Updates on the Epidemiology, Pathophysiology and Management of Uraemic Pruritus

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ABSTRACT

Pruritus is a very common chronic and frustrating symptom that considerably affects the quality of life of patients with end-stage renal disease. The current review examined the updates in the epidemiology, pathophysiology, and management of uraemic pruritus. Recently, there has been reduction in the prevalence of urameic pruritus. With few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age, gender, and type of dialysis. However, pre-dialysis prevalence was lower than during dialysis prevalence. In recent years, new pathophysiologic hypotheses (immune and opioid) have been postulated and other hypotheses have been undermined (serotonin). There have been several anti-pruritic therapies examined among hemodialysis patients, including efficient dialysis, topical medications, systemic medications, physical and alternative treatments, and surgical treatments. However, none is considered the drug of choice or exclusively efficient in all patients. Several new medications have been examined in the last decade. However, for many of these medications, the evidence is still insufficient for their recommendations. After all advances in dialysis techniques and the availability of multiple therapies, uraemic pruritus is still a significant problem among hemodialysis patients that warrant further research.

Key words: Pruritus, uremia, kidney failure, renal dialysis, drug therapy

الملخص

الحكة هي عرض مزمن وشائع جدا لدى مرضى الفشل الكلوي النهائي وهي عرض محبط ويؤثر بشكل كبير على حياة المصابين به. هذه المراجعة تتعلق بدراسة التحديثات في الوبائية، والفسيولوجيا المرضية والعلاج للحكة الناتجة من ارتفاع البولينا. وجد مؤخرا انخفاض في معدل انتشار الحكة الناتجة من ارتفاع البولينا، كما وجد أنه ليس هنالك أي اختلافات كبيرة (مع وجود بعض الاستثناءات القليلة) في معدل انتشار الحكة بحسب السن والجنس ونوع الغسيل الكلوي. ومع ذلك فإن معدل انتشار الحكة قبل الغسيل الكلوي أقل من معدل الانتشار بعد الغسيل الكلوي. في السنوات الأخيرة، افترضت فرضيات فسيولوجية ومرضية جديدة (تتعلق بجهاز المناعة أو بالمادة الأفيونية) وقوضت فرضيات أخرى (السيروتونين). تم اختبار العديد من العلاجات المضادة للحكة وسط مرضى الغسيل الكلوي منها إجراء الغسيل بكفاء، الأدوية الموضعية، الأدوية الشاملة، العلاج الفيزيائي، العلاجات البديلة والعلاجات الجراحية. ومع ذلك لا يعتبر أي منها العلاج الأفضل أو الأكثر كفاءة لكل المرضى. خلال العقد الماضي تم اختبار عدة أدوية جديدة، ومع ذلك فإن الأدلة لاتزال غير كافية بالنسبة لكثير من هذه الأدوية لتتم التوصية بها. بعد كل التقدم في تقنيات غسيل الكلى وتوافر علاجات متعددة، لاتزال الحكة الناتجة من ارتفاع البولينا مشكلة كبيرة بين مرضى غسيل الكلى ويحتاج الأمر لمزيد من البحث.

INTRODUCTION

Pruritus is a very common chronic and frustrating symptom among hemodialysis patients. It affects the quality of life of patients with advanced or end-stage renal disease, because of the serious discomfort, sleeping disorders, anxiety and depression[1,2].

The pathophysiology is complex and incompletely understood. There are several anti-pruritic therapies examined among patients on maintenance hemodialysis. However, none is considered the drug of choice or exclusively efficient in all patients[1-3]. In the last 10 to 15 years, reduction in the prevalence of uraemic pruritus has been observed, new pathophysiologic hypotheses (immune and opioid) have been postulated, and multiple new medications have been examined. Therefore, we thought to review the new changes in the epidemiology,

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pathophysiology, and management of uraemic pruritus.

EPIDEMIOLOGY

Table 1 summarizes the prevalence of uraemic pruritus in studies published between 2000 and 2014. Although it is not easy to compare numbers between different studies due to differences in methodology, differences in pruritus definitions, and the small sample size of many of these studies, some findings can be pointed out. Studies published after 2000 had lower prevalence than studies published before 2000. In the current review, among the 24 studies examined (Table 1), the prevalence of uraemic pruritus ranged between 18% and 74%, with the majority of studies below 50%.[4, 5] For example, in a huge prevalence study (DOPPS) that examined more than 10,000 hemodialysis patients from Northern America, Western Europe, Japan, and Australia, the prevalence of uraemic pruritus was 42% using data collected between 2002 and 2003.[6] On the other hand, a non-comprehensive review for the prevalence studies published before 2000 showed prevalence between 22% and 86%, with the majority of studies above 50%.[7] It has been suggested that improving the quality of dialysis may have contributed to such reduction in the prevalence of uraemic pruritus.[8] There have been considerable geographic variability in the prevalence of uraemic pruritus. For example, in the DOPPS study, the prevalence of uraemic pruritus was lowest in France (36%) and highest in UK (50%).[6] In the 12 studies that calculated the prevalence by age and/or gender,[4,5,9-18] with few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age or gender. For the age, four studies showed significant association between the presence of pruritus and age, being higher in older age.[11,13,18,19] For the gender, two studies showed more prevalence in males[15,16] and one study showed high prevalence in females.[17] The prevalence of pruritus before dialysis was lower than the prevalence during dialysis (during the study).[4,16,17,20] This may be explained by the fact that pre-dialysis prevalence may indicate a lower stage of chronic kidney disease. In the few studies that examined the prevalence of uraemic pruritus among patients on hemodialysis versus peritoneal dialysis, no difference has been found in two studies[16,21] and one study found higher prevalence in hemodialysis compared with peritoneal dialysis.[22]

PATHOPHYSIOLOGY

Several hypotheses have been suggested to explain the underlying pathophysiology of uremic pruritus.[1-3] the presence of several pathophysiologic hypotheses for uremic pruritus is considered a consequence of the complex metabolism in uraemic patients and is considered an indication of inconclusiveness of any single hypothesis. Table 2 summarizes the main pathophysiologic hypotheses for uremic pruritus. These include:

Immune-inflammatory hypothesis: uraemic pruritus is believed to be a systemic inflammation rather than a local skin disorder.[7,23] This new hypothesis is supported by the overexpression of higher T helper-1 (TH1) cells, C-reactive protein and interleukin 6 (IL-6) in hemodialysis patients as well as the efficacy of specific immunomodulating therapies such as ultraviolet B phototherapy, thalidomide, and local tacrolimus in the treatment of uraemic pruritus.[1,24]

Opioid hypothesis: uraemic pruritus is believed to be associated with imbalances in the expression of mu and kappa opioid receptors that cause pruritus.[3] This new hypothesis is supported by the overexpression of mu-receptor agonist (beta-endorphin) to the kappa-receptor agonist (dynorphin-A) in patients with uraemic pruritus as well as the efficacy of nalfurafine, a centrally acting kappa-opioid receptor agonist, in the treatment of uraemic pruritus.[2,3]

Uraemic neuropathy hypothesis: uraemic pruritus is believed to be associated with diminished threshold of sensory perception, due to central sensitization to itch or due to peripheral nerve fiber damage.[1,2,25] This hypothesis is supported by the efficacy of anticonvulsant medications such as gabapentin and pregabalin in treating uraemic pruritus, through blocking neuronal calcium influx and decrease the release of neurotransmitters.[26]

Pruritogenic cytokines hypothesis: uraemic pruritus is believed to be associated with increased release of histamine and mast cells mediators, stimulating local itch receptors. This hypothesis is supported by the higher plasma histamine level[27] and the skin mast cell level[28] in patients with pruritus, without being linked to pruritus itself. Additionally, this hypothesis is supported by the efficacy of cromolyn sodium, a mast cell stabilizer, in treating uraemic pruritus. However,

Table 1: Prevalence of uraemic pruritus and its associations with age, gender, and type of treatment

Study	Number of patients	Age (years)	Country	Prevalence	Associations
Susel et al. (2014)[9]	200 HD	59.1	Poland	Overall: 75 (37.9%) Male: 49 (39.8%) Female: 26 (34.7%)*	No significant differences by age or gender
Tajbakhsh et al. (2013)[84]	100 HD	49 ± 12.3	Iran	Overall: 36/92 (39.1%)	None mentioned
Makhlough et al. (2013)[10]	153 HD	Yes: 59.6 ± 15.7 No: 61.7 ± 13.1	Iran	Overall: 94 (61.4%) Male: 48 (60%.0)* Female: 46 (63.0%)*	No significant differences by age or gender
Deshmukh et al. (2013)[85]	35 HD	48.8 ±13.4	India	Overall: 23 (65.7%)	None mentioned
Lopes et al. (2012)[11]	980 HD	No: 47.6± 14.3 Mild: 49.6±14.1 Severe: 51.2±13.5	Salvador & Brazil	Overall: 429 (43.8%) Severe: 190 (19.4%)	Pruritus was significantly associated with older age but not gender
Welter et al. (2011)[12]	105 HD	51.9	Brazil	Overall: 46 (43.8%) Severe: 9 (19.6%)	No significant differences by age or gender
Falodun et al. (2011)[86]	Total : 120 HD: 76 Conservative: 44	43.1±15.4	Nigeria	Overall: 32 (26.7%) HD: 21 (27.6%) Conservative: 11 (25.0%)	No significant differences between the treatment groups
Attia et al. (2010)[19]			Egypt	Overall: 66 (32.0%) Adult: 58 (35.6%) Children: 8 (18.6)	Pruritus was significantly higher among adults* and diabetics but not HCV
Khanna et al. (2010)[20]	Total: 200 CKD: 150 HD: 50	40.2±15.2	India	Overall: 72 (36%) No dialysis: 43 (28.7%)* Dialysis: 29 (58.0%)*	Significantly higher in CKD with dialysis than CKD without dialysis*
Yong et al. (2009)[21]	Total: 179 PD: 107 HD: 27 Palliative: 45	61.9 ±12.3	Hong Kong	Overall: 114 (63.7%) PD & HD: 88 (65.7%) Palliative: 26 (57.8%)	No significant differences between the treatment groups
Melo et al. (2009)[13]	101 HD	Yes: 54.0 No: 38.5	Brazil	Overall: 31 (30.7%) Males: 19 (32.2%)* Females: 12 (28.6%)*	Pruritus was significantly associated with older age but not gender
Layegh et al. (2007)[22]	Total: 127 HD: 93 PD: 34	HD: 48 PD: 42	Iran	Before dialysis: 60 (47.2%)* Overall dialysis: 70 (55.1%) HD: 59 (63.4%) PD: 11 (32.3%)	Significant differences by type of dialysis (HD>PD)
Resic et al. (2007)[14]	77 HD	55.8 ± 14.1	Bosnia & Herzegovina	Overall: 45 (58.4%) Male: 26 (63.4%)* Female: 19 (52.8%)*	No significant differences by age or gender*

Study	Number of patients	Age (years)	Country	Prevalence	Associations
Pisoni et al. (2006)[6]	DOPPS 1: 10810 HD DOPPS 2: 10265 HD	Yes: 60.7±14.5 No: 60.3 ± 14.6	DOPPS 1: 7 Western countries DOPPS 2: 12 Western countries	Moderate-severe pruritus DOPPS 1: 45% (38-48%) DOPPS 2: 42% (36-50%)	Significant differences by country (36% in France and 50% in UK) and between facilities (5–75%)
Narita et al. (2006)[15]	1773 HD	60.2±12.8	Japan	Moderate-severe pruritus* Overall: 947 (53.4%) Male: 609 (58.3%) Female: 338 (46.5%)	Significant difference by gender (males > females) but not by age
Udayakumar et al. (2006)[87]	100 HD	10-76	India	Overall: 53 (53.0%)	None mentioned
Duque et al. (2006)[88]	105 HD	48±11	USA	Overall: 60 (57.1%)	None mentioned
Mistik et al. (2006)[16]	Total: 341 HD: 289 PD: 52	51.1±15.0	Poland	Before dialysis: 97 (28.4%) Overall dialysis: 177 (51.9%) HD: 145 (50.2%) PD: 32 (61.5%)	Significant difference by gender (63.8% in males vs. 36.2% in females) but not by age or type of dialysis
Dyachenko et al. (2006)[5]	70 HD	62.9 ± 14.1	Israel	Overall: 52 (74.3%)	No significant differences by age, gender or ethnicity
Zucker et al. (2003)[4]	219 HD	62 ± 13.7	Israel	Before dialysis: 40 (18%) During dialysis: 105 (48%)	No significant differences by age or gender
Szepietowski et al. (2002)[17]	130 HD		Poland	Before dialysis: 47 (36.2%) During dialysis: 53 (40.8%)	Significant gender difference (females > males) but no age difference
Subach and Marx (2002)[89]	70 HD			Overall: 49 (70.0%)	None mentioned
Silverberg et al. (2001)[90]	Total: 30 HD: 16 Transplant: 10 Medical: 4	14 (3-18)	USA	Overall: 17 (56.7%) HD: 11 (69%) Transplant: 5 (50%) Medical: 1 (25%)	No significant differences between the treatment groups *
Jamal and Subramanian (2000)[18]	100 HD	13-80	Saudi Arabia	Overall: 67 (67.0%) Males: 27 (67.5%) Females: 40 (66.7%)	Significant age difference (older > younger)* but no overall gender difference

*Calculated from the published data HD: on hemodialysis, PD: on peritoneal dialysis; Yes: patient has pruritus
No: No pruritus

the limited efficacy of classical antihistamines (cetirizine, loratadine, and desloratadine) in treating uraemic pruritus draws doubt over the role of histamine in uraemic pruritus.[1,2]

Skin alteration hypothesis: skin xerosis is believed to promote uraemic pruritus by lowering the perception threshold.[29] This hypothesis is supported by the efficacy of skin emollients in relieving mild and/or localized uraemic pruritus.[30,31]

Uraemia-related alterations hypothesis: uraemic pruritus is believed to be associated with severe secondary hyperparathyroidism, hyperphosphatemia, and elevated calcium–phosphate product.[1,3] Additionally, the serum parathyroid hormone has been shown in some studies to correlate with the severity of pruritus in hemodialysis patients.[10] This may lead to deposition of calcium phosphate crystals in the epidermis, producing peripheral sensitization to itch. This hypothesis is supported by the improvement of uraemic Pruritus after parathyroidectomy.However, the lack of correlation between preoperative levels of calcium, phosphate, and calcium-phosphate product in these patients and pruritus add to the inconclusiveness on this hypothesis.[32]

Serotonin hypothesis: Serotonin that is known to enhance pain perception and pruritic symptoms has been shown to be higher in dialyzed patients, especially those with pruritus, but not linked to pruritus.[33] Therefore, it has been believed that uraemic pruritus is associated with higher serotonin activity. However, the inefficacy of serotonin antagonists as ondansetron in treating uraemic pruritus undermines the serotonin hypothesis.[34]

MANAGEMENT

Similar to the multiple hypotheses suggested to explain the pathophysiology of uraemic pruritus, several anti-pruritic therapies have been examined in hemodialysis patients. However, none is considered the drug of choice or exclusively efficient in all patients.[1-3] Additionally, most available evidence and recommendations are based on limited-quality research in the form for small RCT, uncontrolled trials, pre and post small interventional studies, and case series. Therefore, there are no current standard guidelines. The available therapies published between 2000 and 2014 are discussed here. These include;

- Treatments of uraemia such as adequate dialysis, optimization of metabolic parameters, and renal transplantation which is considered the definitive treatment
- Evidence from a well-conducted trial at one or more institutions
- Topical treatments such as emollients, topical analgesics, and tacrolimus
- Systemic pharmacologic treatments such as antihistamines and mast cell stabilizers, anticonvulsants, opioid receptor medications, serotonin antagonists, antidepressants, and other medications. Table 3 summarize the local and systemic pharmacologic agents.
- Physical and alternative treatments such as phototherapy and acupuncture
- Surgical treatment such as parathyroidectomy

Adequate dialysis: It has been shown that increasing the dose of dialysis may improve pruritus.[32] Additionally, in some studies, higher dialysis efficacy, as expressed by dialyzer clearance, volume distribution of area, and dialysis duration (Kt/v), has been inversely associated with uraemic pruritus.[5,36] However, the lack of association between dialysis efficacy and the degree of pruritus in other studies may be explained by the fact that Kt/v actually quantify urea clearance and does not quantify the removal of mid- and large-sized molecules which may be responsible for uremic pruritus.[15] Interestingly, switching dialyzed patients to polymethylmethacrylate based dialysis membranes (PMMA) has been associated with a significant reduction in the degree of pruritus, irrespective of dialysis efficiency or improvement in other biochemical parameters.[37,38] Although the exact mechanism is not known, it may be due the ability of the PMMA dialyzers to adsorb solutes such as cytokines and some cationic compounds. However, since the evidence has been based on generally small non-randomized studies, the finding should not been overestimated. Additionally, uraemic pruritus is still prevalent problem in the US where almost all patients are already dialyzed against PMMA.[39,40]

Topical treatments: As mentioned above, skin xerosis is believed to promote uraemic pruritus.[29] Therefore emollients with high water content are widely used topical treatment of uremic pruritus, especially if

Table 2: Pathophysiologic hypotheses of uraemic pruritus and related medications

Hypotheses	Mechanism and mediators	Related medications
Immune-inflammation: uraemic pruritus is caused by systemic inflammation rather than a local skin disorder	Higher T helper-1 (TH1) cells, C-reactive protein and interleukin 6 (IL-6) in uraemic pruritus	Immunomodulating therapies: Ultraviolet B phototherapy, thalidomide, tacrolimus
Opioids: uraemic pruritus is associated with imbalances in the expression of mu and kappa opioid receptors	Overexpression of mu-receptor agonist (beta-endorphin) to the kappa-receptor agonist (dynorphin-A) was observed in patients with uraemic pruritus	Kappa-opioid receptor agonist: Nalfurafine Mu-opioid receptor antagonist: Naltrexone
Neuropathy: uraemic pruritus is associated with diminished threshold of perception, due to central sensitization to itch or due to peripheral nerve fiber damage	Increased neuronal calcium influx and increased release of neurotransmitters	Anticonvulsants: Gabapentin and pregabalin
Pruritogenic cytokines: uraemic pruritus is associated with increased release of histamine and mast cells mediators, stimulating local itch receptors	Increased histamine produced by mast cells, keratinocytes, and leukocytes. Increased release of mast cell mediators including histamine, IL2, acethylcholine, TNF-α and proteases.	Classical antihistamines: Cetirizine, loratadine, and desloratadine. Mast cell stabilizer: Cromolyn sodium
Skin alteration: skin xerosis promote uraemic pruritus by lowering the perception threshold	Skin xerosis is caused by decrease in sweat volume, atrophy of sebaceous glands, and dermal dehydration	Topical emollients
Uraemia-Related Alterations: uraemic pruritus is associated with severe secondary hyperparathyroidism, hyperphosphatemia, and elevated calcium–phosphate product	Calcium phosphate deposits in the epidermis produce peripheral sensitization to itch	Treatment of hyperparathyroidism: vitamin D and calcimimetics Surgical parathyroidectomy
Serotonin: uraemic pruritus is associated with higher serotonin activity	Serotonin enhances pain perception and pruritic symptoms through 5-HT3 receptors on the nervous system	Serotonin antagonists: ondansetron and granisetron

xerosis is present on examination. Despite the limited data quality being uncontrolled or non-randomized small-sized studies, emollients have been shown to be a safe and effective initial treatment for uaemic pruritus.[30-31] Topical use of gamma-linolenic acid has been shown to be effective and safe adjuvant agent for refractory uremic pruritus.[41] Although the study was RCT, the small number of studied patients and the lack of other confirmatory evidence, may limit its recommendation at this point. Local use of pramoxine, an analgesic, has been shown in a pharmaceutically-sponsored RCT to be a safe and convenient therapy for hemodialysis patients with persistent moderate to severe pruritus despite appropriate use of emollients.[42] Local use of capsaicin, another analgesic, has been shown to be effective in one recent RCT[43] and ineffective in another earlier interventional study.[44] This conflicting data and being suggested for localized pruritus rather than systemic one may limit its current recommendation. Finally, the earlier efficacy of short-term topical use of tacrolimus ointment in reducing uaremic pruritus[45,46] has not been replicated in a recent RCT.[47] Additionally, the fear from the carcinogenic properties of systemic use of tacrolimus and its relatively high cost limit its use, if any.[45,46]

Antihistamines: Although they are probably the most widely prescribed systemic medications in pruritic diseases including uraemic pruritus, the findings from recent studies are not supportive. Classical antihistamines (cetirizine, loratadine, and desloratadine) have been shown to have no or limited efficacy in controlling uraemic pruritus.[34,48,49] On the other hand some medications with antihistaminic properties and mast cell stabilizers showed promising results. For example, doxepin, a tricyclic antidepressant with anti-H1 receptor effect,

Table 3: Pathophysiologic hypotheses of uraemic pruritus and related medications

Treatment	Studies	Number of patients	Level of evidence	Efficacy	Safety	Comments
TOPICAL TREATMENTS						
Emollients	Okada & Matsumoto (2004)[30]	20	3	Yes	Yes	Effective safe initial treatment but insufficient evidence
	Szepietowski et al. (2005)[31]	19	4	Yes	Yes	
Gamma-linolenic acid	Chen et al. (2006)[41]	17	1	Yes	Yes	Promising probably effective treatment but no sufficient evidence yet
Pramoxine	Young et al. (2009)[42]	28	1	Yes	Yes	
Capsaicin	Weisshaar et al. (2003)[44]	11	3	No	Yes	Conflicting efficacy data. Insufficient evidence
	Makhlough et al. (2010)[43]	34	1	Yes	Yes	
Tacrolimus	Pauli-Magnus et al. (2000)[45]	3	6	Yes	Yes	Conflicted efficacy data and possibility of carcinogenic effect. Not recommended
	Kuypers et al. (2004)[46]	25	4	Yes	Yes	
	Duque et al. (2005)[47]	22	1	No	Yes	
ANTIHISTAMINES AND MAST CELL STABILIZER						
Cetirizine	Weisshaar et al. (2004)[34]	21	4	No	Yes	Widely used despite lack or limited efficacy
Loratadine	Legroux-Crespel et al. (2004)[48]	52	4	No	Yes	
Doxepin	Pour-Reza-Gholi et al. (2007)[50]	24	1	Yes	Yes	
Desloratadine	Marquez et al. (2012)[49]	22	3	Modest	Yes	Promising safe and effective treatment but no sufficient evidence yet
Cromolyn	Rosner (2006)[51]	2	6	Yes	Yes	
	Vessal et al. (2010)[28]	62	1	Yes	Yes	
ANTICONVULSANTS						
Gabapentin	Gunal et al. (2004)[52]	25	1	Yes	Yes	Effective for resistant pruritus unresponsive to antihistamines and emollients and associated with peripheral neuropathy. Adverse reaction may be an issue
	Manenti et al. (2005)[53]	6	6	Yes	Yes	
	Naini et al. (2007)[54]	34	1	Yes	Yes	
	Razeghi et al. (2009)[55]	34	1	Yes	Equivocal	
	Solak et al. (2012)[56]	50	1	Yes	Equivocal	
	Marquez et al. (2012)[49]	22	3	Marginal	No	
	Rayner et al. (2012)[59]	71	4	Yes	Equivocal	
Pregabalin	Aperis et al. (2010)[57]	16	4	Yes	Equivocal	An equally effective alternative drug to gabapentin used for resistant pruritus with probably lower adverse reactions
	Solak et al. (2012)[56]	50	1	Yes	Equivocal	
	Rayner et al. (2012)[59]	15	4	Yes	Yes	
	Shavit et al. (2013)[26]	12	4	Yes	Yes	
	Yue et al. (2014)[58]	188	1	Yes	Yes	
K-OPIOIDS AGONIST						
Naltrexone	Pauli-Magnus et al. (2000)[61]	23	1	No	No	Naltrexone is ineffective in treating uraemic pruritus and has frequent GIT adverse effects. Not recommended
	Legroux-Crespel et al. (2004)[48]	52	1	No	No	

Nalfurafine	Wikstrom et al. (2005)[62]	144	1	Yes	Yes	Nalfurafine is a safe and effective treatment for uremic pruritus refractory to conventional therapies
	Kumagai et al. (2010)[63]	337	1	Yes	Yes	
	Inui et al. (2012)[65]	6	4	Yes	Yes	
	Kumagai et al. (2012)[64]	211	4	Yes	Yes	
SEROTONIN ANTAGONISTS						
Ondansetron	Ashmore et al. (2000)[67]	16	1	No	Yes	Ondansetron is ineffective in treating pruritus and should not be recommended.
	Murphy et al. (2003)[68]	24	1	No	Yes	
	Deshpande (2004)[66]	1	6	Yes	Yes	
	Yue et al. (2014)[58]	188	1	No	Yes	
Granisetron	Albares et al. (2003)[69]	1	6	Yes	Yes	Granisetron is probably effective but no sufficient evidence yet
	Layegh et al. (2007)[22]	14	4	Yes	Yes	
NOVEL AND OTHER THERAPIES						
Sertraline	Shakiba et al. (2012)[70]	19	4	Yes	Yes	Promising safe and effective medication but no sufficient evidence yet
	Chan et al. (2013)[71]	20	4	Yes	Yes	
Montelukast sodium	Nasrollahi et al. (2007)[72]	16	1	Yes	Yes	
Omega-3 fatty acids	Begum et al. (2004)[73]	22	1	No	Yes	
	Ghanei et al. (2012)[74]	22	1	Yes	Yes	

has been shown in one RCT as effective systemic treatment against resistant uraemic pruritus.[50] The main adverse effect doxepin was temporary drowsiness. Additionally, cromolyn sodium, a mast cell stabilizer has been shown in one RCT and a case report as very effective and safe medication for uraemic pruritus.[28,51]

Anticonvulsants: Gabapentin is an anticonvulsant medication used in a variety of neuropathic pain syndromes. Several RCTs and one case series over the last 10 years showed its clear effective management of uraemic pruritus.[49,52-56] The studied patients typically had resistant uraemic pruritus unresponsive to emollients and antihistamines with the majority having additional neurologic problems.[55] The safety of gabapentin has been generally acceptable,[52-54] although in some recent studies has been questionable.[49] Common adverse effects included somnolence, dizziness and fatigue.[49,56] Therefore it has been suggested to gradually use the lowest effective dose to avoid adverse effects.[34] Pregabalin is very similar to gabapentin regarding the structure and mechanism of action.[26] Its effectiveness against resistant uraemic pruritus has been shown in recent RCTs and observational studies.[26, 56-59] Pregabalin has been suggested as an equally effective alternative drug to gabapentin in patients with resistant uraemic pruritus, with probably more rapid effect and with better tolerability.[56,59] Dizziness and somnolence were the most common side effects for pregabalin use.[56,57,59]

Opioid receptor medications: Although initially suggested as an effective treatment of uraemic pruritus,[60] naltrexone, a mu-receptor antagonist, has been shown in 2 recent RCTs as ineffective medication for uremic pruritus.[48,61] Additionally, naltrexone is expensive and accompanied by a high incidence of gastrointestinal side effects.[48,61] Therefore naltrexone should not be currently recommended for uraemic pruritus. Nalfurafine is a recently developed selective

kappa-opioid receptor agonist with a potent antipruritic effect on various types of pruritus. Two recent large RCT[62,63] and two interventional studies [64,65] showed its effectiveness in reducing itch in hemodialysis patients with uremic pruritus refractory to conventional therapies. The most common side effect of nalfurafine was insomnia, seen in only approximately 10% of patients.

Serotonin antagonists: In a pediatric case report, the use of ondansetron was followed by a dramatic improvement of resistant uraemic pruritus, unresponsive to antihistamines.[66] However, a recent large RCT[58] and another two smaller RCTs[67,68] consistently showed negligible effects of ondansetron in treating uraemic pruritus, and therefore, should not be recommended for uraemic pruritus. Granisetron has been shown to be effective against moderate to severe uraemic pruritus.[22,69] However, the limited quality of data and small number of examined patients preclude current recommendation of granisetron. Inconsistent data about the role of serotonin antagonists in controlling uraemic pruritus undermine the serotonin hypothesis to explain the pathophysiology of uraemic pruritus.

Novel and other medications: Few additional drugs have been suggested as a promising anti-pruritic agents but the current data quality does not allow its current recommendations. Sertraline, antidepressant that has been used for the treatment of non-renal pruritus, has been found to be effective for antihistamine-refractory uremic pruritus in renal palliative care patients.[70,71] However, since the available data were based on small uncontrolled studies, confirmation of these findings in RCTs is required before its recommendation. One small-sized RCT found montelukast, a leukotriene receptor antagonist, safe and effective medication in the treatment of uremic pruritus not responding to the currently available antipruritus medications.[72] Finally, two RCTs showed conflicting data about the efficacy of omega-3 fatty acids for treatment of itching in hemodialysis patients.[73,74]

Parathyroidectomy: Despite the lack of correlation between pruritus and preoperative levels of calcium, phosphate, and calcium-phosphate product, parathyroidectomy has been associated with significant improvement of pruritus among 37 patients on hemodialysis who suffered from secondary hyperparathyroidism.[32] Additionally, medical treatment of hyperparathyroidism using calcimimetics has been associated with reduced itching among hemodialysis patients.[75]

Ultraviolet-based therapy: Ultraviolet irradiation has been used in treating various types of pruritus, including uraemic pruritus.[76] The exact mechanism is not exactly known but a decrease in proinflammatory cytokine levels and induction of mast cell apoptosis have been suggested.[77] Two cases series and one interventional study showed beneficial effect of narrowband ultraviolet B phototherapy in alleviating renal pruritus.[78-80] However, the same results could not be replicated in a small recent RCT.[81] Additionally, the possibility of recurrence, the risk of long-term carcinogenic effect, and the interaction with concomitant immunosuppressive therapy should be weighted before starting ultraviolet B phototherapy for renal patients with pruritus.[79-80]

Acupunture: A recent systematic review of 3 RCTs and three uncontrolled observational studies found acupunture as an easy, safe and effective means of relieving uraemic pruritus.[82] However, these studies had a significant design flaw and high risk of bias, which make the current evidence insufficient to recommend acupuncture for treatment for uraemic pruritus.

Suggested step-wise treatment: Due to current lack of standard guidelines for the management of uraemic pruritus, several authors proposed a step-wise approach in treating patients with uraemic pruritus.[3,24,83] Initial therapy should include more efficient dialysis and topical emollients and/or analgesics (such as pramoxine lotion). Resistant pruritus not responding to previous treatment should be started on oral antihistamines and if not sufficient then oral anticonvulsants as gabapentin or pregabalin. Refractory pruritus not responding to previous treatments should be started on intravenous nalfurafine, ultraviolet B phototherapy, or other novel medications that did not have sufficient evidence for current recommendations.

CONCLUSION

The prevalence of uraemic pruritus has been reduced in recent years. Although still complex, recent years

improved our understanding in the pathophysiology of uraemic pruritus. Several new medications have been examined in the last decade. However, in many of these medications, the evidence is still insufficient for their recommendations. After all advances in dialysis techniques and the availability of multiple therapies, uraemic pruritus is still a significant problem among hemodialysis patients that warrant further research.

KEY POINT BOX

- With few exceptions, there have been no significant differences in the prevalence of uraemic pruritus by age, gender, and type of dialysis.
- Although still complex, recent years improved our understanding in the pathophysiology of uraemic pruritus.
- We reviewed the available therapies published between 2000 and 2014, and we conclude that uraemic pruritus is still a significant problem that warrant further research.

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