Introduction

Pruritus is an unpleasant sensation that evolved for the purpose of defense against harmful ectoparasites. Physiologically, it simulates pain in terms of genesis and transmission but evokes a different behavioral response of scratching. The itch-scratch reflex is executed locally at the spinal level with precise regulation by higher brain centers. Clinically, pruritus can be defined as localized or generalized, depending on the extent of involvement or as acute and chronic, depending on the duration of the symptom. In the past, pruritus was regarded solely due to the dermatological origin, but now, it is better understood that it can be a signaling symptom of several systemic disorders such as hepatobiliary disorders, chronic kidney disease, hematological, endocrine abnormalities, neuropsychiatric diseases, and even malignancies. This review will focus on various topical and systemic pharmacological agents used in the management of pruritus of systemic origin.

Key words: Itch, pruritus, review, scratch

Pruritus of Hepatobiliary Origin (Cholestatic Pruritus)

Pruritus occurs in approximately one-fifth of the hepatic patients. Prevalence is greater in intrahepatic causes as compared to extrahepatic cholestasis. Several mechanisms explain pruritus in cholestatic liver disease:

- Accumulation of toxic pruritogens
- Imbalance in endogenous opioid system
- Autotaxin (ATX), mediated conversion of lysophosphatidylcholine into lysophosphatidic acid (LPA), which, in turn, correlates with the itch response.

Commonly used antipruritic medications such as antihistamines and glucocorticoids are ineffective in cholestatic pruritus; however, partial benefits may be observed due to their sedative properties. Pruritus associated with extrahepatic bile duct obstruction responds promptly to the restoration of biliary drainage. The following drugs are frequently used:

Bile acid therapy

Drug in this class is ursodeoxycholic acid (UDCA). It is frequently used to treat cholestasis of a range of causes, including cholestasis of pregnancy and primary biliary cholangitis. In intrahepatic cholestasis of pregnancy (ICP), UDCA improved itch and liver enzymes in several randomized placebo-controlled trials. It is the preferred drug for the management of ICP. The recommended dose is 10–15 mg/kg in two to three divided doses.

Anion exchange resins

Cholestyramine, colestipol, and colesvelam are nonabsorbable anion exchange resins enhancing the intestinal excretion of pruritogens in bile. Several randomized controlled trials (RCTs)
involving cholestyramine use have derived heterogeneous results. However, one small, double-blinded RCT showed a beneficial effect in ten patients, using cholestyramine 9 g daily orally.[6] The recommended dose of cholestyramine is 4–16 g daily, initiated with 4 g administered orally before and after breakfast. Common adverse effects include bloating, constipation, malabsorption of nutrients, and coagulopathy. It can be considered as a first-line treatment in patients with hepatic pruritus.

**Hepatic enzyme inducer**

Drug in this class is rifampicin. It is regarded as a second-line treatment for cholestatic pruritus. It partially ablates cholestatic pruritus by the pregnane X receptor-dependent transcriptional inhibition of ATX expression.[7] Furthermore, it may have an anti-opiate effect. It should be started at a dose of 150 mg twice daily if serum bilirubin is >3 mg/dl and 150 mg three times daily if serum bilirubin is <3 mg/dl, with gradual dose escalation to 600 mg twice daily. Rifampicin can be hepatotoxic, and liver tests should be monitored.

**Opioid agonists/antagonists**

These are recommended as third-line therapy. The μ-opioid antagonist, naltrexone, in a daily dose of 50 mg orally is found to be effective in pruritus of hepatobiliary disease. Nalmefene (0.25–1 μg/kg/day intravenously), methyl naltrexone, and naloxone may be alternative opioid antagonists to naltrexone.[8] Possible adverse effects with these agents are opiate withdrawal-like syndrome, but this can be avoided by initiating treatment with naltrexone at a low dose of 12 mg or intravenous infusion of naloxone, followed by stepwise dose increase. Naltrexone can be hepatotoxic.

**Selective serotonin reuptake inhibitor**

Selective serotonin reuptake inhibitors (SSRIs) increase the threshold of itch generation. Several RCTs revealed the efficacy of sertraline in hepatic pruritus in a daily dose of 75–100 mg.[9] Sertraline is considered the fourth-line treatment option in the management of cholestatic pruritus. Ancedotal reports of successful treatment of cholestatic pruritus include the use of intravenous lidocaine, flumecinol, antioxidants, parenteral ondansetron (5-HT3-receptor antagonist), ultraviolet B phototherapy, and androgens.[10]

**Future prospects**

A novel approach could be inhibiting the apical sodium-dependent bile acid transporter that plays a physiological role in the absorption of the bile acid in the ileum. Several studies including Phase 2 trials have shown their possible effectiveness in the treatment of cholestatic itch.[11] Agents inhibiting ATX or its product, LPA, may also be of interest in the future therapy of cholestatic itch.[12]

**Uremic Pruritus**

Uremic pruritus (UP) is a consequence of underlying pathophysiologic alterations related to chronic kidney disease. Nearly 40% of patients with end-stage renal disease experience moderate-to-severe pruritus. There is a proposed role of several factors including increased systemic inflammation, abnormal serum parathyroid hormone, calcium and phosphorus levels, an imbalance in opiate receptors, and a neuropathic process. Additional contributors are xerosis and anemia. Therapeutic modalities available are topical and systemic agents, phototherapy, acupuncture, and surgical methods. Adequate dialysis, calcium and phosphate homeostasis, correcting anemia, and xerosis are prerequisite before shifting to antipruritic medication.

UP is often generalized in nature. Thus, it would be impractical to use topical agents. However, liberal use of emollients for adequate skin hydration is an important component of therapy.[13] Drugs frequently used in battling UP include:

**Topical pharmacotherapy**

The evidence for most of the topical therapies is not of high quality; still, the following drugs find mention in the literature.

a. A single-center, double-blind RCT observed superior antipruritic action of 1% pramoxine hydrochloride as compared to placebo, in patients on hemodialysis.[14]

b. Cromolyn sodium (4%) relieves UP by stabilizing mast cells and indirectly inhibiting the activation of sensory nerves.[15] Tacrolimus and calcitriol have antipruritic effects by virtue of alteration of local immunological milieu.[16,17]

c. Capsaicin (0.025%) is a natural alkaloid extracted from chili peppers. It alleviates uremic pruritus by depleting neuropeptides in peripheral sensory neurons which, in turn, interferes with the conduction of itch.[18]

d. Topical gamma-linolenic acid relieves the uremic itch by modulating lymphokines and prostaglandin synthesis.[19]

e. A recent observation found a significant reduction of uremic xerosis and pruritus with topical preparation containing structured lamellar lipids and endocannabinoids: N-acetylethanolamine and N-palmitoylethanolamine.[20]

**Systemic pharmacotherapy**

Systemic medications reported to be beneficial in patients with UP are exhaustive and include gabapentinoids, activated carbon, cholestyramine, opioid agonists/antagonists, thalidomide and pentoxifylline, nicergoline, a leukotriene inhibitor, and antihistamines. However, evidence for the efficacy of most of these systemic therapies is not robust and derived out of small open-label studies and case series.

a. Gabapentinoids suppress UP by their neuromodulatory action mediated through binding voltage-gated calcium channels.[21] This class includes gabapentin and pregabalin. Gabapentin is typically dosed at 50–100 mg at night. About 300 mg three times weekly for 4 weeks has also been found to be safe and effective in double-blind studies.[22] Pregabalin is a similar drug that has been reported to reduce chronic itch in dialysis. Therapy with 75 mg of pregabalin orally twice weekly was compared, either to ondansetron or placebo, and was found effective.[23] The
only oral agents that have produced consistent results in UP are gabapentinoids.

- Activated carbon and cholestyramine may abate UP by sequestering putative pruritogens in the intestinal lumen.[24,25]
- Presuming the imbalance in opioid receptor expression as one of the mechanisms in UP. Naltrexone (µ-receptor antagonist), nal啡urine (κ-receptor agonist), and butorphanol (κ-agonist and µ-antagonist) have been evaluated in various clinical trials with variable efficacy.[26,27]
- Thalidomide and pentoxifylline are anti-inflammatory agents with TNF-alpha antagonizing action. These agents have been found useful in refractory UP across different studies.[28,29]
- As for other oral medications, few small-scale studies have shown the efficiency of ketotifen 1 mg daily and doxepin 10 mg twice daily in the treatment of UP due to their additional mast cell stabilizing property.[30] There have been conflicting reports of the efficacy of 5-HT3 receptor antagonists (ondansetron) in UP. Uremic itch threshold can be modified using serotonin–norepinephrine reuptake inhibitors (SNRIs) (mirtazapine) and SSRIs (sertraline).[31]

UP is associated with increased mortality. Renal transplantation is the only definitive treatment for this condition.

### Hematological Pruritus

Pruritus is often associated with hematological disorders including iron deficiency, hemochromatosis (iron overloading state), myeloproliferative disorders, lymphomas, and leukemias.

- Iron deficiency may present with generalized pruritus with or without anemia and other signs of iron deficiency. Iron is an important cofactor for enzymatic activities, and its deficiency may lead to metabolic alteration and thus pruritus.[32] The management of such pruritus includes iron supplementation in addition to treating underlying causes of iron deficiencies such as alcoholism, malabsorption, occult bleeding, and malignancies
- Pruritus in lymphoma and leukemia may imply bad prognosis but improves after radiation therapy or chemotherapy
- Aquagenic pruritus of myeloproliferative disorder is characteristically precipitated by contact with hot and cold water, sweating, and alcohol. Basophilic granulocytes play a key role in triggering the symptoms.

The recommended measures to manage pruritus in such disorders are the use of salicylates, alkalinization of bathing water, topical capsaicin treatment, systemic therapy with antihistaminic and antiserotonergic drugs (cyproheptadine, paroxetine, and pizotifen), or phototherapy.[33] Cytochrome therapy with agents such as hydroxyurea and interferon-alpha 21 has also been found to be effective in the control of pruritus associated with polycythemia vera.[34]

### Endocrine Disorders

- **Pruritus is common in thyroid diseases.** About 4%–11% of hyperthyroid patients present with pruritus which is attributed to increased skin temperature and decreased itch threshold. Treatment with antithyroid medication along with antihistamines would effectively suppress the itch. Hypothyroidism-associated xerosis is responsible for evoking pruritus which usually responds to liberal use of emollients and thyroid hormone replacement.[35] Subtotal parathyroidectomy may improve pruritus associated with abnormal parathyroid gland activity.[36]

- **Pruritus associated with diabetes mellitus has multiple mechanisms, i.e.,** due to bacterial and fungal infection, metabolic abnormalities, autonomic dysfunction with anhidrosis, diabetic neuropathy, and antidiabetic drugs.[37] Judicious use of antibiotics, barrier restoration, hygroscopic emollients, and neuromodulators along with strict control of blood sugar is all that is required
- It is to be emphasized that hormonal replacement therapy in women may relieve vulvar pruritus of postmenopausal period.[38]

### Pruritus Associated with Malignant Solid Tumors

Solid malignant tumors are a relatively rare cause of pruritus. Generalized pruritus in malignancy can be multifactorial—a true paraneoplastic symptom, secondary to paraneoplastic neuropathy, a consequence of secondary skin involvement by cutaneous or noncutaneous primary tumors, or a side effect of cancer treatment. Generalized pruritus has been described in breast, colon, lung, testicular, and stomach cancers; insulinoma; gastric carcinoid; and thymoma.[39]

Treatment of the malignancy can often help to resolve pruritus.

- **Anticancer drugs and biologics can also trigger pruritus and require modification or discontinuation of medications**[40]
- **Antihistamines are generally ineffective in pruritus due to solid tumors**
- **Kappa opioids and neuroleptics are of some use in reducing bothersome pruritus**
- **SSRIs such as paroxetine 20 mg daily, and SNRI such as mirtazapine 15–30 mg daily, may have a role in the management of malignant pruritus.**[41] These medicines are thought to act centrally and may take up to 2–3 weeks to become clinically beneficial
- **Granisetron, a 5-HT3 receptor antagonist, has been used in a case of pruritus in advanced malignancy, where a continuous infusion (3 mg/24 h) resulted in a prompt reduction in pruritus in 2 h.[42]**
- **Substance P is a key mediator of pruritus, and blockade of its receptor, neurikinin-1 (NK-1), can be of some use. NK-1 receptor antagonist aprepitant had a 91% response rate, defined by >50% reduction in pruritus response at week 12, was non-inferior to placebo in reducing pruritus in patients with advanced cancer.**[43]
intensity in 45 patients with metastatic solid tumors.\textsuperscript{43} Aprepitant treatment has been used with success for pruritus associated with both malignant and nonmalignant conditions in at least 74 patients\textsuperscript{44}
g. Thalidomide may be used as a last resort for the management of cancer-related pruritus in a palliative care situation.\textsuperscript{45}

**Neuropathic and Psychogenic Pruritus**

Neuropathic pruritus refers to any dysfunction along the afferent itch pathway that results in a feeling to scratch. Nearly 8\%–19\% of patients with chronic pruritus have an underlying neuropathic cause.\textsuperscript{46} Allokinesis resulting from neural sensitization is frequently associated with neuropathic itch. Disorders of the peripheral nervous system associated with neuropathic pruritus are postherpetic neuralgia, nostalgia paraesthetica, brachioradial pruritus, and prurigo nodularis. Structural or functional dysfunction in the central nervous system may underlie the pruritus of transverse myelitis, syringomyelia, stroke, and multiple sclerosis.

Psychogenic itch can be defined as an itch disorder where the itch is at the center of the symptomatology and where psychological factors play an evident role in the triggering, intensity, aggravation, or persistence of the pruritus. Although a purely psychogenic itch is a rare phenomenon in dermatology clinics, diagnosis can be established after ruling out related organic causes and with aid of the French Psychodermatology Group Diagnostic Criteria.\textsuperscript{67}

Commonly prescribed antipruritic medicines such as antihistamines and corticosteroids have a limited role in management. Treatment options include:

- Mild-to-moderate neuropathic itch can be controlled by topical application of local anesthetic preparations (lidocaine, pramoxine, and eutectic mixtures), cooling agents (menthol), capsaicin, and strontium hydrogel\textsuperscript{48}
- Topical acetylsalicylic acid may be helpful in reducing itch intensity in postherpetic neuralgia\textsuperscript{49}
- Systemic agents are required for severe and refractory cases. These agents have a direct or indirect influence on the neural transmission by blocking either ion channels or modifying neurotransmitters level at the synapse
- The most widely used agents are gabapentinoids. Gabapentin is approved by the USFDA for the treatment of postherpetic neuralgia and is also effective for postherpetic itch and other neuropathic itches
- Additional alternatives are oxcarbazepine, SSRIs (serotonin), tricyclic antidepressants (amitriptyline), SNRIs (mirtazapine), and neurokinin receptor antagonist (aprepitant)\textsuperscript{50}
- About 1–4 mg of intranasal butorphanol can reduce symptoms in patients with a refractory itch.\textsuperscript{51} However, clinical evidence for the use of opioid agonist and antagonists for neuropathic itch is lacking
- NMDA receptor antagonist (intravenous ketamine: 0.5 mg/kg) and oral lidocaine analogs, mexiletine, are the potential therapeutic option for the treatment-refractory neuropathic itch\textsuperscript{52}
- For psychogenic pruritus, the drug armamentarium is the same as that for neurological itch with an addition of antipsychotic preparation for delusional disorders such as pimozide and risperidone\textsuperscript{63}
- Potential future treatments involve the development of agents targeting neurokinin-1 receptors, transient receptor potential channels, and Mas-related G-protein-coupled receptor.

**Conclusion**

Systemic diseases can be a cause of chronic intractable pruritus. Although there are a number of topical and systemic medications available for use, the evidence for a large number of these therapies is not of a very high order. The better understanding of the pathophysiology of itch will lead to a more targeted approach in the future.

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There are no conflicts of interest.

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