Pruritus in palliative care

Getting up to scratch

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Mrs P. is an engaging 75-year-old woman you have known for more than 20 years. She has end-stage renal disease and is receiving hemodialysis 3 times a week. Over the past few months, her function has declined considerably. She has had mild pruritus for a long time, but recently it has been worse, keeping her up at night and "making her crazy." Today she tells you that she has "a terrible itch all over." Antihistamines are not helping.

Pruritus or itch (both terms are used interchangeably throughout this article) is not the most common symptom seen in palliative care, but can be very distressing and can adversely affect quality of life. Pruritus can be described as an unpleasant sensation of the skin or mucous membranes that provokes the desire to scratch or rub.[1-3] Pathophysiology of pruritus is important and guides effective therapeutic choices. There are 4 categories of pruritus: prurioreceptive, neuropathic, neurogenic, and psychogenic.[2,3]

Prurioreceptive pruritus occurs when the itch originates in the skin. The sensation begins in the free nerve endings of the skin; it is transmitted by dedicated unmyelinated C fibres to the posterior horn and relayed via the spinothalamic tract to the brain, where it is perceived as itch. The motor reflex to scratch stimulates Aδ sensory fibres, which in turn block the sensation of itch.[2-5]

Several chemical mediators (ie, pruritogens) stimulate the C fibres. Although histamine (through histamine–type 1 [H_1] receptors) is the best known pruritogen, there are several others, including serotonin (through 5-hydroxytryptamine [HT] receptors 2 and 3), cytokines, opioids (endogenous and exogenous, through μ-opioid and κ–opioid receptors), and neuropeptides (such as substance P), that can play a role.[2] Both opioidergic and serotonergic systems have been proposed as central regulators of pruritus.[6] Some pruritogens act by releasing histamine from mast cells and others act independently, which explains why not all itching sensations respond to treatment with antihistamines. Even when pruritus is responsive to antihistamines, there might be central sensitization and decreased response if the itch is chronic.[4] Further study is needed to understand this process.

Neuropathic pruritus, another category of pruritus, occurs when there is damage anywhere along the afferent pathway, as with postherpetic itch or itch secondary to brain tumour.

The third category of pruritus, neurogenic, is centrally induced and is unresponsive to antihistamines.[4,5] Both opioid and serotonin receptors can reset the itch threshold centrally by altering the central inhibitory circuits.[6] Examples of neurogenic pruritus include uremic and cholestatic itch.

The fourth and least common category, psychogenic pruritus, is associated with psychiatric disorders.[3,5]

Clinical manifestation

Although it is normal to experience occasional mild or moderate pruritus, the severe pruritus seen in patients with advanced disease is usually associated with uremia (chronic renal failure), cholestasis, opioids, solid tumours (paraneoplasia), and hematologic disorders. Dry skin also accompanies many of these conditions.

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BOTTOM LINE

- Histamine release does not play a meaningful role in the pruritus typically observed in palliative patients; therefore, antihistamines are not usually beneficial.
- Emollients should always be considered, as dry skin is often an exacerbating factor for most palliative patients with pruritus.
- Consider treating pruritus secondary to uremia, cholestasis, or malignancy with paroxetine or mirtazapine.
- In certain cases, stenting for biliary obstruction is an effective nonpharmacologic treatment that often obviates pharmacotherapy, eliminating potentially adverse side effects.

POINTS SAILLANTS

- La libération d'histamine ne joue pas de rôle important dans le prurit typiquement observé chez les patients en soins palliatifs. Par conséquent, les antihistaminiques ne sont habituellement pas bénéfiques.
- Il faudrait toujours envisager l'utilisation d'émollients parce que la sécheresse de la peau est souvent un facteur d'exacerbation du prurit chez la plupart des patients en soins palliatifs.
- Envisagez de traiter le prurit secondaire à l'urémie, à la cholestase ou au cancer avec de la paroxétine ou de la mirtazapine.
- Dans certains cas, un stent pour une obstruction biliaire est un traitement non pharmacologique efficace qui élimine souvent la nécessité d'une pharmacothérapie et la possibilité d'effets secondaires indésirables.

Chronic renal failure. Pruritus secondary to chronic renal failure presents in nondialysis and dialysis patients alike. It can be generalized or localized and paroxysmal or continuous. There are multiple possible causal factors and current treatments to target these factors. For example, most uremic patients have dry skin, in which case emollients are suggested and can be combined with all treatments.[5,7] Ultraviolet B light therapy can be helpful, although the exact mechanism of action remains unknown. Antihistamines are not usually helpful in pruritus secondary to chronic renal failure, so histamine is unlikely to be a contributing factor.[5,7-9] Paroxetine and mirtazapine can be tried, as serotonin regulation is likely involved.[10,11] Cholestyramine might help with increased concentrations of bile acids seen in uremic patients. Opioid antagonists have been used for the purported opioid receptor imbalance.[7]

Cholestasis. Cholestasis is commonly associated with pruritus, but the pathogenesis is still unclear. There is no correlation between the level of bile acids and the degree of pruritus, which explains why lowering the level of bile acids with cholestyramine is often ineffective. Another postulated mechanism is altered central opioidergic transmission; for that reason, opioid antagonists are used.[8,9] Other possibilities include increased serotonin release, for which paroxetine, mirtazapine, or ondansetron can be prescribed. Again, histamine might be involved but to a lesser extent, as antihistamines are generally ineffective. Ultraviolet B light therapy is also an option.[5,8,9,12-15]

Opioid-induced itch. Opioid-induced itch is more common with spinal opioids than with systemic opioids. The exact mechanism of opioid-induced pruritus is unknown; however, it is thought to be centrally mediated by μ-opioid receptors and inhibited by κ-opioid receptors. Opioids might also activate serotonin pathways, which explains why ondansetron (a 5-HT_3 receptor antagonist) relieves itch secondary to spinal morphine.[5,16,17]

Solid tumours. Solid tumours can be associated with paraneoplastic pruritus, which in fact might be the presenting symptom that precedes the diagnosis by months or years. The pathophysiology is not well understood, but appears to involve an immunologic reaction to tumour-specific antigens. Antihistamines are ineffective. The itch can be generalized or tumour specific: scrotal itch in prostate cancer, perianal itch in colorectal cancer, or vulvar itch in cervical cancer. Solid tumours can also cause pruritus via biliary obstruction (eg, in pancreatic cancer); in such cases, decompression through stenting can be very effective.[5,6,8,9,16]

Hematologic disorders. Pruritus associated with hematologic disorders, such as lymphoma and polycythemia vera, is more common than pruritus associated with solid tumours. Pruritus is present in approximately 30% of patients with Hodgkin disease and might precede the diagnosis by up to 5 years. In polycythemia vera, 30% to 50% of patients have itching after contact with water. Although these patients have increased histamine levels, H_1 receptor antagonists are ineffective.[5,6,8,9,17]

Treatment

Regardless of the cause of pruritus in palliative patients, general skin care measures are important. Xerosis, or dry skin, can accompany all causes of pruritus in palliative patients; therefore, a mainstay of general management is to regularly lubricate the skin, especially after bathing. Bathing should be minimized and tepid water with mild, unscented soap should be used. Other general measures include wearing loose, nonirritating clothing and avoiding fragrant topical agents. A cool, humidified environment is ideal.[2,5,18]

Topical agents other than emollients can also be helpful. Substituting itch with the preferred sensation of cooling can be achieved with topical agents containing 1% menthol or 0.5% to 2% phenol. For localized areas of itch, agents such as 2.5% lidocaine cream can anesthetize sensory nerve endings; however, large quantities of lidocaine cream should be avoided owing to potential toxicity when absorbed. Localized areas of itch might also respond to agents that block mediators of pruritus—for example, capsaicin, which depletes the neuropeptide substance P. If there is localized inflammation, topical corticosteroids can also be useful.[5,18]

Nonpharmacologic treatments. Ultraviolet B light therapy is thought to act by decreasing the number of mast cells and free nerve endings in the skin. It is often done 3 times a week; although it is most useful in pruritus secondary to uremia, it can also help with cholestasis and malignant skin infiltrations.[5,19] This regimen, however, is impractical for palliative patients toward end of life.

Another nonpharmacologic approach to pruritus, specific to cholestasis, is the placement of a stent to decompress biliary obstruction. Such obstructions are commonly observed in pancreatic cancer patients. This procedure might negate the need for any pharmacologic treatment, thus eliminating potential adverse side effects of certain drugs.

Pharmacologic treatments. Previously, H_1 receptor antagonists were the drug of choice for any type of pruritus. In fact, they are helpful only in cases in which histamine release occurs in the skin. This is, unfortunately, neither the only nor the biggest cause of pruritus seen in palliative care. In the past they might have appeared to work ubiquitously, perhaps owing to first-generation sedating effects.

Paroxetine is a serotonin reuptake inhibitor; because serotonin might have a role in pruritus secondary to

Table 1. Treatment options for pruritus secondary to advanced disease in palliative care

TREATMENT	MECHANISM OF ACTION	INDICATION(S)	CONSIDERATIONS	
			POSITIVE	NEGATIVE
Nonpharmacologic				
General skin care[2,5,7,20] • Emollients • Minimize bathing • Tepid water • Mild, unscented soap • Loose, nonirritating clothing • Avoid fragrant topical agents • Cool, humidified environment	Soothes inflamed skin and prevents futher abrasions, eruptions, or irritations	Dry skin	Dry skin is associated with many other causes of pruritus	NA
UVB light therapy[5,21]	Decreases the number of mast cells and free nerve endings in the skin	Cholestasis Uremia Malignant skin infiltration	NA	Procedure often required 3 times/wk; impractical at end of life
Biliary stenting[5,6,8,9,18]	Relieves obstruction in the bile ducts	Cholestasis due to biliary obstruction	Might negate need for pharmacotherapy	NA
Pharmacologic				
Lidocaine 2.5% cream (topical anesthetic)[18]	Anesthetizes sensory nerve endings	Localized areas of itch	Appropriate regardless of cause of pruritus	Large quantities of cream can cause toxicity when absorbed
Paroxetine (antidepressant)[5,10,11,21,22]	5-HT_3 reuptake inhibition	Cholestasis Uremia Opioid-induced pruritus Malignancy	Effects within 24 to 48 h Few side effects	NA
Mirtazapine (antidepressant)[10,11,21,22]	5-HT_2, 5-HT_3, and H_1 receptor antagonists	Cholestasis Uremia Opioid-induced pruritus Malignancy	Effective	Sedation Weight gain
Ondansetron (antiemetic)[5,14,15,17,22]	5-HT_3 receptor antagonist	Cholestasis Uremia Opioid	NA	Expensive Constipation
Dipenhydramine (antihistamine)[5,7,8,9]	H_1 receptor antagonist	Allergy Histamine-mediated pruritus	Inexpensive	Sedation Rarely effective
Naloxone or naltrexone (opioid antagonist)[5,16,17,22]	μ-Opioid receptor antagonist	Cholestasis Uremia Opioid-induced pruritus	NA	Reverses analgesia Expensive

5-HT—5-hydroxytryptamine (serotonin), H_1—histamine–type 1, NA—not applicable, UVB—ultraviolet B.

malignant disease, as well as cholestasis, uremia, and opioids, it is therefore reasonable to try the drug in palliative patients with pruritus secondary to any of these illnesses. Patients can start with small doses, such as 5 to 10 mg nightly, which will cause fewer side effects than higher doses. Effects can usually be observed within 24 to 48 hours.[5,11,19,20]

Mirtazapine is an antidepressant with 5-HT_2, 5-HT_3, and H_1 receptor antagonist properties. As with paroxetine, it can be used for uremic, cholestatic, and malignant pruritus. Treatment usually begins with a 15-mg dose nightly, but a lower dose of 7.5 mg to begin is also effective. Mirtazapine has few side effects.[10,19,20]

Ondansetron, a 5-HT_3 receptor antagonist, can be used for pruritus associated with opioids, cholestasis, and uremia. It is fairly expensive though and can cause constipation, with which palliative patients are often afflicted.[5,14,20]

Naltrexone and naloxone have previously been used to treat uremia, cholestasis, and opioid-induced pruritus, as μ-opioid receptor agonists are central mediators of pruritus.[5,20-22] However, these drugs are often inappropriate in the palliative population. Palliative patients might be using opioids for the management of pain or dyspnea, and opioid antagonists could reverse analgesia or lead to withdrawal symptoms. For opioid-induced pruritus secondary to systemic opioids, the initial strategy is to rotate to a different opioid. Spinal opioids are often given with bupivacaine, which decreases itch as well.

Treatment options are summarized in **Table 1.**[2,5-11,14,16-18,20-22]

You advise Mrs P. to discontinue the antihistamines, as they are not likely helping with her itch. You review the general principles of dry skin care and recommend emollients, bathing less often, etc. You also prescribe a small dose of paroxetine (5 mg each night at bedtime). Within 48 hours, her pruritus has improved dramatically.

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Competing interests
None declared

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