Palliative Meds Info
tel: 01 4912578
palliativemedsinfo@olh.ie

Our Lady's Hospice & Care Services
Respite Rehabilitation Reassurance
Harold's Cross & Blackrock

Question: What are the treatment options for pruritus?

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Summary

Pruritus, from the latin “to itch”, is defined as an unpleasant sensation that elicits a desire to scratch, subjectively quantified by intensity, severity, location, and intractability[2]. In patients with palliative care needs, pruritus may originate from more than one cause and may be challenging to treat. Therefore, careful consideration should be given to each possible cause before choosing a treatment approach.

Classification of Pruritus and Overview of Treatment Approaches

- *Cholestatic pruritus:*

Cholestasis is seen in many hepatobillary disorders and associated pruritus is a common troublesome symptom[3]. Cholestatic pruritus can be localised or generalised with severity generally not correlating to severity of the underlying disease[3]. It is commonly more troublesome at bedtime and is also exacerbated by stress[3].

If the pruritus is mild, treatments such as warm baths and emollients may help[3]. Oral antihistamines may also be helpful in mild pruritus, particularly for patients with associated insomnia[3]. However, these measures often fail when pruritus is moderate to severe[3]. Pharmacological therapy is generally necessary for all patients with moderate to severe cholestatic itch.

- *Uraemic pruritus:*

Uraemic pruritus frequently presents in patients with end stage renal disease (ESRD). Uraemic pruritus most commonly affects the back but may also involve the arms, head, and abdomen[4]. Generalized pruritus is also noted in a significant number of patients[4]. Symptoms tend to be worse at night, resulting in sleep disruption[4]. High quality evidence on the management of uraemic pruritus is limited. Initial treatment involves optimal dialysis (since under dialysis is a common precipitant), treatment of hyperparathyroidism, hyperphosphataemia, and hypermagnesaemia and the regular use of emollients and/or topical analgesics[4].

- *Opioid induced pruritus*

There are two types of opioid-induced pruritus – one due to spinal opioid administration, the other caused by systemic opioids[5]. Pruritus associated with systemic opioid exposure is thought to be related to cutaneous histamine release[5], and possibly occurs in only ~1% of patients receiving an opioid systemically[4,5]. Generally, this type of reaction to systemic opioids responds to H_1 antihistamines and a switch in opioid[4]. Pruritus associated with the spinal administration of opioids occurs in ≤ 80% of opioid naïve patients[4,5], but interestingly in just 10 – 15% of patients with chronic pain already taking opioids by another route[4,5]. Intrathecal opioids tend to cause a central reaction, which does not respond to anti-histamine therapy[4,5].

- *Hodgkin's Lymphoma*

Hodgkin's lymphoma causes pruritus in 10%—30% of patients[5,6]. In some instances, pruritus precedes diagnosis of the lymphoma, and may be an indicator of a less favourable prognosis[6]. Pruritus associated with Hodgkin's lymphoma is characterized by symptoms of burning and intense itching occurring initially on a localized skin area, frequently on the lower legs[6,7]. Pruritus commonly progresses, becoming generalized[6,7]. Pruritus related to Hodgkin's lymphoma is often more severe in older patients and patients with more advanced disease[7]. Symptoms may be aggravated at night[7.]

- *Idiopathic Itch*

Idiopathic itch is that which arises spontaneously and for which the cause is unknown.

Non-Pharmacological Management Strategies:

Most patients with pruritus have dry skin even when there is a definitive endogenous cause[4].

Rehydration of the skin may prevent the need for pharmacological therapy[5].

- Emollients[4,8,9,10]:
  Apply twice-three times daily[4,11] i.e. Diprobase cream[11], Aqueous cream[8,10,11] or Aveeno[11]
- Review medication as a suspecting cause of pruritus[5]. If a drug cause is identified this medication should be discontinued where possible[5,8]
- Discourage scratching and cut finger nails short [45,8,11]
- Avoid prolonged baths[5]
- Avoid sweating and over-heating[5,8]

Topical management of Pruritus:

Topical antipruritic agents should be considered for patients with mild to moderate pruritus[8].

- *Menthol (Aveeno® menthol)*

  Menthol acts as a counter-irritant by cooling the skin[11]. Aveeno menthol is widely available, and can be bought over the counter by patients in the community. Generally topical antipruritics should be applied after washing in the morning and again in the evening.

- *Calamine*

  Calamine is a mild astringent and may help relive pruritus. It can be applied topically to the affected area with cotton wool and allowed to dry[12]. Of note, the Palliative Care Formulary cautions that calamine has a drying effect which may be irritant to already itchy skin[11]. Calamine Lotion® (calamine 15%, zinc oxide 5%) is available without a prescription in the community pharmacy setting[12].

- *Topical antihistamines*

  Several topical H1 antihistamines are suggested in the literature, but mepyramine (Anthisan®) is the only licensed product available in Ireland. It is an over-the-counter product and is widely available. It has antihistaminic and anti-pruritic properties[13]. It can be applied two to three times daily for up to three days[13]. Of note, the PCF states that the use of topical H_1 antihistamines should be discouraged based on their risk of causing contact dermatitis[5,11].

- *Crotamiton*

  Crotamiton 10% (Eurax®) is available as both a lotion and cream[15]. Its mild

antiscabetic effect gives it its reputation as an antipruritic[5,11]. However, it has been shown to be no better than placebo as an antipruritic, therefore cannot be recommended[5,11].

- *Capsaicin cream*

  Capsaicin acts to deplete substance P at sensory nerve endings[16]. A systematic review in 2010 considered that there was no convincing evidence that topical capsaicin was effective for the treatment of pruritus in any medical condition[16]. A Cochrane review of pruritus in adult palliative care patients (2016) did find benefit with capsaicin in uraemic pruritus, but the methodological quality of the studies was low, introducing a risk of bias and thus preventing meaningful interpretation of the results[17].

  Capsaicin cream should initially be used t.d.s.–q.d.s. (leaving at least 4h between applications; the manufacturers specify q.d.s. for the 0.025% cream) to overcome the irritation, after which the frequency of applications can be reduced[11]. Capsaicin cream is not licensed for the treatment of pruritus[18].

- *Local Anaesthetics*

  It is suggested that topical anaesthetics exhibit antipruritic effects[19]. Several preparations are available. Prilocaine and lidocaine (lignocaine) are the most common but some preparations contain tetracaine. EMLA® cream (available from OLH pharmacy) is available on prescription, and contains 2.5% lidocaine in combination with 2.5% prilocaine[20]. Dolocopin® cream contains lidocaine 4%[21]. Pliaglis cream is a combination of 7% lidocaine and 7% tetracaine[22]. Importantly, none of these products are licensed for the management of itch. With the exception of lidocaine, local anaesthetics can cause contact dermatitis[23]. They are also absorbed to a variable extent and, if large amounts are applied, could cause cardiac arrhythmias[23]. Use is best restricted to a few days[23].

Pharmacological management:

An *Exempt Medicinal Product (*EMP) is one which does not carry either a Product Authorisation (PA) number issued by the Health Products Regulatory Authority (HPRA) or a European Union authorisation number issued by the European Medicines Evaluation Agency (EMEA). An exempt medicinal product should only be prescribed when an equally safe and effective licensed alternative, in a similar/suitable formulation, is not available.

1. *Antihistamine; for histamine mediated pruritus*

Antihistamine	Dosage
Cetirizine (Zirtek®) Non-sedating antihistamine	5mg BD or 10mg OD[9]. Best choice if sedation is undesirable.
Chlorphenamine (Piriton®) Sedating antihistamine	4mg TDS. Doses up to 12mg QDS may be used to determine if an antihistamine may be of benefit[9]. The max licensed dose is 24mg/day[25].
Hydroxyzine (Ucerax®) Sedating antihistamine	25 mg before resting, to be followed if necessary with doses up to 25 mg 3 to 4 times daily[26].
Levomepromazine (EMP) Sedating antihistamine	12.5mg SC; if beneficial convert to 6-25mg PO at bedtime[9]. Unlicensed in Ireland, but available.
Promethazine (Phenergan®) Sedating antihistamine	25-50mg BD[9]. The licensed dose is 25-75 mg either as a single daily dose at bedtime or in 3 divided doses[27].

2. *Pharmacological management of cholestatic pruritus(CP)*

Drug	*Drug class*	*Evidence*	*Dose*	*Other Information*
Colestyramine (EMP)	An intestinally active anion exchange resin – acts by chelating bile acids in the intestines[17,28]	Colestyramine is licensed for the relief of pruritus associated with partial biliary obstruction and primary biliary cirrhosis[32]. Benefit has been claimed only in an open label; non-randomised long-term study of 27 patients[28]. Cholestyramine is not effective in itch associated with complete large-duct biliary obstruction[28].	4-8g OD[29,30]	Patients should take other drugs at least one hour before or 4-6 hours after colestyramine to minimise possible interference with their absorption[29]. This is not always practical in palliative care populations.
Danazol (EMP)	Chemically modified testosterone (androgen derivative)	The PCF recommends danazol as a 2nd line choice for the management of CP[5].	200-800mg daily PO, with food[31]	Androgens themselves can cause cholestatic jaundice and severe hepatic impairment. The antipruritic effect is maintained even if the cholestasis is exacerbated by the androgen itself. Will cause masculinization in women – avoid long-term use[32].
Naltrexone (EMP)	Complete opioid antagonist	Two studies including 36 patients have been found which evaluated naltrexone for CP. The pooled results showed a statistically significant effect in	12.5–250mg once daily[5]	Available as a 50mg tablet. Naltrexone is contraindicated in patients with acute

		terms of improvement of itching versus placebo but huge inconsistencies in the data is reported[8,17]. Naltrexone showed the most adverse effects of all medicines used for the management of pruritus[17]. The PCF recommends naltrexone third line for the pharmacological management of CP[5].		hepatitis or liver failure.[33]
Rifampicin	Antibacterial	3 studies including 45 patients have investigated the utility of rifampicin in treating CP (Bachs 1989; Ghent 1988; Podesta 1991)[17]. The pooled estimate of the three studies indicates that rifampicin may improve pruritus in participants suffering from CP[17]. Overall, investigators observed very few adverse events for short-term use of rifampicin[17]. The PCF recommends rifampicin as a first line pharmacological choice for CP[5].	75 - 150mg OD to start, up to max. 600mg in divided doses[5,8]	Available as 150mg, 300mg, 600mg capsules. 100mg/5mL oral suspension also available Hyperbilirubinaemia resulting from competition between rifampicin and bilirubin for excretory pathways can occur in early days of treatment[34].
Sertraline	SSRI	Mayo 2007 described that sertraline was effective and well-tolerated in participants with CP[35]. However, the sample size of 12 participants was very small, and the blinding of outcome assessment was somewhat precarious[35]. The PCF5 recommends it as a first line pharmacological choice for CP[5].	50 – 100mg OD[5,8,17]	Available as 50mg tablet. (can be crushed)

3. Pharmacological management of uraemic pruritus

Drug	*Drug class*	*Evidence*	*Dose*	*Other information*
Topical Capsaicin	Naturally occurring alkaloid which depletes substance P	4 RCTs have assessed the efficacy of capsaicin in UP but, just 2 (112 participants) provided sufficient data and statistics to be assessed by Cochrane[17]. Topical capsaicin was found to be superior to placebo in relieving UP associated itch, though the quality of evidence is only moderate[17]. Recommended first-line in the management of UP by PCF5[5].	0.025 – 0.075% once daily– q.d.s[5,11]	Available as a 0.025% or 0.075% cream.
Doxepin (EMP)	Tricylic antidepressant	In a cross-over RCT by Pour-Reza-Gholi 2007, performed on 24 participants with UP, investigators described complete (58.3%) or partial improvement in 87.5% of participants treated with doxepin[36]. This was significantly higher than improvements with placebo[17,36].	10mg BD[5,36]	Available only as Doxepin 50mg capsules and accordingly dosing is impractical.
Naltrexone (EMP)	Opioid Antagonist	Three studies (90 participants) researched the antipruritic effect of the opioid antagonist naltrexone in participants suffering from UP[17]. Results of the RCTs regarding the effects of naltrexone in UP were contradictory[17]. 2 studies showed improvement in pruritus with short-term use of naltrexone, and the other showed no benefit over placebo[17]. The PCF recommends sertraline as a 3rd line choice for the management of UP[5]	12.5–250mg once daily[5]	Available as a 50mg tablet.
Ondansetron	5HT3 receptor antagonist	Among 3 RCTs comparing ondansetron to placebo for benefit in UP, there was a very small but statistically significant effect in favour of the ondansetron group of patients with UP[17]. The PCF5 states that ondansetron does not relieve uraemic pruritus[5].	8mg BD PO/SC[5,8]	Available as 4mg and 8mg tablets, 4mg/5mL oral solution and 4mg/mL solution for injection. Zofran 4mg oral lyophilisate also available.
Sertraline	SSRI	A Cochrane review in 2016 found no clinical evidence for the use of sertraline in the treatment of UP[17]. The PCF recommends sertraline as a 3rd line choice for the management of UP[5]		Available as 50mg tablet. (can be crushed)

4. *Pharmacological management of opioid induced pruritus*

- Step 1: Stat dose of H1 antihistamine[5]

Chlorphenamine (Piriton®)/Cetirizine (Zirtek®)

Dose: Chlorphenamine 4-12mg PO[4,9] or 10mg SC[37]

OR Cetirizine 10mg PO[9]

- Step 2: Switch opioid[5]

See the Palliative Medicines Information website (https://olh.ie/our-services/palliative-care/palliative-meds-info) to access our documents *"Will opioid rotation resolve an opioid induced itch?"*[38] and *"A patient presents with an allergy to an opioid, can an alternative opioid be prescribed?"*[39] for further information.

- Other Options:

Ondansetron[5]

Limited evidence suggests that ondansetron may ease opioid associated itch[5].

Ondansetron is not licensed for the treatment of pruritus.

Dose: 8mg BD PO/SC[5]

5. *Pharmacological management of pruritus associated with Hodgkin's lymphoma*

- Step 1: **Prednisolone** 10-20mg TDS[5] – recommended in HL based on case reports[23]
- Other Options:

Cimetidine 800mg/24 hour[5] – a H2-antagonist which enhances the effects of H1 antihistamines in utricaria[23]

Carbamazepine 200mg BD[5] – based on its successful use in just four patients (three with B-cell lymphoma and one with myeloma)[5]

6. *Pharmacological options for paraneoplastic itch or idiopathic itch*

- Suggested Options:

Paroxetine 5-20mg OD[5] – often effective for paraneoplastic itch [17,23]. Effect often wears off after 4 – 6 weeks[23].

Sertraline 50-100mg[4] OD – reasonable results for non-specific itch[17]

Mirtazapine 7.5 - 30mg at bedtime[5,23] – has demonstrated efficacy in lymphoma patients[23].

Thalidomide (only when all else fails)[5] – cost is prohibitive and it may cause severe neuropathy when used long-term.

Other pharmacological therapies suggested in the literature:

Ursodeoxycholic acid

In primary biliary cholangitis ursodexoycholic acid has been effective when used in combination with cholestyramine[3]. Ursodeoxycholic acid is not licensed for the treatment of pruritus.
Dose: 200-300mg daily and then gradually increased to 13-15mg/kg/day in 2-3 divided doses over a few weeks[3].

Aprepitant

Aprepitant is an antagonist of the neurokinin 1 receptor, a receptor for substance P, which is a mediator in the itch sensation, and has been trialled in the relief of pruritus[40]. Aprepitant has demonstrated efficacy in the management of severe pruritus related to targeted biological cancer treatment with anti-EGFR antibodies and tyrosine-kinase inhibitors[5]. Additional studies are required to confirm efficacy[19] and its high cost currently limits its utility.

Thalidomide

The antipruritic action of this drug may be secondary to inhibition of TNF[17]. Another possibility is that thalidomide can act as both a peripheral and a central nerve depressant[17]. Thalidomide is associated with high cost and may cause severe neuropathy when used long term[5]. Thalidomide is a high-tech medicine with 28 x 50mg capsules costing the state €391.18. Its use must be restricted to patients in whom other interventions for itch have been exhausted.
Dose: 100-200mg at bedtime in uraemic pruritus has been successful[5]

Mirtazapine

Mirtazapine is a centrally active presynaptic 2-antagonist, which increases central noradrenergic and serotonergic neurotransmission and has H1-antihistamine properties[41]. It has been used successfully to relieve itch in patients with malignant cholestasis, lymphoma and uraemia[8,23]. Doses of 15-30mg at night were used but success with a dose of 7.5mg has been reported in unpublished observations[23]. It is possible, of course, that the antipruritic effect of mirtazapine is at least partly a consequence of non-specific sedation[23].
Dose: 15-30mg at bedtime[8,23]

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