Pruritus (severe itching) associated with advanced disease is an under-recognised and under-treated symptom (Hudson et al, 2015). Although severe itching is a common symptom that usually causes no concern, when it occurs as a result of advanced disease it can become overwhelming. The effects are outlined in Box 1.

The prevalence of pruritus within the palliative care setting is uncertain. Teunissen et al (2007) suggested that problematic itching is experienced by 10% of patients with incurable cancer. However, estimates are influenced by underlying diagnosis (Weisshaar et al, 2015) and the source of information; for example, a lower prevalence is found when information is obtained from medical records than when obtained via patient questionnaire (Teunissen et al, 2007).

Although the presenting symptom of itching is the same, pruritus may be the consequence of a variety of underlying diseases and pathological mechanisms (Xander et al, 2013); management is therefore challenging because there are no definitive treatment options. While a limited number of controlled trials have been undertaken assessing treatments for systemic itch, study sizes are often small and results difficult to generalise (Xander et al, 2013; Zylicz and Krajnik, 2009).

Pathophysiology

Although the sensation of itch is confined to the skin and mucous membranes, the underlying cause of pruritus may originate peripherally in the skin or centrally (Twycross et al, 2003). Four classes of itch have been identified, depending on the underlying mechanism (Table 1):

- Pruritceptive;
- Neuropathic;
- Neurogenic;
- Psychogenic (Twycross et al, 2003).

Pruritceptive itch originates from the skin due to the stimulation of free nerve endings of specialised C-fibres, which lie close to the junction between the epidermis and dermis. The C-fibres are similar but distinct from nerves associated with transmission of pain.

Several chemical mediators (pruritogens) are known to stimulate the specialised C-fibres and induce itch; the best known is histamine, which is implicated as the cause of itch in several frequently encountered conditions, including insect bites and stings. However, histamine seems to play little or no part in other forms of itch, such as symptoms relating to systemic disease.

The sensation of itch may be modified by a number of underlying mechanisms (Table 1):

- Psychological
- Social

In this article...

- The pathophysiology of pruritus in patients at the end of life
- Advice on skin care
- Treating this symptom

5 key points

1. Pruritus (severe itching) can be extremely distressing to patients nearing the end of life.
2. The pathophysiology of pruritus in advanced disease is complex and not fully understood.
3. There is no specific treatment for pruritus in advanced disease.
4. Holistic assessment is required to create an individualised plan of care.
5. General skin-care measures are important to alleviate itch.

---

**Box 1. Potential Effect of Severe Itch**

**Physical**
- Reduced skin integrity (due to scratching) with increased risk of infection
- Altered body image
- Sleep disturbance
- Poor appetite

**Psychological**
- Anxiety
- Depression
- Irritability

**Social**
- Isolation
- Embarrassment
- Tension between patient and family

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Some patients nearing the end of life experience severe itching, which can be extremely distressing. The symptom has a number of causes but can be managed...
including the peripheral nervous system, spinal cord or central nervous system. The transmission of itch impulses (and therefore the sensation of itch) may be modified by the opioid and serotonin system, hence the potential role for opioid antagonists and selective serotonin reuptake inhibitors (SSRIs) in managing itch.

Neuropathic itch results from damage to an afferent nerve pathway (these conduct impulses to the spinal cord and brain), while neurogenic itch is induced centrally (with no evident nerve damage), for example, as a result of an underlying condition, such as cholestasis. Psychogenic itch is associated with psychiatric disorders. Patients may experience more than one class of itch simultaneously.

Causes
Pruritus may be associated with a range of systemic diseases, including hyperthyroidism, hypothyroidism, diabetes, iron deficiency anaemia and multiple sclerosis. The ageing process also makes the body more prone to itching, possibly due to increasingly dry skin or an increased sensitivity to histamine (Twycross et al, 2003; Krajnik and Zylicz, 2001). Conditions that may cause pruritus in patients receiving palliative care are outlined below.

Cholestasis
Cholestasis occurs when there is an interruption to the flow of bile due to an obstruction or when there is a disruption to bile formation; the result of either is deranged liver function and jaundice. It is considered to be the most common systemic cause of pruritus, with 20-25% of patients with end-stage liver disease reporting the symptom (Alshammary et al, 2016).

Pruritus in patients with cancer is likely to be associated with underlying cholestasis (Zyllicz and Krajnik, 2007). This may be the result of extrahepatic causes, such as pancreatic cancer or intrahepatic causes, for example, liver metastases. Itching may be experienced regardless of whether jaundice is present.

The mechanism by which cholestasis causes pruritus is poorly understood. The accumulation of bile acids in the skin has long been considered a primary factor. However, it is now recognised that endogenous opioids and the serotonin system have an important role in itch related to cholestasis (Seccareccia and Gebara, 2011; Twycross et al, 2003). Reasons for this changing view include:

- There is a poor relationship between the degree of cholestasis and the severity of itch;
- Increased plasma levels of endogenous opioids are detected in patients with chronic cholestasis;
- Opioid antagonists reduce the sensation of itch in patients with cholestasis;
- Opioid antagonists may cause an opioid withdrawal-like reaction in patients with cholestasis, even when they are not receiving opioid analgesia;
- SSRIs may relieve itch associated with cholestasis;
- Antihistamine drugs are often ineffective, suggesting that histamine release does not have a significant role in itch related to cholestasis.

Uraemia
Although the incidence is uncertain, itch is a recognised symptom associated with uraemia and end-stage renal failure. Uraemic itch is poorly understood, but is thought to have neuropathic and neurogenic elements (Manenti, 2009), and the opioid and serotonin systems are likely to have a role. It is also suggested that the sensation may be a result of neuropathy, which is common in patients with uraemia (Gunal et al, 2004).

Plasma histamine levels are higher in uraemic patients experiencing itch, but no obvious link has been noted between histamine levels and severity of the sensation. Antihistamines do not appear to offer relief.

Paraneoplastic itch
Paraneoplastic itch is defined as a systemic itch that occurs as a reaction to the presence of a tumour or haematological malignancy, but it is not induced by the local presence of cancer cells or by anti-cancer therapy (Weisshaar et al, 2015). The underlying mechanism that causes the problem is unknown but appears to involve an immunological reaction to tumour-specific antigens (Seccareccia and Gebara, 2011).

Human immunodeficiency virus
Itch may be a presenting symptom of HIV or occur in established disease. The underlying mechanism is thought to include increased cytokine activity, which is part of the immune response, neuropathy, and secondary skin infections/infestations due to a weakened immune system (Krajnik and Zylicz, 2001).

Opioid-induced itch
Localised itch at the site where an opioid has been administered by subcutaneous injection may be caused by histamine release. Generalised itch associated with opioids administered orally or by subcutaneous injection is uncommon; incidence is estimated as less than 1% (Alshammary et al, 2016; Twycross et al, 2014). Itch is a well-known adverse effect when opioids are administered as a spinal injection, but this route of administration is not regularly used in palliative care.

Assessment
A holistic assessment is required to identify the most likely cause of pruritus and to develop a care plan (Box 2). Assessment must include the impact of the itch on both the patient’s wellbeing and that of the family; itch is a subjective experience and, when making an assessment, it is important to note the patient’s own words.

<table>
<thead>
<tr>
<th>TABLE 1. CLASSIFICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Peripheral</strong></td>
</tr>
<tr>
<td>Pruritoceptive</td>
</tr>
<tr>
<td>- Most forms of urticaria</td>
</tr>
<tr>
<td>- Insect bites</td>
</tr>
<tr>
<td>- Drug allergies</td>
</tr>
</tbody>
</table>

**Neuropathic**
- Post-herpetic neuralgia

**Neurogenic**
- Cholestasis
- Opioids
- Anxiety
- Paraneoplastic

**Human immunodeficiency virus**
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The use of a visual analogue scale (0 = no itch, 10 = worst itch imaginable) may enable patients to describe severity of itch experienced at different times and monitor response to treatments. Changes in skin scratching may provide more objective data.

**Treatment**

Regardless of the cause of pruritus, treating dry skin and general skin-care measures are an important aspect of its management (Box 3). Unrelenting itch can lead to a sense of helplessness and frustration that in turn may exacerbate distress. Discussing the likely cause of the itch and rationale for chosen treatments, allowing the expression of feelings and, where appropriate, supporting family members’ involvement in management may help patients and families to regain a sense of control. Relief may be obtained by treating the underlying cause (Twycross et al, 2014). For example:

- Insertion of a stent to relieve cholestasis caused by a blocked common bile duct;
- Treatment of underlying malignancy;
- Discontinuation of itch-inducing medication or change of medication; for example, if itching is associated with opioid use, consider a different opioid.

The management of pruritus in advanced disease is likely to involve a combination of topical treatments (Table 2) and systemic drugs, although few systemic interventions have been subjected to high-quality studies or provided consistently positive results. A Cochrane review identified 40 randomised control trials and concluded that there is no universally accepted therapy for itch (Xander et al, 2013).

Many of the drugs that may be used have been developed for indications other than itch and their mechanism of action is incompletely understood. Table 3 lists possible systemic treatments.

**Non-pharmacological intervention**

Ultraviolet B light (UVB) therapy can be beneficial for itch associated with T-cell lymphoma and uraemia. However, it can be difficult for patients to attend appointments for therapy as they near the end of life (Secchareccia and Gebbara, 2011).

Acupuncture may be effective in reducing itch (Manenti et al, 2009) and transcutaneous electrical nerve stimulation, commonly used to manage localised pain, may also provide relief (Yosipovitch et al, 2003; Krajnik and Zylicz, 2001). Hypnotherapy has been shown to reduce the distress of itch in a small study of patients with HIV/AIDS (Rucklidge and Saunders, 2002), while techniques such as imagery and relaxation may help reduce the severity of itch sensation (Yosipovitch and Samuel, 2008).

It has also been suggested that supporting a positive patient attitude may increase the effectiveness of treatments to reduce itch (Bergasa et al, 2006).

**Case study**

Caroline Fallows*, aged 95, had lived independently following the death of her husband 20 years previously. Her daughter lived 100 miles away and visited her mother two or three times a month.

After noticing that Mrs Fallows appeared to be losing weight, seemed fatigued and looked jaundiced, her daughter took her to see her GP. Blood tests revealed a deranged liver function and Mrs Fallows appeared to have obstructive jaundice with a possible underlying malignancy. The potential seriousness of the diagnosis was explained to Mrs Fallows, who refused investigations or interventions. She was already experiencing generalised itch and was prescribed chlorphenamine 4mg three times daily (a sedating antihistamine).

I first met Mrs Fallows two weeks later and she denied experiencing pain, nausea or vomiting. She appeared jaundiced and was troubled by severe and continuous itching, which was worse at night and disturbed her sleep. Her skin appeared dry and numerous scratch marks were evident.

Mrs Fallows continued to decline any invasive interventions, such as insertion of a biliary stent, which could have helped her symptoms. General skin-care measures were advised and emollients prescribed to add to bathing water, and to apply directly to her skin.

A buprenorphine 5mcg/hour patch was applied but discontinued after three days, as there was no improvement. Mrs Fallows was commenced on sertraline 50mg daily, and general skin-care measures and application of emollient continued. Within a week she reported a reduction in the severity of itch and her daughter noticed her mother was scratching less. After two weeks she reported complete resolution. During this time, her general condition continued to deteriorate and she died at home three weeks later. Although unable to take sertraline in the last week of life, her itch did not return and her death was peaceful.

**Conclusion**

Although a relatively uncommon symptom, pruritus associated with advanced disease can be extremely debilitating for patients and adversely affect their physical, psychological and social wellbeing. Unresolved...
itch can also be upsetting for family members and put a strain on relationships.

The management of itch can be challenging and nurses play a pivotal role by completing a holistic assessment, delivering and monitoring treatment, and providing support to patients and family.

* The patient’s name has been changed

### References


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- Ethical issues around continuous deep sedation without hydration
- Bit.ly/NTEthicHydration

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### TABLE 3. SYSTEMIC TREATMENTS

<table>
<thead>
<tr>
<th>Class and drug</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic Buprenorphine</td>
<td>Cholestasis</td>
<td>Transdermal patch may be better tolerated than sublingual preparations</td>
</tr>
<tr>
<td>Antibiotic Rifampicin</td>
<td>Cholestasis</td>
<td>May cause hepatotoxicity</td>
</tr>
<tr>
<td>Anticonvulsant Gabapentin</td>
<td>Uraemia</td>
<td>May exacerbate itch secondary to cholestasis</td>
</tr>
<tr>
<td>- Pregabalin</td>
<td>Neupathic pruritus</td>
<td>Increased risk of side-effects for patients with renal impairment: start at low doses</td>
</tr>
<tr>
<td>- Carbamazepine</td>
<td>Haematological malignancies</td>
<td>For patients receiving haemodialysis, single dose should be given after each dialysis session</td>
</tr>
<tr>
<td>Antidepressant Paroxetine</td>
<td>Uraemia</td>
<td>May be helpful, even if sertraline or paroxetine have not provided relief</td>
</tr>
<tr>
<td>- Sertraline</td>
<td>Cholestasis</td>
<td>Sedative effect may be beneficial when taken at night</td>
</tr>
<tr>
<td>Antihistamine Chlorphenamine Promethazine Hydroxyzine</td>
<td>Allergic reaction</td>
<td>Not considered effective with itch related to systemic disease</td>
</tr>
<tr>
<td>- Hydroxyzine</td>
<td>Unknown cause</td>
<td>Sedative effect may be beneficial when taken at night</td>
</tr>
<tr>
<td>Bile acid sequestrant Colestyramine</td>
<td>Cholestasis</td>
<td>Limited use in palliative care as unpalatable; may cause nausea/diarrhoea</td>
</tr>
<tr>
<td>Corticosteroids Prednisolone Dexamethasone</td>
<td>Haematological malignancy</td>
<td>Dose should be gradually reduced to stop or maintenance dose</td>
</tr>
<tr>
<td>- Dexamethasone</td>
<td>Cholestasis</td>
<td>Potential for adverse effects increases with longer-term use</td>
</tr>
<tr>
<td>H2 receptor antagonist Cimetidine</td>
<td>Hodgkin’s disease</td>
<td></td>
</tr>
<tr>
<td>Immunomodulator Thalidomide</td>
<td>Paraneoplastic Hodgkin’s disease</td>
<td>Long-term use may cause severe neuropathy</td>
</tr>
<tr>
<td>- Uraemia</td>
<td>Expensive</td>
<td></td>
</tr>
<tr>
<td>Non-steroidal anti-inflammatory drug Indomethacin</td>
<td>HIV/AIDS</td>
<td>Use may cause gastric irritation – gastric protection required (for example, concurrent use of a proton-pump inhibitor)</td>
</tr>
<tr>
<td>Opioid antagonist Naltrexone</td>
<td>Uraemia</td>
<td>Not appropriate for patients taking opioids for pain or breathlessness as will reverse the desired effect</td>
</tr>
<tr>
<td>Nalmefene</td>
<td>Cholestasis</td>
<td></td>
</tr>
</tbody>
</table>

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**Itch:**

- In cancer patients, pruritus can occur due to various reasons such as cholestasis, unknown cause, or related to systemic disease.
- Gabapentin and pregabalin can be used to manage pruritus associated with cholestasis.
- Carbamazepine can be effective for pruritus related to haematological malignancies.
- Sertraline may be helpful, even if other antidepressants have not provided relief.
- Hydroxyzine can be used as an antihistamine to manage pruritus.
- Colestyramine is limited in use due to its unpalatability.
- Corticosteroids can be used for haematological malignancy-related pruritus.
- Cimetidine can be used for patients with Hodgkin’s disease.
- Thalidomide can be used for paraneoplastic pruritus.
- Indomethacin can be used for HIV/AIDS-related pruritus.
- Nalmefene can be used for opioid-induced pruritus.

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**References:**


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