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Post-Burn Pruritus and Its Management—Current and New Avenues for Treatment

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Abstract

Purpose of Review This article seeks to review the current literature on post-burn pruritus and its treatments, as well as to propose new treatments that may be of potential benefit for these patients.

Recent Findings Post-burn pruritus has been reported to affect as many as 93% of patients after a burn injury. Pruritus is extremely distressing to these patients, yet the current state of treatment, mostly antihistamines and emollients, is still widely ineffective in providing relief of itch.

Summary Therapies that are effective in treating pruritus and that may act as superior treatment options for patients suffering from post-burn pruritus include gabapentin and pregabalin, topical ketamine-lidocaine-amitriptyline, opioid medications, neurokinin-1 inhibitors, antidepressants, anti-cytokines, PAR-2 inhibitors, and botulinum toxin among others.

Keywords Pruritus · Itch · Post-burn pruritus · Post-burn itch · Burn injury · Burn scar

Introduction

Pruritus is a frequent and distressing symptom of burn injuries. The vast majority of burn patients experience acute itch after their initial burn injury, and a subset of these patients continue to experience chronic itch after their scars are healed [1].

Suffering from pruritus after a burn can drastically impact one's quality of life. Itch may affect patients' mood, causing agitation, anxiety, aggression, and difficulty concentrating [1]. Activities of daily living as well as sleep are also affected by post-burn pruritus [2•]. In addition, because itch causes a scratching reflex, the wound healing process will be disrupted and infections may ensue [3].

Post-burn pruritus has been recognized for at least three decades, yet the current state of therapy is unsatisfactory [4]. This article aims to review the current literature on post-burn pruritus and its current state of treatment, as well as to discuss therapies that have potential for these patients.

This article is part of the Topical Collection on *Burns*

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Definition

Pruritus, or itch, is defined as an unpleasant sensation eliciting a desire to scratch. Post-burn pruritus is a persistent desire to scratch on a scar formed from a healing burn wound [5]. In the dermatology literature, chronic pruritus is typically defined as the sensation of itch persisting for over 6 weeks [6]. However, in the context of burns, chronic pruritus is defined as itch lasting for at least 6 months. This discrepancy in definitions is due to the changing scar environment. The literature on burns considers acute itch to last for less than 6 months, while the wound closes before the remodeling phase ensues [7••].

Epidemiology of Post-Burn Itch

The prevalence of patients experiencing pruritus following a burn injury has been noted to be as high as 93% [2•]. Although the rates of pruritus trend down as the burn injury heals, a vast majority of burn patients continue to suffer from pruritus for months and even years after the initial injury. 70–83% of

patients continue to be affected by pruritus 1 year after their burn injury, and 67–73% are affected 2 years post-burn injury [2•, 8].

It is difficult to predict who will be affected the most by pruritus following a burn, as the mechanism of post-burn pruritus is yet to be fully elucidated. However, studies have defined some risk factors that predict development of post-burn pruritus.

In Van Loey et al.'s prospective cohort study, deep dermal injury and early post-traumatic stress symptoms predicted development of itch at 3 months, 12 months, and 24 months post-burn injury. In addition, female gender predicted itching at 3 months and 12 months, but not 24 months post-burn. Finally, total body surface area (TBSA) predicted itch only at 3 months [8].

Carrougher et al. corroborated these results, finding that female gender and TBSA were early predictors of post-burn pruritus. They also found that TBSA grafted, a reflection of deep dermal injury, predicted post-burn pruritus consistently throughout the healing process. Furthermore, this study found that dry skin and thick or raised scars were predictors, while ethnicity was not a predictor in developing itch [2•].

Pathophysiology of Itch in Burns

The exact pathophysiology of developing itch in burn wounds is yet to be fully elucidated. The mechanism of pruritus itself is complex and involves various chemical mediators.

Basic Mechanism of Pruritus

In short, pruritogens activate unmyelinated C fibers in the skin. These unmyelinated C fibers have their cell bodies in the dorsal root ganglion (DRG) and transmit itch sensations centrally by way of the lateral spinothalamic tract [9••]. The C fibers can be broadly characterized as either histaminergic or nonhistaminergic neurons. Pruritogens can include molecules such as histamine, serotonin, proteases, cytokines, and neurotransmitters such as opioids and substance P [10, 11].

Histaminergic itch encompasses mainly acute itch. Chronic itch, on the other hand, stems from nonhistaminergic pathways. Nonhistaminergic itch can be activated by a variety of pruritogens other than histamine, including proteases, cytokines, and amines that activate G protein–coupled receptors (GPCRs), ion channels, and transient receptor potential (TRP) channels [9••].

Mechanism of Burn-Induced Pruritus

After experiencing a burn, the skin undergoes a process of healing consisting of three phases: an inflammatory phase, a proliferative phase, and a remodeling phase. The inflammatory phase begins in the initial days following the burn injury and consists of mediator release, tissue vasodilation, and an influx of white blood cells. The proliferative phase begins at day 4 and lasts until the third week after the injury. This is when fibroblasts are activated and collagen is secreted. The remodeling phase, when collagen is produced and broken down leading to wound contracture, continues for 6 to 18 months post-injury [7••].

Post-burn pruritus is deemed an intricate process and involves many chemical mediators. The most well-known mediator is histamine, which is released during acute inflammation in the inflammatory and proliferative phases of healing. This is due to activation of mast cells, which release histamine, and collagen production, which forms histamine as a byproduct [7••]. Therefore, histamine may play a role in the early phase of post-burn pruritus, shortly after the injury.

There are numerous other mediators released in the burn wound environment that may contribute to post-burn pruritus. Local release of substance P, neurokinin A, eicosanoids, bradykinin, and other tachykinins can bind unmyelinated C fibers and upregulate their activation [12].

Immunohistochemistry studies have shown that the burn wound environment contains numerous pruritus mediators, contributing to the complex pathophysiology of post-burn pruritus. Yang et al. found that TRPV3, a transient receptor potential vanilloid channel linked to the itch pathway, stained more strongly in the epidermis of burn scars in patients with post-burn pruritus compared with healthy skin in those same patients. Furthermore, mRNA of TRPA1 and TRPV4, known TRP channels involved in itch, showed increased expression in burn scars of patients with post-burn pruritus compared with burn scars in patients without itch [13].

Immunohistochemistry studies have also shown a significant increase in the expression of interleukin-31 (IL-31), an itchy cytokine, and its receptors, IL-31Rα and oncostatin M receptor (OSMR), in hypertrophic burn scars of patients suffering from post-burn pruritus. IL-31 and its receptors play a role in the induction of itch and have been found to be elevated in other pruritic conditions such as atopic dermatitis and prurigo nodularis [14].

Staining of deep partial-thickness burns revealed a loss of substance P–positive nerve fibers immediately after the initial burn injury. In contrast, 2 weeks post-burn, these same burn wounds reveal a higher density of substance P–positive fibers compared with healthy skin [15]. Substance P is known to activate mast cells and is implicated in the itch pathway [16].

We must also examine the central nervous system as contributing to post-burn pruritus. In an experiment by Palanivelu et al., DRG cell bodies conveying pressure, touch, and vibration sensation were decreased ipsilateral to the burn injury in rats. This subsequently caused an increase in proportion of DRG cell bodies conveying pain and itch sensations. The authors theorize that this change may cause an increase in

sensitivity of pain and itch sensations [17]. This supports the theory that post-burn pruritus is mediated at the neuronal level.

In fact, a common notion is that chronic itch involves neural sensitization, both at the peripheral and central levels. Inflammatory mediators can lead to sensitization of peripheral pruritoceptive neurons. Central sensitization, involving the spinothalamic tract, also plays a role in chronic itch, as demonstrated by alloknesis, in which a nonpruritic stimulus induces an itch sensation. The exact mechanisms of peripheral and central neural sensitization related to itch are still unclear, but the closer we get to understanding it, the better we will be able to treat pruritus [18].

Neural damage is also suggested to play a role in itch occurring in keloids, where neuropathic damage may result from scar tissue deposition. In a study by Lee et al., 86% of keloids had itch, with a portion experiencing alloknesis. These findings in combination with quantitative thermosensory testing revealing abnormal thermal and pain thresholds suggest that keloids may have a small nerve fiber neuropathy; the damage of which correlates with intensity of itch [19].

All in all, post-burn pruritus is a complicated process and involves numerous mediators of itch. To better manage this condition, we must aim treatment at both the local environment of the burn wound and the peripheral and central nervous systems.

Topical Treatments for Post-Burn Pruritus

Topical treatments can be applied directly at the site of pruritus. They are safe therapies and tend to be used as first-line agents. Figure 1 proposes a therapeutic ladder for the treatment of post-burn pruritus, starting with topical agents and working up to systemic agents.

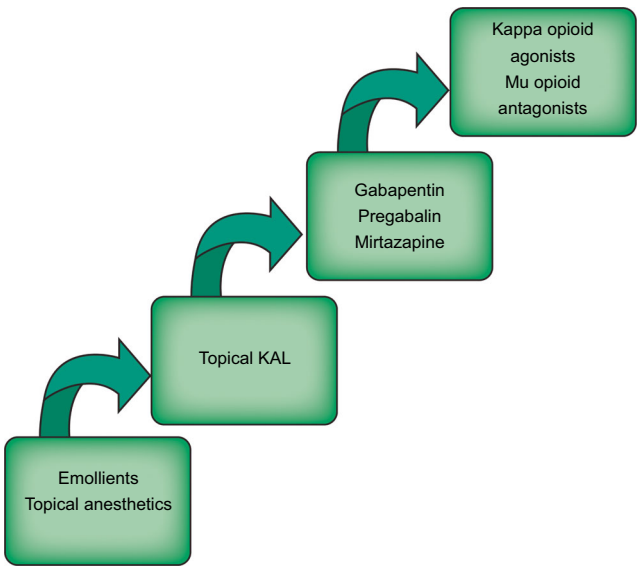

Fig. 1 Proposed therapeutic ladder for post-burn pruritus based on author's experience

Emollients

Emollients are considered a backbone for the treatment of burn injuries. Emollients include basic moisturizers, *Aloe vera*, and coconut oil. They work to moisturize the skin and improve skin barrier function [5].

Emollients are thought to be antipruritic in that they soften the stratum corneum of dry skin. When the skin barrier is impaired, more water is lost which can lead to a greater sensation of itch. This is illustrated by atopic dermatitis patients who have dramatically impaired skin barrier function, and who itch more at night when their transepidermal water loss is heightened [20].

Emollients are a necessity in healing burn wounds, to improve skin barrier function and facilitate healing. However, they may have less effect as anti-pruritics in chronic post-burn pruritus, as patients may require additional, more potent therapies.

Local Anesthetics

Topical anesthetics include pramoxine 1% cream and eutectic mixtures of lidocaine 2.5–5% and prilocaine 2.5% (EMLA) creams [20]. They work by reversibly inhibiting nerve conduction and are offered at low costs and minimal risks to patients.

Topical anesthetics only offer a short-term benefit for pruritus and are less beneficial for treatment of itch that is chronic. Additionally, use of topical anesthetics is only feasible in burns with low TBSA, as application to an increased TBSA may lead to systemic toxicity [21]. However, they may be of use for some cases of post-burn pruritus, especially pramoxine which does not cause general toxicity, as they can also treat concurrent pain that is present in the burn injury.

Topical Ketamine-Lidocaine-Amitriptyline

Topical 5–10% ketamine in combination with 5% lidocaine and 5% amitriptyline is an effective treatment for pruritus, especially neuropathic itch [22]. It is thought to work by reducing neural transmission from hypersensitive peripheral nerves. IV ketamine, which differs from topically applied ketamine in that it has central neural anti-nociceptive effects, has been studied in burn patients as an analgesic and anesthetic [23], but has yet to be studied in cases of post-burn pruritus.

Topical combination of ketamine-lidocaine-amitriptyline is a reasonable option in patients with post-burn pruritus as it will reduce firing of defective nerves by multiple mechanisms. When administered topically, ketamine carries no risk of hallucinations or delirium as seen when it is administered systemically.

Systemic Treatments for Post-Burn Pruritus

Most patients with post-burn pruritus will require a systemic agent in order to eradicate their itch. As we discuss different treatment options for post-burn pruritus, please refer to Table 1 for an outline of these systemic medications and their dosing.

Antihistamines

Antihistamines have long been the mainstay of treatment in post-burn pruritus, yet they continue to perform poorly in the treatment of burn victims' itch, similar to their lack of effect in the majority of other types of chronic itch. Antihistamines act mainly as H1 receptor antagonists and are divided into first- and second-generation antihistamines. First-generation antihistamines (e.g., diphenhydramine, hydroxyzine, and promethazine) are selective for the H1 receptor, but also bind to muscarinic, alpha-adrenergic, dopaminergic, and serotonergic receptors. This causes a side effect of sedation, which is a fundamental part of their antipruritic effect. Second-generation antihistamines (e.g., cetirizine, loratadine, and fexofenadine) are more specific antagonists of the H1 receptor and cause fewer side effects [24].

The motivation behind using antihistamines as the usual first-line therapy for post-burn pruritus rests on the increased predominance of histamine within the wound during the initial phases of healing. As mentioned before, histamine is increased during the initial inflammatory and proliferative phases of healing and by blocking its receptor, patients' pruritic symptoms may be diminished.

Although they are commonly used, their clinical utility is of minimal effect. A study by Goutos et al. found that in the acute setting, post-burn pruritus is less effectively treated with antihistamine monotherapy compared with gabapentin monotherapy. Their results indicated that only 10% of patients given chlorpheniramine monotherapy achieved satisfactory control of their pruritus compared with 41% of patients on gabapentin monotherapy. In addition, 95% of patients who received a combination of gabapentin and two antihistamines (cetirizine and cyproheptadine) received relief of their pruritus, while only 84% of patients who received combination therapy with three antihistamines (chlorpheniramine, hydroxyzine, and cyproheptadine) received pruritic relief [25].

The evidence presented in studies on antihistamines in post-burn pruritus suggests that antihistamines may be useful in relieving pruritus during the early stages of wound healing; however, during the late stages of healing burn wounds, it becomes increasingly less responsive to them [7••]. Additionally, there are more efficacious treatments available for post-burn pruritus than antihistamines, and the standard practice of antihistamines as first-line therapies should be revisited.

Gabapentin and Pregabalin

Gabapentin, a structural analog of the inhibitor neurotransmitter, gamma-aminobutyric acid (GABA), is an antiepileptic

Table 1 Systemic nonhistaminergic treatments for post-burn pruritus

Drug class	Drug name	Dosage
Neuroleptics	Gabapentin	Adults and children ≥12 years: 300–3600 mg daily, in 3 divided doses Children ≥4 years: Initial dose 10–15 mg/kg/day, can titrate up to 40–50 mg/kg/day Reduce dose in renal insufficiency
	Pregabalin	Adults: 150–600 mg daily, in 2–3 divided doses Children ≥4 years: Initial dose 2.5 mg/kg/day, can titrate up to maximum daily dose of 600 mg Reduce dose in renal insufficiency
Tricyclic antidepressants	Doxepin	10–30 mg daily
	Amitriptyline	Initial 10–50 mg daily, can titrate up to 150 mg daily
SSRIs	Paroxetine	10–50 mg daily
	Sertraline	Initial dose 24–50 mg daily, can titrate up to 150–200 mg daily
SNRIs	Mirtazapine	Initial dose 7.5–15 mg, can titrate to 45 mg daily
Mu-opioid antagonists	Naltrexone	12.5–50 mg daily
Mixed opioids	Butorphanol	1–4 mg intranasally per day
NK-1 inhibitors	Aprepitant	80 mg daily
JAK inhibitors	Tofacitinib	5–10 mg twice daily

drug and is useful in neuropathic disorders, such as those causing itch and pain [20]. Pregabalin, another structural analog of GABA, has a similar mechanism to gabapentin, but is more potent and given in lower doses. Both drugs have achieved much success in the treatment of post-burn pruritus and are becoming a standard of care.

The results of a study comparing antihistamine to gabapentin monotherapy in the remodeling phase of burn wound healing reveal gabapentin's superiority. The initial mean VAS score of patients given cetirizine monotherapy was reduced by 52%, compared with a 95% reduction seen in the gabapentin monotherapy group. When gabapentin and cetirizine were combined, patients received a 94% reduction in mean VAS scores, which was not statistically significantly different from that of gabapentin alone. Furthermore, all patients receiving gabapentin (both with monotherapy and combination therapy) reached complete relief of their pruritus by day 28, while only 3 out of 20 patients receiving cetirizine monotherapy were pruritus-free by then [26].

Pregabalin has likewise shown success in treatment of post-burn pruritus. In a randomized, placebo-controlled study, pregabalin had much greater reductions of itch compared with cetirizine and placebo. Furthermore, combination therapy of pregabalin with cetirizine produced a similar reduction in itch to pregabalin alone [24].

Gabapentin and pregabalin can even be given in combination, perhaps for patients with severe, refractory post-burn pruritus. In a study of burn patients under age 20, 91.4% of patients received pruritic relief by treatment with gabapentin monotherapy, while 100% of patients received pruritic relief with combination therapy of gabapentin and pregabalin. Researchers could not explain this finding but suggest that although similar in their molecular mechanisms, gabapentin and pregabalin do not have identical effects on target nerve fibers, but they both reduce neural itch sensitization [27].

Overall, gabapentin and pregabalin are useful drugs for post-burn pruritus. Additionally, these drugs are beneficial to burn patients as they can improve their pain management. A study showed that burn patients taking gabapentin required less morphine and rated their pain significantly lower than burn patients not receiving gabapentin [28].

Antidepressants

Antidepressants have been used successfully in the treatment of pruritus of varying etiologies. No clinical trials have evaluated the efficacy of these drugs in treating post-burn pruritus; however, they are relatively safe and reasonable options for patients suffering from pruritus refractory to other therapies. They can even be combined with gabapentin or pregabalin, to induce a stronger therapeutic effect and reduce neural sensitization, which is a common phenomenon in chronic itch. Antidepressants effective for itch include tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

Tricyclic Antidepressants

TCAs mainly work to increase serotonin and norepinephrine at nerve synapses by inhibiting their reuptake. Additionally, they are antagonists at histaminic, muscarinic, and alpha-adrenergic receptors. They can be used either as topical creams or oral medications for treatment of pruritus.

Doxepin, a particularly potent antagonist of histamine receptors, has been applied topically for treatment of pruritus for decades. Topical 5% doxepin cream has been used successfully in pruritus of varying etiologies, including atopic dermatitis, chronic urticaria, lichen simplex chronicus, and uremic pruritus. However, because of its risk of sedation and contact dermatitis when used in large amounts, 5% doxepin cream should only be applied onto limited areas of the skin and only for a short period of time [29].

Oral TCAs, including doxepin and amitriptyline, have shown success in treating pruritus of differing etiologies. They may be helpful in post-burn pruritus as they also play a role in managing neuropathic pain, and burn patients often suffer from both [4].

Unfortunately, TCAs are associated with numerous adverse effects and thus are not frequently used. These include drowsiness, blurry vision, dizziness, constipation, and urinary retention [29]. Most importantly, they are life-threatening if taken in overdoses, for they increase the QT interval leading to fatal cardiac arrhythmias and can also lower the seizure threshold [30].

Selective Serotonin Reuptake Inhibitors

SSRIs are another class of antidepressants. They work both centrally and peripherally and increase serotonin at the nerve synapse by inhibiting its reuptake. They can be useful in treating pruritus, especially when other therapies have failed [31].

Currently, there is no data on whether SSRIs would help patients with post-burn pruritus, but they should certainly be considered for refractory cases. They can especially be of use in patients with comorbid depression, anxiety, or post-traumatic stress disorder.

Serotonin Norepinephrine Reuptake Inhibitors

SNRIs work similarly to SSRIs, but inhibit the reuptake of both serotonin and norepinephrine at the presynaptic nerve terminals.

Mirtazapine, an atypical antidepressant, also has anti-adrenergic and antihistaminic properties. This medication is helpful for chronic itch, especially in cases of nocturnal pruritus. In addition, mirtazapine also helps to reduce anxiety and

depressive symptoms, and so may similarly be of use in burn patients with these concomitant symptoms [30].

Opioids

Opioid medications are often prescribed for management of pain from burn injuries. However, certain opioids may also be effective in the management of post-burn pruritus. All three types of opioid receptors (mu, kappa, and delta) show an increase in density in keratinocytes and fibroblasts of hypertrophic scars compared with that of healthy skin [32].

Opioid receptors are found both peripherally and centrally throughout the nervous system, including the skin, dorsal horn of the spinal cord, and brain. Only mu- and kappa-opioid receptors are relevant to the discussion of pruritus. Ligand binding to mu-opioid receptors induces pruritus, while ligand binding to kappa-opioid receptors inhibits pruritus.

Mu-Opioid Antagonists

Mu-opioid antagonists (e.g., naltrexone, naloxone) have shown effectiveness in the treatment of itch due to chronic urticaria, atopic eczema, end-stage renal disease, and cholestasis [33]. A case series of 15 patients receiving naltrexone for antihistamine-refractory post-burn pruritus reported that naltrexone provided relief of pruritus and improved quality of life [34]. These results were corroborated by an open trial where patients with burns covering greater than 40% of TBSA received naltrexone after unsuccessful treatment with antihistamines and/or gabapentin. Patients reported a statistically significant reduction in itch [35].

Kappa-Opioid Agonists

Kappa-opioid agonists have yet to be studied in post-burn pruritus. However, they show potential in treatment of pruritus of other etiologies. Nalfurafine, a kappa-opioid agonist available only in Japan, showed success in a phase III trial of hemodialysis patients suffering from pruritus [36, 37]. Other kappa-opioid agonists on the horizon include asimadoline, which showed reduction of pruritus in preclinical studies, and CR845, which had success in treatment of pruritus in phase II clinical trials [38].

Mixed Opioid Agonists and Antagonists

Butorphanol, a kappa-opioid agonist and partial mu-opioid antagonist administered intranasally, has shown effectiveness in treatment-refractory pruritus of differing etiologies [20]. It has yet to be studied in patients suffering from post-burn pruritus, but should be considered an option as it has a safe side effect profile, has minimal abuse potential, and has shown success in other difficult-to-treat pruritic conditions. In addition, it does not reverse the analgesic effects of coadministered opioid medications, which may be particularly of use in severely burned patients receiving pain management [39].

Nalbuphine, a newer mixed kappa-opioid agonist and mu-opioid antagonist, has been shown to have anti-pruritic effects in uremic pruritus [40]. Currently, it is undergoing clinical trials for treatment of pruritus in prurigo nodularis.

Neurokinin-1 Inhibitors

Neurokinin-1 (NK-1) inhibitors (e.g., aprepitant, serlopitant, and tradipitant) have not been studied in post-burn pruritus. Nevertheless, they have shown positive results in pruritus of other etiologies [20] and are promising drugs for reduction of itch of differing etiologies.

By antagonizing NK-1, these drugs inhibit substance P binding, preventing the release of histamine and pro-inflammatory cytokines by mast cells and keratinocytes expressing NK-1 [41]. As discussed above, burn wounds express an increased density of substance P–positive nerve fibers and since substance P is a known mediator of pruritus, these drugs may help manage this distressing symptom.

Unfortunately, aprepitant has the potential for metabolic drug interactions, as it is a weak-to-moderate inhibitor as well as inducer of CYP3A4 and CYP2C9 [42]. In addition, it is extremely expensive. Serlopitant and tradipitant, currently undergoing investigation in clinical trials, have demonstrated better side effect profiles in patients suffering from chronic pruritus, and therefore may be better tolerated by patients [43, 44].

Anti-Cytokines

Janus kinase (JAK) inhibitors, such as tofacitinib, are antipruritic and have recently shown anti-pruritic effects for itch from psoriasis and eczema. They have not yet been studied in post-burn pruritus.

Tofacitinib, an oral JAK inhibitor, was studied in two randomized phase III trials in patients with moderate-to-severe plaque psoriasis and was found to improve pruritus compared with placebo treatment [45]. Similarly, topical tofacitinib was studied in a randomized phase IIa trial, where it was found to significantly decrease pruritus in patients with atopic dermatitis, even as early as after 1 day of treatment [46].

Pruritus induced by cytokines is mediated in part by the JAK/STAT pathway, which can drive chronic pruritus [9••]. Post-burn pruritus involves numerous cytokines, and sometimes, treatment requires targeting of multiple pathways involved in mediating pruritus. JAK inhibitors may be useful in post-burn pruritus because by blocking this pathway, signaling through IL-2, IL-4, IL-7, IL-9, IL-13, IL-15, IL-21, and IL-31 is inhibited, thereby downregulating inflammation through multiple targets [46].

Another method to treat pruritus is to block specific cytokines through their receptor antibodies. Nemolizumab, an IL-31 receptor antibody, was effective and well-tolerated in patients with pruritus from atopic dermatitis in a phase II randomized, double-blind, placebo-controlled trial [47]. Nemolizumab is currently undergoing phase II clinical trial for treatment of itch in prurigo nodularis.

PAR-2 Inhibitors

Protease-activated receptor-2 (PAR-2) is a cell surface sensor that mediates itch by binding proteinases such as tryptase and chymase, leading to C fiber activation [12]. The cell-penetrating pepducin, PZ-235, is a potent inhibitor of PAR-2 and was shown to reduce itch in mouse models of atopic dermatitis [48].

Thalidomide

Thalidomide can be used off-label as an anti-pruritic agent and has been reported to be useful in cases of prurigo nodularis and uremic pruritus. Its anti-pruritic effects are thought to be due to its mechanism of central depression, anti-inflammatory properties, and immunomodulatory and neuromodulatory actions [49]. However, thalidomide carries risk of teratogenicity and other adverse effects such as neuropathy. Therefore, it is limited in its use and can only be used for periods of up to 1 year [20].

Ondansetron

Ondansetron is a 5HT-3 receptor antagonist primarily used for prevention of nausea and vomiting in chemotherapy patients. As for itch, there is limited literature that mentions ondansetron as being helpful in treatment of pruritus secondary to uremia and cholestasis, and a systematic review comparing five randomized clinical trials concluded that ondansetron has negligible effect in treating pruritus from these conditions [50].

A double-blind, randomized, crossover trial comparing a single dose of ondansetron to diphenhydramine for treatment of pruritus in burn wounds found that ondansetron created a greater reduction in itch scores [51]. This is the only study available on ondansetron treatment in post-burn pruritus. Reduction of itch scores in this study was not dramatically greater in the ondansetron group compared with the diphenhydramine group, there was a small sample size of patients, and the study duration was only 2 days long. In our opinion, ondansetron arguably has no clinical significance in the treatment of pruritus.

Alternative Treatments

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) is a non-invasive therapy involving application of electrodes onto the skin that transmit controlled, low-voltage electrical impulses targeting the nervous system [7••]. Most of the burn literature on TENS discusses its efficacy in the management of pain. However, TENS has also been shown to significantly reduce post-burn pruritus. A pilot study by Hettrick et al. showed a statistically significant reduction in VAS scores of patients with post-burn pruritus after undergoing TENS for a 3-week period [52]. TENS can be considered as an option for post-burn pruritus patients refractory to other therapies, or for those who do not want drugs or invasive treatment.

Botulinum Toxin

From the bacterium *Clostridium botulinum*, botulinum toxin prevents release of acetylcholine at receptors on C fibers, thereby preventing their activation and sensitization [53]. By this mechanism, botulinum toxin has shown effectiveness in the treatment of pruritus, particularly of neuropathic origin [54].

A prospective study showed favorable results in patients with post-burn pruritus injected with botulinum toxin. After only 4 weeks, all nine burn patients with recalcitrant itch no longer reported having pruritus and spent an average of 6.3 months pruritus-free (range 3–18 months) [53]. More clinical studies need to be performed on the utilization of botulinum toxin for post-burn pruritus to further evaluate its efficacy.

Progressive Muscle Relaxation

Several stress reduction methods and psychological interventions have been used to help reduce itch intensity, such as progressive muscle relaxation (PMR). This technique has shown success in patients suffering from chronic itch [55].

Other additional stress reduction methods that may be considered for treatment of post-burn pruritus include autogenic training, another form of relaxation therapy, and meditation. These stress reduction techniques may be especially useful in patients who report that their itch intensifies during periods of stress and should be considered as adjunctive treatments [55].

Conclusion

Post-burn pruritus is a bothersome complaint that affects the quality of life and the recovery of burn patients. It is critical to be able to recognize and to develop an understanding of this condition. In a study evaluating the priorities of burn

survivors, they ranked "itching and edema on scars and donor places" as what they would place highest priority to in research [56]. Therefore, it should also be of concern to physicians and researchers in the field.

In this review, we outlined various treatments for pruritus, wherein some of which have already been reported for post-burn patients, as well as other novel ones that have the potential in reducing post-burn pruritus. Therefore, as we better recognize the specific pathophysiology of post-burn itch, we will be able to develop more targeted treatments for this relentless itch.

Compliance with Ethical Standards

Conflict of Interest Dr. Yosipovitch reports grants and personal fees from TREVI, grants and personal fees from Menlo, personal fees from Sienna, personal fees from Galderma, grants and personal fees from Pfizer, grants and personal fees from Sanofi/ Regeneron, personal fees from Novartis, personal fees from Opko, personal fees from Bayer, and grants from Sun Pharma, outside the submitted work. Dr. Fowler has nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
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