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

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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 guidance – 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 methodology[3] 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 Index[19] 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 $\mu g\ L^{-1}$ 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 infiltration[35] (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] mirtazapine[51] 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] cimetidine[61] 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 $(5\text{-HT})_2$ and 5-HT_3 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]

Granisetron, a 5-HT_3 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] obesity[86] and insulinoma[96] (*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 × 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-HT_3 receptor antagonists that have been tried in uraemic pruritus are ondansetron, granisetron and tropisetron. Initial case reports suggested that both ondansetron 8 mg daily orally[131] and granisetron 1 mg daily orally[132] 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 ondansetron[130] 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 antianxiety 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 (0·25–1 $\mu g\ kg^{-1}$ per day intravenously) may be an alternative opioid antagonist to naltrexone,[150,151] as may methylnaltrexone[152] 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] phenobarbitone[159] 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 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]

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

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 toxaemic 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 nalbuphine[209] and butorphanol,[211] but these are unlikely to be useful outside the critical care setting.

Ondansetron and other 5-HT_3 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 orally[215] and gabapentin 1200 mg daily in divided doses orally[216] 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% lotion[227] 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 control[232] 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 H_1 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 (H_1 and H_2 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*)
  - H_1 and H_2 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 turmeric[285] 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 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.

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

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 H_4 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)	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*) Patients with generalized pruritus associated with either PV or suspected lymphoma should be referred to haematology (*Strength of recommendation D*) Patients with persistent, unexplained generalized pruritus should perhaps have a skin biopsy carried out to ascertain potential cutaneous lymphoma (*Strength of recommendation D*) 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*) 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*)
Generalized pruritus (malignancy)	A thorough history and physical examination should be performed. Full investigation to rule out malignancy is not routinely recommended (*Strength of recommendation C*) Pruritus with appropriate systemic symptoms of malignancy needs tailored investigations to rule out specific cancers (*Strength of recommendation D (GPP)*) Oncology patients receiving biological therapies should be asked about pruritus on review (*Strength of recommendation A*)
Generalized pruritus (endocrinopathy)	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*) Vitamin D supplementation may help some affected by GPWOR (*Strength of recommendation D*)
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)	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)*) Detailed further investigation of the nervous system is advised only if it is clinically indicated (*Strength of recommendation D (GPP)*) 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)*)
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)	Patients with generalized pruritus associated with lymphoma may have their itch resolved by treatment with cimetidine, carbamazepine, gabapentin or mirtazapine (*Strength of recommendation D*) Patients with generalized pruritus associated with incurable lymphoma may have their itch relieved with oral corticosteroids (*Strength of recommendation D*) Patients with pruritus associated with Hodgkin lymphoma may benefit from BB-UVB for temporary relief from itch (*Strength of recommendation D*) Patients with pruritus associated with non-Hodgkin lymphoma may benefit from NB-UVB for temporary relief from itch (*Strength of recommendation D*)
Generalized pruritus (polycythaemia vera; PV)	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*) 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*) Patients with aquagenic pruritus may benefit from NB-UVB, BB-UVB or combined UVA and UVB to relieve itch (*Strength of recommendation D*)
Generalized pruritus (solid cancers)	Paraneoplastic pruritus may be relieved with paroxetine, mirtazapine, granisetron or aprepitant (*Strength of recommendation D*)
Generalized pruritus (uraemia)	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*) No single topical/systemic treatment strategy is effective • 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*) BB-UVB is an effective treatment for many patients with uraemic pruritus (*Strength of recommendation A*) Patients with uraemic pruritus should consider auricular acupressure or aromatherapy (*Strength of recommendation D (GPP)*) Renal transplantation is the only definite treatment (*Strength of recommendation D*)
Generalized pruritus (liver disease)	In hepatic pruritus consider rifampicin as first-line treatment (*Strength of recommendation A*) In hepatic pruritus, do not use gabapentin (*Strength of recommendation D (GPP)*) In hepatic pruritus consider cholestyramine as second-line treatment (*Strength of recommendation D (GPP)*) In hepatic pruritus consider sertraline as third-line treatment before naltrexone or nalmefene (*Strength of recommendation D (GPP)*) In hepatic pruritus consider as fifth-line treatment: • 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*) Patients with cholestatic pruritus may benefit from BB-UVB or combined UVA and UVB to relieve itch (*Strength of recommendation D*) Patients with hepatic pruritus may benefit from transcutaneous electrical nerve stimulation (*Strength of recommendation D*)
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)	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)*) Patient support groups can be beneficial (*Strength of recommendation D (GPP)*) Referral to social workers, liaison psychiatry and psychologists may be helpful in individual cases (*Strength of recommendation D (GPP)*) Patients with psychogenic pruritus (functional itch disorder) may benefit from NB-UVB (*Strength of recommendation D*)

(continued)

Table 7 (continued)

Generalized pruritus (infections and infestations)	In patients with generalized pruritus associated with HIV consider: • indomethacin (*Strength of recommendation D*) or • less toxic cyclooxygenase inhibitors (*Strength of recommendation D (GPP)*) Patients with HIV-associated pruritus may benefit from UVB phototherapy (*Strength of recommendation D*) Patients with HIV-associated pruritus may benefit from oral PUVA (*Strength of recommendation D*) In patients with generalized pruritus associated with HIV consider hypnosis to relieve itch (*Strength of recommendation D*)
Generalized pruritus (drug induced)	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*) 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)*) In patients with postoperative generalized pruritus without visible skin signs consider diclofenac 100 mg given rectally (*Strength of recommendation D (GPP)*) 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)*) In patients with chloroquine-induced generalized pruritus without visible skin signs consider dapsone to relieve itch (*Strength of recommendation D (GPP)*)
Generalized pruritus of unknown origin (GPUO)	Patients with GPUO should receive self-care advice and emollients (*Strength of recommendation D (GPP)*) 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)*) 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)*) Patients with GPUO may benefit from topical clobetasone butyrate or menthol (*Strength of recommendation D*) Patients with GPUO should not use crotamiton cream (*Strength of recommendation B*) Patients with GPUO should not use topical capsaicin or calamine lotion (*Strength of recommendation D (GPP)*) In GPUO, consider nonsedative antihistamines (H_1 antagonists) such as fexofenadine 180 mg or loratadine 10 mg, or mildly sedative agents such as cetirizine 10 mg orally (*Strength of recommendation D*) In GPUO, consider H_1 and H_2 antagonists in combination, for example fexofenadine and cimetidine (*Strength of recommendation D (GPP)*) In GPUO, consider paroxetine, fluvoxamine, mirtazapine, naltrexone, butorphanol, gabapentin, pregabalin, ondansetron or aprepitant orally (*Strength of recommendation D*) Sedative antihistamines are recommended in GPUO only in the short-term or palliative setting, such as hydroxyzine (*Strength of recommendation D*) Patients with GPUO should consider acupuncture in combination with Chinese herbal remedies (*Strength of recommendation D*) Patients with GPUO should consider acupuncture as a second-line therapy (*Strength of recommendation D*)
Pruritus in elderly skin	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*) Moisturizers with high lipid content may be preferred in the elderly (*Strength of recommendation D*) Patients with pruritus in elderly skin may benefit from gabapentin (*Strength of recommendation D*) Patients with pruritus in elderly skin should not be prescribed sedative antihistamines (*Strength of recommendation C*) Patients with pruritus in elderly skin who have not responded to the initial treatment should be reassessed (*Strength of recommendation D*) 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)*)

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:

a. Ferritin
b. Full blood count
c. Urea and electrolytes
d. Liver function tests
e. Erythrocyte sedimentation rate (if available locally)
f. 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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References

1 Metz M, Wahn U, Gieler U *et al.* Chronic pruritus associated with dermatologic disease in infancy and childhood: update from an interdisciplinary group of dermatologists and pediatricians. *Pediatr Allergy Immunol* 2013; **24**:527–39.
2 Rungsiprakarn P, Laopaiboon M, Sangkomkamhang US *et al.* Pharmacological interventions for generalised itching (not caused by systemic disease or skin lesions) in pregnancy. *Cochrane Database Syst Rev* 2016; **2**:CD011351.
3 Bell HK, Ormerod AD. Writing a British Association of Dermatologists clinical guideline: an update on the process and guidance for authors. *Br J Dermatol* 2009; **160**:725–8.
4 Brouwers MC, Kho ME, Browman GP *et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. *CMAJ* 2010; **182**:E839–42.
5 Weisshaar E, Szepietowski JC, Darsow U *et al.* European guideline on chronic pruritus. *Acta Derm Venereol* 2012; **92**:563–81.
6 Leslie TA. Itch. *Medicine* 2013; **41**:367–71.
7 Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus. *N Engl J Med* 2013; **368**:1625–34.
8 Weisshaar E, Apfelbacher C, Jäger G *et al.* Pruritus as a leading symptom: clinical characteristics and quality of life in German and Ugandan patients. *Br J Dermatol* 2006; **155**:957–64.
9 Matterne U, Apfelbacher CJ, Loerbroks A *et al.* Prevalence, correlates and characteristics of chronic pruritus: a population-based cross-sectional study. *Acta Derm Venereol* 2011; **91**:674–9.
10 Weisshaar E, Dalgard F. Epidemiology of itch: adding to the burden of skin morbidity. *Acta Derm Venereol* 2009; **89**:339–50.
11 Luo J, Feng J, Liu S *et al.* Molecular and cellular mechanisms that initiate pain and itch. *Cell Mol Life Sci* 2015; **72**:3201–23.
12 Shiratori-Hayashi M, Koga K, Tozaki-Saitoh H *et al.* STAT3-dependent reactive astrogliosis in the spinal dorsal horn underlies chronic itch. *Nat Med* 2015; **21**:927–31.
13 Chen L, Wang W, Tan T *et al.* $GABA_A$ receptors in the central nucleus of the amygdala are involved in pain- and itch-related responses. *J Pain* 2016; **17**:181–9.
14 Kleyn CE, McKie S, Ross A *et al.* A temporal analysis of the central neural processing of itch. *Br J Dermatol* 2012; **166**:994–1001.
15 Ständer S, Schäfer I, Phan NQ *et al.* Prevalence of chronic pruritus in Germany: results of a cross-sectional study in a sample working population of 11,730. *Dermatology* 2010; **221**:229–35.
16 Berger TG, Shive M, Harper GM. Pruritus in the older patient: a clinical review. *JAMA* 2013; **310**:2443–50.
17 Hartmann EM, Handwerker HO, Forster C. Gender differences in itch and pain-related sensations provoked by histamine, cowhage and capsaicin. *Acta Derm Venereol* 2015; **95**:25–30.
18 Phan NQ, Blome C, Fritz F *et al.* Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. *Acta Derm Venereol* 2012; **92**:502–7.
19 Warlich B, Fritz F, Osada N *et al.* Health-related quality of life in chronic pruritus: an analysis related to disease etiology, clinical skin conditions and itch intensity. *Dermatology* 2015; **231**:253–9.
20 Ständer S, Augustin M, Reich A *et al.* Pruritus assessment in clinical trials: consensus recommendations from the International

Forum for the Study of Itch (IFSI) Special Interest Group Scoring Itch in Clinical Trials. *Acta Derm Venereol* 2013; **93**:509–14.
21 Fritz F, Blome C, Augustin M *et al.* Differences in patient and physician assessment of a dynamic patient reported outcome tool for chronic pruritus. *J Eur Acad Dermatol Venereol* 2016; **30**:962–5.
22 Desai NS, Poindexter GB, Monthrope YM *et al.* A pilot quality-of-life instrument for pruritus. *J Am Acad Dermatol* 2008; **59**:234–44.
23 Haydek CG, Love E, Mollanazar NK *et al.* Validation and banding of the ItchyQuant: a self-report itch severity scale. *J Invest Dermatol* 2017; **137**:57–61.
24 Tan EK, Millington GWM, Levell NJ. Acupuncture in dermatology: an historical perspective. *Int J Dermatol* 2009; **48**:648–52.
25 Xander C, Meerpohl JJ, Galandi D *et al.* Pharmacological interventions for pruritus in adult palliative care patients. *Cochrane Database Syst Rev* 2010; **6**:CD008320.
26 Lewiecki EM, Rahman F. Pruritus. A manifestation of iron deficiency. *JAMA* 1976; **236**:2319–20.
27 Vickers CF. Iron-deficiency pruritus. *JAMA* 1977; **238**:129.
28 Valsecchi R, Cainelli T. Generalized pruritus: a manifestation of iron deficiency. *Arch Dermatol* 1983; **119**:630.
29 Bharati A, Yesudian PD. Positivity of iron studies in pruritus of unknown origin. *J Eur Acad Dermatol Venereol* 2008; **22**:617–18.
30 Sato S. Iron deficiency: structural and microchemical changes in hair, nails, and skin. *Semin Dermatol* 1991; **10**:313–19.
31 Lau MS, Mooney P, White W *et al.* Pre-endoscopy point of care test (Simtomax- IgA/IgG-Deamidated Gliadin Peptide) for coeliac disease in iron deficiency anaemia: diagnostic accuracy and a cost saving economic model. *BMC Gastroenterol* 2016; **16**:115.
32 Kluger N, Raison-Peyron N, Rigole H *et al.* Generalized pruritus revealing hereditary haemochromatosis. *Acta Derm Venereol* 2007; **87**:277.
33 Hamilton DV, Gould DJ. Generalized pruritus as a presentation of idiopathic haemochromatosis. *Br J Dermatol* 1985; **112**:629.
34 Nestler JE. Hemochromatosis and pruritus. *Ann Intern Med* 1983; **98**:1026.
35 Brigant F, Hautefeuille V, Dadban A *et al.* Generalized pruritus in dysmetabolic hyperferritinemia treated by phlebotomy. *Dermatol Online J* 2015; **21**: 13030/qt4qg8 m234.
36 Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. *Br J Haematol* 2001; **115**:619–21.
37 Krajnik M, Zylicz Z. Pruritus in advanced internal diseases. *Pathogenesis and treatment. Neth J Med* 2001; **58**:27–40.
38 Erskine JG, Rowan RM, Alexander JO *et al.* Pruritus as a presentation of myelomatosis. *BMJ* 1977; **1**:687–8.
39 Hanes D, Jefferson-Gordon J, Lindsey A *et al.* Assessment and prediction of pruritus in sickle cell disease patients: a preliminary study. *Clin Nurse Spec* 2013; **27**:255–61.
40 Polat M, Öztas P, Ilhan MN *et al.* Generalized pruritus: a prospective study concerning etiology. *Am J Clin Dermatol* 2008; **9**:39–44.
41 Parker A, Bain B, Devereux S *et al.*; British Committee for Standards in Haematology. Guideline: best practice in lymphoma diagnosis and reporting. Available at: http://www.bcshguidelines.com/documents/Lymphoma_disease_app_bcsh_042010.pdf (last accessed 19 October 2017).
42 Mallo S, Coto P, Caminal L *et al.* Generalized pruritus as presentation of T-cell large granular lymphocyte leukaemia. *Clin Exp Dermatol* 2008; **33**:348–9.
43 Pujol RM, Gallardo F, Llistosella E *et al.* Invisible mycosis fungoides: a diagnostic challenge. *J Am Acad Dermatol* 2002; **47**:S168–71.
44 Deen K, O'Brien B, Wu J. Invisible mycosis fungoides: not to be missed in chronic pruritus. *Dermatol Ther (Heidelb)* 2015; **5**:213–16.
45 García R, Hernández JM, Caballero MD *et al.* Serum lactate dehydrogenase level as a prognostic factor in Hodgkin's disease. *Br J Cancer* 1993; **68**:1227–31.
46 Baxter EJ, Scott LM, Campbell PJ *et al.* Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders. *Lancet* 2005; **365**:1054–61.
47 McMullin MF, Bareford D, Campbell P *et al.* Guidelines for the diagnosis, investigation and management of polycythaemia/erythrocytosis. *Br J Haematol* 2005; **130**:174–95.
48 Passamonti F, Griesshammer M, Palandri F *et al.* Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol* 2017; **18**:88–99.
49 Aymard JP, Lederlin P, Witz F *et al.* Cimetidine for pruritus in Hodgkin's disease. *BMJ* 1980; **280**:151–2.
50 Korfitis C, Trafalis DT. Carbamazepine can be effective in alleviating tormenting pruritus in patients with hematologic malignancy. *J Pain Symptom Manage* 2008; **35**:571–2.
51 Davis MP, Frandsen JL, Walsh D *et al.* Mirtazapine for pruritus. *J Pain Symptom Manage* 2003; **25**:288–91.
52 Kaptanoglu AF, Oskay T. Ultraviolet B treatment for pruritus in Hodgkin's lymphoma. *J Eur Acad Dermatol Venereol* 2003; **17**:489–90.
53 Twycross R, Greaves MW, Handwerker H *et al.* Itch: scratching more than the surface. *QJM* 2003; **96**:7–26.
54 Fjellner B, Hagermark O. Pruritus in polycythemia vera: treatment with aspirin and possibility of platelet involvement. *Acta Derm Venereol* 1979; **59**:505–12.
55 Jackson N, Burt D, Crocker J *et al.* Skin mast cells in polycythaemia vera: relationship to the pathogenesis and treatment of pruritus. *Br J Dermatol* 1987; **116**:21–9.
56 Bircher AJ. Water-induced itching. *Dermatologica* 1990; **181**:83–7.
57 Finelli C, Gugliotta L, Gamberi B *et al.* Relief of intractable pruritus in polycythemia vera with recombinant interferon alfa. *Am J Hematol* 1993; **43**:316–18.
58 Tefferi A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. *Blood* 2002; **99**:2627.
59 Baldo A, Sammarco E, Monfrecola G *et al.* UVB phototherapy for pruritus in polycythaemia vera. *J Dermatolog Treat* 1996; **7**:245–6.
60 Jeanmougin M, Rain JD, Najean Y. Efficacy of photochemotherapy on severe pruritus in polycythemia vera. *Ann Hematol* 1996; **73**:91–3.
61 Weick JK, Donovan PB, Najean Y *et al.* The use of cimetidine for the treatment of pruritus in polycythemia vera. *Arch Intern Med* 1982; **142**:241–2.
62 Cao T, Yong AA, Tan KB *et al.* Idiopathic aquagenic pruritus: pathogenesis and effective treatment with atenolol. *Dermatol Ther* 2015; **28**:118–21.
63 Lidstone V, Thorns A. Pruritus in cancer patients. *Cancer Treat Rev* 2001; **27**:305–12.
64 Chiang HC, Huang V, Cornelius LA. Cancer and itch. *Semin Cutan Med Surg* 2011; **30**:107–12.
65 Cormia FE. Pruritus, an uncommon but important symptom of systemic carcinoma. *Arch Dermatol* 1965; **92**:36–9.
66 Hebant B, Miret N, Berthelot L *et al.* Generalized pruritus preceding paraneoplastic neuropathy. *J Clin Neurosci* 2016; **26**:156–7.
67 Fett N, Haynes K, Propert KJ *et al.* Predictors of malignancy development in patients with chronic pruritus. *J Dermatol Sci* 2016; **82**:123–8.
68 Atkar R, Sterling JC. Testicular cancer as an underlying cause of intractable chronic pruritus. *Clin Exp Dermatol* 2015; **40**:694–5.
69 Padda SK, Shrager JB, Riess JW *et al.* Pruritus as a paraneoplastic symptom of thymoma. *J Thorac Oncol* 2015; **10**:e110–12.

70 Lober CW. Should the patient with generalized pruritus be evaluated for malignancy? *J Am Acad Dermatol* 1988; **19**:350–2.

71 Paul R, Paul R, Jansen CT. Itch and malignancy prognosis in generalized pruritus: a 6-year follow-up of 125 patients. *J Am Acad Dermatol* 1987; **16**:1179–82.

72 Fett N, Haynes K, Propert KJ *et al.* Five-year malignancy incidence in patients with chronic pruritus: a population-based cohort study aimed at limiting unnecessary screening practices. *J Am Acad Dermatol* 2014; **70**:651–8.

73 Johannesdottir SA, Farkas DK, Vinding GR *et al.* Cancer incidence among patients with a hospital diagnosis of pruritus: a nationwide Danish cohort study. *Br J Dermatol* 2014; **171**:839–46.

74 Chiang C, Price V, Mirmirani P. Central centrifugal cicatricial alopecia: superimposed tinea capitis as the etiology of chronic scalp pruritus. *Dermatol Online J* 2008; **14**:3.

75 Santoni M, Conti A, Andrikou K *et al.* Risk of pruritus in cancer patients treated with biological therapies: a systematic review and meta-analysis of clinical trials. *Crit Rev Oncol Hematol* 2015; **96**:206–19.

76 Clabbers JMK, Boers-Doets CB, Gelderblom H *et al.* Xerosis and pruritus as major EGFRI-associated adverse events. *Support Care Cancer* 2016; **24**:513–21.

77 Zylicz Z, Krajnik M, Sorge AA *et al.* Paroxetine in the treatment of severe non-dermatological pruritus: a randomized, controlled trial. *J Pain Symptom Manage* 2003; **26**:1105–12.

78 Yosipovitch G. Chronic pruritus: a paraneoplastic sign. *Dermatol Ther* 2010; **23**:590–6.

79 Porzio G, Aielli F, Narducci F *et al.* Pruritus in a patient with advanced cancer successfully treated with continuous infusion of granisetron. *Support Care Cancer* 2004; **12**:208–9.

80 Santini D, Vincenzi B, Guida FM *et al.* Aprepitant for management of severe pruritus related to biological cancer treatments: a pilot study. *Lancet Oncol* 2012; **13**:1020–4.

81 Vincenzi B, Fratto ME, Santini D *et al.* Aprepitant against pruritus in patients with solid tumours. *Support Care Cancer* 2010; **18**:1229–30.

82 Lowney AC, McAleer MA, Kelly S *et al.* Thalidomide therapy for pruritus in the palliative setting – a distinct subset of patients in whom the benefit may outweigh the risk. *J Pain Symptom Manage* 2014; **48**:e3–5.

83 Cassano N, Tessari G, Vena GA *et al.* Chronic pruritus in the absence of specific skin disease: an update on pathophysiology, diagnosis, and therapy. *Am J Clin Dermatol* 2010; **11**:399–411.

84 Greaves MW. Pruritus. In: *Rook's Textbook of Dermatology* (Burns A, Breathnach S, Cox N, Griffiths C, eds), 8th edn. Oxford: Blackwell Publishing, 2010; Chapter 21.

85 Artantaş S, Gül U, Kiliç A *et al.* Skin findings in thyroid diseases. *Eur J Intern Med* 2009; **20**:158–61.

86 Sommer F, Hensen P, Böckenholt B *et al.* Underlying diseases and co-factors in patients with severe chronic pruritus: a 3-year retrospective study. *Acta Derm Venereol* 2007; **87**:510–16.

87 Jabbour SA. Cutaneous manifestations of endocrine disorders: a guide for dermatologists. *Am J Clin Dermatol* 2003; **4**:315–31.

88 Hampers CL, Katz AI, Wilson RE *et al.* Disappearance of 'uremic' itching after subtotal parathyroidectomy. *N Engl J Med* 1968; **279**:695–7.

89 Massry SG, Popovtzer MM, Coburn JW *et al.* Intractable pruritus as a manifestation of secondary hyperparathyroidism in uremia. Disappearance of itching after subtotal parathyroidectomy. *N Engl J Med* 1968; **279**:697–700.

90 Chou FF, Ho JC, Huang SC *et al.* A study on pruritus after parathyroidectomy for secondary hyperparathyroidism. *J Am Coll Surg* 2000; **190**:65–70.

91 Shirazian S, Kline M, Sakhiya V *et al.* Longitudinal predictors of uremic pruritus. *J Ren Nutr* 2013; **23**:428–31.

92 El-Shafey EM, Alsahow AE, Alsaran K *et al.* Cinacalcet hydrochloride therapy for secondary hyperparathyroidism in hemodialysis patients. *Ther Apher Dial* 2011; **15**:547–55.

93 Wu HY, Peng YS, Chen HY *et al.* A comparison of uremic pruritus in patients receiving peritoneal dialysis and hemodialysis. *Medicine (Baltimore)* 2016; **95**:e2935.

94 Gatmiri SM, Mahdavi-Mazdeh M, Lessan-Pezeshki M *et al.* Uremic pruritus and serum phosphorus level. *Acta Med Iran* 2013; **51**:477–81.

95 Goetz DW. Idiopathic itch, rash, and urticaria/angioedema merit serum vitamin D evaluation: a descriptive case series. *W V Med J* 2011; **107**:14–20.

96 King NK, Siriwardana HP, Coyne JD *et al.* Intractable pruritus associated with insulinoma in the absence of multiple endocrine neoplasia: a novel paraneoplastic phenomenon. *Scand J Gastroenterol* 2003; **38**:678–80.

97 Yamaoka H, Sasaki H, Yamasaki H *et al.* Truncal pruritus of unknown origin may be a symptom of diabetic polyneuropathy. *Diabetes Care* 2010; **33**:150–5.

98 Szepietowski JC, Balaskas E, Taube KM *et al.* Quality of life in patients with uraemic xerosis and pruritus. *Acta Derm Venereol* 2011; **91**:313–17.

99 Pisoni RL, Wikstrom B, Elder SJ *et al.* Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2006; **21**:3495–505.

100 Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis* 2007; **50**:11–20.

101 Masmoudi A, Hajjaji Darouiche M, Ben Salah H *et al.* Cutaneous abnormalities in patients with end stage renal failure on chronic hemodialysis. A study of 458 patients. *J Dermatol Case Rep* 2014; **8**:86–94.

102 Malekmakan L, Malekmakan A, Sayadi M *et al.* Association of high-sensitive C-reactive protein and dialysis adequacy with uremic pruritus. *Saudi J Kidney Dis Transpl* 2015; **26**:890–5.

103 Yosipovitch G, Reis J, Tur E *et al.* Sweat secretion, stratum corneum hydration, small nerve function and pruritus in patients with advanced chronic renal failure. *Br J Dermatol* 1995; **133**:561–4.

104 Ståhle-Bäckdahl M. Uremic pruritus. *Semin Dermatol* 1995; **14**:297–301.

105 Zucker I, Yosipovitch G, David M *et al.* Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol* 2003; **49**:842–6.

106 Karadag E, Kilic SP, Karatay G *et al.* Effect of baby oil on pruritus, sleep quality, and quality of life in hemodialysis patients: pretest–post-test model with control groups. *Jpn J Nurs Sci* 2014; **11**:180–9.

107 De Marchi S, Cecchin E, Villalta D *et al.* Relief of pruritus and decreases in plasma histamine concentrations during erythropoietin therapy in patients with uremia. *N Engl J Med* 1992; **326**:969–74.

108 Hiroshige K, Kabashima N, Takasugi M *et al.* Optimal dialysis improves uremic pruritus. *Am J Kidney Dis* 1995; **25**:413–19.

109 Ko MJ, Wu HY, Chen HY *et al.* Uremic pruritus, dialysis adequacy, and metabolic profiles in hemodialysis patients: a prospective 5-year cohort study. *PLOS ONE* 2013; **8**:e71404.

110 Jiang X, Ji F, Chen Z-W *et al.* Comparison of high-flux hemodialysis with hemodialysis filtration in treatment of uraemic pruritus: a randomized controlled trial. *Int Urol Nephrol* 2016; **48**:1533–41.

111 Tarng DC, Cho YL, Liu HN *et al.* Hemodialysis-related pruritus: a double-blind, placebo-controlled, crossover study of capsaicin 0.025% cream. *Nephron* 1996; **72**:617–22.

112 Makhlough A. Topical capsaicin therapy for uremic pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2010; **4**:137–40.

113 Breneman DL, Cardone JS, Blumsack RF *et al.* Topical capsaicin for treatment of hemodialysis-related pruritus. *J Am Acad Dermatol* 1992; **26**:91–4.

114 Pauli-Magnus C, Mikus G, Alscher DM *et al.* Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol* 2000; **11**:514–19.

115 Kuypers DR, Claes K, Evenepoel P *et al.* A prospective proof of concept study of the efficacy of tacrolimus ointment on uraemic pruritus (UP) in patients on chronic dialysis therapy. *Nephrol Dial Transplant* 2004; **19**:1895–901.

116 Ghorbani AR, Feily A, Khalili A *et al.* Lack of efficacy of topical calcineurin inhibitor pimecrolimus 1% on pruritus of severely uremic patients: a randomized double-blind study in 60 patients. *Dermatitis* 2011; **22**:167–8.

117 Duque MI, Yosipovitch G, Fleischer AB Jr, *et al.* Lack of efficacy of tacrolimus ointment 0.1% for treatment of hemodialysis-related pruritus: a randomized, double-blind, vehicle-controlled study. *J Am Acad Dermatol* 2005; **52**:519–21.

118 Jung KE, Woo YR, Lee JS *et al.* Effect of topical vitamin D on chronic kidney disease-associated pruritus: an open-label pilot study. *J Dermatol* 2015; **42**:800–3.

119 Feily A, Dormanesh B, Ghorbani AR *et al.* Efficacy of topical cromolyn sodium 4% on pruritus in uremic nephrogenic patients: a randomized double-blind study in 60 patients. *Int J Clin Pharmacol Ther* 2012; **50**:510–13.

120 Chen Y-C, Chiu W-T, Wu M-S. Therapeutic effect of topical gamma-linolenic acid on refractory uremic pruritus. *Am J Kidney Dis* 2006; **48**:69–76.

121 Francos GC, Kauh YC, Gittlen SD *et al.* Elevated plasma histamine in chronic uremia. Effects of ketotifen on pruritus. *Int J Dermatol* 1991; **30**:884–9.

122 Pour-Reza-Gholi F, Nasrollahi A, Firouzan A *et al.* Low-dose doxepin for treatment of pruritus in patients on hemodialysis. *Iran J Kidney Dis* 2007; **1**:34–7.

123 Gray SL, Anderson ML, Dublin S *et al.* Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med* 2015; **175**:401–7.

124 Weisshaar E, Dunker N, Rohl FW *et al.* Antipruritic effects of two different 5-HT_3 receptor antagonists and an antihistamine in haemodialysis patients. *Exp Dermatol* 2004; **13**:298–304.

125 Naini AE, Harandi AA, Khanbabapour S *et al.* Gabapentin: a promising drug for the treatment of uremic pruritus. *Saudi J Kidney Dis Transpl* 2007; **18**:378–81.

126 Gunal AI, Ozalp G, Yoldas TK *et al.* Gabapentin therapy for pruritus in haemodialysis patients: a randomized, placebo-controlled, double-blind trial. *Nephrol Dial Transplant* 2004; **19**:3137–9.

127 Tol H, Atalay H, Güney I *et al.* The effects of gabapentin therapy on pruritus, quality of life, depression and sleep quality in pruritic hemodialysis patients. *Trakya Univ Tip Fak Derg* 2010; **27**:1–5.

128 Razeghi E, Eskandari D, Ganji MR *et al.* Gabapentin and uremic pruritus in hemodialysis patients. *Ren Fail* 2009; **31**:85–90.

129 Amirkhanlou S, Rashedi A, Taherian J *et al.* Comparison of gabapentin and ketotifen in treatment of uremic pruritus in hemodialysis patients. *Pak J Med Sci* 2016; **32**:22–6.

130 Yue J, Jiao S, Xiao Y *et al.* Comparison of pregabalin with ondansetron in treatment of uraemic pruritus in dialysis patients: a prospective, randomized, double-blind study. *Int Urol Nephrol* 2015; **47**:161–7.

131 Andrews PA, Quan V, Ogg CS. Ondansetron for symptomatic relief in terminal uraemia. *Nephrol Dial Transplant* 1995; **10**:140.

132 Albares MP, Betlloch I, Guijarro J *et al.* Severe pruritus in a haemodialysed patient: dramatic improvement with granisetron. *Br J Dermatol* 2003; **148**:376–7.

133 Peer G, Kivity S, Agami O *et al.* Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet* 1996; **348**:1552–4.

134 Wikström B, Gellert R, Ladefoged SD *et al.* Kappa-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol* 2005; **16**:3742–7.

135 Silva SR, Viana PC, Lugon NV *et al.* Thalidomide for the treatment of uremic pruritus: a crossover randomized double-blind trial. *Nephron* 1994; **67**:270–3.

136 Chan KY, Li CW, Wong H *et al.* Use of sertraline for antihistamine-refractory uremic pruritus in renal palliative care patients. *J Palliat Med* 2013; **16**:966–70.

137 Pederson JA, Matter BJ, Czerwinski AW *et al.* Relief of idiopathic generalized pruritus in dialysis patients treated with activated oral charcoal. *Ann Intern Med* 1980; **93**:446–8.

138 Kremer AE, Bolier R, van Dijk R *et al.* Advances in pathogenesis and management of pruritus in cholestasis. *Dig Dis* 2014; **32**:637–45.

139 Dogra S, Jindal R. Cutaneous manifestations of common liver diseases. *J Clin Exp Hepatol* 2011; **1**:177–84.

140 Beard MP, Millington GWM. Recent developments in the specific dermatoses of pregnancy. *Clin Exp Dermatol* 2012; **37**:1–4.

141 Goldman RD, Rea TH, Cinque J. The 'butterfly' sign. A clue to generalized pruritus in a patient with chronic obstructive hepatobiliary disease. *Arch Dermatol* 1983; **119**:183–4.

142 Quarneti C, Muratori P, Lalanne C *et al.* Fatigue and pruritus at onset identify a more aggressive subset of primary biliary cirrhosis. *Liver Int* 2015; **35**:636–41.

143 Eisendle K, Muller H, Ortner E *et al.* Pruritus of unknown origin and elevated total serum bile acid levels in patients without clinically apparent liver disease. *J Gastroenterol Hepatol* 2011; **26**:716–21.

144 Tandon P, Bain VG, Rowe BH *et al.* The efficacy and safety of bile acid binding agents, opioid antagonists, or rifampin in the treatment of cholestasis-associated pruritus. *Am J Gastroenterol* 2007; **102**:1528–36.

145 Di Padova C, Tritapepe R, Rovagnati P *et al.* Double-blind placebo-controlled clinical trial of microporous cholestyramine in the treatment of intra- and extra-hepatic cholestasis: relationship between itching and serum bile acids. *Methods Find Exp Clin Pharmacol* 1984; **6**:773–6.

146 Ghent CN, Carruthers SG. Treatment of pruritus in primary biliary cirrhosis with rifampin. Results of a double-blind, crossover, randomized trial. *Gastroenterology* 1988; **94**:488–93.

147 Khurana S, Singh P. Rifampin is safe for treatment of pruritus due to chronic cholestasis: a meta-analysis of prospective randomized-controlled trials. *Liver Int* 2006; **26**:943–8.

148 Phan NQ, Bernhard JD, Luger TA *et al.* Antipruritic treatment with systemic μ-opioid receptor antagonists: a review. *J Am Acad Dermatol* 2010; **63**:680–8.

149 Mayo MJ, Handem I, Saldana S *et al.* Sertraline as a first-line treatment for cholestatic pruritus. *Hepatology* 2007; **45**:666–74.

150 Bergasa NV, Schmitt JM, Talbot TL *et al.* Open-label trial of oral nalmefene therapy for the pruritus of cholestasis. *Hepatology* 1998; **27**:679–84.

151 Bergasa NV, Alling DW, Talbot TL *et al.* Oral nalmefene therapy reduces scratching activity due to the pruritus of cholestasis: a controlled study. *J Am Acad Dermatol* 1999; **41**:431–4.

152 Hohl CM, Wong JK, Harlos MS. Methylnaltrexone to palliate pruritus in terminal hepatic disease. *J Palliat Care* 2015; **31**:124–6.

153 Joshi GG, Thakur BS, Sircar S *et al.* Role of intravenous naloxone in severe pruritus of acute cholestasis. *Indian J Gastroenterol* 2009; **28**:180–2.
154 Schwörer H, Hartmann H, Ramadori G. Relief of cholestatic pruritus by a novel class of drugs: 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists: effectiveness of ondansetron. *Pain* 1995; **61**:33–7.
155 Müller C, Pongratz S, Pidlich J *et al.* Treatment of pruritus in chronic liver disease with the 5-hydroxytryptamine receptor type 3 antagonist ondansetron: a randomized, placebo-controlled, double-blind cross-over trial. *Eur J Gastroenterol Hepatol* 1998; **10**:865–70.
156 O'Donohue JW, Pereira SP, Ashdown AC *et al.* A controlled trial of ondansetron in the pruritus of cholestasis. *Aliment Pharmacol Ther* 2005; **21**:1041–5.
157 Jones EA, Molenaar HAJ, Oosting J. Ondansetron and pruritus in chronic liver disease: a controlled study. *Hepatogastroenterology* 2007; **54**:1196–9.
158 Neff GW, O'Brien CB, Reddy KR *et al.* Preliminary observation with dronabinol in patients with intractable pruritus secondary to cholestatic liver disease. *Am J Gastroenterol* 2002; **97**:2117–19.
159 Bachs L, Parés A, Elena M *et al.* Comparison of rifampicin with phenobarbitone for treatment of pruritus in biliary cirrhosis. *Lancet* 1989; **1**:574–6.
160 Borgeat A, Wilder-Smith O, Mentha G *et al.* Propofol and cholestatic pruritus. *Am J Gastroenterol* 1992; **87**:672–4.
161 Borgeat A, Savioz D, Mentha G *et al.* Intractable cholestatic pruritus after liver transplantation – management with propofol. *Transplantation* 1994; **58**:727–9.
162 Aguilar-Bernier M, Bassas-Vila J, Sanz-Munoz C *et al.* Successful treatment of pruritus with topical tacrolimus in a patient with primary biliary cirrhosis. *Br J Dermatol* 2005; **152**:808–9.
163 Bergasa NV, McGee M, Ginsburg IH *et al.* Gabapentin in patients with the pruritus of cholestasis: a double-blind, randomized, placebo-controlled trial. *Hepatology* 2006; **44**:1317–23.
164 Hegade VS, Krawczyk M, Kremer AE *et al.* The safety and efficacy of nasobiliary drainage in the treatment of refractory cholestatic pruritus: a multicentre European study. *Aliment Pharmacol Ther* 2016; **43**:294–302.
165 Hegade VS, Kendrick SF, Jones DE. Drug treatment of pruritus in liver diseases. *Clin Med (Lond)* 2015; **15**:351–7.
166 Yosipovitch G, Samuel LS. Neuropathic and psychogenic itch. *Dermatol Ther* 2008; **21**:32–41.
167 Brenaut E, Nizery-Guermeur C, Audebert-Bellanger S *et al.* Clinical characteristics of pruritus in neurofibromatosis 1. *Acta Derm Venereol* 2016; **96**:398–9.
168 Stumpf A, Ständer S. Neuropathic itch: diagnosis and management. *Dermatol Ther* 2013; **26**:104–9.
169 Fjellner B, Arnetz BB. Psychological predictors of pruritus during mental stress. *Acta Derm Venereol* 1985; **65**:504–8.
170 Robinson P, Szewczyk M, Haddy L *et al.* Outbreak of itching and rash. Epidemic hysteria in an elementary school. *Arch Intern Med* 1984; **144**:1959–62.
171 Schut C, Grossman S, Gieler U *et al.* Contagious itch: what we know and what we would like to know. *Front Hum Neurosci* 2015; **9**:57.
172 Niemeier V, Kupfer J, Gieler U. Observations during an itch-inducing lecture. *Dermatol Psychosom* 2000; **1**(Suppl. 1):15–18.
173 Bartels DJ, van Laarhoven AI, Haverkamp EA *et al.* Role of conditioning and verbal suggestion in placebo and nocebo effects on itch. *PLOS ONE* 2014; **9**:e91727.
174 Gupta MA, Gupta AK. Stressful major life events are associated with a higher frequency of cutaneous sensory symptoms: an empirical study of non-clinical subjects. *J Eur Acad Dermatol Venereol* 2004; **18**:560–5.
175 Verhoeven EW, de Klerk S, Kraaimaat FW *et al.* Biopsychosocial mechanisms of chronic itch in patients with skin diseases: a review. *Acta Derm Venereol* 2008; **88**:211–18.
176 Kim HJ, Park JB, Lee JH *et al.* How stress triggers itch: a preliminary study of the mechanism of stress-induced pruritus using fMRI. *Int J Dermatol* 2016; **55**:434–42.
177 Kini SP, DeLong LK, Veledar E *et al.* The impact of pruritus on quality of life: the skin equivalent of pain. *Arch Dermatol* 2011; **147**:1153–6.
178 Sheehan-Dare RA, Henderson MJ, Cotterill JA. Anxiety and depression in patients with chronic urticaria and generalized pruritus. *Br J Dermatol* 1990; **123**:769–74.
179 Lopes GB, Nogueira FC, de Souza MR *et al.* Assessment of the psychological burden associated with pruritus in hemodialysis patients using the kidney disease quality of life short form. *Qual Life Res* 2012; **21**:603–12.
180 Stumpf A, Ständer S, Warlich B *et al.* Relations between the characteristics and psychological comorbidities of chronic pruritus differ between men and women: women are more anxious than men. *Br J Dermatol* 2015; **172**:1323–8.
181 Stumpf A, Stander S, Phan NQ *et al.* Body concept of patients with chronic pruritus in relation to scratch lesions and psychic symptoms. *Dermatology* 2013; **227**:263–9.
182 Misery L, Alexandre S, Dutray S *et al.* Functional itch disorder or psychogenic pruritus: suggested diagnosis criteria from the French psychodermatology group. *Acta Derm Venereol* 2007; **87**:341–4.
183 Kretzmer GE, Gelkopf M, Kretzmer G *et al.* Idiopathic pruritus in psychiatric inpatients: an explorative study. *Gen Hosp Psychiatry* 2008; **30**:344–8.
184 Ferm I, Sterner M, Wallengren J. Somatic and psychiatric comorbidity in patients with chronic pruritus. *Acta Derm Venereol* 2010; **90**:395–400.
185 Kimsey LS. Delusional infestation and chronic pruritus: a review. *Acta Derm Venereol* 2016; **96**:298–302.
186 van Os-Medendorp H, Eland-de Kok P, van Linge R *et al.* The tailored implementation of the nursing programme 'Coping with Itch'. *J Clin Nurs* 2008; **17**:1460–70.
187 van Os-Medendorp H, Eland-de Kok PC, Ros WJ *et al.* The nursing programme 'Coping with itch': a promising intervention for patients with chronic pruritic skin diseases. *J Clin Nurs* 2007; **16**:1238–46.
188 van Os-Medendorp H, Ros WJ, Eland-de Kok PC *et al.* Effectiveness of the nursing programme 'Coping with itch': a randomized controlled study in adults with chronic pruritic skin disease. *Br J Dermatol* 2007; **156**:1235–44.
189 Calabrò RS, Bramanti P, Digangi G *et al.* Psychogenic itch responding to topiramate. *Psychosomatics* 2013; **54**:297–300.
190 Signorelli MS, Cinconze M, Nasca MR *et al.* Can topiramate induce pruritus? A case report and review of literature. *CNS Neurol Disord Drug Targets* 2015; **14**:309–12.
191 Schut C, Mollanazar NK, Kupfer J *et al.* Psychological interventions in the treatment of chronic itch. *Acta Derm Venereol* 2016; **96**:157–61.
192 Bonney JH, Kwame-Aryee RA, Obed S *et al.* Fatal hepatitis E viral infection in pregnant women in Ghana: a case series. *BMC Res Notes* 2012; **5**:478.
193 Shapiro RS, Samorodin C, Hood AF. Pruritus as a presenting sign of acquired immunodeficiency syndrome. *J Am Acad Dermatol* 1987; **16**:1115–17.
194 Milazzo F, Piconi S, Trabattoni D *et al.* Intractable pruritus in HIV infection: immunologic characterization. *Allergy* 1999; **54**:266–72.
195 Zuger A. Intolerable pruritus in an HIV-infected man. *AIDS Clin Care* 1995; **7**(23):26.

196 Smith KJ, Skelton HG, Yeager J *et al.* Pruritus in HIV-1 disease: therapy with drugs which may modulate the pattern of immune dysregulation. *Dermatology* 1997; **195**:353–8.
197 Rucklidge JJ, Saunders D. The efficacy of hypnosis in the treatment of pruritus in people with HIV/AIDS: a time-series analysis. *Int J Clin Exp Hypn* 2002; **50**:149–69.
198 Lee HJ, Kim GW, Kim WJ *et al.* Clinical characteristics of postherpetic pruritus: assessment using a questionnaire, von Frey filaments and Neurometer. *Br J Dermatol* 2015; **172**:1672–3.
199 Funkhouser TA, Carr WW. A 34-year-old man with chronic itching and peripheral and submucosal eosinophilia. *Allergy Asthma Proc* 2006; **27**:77–81.
200 Awadzi K. Clinical picture and outcome of serious adverse events in the treatment of onchocerciasis. *Filaria J* 2003; **2** (Suppl. 1):S6.
201 Kolárová L. Schistosomes causing cercarial dermatitis: a mini-review of current trends in systematics and of host specificity and pathogenicity. *Folia Parasitol (Praha)* 2007; **54**:81–7.
202 Evans AC, Martin DJ, Ginsburg BD. Katayama fever in scuba divers. A report of 3 cases. *S Afr Med J* 1991; **79**:271–4.
203 Cunha BA, Leonichev VB, Raza M. Chikungunya fever presenting with protracted severe pruritus. *IDCases* 2016; **6**:29–30.
204 Raksha MP, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. *Indian J Dermatol Venereol Leprol* 2008; **74**:80.
205 Reich A, Stander S, Szepietowski JC. Drug-induced pruritus: a review. *Acta Derm Venereol* 2009; **89**:236–44.
206 Niklasson O, Boman K, Stenberg B. The prevalence and characteristics of pruritus in patients with heart failure. *Br J Dermatol* 2015; **172**:1541–6.
207 Miller JL, Hagemann TM. Use of pure opioid antagonists for management of opioid-induced pruritus. *Am J Health Syst Pharm* 2011; **68**:1419–25.
208 Bart G. Maintenance medication for opiate addiction: the foundation of recovery. *J Addict Dis* 2012; **31**:207–25.
209 Kjellberg F, Tramèr MR. Pharmacological control of opioid-induced pruritus: a quantitative systematic review of randomized trials. *Eur J Anaesthesiol* 2001; **18**:346–57.
210 Yuan CS, Foss JF, O'Connor M *et al.* Efficacy of orally administered methylnaltrexone in decreasing subjective effects after intravenous morphine. *Drug Alcohol Depend* 1998; **52**:161–5.
211 Wu Z, Kong M, Wang N *et al.* Intravenous butorphanol administration reduces intrathecal morphine-induced pruritus after cesarean delivery: a randomized, double-blind, placebo-controlled study. *J Anesth* 2012; **26**:752–7.
212 George RB, Allen TK, Habib AS. Serotonin receptor antagonists for the prevention and treatment of pruritus, nausea, and vomiting in women undergoing cesarean delivery with intrathecal morphine: a systematic review and meta-analysis. *Anesth Analg* 2009; **109**:174–82.
213 Brião FF, Horta ML, Horta BL *et al.* Comparison of droperidol and ondansetron prophylactic effect on subarachnoid morphine-induced pruritus. *Braz J Anesthesiol* 2015; **65**:244–8.
214 Colbert S, O'Hanlon DM, Galvin S *et al.* The effect of rectal diclofenac on pruritus in patients receiving intrathecal morphine. *Anaesthesia* 1999; **54**:948–52.
215 Sheen MJ, Ho ST, Lee CH *et al.* Prophylactic mirtazapine reduces intrathecal morphine-induced pruritus. *Br J Anaesth* 2008; **101**:711–15.
216 Sheen MJ, Ho S-T, Lee C-H *et al.* Preoperative gabapentin prevents intrathecal morphine-induced pruritus after orthopedic surgery. *Anesth Analg* 2008; **106**:1868–72.
217 Adebayo RA, Sofowora GG, Onayemi O *et al.* Chloroquine-induced pruritus in malaria fever: contribution of malaria parasitaemia and the effects of prednisolone, niacin, and their combination, compared with antihistamine. *Br J Clin Pharmacol* 1997; **44**:157–61.
218 Ajayi AA, Kolawole BA, Udoh SJ. Endogenous opioids, μ-opiate receptors and chloroquine-induced pruritus: a double-blind comparison of naltrexone and promethazine in patients with malaria fever who have an established history of generalized chloroquine-induced itching. *Int J Dermatol* 2004; **43**:972–7.
219 Spencer HC, Poulter NR, Lury JD *et al.* Chloroquine-associated pruritus in a European. *BMJ (Clin Res Ed)* 1982; **285**:1703–4.
220 Onyeji CO, Ogunbona FA. Pharmacokinetic aspects of chloroquine-induced pruritus: influence of dose and evidence for varied extent of metabolism of the drug. *Eur J Pharm Sci* 2001; **13**:195–201.
221 Aghahowa SE, Obianwu HO, Isah AO *et al.* Chloroquine-induced pruritus. *Indian J Pharm Sci* 2010; **72**:283–9.
222 Asawalam B, Osifo NG, Haller L. Drugs against chloroquine antimalarial itch. *J Eur Acad Dermatol Venereol* 1993; **2**:193–9.
223 El Abd O, Pimentel DC, Amadera JE. Generalized pruritus as an unusual side effect after epidural injection with dexamethasone. *PM R* 2015; **7**:206–9.
224 Szczepanowska J, Reich A, Szepietowski JC. Emollients improve treatment results with topical corticosteroids in childhood atopic dermatitis: a randomized comparative study. *Pediatr Allergy Immunol* 2008; **19**:614–18.
225 Eschler DC, Klein PA. An evidence-based review of the efficacy of topical antihistamines in the relief of pruritus. *J Drugs Dermatol* 2010; **9**:992–7.
226 Bonnel RA, La Grenade L, Karwoski CB *et al.* Allergic contact dermatitis from topical doxepin: Food and Drug Administration's postmarketing surveillance experience. *J Am Acad Dermatol* 2003; **48**:294–6.
227 Smith EB, King CA, Baker MD. Crotamiton lotion in pruritus. *Int J Dermatol* 1984; **23**:684–5.
228 Yosipovitch G, Szolar C, Hui XY *et al.* Effect of topically applied menthol on thermal, pain and itch sensations and biophysical properties of the skin. *Arch Dermatol Res* 1996; **288**:245–8.
229 Gooding SM, Canter PH, Coelho HF *et al.* Systematic review of topical capsaicin in the treatment of pruritus. *Int J Dermatol* 2010; **49**:858–65.
230 Gal-Oz A, Rogowski O, Swartzon M *et al.* Ethyl chloride as an antipruritic agent: a double-blind placebo-controlled prospective study. *Dermatology* 2010; **221**:373–7.
231 Gal-Oz A, Kivity S, Shacham Y *et al.* Prevention of pruritus with ethyl-chloride in skin prick test: a double-blind placebo-controlled prospective study. *Allergy Asthma Clin Immunol* 2015; **11**:25.
232 Bernstein JE, Whitney DH, Soltani K. Inhibition of histamine-induced pruritus by topical tricyclic antidepressants. *J Am Acad Dermatol* 1981; **5**:582–5.
233 Yosipovitch G, Szolar C, Hui XY *et al.* High-potency topical corticosteroid rapidly decreases histamine-induced itch but not thermal sensation and pain in human beings. *J Am Acad Dermatol* 1996; **35**:118–20.
234 Buddenkotte J, Steinhoff M. Pathophysiology and therapy of pruritus in allergic and atopic diseases. *Allergy* 2010; **65**:805–21.
235 Davies MG, Marks R, Horton RJ *et al.* The efficacy of histamine antagonists as antipruritics in experimentally induced pruritus. *Arch Dermatol Res* 1979; **266**:117–20.
236 Arnold AJ, Simpson JG, Jones HE *et al.* Suppression of histamine-induced pruritus by hydroxyzine and various neuroleptics. *J Am Acad Dermatol* 1979; **1**:509–12.
237 Zuberbier T, Aberer W, Asero R *et al.* The EAACI/GA^{2}LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. *Allergy* 2014; **69**:868–87.

238 Gokdemir G, Doruk T. Treatment of generalized pruritus: comparison of narrowband ultraviolet-B with oral cetirizine. *J Eur Acad Dermatol Venereol* 2011; **25**:1484–5.

239 Ständer S, Böckenholt B, Schürmeyer-Horst F *et al.* Treatment of chronic pruritus with the selective serotonin re-uptake inhibitors paroxetine and fluvoxamine: results of an open-labelled, two-arm proof-of-concept study. *Acta Derm Venereol* 2009; **89**:45–51.

240 Hundley JL, Yosipovitch G. Mirtazapine for reducing nocturnal itch in patients with chronic pruritus: a pilot study. *J Am Acad Dermatol* 2004; **50**:889–91.

241 Metze D, Reimann S, Luger TA. Effective treatment of pruritus with naltrexone, an orally active opiate antagonist. *Ann N Y Acad Sci* 1999; **885**:430–2.

242 Dawn AG, Yosipovitch G. Butorphanol for treatment of intractable pruritus. *J Am Acad Dermatol* 2006; **54**:527–31.

243 Yesudian PD, Wilson NJ. Efficacy of gabapentin in the management of pruritus of unknown origin. *Arch Dermatol* 2005; **141**:1507–9.

244 Ruiz-Villaverde R, Sánchez-Cano D. [Idiopathic senile pruritus: therapeutic response to gabapentin]. *Rev Esp Geriatr Gerontol* 2009; **44**:355–6 (in Spanish).

245 Ehrchen J, Ständer S. Pregabalin in the treatment of chronic pruritus. *J Am Acad Dermatol* 2008; **58**:S36–7.

246 Schwörer H, Ramadori G. Treatment of pruritus: a new indication for serotonin type 3 receptor antagonists. *Clin Investig* 1993; **71**:659–62.

247 Maley A, Swerlick RA. Azathioprine treatment of intractable pruritus: a retrospective review. *J Am Acad Dermatol* 2015; **73**:439–43.

248 Stander S, Siepmann D, Herrgott I *et al.* Targeting the neurokinin receptor 1 with aprepitant: a novel antipruritic strategy. *PLOS ONE* 2010; **5**:e10968.

249 Tan JK, Haberman HF, Coldman AJ. Identifying effective treatments for uremic pruritus. *J Am Acad Dermatol* 1991; **25**:811–18.

250 Gilchrest BA, Rowe JW, Brown RS *et al.* Ultraviolet phototherapy of uremic pruritus. Long-term results and possible mechanism of action. *Ann Intern Med* 1979; **91**:17–21.

251 Seckin D, Demircay Z, Akin O. Generalized pruritus treated with narrowband UVB. *Int J Dermatol* 2007; **46**:367–70.

252 Ada S, Seçkin D, Budakoğlu I *et al.* Treatment of uremic pruritus with narrowband ultraviolet B phototherapy: an open pilot study. *J Am Acad Dermatol* 2005; **53**:149–51.

253 Hsu MM, Yang CC. Uraemic pruritus responsive to broadband ultraviolet (UV)B therapy does not readily respond to narrowband UVB therapy. *Br J Dermatol* 2003; **149**:888–9.

254 Ko MJ, Chiu HC, Jee SH *et al.* Narrowband ultraviolet B phototherapy for patients with refractory uraemic pruritus: a randomized controlled trial. *Br J Dermatol* 2011; **165**:633–9.

255 Steinman HK, Greaves MW. Aquagenic pruritus. *J Am Acad Dermatol* 1985; **13**:91–6.

256 Greaves M, Handfield-Jones S. Aquagenic pruritus, pharmacological findings and treatment. *Eur J Dermatol* 1992; **2**:482–4.

257 Baldo A, Sammarco E, Plaitano R *et al.* Narrowband (TL-01) ultraviolet B phototherapy for pruritus in polycythaemia vera. *Br J Dermatol* 2002; **147**:979–81.

258 Madkan VK, Bandow GD, Koo JY. Resolution of pruritus secondary to polycythemia vera in a patient treated with narrowband ultraviolet B phototherapy. *J Dermatolog Treat* 2005; **16**:56–7.

259 Menagé HD, Norris PG, Hawk JL *et al.* The efficacy of psoralen photochemotherapy in the treatment of aquagenic pruritus. *Br J Dermatol* 1993; **129**:163–5.

260 Swerlick RA. Photochemotherapy treatment of pruritus associated with polycythemia vera. *J Am Acad Dermatol* 1985; **13**:675–7.

261 Holme SA, Anstey AV. Aquagenic pruritus responding to intermittent photochemotherapy. *Clin Exp Dermatol* 2001; **26**:40–1.

262 Smith RA, Ross JS, Staughton RC. Bath PUVA as a treatment for aquagenic pruritus. *Br J Dermatol* 1994; **131**:584.

263 Goodkin R, Bernhard JD. Repeated PUVA treatment of aquagenic pruritus. *Clin Exp Dermatol* 2002; **27**:164–5.

264 Xifra A, Carrascosa JM, Ferrandiz C. Narrow-band ultraviolet B in aquagenic pruritus. *Br J Dermatol* 2005; **153**:1233–4.

265 Ingber S, Cohen PD. Successful treatment of refractory aquagenic pruritus with naltrexone. *J Cutan Med Surg* 2005; **9**:215–16.

266 Koh MJA, Chong WS. Aquagenic pruritus responding to combined ultraviolet A/narrowband ultraviolet B therapy. *Photodermatol Photoimmunol Photomed* 2009; **25**:169–70.

267 Hanid MA, Levi AJ. Phototherapy for pruritus in primary biliary cirrhosis. *Lancet* 1980; **2**:530.

268 Perlstein SM. Treatment of primary biliary cirrhosis. *Arch Dermatol* 1974; **110**:132.

269 Decock S, Roelandts R, Steenbergen WV *et al.* Cholestasis-induced pruritus treated with ultraviolet B phototherapy: an observational case series study. *J Hepatol* 2012; **57**:637–41.

270 Cerio R, Murphy GM, Sladen GE *et al.* A combination of phototherapy and cholestyramine for the relief of pruritus in primary biliary cirrhosis. *Br J Dermatol* 1987; **116**:265–7.

271 Person JR, Ultraviolet A. (UV-A) and cholestatic pruritus. *Arch Dermatol* 1981; **117**:684.

272 Breuer-McHam J, Marshall G, Adu-Oppong A *et al.* Alterations in HIV expression in AIDS patients with psoriasis or pruritus treated with phototherapy. *J Am Acad Dermatol* 1999; **40**:48–60.

273 Gorin I, Lessana-Leibowitch M, Fortier P *et al.* Successful treatment of the pruritus of human immunodeficiency virus infection and acquired immunodeficiency syndrome with psoralens plus ultraviolet A therapy. *J Am Acad Dermatol* 1989; **20**:511–13.

274 Özden MG, Aydin F, Şentürk N, *et al.* Narrow-band ultraviolet B as a potential alternative treatment for resistant psychogenic excoriation: an open-label study. *Photodermatol Photoimmunol Photomed* 2010; **26**:162–4.

275 Xiao F. Cutaneous pruritus treated by Chinese medicine. *J Chin Med* 2002; **69**:30–2.

276 Ma KW. Acupuncture: its place in the history of Chinese medicine. *Acupuncture Med* 2000; **18**:88–99.

277 Pfab F, Hammes M, Bäcker M *et al.* Preventive effect of acupuncture on histamine-induced itch: a blinded, randomized, placebo-controlled, crossover trial. *J Allergy Clin Immunol* 2005; **116**:1386–8.

278 Che-Yi C, Wen CY, Min-Tsung K *et al.* Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. *Nephrol Dial Transplant* 2005; **20**:1912–15.

279 Kim KH, Lee MS, Choi S-M. Acupuncture for treating uremic pruritus in patients with end-stage renal disease: a systematic review. *J Pain Symptom Manage* 2010; **40**:117–25.

280 Jiang Y-H, Jiang W, Jiang L-M *et al.* Clinical efficacy of acupuncture on the morphine-related side effects in patients undergoing spinal-epidural anesthesia and analgesia. *Chin J Integr Med* 2010; **16**:71–4.

281 Yan CN, Yao WG, Bao YJ *et al.* Effect of auricular acupressure on uremic pruritus in patients receiving hemodialysis treatment: a randomized controlled trial. *Evid Based Complement Alternat Med* 2015; **2015**:593196.

282 Cürcani M, Tan M. The effect of aromatherapy on haemodialysis patients' pruritus. *J Clin Nurs* 2014; **23**:3356–65.

283 Ro YJ, Ha HC, Kim CG *et al.* The effects of aromatherapy on pruritus in patients undergoing hemodialysis. *Dermatol Nurs* 2002; **14**:231–4, 237–8, 256.

284 Aramwit P, Keongamaroon O, Siritientong T *et al.* Sericin cream reduces pruritus in hemodialysis patients: a randomized, double-blind, placebo-controlled experimental study. *BMC Nephrol* 2012; **13**:119.

285 Pakfetrat M, Basiri F, Malekmakan L *et al.* Effects of turmeric on uremic pruritus in end stage renal disease patients: a double-blind randomized clinical trial. *J Nephrol* 2014; **27**:203–7.
286 Ghanei E, Zeinali J, Borghei M *et al.* Efficacy of omega-3 fatty acids supplementation in treatment of uremic pruritus in hemodialysis patients: a double-blind randomized controlled trial. *Iran Red Crescent Med J* 2012; **14**:515–22.
287 Mohammad Ali BM, Hegab DS, El Saadany HM. Use of transcutaneous electrical nerve stimulation for chronic pruritus. *Dermatol Ther* 2015; **28**:210–15.
288 Kantor GR, Lookingbill DP. Generalized pruritus and systemic disease. *J Am Acad Dermatol* 1983; **9**:375–82.
289 National Institute for Health and Care Excellence. Clinical knowledge summaries. Itch – widespread. Available at: http://cks.nice.org.uk/itch-widespread#!backgroundsub (last accessed 19 October 2017).
290 National Health Service Scotland. Dermatology patient pathways. Available at: http://www.dermatology.nhs.scot/dermatology-pathways (last accessed 19 October 2017).
291 Ward JR, Bernhard JD. Willan's itch and other causes of pruritus in the elderly. *Int J Dermatol* 2005; **44**:267–73.
292 Grundmann SA, Ständer S. Evaluation of chronic pruritus in older patients. *Aging Health* 2010; **6**:53–66.
293 Thaipisuttikul Y. Pruritic skin diseases in the elderly. *J Dermatol* 1998; **25**:153–7.
294 Bakker CV, Terra JB, Pas HH *et al.* Bullous pemphigoid as pruritus in the elderly: a common presentation. *JAMA Dermatol* 2013; **149**:950–3.
295 Levell NJ. Recognition and management of common causes of itchy skin. *Nurs Resid Care* 2008; **10**:188–91.
296 Yong AA, Cao T, Tan V *et al.* Skin physiology in pruritus of advanced ageing. *J Eur Acad Dermatol Venereol* 2016; **30**:549–50.
297 van Os-Medendorp H, Guikers CLH, Eland-de Kok PCM *et al.* Costs and cost-effectiveness of the nursing programme 'Coping with itch' for patients with chronic pruritic skin disease. *Br J Dermatol* 2008; **158**:1013–21.

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
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. [a]Studies 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.