

British Association of Dermatologists' guidelines for the investigation and management of generalized pruritus in adults without an underlying dermatosis, 2018*

G.W.M. Millington¹, A. Collins,² C.R. Lovell,³ T.A. Leslie,⁴ A.S.W. Yong,¹ J.D. Morgan,⁵ T. Ajithkumar,⁶ M.J. Andrews,⁷ S.M. Rushbook,⁸ R.R. Coelho,⁹ S.J. Catten,¹ K.Y.C. Lee,¹ A.M. Skellett,¹ A.G. Affleck,¹⁰ L.S. Exton,¹¹ M.F. Mohd Mustapa¹¹ and N.J. Levell¹

¹Dermatology Department, ²Haematology Department, ³Nephrology Department and ⁸Hepatology Unit, Norfolk and Norwich University Hospital, Colney Lane, Norwich NR4 7UY, U.K.

³Dermatology Department, Royal United Hospital, Combe Park, Bath BA1 3NG, U.K.

⁴Dermatology Department, Royal Free Hospital, Pond Street, London NW3 2QG, U.K.

⁵General Practitioner, Chet Valley Medical Practice, 40–48 George Lane, London NR14 6QH, U.K.

⁶Oncology Department, Addenbrooke's Hospital, Hills Road, Cambridge CB2 2QQ, U.K.

⁹Dermatology Department, St George's Hospital, Blackshaw Road, London SW17 0QT, U.K.

¹⁰Dermatology Department, Ninewells Hospital, Dundee DD1 9SY, U.K.

¹¹British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.

Correspondence

George Millington.

E-mail: george.millington@nnuh.nhs.uk; guidelines@bad.org.uk

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Administrator), A.G. Brain (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist) and M.F. Mohd Mustapa (BAD Clinical Standards Manager).

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NICE has accredited the process used by the British Association of Dermatologists to produce clinical guidelines. The renewed accreditation is valid until 31 May 2021 and applies to guidance produced using the process described in the updated guidance for writing a British Association of Dermatologists clinical guideline – the adoption of the GRADE methodology 2016. The original accreditation term began on 12 May 2010. More information on accreditation can be viewed at www.nice.org.uk/accreditation.

1.0 Purpose and scope

The overall objective of the guidelines is to provide up-to-date, evidence-based recommendations on the investigation and management of secondary pruritus without underlying skin disorder and generalized pruritus of unknown origin (GPUO) in adults (excluding children aged < 18 years). The document aims to: (i) offer an appraisal of all relevant literature up to November 2016, focusing on any key developments; (ii) address important, practical clinical questions relating to the primary guidelines objective (i.e. accurate diagnosis and identification of cases and suitable treatment); (iii) provide guideline recommendations; (iv) where appropriate, provide practical and health economic implications; and (v) discuss potential developments and future directions.

The guidelines are presented as a detailed review with highlighted recommendations for practical use in the clinic (see section 13), in addition to an updated patient information leaflet [available on the British Association of Dermatologists

(BAD) website, <http://www.bad.org.uk/for-the-public/patient-information-leaflets>].

1.1 Exclusions

These guidelines do not cover primary dermatological pruritic conditions, localized pruritus or pruritus in children.¹ Also, the management of pruritus associated with pregnancy is not covered, as there has been a recent Cochrane review of this topic.²

2.0 Stakeholder involvement and peer review

The Guidelines Development Group (GDG) consisted of clinicians from dermatology, nursing, primary care, oncology, nephrology, hepatology and haematology. The draft document was circulated to the BAD membership, the British Dermatological Nursing Group and the Primary Care Dermatological Society for comments, which were considered by the GDG, and peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines subcommittee) prior to publication.

3.0 Methodology

This set of guidelines has been developed using the BAD recommended methodology³ and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).⁴ Recommendations were developed for implementation in the National Health Service using a process of considered judgement based on the evidence. Targeted literature searches were carried out in the PubMed, MEDLINE and Embase databases for meta-analyses, randomized and nonrandomized controlled clinical trials, case series, case reports and open studies involving treatments for pruritus published in the English language up to November 2016. The search terms and strategies are detailed in Appendix S1 (see Supporting Information). Additional relevant references were identified from citations in the reviewed literature. All identified titles were screened and those relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed by the GDG and the full papers of relevant material obtained; disagreements in the final selections were resolved by discussion with the entire GDG. The structure of the guidelines was then discussed, with headings and subheadings decided; different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the selected literature with discussions within the GDG to resolve any issues. All subsections were subsequently collated and edited to produce the final set of guidelines.

4.0 Limitations of the guidelines

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations

herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English-language references was a pragmatic decision but the authors recognize this may exclude some important information published in other languages. For example, certain papers cited in the European guidelines on chronic pruritus, published in 2012, are not written in English.⁵

5.0 Plans for guideline revision

The proposed revision for this set of recommendations is scheduled for 2023; where necessary, important interim changes will be updated on the BAD website.

6.0 Introduction

Pruritus (itch) is a common and distressing symptom of many dermatological, systemic and psychological disorders (Table 1). It is perhaps the most common presenting symptom in dermatology (Table 2).^{6,7} The focus of these guidelines is the investigation and management of both noncutaneous secondary causes of pruritus due to an underlying disorder, and GPUO, which forms about 8% of all cases of pruritus.⁸ There is a significantly impaired quality of life associated with itch, similar to that of chronic pain.^{5,9,10}

Pruritus can be defined as 'the sensation that is relieved by scratching the skin'.^{6,7} Somatosensory neurones carry the sense of touch, as well as pain and itch.¹¹ Any tissue damage or inflammation can produce either localized or generalized pruritus.¹¹ Both pain and itch sensations arise by activation of primary sensory neurones, but there is experimental evidence that these two sensations are transduced by distinct subpopulations of sensory neurones and spinal afferent pathways, although there may be 'cross-talk' between these two distinct neuronal circuits.¹¹ Various centres within the central nervous system have been implicated in the perception of chronic pruritus, including signal transducer and activator of transcription 3- and lipocalin-2-mediated signalling in astrocytes,¹² γ -aminobutyric acid (GABA)_A receptor activation in the central nucleus of the amygdala,¹³ and signalling in the middle superior temporal gyrus and right inferior frontal gyrus/insula.¹⁴

Itch is a common symptom in the general population, with a 2-week-period prevalence of acute itch of 8.4%.¹⁰ The

Table 1 Basic classification of pruritus

| |
|--|
| 1. Pruritus with associated underlying dermatosis |
| 2. Pruritus with no underlying dermatosis |
| 2a. Secondary pruritus due to underlying systemic disorder (secondary pruritus) |
| 2b. Generalized pruritus of unknown origin (GPUO) |
| Note that type 2a and 2b pruritus may have secondary changes due to rubbing or excoriation |
| Acute: < 6 weeks; chronic: > 6 weeks |

Table 2 Causes of generalized pruritus without rash

| |
|--|
| Pruritic skin diseases before rash |
| Disorders of iron metabolism |
| Uraemia |
| Hepatic disease (especially cholestasis) |
| Malignancy |
| Haematological disorders |
| Infection |
| Endocrine disease |
| Neurological disorders |
| Psychological and emotional factors |
| Adverse drug reactions |
| Heart failure |
| Pregnancy |
| Pruritus of elderly skin |
| Pruritus of unknown origin (GPUO) |

pathophysiology of itch is the subject of a number of reviews to which the reader is referred^{6,7,11} and is beyond the scope of these guidelines.

Itch may be acute (< 6 weeks) or chronic (> 6 weeks). Chronic itch has a prevalence of approximately 17% in adults;¹⁵ however, this may be much higher in the elderly (> 65 years), where the figure is likely to be 50% or higher.¹⁶ The quality of perception of itch may be sex dependent.¹⁷

The management of pruritus requires a detailed history and examination coupled with appropriate investigations, directed from the initial clinical assessment. A major aim of these guidelines is to evaluate screening investigations in generalized pruritus without cutaneous signs and their value in the absence of clinical evidence of systemic disease such as blood disorders, renal disease, liver disease or malignancy.

It is difficult to assess the intensity, severity and course of pruritus accurately. It is also hard to characterize and define the sensation. Tools have been developed and validated for baseline assessment and evaluation of treatment efficacy of pruritus, thus allowing comparison between clinical studies. Commonly used tools for self-reporting of pruritus intensity are the visual analogue scale (VAS), numerical rating scale and verbal rating scale.¹⁸ The use of a patient-completed 10-cm VAS and perhaps the Dermatology Life Quality Index¹⁹ is recommended to provide a baseline measure of itch activity to help quantify management outcomes. However, as yet, there is no international consensus on how to measure the severity of itch.²⁰ Moreover, there may be differences in how patients and physicians assess the severity of pruritus.^{21–23}

The management of pruritus depends on the treatment of any underlying disease. Symptomatic measures may be appropriate in patients where no cause can be identified or treated. More directed management can be divided into topical treatments, systemic treatments, phototherapy, psychological approaches or alternative therapies.^{5,24} Palliative care is a specialized situation and, in general, the therapy of the pruritus should be centred on the individual circumstances of the patient.²⁵

7.0 Investigation of generalized pruritus without rash and interventions for secondary generalized pruritus

7.1 Iron deficiency and pruritus

In all cases of generalized pruritus without rash (GPWOR), but especially where iron loss is suspected, it is important to enquire about diet (vegetarian or vegan), potential sources of blood loss and gastrointestinal symptoms. Generalized pruritus associated with iron deficiency was first described over 40 years ago.^{26–29} Iron replacement leads in some cases to complete cessation of pruritus very shortly after commencement of therapy.^{26,28}

A prospective case–control study showed that the mean serum iron levels in the population of patients with pruritus was significantly lower than that in the control group, with no median age difference between the two groups. Furthermore, the most common cause of generalized pruritus in patients with underlying systemic disease was found to be iron deficiency anaemia, which responded to iron replacement (25% of all patients with pruritus with systemic disease).³⁰ Therefore, we recommend that full blood count and ferritin levels should be checked in all patients with chronic GPWOR. Note that ferritin is an acute-phase protein and may be elevated in a situation of iron deficiency.

Where iron deficiency is suspected, and ferritin is apparently ‘normal’, it may be necessary to check serum iron and total iron binding capacity as well. A trial of iron replacement should be given if the ferritin is below the lower limit of the reference range (between 15 and 25 $\mu\text{g L}^{-1}$ in most U.K. laboratories) or if there is anaemia or microcytosis not attributable to any other cause (e.g. gastrointestinal blood loss, loss in the urine, thalassaemia trait or polycythaemia). Those who have unexplained iron deficiency should also be tested for tissue transglutaminase (TTG) antibodies. This is assuming they have not been excluding gluten for at least 6 weeks. If this is abnormal, they should be referred to a gastroenterologist for consideration of endoscopy and small bowel biopsy. A biopsy may be indicated anyway, even with a negative TTG.³¹ IgA deficiency is relatively common in the population and, if present, TTG measurement may give a falsely negative reading.

Recommendation

- Full blood count and ferritin levels should be checked in all patients with chronic GPWOR (Strength of recommendation C; Level of evidence 2++) (see Appendix)

7.2 Iron overload

Iron overload may also be associated with generalized pruritus, either in association with haemochromatosis^{32–34} or with hyperferritinaemia in the absence of haemochromatosis.³⁵ Important confounding variables are that iron overload is associated with both liver infiltration³⁵ (see section 7.7) and

diabetes mellitus (see section 7.5).^{32–34} Treatment of iron overload by venesection in such cases can reduce or remove the sensation of pruritus.^{32–35}

Recommendation

- Liver functions tests should be considered for patients with generalized pruritus associated with iron overload (Strength of recommendation D; Level of evidence 3)

7.3 Haematological causes of pruritus

GPWOR can be the presenting symptom of essential polycythaemia vera (PV) and secondary polycythaemia, due to lung or kidney disease.³⁶ It is also associated with Hodgkin lymphoma,³⁷ but is unusual in other types of lymphoma, such as non-Hodgkin lymphoma (NHL). Myeloma presents with GPWOR extremely rarely.³⁸ It is also linked with sickle cell disease, but this is probably due to opiates (see section 7.11), which are commonly used to treat pain in this disorder.³⁹ Haematological causes of GPWOR account for approximately 2% of the total.⁴⁰

Evidence of an underlying haematological disorder may be identified from the history and examination. Aquagenic pruritus is characterized by the development of intense itching, without the development of skin lesions, evoked by contact with water. It is characteristic of PV,³⁶ although there are other causes. Itching at night in association with weight loss, fevers and night sweats is suggestive of lymphoma.³⁷ Any enlarged lymph nodes or masses should be referred for excision or ultrasound-assisted core biopsy.⁴¹

A skin biopsy may very occasionally be necessary in persistent, unexplained pruritus, as patients may very rarely present with pruritus and normal-looking skin, who subsequently prove to have skin lymphoma on biopsy, usually taken from the trunk.^{42–44}

Initial investigation of patients with pruritus, where haematological involvement is suspected, should include full blood count, blood film, erythrocyte sedimentation rate (ESR, if available) and lactate dehydrogenase.⁴⁵ PV should be considered in the presence of a raised haemoglobin or haematocrit, especially in association with microcytosis (suggesting secondary iron deficiency), raised white cell or platelet count and low ESR. If PV is suspected, blood should be analysed for the Janus kinase (JAK)2 V617F mutation, which is present in up to 97% of cases.⁴⁶ In the absence of the JAK2 mutation, secondary causes of polycythaemia should be investigated where possible by means of clinical assessment, renal and liver function tests, serum erythropoietin level, measurement of oxygen saturation, chest X-ray and abdominal ultrasound.⁴⁷ A recent randomized controlled trial (RCT) showed that ruxolitinib (an antibody against JAK1/JAK2) was very effective at treating PV, producing rapid reductions in pruritus scores.⁴⁸

Curative treatment of lymphoma invariably resolves the associated pruritus.⁷ However, symptomatic management may

be required while the patient is receiving definitive treatment or if the lymphoma is incurable. Cimetidine controlled the pruritus in a series of four patients with Hodgkin lymphoma.⁴⁹ Small case series and case reports have reported success with the use of carbamazepine,⁵⁰ mirtazapine⁵¹ and phototherapy.⁵² High-dose oral corticosteroids are frequently used in the treatment and palliation of patients with lymphoma, and can also provide symptomatic relief from itching.⁵³

The pruritus associated with PV can persist despite normalization of blood counts with venesection or cytoreductive therapy.³⁶ Aspirin 300 mg daily has been shown to be effective in relieving pruritus in a number of patients with PV.^{54,55} There is evidence from case reports that pruritus associated with PV may be helped by sodium bicarbonate baths.⁵⁶ However, this has not been confirmed in all cases.

Interferon alpha therapy may also be useful.⁵⁷ It has the added advantage of being a cytoreductive therapy and therefore a treatment for PV, but is poorly tolerated due to myalgia, arthralgia, nausea and diarrhoea. Other agents for which the evidence is limited to case series or reports are selective serotonin reuptake inhibitors (SSRIs),⁵⁸ psoralen–ultraviolet A (PUVA) or ultraviolet (UV)B phototherapy,^{59,60} cimetidine⁶¹ and atenolol.⁶²

In summary, haematological conditions should be considered in the initial work-up of a patient with pruritus. The evidence for the treatments used in pruritus associated with haematological conditions is primarily from case reports and case series.

Recommendations (investigation)

- Patients with generalized pruritus with suspicion of haematological involvement should have initial investigations including full blood count, blood film, lactate dehydrogenase and ESR (if available). Immunoglobulins and urinary paraproteins may also be requested, but will have a low yield, as myeloma is rarely associated with GPWOR (Strength of recommendation D; Level of evidence 3)
- Patients with generalized pruritus associated with either PV or suspected Hodgkin lymphoma should be referred to haematology (Strength of recommendation D; Level of evidence 4)
- Patients with generalized pruritus with suspicion of PV (raised haemoglobin or haematocrit) should have blood samples sent for JAK2 V617F mutation analysis and/or be referred to haematology (Strength of recommendation D; Level of evidence 4)
- In the absence of JAK2 mutation, secondary causes of PV should be investigated by means of clinical assessment, renal and liver function tests, serum erythropoietin level, measurement of oxygen saturation, chest X-ray and abdominal ultrasound (Strength of recommendation D; Level of evidence 4)

Recommendations (treatment)

- Patients with generalized pruritus associated with lymphoma may have their itch resolved by treatment with cimetidine, gabapentin, carbamazepine, mirtazapine or phototherapy (Strength of recommendation D; Level of evidence 3)
- Patients with generalized pruritus associated with incurable lymphoma may have their itch relieved with oral corticosteroids (Strength of recommendation D; Level of evidence 4)
- Patients with generalized pruritus associated with PV may have their itch relieved with cytoreductive therapy, aspirin, interferon- α , SSRIs, PUVA, UVB phototherapy, cimetidine or atenolol (Strength of recommendation D; Level of evidence 3)

7.4 Pruritus associated with malignant solid tumours

Solid malignant tumours are a relatively rare cause of pruritus, and the true prevalence of itch in malignancy is not known.⁶³ Generalized pruritus in malignancy can be multifactorial. It can be a true paraneoplastic symptom, a feature of paraneoplastic dermatoses, secondary to paraneoplastic neuropathy, a consequence of secondary skin involvement by cutaneous or noncutaneous primary tumours or a side-effect of cancer treatment (Table 3). Melanomatosis and skin infiltration by tumours can also cause itching.^{63–66}

When generalized paraneoplastic pruritus is suspected, investigations should be guided by a thorough history and physical examination. Features in the history of a patient with chronic unexplained pruritus that favour a possibility of underlying

malignancy include older age, male sex, possible liver disease and chronic tobacco usage.⁶⁷ Generalized pruritus has been described in breast, colon, lung, testicular and stomach cancers; insulinoma; gastric carcinoid and thymoma.^{63,68,69}

Although GPWOR can be an initial manifestation of cancer prior to clinically detectable disease, a full investigation to rule out malignancy is not necessarily beneficial to patients or cost-effective, and is therefore not routinely recommended.^{70,71} A 5-year cohort study found that GPWOR statistically correlated with an increased risk of later haematological malignancies or cholangiocarcinoma, but not other cancers.⁷² This finding was complemented by a cohort that recently found that the risk of manifesting any malignancy was significantly higher in the first 3 months after developing itch.⁷³ Pruritus with systemic symptoms of malignancy needs tailored investigations to rule out specific malignancies. Thus, in those with persistent sudden onset of severe pruritus, in the absence of any obvious trigger or other symptoms or signs or abnormal basic investigations, it may be appropriate to consider a computed tomography scan of the neck, chest, abdomen and pelvis.

A number of cancer treatments, including radiotherapy, can lead to pruritus by a variety of mechanisms.^{63–65} Treatment of the malignancy can often help to resolve pruritus.^{63,65,74} Cancer-drug-induced pruritus requires modification or discontinuation of medications.^{63,64} Biological therapies are now commonly used in oncology. A recent meta-analysis of 33 RCTs concluded that pruritus was a significant side-effect of cancer treatment with this class of agent.⁷⁵ Pruritus is a common side-effect of epidermal growth factor inhibitors, which have either biological or intracellular mechanisms of action.⁷⁶ Oncology patients receiving biological therapies should be asked about pruritus on review.

Table 3 Clinical features of cancers associated with generalized pruritus without rash

| Pruritus-associated cancers | Symptoms | Signs |
|--------------------------------|--|--|
| Any (including haematological) | Loss of appetite, lethargy | Weight loss, lymphadenopathy, fever |
| Breast cancer | Breast or axillary lump, change in breast shape, bloodstained nipple discharge | Breast or axillary lump, change in breast shape, bloodstained nipple discharge |
| Colorectal cancer | A persistent change in bowel habit, diarrhoea, abdominal pain, discomfort or bloating brought on by eating | Blood in the motions, in the absence of haemorrhoids on examination |
| Lung cancer | Persistent cough and breathlessness, persistent chest or shoulder pain | Persistent chest infections and wheeze, facial swelling, hoarse voice, finger clubbing |
| Gastric cancer | Persistent nausea, reflux symptoms, dysphagia or vomiting | Melaena, jaundice |
| Cholangiocarcinoma | Nonspecific upper abdominal discomfort | Jaundice, pale stools, dark urine |
| Testicular cancer | Intermittent dull ache or sharp pain in the testicle or scrotum | Clinical difference between one testicle and the other in texture or firmness |
| Thymoma | Persistent cough, shortness of breath, pain or pressure in the chest, diplopia, dysphagia | Anaemia, frequent infections, muscle weakness, ptosis, arm or facial swelling |
| Insulinoma | Intermittent double vision or blurred vision, confusion, anxiety and irritability, dizziness, mood swings, weakness, sweating and hunger | Symptoms correlate with episodic hypoglycaemia |
| Gastric carcinoid tumour | Abdominal pain, diarrhoea, intermittent facial flushing | Very rarely, cardiac valve murmurs, cutaneous stigmata of neurofibromatosis type 1 or tuberous sclerosis |

Antihistamines are generally ineffective in pruritus due to solid tumours.^{63–65}

Paroxetine 20 mg daily, a serotonin reuptake inhibitor (as shown in an RCT), and mirtazapine 15–30 mg daily, a 5-hydroxytryptamine (5-HT)₂ and 5-HT₃ antagonist (as shown in a case series), may have a role in the management of malignant pruritus.^{51,77} These medicines are thought to act centrally and may take up to 2–3 weeks to become clinically beneficial.⁷⁸

Granisetrone, a 5-HT₃ receptor antagonist, has been used in a case of pruritus in advanced malignancy, where a continuous infusion (3 mg per 24 h) resulted in prompt reduction in pruritus in 2 h.⁷⁹

Aprepitant (a neurokinin-1 receptor antagonist) has been used in malignancy/cancer treatment-associated pruritus, including that secondary to biological agents, although there have been no RCTs, only case reports (125 mg initial dose, then 80 mg daily dosage).^{80,81}

The management of cancer-related pruritus in a palliative-care situation may involve use of medicines, such as thalidomide, that would not necessarily be chosen in the conventional oncology setting, because of the side-effect profile.⁸²

Recommendations (investigation)

- If paraneoplastic pruritus is suspected, investigations should be guided by a thorough, regular history and physical examination, although a full investigation to rule out malignancy is not routinely recommended (Strength of recommendation D; Level of evidence 3)
- Pruritus with systemic symptoms of malignancy needs tailored investigations to rule out specific cancers (Strength of recommendation D (GPP); Level of evidence 4)
- Oncology patients receiving biological and other therapies should be asked about pruritus on review (Strength of recommendation A; Level of evidence 1+)

Recommendations (treatment)

- Paraneoplastic pruritus may be relieved with paroxetine, mirtazapine, granisetron or aprepitant (Strength of recommendation D; Level of evidence 3)
- The management of paraneoplastic pruritus in the palliative care setting may include a wider range of therapies, such as thalidomide (Strength of recommendation D; Level of evidence 3)

7.5 Endocrine causes of generalized pruritus

Conventional reviews and medical textbooks state that both hyperthyroidism and hypothyroidism are associated with generalized pruritus.^{83,84} There is limited evidence of this in clinical experimental studies. In a prospective study comparing 55 patients with pruritus and 41 age- and sex-matched controls, 12 patients had a systemic cause of pruritus.³⁰ One of these 12 was hypothyroid and the pruritus responded to thyroxine replacement.³⁰ Haemoglobin, iron and vitamin B12 levels

were significantly lower in the pruritus group. Thyroid function tests (TFTs) were not different between the two groups.³⁰ A larger study examined 220 newly diagnosed patients with thyroid disease and 90 healthy controls for the presence of skin disease. Chronic nonspecific pruritus, urticaria and vitiligo were all significantly more common in those diagnosed with thyroid disease, but pruritus was not a common finding in the thyroid group (2.7%).⁸⁵ Another retrospective study, following up 263 patients with pruritus for 3 years, found only three instances of associated thyroid disease.⁸⁶ If thyroid disease is causative in pruritus, it is uncommon.

Some textbooks and reviews state that primary hypoparathyroidism may be associated with pruritus, particularly if there are cutaneous calcium deposits,⁸⁷ but this is not borne out by larger studies.^{30,86} Early case reports suggested that subtotal parathyroidectomy for secondary hyperparathyroidism of renal failure improved uraemic pruritus,^{88,89} and a larger case series supported this observation.⁹⁰ However, in a study of 50 uraemic patients receiving haemodialysis, levels of parathyroid hormone (PTH), calcium, phosphate, calcium phosphate product or serum phosphorus were found not to correlate with pruritus.⁹¹ Cinacalcet hydrochloride binds to calcium-sensing receptors in the parathyroid gland to treat secondary hyperparathyroidism.⁹² It may be useful in treating the pruritus of secondary hyperparathyroidism.⁹² However, vitamin D may alleviate pruritus in uraemic patients undergoing either peritoneal dialysis or haemodialysis; it should be noted that in that study it is not clear whether the patients were vitamin D deficient, nor is the replacement dose specified.⁹³

Reducing the phosphate levels in patients with uraemic pruritus might also reduce pruritus, as shown in one cross-sectional study.⁹⁴ In a descriptive case series including patients with GPWOR, as well as pruritic dermatoses, 90% were found to be vitamin D deficient. These often benefited from oral supplementation with vitamin D, at a dose of 50 000 IU weekly for 8–12 weeks.⁹⁵ In conclusion, the evidence regarding calcium metabolism and its effects on pruritus is not clear, although some may benefit from vitamin D supplementation.

Other endocrine conditions that may occasionally be linked with nonspecific pruritus include diabetes mellitus,^{30,86} obesity⁸⁶ and insulinoma⁹⁶ (Level of evidence 3.) Recently, diabetic neuropathy has been associated with pruritus affecting predominantly the trunk.⁹⁷ Diabetes and obesity are such common problems that it may be difficult to make any significant epidemiological link with pruritus, which is also common.⁸⁶

In summary, there is little evidence to support routine endocrine investigations (including TFTs) in the investigation of nonspecific, generalized pruritus, in the absence of any supporting clinical features suggesting diabetes, endocrinopathy or renal disease.

Recommendations (investigation)

- Patients with generalized pruritus should not undergo routine endocrine investigations (including TFTs) unless they present with additional clinical features

suggesting diabetes, other endocrinopathy or renal disease (Strength of recommendation D; Level of evidence 3)

- Vitamin D supplementation may help some people affected by GPWOR (Strength of recommendation D; Level of evidence 3)

7.6 Uraemic pruritus

Pruritus is a common feature of patients with end-stage renal disease (ESRD) or chronic kidney disease.^{98–100} The symptoms vary from mild intermittent irritation to intractable itch associated with very poor sleep and diminished quality of life. In two-thirds of patients, the pruritus is generalized, while in others it affects mainly the back, face or arteriovenous fistula arm. Uraemia causes severe episodes of pruritus, especially during the summer or at night. Although pruritus sometimes improves at the start of dialysis,¹⁰¹ some patients experience itch, during or soon after treatment, usually beginning within 6 months of the onset of dialysis.^{98–100} In the Dialysis Outcomes and Practice Patterns Study of over 1800 patients, the incidence of pruritus in patients on haemodialysis was 42%.⁹⁹ Overall, the severity of pruritus is lower in ESRD treated with peritoneal dialysis, rather than haemodialysis.⁹³ ESRD may be asymptomatic other than pruritus,^{98,99,101} and so urea and electrolytes should be included in a screen for GPWOR. A recent study suggests that C-reactive protein levels in any one patient positively correlate with the incidence of uraemic pruritus.¹⁰²

Dry skin (xerosis) is the most common cutaneous sign in patients on dialysis, although this does not necessarily correlate with pruritus.^{103,104} Perhaps uraemic xerosis, even if it is not the principal cause of pruritus, has a permissive effect by lowering the threshold for itch.¹⁰⁵ Use of emollients is essential.

No single treatment has been shown overwhelmingly to be effective. Although the evidence is not compelling, it is common practice to ensure adequate dialysis, normalize calcium-phosphate balance, control PTH to accepted levels, correct any anaemia with erythropoietin and use emollients (for xerosis) before using other treatment strategies.^{99,106,107}

Pruritus is more common in underdialysed patients and symptoms may be improved by increasing the dialysis dose.¹⁰⁸ The problem is that dialysis adequacy measured by Kt/V [(dialyser urea clearance \times time)/urea distribution volume] is now generally at least as high as, or higher than, in the intervention group in these trials. There are no data correlating an optimum dialysis adequacy to reduce symptoms such as pruritus, but current guidelines suggest that a Kt/V of around 1.6 is optimal.¹⁰⁹ In addition, an RCT has shown that high-flux haemodialysis is more effective in treating uraemic pruritus than haemodialysis filtration.¹¹⁰

Secondary and tertiary hyperparathyroidism often accompany ESRD and may contribute to pruritus (see section 7.5).

Topical capsaicin, a natural alkaloid extracted from chilli peppers, depletes neuropeptides including substance P in peripheral

sensory neurons. A randomized, double-blind crossover trial of 19 patients on haemodialysis with severe pruritus showed a statistically and clinically significant effect of capsaicin 0.025% cream applied four times daily for 4 weeks compared with placebo cream. Fourteen (out of 17) patients completing the study reported marked relief, with five of the 14 reporting complete remission of pruritus. Furthermore, in the responders, there was a prolonged antipruritic effect up to 8 weeks after cessation of treatment. There were no serious side-effects, but one patient died of unrelated myocardial infarction and another had an insufficient response to treatment.¹¹¹

A double-blind crossover RCT with 34 patients on haemodialysis using capsaicin 0.03% cream four times a day for 4 weeks on itchy areas also showed a statistically significant improvement in pruritus scores (based on severity, distribution and sleep disorder).¹¹² A further open-label study of 22 patients on haemodialysis showed some improvement with topical capsaicin 0.025% cream for 6 weeks; however, 12 patients did not complete the trial, with eight citing unacceptable cutaneous 'burning sensation'. A total of seven (out of nine) patients completing the trial showed improvement in symptoms.¹¹³ In summary, there is evidence for a positive effect of capsaicin cream, although trial numbers have been small.

Topical tacrolimus may be effective at controlling uraemic pruritus in individual cases.^{114,115} However, these observations are not confirmed in RCTs in uraemic pruritus.^{116,117} Recently, topical calcipotriol has been shown to have antipruritic effects in renal itch, in an open-label, pilot study on 23 patients.¹¹⁸

An RCT comparing topical cromolyn sodium (sodium cromoglicate) 4% with placebo showed that the former was effective at treating uraemic pruritus.¹¹⁹ A double-blind crossover RCT of γ -linolenic acid in 14 patients on haemodialysis and three patients on peritoneal dialysis showed significant improvement of visual analogue rating in the treatment group (by approximately 50%). Treatment included daily application to the whole body (after bathing) and thrice-daily application to pruritic sites with evening primrose oil for 2 weeks. Only one patient withdrew from the study due to a skin rash.¹²⁰

Oral antihistamines may be effective in uraemic pruritus, but there are no RCTs. Ketotifen 1 mg daily, in five patients, showed marked improvement in symptoms over 8 weeks.¹²¹ A study of 24 patients on haemodialysis used doxepin 10 mg twice daily followed by washout and crossover with placebo for 1 week each. Complete resolution of symptoms was reported in 58% of the treatment group vs. 8% on placebo, and relative improvement in 29% vs. 17%, respectively. One-half of patients (50%) reported drowsiness and one patient withdrew from the study.¹²² A recent prospective cohort study suggested that long-term sedative antihistamines may predispose to dementia and should be avoided, except in palliative situations, although this was not in a specific uraemic population.¹²³ Cetirizine 10 mg daily, a mildly sedating antihistamine, did not help with uraemic pruritus in patients on haemodialysis.¹²⁴

Oral gabapentin has been shown to be effective in uraemic pruritus, usually given in a dose of 100–300 mg after dialysis three times per week. A double-blind, placebo-controlled trial of 34 patients on haemodialysis with pruritus unresponsive to oral antihistamines received 400 mg gabapentin twice weekly after the haemodialysis session for 4 weeks. Note that these are low doses compared with the non-ESRD population. There was a significant improvement in the treatment group compared with placebo, with mild side-effects of drowsiness in the treatment group.¹²⁵ Gabapentin 300 mg given three times a week after dialysis sessions, with a crossover and washout period with placebo, reduced pruritus in 25 adult patients on haemodialysis.¹²⁶ Gabapentin has been shown in a small study ($n = 14$) to improve sleep and depression associated with pruritus in patients on dialysis.¹²⁷ The minimal effective dose of gabapentin is not known, but a multicentre, double-blind, placebo-controlled trial of 34 patients receiving 100 mg postdialysis, three times a week, showed good response rates, with the visual analogue rating falling in excess of 50% compared with placebo.¹²⁸ A recent RCT suggested that the beneficial effect of gabapentin in treating pruritus in patients receiving haemodialysis was not significantly different from the effect of ketotifen.¹²⁹

One RCT showed that another GABA analogue, pregabalin, may also be effective in uraemic pruritus at a dose of 75 mg twice daily orally.¹³⁰

Three 5-HT₃ receptor antagonists that have been tried in uraemic pruritus are ondansetron, granisetron and tropisetron. Initial case reports suggested that both ondansetron 8 mg daily orally¹³¹ and granisetron 1 mg daily orally¹³² were effective. However, a larger open study looking at the effects of ondansetron (8 mg daily orally) and tropisetron (5 mg daily orally)¹²⁴ and an RCT looking at ondansetron¹³⁰ do not support the use of these agents.

Naltrexone is an opioid antagonist used 50 mg daily orally, which has been used with mixed results in uraemic pruritus. An earlier RCT showed that it was effective,¹³³ but a more recent RCT found that it was ineffective and had a high incidence of adverse effects.¹¹⁴ Naltrexone is not a first-choice agent in treating uraemic pruritus.¹³⁴

Thalidomide has been trialled in 11 patients with severe uraemic pruritus with seven in a control arm. The treatment group received thalidomide 100 mg at night for 7 days followed by washout and crossover to placebo. The mean pruritus score was decreased by more than 50% in six of the 11 patients in the thalidomide group and in none of the placebo group. One limitation of this study was the fact that pruritus was scored on a scale of 1 to 3.¹³⁵

Mirtazapine 15–30 mg daily orally may have a role in managing cases of uraemic pruritus, through its anti-anxiety properties,⁵¹ as may sertraline 25–200 mg daily orally, as shown in a large case series.¹³⁶

An RCT of oral activated charcoal in uraemic pruritus in individuals on chronic renal dialysis showed significant improvements in symptoms.¹³⁷

The effects of phototherapy on uraemic pruritus are discussed in section 8.3. The role of acupuncture in treating

uraemic pruritus is discussed in the section on alternative therapies (section 8.4).

In summary, urea and electrolytes should form part of the investigation of GPWOR. There is some evidence to support treatment of uraemic pruritus with a variety of topical and oral agents. Uraemic pruritus is associated with increased mortality, and renal transplantation is the only definitive treatment for this condition.⁹⁹

Recommendations (investigation)

- Urea and electrolytes should form part of the investigation of GPUO (Strength of recommendation D; Level of evidence 3)

Recommendations (treatment)

- Ensure adequate dialysis, normalize calcium–phosphate balance, control PTH to accepted levels, correct any anaemia with erythropoietin and use simple emollients (for xerosis) in patients with uraemic pruritus before using other treatment strategies (Strength of recommendation D; Level of evidence 3)
- No single topical or systemic treatment strategy is effective:
 - Consider capsaicin cream, topical calcipotriol or oral gabapentin (Strength of recommendation D; Level of evidence 3)
 - Sedative antihistamines long term may predispose to dementia and should be avoided, except in palliative care (Strength of recommendation B; Level of evidence 2++)
 - Cetirizine is not an effective antihistamine in uraemic pruritus (Strength of recommendation D; Level of evidence 3)
- Renal transplantation is the only definite treatment (Strength of recommendation D; Level of evidence 3)

7.7 Hepatic pruritus

Pruritus is a common symptom in patients with various hepatobiliary disorders, including cholestasis of pregnancy.^{138–140} The skin in hepatic pruritus is often generally hyperpigmented and excoriated.¹⁴¹ The hands and feet are often the worst-affected areas.¹³⁹ Pruritus in association with fatigue at presentation may be a marker for more aggressive disease, for example primary biliary cholangitis.¹⁴²

There is a poor correlation between pruritus and bile acid levels, suggesting that other factors may be relevant.^{138,139} In patients with large bile duct obstruction, treatment is directed at restoration of biliary drainage, which is often associated with a prompt resolution of symptoms.^{138,139} Nevertheless, measurement of serum bile acids may be important in detecting asymptomatic cholestasis in association with pruritus.¹⁴³ Ursodeoxycholic acid is frequently used to treat cholestasis of a range of causes, including cholestasis of pregnancy and primary biliary cholangitis.

For pruritus associated with parenchymal liver disease, cholestyramine is often given as first-line therapy, although there is limited evidence. Cholestyramine, colestipol and colesevelam (anion exchange binding resins) bind bile salts in the gut lumen, thus preventing absorption of bile acids in the terminal ileum.^{144,145} A meta-analysis of several RCTs involving cholestyramine use suggested that the data were too heterogeneous to pool.¹⁴⁴ However, one small, double-blinded RCT showed a beneficial effect in 10 patients, using cholestyramine 9 g daily orally.¹⁴⁵

Rifampicin is often considered the second-line choice. Starting at a dose of 150 mg twice daily, the dose can be increased to 600 mg twice daily.¹⁴⁶ Patients should be monitored for hepatotoxicity and informed about the change of colour to secretions.¹⁴⁶ Two meta-analyses of a small number of RCTs suggest that rifampicin is effective in reducing hepatic pruritus.^{144,147} Given this evidence, rifampicin should now be the drug of first choice in treating hepatic pruritus.

Naltrexone 50 mg daily orally or sertraline 75–100 mg daily orally have been considered as third-line choices.^{138,139} In a meta-analysis comparing the effects of cholestyramine, rifampicin and opioid antagonists, both opioid antagonists and rifampicin were shown to reduce pruritus.¹⁴⁴ However, rifampicin was not found to have increased side-effects when compared with placebo, unlike the opioid antagonists.¹⁴⁴ Opioid antagonists have significantly more side-effects than cholestyramine and rifampicin, and this may limit their use in hepatic pruritus.^{144,148} There is one small RCT that supports the use of sertraline 75–100 mg in hepatic pruritus. The drug was well tolerated.¹⁴⁹ Sertraline should be the third-line choice before naltrexone. Nalmefene ($0.25\text{--}1\ \mu\text{g kg}^{-1}$ per day intravenously) may be an alternative opioid antagonist to naltrexone,^{150,151} as may methylnaltrexone¹⁵² and naloxone.¹⁵³

Ondansetron was found to be helpful in hepatic pruritus in two early RCTs,^{154,155} but not in two more recent RCTs.^{156,157} There has been no meta-analysis of its role in therapy as yet. It is difficult to support the routine use of ondansetron in the management of hepatic pruritus.

A number of agents have had beneficial effects in individual cases or case series of hepatic pruritus, including systemic dronabinol,¹⁵⁸ phenobarbitone¹⁵⁹ and propofol,^{160,161} as well as topical tacrolimus ointment.¹⁶²

Gabapentin did not improve hepatic pruritus in an RCT. In fact, it made the itch worse in general.¹⁶³ Gabapentin cannot be recommended in hepatic pruritus.

Physical treatments that have been tried in hepatic pruritus include phototherapy (see section 8.3), extracorporeal dialysis techniques, nasobiliary drainage and liver transplantation.^{138,139,164} These latter three are part of specialist hepatological practice and are not detailed further.

Experimental evidence suggests that new specific agents based on blockade of bile acid transport, autotaxin and lysophosphatidic acid metabolism in the liver may improve hepatic pruritus in the future.¹⁶⁵

Hepatitis in GPWOR is discussed in section 7.10: infections, infestations and generalized pruritus.

Recommendations (investigation)

- Liver function tests should form part of the investigation of GPWOR. Perhaps consider bile acids and antimitochondrial antibodies. Any suggestion of significant hepatic impairment should lead to a referral to a hepatology centre (Strength of recommendation D; Level of evidence 3)

Recommendations (treatment)

- In patients with hepatic pruritus, consider rifampicin as first-line treatment (Strength of recommendation A; Level of evidence 1+)
- In patients with hepatic pruritus consider cholestyramine as second-line treatment (Strength of recommendation D (GPP); Level of evidence 4)
- In patients with hepatic pruritus consider sertraline as third-line treatment (Strength of recommendation D (GPP); Level of evidence 4)
- Naltrexone or nalmefene are considered fourth-line treatments (Strength of recommendation D (GPP); Level of evidence 4)
- In patients with hepatic pruritus consider as fifth-line treatment
 - systemic dronabinol, phenobarbitone, propofol or topical tacrolimus ointment (Strength of recommendation D; Level of evidence 3)
 - new specific agents based on blockade of bile acid transport, autotaxin and lysophosphatidic acid metabolism (Strength of recommendation D; Level of evidence 4)
 - phototherapy, extracorporeal dialysis techniques, nasobiliary drainage and liver transplantation (Strength of recommendation D; Level of evidence 3)
- In patients with hepatic pruritus do not use gabapentin (Strength of recommendation D (GPP); Level of evidence 4)

7.8 Neuropathic pruritus

Neuropathic pruritus is caused by pathology located at any point along the afferent pathway of the nervous system.¹⁶⁶ This can arise due to pathology affecting the peripheral nervous system causing postherpetic neuropathy, brachioradial pruritus or notalgia paraesthetica, or due to lesions affecting pathways of the central nervous system, for example as a result of spinal cord tumours, neurofibromatosis type 1 or multiple sclerosis.^{166,167} Sensory symptoms including burning, paraesthesia, stinging and tingling can accompany neuropathic pruritus.^{166,167}

Nerve fibre compression can cause pruritus in the corresponding dermatome, and nerve fibre degeneration (such as small fibre neuropathy) can cause a localized or generalized pruritus. Small fibre neuropathy can occur in systemic diseases such as diabetes mellitus, Guillain-Barré syndrome, sarcoidosis, neurofibromatosis type 1 and HIV.^{167,168} Diabetic neuropathy can lead to a regional pruritus affecting the trunk.⁹⁷ Small fibre neuropathy may be too small to produce clinical or

electrophysiological changes, and the only investigation that may reveal anything is skin biopsy.

As in the majority of cases, the pruritus is not generalized; neurological causes of pruritus will not be discussed further in this review.^{166,168} Following a detailed history, examination and initial investigations, the patient should be referred to the relevant specialist, except in the case of clinically obvious notalgia paraesthetica or brachioradial pruritus, which can often be managed in primary care.^{166,168} Detailed investigation of the nervous system is not usually part of the investigation of generalized pruritus, unless it is clinically indicated.

Recommendations (investigation)

- Following a detailed history, examination and initial investigations, a patient with neuropathic pruritus may need to be referred to the relevant specialist (Strength of recommendation D (GPP); Level of evidence 4)
- Detailed further investigation of the nervous system is advised only if it is clinically indicated (Strength of recommendation D (GPP); Level of evidence 4)

Recommendations (treatment)

- Patients with neuropathic pruritus should be referred to the relevant specialist for treatment (Strength of recommendation D (GPP); Level of evidence 4)

7.9 Psychological and emotional factors in pruritus

Pruritus can be triggered or worsened by negative feelings such as stress or emotional excitation including rage, fear, annoyance and embarrassment, as well as other cognitive factors.^{169–171} Viewing itch-related images and simple verbal suggestion have also been shown to elicit pruritus, clearly demonstrating the importance of psychological factors.^{172,173}

There appears to be a direct correlation between the incidence of stressful major life events and cutaneous sensory symptoms, including pruritus.¹⁷⁴ Minor daily stressors may also contribute to pruritus.¹⁷⁵ Stress may cause pruritus via activation of neural circuits in the hippocampus and subcortical structures.¹⁷⁶ Scratching appears to have a similar effect to sedative antihistamines, in terms of effects on neural activity, in relieving stress-induced pruritus.¹⁷⁶

Chronic generalized pruritus of any cause significantly reduces quality of life in a manner akin to chronic pain.^{7,177} Deranged sleep patterns are common and contribute to exacerbations of itching and further difficulty coping.⁷ Significant psychosocial morbidity, including anxiety and depressive disorder, develops in up to one-third of individuals with chronic pruritus.^{7,178–180} Feelings of stigmatization are common, and perceived body image may become distorted.¹⁸¹

Chronic generalized pruritus is found commonly in several psychiatric disorders including depression, anxiety disorder, obsessive compulsive disorder, substance abuse and delusional infestation.^{7,182–185} However, one should always look

Table 4 Proposed diagnostic criteria for psychogenic pruritus (functional itch disorder)

| Three compulsory criteria | Three out of seven optional criteria are also required |
|---|--|
| Generalized pruritus without primary skin disease | Chronological relationship of the occurrence of pruritus with one or several life events that could have psychological repercussions |
| Chronic pruritus (> 6 weeks) | Variations in intensity associated with stress |
| No somatic cause (cutaneous or systemic) | Pruritus that is worse at night |
| | Predominance during rest or inaction |
| | Associated psychological disorder |
| | Pruritus that could be improved by psychotropic drugs |
| | Pruritus that could be improved by psychological therapy |

for a physical cause before labelling such patients as 'psychogenic'. The French psychodermatology group proposed that psychogenic pruritus should be renamed 'functional itch disorder'. Relevant diagnostic criteria are outlined in Table 4.¹⁸²

A nursing programme 'Coping with Itch' included education on how to avoid trigger factors, how to apply treatments, lifestyle interventions, patient support groups, relaxation techniques and changes to cognition and behaviour.¹⁸⁶ A controlled study found no significant difference in the intensity of itch; however, a significant improvement in itch-related coping was found in the intervention group.^{187,188} The frequency of visits was reduced, with 59% of the intervention group visiting the dermatologist in the first 3 months compared with 86% of the controlled group. The programme led to a reduction in the frequency of itch and scratching, a reduction in catastrophizing thoughts and improvements in coping with helplessness in patients in the period immediately following the intervention.

A holistic biopsychosocial assessment of any distressed patient with chronic pruritus is recommended. This includes screening for depression and anxiety, quality-of-life impact, ongoing stressors and recent major life events, and beliefs related to pruritus. Neuroactive medications are often used in psychogenic pruritus (functional itch disorder), including gabapentin, antidepressants, low-dose neuroleptics and mirtazapine.⁷ However, medications that may benefit psychogenic pruritus can also cause drug-induced pruritus (see section 7.11), for example topiramate.^{189,190}

Input from clinical psychology and/or psychiatry should always be considered. The potential role of new psychological approaches that have proved effective in chronic pain is also promising in the management of chronic pruritus and merits further research including acceptance and commitment therapy and mindfulness-based stress reduction.¹⁹¹

Recommendations (treatment)

- In distressed patients with chronic pruritus including likely psychogenic origin, consider psychosocial and behavioural interventions including education on how to avoid trigger factors, how to apply treatments, lifestyle interventions, relaxation techniques, cognitive restructuring and behaviour modification including habit reversal training (Strength of recommendation D (GPP); Level of evidence 4)
- Patient support groups can be beneficial (Strength of recommendation D (GPP); Level of evidence 4)
- Referral to social workers, liaison psychiatry and psychologists may be helpful in individual cases (Strength of recommendation D (GPP); Level of evidence 4)

Recommendations (investigation)

- Take a full history (including travel history, sexual history and history of potential intravenous drug abuse) and examination; consider:
 - HIV, hepatitis A, B and C serology
 - Screening for malaria, strongyloidiasis and schistosomiasis (Strength of recommendation D (GPP); Level of evidence 4)

Recommendations (treatment)

- In patients with generalized pruritus associated with HIV consider indomethacin 25 mg three times per day, orally (Strength of recommendation D; Level of evidence 3)
- In patients with generalized pruritus associated with HIV consider hypnosis to relieve itch (Strength of recommendation D; Level of evidence 3)

7.10 Infections, infestations and generalized pruritus

Pruritus due to cholestasis is associated with many viral infections, including hepatitis A, B, C and E.^{138,192} Pruritus typically occurs at a late stage of infection with HIV, although occasionally it may be a presenting feature.¹⁹³ The degree of pruritus in HIV infection often correlates directly with the viral load and can be associated with eosinophilia.¹⁹⁴ Causes of pruritus in HIV include xerosis, drug therapies and photosensitivity, together with specific follicular and papular dermatoses, such as eosinophilic folliculitis.¹⁹³ Scabies should always be considered, which can present with severe pruritus and minimal skin signs, particularly in patients with HIV.¹⁹⁵ Phototherapy in HIV-induced pruritus is discussed later (see section 8.3). In one case-control study, indomethacin (25 mg, three times per day) proved more effective at reducing HIV pruritus than sedating antihistamines, although gastric intolerance was observed in several patients.¹⁹⁶ In one case series, hypnosis significantly reduced HIV-related itch.¹⁹⁷ Varicella zoster infection, which is also commonly associated with HIV infection, may be associated with postherpetic pruritus, rather than neuralgia.¹⁹⁸

Eosinophilia and generalized pruritus are features of parasitic infections, notably helminths such as *Strongyloides stercoralis*.¹⁹⁹ Treatment of onchocerciasis with any microfilaricide may cause prolonged itching, with or without oedema and exfoliation.²⁰⁰ Swimmers bathing in lakes and rivers worldwide are at risk of intense pruritus within minutes, due to skin penetration by cercariae of schistosomes (*Trichobilharzia* spp. in Western Europe).²⁰¹ In some schistosome infections this is followed by a toxæmic phase (e.g. Katayama fever due to *Schistosoma japonicum*).²⁰² Chikungunya fever may also present with generalized pruritus.²⁰³

Chloroquine therapy of malaria is considered in section 7.11.

7.11 Drug-induced pruritus

Pruritus secondary to the effects of medication may occur with or without a rash. It is important to obtain a history of all ingested medication, including over-the-counter pharmaceuticals and herbal remedies. In a study of 200 patients with cutaneous drug reactions, 12.5% had pruritus without a rash.²⁰⁴ Proposed mechanisms of drug-induced pruritus include cholestasis, direct drug or metabolite deposition and alteration of neural signalling.²⁰⁵ However, the majority of cases are idiopathic.²⁰⁵ Recently, generalized pruritus has been associated with chronic heart failure, but this is currently thought to be related to the treatment of the underlying cardiac condition, rather than any effect of chronic heart failure on the skin.²⁰⁶ Cholestatic pruritus and its management are discussed elsewhere in these guidelines (see section 8.3). This section will focus on the management of opioid- and chloroquine-induced generalized pruritus without visible skin signs.

Opioid-induced pruritus is common and affects 2–10% of patients receiving oral, 10–50% intravenous and 20–100% epidural and intrathecal opioids.²⁰⁷ The frequency increases with increased dosage of opioids.²⁰⁷ Treatments include opioid antagonists (naloxone, naltrexone, nalmefene, methylnaltrexone), opioid agonist antagonists (nalbuphine, butorphanol), droperidol, ondansetron, propofol, diclofenac and antihistamines.²⁰⁷ The use of opioid antagonists in treating opioid-induced pruritus clearly risks inducing significant pain.

Naltrexone is a commonly used μ -opioid receptor antagonist useful for treatment of opioid and alcohol dependence.²⁰⁸ It was tested in two studies at 3-mg, 6-mg and 9-mg doses in women receiving epidural morphine as postcaesarean section analgesia. Both 6 mg and 9 mg were effective in reducing

pruritus, but with reduction of duration of analgesia compared with control.²⁰⁹

Methylnaltrexone is a derivative of naltrexone with less lipid solubility than naltrexone, which reduces its ability to cross the blood–brain barrier.²⁰⁷ In a double-blind, placebo-controlled study, it reduced the subjective feeling of ‘skin itch’ at an oral dose of 19.2 mg kg⁻¹, 3 min after injection of 0.05 mg kg⁻¹ of intravenous morphine.²¹⁰

Nalbuphine and butorphanol are synthetic κ -opioid receptor agonists that are available only as injections. There are data to suggest antipruritic efficacy of nalbuphine²⁰⁹ and butorphanol,²¹¹ but these are unlikely to be useful outside the critical care setting.

Ondansetron and other 5-HT₃ receptor antagonists (tropisetron and granisetron) do not reduce the incidence of opiate-induced pruritus or time to onset of pruritus when compared with placebo.²¹² However, ondansetron 4 mg or 8 mg may reduce the severity or the need for treatment of pruritus secondary to opiates,²¹² although this has been refuted in a more recent study.²¹³

Droperidol is a parenteral antidopaminergic drug. It may prevent opiate-induced pruritus when given intravenously (2.5–5 mg).²⁰⁹

Diclofenac 100 mg, given rectally to 105 patients postinduction for abdominal surgery in an unblinded RCT, reduced postoperative pruritus.²¹⁴

Mirtazapine 30 mg daily orally²¹⁵ and gabapentin 1200 mg daily in divided doses orally²¹⁶ in RCTs have both been shown to prevent morphine-induced pruritus in a surgical setting.

Chloroquine-induced pruritus during malaria treatment occurs in 60–70% of patients of African background.^{217,218} It is often severe and generalized without skin lesions. It is uncommon in other ethnic groups and the molecular basis for this potential pharmacogenetic effect is unclear.^{217–219} There may be interindividual variation in chloroquine metabolism.²²⁰ Other potential aetiological factors in chloroquine-induced pruritus include the age of the affected individual, degree of plasmodium parasitaemia, species of plasmodium, dosage form of chloroquine and excipients of the preparation.²²¹

A double-blind RCT compared promethazine (25 mg daily orally), prednisolone (10 mg daily orally), niacin (50 mg daily orally) and a combination of prednisolone with niacin.²¹⁷ Pruritus was reduced by prednisolone alone, niacin alone and a combination of prednisolone and niacin. The prednisolone-only and combination groups showed the greatest efficacy when the severity was adjusted to plasmodium parasite density.²¹⁷

Naltrexone (50 mg daily orally) showed no effect on chloroquine-induced pruritus intensity, when compared with promethazine in a small, double-blind RCT involving 18 patients of whom six dropped out.²¹⁸

Dapsone (50 mg daily orally) reduced chloroquine-induced pruritus and limb-scratching activity significantly, whereas ketotifen, clemastine and prednisolone had no effect in a parallel-group trial.²²²

Apart from the opioids and chloroquine, some drugs commonly reported to cause pruritus include angiotensin-

converting enzyme inhibitors and statins, although the list of potential drugs is extensive.²⁰⁵ Interestingly, epidural dexamethasone has been associated with causing generalized pruritus.²²³

A trial of cessation of medications should be undertaken if the risk vs. benefit analysis is acceptable to the clinician and patient.

Recommendations (investigations)

- In patients with drug-induced pruritus, a trial of cessation of medications should be undertaken if the risk vs. benefit analysis is acceptable to both clinician and patient (Strength of recommendation D (GPP); Level of evidence 4)

Recommendations (treatment)

- Naltrexone is effective in treating opioid-induced generalized pruritus without visible skin signs and is the first-choice recommendation in this situation (if cessation of opioid therapy is impossible). Methylnaltrexone may be an alternative (Strength of recommendation B; Level of evidence 1+)
- In patients with opioid-induced generalized pruritus without visible skin signs consider methylnaltrexone, ondansetron, droperidol, mirtazapine or gabapentin as alternative antipruritic agents (Strength of recommendation D (GPP); Level of evidence 4)
- In patients with postoperative generalized pruritus without visible skin signs consider diclofenac given rectally (Strength of recommendation D (GPP); Level of evidence 4)
- In patients with chloroquine-induced generalized pruritus without visible skin signs consider prednisolone 10 mg, niacin 50 mg or a combination of prednisolone and niacin (Strength of recommendation D (GPP); Level of evidence 4)
- In patients with chloroquine-induced generalized pruritus without visible skin signs consider dapsone to relieve itch (Strength of recommendation D (GPP); Level of evidence 4)

8.0 Treatment of generalized pruritus of unknown origin

Once both underlying pruritic skin disease and other secondary causes of pruritus have been excluded, an individual can be considered to have idiopathic GPUO. This must also be distinguished from pruritus of elderly skin (see section 9.2). It is important to keep an open mind to the possibility of symptoms and signs of secondary pruritus developing later in an apparent case of GPUO, therefore necessitating reinvestigation.

8.1 Topical treatments for generalized pruritus of unknown origin

For treatment of secondary pruritus, see sections 8.3 and 8.4.

Although most dermatologists would recommend that patients with pruritus should use emollients to wash and moisturize the skin, and avoid the use of soaps and physical triggers to pruritus such as wearing clothing made of wool,

there is little direct evidence to support these practices in the literature. The evidence is mostly indirect extrapolation from studies involving the management of xerosis and eczema.²²⁴ Many patients will self-medicate with proprietary emollients and most dermatologists will prescribe these as the first step in managing GPUO, despite the lack of objective evidence.

A recent meta-analysis of 19 RCTs and other trials of topical antihistamines suggested that topical doxepin has a role in the management of generalized pruritus, but the evidence for other compounds was lacking.²²⁵ However, concerns about the risk of allergic contact dermatitis to topical doxepin suggest that treatment should be limited to 8 days, and toxicity concerns limit use to 10% of body surface area (maximum 12 g daily).²²⁶

Crotamiton 10% lotion²²⁷ was considered not to have a significant antipruritic effect compared with vehicle in an RCT. Menthol was thought to have a counter-irritant effect (which may be beneficial), rather than a true antipruritic effect compared with vehicle control.²²⁸ Calamine lotion is not recommended in the treatment of pruritus, as there is no literature to support its use in GPUO.

Topical capsaicin has been promoted as an antipruritic agent in a variety of small studies. However, a systemic review of the literature does not support its use in this context,²²⁹ except in uraemic pruritus (see section 7.6). We do not recommend its use in treating GPUO.

Other agents that have been promoted as having a topical antipruritic effect in double-blind RCTs include the topical anaesthetic spray ethyl chloride in placebo-controlled studies,^{230,231} the topical tricyclic antidepressants amitriptyline and diphenhydramine, compared with vehicle control²³² and the moderate-potency topical steroid clobetasone butyrate.²³³ Only clobetasone butyrate and hydrocortisone are available for over-the-counter use in the U.K.

Recommendations

- Patients with GPUO may be prescribed topical doxepin. Treatment should be limited to 8 days, 10% of body surface area and 12 g daily (Strength of recommendation D (GPP); Level of evidence 4)
- Patients with GPUO may benefit from topical clobetasone butyrate or menthol (Strength of recommendation D; Level of evidence 4)
- Patients with GPUO should not use crotamiton cream (Strength of recommendation B; Level of evidence 1+)
- Patients with GPUO should not use topical capsaicin or calamine lotion (Strength of recommendation D (GPP); Level of evidence 4)

8.2 Systemic treatments for generalized pruritus of unknown origin

Various systemic treatments have been used in the management of idiopathic GPUO. However, no RCTs have found any

one therapy to be effective and safe. Most publications are case reports, case series or open trials with no long-term follow-up. It is important to exclude secondary causes of pruritus that have specific treatments.

Blockade of the histamine H₁ receptor subtype, either peripherally or in the central nervous system, may help reduce the sensation of itch.²³⁴ Chlorpheniramine 4 mg and cimetidine 400 mg (H₁ and H₂ antagonists) in combination, taken four times per day, showed suppression of pruritus artificially induced by intraepidermal histamine and the artificial pruritogen papain, suggesting the need for simultaneous antagonism of more than one histamine receptor to control itch.²³⁵ Other sedative antihistamines, such as hydroxyzine 25 mg daily orally, improved histamine-induced pruritus.²³⁶ Nonsedative drugs such as fexofenadine 180 mg or loratadine 10 mg, or mildly sedative agents such as cetirizine 10 mg are now preferred to sedative drugs such as chlorpheniramine and hydroxyzine, because of the risk of potentiating dementia.^{123,237} Nonsedative antihistamines may be used once daily, or up to four times a day as required.²³⁷ An open-label study suggested that oral cetirizine (dose not specified) was preferable, more cost-effective and less time consuming than narrowband (NB)-UVB phototherapy in the management of generalized pruritus.²³⁸

Tricyclic and SSRI antidepressants are often prescribed by clinicians in the management of GPUO, in the absence of psychological disease. In a large case series in GPUO, and in non-dermatological secondary pruritus, both paroxetine 10 mg daily and fluvoxamine 25 mg daily improved pruritus in GPUO.^{238,239} Mirtazapine 15 mg daily orally had similar effects in a smaller case series.²⁴⁰

Naltrexone 50 mg daily orally, an oral opioid antagonist, has been shown to reduce histamine-induced pruritus.²⁴¹ Butorphanol (1 mg daily or every other day), a κ -opioid agonist and μ -opioid antagonist, also suppressed itch in cases of GPUO.²⁴²

Two GABA analogues, gabapentin^{243,244} and pregabalin,²⁴⁵ reduced itch in cases of GPUO. Gabapentin should be started at 300 mg on the first day, then 300 mg twice a day and then increased to 300 mg three times a day on the third day.^{243,244} Gabapentin can then be increased up to 600 mg three times a day over 3–4 weeks if there is no effect.²⁴³ In one study pregabalin was started at a dose of 75 mg twice daily and increased to 150 mg twice daily after 5–8 weeks.²⁴⁵

Ondansetron 8 mg, administered intravenously, may be of benefit in isolated cases of GPUO.²⁴⁶

Azathioprine, in a dosage range between 25 mg and 175 mg daily, appeared to reduce pruritus in a large case series of GPUO, although a high proportion of patients had side-effects, with some serious enough to stop therapy.²⁴⁷ Aprepitant 80 mg daily orally, an antagonist of neurokinin receptor 1 that mediates the actions of substance P on somatosensory neurones, reduced pruritus in a few cases of GPUO, as well as other cases of secondary pruritus.²⁴⁸

Recommendations

- In patients with generalized pruritus no one therapy has been found to be effective and safe. Consider the following to relieve itch:
 - nonsedative antihistamines such as fexofenadine 180 mg, loratadine 10 mg or mildly sedative agents such as cetirizine 10 mg before sedative antihistamines (Strength of recommendation D; Level of evidence 2+)
 - paroxetine, fluvoxamine, mirtazapine, naltrexone, butorphanol, gabapentin, pregabalin, ondansetron or aprepitant (Strength of recommendation D; Level of evidence 3)
 - H₁ and H₂ antagonists in combination, for example fexofenadine and cimetidine (Strength of recommendation D (GPP); Level of evidence 4)
 - sedative antihistamines in the short-term or palliative setting, for example hydroxyzine (Strength of recommendation D; Level of evidence 3)

8.3 Phototherapy in generalized pruritus without rash

There is now some evidence for phototherapy in the management of secondary pruritus due to underlying systemic disease, rather than GPUO, although expert opinion suggests benefit in GPUO. The best-quality evidence for use of phototherapy for pruritus is in treating uraemic pruritus.²⁴⁹ A meta-analysis of RCTs in treating moderate-to-severe uraemic pruritus concluded that broadband (BB)-UVB phototherapy was the treatment of choice, as it was the only therapy to reach clinical significance.²⁴⁹ In a half-body BB-UVB trial in which UVA was used as an active comparator, all patients with uraemic pruritus improved with BB-UVB only on the half-side treated, and the authors suggested that BB-UVB had systemic actions in relieving pruritus.²⁵⁰ Onset of effect was noticed from 2 weeks into treatment and lasted up to 7 months.²⁵⁰ Two prospective studies of NB-UVB showed that 60–80% of patients were responders with a decrease in visual analogue scale scores of 54.2% and 70.8%, respectively.^{251,252} However, some have not been able to replicate the beneficial response with NB-UVB.^{253,254}

The first single-blind RCT looking at NB-UVB rather than BB-UVB found no difference between NB-UVB and placebo in reducing itch in uraemic pruritus.²⁵⁴ Further NB-UVB RCTs are needed to ascertain any benefit and confirm the optimal dose and frequency in the management of uraemic pruritus.

There are case series and case reports demonstrating that both NB-UVB and BB-UVB are effective in providing some relief of the pruritus associated with PV.^{59,255–258} Response rates varied from 50% to 80%.⁵⁹ Relapses often occurred after stopping treatment, but maintenance was reported up to 8 months.⁵⁹ PUVA gave benefit after UVB failed to achieve complete remission, but again relapses were reported from as

early as 2 weeks after stopping.²⁵⁹ PUVA with natural sunlight may also be beneficial.²⁶⁰

Temporary relief of pruritus associated with Hodgkin disease and NHL was reported when treated with BB-UVB and NB-UVB, respectively.^{42,52}

The use of both PUVA and UVB in case reports and series has been reported for aquagenic pruritus not associated with an underlying disorder. Remission was short lived in all patients, with symptoms recurring 3–24 weeks later.^{261–263}

NB-UVB and BB-UVB gave symptomatic relief in some cases of aquagenic pruritus,^{256,264} but in others it was not reported to be of any benefit.²⁶⁵ After relief obtained with NB-UVB, once-weekly continued maintenance treatment prevented relapse of the pruritus.²⁶⁴ Remission for over 1 year was achieved using combined UVA and UVB.²⁶⁶

BB-UVB may be effective in the management of cholestatic pruritus, according to several case series.^{267–269} One single case used UV (presumably BB-UVB, as it is not stated in the paper) to induce remission of pruritus that was maintained with oral cholestyramine.²⁷⁰ Combined UVA and UVB was used to induce remission of pruritus in a single case of cholestatic pruritus, whereas UVB alone was of no benefit.²⁷¹

Phototherapy with UVB was found to be an effective treatment for HIV-associated pruritus, with no adverse effects on viral load in standard doses, in a prospective cohort of 17 patients, with a larger nontreated control group.²⁷² Oral PUVA therapy has also been effective in treating HIV-associated pruritus, in a small case series.²⁷³ Psychogenic excoriation has responded to NB-UVB in a case series of seven patients.²⁷⁴

Recommendations

- BB-UVB is an effective treatment for many patients with uraemic pruritus (Strength of recommendation A; Level of evidence 1+)
- Patients with pruritus associated with Hodgkin disease may benefit from BB-UVB for temporary relief from itch (Strength of recommendation D; Level of evidence 3)
- Patients with pruritus associated with NHL may benefit from NB-UVB for temporary relief from itch (Strength of recommendation D; Level of evidence 3)
- Patients with pruritus associated with PV may benefit from NB-UVB, BB-UVB, PUVA or PUVA in combination with sunlight to relieve itch, although relapse is common after stopping treatment (Strength of recommendation D; Level of evidence 3)
- Patients with aquagenic pruritus may benefit from NB-UVB, BB-UVB or combined UVA and UVB to relieve itch (Strength of recommendation D; Level of evidence 3)
- Patients with cholestatic pruritus may benefit from BB-UVB or combined UVA and UVB to relieve itch (Strength of recommendation D; Level of evidence 3)
- Patients with HIV-associated pruritus may benefit from UVB phototherapy (Strength of recommendation D; Level of evidence 2+)

- Patients with HIV-associated pruritus may benefit from oral PUVA (Strength of recommendation D; Level of evidence 3)
- Patients with psychogenic pruritus (functional itch disorder) may benefit from NB-UVB (Strength of recommendation D; Level of evidence 2+)
- Patients with GPUO often benefit from phototherapy (Strength of recommendation D (GPP); Level of evidence 4)

8.4 Alternative therapies in generalized pruritus of unknown origin and secondary pruritus

Traditional Chinese medicine combines acupuncture, a technique using needles to exert effects through pressure points in the body, with established herbal remedies. Traditionally, acupuncture is only part of a range of treatments available in Chinese medicine and is usually used in combination with these other therapeutic approaches.²⁴ This approach has been shown to be successful in generalized pruritus in a single case.²⁷⁵

Acupuncture may be carried out independently of Chinese herbal medicine.²⁷⁶ An RCT showed that acupuncture can prevent histamine-induced itch.²⁷⁷ There is also some evidence for the use of acupuncture in the management of uraemic pruritus. An RCT showed that acupuncture may be beneficial,²⁷⁸ but a systematic review suggests that acupuncture does not have a role in the management of uraemic pruritus.²⁷⁹ Acupuncture was shown, in a partially controlled study, to reduce the pruritus induced by morphine used for patient-controlled analgesia.²⁸⁰ Currently there is no robust evidence to recommend acupuncture as a first-line therapy of pruritus, but as it is relatively safe and has few side-effects it may always be considered in an individual situation.²⁴

Acupressure combines massage and pressure to specific points, along a defined meridian, similar to those used for acupuncture. Auricular acupressure may be beneficial in uraemic pruritus as reported in an unblinded, placebo-controlled trial.²⁸¹

Two uncontrolled studies suggest the benefits of aromatherapy in uraemic pruritus.^{282,283}

Treatments in other uncontrolled studies that may show benefit in uraemic pruritus include Sericin cream, derived from silkworms,²⁸⁴ topical turmeric²⁸⁵ and oral omega-3 fatty acid supplements.²⁸⁶

Transcutaneous electrical nerve stimulation may be of benefit in some patients, as shown by the results of an uncontrolled study in hepatic pruritus.²⁸⁷

Recommendations

- Patients with GPUO may consider acupuncture in combination with Chinese herbal remedies as referenced (Strength of recommendation D; Level of evidence 3)

- Patients with GPUO may consider acupuncture as a second-line therapy (Strength of recommendation D; Level of evidence 3)
- Patients with uraemic pruritus may consider auricular acupressure, topical Sericin, topical turmeric, oral omega-3 supplements or aromatherapy (Strength of recommendation D (GPP); Level of evidence 3)
- Patients with hepatic pruritus may benefit from transcutaneous electrical nerve stimulation (Strength of recommendation D; Level of evidence 3)

9.0 Management in primary care

9.1 Community perspective

General practice is usually the first point of contact for patients with pruritus in the U.K. and in other countries with primary care-based healthcare systems, and therefore all primary care providers should have an understanding of this condition. Generalized pruritus may have a significant underlying cause in 20–30% of cases, and so the general practitioner (GP) or family physician's input in diagnosis and management is invaluable, given the GP's broad view of the individual's overall health status.^{30,288} For example, GPs may have invaluable insight into patients' drug histories, family history, risk factors for underlying disease and psychosocial issues.^{30,288} The nature of general practice also ensures continuity of long-term care and, as the underlying systematic cause of pruritus may not be evident initially, it is important for GPs to follow up these patients.²⁸⁸

If the initial patient assessment suggests generalized idiopathic pruritus, then simple self-care advice (such as keeping the individual's nails short) and emollients should be used, followed by a short trial of a nonsedating antihistamine,¹²³ if warranted.

There is little evidence on when to refer a patient with generalized idiopathic pruritus to secondary care, but it is recommended to refer patients where there is diagnostic doubt, or in those who are distressed by their symptoms, despite primary care management.^{289,290}

9.2 Pruritus in the elderly

Pruritus in the elderly (Willan's itch) is very common and is defined as chronic itching occurring in those aged over 65 years. It is commonly associated with dry skin or xerosis, but there may be other factors, including GPUO, malignancy, ageing in nerve fibre bundles and drug-induced pruritus.^{291–293} Pruritus alone can very rarely be the presenting feature of bullous pemphigoid, particularly in the elderly, and so it may be necessary to request relevant investigations, such as a skin biopsy and indirect immunofluorescence.²⁹⁴ Loss of free fatty acids in the

stratum corneum leads to superficial cracks and fissures in the epidermis,²⁹² which can cause pruritus by producing asteatotic eczema. This should be managed by emollients and topical steroids, ideally for at least 2 weeks, prior to reassessment for alternative underlying causes of pruritus.²⁹⁵ Moisturizers with high lipid content may be preferred in the elderly.²⁹⁶ The use of sedating antihistamines should be avoided in the elderly, because of the potential causal association with dementia.¹²³ Gabapentin (300 mg daily) has been shown to be of benefit in pruritus of elderly skin in a small case series of seven patients.²⁴⁴

Recommendations (community)

- GPs should regularly follow up patients with generalized pruritus where the underlying systematic cause is not evident (Strength of recommendation D (GPP); Level of evidence 4)
- Patients with GPUO should receive
 - self-care advice and emollients (Strength of recommendation D (GPP); Level of evidence 4)
 - followed by a short course of nonsedating antihistamine (Strength of recommendation B; Level of evidence 2++)
- Patients with GPUO should be referred to secondary care if there is diagnostic doubt, or if primary care management does not relieve symptoms (Strength of recommendation D (GPP); Level of evidence 4)

Recommendations (elderly)

- Patients with pruritus in elderly skin should initially receive emollients and topical steroids for a least 2 weeks to treat any asteatotic eczema (Strength of recommendation D; Level of evidence 4)
- Patients with pruritus in elderly skin who have not responded to the initial treatment should be reassessed (Strength of recommendation D; Level of evidence 4)
- Moisturizers with high lipid content may be preferred in the elderly (Strength of recommendation D; Level of evidence 4)
- Patients with pruritus in elderly skin may benefit from gabapentin (Strength of recommendation D; Level of evidence 3)
- Patients with pruritus in elderly skin should not receive sedating antihistamines (Strength of recommendation C; Level of evidence 2++)
- Patients with GPUO should be referred to secondary care if there is diagnostic doubt, or if primary care management does not relieve symptoms (Strength of recommendation D (GPP); Level of evidence 4)

10.0 Economic considerations

There have not been many studies evaluating the economic impact of secondary pruritus and GPUO. However, there have been a number of studies from a group looking at psychosocial nursing interventions in the management of pruritus (see section 7.9). One particular RCT looked at the health

Table 5 Summary of screening in generalized pruritus without rash

| | |
|---|---|
| Recommended screening in generalized pruritus (Strength of recommendation D) | Detailed history Detailed examination Ferritin Full blood count Urea and electrolytes Liver function tests Erythrocyte sedimentation rate (or C-reactive protein if unavailable) Chest X-ray |
| Optional screening tests, where there is additional clinical suspicion (Strength of recommendation D) | Investigation of potential blood loss Serum bile acids C-reactive protein Lactate dehydrogenase Thyroid function tests Fasting glucose and glycated haemoglobin Calcium and phosphate (and parathyroid hormone) Vitamin D Immunoglobulins HIV and hepatitis A, B and C serology Computed tomography scan of the neck, thorax, abdomen and pelvis Magnetic resonance imaging of the brain and spinal cord Nerve conduction studies Malaria, strongyloidiasis and schistosomiasis screening Skin biopsy |

economic implications and found that most expenses were associated and incurred in the first 3 months of the programme.²⁹⁷ The benefits, with regard to days with little itch, increased beyond 3 months, thus leading to a favourable incremental and cost-effectiveness ratio.

11.0 Future directions

Future directions in investigation and management of secondary pruritus and GPUO should reflect the human and psychological elements of what is a distressing, chronic condition for the patient. Recent advances in both the neuroscience and immunopharmacology of pruritus should lead to new therapies. Molecular studies, perhaps using DNA subtraction analyses, could be used to look for the core abnormalities common to all the forms of secondary pruritus. These key pathological steps could be the best targets for future therapies. However, without recognition of the clinical psychopathological dimension and cross-cultural agreement about clinical assessment of pruritus severity, it will continue to be difficult to implement new therapies.

An important research and clinical objective is to agree on standardized approaches to assessing severity of pruritus and its effect on activities of daily living. Another important question is whether 'up-dosing' of nonsedative antihistamines, in a similar fashion to their use in urticaria, is of benefit. There

are some types of medication that do not appear to have been tried in pruritus, such as the leukotriene inhibitors – montelukast and zafirlukast – or the new H₄ histamine antagonists.

Additionally, further RCTs of NB-UVB are needed to ascertain its effectiveness in the management of uraemic pruritus.

Table 6 Summary of investigations

| | |
|--|--|
| Generalized pruritus (iron deficiency) | Full blood count and ferritin levels should be checked in all patients with chronic GPWOR (Strength of recommendation C) |
| Generalized pruritus (iron overload) | LFTs should be considered for patients with generalized pruritus associated with iron overload (Strength of recommendation D) |
| Generalized pruritus (blood disorders) | <p>Patients with generalized pruritus with suspicion of haematological involvement should have initial investigations including full blood count, blood film, lactate dehydrogenase and erythrocyte sedimentation rate (Strength of recommendation D)</p> <p>Patients with generalized pruritus associated with either PV or suspected lymphoma should be referred to haematology (Strength of recommendation D)</p> <p>Patients with persistent, unexplained generalized pruritus should perhaps have a skin biopsy carried out to ascertain potential cutaneous lymphoma (Strength of recommendation D)</p> <p>Patients with generalized pruritus with suspicion of PV (raised haemoglobin or haematocrit) should have blood samples sent for JAK2 V617F mutation analysis and/or be referred to haematology (Strength of recommendation D)</p> <p>In the absence of JAK2 mutation, secondary causes of PV should be investigated by means of clinical assessment, renal and liver function tests, serum erythropoietin level, measurement of oxygen saturation, chest X-ray and abdominal ultrasound (Strength of recommendation D)</p> |
| Generalized pruritus (malignancy) | <p>A thorough history and physical examination should be performed. Full investigation to rule out malignancy is not routinely recommended (Strength of recommendation C)</p> <p>Pruritus with appropriate systemic symptoms of malignancy needs tailored investigations to rule out specific cancers (Strength of recommendation D (GPP))</p> <p>Oncology patients receiving biological therapies should be asked about pruritus on review (Strength of recommendation A)</p> |
| Generalized pruritus (endocrinopathy) | <p>Patients with generalized pruritus should not undergo routine endocrine investigations (including thyroid function tests), unless they present with additional clinical features suggesting diabetes, other endocrinopathy or renal disease (Strength of recommendation D)</p> <p>Vitamin D supplementation may help some affected by GPWOR (Strength of recommendation D)</p> |
| Generalized pruritus (uraemia) | Urea and electrolytes should form part of the investigation of GPUO (Strength of recommendation D) |
| Generalized pruritus (liver disease) | LFTs should form part of the investigation of GPUO. Perhaps consider bile acids and antimitochondrial antibodies. Any suggestion of significant hepatic impairment should lead to a referral to a hepatology centre (Strength of recommendation D) |
| Generalized pruritus (neuropathy) | <p>Following a detailed history, examination and initial investigations, a patient with neuropathic pruritus may need to be referred to the relevant specialist (Strength of recommendation D (GPP))</p> <p>Detailed further investigation of the nervous system is advised only if it is clinically indicated (Strength of recommendation D (GPP))</p> <p>Patients with suspected neuropathic pruritus should perhaps have a skin biopsy carried out to try to confirm the diagnosis, if small fibre neuropathy is suspected (Strength of recommendation D (GPP))</p> |
| Generalized pruritus (infections and infestations) | Take a full history (including travel history) and examination. Consider HIV and hepatitis A, B and C serology. Consider screening for malaria, strongyloidiasis and schistosomiasis (Strength of recommendation D (GPP)) |
| Generalized pruritus (drug induced) | A trial of cessation of medications should be undertaken, if the risk vs. benefit analysis is acceptable to both clinician and patient (Strength of recommendation D (GPP)) |

GPUO, generalized pruritus of unknown origin; GPWOR, generalized pruritus without rash; JAK, Janus kinase; LFT, liver function test; PV, polycythaemia vera.

Table 7 Summary of treatments

| | |
|--|---|
| Generalized pruritus (iron deficiency) | Iron replacement (Strength of recommendation C) |
| Generalized pruritus (iron overload) | Venesection or desferrioxamine infusion (Strength of recommendation D) |
| Generalized pruritus (lymphoma) | <p>Patients with generalized pruritus associated with lymphoma may have their itch resolved by treatment with cimetidine, carbamazepine, gabapentin or mirtazapine (Strength of recommendation D)</p> <p>Patients with generalized pruritus associated with incurable lymphoma may have their itch relieved with oral corticosteroids (Strength of recommendation D)</p> <p>Patients with pruritus associated with Hodgkin lymphoma may benefit from BB-UVB for temporary relief from itch (Strength of recommendation D)</p> <p>Patients with pruritus associated with non-Hodgkin lymphoma may benefit from NB-UVB for temporary relief from itch (Strength of recommendation D)</p> |
| Generalized pruritus (polycythaemia vera; PV) | <p>Patients with generalized pruritus associated with PV may have their itch relieved with cytoreductive therapy, aspirin, interferon-α, SSRIs, PUVA, UVB phototherapy, cimetidine or atenolol (Strength of recommendation D)</p> <p>Patients with pruritus associated with PV may benefit from NB-UVB, BB-UVB, PUVA or PUVA in combination with sunlight to relieve itch (although relapse is common after stopping treatment) (Strength of recommendation D)</p> <p>Patients with aquagenic pruritus may benefit from NB-UVB, BB-UVB or combined UVA and UVB to relieve itch (Strength of recommendation D)</p> |
| Generalized pruritus (solid cancers) | Paraneoplastic pruritus may be relieved with paroxetine, mirtazapine, granisetron or aprepitant (Strength of recommendation D) |
| Generalized pruritus (uraemia) | <p>Ensure adequate dialysis, normalize calcium–phosphate balance, control parathyroid hormone to accepted levels, correct any anaemia with erythropoietin and use simple emollients (for xerosis) in patients with uraemic pruritus before using other treatment strategies (Strength of recommendation D)</p> <p>No single topical/systemic treatment strategy is effective</p> <ul style="list-style-type: none"> • Consider capsaicin cream, topical calcipotriol or oral gabapentin (Strength of recommendation D) • Sedative antihistamines long term may predispose to dementia and should be avoided, except in palliative care (Strength of recommendation B) • Cetirizine is not effective in uraemic pruritus (Strength of recommendation D) <p>BB-UVB is an effective treatment for many patients with uraemic pruritus (Strength of recommendation A)</p> <p>Patients with uraemic pruritus should consider auricular acupressure or aromatherapy (Strength of recommendation D (GPP))</p> <p>Renal transplantation is the only definite treatment (Strength of recommendation D)</p> |
| Generalized pruritus (liver disease) | <p>In hepatic pruritus consider rifampicin as first-line treatment (Strength of recommendation A)</p> <p>In hepatic pruritus, do not use gabapentin (Strength of recommendation D (GPP))</p> <p>In hepatic pruritus consider cholestyramine as second-line treatment (Strength of recommendation D (GPP))</p> <p>In hepatic pruritus consider sertraline as third-line treatment before naltrexone or nalmeferne (Strength of recommendation D (GPP))</p> <p>In hepatic pruritus consider as fifth-line treatment:</p> <ul style="list-style-type: none"> • systemic dronabinol, phenobarbitone, propofol or topical tacrolimus ointment (Strength of recommendation D) • new specific agents based on blockade of bile acid transport, autotaxin and lysophosphatidic acid metabolism (Strength of recommendation D) • extracorporeal dialysis techniques, nasobiliary drainage and liver transplantation (Strength of recommendation D) <p>Patients with cholestatic pruritus may benefit from BB-UVB or combined UVA and UVB to relieve itch (Strength of recommendation D)</p> <p>Patients with hepatic pruritus may benefit from transcutaneous electrical nerve stimulation (Strength of recommendation D)</p> |
| Generalized pruritus (neuropathy) | Patients with neuropathic pruritus should be referred to the relevant specialist for treatment (Strength of recommendation D (GPP)) |
| Generalized pruritus (psychological and emotional factors) | <p>In distressed patients with chronic pruritus including likely psychogenic origin, consider psychosocial and behavioural interventions including education on how to avoid trigger factors and apply treatments, lifestyle interventions, relaxation techniques, cognitive restructuring and behaviour modification including habit reversal training (Strength of recommendation D (GPP))</p> <p>Patient support groups can be beneficial (Strength of recommendation D (GPP))</p> <p>Referral to social workers, liaison psychiatry and psychologists may be helpful in individual cases (Strength of recommendation D (GPP))</p> <p>Patients with psychogenic pruritus (functional itch disorder) may benefit from NB-UVB (Strength of recommendation D)</p> |

(continued)

Table 7 (continued)

| | |
|--|--|
| Generalized pruritus (infections and infestations) | <p>In patients with generalized pruritus associated with HIV consider:</p> <ul style="list-style-type: none"> • indomethacin (Strength of recommendation D) or • less toxic cyclooxygenase inhibitors (Strength of recommendation D (GPP)) <p>Patients with HIV-associated pruritus may benefit from UVB phototherapy (Strength of recommendation D)</p> <p>Patients with HIV-associated pruritus may benefit from oral PUVA (Strength of recommendation D)</p> <p>In patients with generalized pruritus associated with HIV consider hypnosis to relieve itch (Strength of recommendation D)</p> |
| Generalized pruritus (drug induced) | <p>Naltrexone is effective in treating opioid-induced generalized pruritus without visible skin signs and is the first-choice recommendation in this situation (if cessation of opioid therapy is impossible). Methylnaltrexone may be an alternative (Strength of recommendation B)</p> <p>In patients with opioid-induced generalized pruritus without visible skin signs consider methylnaltrexone, ondansetron, droperidol, mirtazapine or gabapentin as alternative antipruritic agents (Strength of recommendation D (GPP))</p> <p>In patients with postoperative generalized pruritus without visible skin signs consider diclofenac 100 mg given rectally (Strength of recommendation D (GPP))</p> <p>In patients with chloroquine-induced generalized pruritus without visible skin signs consider prednisolone 10 mg, niacin 50 mg or a combination of prednisolone and niacin (Strength of recommendation D (GPP))</p> <p>In patients with chloroquine-induced generalized pruritus without visible skin signs consider dapsone to relieve itch (Strength of recommendation D (GPP))</p> |
| Generalized pruritus of unknown origin (GPUO) | <p>Patients with GPUO should receive self-care advice and emollients (Strength of recommendation D (GPP))</p> <p>Patients with GPUO should be referred to secondary care if there is diagnostic doubt, or if primary care management does not relieve symptoms (Strength of recommendation D (GPP))</p> <p>Patients with GPUO could be prescribed topical doxepin. Treatment should be limited to 8 days, 10% of body surface area and 12 g daily (Strength of recommendation D (GPP))</p> <p>Patients with GPUO may benefit from topical clobetasone butyrate or menthol (Strength of recommendation D)</p> <p>Patients with GPUO should not use crotonamiton cream (Strength of recommendation B)</p> <p>Patients with GPUO should not use topical capsaicin or calamine lotion (Strength of recommendation D (GPP))</p> <p>In GPUO, consider non-sedative antihistamines (H₁ antagonists) such as fexofenadine 180 mg or loratadine 10 mg, or mildly sedative agents such as cetirizine 10 mg orally (Strength of recommendation D)</p> <p>In GPUO, consider H₁ and H₂ antagonists in combination, for example fexofenadine and cimetidine (Strength of recommendation D (GPP))</p> <p>In GPUO, consider paroxetine, fluvoxamine, mirtazapine, naltrexone, butorphanol, gabapentin, pregabalin, ondansetron or aprepitant orally (Strength of recommendation D)</p> <p>Sedative antihistamines are recommended in GPUO only in the short-term or palliative setting, such as hydroxyzine (Strength of recommendation D)</p> <p>Patients with GPUO should consider acupuncture in combination with Chinese herbal remedies (Strength of recommendation D)</p> |
| Pruritus in elderly skin | <p>Patients with GPUO should consider acupuncture as a second-line therapy (Strength of recommendation D)</p> <p>Patients with pruritus in elderly skin should initially receive emollients and topical steroids for a least 2 weeks to exclude asteatotic eczema (Strength of recommendation D)</p> <p>Moisturizers with high lipid content may be preferred in the elderly (Strength of recommendation D)</p> <p>Patients with pruritus in elderly skin may benefit from gabapentin (Strength of recommendation D)</p> <p>Patients with pruritus in elderly skin should not be prescribed sedative antihistamines (Strength of recommendation C)</p> <p>Patients with pruritus in elderly skin who have not responded to the initial treatment should be reassessed (Strength of recommendation D)</p> <p>Patients with pruritus in elderly skin should be referred to secondary care if there is diagnostic doubt, or if primary care management does not relieve symptoms (Strength of recommendation D (GPP))</p> |

BB, broadband; NB, narrowband; PUVA, psoralen–ultraviolet A; SSRI, selective serotonin reuptake inhibitor; UV, ultraviolet.

12.0 Recommended audit points

In the last 20 consecutive patients presenting with possible GPWOR, were the following items recorded:

- Ferritin
- Full blood count
- Urea and electrolytes
- Liver function tests

- Erythrocyte sedimentation rate (if available locally)
- Chest X-ray

Healthcare professionals treating patients presenting with possible GPUO at follow-up, where initial tests were negative, may wish to audit the recording of the following additional items, dependent on clinical findings. However, these do not form part of our core recommended audit points:

- a. Investigation of potential blood loss
- b. Serum bile acids
- c. C-reactive protein
- d. Lactate dehydrogenase
- e. Thyroid function tests
- f. Fasting glucose and glycated haemoglobin
- g. Calcium and phosphate (and parathyroid hormone)
- h. Vitamin D
- i. Immunoglobulins
- j. HIV and hepatitis A, B and C serology
- k. Computed tomography scan of the neck, thorax, abdomen and pelvis
- l. Magnetic resonance imaging of the brain and spinal cord
- m. Nerve conduction studies
- n. Malaria, strongyloidiasis and schistosomiasis screening
- o. Skin biopsy

The audit recommendation of 20 cases per department is to reduce variation in the results due to a single patient, and allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months. A summary of the screening recommendations for GPWOR is provided in Table 5.

13.0 Summary

See the full manuscript for details of the evidence. A summary of investigations is provided in Table 6, with treatments summarized in Table 7.

Pruritus or itch is a common and distressing symptom of many dermatological, systemic and psychological disorders. These guidelines explore the investigation and management of generalized pruritus, whether due to problems with iron metabolism, renal disease, hepatic cholestasis, malignancy, other haematological disorders, endocrine disease, infection, neurological and psychological dysfunction or ageing, as well as pruritus of unknown origin. It is important to exclude as many of the secondary causes of pruritus as possible in any patient with pruritus, because many of these secondary causes have specific treatments, including the management of the underlying disease. The guidelines do not cover primary dermatological pruritic conditions, nor do they cover pruritus in children or in pregnancy (Table 1). They also do not cover the pathophysiology of itch in great detail. Producing guidelines for the investigation and management of pruritus is not straightforward. Many publications reviewed are case reports, case series or open trials with no long-term follow-up, so firm evidence-based conclusions are not always possible. Nevertheless, these guidelines form a framework for the investigation and management of generalized secondary pruritus and GPUO in adults.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Appendix S1. Literature search strategy.

Appendix

Levels of evidence

| Level of evidence ^a | Type of evidence |
|--------------------------------|---|
| 1++ | High-quality meta-analyses, systematic reviews of RCTs or RCTs with a very low risk of bias |

(continued)

Appendix (continued)

| | |
|-----|---|
| 1+ | Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias |
| 1– | Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias |
| 2++ | High-quality systematic reviews of case-control or cohort studies. High-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal |
| 2+ | Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal |
| 2– | Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal |
| 3 | Nonanalytical studies (e.g. case reports, case series) |
| 4 | Expert opinion, formal consensus |

RCT, randomized controlled trial. ^aStudies with a level of evidence '–' should not be used as a basis for making a recommendation.

Strength of recommendation

| Class | Evidence |
|---------|--|
| A | At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results, or Evidence drawn from a NICE technology appraisal |
| B | A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+ |
| C | A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++ |
| D | Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus |
| D (GPP) | A good practice point (GPP) is a recommendation for best practice based on the experience of the guidelines development group |

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.