On the molecular level there are many additional receptors for which targets have not yet been developed, such as Mas-related G protein-coupled receptors (MRGPRs) and gastrin-related peptide receptor (GRPR).

Non-Immunological Management of Chronic Itch

Chronic itch can be difficult to manage, however with a deeper understanding of the mechanism of itch, effective therapies have been developed and many more are on the horizon. Figure 3 illustrates where each therapy carries out its mechanism of action.

Topical Therapies

Topical Anesthetics

Topical anesthetics such as pramoxine 1%, lidocaine 2.5-5%, and prilocaine 2.5% creams, come at low-cost and minimal risk when treating pruritus.^{6,7} They may be used individually or as a eutectic mixture of local anesthetic (EMLA), a cream made up of equal parts

70 lidocaine 2.5% and prilocaine 2.5%. Topical anesthetics work by reversibly antagonizing sodium
71 channels, interfering with impulse production and action potential conduction in nerves.⁸

72 Due to their action on nerves topical anesthetics are useful in the treatment of neuropathic
73 pruritus, but reports have also shown benefit in anogenital and facial itch, as well as uremic
74 pruritus.^{6,9} Results vary among patients, but topical anesthetics may be considered for providing
75 some relief in patients with chronic localized pruritus, even if only for short-term.

77 *Ketamine-Amitriptyline-Lidocaine*

78 Another topical anesthetic preparation includes a combination of 5% lidocaine with 5-
79 10% ketamine and 5% amitriptyline.⁷ Currently, this is perhaps the most effective form of topical
80 anesthetic preparation given for chronic itch in the authors' experience. Although the mechanism
81 of this combination has yet to be fully elucidated, it is thought to work by reducing the
82 hypersensitivity of peripheral afferent nerve fibers, through blockage of N-methyl-D-aspartate
83 (NMDA) receptors and sodium channels.¹⁰

84 This combination has helped patients with neuropathic itch such as brachioradial pruritus,
85 postherpetic neuralgia, and notalgia paresthetica, as well as patients with prurigo nodularis and
86 itch of advanced age.^{7,10}

88 *Capsaicin*

89 The spice from hot chili peppers is generated by the active ingredient capsaicin, the
90 therapeutic use of which dates back to the 19th century.¹¹ Capsaicin binds to TRPV1 on C nerve
91 fibers, causing activation that leads to intense depolarization, thereby causing neural

desensitization. The intense depolarization of these fibers stimulate release of substance P, which can cause an initial burning sensation on application.^{7,11}

Topical capsaicin can be found over-the-counter in concentrations of 0.025-0.1%, but treatment of pruritus frequently requires higher concentrations of 0.075-0.1% available by prescription.⁷ Capsaicin can be useful for localized neuropathic chronic itch, in particular those with spinal cord compression such as brachioradial pruritus, notalgia paresthetica, and genital itch, as well as small fiber neuropathies such as postherpetic neuralgia.⁶ Other itchy conditions like prurigo nodularis, aquagenic pruritus, and uremic pruritus have also reported relief of itch with capsaicin.^{11,12} Additionally, a more potent 8% capsaicin patch can provide prolonged relief in neuropathic itch when applied for an hour. However, as with any treatment for itch, responses are variable and can last from a few days to over a year.¹³⁻¹⁵ Differences among ethnic groups have also been noted, with African Americans having a limited response.¹⁶

Menthol

Menthol, known for its cooling effects, has been shown to reduce itch when given in low concentrations of 1-5% creams.⁶ Menthol binds to TRPM8, a thermosensitive ion channel present on afferent nerves transmitting itch. By activating TRPM8, inhibitory pathways in the spinal cord are activated leading to a reduction in pruritus.^{3,17}

A subset of patients endorse that ice packs or cooling sensations relieve their itch. These patients, therefore, may benefit from application of menthol to their itchy skin.¹⁸

Strontium

Strontium is a calcimimetic whose antipruritic effect may result from inhibition of calcium-dependent depolarization of itch-selective C nerve fibers, interference with synaptic transmission, or disruption of neurotransmitter release.¹⁹ Although it is still unclear as to how it exerts its antipruritic effect, strontium has shown to be beneficial in both nonhistaminergic and histaminergic itch.^{19,20}

In a double blind vehicle-controlled crossover study, strontium chloride hydrogel was shown to be more effective in treating cowhage-induced pruritus compared to other over-the-counter topical preparations.¹⁹ Topical strontium, therefore, may present a cheap over-the-counter solution for treating localized chronic itch.

Cannabinoids

The cannabinoid receptors, CB1 and CB2, are present in the skin as well as the nervous system, and therefore can be targets for modulation of itch at various levels. CB1 and CB2 are GPCRs that when activated cause an inhibitory effect.²¹

Topical cannabinoid medications can be antipruritic by directly activating cannabinoid receptors or indirectly by increasing the activity of endogenous cannabinoids.

Palmitoylethanolamide (PEA), for example, works by stimulating anandamide, an endocannabinoid that activates CB1 receptors. Topical cannabinoid therapies have shown to have antipruritic effects in a variety of non-inflammatory itch conditions, such as postherpetic neuralgia, uremic pruritus, and aquagenic pruritus.^{3,22,23}

Botulinum Toxin

A more invasive treatment administered for chronic pruritus is botulinum toxin. It is administered by injection into the pruritic areas of the skin. Its mechanism of action involves cleavage of proteins that lead to inhibition of acetylcholine release at the neurotransmitter junction. Additionally, the release of other neuropeptides, including substance P, glutamate, and calcitonin gene-related protein, is inhibited. These neuropeptides are all involved in neuropathic pruritus and inflammation.³

Botulinum toxin works best for treatment-refractory chronic pruritus that is localized, since it works directly on the nerves at the site of injection. It has relieved pruritus successfully in cases of neuropathic itch, notalgia paresthetica, brachioradial pruritus, lichenified areas caused by scratching, and burn wounds.²⁴⁻²⁶ Although invasive, botulinum toxin offers the advantage of being administered by a healthcare provider with an effect that can last for several months. Therefore, patients may require only three to four injections per year²⁴

Systemic Therapies

Systemic treatments are useful for treating chronic itch that is more generalized, but come with a potential for more adverse effects (Table 1).

Gabapentin & Pregabalin

Gabapentin and pregabalin are analogs of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter. Referred to as anticonvulsants, gabapentin and pregabalin were originally manufactured as medications to treat epilepsy. Today, these drugs are given for a variety of neuropathic conditions, including postherpetic neuralgia, diabetic neuropathy, and

various forms of chronic itch.²⁷ Their mechanism of action involves inhibition of voltage-gated calcium channels in the spinal cord, thereby reducing central neural hypersensitization.^{3,27}

Gabapentin is an effective drug in patients suffering from neuropathic causes of pruritus. It has been shown to reduce itch in patients with postherpetic pruritus, notalgia paresthetica, brachioradial pruritus, and prurigo nodularis.^{7,23,27-29} There are also reports of gabapentin being useful in other causes of chronic itch such as chronic kidney disease, cutaneous lymphoma, and prurigo nodularis.^{6,30}

Pregabalin is another gabapentinoid with supposedly less adverse effects and easier administration.⁶ It can similarly be used for neuropathic itch. If a patient's pruritus fails to improve on one of these agents, the other agent may be tried and in some cases can be successful in relieving pruritus.⁷

Tricyclic Antidepressants

Tricyclic antidepressants (TCAs) are antidepressants that inhibit reuptake of serotonin in nerve synapses, leading to an increase in its concentration and causing increased neural impulses. TCAs are nonspecific and can antagonize other receptors including muscarinic, adrenergic, and histaminergic receptors. Antagonism of histamine receptors may contribute to their antipruritic effect. TCAs have limited use in the treatment of chronic itch, especially that mediated by non-histaminergic mechanisms.

Amitriptyline, a TCA, has been shown to alleviate pruritus in cases of notalgia paresthetica, brachioradial pruritus, and uremic pruritus when given orally.³¹⁻³³ Doxepin, the most potent antihistaminic TCA, is well known for its antipruritic effects.³⁴ However, doxepin is not a great option for chronic itch, which in the majority of cases is nonhistaminergic.

Adverse effects of TCAs include sedation, blurry vision, dry mouth, urinary retention, orthostatic hypotension, and cardiotoxicity causing conduction abnormalities. Many patients may not be able to tolerate these adverse effects and frequent monitoring with ECGs is required.⁶

Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors

Serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are antidepressants that inhibit presynaptic reuptake of serotonin and norepinephrine, allowing these neurotransmitters to increase in concentration at the nerve synapse, causing an increase in neurotransmission. SSRIs including sertraline, paroxetine, and fluvoxamine, have shown improvement in various forms of chronic pruritus, although are limited in use for neuropathic causes of pruritus.³

Mirtazapine, an atypical SNRI, antagonizes serotonergic and noradrenergic receptors, causing an increase in their central neurotransmission.³⁵ It may be used as adjunct therapy in numerous forms of itch.⁶ Mirtazapine also has antinociceptive properties and in low doses has sedative effects that make it useful for nocturnal pruritus.³⁵

Opioids

Opioid receptors are found in both the peripheral and central nervous system. In the context of itch, we are concerned with mu- and kappa-opioid receptors. Mu-opioid agonists, such as morphine, induce itch. Kappa-opioid agonists, on the other hand, are antipruritic. Therefore using agonists of kappa-opioid receptors and antagonists of mu-opioid receptors can lead to relief of pruritus.

Butorphanol is a mixed kappa-opioid agonist and mu-opioid antagonist that is administered intranasally. Since it has antipruritic effects at both opioid receptors involved in itch, it is quite effective, especially for cases of intractable itch. Additionally, it has a rapid onset of action and little abuse potential.³⁶

Nalbuphine is another mixed kappa-opioid agonist and mu-opioid antagonist that is used off-label in treatment of pruritus caused by opioid intake.³⁷ Clinical trials studying nalbuphine therapy for other pruritic conditions, such as uremic pruritus³⁸ and prurigo nodularis³⁹, have shown promising results (Table 2).

Less commonly used for pruritus are the mu-opioid antagonists, which include naloxone and naltrexone. Randomized controlled trials have reported some benefit in relieving pruritus.⁴⁰ However, mu-opioid antagonists are not frequently used antipruritic agents due to adverse effects which include nausea, abdominal cramps, and diarrhea.^{6,40}

Kappa-opioid agonists have shown antipruritic efficacy but are not yet available in the United States. In Japan, nalfurafine is a kappa-opioid agonist used to treat pruritus in hemodialysis patients.⁴¹ Newer kappa-opioid agonists on the horizon include asimadoline and CR845. Asimadoline is currently being investigated in phase II studies for treating pruritus in atopic dermatitis. Additionally, phase III trials are currently underway studying the efficacy of intravenous CR845 in uremic pruritus. In phase II trials, CR845 had shown significant antipruritic effects for uremic pruritus.⁴² (Table 2)

Neurokinin-1 Inhibitors

The NK-1 receptor is located throughout the central nervous system and skin. NK-1 is activated by binding the neuropeptide substance P, a mediator of pruritus.⁴³

Aprepitant, an NK-1 inhibitor, has relieved itch in patients with prurigo nodularis and cutaneous T-cell lymphoma.^{43,44} It is given in cases of chronic itch that are refractory, and has been reported to be effective, for example in brachioradial pruritus.⁴⁵ A major drawback of aprepitant, however, is its wide range of potential drug interactions.³

Newer NK-1 inhibitors, serlopitant and tradipitant, have less adverse effects and so far have shown potential as antipruritic therapies. In a randomized, placebo-controlled, phase 2 clinical trial, serlopitant showed a statistically significant reduction in chronic itch.⁴⁶ Similarly, tradipitant, in a randomized, double-blind, placebo-controlled, phase 2 trial, improved itch in patients with atopic dermatitis.⁴⁷ (Table 2)

Thalidomide

Thalidomide may be used in cases of chronic pruritus refractory to other treatments, in particular prurigo nodularis. Thalidomide acts as a central depressant, has anti-inflammatory properties, and acts as an immunomodulator and neuromodulator, which all together make it a robust antipruritic drug.⁴⁸

Of course, thalidomide must be used with caution due to its potential for teratogenicity and peripheral neuropathy.⁴⁸ Therefore, it is reserved for cases of severe treatment-refractory chronic pruritus, and has shown success in randomized trials for treatment of prurigo nodularis and uremic pruritus.⁴⁸⁻⁵⁰

Therapies on the Horizon

Intravenous Ketamine

Intravenous (IV) ketamine is a therapy used off-label for severe, treatment-refractory depression and chronic, intractable pain. Ketamine is an NMDA receptor antagonist and has neuromodulatory effects, altering brain plasticity.⁵¹

With its success in treating chronic intractable pain, it has a potential in the treatment of chronic, treatment-refractory itch. So far, there is only anecdotal evidence available for its therapeutic success in treating chronic pruritus, however it can be considered an option when chronic itch is severe and unresponsive to all other available therapies.⁵²

TrkA Antagonists and NGF Inhibitors

Tropomyosin receptor kinase A (TrkA) and nerve growth factor (NGF) are important in mediation of the neural sensitization of itch at the peripheral level. NGF, released by keratinocytes and eosinophils, binds to its receptor, TrkA. TrkA sensitizes TRPV1 on the peripheral nerves, which increases neural sensitivity to pruritic mediators including substance P, CGRP, and others. Additionally, NGF sensitizes skin to cowhage-induced itch, a form of nonhistaminergic itch.³ Therefore, by blocking this pathway, symptoms of pruritus can be reduced.

A clinical trial demonstrated that a topical TrkA antagonist, CT327, was able to reduce itch in psoriasis patients.⁵³ So far this drug has only been shown to reduce itch in psoriasis, but it will be interesting to see in what other pruritic conditions that TrkA antagonists and NGF inhibitors can be helpful.

Nav 1.7 Antagonists

Nav 1.7 is another receptor implicated in propagating the sensation of itch. In mice, an antibody developed targeting Nav 1.7 was shown to suppress both chronic and acute itch, making it a potential therapeutic target for future itch therapy.⁵⁴

Protease Activated Receptor-2 Inhibitors

PAR-2 is a GPCR involved in the transmission of nonhistaminergic itch. It may also play a role in neural sensitization of chronic itch by direct action on pruritoceptive nerve endings in the skin.⁵⁵

In mouse models of atopic dermatitis, PZ-235, a peptidic inhibitor of PAR-2, reduced acute and chronic itch.⁵⁶ Clinical studies are necessary to conclude whether or not targeting PAR-2 effectively reduces itch in humans, and whether it has any effect on non-inflammatory pruritic conditions.

Mas-Related G Protein-Coupled Receptor Inhibitors

MRGPRs are receptors located on peripheral sensory neurons transmitting non-histaminergic itch.⁵⁷ Human mast cells have also been found to express MRGPRX2. MRGPRs are involved in the perpetuation of chronic itch, which have made them new potential targets for drug development.³

Holistic Approaches

Holistic approaches may be implemented as adjuvant therapy in patients suffering from chronic itch. Stress has been shown to aggravate itch and to increase its perceived intensity.⁵⁸ By controlling stress, one may improve their itch and quality of life.⁵⁹

Progressive muscle relaxation (PMR) and autogenic training are two relaxation techniques that have been shown to reduce pruritus. Psychological therapies such as cognitive behavioral therapy (CBT) and habit reversal training (HRT) may also help control scratching behavior.⁵⁹ Additionally, in cases of neuropathic pruritus, such as those involving nerve impingement, stretching and strengthening exercises may also be beneficial adjunctive therapies.⁶⁰

Conclusion

Understanding that chronic pruritus is not solely inflammatory in nature has led to advances in the treatment of itch. Nerves are the final common pathway of itch processing. The process of neural sensitization perpetuates the condition of chronic pruritus, a symptom that is complicated and often multifactorial in nature. In this review, we outlined many effective therapeutic options available, as well as novel therapies. Figure 4 illustrates a therapeutic ladder of treatments targeting the nerves that may be used for patients with multiple types of idiopathic chronic itch. By using treatments targeting the nerves, instead of those working only on the immune system, relief of chronic itch may be achieved in these patients.

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Figure 1. Neural pathway of itch, originating in the skin and ending in the brain.

Figure 2. Major neural receptors involved in transduction of itch in the skin and spinal cord.

Abbreviations: CB1/CB2, cannabinoid receptor 1/cannabinoid receptor 2; GABA, gamma-aminobutyric acid; GRP, gastrin-related peptide; GRPR, gastrin-related peptide receptor; H1R/H4R, histamine receptor 1/ histamine receptor 4; Mrgpr, mas-related G protein-coupled receptor; Nav 1.7, voltage-gated sodium channel 1.7; Nav 1.9, voltage-gated sodium channel 1.9; NGF, nerve growth factor; NK-1, neurokinin receptor 1; NMDA, N-methyl-D-aspartate; PAR, protease activated receptor; MOR/KOR, mu-opioid receptor/kappa-opioid receptor; TrkA, tropomyosin receptor kinase A; TRPA1 transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV1, transient receptor potential vanilloid 1.

Figure 3. Treatments for chronic itch and where they work in the central and/or peripheral nervous systems. Abbreviations: DRG, dorsal root ganglion; IV, intravenous; KAL, ketamine-amitriptyline-lidocaine; NK-1, neurokinin receptor-1; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, serotonin reuptake inhibitor.

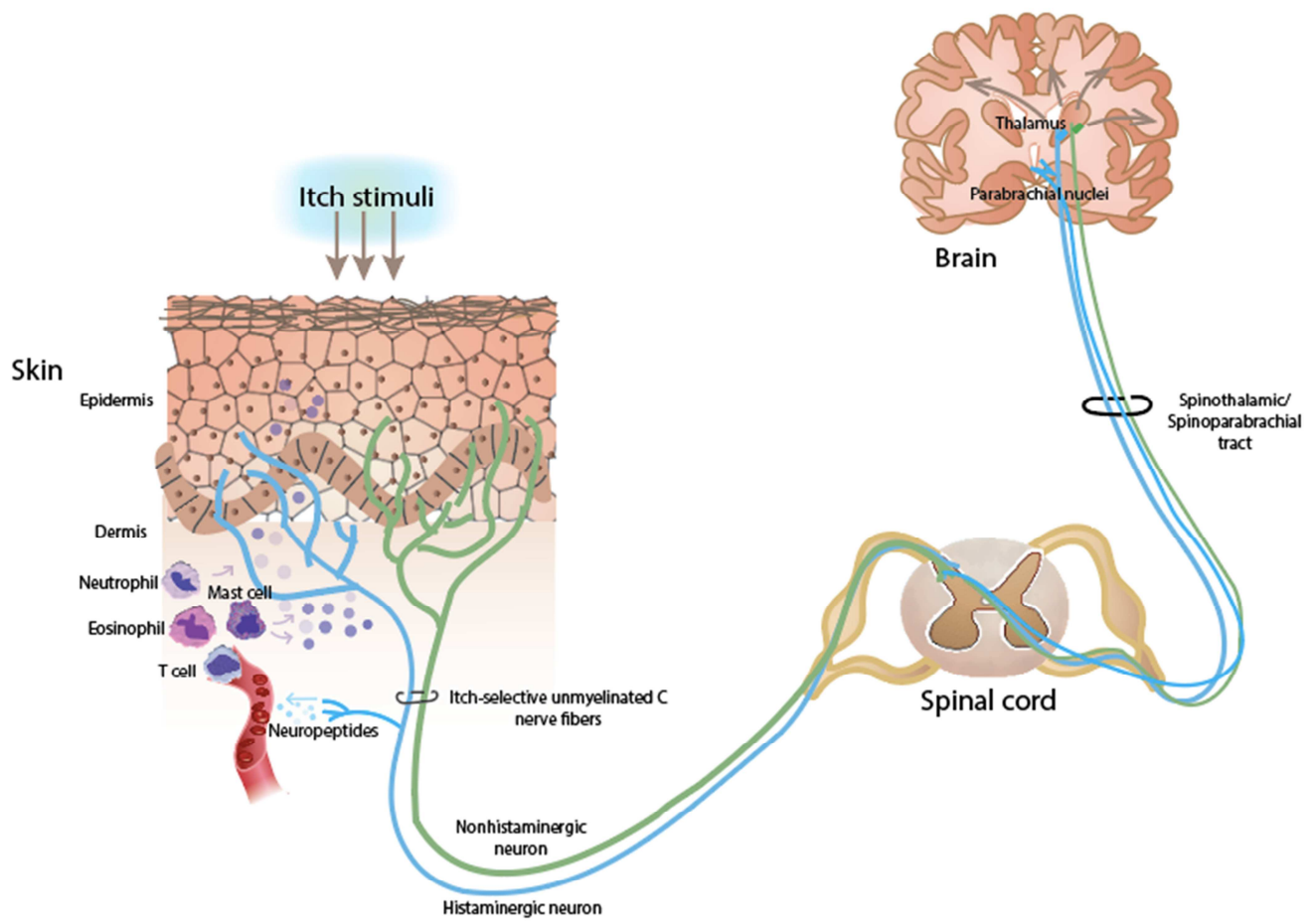
Figure 4. Proposed therapeutic ladder for non-immunological treatment of chronic itch.

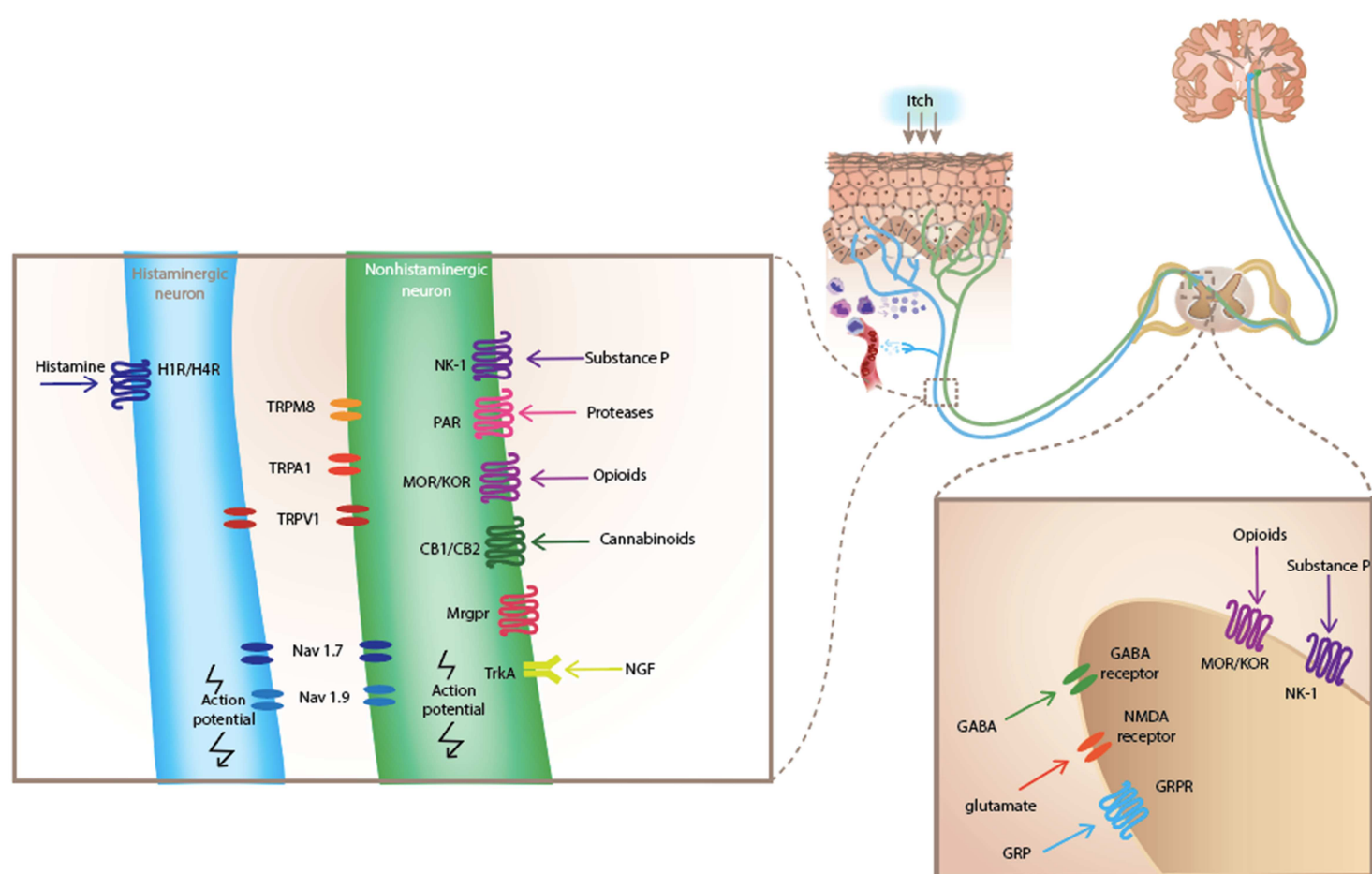
Drug Class	Medication	Dosing	Adverse Effects
Anti-Epileptics	Gabapentin	start with 300-600 mg at night, can titrate up to 3600 mg/day divided into 3 doses *dose adjustment in renal insufficiency	Drowsiness Increased appetite Weight gain Constipation Lower extremity swelling
	Pregabalin	start with 75 mg twice a day, can titrate up to 600 mg daily *dose adjustment in renal insufficiency	
Antidepressants	Amitriptyline	10-50 mg daily, can titrate up to 150 mg	Sedation Blurry vision Dry mouth Orthostatic hypotension Urinary retention Cardiac conduction abnormalities
	Doxepin	10-30 mg daily	
	Paroxetine	10-50 mg daily	
	Sertraline	75-150 mg daily	Drowsiness Sexual Dysfunction Insomnia
	Fluvoxamine	start at 25 mg, titrate to 50-150 mg daily	
	Mirtazapine	7.5-15 mg daily	Drowsiness Weight gain
Mu-Opioid Antagonists	Naltrexone	12.5-50 mg daily	Nausea, vomiting Reversal of analgesia Hepatotoxicity
Mixed Opioids	Butorphanol	1-4 mg daily, intranasal administration	Drowsiness
NK-1 Inhibitors	Aprepitant	80 mg daily	Nausea Dizziness
Thalidomide		100-200 mg daily	Teratogenicity Peripheral neuropathy

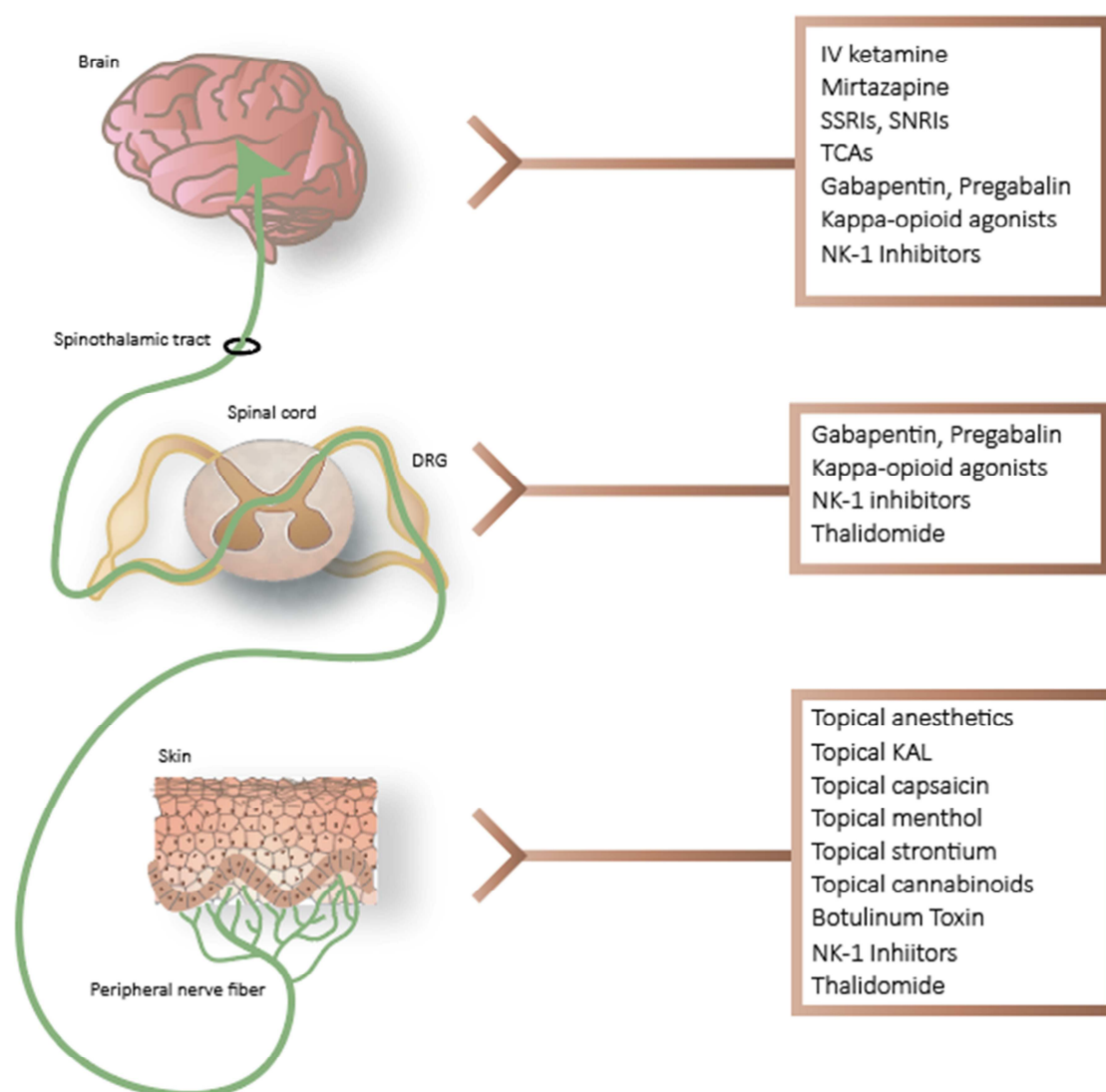
Table1. Adult Dosing and Notable Adverse Effects of Non-Immunological Systemic Drugs Available for Treatment of Chronic Itch. Abbreviations: mg, milligrams; NK-1, neurokinin receptor-1.

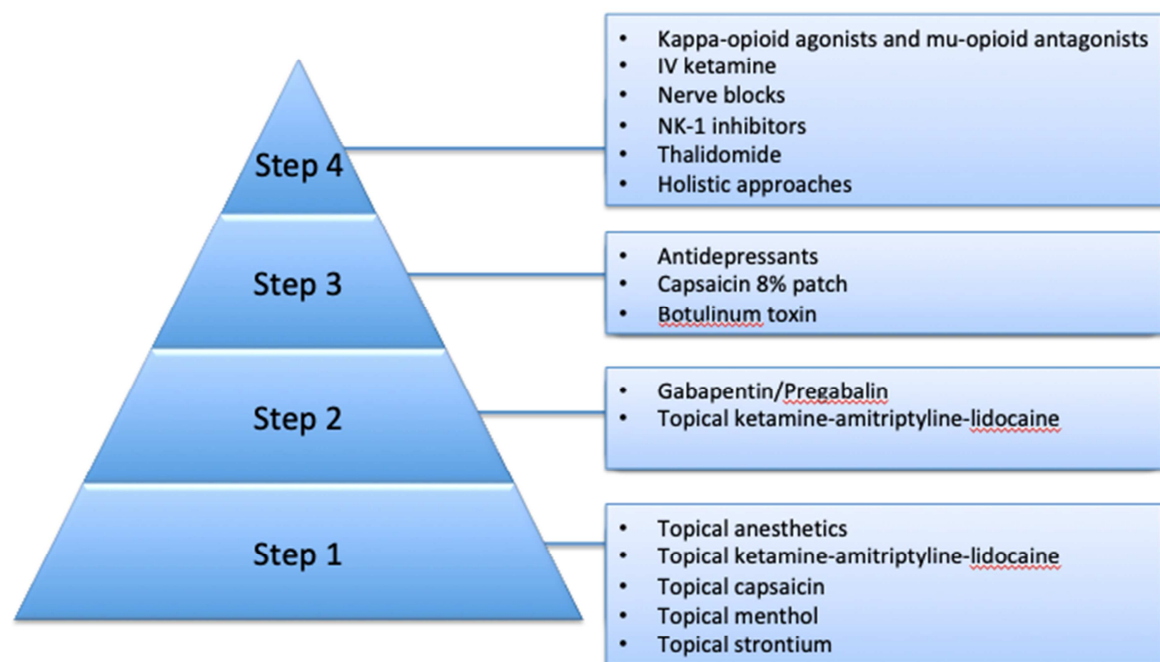
Drug	Phase of Study	Patient Population	Duration of Study	Dose	Resulting Itch Reduction
Nalbuphine	Phase II/III	Uremic pruritus ³⁸	8 weeks	60 mg daily	NRS score mean change from baseline vs placebo was not statistically significant.
				120 mg daily	NRS score mean change from baseline vs placebo: -3.5 vs -2.8 (p = 0.017)
Nalfurafine	Phase II	Prurigo nodularis ³⁹	8 weeks	180 mg twice daily	50% of treated patients vs 20% of patients treated with placebo obtained a >50% reduction in worst itch NRS from baseline
				5 ug daily	Average VAS reduction vs placebo: -22 vs -13 (p = 0.0002)
CR845	Phase III	Hemodialysis patients ⁴¹	2 weeks	2.5 ug daily	Average VAS reduction vs placebo: -23 vs -13 (p = 0.0001)
				0.5 ug/kg, 1.0 ug/kg, or 1.5 ug/kg IV three times weekly	68% greater reduction from baseline in worst itch scores vs placebo (p < 0.0019)
Serlopitant	Phase II	Chronic pruritus ⁴⁶	6 weeks	5 mg daily	Average VAS reduction vs placebo: -42.5 vs -28.3 (p = 0.013)
				1 mg daily	Average VAS reduction vs placebo: -41.4 vs -28.3 (p = 0.22)
Tradipitant	Phase II	Atopic dermatitis ⁴⁷	8 weeks	85 mg twice daily	Average VAS reduction compared to placebo was not statistically significant. Worst itch VAS reduction compared to placebo: -44.2 vs -30.6 (p = 0.019)

Table 2. New Anti-Pruritic Therapies and Magnitude of Itch Reductions from Randomized, Double-Blind, Placebo-Controlled Trials. Abbreviations: IV, intravenous; mg, milligrams; ug, micrograms; NRS, numerical rating scale; VAS, visual analogue scale; vs, verses.









Key Messages

- Chronic itch is nonhistaminergic in nature, and often requires treatments that work on the nerves, rather than those targeting the immune system.
- The sensation of itch is mediated by nerves in the skin, spinal cord, and brain, and involves a phenomenon of neural sensitization at each of these levels.
- Unmyelinated C nerve fibers responsible for transmitting itch sensation have a variety of receptors that may be targeted for therapy, including GPCRs, TRPs, Nav channels, NK receptors, and PARs.
- Topical treatments such as capsaicin, menthol, anesthetics, ketamine-amitriptyline-lidocaine, strontium, cannabinoids, and injections of botulinum toxin may relieve chronic pruritus.
- Systemic therapies that provide relief to chronic itch patients include gabapentin, pregabalin, tricyclic antidepressants, SSRIs, mirtazapine, mu-opioid antagonists, kappa-opioid agonists, neurokinin-1 inhibitors, and thalidomide.