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Uraemic Pruritus

Clinical Characteristics, Pathophysiology and Treatment

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Abstract

Pruritus is a common complication of end-stage renal disease (ESRD), affecting about one-third of dialysis patients. It is a chronic, unpleasant symptom with a strong negative impact on patients' quality of life, often inducing sleeplessness and mood disorders. Recent data show that it is also associated with increased mortality.

The pathogenesis of uraemic pruritus (UP) is multifactorial. Triggering factors may include uraemia-related abnormalities (particularly involving calcium, phosphorus and parathyroid hormone metabolism), accumulation of uraemic toxins, systemic inflammation, cutaneous xerosis, and common co-morbidities such as diabetes mellitus and viral hepatitis. Recent findings suggest that the neurophysiology of itch is similar to that of pain; this has led to the hypothesis that the two phenomena also closely interact in ESRD patients, who often also experience uraemic neuropathy.

The management of UP needs to address several different issues, such as optimization of dialysis efficacy and skin hydration, and correction of calcium-phosphorus metabolism abnormalities. A wide range of antipruritic drugs have been suggested for the treatment of UP, although most of them have only been tested in small, uncontrolled trials, which have yielded conflicting results. Antihistamines are now known to have little or no

efficacy, although they are still often prescribed. Novel neurotropic drugs such as gabapentin, along with opioid receptor modulators such as nalfurafine, appear to be effective and well tolerated, but their efficacy has not yet been directly compared. Finally, physical therapies, including UV radiation, may also have a role in patients with refractory symptoms.

1. Clinical Characteristics

Pruritus associated with end-stage renal disease (ESRD) has been recognized for over a century. Before dialysis became available, it was known to occur in <30% of patients with renal failure. In the early haemodialysis era, the prevalence of uraemic pruritus (UP) was nearly 100%; thereafter, it decreased thanks to improved haemodialysis techniques and efficacy.[1] More recently, the prevalence of UP was estimated to be around 50%, with unexplained differences between countries.[2]

The prevalence of UP in peritoneal dialysis (PD) patients was found to be similar to that observed in haemodialysis,[3] thus downsizing the importance of contact reaction to haemodialysis devices as a possible causative factor. Moreover, kidney transplant patients almost never report UP.[4]

The current opinion is that, albeit that the prevalence of severe UP has decreased, UP is still a major problem affecting the quality of life (QOL) of dialysis patients.

Only a few studies have evaluated the clinical characteristics of UP. Uraemic patients usually develop pruritus before starting dialysis; no correlation has been found between UP severity or prevalence, and age, sex or type of underlying renal disease. UP is either generalized (more than one-third of patients) or localized, especially on the back, abdomen, head and arms.[5] UP is characterized by daily itching bouts with a symmetric distribution, the intensity of which worsens during the night, thus causing sleeplessness. It generally presents with cutaneous manifestations such as scratching excoriations with or without impetigo, prurigo lesions and lichenification that occur as secondary phenomena. Duration of UP tends to be prolonged (more than 1 year in one-third of patients) and about half of the patients report secondary agitation or depression.[5]

In the recent DOPPS II (Dialysis Outcomes and Practice Patterns Study II) trial,[2] which evaluated more than 18 000 patients on haemodialysis, pruritus was associated with an increase of 17% in the mortality risk. UP was also associated with a poorer QOL and particularly with disturbed sleep, confirming the importance of an appropriate treatment of this vexing symptom.

This article reviews the current understanding of the pathophysiology of UP and the available therapeutic options. For these purposes, we performed a MEDLINE search using PubMed without any date limits, mainly using the search terms 'pruritus', 'itch', 'uraemia', 'uremia', 'treatment', 'pathophysiology' and 'mechanisms'. The reference lists of the retrieved articles were also considered.

2. Pathophysiology

Itch is a major symptom in a variety of dermatological conditions as well as in systemic disorders such as uraemia, chronic hepatic obstruction and haematological disorders. Itch is transmitted by dedicated C neurons, which are distinct from the nociceptors implicated in pain processing. Moreover, a specific class of dorsal horn neurons projecting to the thalamus has been identified in animal models. Thus, like pain, itch originating in the skin is induced by the stimulation of the free nerve endings of specialized C-fibres by one or more peripheral pruritogens, the effects of which are processed by CNS.

On the basis of this concept, itch has generally been classified as pruritoceptive, neuropathic, neurogenic or psychogenic.[6] UP seems to take place in the setting of a complex metabolic

environment and does not fit any of these specific categories. It seems reasonable to hypothesize that more than just one pruritogen can precipitate a predisposing *pabulum* (i.e. the concomitant presence of advanced age, diabetes mellitus, iron deficiency, anaemia, and intrahepatic cholestasis associated with hepatitis B and C virus infections, which are common among patients on long-term haemodialysis), and this is probably why every attempt to find a single cause has so far failed.

2.1 Skin Xerosis and Cutaneous Alterations

The skin of patients with ESRD is usually atrophic and dry, but a correlation between xerosis and UP has not been clearly demonstrated; skin xerosis may act as a co-factor in promoting pruritus by lowering the perception threshold. Interestingly, xerosis and hypohydrosis are often a consequence of reduced sweat secretion due to sympathetic nerve damage,[7] and are therefore suggestive of dysautonomia.

Nephrogenic systemic fibrosis, a rare cutaneous manifestation associated with gadolinium administration in ESRD patients is extremely itchy. Conversely, other specific ESRD-related skin abnormalities, such as perforating disorders, calcifying diseases (e.g. calciphylaxis), bullous dermatoses and foot ulcers are frequent in haemodialysis patients: these are often itchy but also frequently associated with pain.

2.2 Pruritogenic Cytokines Produced in the Dermis

Pruritogenic cytokines may be produced in the dermis by various activated cells and act locally on itch receptors in a paracrine manner. Initially, UP seemed to be present in patients with enhanced sensitivity to pruritogens[8] and, *in vitro*, a higher histamine release was induced using UP patient sera compared with control sera.[9] Plasma histamine levels are much higher in uraemic patients with itch than in nonuraemic or nonitching individuals, but there is no correlation between UP severity and plasma histamine levels. More recently, controversy has arisen as to whether histamine, secreted by proliferating skin-resident mast cells, might cause UP without necessarily increasing plasma histamine levels.[10] This theory has since been dropped because of conflicting results of trials.[11,12] Recently, the role of the histamine receptor in cutaneous peripheral nerves has been considered. The histamine H_1 receptor does not seem to be exclusively responsible for histamine itch transduction. Indeed, the H_4 receptor in cutaneous sensory neurons has now been identified, and experimental studies in mice showed that an H_4 receptor agonist induced and its antagonist completely inhibited scratching behaviour.[13] This would explain the unsatisfactory results of selective anti-H_1 receptor antagonists in controlling UP. Other pruritogenic mediators may include kallikrein, interleukin (IL)-2, acethylcholine and others released under histamine-mediated mast cell stimulation. All these cytokines are likely to play a role in determining an inflammatory basis that causes a lower UP threshold.

2.3 Uraemia-Related Alterations

It has been suggested that UP is related to marked elevation of serum parathyroid hormone (PTH) levels, although PTH itself is not pruritogenic when injected into the skin. A number of authors[14,15] have also suggested that itch intensity correlates with the calcium-phosphorus product, with some studies[16] showing that bivalent ions (calcium, phosphorus, magnesium) precipitate to a greater extent in uraemic patients with UP than in those without UP. An histological study in UP patients showed a significantly higher calcium deposition in basal and spinous cells when compared with non-UP patients. However, many clinical studies[17-19] have failed to find a correlation between bivalent ion or PTH levels and UP; recently, the large epidemiological DOPPS II study[2] showed that only a very high calcium-phosphorus product (i.e. $>80\,mg^2/dL^2$) correlates with UP frequency. Reduced calcium excretion in ESRD, vitamin D supplementation and use of calcium-containing phosphorus binders, such as calcium carbonate or calcium acetate, would facilitate itch through deposition

in the epidermal layers[16] producing a peripheral sensitization to itch.

Surprisingly, dialysis adequacy, assessed as K_t/V values using the method described by Daugirdas,[20] did not correlate with the frequency of UP in large epidemiological studies.[2,21,22] Conversely, a relationship between circulating levels of β_2-microglobulin (which often accumulates in ESRD patients) and UP has been shown.[21] Middle molecular weight proteins, the haemodialysis clearance of which is indirectly monitored by means of β_2-microglobulin levels, would be responsible for uraemic neuropathy and thus the onset of UP.

2.4 Immune-Inflammatory Hypothesis

Taking into account the body of evidence suggesting that uraemia is an inflammatory state, some authors consider UP as a skin manifestation of chronic inflammation.[22] Recently, a theory of persistent 'microinflammation' suggested that malnutrition and inflammation may be related to the genesis of UP; in this setting, derangements of the immune system with a proinflammatory pattern may be involved. A recent study showed a significantly enhanced proportion of T helper (T_h)-1 cells, C-reactive protein and IL-6, and decreased serum albumin and transferrin levels in UP patients, suggesting an up-regulated inflammatory state. Moreover, multiple factors potentiate inflammation in haemodialysis patients including oxidative stress, nonbiocompatible dialysers, vascular access infections and less-than sterile dialysers.[23] To corroborate these findings is the observation that UP correlates with poor survival.

2.5 Opioid Hypothesis

The observation that several μ-opioid receptor agonist drugs induce pruritus, particularly after intrathecal or epidural administration, led to the hypothesis that opioid receptors are involved in UP.[24] Although no correlation has been found between the prevalence and severity of pruritus and serum levels of β-endorphins before or after dialysis,[25] many studies have underlined the role of the opioid system in the pathogenesis of cholestatic pruritus, and in recent years the opioid hypothesis has emerged as a possible explanation of UP.[24] However, this hypothesis was not confirmed by the results of a placebo-controlled trial,[24] with the μ-receptor antagonist naltrexone showing no effect in reducing UP.

κ-Opioid system agonists show a satisfactory antipruritic activity, as they have been demonstrated to inhibit substance P- and histamine-induced scratching in mice.[26]

Moreover, μ-opioid antagonism receptor plus κ-opioid receptor stimulation seems to alleviate itch, and mixed opioid receptor agonist-antagonists are under evaluation in animal models, with interesting results in inhibiting induced scratching behaviour.[26]

2.6 Uraemic Neuropathy Hypothesis and 'Wind-Up Phenomenon'

A relationship between UP and uraemic (somatic and autonomic) neuropathy has been hypothesized in a few studies.[5] Interestingly, a significant correlation between paresthesia and UP was shown, along with a correlation between the severity of UP and the occurrence of restless leg syndrome. Moreover, a recent study[27] tested histamine and serotonin-induced cutaneous flare sizes in haemodialysis patients and concomitantly measured subjective itch sensation. Interestingly, haemodialysis patients had smaller flare reactions but higher itch perception confirming an altered neurophysiological response. UP, supposedly of central origin, could be as a result of a diminished threshold of perception, regardless of the specific causative factor. This could be the result of peripheral nerve fibre damage as a result of the uraemic neuropathy associated with a central sensitization to itch, which could be chronically sustained by uraemic toxins.[7] This hypothesis is similar to that proposed for neuropathic pain, in which nerve fibre damage and central 'wind up' phenomenon are thought to be pathogenic factors.[28]

An emerging pathogenetic hypothesis strictly correlates itch and pain. The neurophysiology of itch and pain is similar: both are conveyed by a subset of specialized C-fibres in the dorsal horns

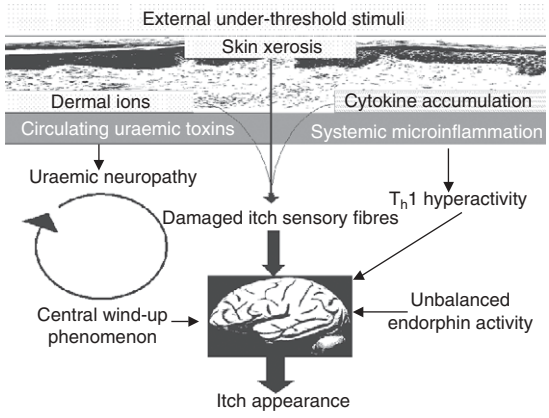

Fig. 1. Proposed pathogenetic model for uremic itch (see text for details). T_h1 = T-helper 1 cell.

of two separate systems, and transmitted to the thalamus and the somatosensory cortex via the lateral spinothalamic tract.[29] Furthermore, itch and pain present concomitantly in diseases such as postherpetic neuralgia, notalgia paresthetica, HIV infection and multiple sclerosis. Moreover, various inflammatory mediators (e.g. bradykinin, serotonin, prostanoids, interleukins and a low pH) may be peripheral mediators not only of itch but also of pain, as it has been demonstrated that they acutely sensitize nociceptors to enhance their responses to external stimulation.[30] It can be hypothesized that the two pathways interact and modulate each other at different levels (both centrally and peripherally).[29]

Haemodialysis patients typically experience both chronic pain and itch, and it is possible that the two distinct populations of sensory fibres modulate itch sensations centrally and not at the peripheral level.

Figure 1 summarizes the potential pathogenetic mechanisms of uraemic pruritus.

3. Management

Currently, there are no general purpose antipruritus drugs for chronic itch. Obviously, before considering the treatment of UP, physicians should evaluate whether the itch is caused by uraemia alone or is related to other dermatological or systemic diseases, such as atopic dermatitis, drug allergy, lymphomas and cholestasis, as each of them requires a focused approach.

Patients troubled with itch generally benefit from keeping cool, by for example, wearing light cool clothes, maintaining a not too dry environment and avoiding alcohol. Patients should be advised to keep their nails short and to rub skin gently.

The complex pathophysiology of UP makes it challenging to find an effective treatment. The proposed therapeutic options derive from anecdotal reports and small clinical trials, which at best compare the test drug against placebo. In the clinical scenario, lots of patients bear this chronic unpleasant distress, which significantly worsens their QOL.[2]

In this review, we classify the myriad of therapeutic options proposed for UP as uraemia treatments, topical treatments, physical and systemic treatments. A common consideration in evaluating UP studies is the score used to test itch severity. Almost all studies uniformly use the visual analogue scale (VAS) score, which consists of a 10-cm line labelled on the extremes with '0' and '10', which respectively indicate 'no itch' and 'very strong itch, as bad as it can possibly be'. This score was validated by Yosipovitch et al.[31] in UP patients; the test is self-administered, almost always twice daily. In addition to the VAS score, some studies used a detailed questionnaire evaluating severity and distribution of UP, and the presence of a sleep disorder;[10] this results in an Itching Score (IS), providing a value that usually parallels VAS changes. A few studies used IS alone. Another common consideration is the presence of a number of small exploratory studies (phase II), which have not been followed by phase III trials. Therefore, we cannot exclude the fact that inconclusive studies remain unpublished in the medical literature.

To develop evidence-based treatment recommendations and to highlight as much as possible the weight given to a study, we reviewed articles using levels of evidence (table I).[32] Moreover, we primarily considered the size of the study cohorts and the presence of validated scores to assess itch severity. We deduced, when

Table I. Levels of evidence for therapy studies used to assess reports[32]

Level	Evidence
1	RCT with hard endpoint
2	RCT with surrogate endpoint
3	Non-randomized trial with a control group, or subgroup analysis of an RCT
4	Before and after study
5	Case series >10 patients
6	Case series <10 patients

RCT = randomized controlled trial.

possible, the percentage reduction in itch severity (table II).

3.1 Uraemia Treatment

As mentioned in section 2.3, a significant (inverse) correlation between dialysis efficacy (as assessed using K_t/V) and frequency/severity of UP has not been clearly demonstrated so far,[2,21] although a small pilot trial initially demonstrated that enhancing dialysis efficacy could control UP.[12] It must be acknowledged that K_t/V assesses dialysis efficacy by calculating the clearance of urea and does not take into account the removal of middle molecular weight toxins, which are implicated in the pathogenesis of UP.[21] Therefore, the possibility that K_t/V is not a reliable tool in this setting needs to be considered. In essence, although not supported by rigorous evidence-based findings, the optimization of dialysis efficacy remains one of the basic approaches in the treatment of UP.

The importance of an appropriate regulation of mineral metabolism without an increase in calcium load (reducing dialysate calcium content, and limiting vitamin D and oral calcium supplementation), proposed by some authors as a potential approach to reduce or prevent UP, is now part of the nephrologists' armamentarium against progressive vascular calcification in dialysis patients.

The introduction of polymethylmethacrylate (PMMA) filters for haemodialysis resulted in itch reduction in three small studies. The rationale would be that PMMA filters may improve UP by adsorption and permeation of ionic substances or cytokines.[33-35] Hypothetically, uraemic blood contains a number of solutes that differ from those in healthy individuals. PMMA filters may remove solutes of greater molecular weight by adsorption and permeation. Moreover, like other biocompatible dialysers, PMMA induces a less pronounced release of cytokines, which are believed to contribute to the development of UP.

However, the suggestion that the reduction in UP is as a result of these more biocompatible dialysers is still a matter of debate. The absence of significant differences in UP frequency or severity between haemodialysis and PD patients[3] has resulted in the role of blood-to-filter contact reaction as one of the potential causative factors of UP being questioned.

3.2 Topical Treatments

The use of skin emollients, such as aqueous gels containing 80% water, has been shown to significantly reduce UP in uncontrolled studies.[36-38] The use of essential oils improved UP by increasing stratum corneum hydration.[65,66] Patients can be advised to use mild soaps along with these emollients at least twice daily. In a randomized, placebo-controlled, crossover trial, patients were assigned to treatment with either 2.2% γ-lynolenic acid (GLA) cream or placebo cream administered three times daily for 2 weeks and then switched to the other treatment. An impressive itch reduction was obtained with GLA compared with placebo.[39]

Interestingly, whereas a randomized controlled trial[41] reported capsaicin 0.025% cream to be efficacious, another more recent trial found topical capsaicin ointment 0.05% did not significantly reduce itch.[42] Capsaicin owes its potential antipruritic properties to desensitization of nociceptive nerve endings depleting the peripheral neurons of substance P and perhaps blocking the conduction of pain or pruritus. Moreover, it is highly likely that capsaicin preferentially activates nociceptive fibres and, probably, acting as analgesic, indirectly affects itch inhibition. However, the painful burning sensation associated with capsaicin use frequently leads to treatment withdrawal.[40]

Table II. Treatment options for uraemic pruritus (UP)

Study (y)	UP treatment	No. of patients	Level of evidence	Efficacy	Mean worst VAS score (% response itch reduction)
Uraemia					
Hiroshige et al.[11] (1995)	↑ Dialysis efficacy	22	4	Yes	NA
Kato et al.[33] (2001)	PMMA	19	3	Yes	NA
Lin et al.[34] (2008)	PMMA	30	4	Yes	NA
Aoike[35] (2007)	PMMA	69	4	Yes	5.7 (20)
Topical					
Morton et al.[36] (1996)	Emollients	21	4	Yes	5.0 (48)
Okada and Matsumoto[37] (2004)	Emollients	20	3	Yes	3.5 (85)
Szepietowski et al.[38] (2005)	Emollients	19	4	Yes	6.2 (80)
Chen et al.[39] (2006)	Gamolenic acid (γ-linolenic acid)	17	1	Yes	7.5 (60)
Breneman et al.[40] (1992)	Capsaicin	22	4	Yes	NA
Tarng et al.[41] (1996)	Capsaicin	17	1	Yes	NA (39)
Weisshaar et al.[42] (2003)	Capsaicin	11	3	No	NA
Kuypers et al.[43] (2004)	Tacrolimus	25	4	Yes	6.7 (43)
Duque et al.[44] (2005)	Tacrolimus	22	1	No	7.9 (72)
Physical					
Gilchrest et al.[45] (1977)	BB-UVB	26	1	Yes	NA
Schultz and Roenigk[46] (1980)	BB-UVB	10	4	Yes	NA
Seckin et al.[47] (2007)	NB-UVB	15	4	Yes	8.2 (54)
Gao et al.[48] (2002)	Acupunture	32	4	Yes	NA
Che-yi et al.[49] (2005)	Acupunture	40	1	Yes	NA (67)
Systemic					
Russo et al.[50] (1986)	Terfenadine	27	1	Yes	NA
Balaskas et al.[51] (1998)	Ondansetron	11	4	Yes	NA (62)
Ashmore et al.[52] (2000)	Ondansetron	16	1	No	5.3 (26)
Murphy et al.[53] (2003)	Ondasentron	24	1	No	6.1 (16)
Layegh et al.[54] (2007)	Granisetron	14	4	Yes	NA (75)
Peer et al.[55] (1996)	Naltrexone	15	1	Yes	9.9 (79)
Legroux-Crespel et al.[56] (2004)	Naltrexone	52	1	No	6.0 (25)
Wikstrom et al.[26] (2005)	Nalfurafine	144	1	Yes	6.4 (36)
Manenti et al.[57] (2005)	Gabapentin	6	6	Yes	8.2 (83)
Gunal et al.[58] (2004)	Gabapentin	25	1	Yes	7.9 (85)
Naini et al.[59] (2007)	Gabapentin	34	1	Yes	7.2 (79)
Silva et al.[60] (1994)	Thalidomide	18	1	Yes	NA (36)
De Marchi et al.[61] (1992)	Erythropoietin	20	1	Yes	NA (76)
Giovannetti et al.[62] (1995)	Oral-activated charcoal	23	4	Yes	NA (70)
Pederson et al.[63] (1980)	Oral-activated charcoal	22	1	Yes	NA
Bousquet et al.[64] (1989)	Nicergoline	15	1	Yes	NA

BB-UVB = broadband UVB; **NA** = not applicable; **NB-UVB** = narrow band-UVB; **PMMA** = polymethylmethacrylate; **VAS** = visual analogue scale; ↑ indicates increased.

An uncontrolled prospective trial in 25 patients showed that 6 weeks of treatment with tacrolimus ointment reduced itch;[43] however, a subsequent randomized controlled trial failed to confirm these data. In this latter study, itch severity reduction was >70% of the basal value

in both the treatment and vehicle group, and according to the authors, this strong placebo effect was partly attributable to vehicle-induced skin moisturization and partly attributable to better care by the physicians, who had to administer the ointment themselves.[44]

3.3 Physical Treatment

Phototherapy, especially UVB radiation, is considered to be effective in UP patients.[45,46] In a small, randomized controlled trial by Gilchrest et al.,[45] 9 of 10 patients experienced a marked improvement in pruritus after six broadband UVB (BB-UVB) exposures; the beneficial effect was sustained, lasting at least 6 months. Recently, narrow band-UVB (NB-UVB) was shown to be effective in an open study.[47] NB-UVB-induced VAS reduction over 6 weeks was considerable, but remission was not prolonged. Therefore, further investigations are needed to define the more appropriate phototherapy protocol. UVB hypothetically acts by inactivating circulating pruritogenic substances, suppression of histamine release, apoptosis of mast cells and an attenuated T_h1 differentiation.[67]

Some studies have also shown acupuncture to be efficacious. The Quchi (LI11) acupoint was effective in reducing UP versus control (a non-acupoint needle was placed in the placebo group) in a randomized trial conducted on 40 uraemic patients; pruritus score reduction was impressive.[49] This finding was supported by the results of another open-label study on 34 patients.[48] The authors raised the old 'gate theory', suggesting that acupunture generates impulses, which, carried by the smaller, myelinated and rapidly conductive β and δ fibres, reach the spinal chord; there, opioid-like substances are released that block the slower C fibre impulses.[68]

3.4 Systemic Treatments

In the past, the use of antihistamines, particularly H_1-receptor antagonists, found support from an old trial involving terfenadine.[50] Perhaps the study was positive for the considerable sedative effect of this older H_1-receptor antagonist, more than for the direct antipruritic effect. Subsequent studies involving H_1-receptor antagonists failed to confirm the initially positive results and in recent studies H_1-receptor antagonists are considered equivalent to placebo.[56] However, in clinical settings, although a well conducted randomized controlled trial on H_1-receptor antagonists in UP has never been published, these antihistamines are still used as first-line therapy for UP, with frustrating results for both the patient and the physician.

A number of successful case reports led to randomized trials of serotonin receptor antagonists for the treatment of UP; however, these trials reported negative results.[51,52-54,69] Moreover, in an experimental setting, serotonin $5\text{-}HT_3$ receptor antagonists (tropisetron, ondansetron), similarly to cetirizine, failed to control iontophoresis-induced itching in haemodialysis patients.[27]

There is increasing evidence that UP, like other forms of chronic itch,[6] is a neurological expression rather than an isolated skin disease. The emerging pathogenetic hypothesis (opioid and neuropathic) originates from the assumption of a disequilibrium in the nervous system.

Opiate use is associated with the appearance of itch, thus opiate antagonists were tested in some trials after an initial case report describing successful treatment of UP by intravenous administration of naloxone.[70] Although an initial randomized controlled trial (performed on a small patient sample) showed positive results,[55] two subsequent randomized studies showed no statistically significant difference between the study drug and placebo or antihistamine groups.[25,50] The studies differed in terms of itch severity at study entry, so Pauli-Magnus et al.,[24] searching an explanation for such conflicting results, reasoned that naltrexone could be more effective in the severest forms of UP, suggesting that the pathophysiology of UP may follow different pathways in patient subsets with different symptom severity. Additionally, naltrexone therapy resulted in a high incidence of gastrointestinal adverse effects, which advise against its routine clinical use.

A novel κ-opioid receptor agonist, nalfurafine (TRK-820), was recently tested in two randomized

controlled trials.[26] Nalfurafine was synthesized as an analgesic and acts not only as an antinociceptive agent, but also as an antipruritic by inhibiting substance P- and histamine-induced scratching in mice. Furthermore, nalfurafine suppressed morphine-induced scratching behaviour in monkeys.[26] Wikstrom et al.[26] reported the results of the two different randomized, multicentre, phase II studies together, using a meta-analysis approach. The results of these trials showed that nalfurafine is effective in patients with UP. The two studies had adequate sample sizes (144 patients in total); however, the net effect (weighted against placebo) of the study drug in reducing UP intensity was mild, as only one-third of UP patients had a reduction of > 50% of worst itching VAS score. Nalfurafine was well tolerated, with rare drug-related adverse events, similar to placebo. Confirmatory large-scale trials to further explore the clinical efficacy of this promising agent are warranted given these interesting results. Interesting advances may originate from the novel class of opioid receptor agonist-antagonists, which are thought to be more effective as antipruritics than pure agonists.

The mechanism of action of gabapentin, a novel antiepileptic agent, is still not fully understood; however, it is known to modulate various receptor sites, and alter dopamine, serotonin and noradrenaline (norepinephrine) release. It is worth noting that gabapentin is an emerging drug in the treatment of brachioradial pruritus, a chronic localized form of pruritus probably caused by nerve root injury secondary to cervical spine disease (a typical 'neuropathic' pruritus), and some authors have suggested that it could be used for chronic itch unresponsive to other treatments.[29] An index case and a small pilot study on five haemodialysis patients showed dramatic improvement in UP after gabapentin administration (100 mg after every haemodialysis session).[57] Two small randomized controlled trials subsequently confirmed the positive effects of this drug (300 mg after every haemodialysis session or 400 mg twice weekly), sharing identical dramatic mean itch reduction versus placebo ($p < 0.0001$).[58,59] All of these studies showed a favourable safety profile of this agent; however, since gabapentin is primarily eliminated through the kidney and its half-life is significantly longer in haemodialysis patients, its Achille's heel is the narrow therapeutic window and the consequent risk of neurotoxicity. In our opinion, gabapentin therapy should be started at a dosage of 100 mg after every haemodialysis session, under nurse supervision, and then titrated on the basis of the clinical response.

Several other agents have been proposed for UP and isolated trials have been conducted, without larger confirmatory randomized controlled studies. The impressive list of tested agents includes: (i) thalidomide,[60] a suppressor of tumour necrosis factor-α that leads to suppression of IL-2-producing T_h1 cells, but that has an important sedative effect and probably acts on peripheral neuropathy; (ii) nicergoline, which was tested in a small randomized study[64] with good results that were never reconfirmed; (iii) oral activated charcoal and neurotropins, tested with good results in uncontrolled studies;[62,63,71] and (iv) recombinant erythropoietin, which appeared to produce a marked improvement in UP[61] in haemodialysis patients in a small randomized trial, the results of which were not confirmed in a later study.[72] A case series showed promising results with intravenous lidocaine[73] and pentoxifylline,[74] but the high rate of adverse effects means its extensive use can not be recommended. Finally, an isolated small randomized controlled study reported homeopathic treatment was efficacious in UP.[75]

4. Conclusions

UP is a significant problem in ESRD patients and, up until a few years ago, its treatment was largely empirical and ineffective. Despite recent advances, about 40% of ESRD patients still experience very annoying, potentially disabling itching; this symptom significantly affects their QOL, particularly sleep quality, mood and ultimately self-esteem. Recently,[2] the large DOPPS II study confirmed the impact of UP on sleep disorders and showed an association with increased mortality.

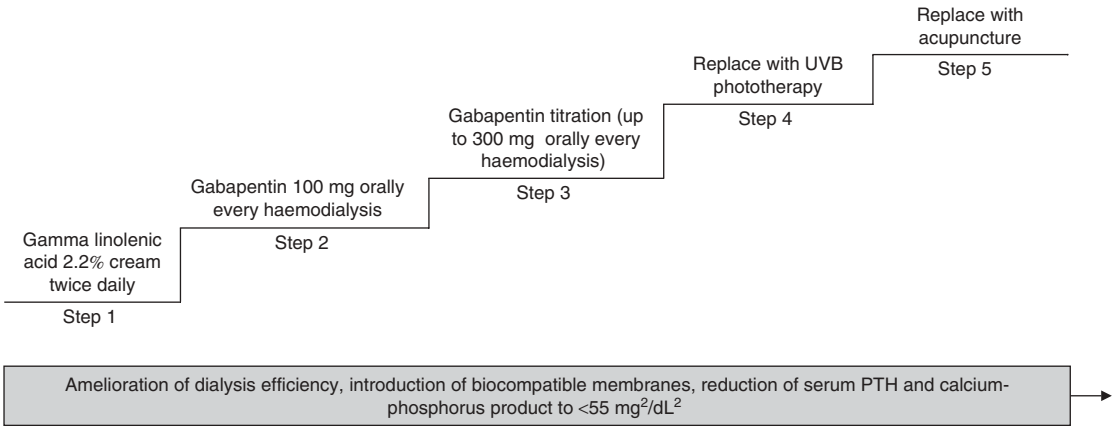

Fig. 2. Treatment hierarchy for uraemic pruritus treatment. **PTH** = parathyroid hormone.

Although the association of uraemia and pruritus has been recognized for more than 100 years, the precise pathophysiological mechanisms of UP remain unclear. Historical data on UP treatment are often contradictory, based on personal experiences or at best small randomized placebo-controlled trials, so it is difficult to generate evidence-based recommendations. A quality jump is needed in this research field; patient enrolment is not difficult, given the relatively high prevalence of UP and thus larger studies are feasible.

On the basis of the available literature, we recommend that a stepwise protocol for UP treatment should be followed (figure 2). Initially, a correct diagnosis is needed and concurrent illnesses must be treated. To obtain a sustained reduction/resolution in UP, the treating physicians should aim at normalizing PTH, calcium and phosphorus levels, optimizing haemodialysis efficacy ($K_t/V > 1.2$) and using biocompatible dialysers, particularly PMMA, to obtain a reduction of inflammation and a more efficient removal of uraemic toxins. Skin xerosis and hypohydrosis must be addressed, and, thereafter, the use of nonocclusive skin emollients rich in water or topical treatments with GLA is advisable.

If no response is obtained after 2 weeks with skin emollients, the second step we would suggest is introducing gabapentin.[57-59] Gabapentin is being more extensively used in haemodialysis patients for the treatment of other ESRD-related conditions such as restless leg syndrome, diabetic neuropathy or chronic pain, without important adverse effects, provided that the dosage is appropriately monitored. In our opinion, it is better to start with the lowest available dose (100 mg after every haemodialysis session administered under nurse supervision) and then titrate it on the basis of patient response.

In patients not responding to gabapentin after a 2-week titration period, a 6-week course of BB- or NB-UVB treatment is suitable. Antihistamines are not advisable for UP because of their limited efficacy. The myriad of other drugs tested so far need confirmatory studies before they can be recommended. In particular, opioid receptor antagonists (nalfuralfine, naltrexone) showed only mild or no efficacy, whereas mixed opioid receptor agonist-antagonists such as butorphanol may represent a promising option, having shown efficacy for opioid-induced pruritus.[76,77]

In conclusion, an integrated approach for the treatment of UP is advisable, and the available treatment options should be used sequentially on the basis of their efficacy and toxicity. In all situations, the patient should feel that their physician shares their concerns regarding the difficulties in treating UP, and this should help reduce any negative feelings of helplessness and frustration the patient may have.

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