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Review Article

Western and complementary alternative medicine treatment of uremic pruritus: A literature review

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Abstract

Uremic pruritus (UP), also called chronic kidney disease-associated pruritus (CKD-aP), is a bothersome symptom that causes sleep disturbance, anxiety, depression, and reduced quality of life. Pruritus often occurs in patients with end-stage renal disease. There is still no definite treatment for UP due to its unclear pathogenesis. We searched electronic databases (PubMed and Google Scholar) and gathered the latest clinical trials and pilot studies of Western and complementary alternative medicine (CAM) therapies for UP in English. These UP studies were separated into three main groups: systemic, topical, and others and CAM. Gabapentin, nalfurafine, acupuncture, and Chinese herbal bath therapy (CHBT) show antipruritic effects, with higher evidence grades in the meta-analysis. Emollients with additive compounds are more effective for reducing itch than emollients without additives. Supplements for deficient elements, such as zinc, omega-3, and omega-6, also show benefits for pruritus improvement. CAM therapies such as acupuncture, herbs, and herbal baths or creams all have good results for UP treatment. We summarize the treatments and suggest a treatment algorithm for UP according to severity. Some UP therapies are already supported by large-scale clinical evidence, and some new treatments can provide patients with new hope and treatment options. However, these new methods still need large population studies and further exploration.

Keywords: *Chronic kidney disease, Complementary and alternative medicine, Dialysis, End-stage renal disease, Uremic pruritus*

Introduction

Uremic pruritus (UP) often occurs in patients with end-stage renal disease (ESRD). With improvements in dialysis techniques, the prevalence of UP ranged from 90% between 1980 and 1993 and 18% between 2012 and 2015. However, the prevalence of UP seems to be underestimated by medical directors, and 18% of UP patients do not receive treatment [1]. The prevalence of UP in patients receiving hemodialysis (HD) and peritoneal dialysis was equal [2]. UP can be localized, mainly affecting the back, face, limbs, and abdomen; however, up to 50% of patients experience generalized pruritus. Itching related to UP can last a few minutes to whole days. The itching worsens at night and interrupts sleep, which causes fatigue and depression and reduces quality of life; furthermore, it increases the risk of mortality [1,3,4]. Clinical findings are limited because most patients present dry and scaly skin without apparent changes. Severe scratching results in secondary skin changes, such as ulcerations, linear crust, impetigo, papules, and prurigo nodularis [3]. Approximately 10% of dialysis patients will develop Kyrle's disease, an acquired perforating dermatosis [5]. Laboratory findings suggestive of UP may include elevated blood urea nitrogen, calcium/phosphate or parathyroid hormone (PTH) [6,7]. The pathogenesis of UP is not well understood, and two major hypotheses have been proposed, implicating the immune and opioid systems [8,9]. Microinflammation of the skin, histamines and the release of pro-inflammatory cytokines, such as serum C-Reactive protein (CRP) and interleukin-6 (IL-6), have been observed in UP patients [8]. A study showed that the pro-inflammatory levels of HD patients with itching are higher than those of HD patients without itching, supporting the immune hypothesis [10]. Toxins, such as uremic toxins, PTH, calcium, phosphorus, magnesium and aluminum, deposit in the skin or tissue and act as pruritogens to induce UP. Pruritogens (accumulated toxin, histamine and pro-inflammatory cytokines)

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cause peripheral neuropathy and induce UP [11]. Most UP patients show signs of peripheral sensorimotor neuropathy and dysautonomia [12]. The opioid hypothesis was proven by the finding that κ-opioid receptor expression was significantly decreased in HD patients with UP compared to those without UP [13]. A cohort study showed that the frequency of pruritus is correlated with psychological stress [14], and two randomized controlled trials (RCT) reported that oral antidepressants could significantly improve pruritus severity [15]. UP patients show significantly decreased stratum corneum hydration, and a high proportion have severe xerosis, especially relative to those with no xerosis. Xerosis has a direct clinical relationship with UP[16] [Figure 1].

Xerosis [17], hyperparathyroidism, hepatitis C virus infection [18], inadequate dialysis [19], and elevated serum electrolytes such as calcium, phosphorus, magnesium, aluminum, and lead are risk factors most strongly associated with UP [6,20,21]. Male sex, anemia and comorbidities such as neurologic disease and congestive heart failure are the least strongly associated risk factors [22,23]. Ethnicity, underlying renal disease and dialysis type are irrelevant to UP [24]. The pathophysiology of UP is still not well understood; therefore, effective treatments are lacking. In addition, there are only a few randomized, placebo-controlled trials with limited therapeutic effects. In this paper, we screen review articles and the latest clinical trials of systemic, topical and complementary and alternative medicine (CAM) therapies to summarize the available evidence regarding treatment strategies for UP.

Uremic pruritus treatment

Dialysis modification and surgical intervention

A 5-year prospective cohort study of 111 UP patients showed that the group with Kt/V (delivered dialysis amount: K = clearance of urea, t = time on dialysis, V = estimated total body water) ≥1.5 and the use of a high-flux dialyzer with high-flux polysulfone membrane using reverse osmosis purified water and bicarbonate dialysate had a decreased extent of pruritus compared with those with Kt/V <1.5 and the use of a low-flux dialyzer [25]. A retrospective study conducted over a 5-year period recruited 36 renal hyperparathyroidism patients refractory to medical treatment and showed not only high levels of PTH, hypercalcemia and/or hyperphosphatemia but also adverse effects such as pruritus. After parathyroidectomy with autotransplantation, PTH, hypercalcemia, hyperphosphatemia and pruritus were improved [26]. However, a higher PTH could be adjusted with Vitamin D analogs and calcimimetics [27]; therefore, parathyroidectomy should be recommended for UP patients after standard therapy, such as Vitamin D analogs and calcimimetics. Recently, a review that included 7 articles stated that kidney transplantation (KTx) can reduce the incidence of UP [28].

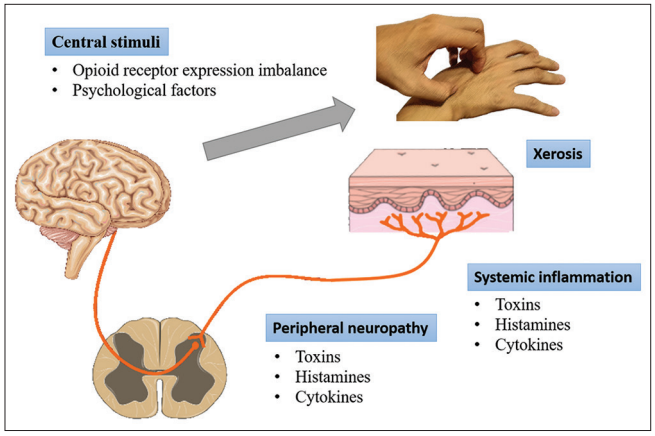

Figure 1: Proposed mechanism and pathogenic factors in uremic pruritus

Systemic treatments

A study of three antihistamines by Kalili *et al*. showed that hydroxyzine decreased the pruritus severity score (33%) more than chlorpheniramine (20%) and ketotifen (4.5%) did [29]. A RCT of 40 UP patients showed that the mean reduction in the visual analog scale (VAS) scores of the group taking oral cromolyn sodium (CS) was significantly greater than that in the placebo group. However, CS did not decrease the serum tryptase level, indicating that its antipruritic effect is not the result of inhibiting mast cells from releasing tryptase [30]. Montelukast was applied in an RCT that recruited 80 UP patients, and the mean reduction in VAS scores and CRP in the montelukast group was considerably higher than that in the placebo group [31]. Fifty-two UP patients were included in an RCT comparing naltrexone, a μ-opioid antagonist, and loratadine, an antihistamine agent; the study found that there were no statistically significant differences in VAS scores between the two groups. Although naltrexone showed a significant decrease in pruritus in 7 patients, it was associated with frequent adverse events [32]. A meta-analysis pooled 2 RCTs of nalfurafine, a κ-opioid agonist, and found that it led to better improvement of VAS scores than placebo in the treatment of UP; however, a higher occurrence of side effects was also noticed [33]. Recently, a case report indicated that a refractory UP patient experienced worsened UP after using topical triamcinolone and oral gabapentin, and his VAS scores decreased from 10 to 0 after the use of intranasal butorphanol spray 1 mg once daily [34]. A systematic review (SR) of two RCTs showed that ondansetron had no benefit over placebo in the treatment of UP [35]. An SR examined the antipruritic effect of the current oral antidepressants used in chronic pruritus treatment. Three oral antidepressants, sertraline, amitriptyline, and doxepin, were applied for the treatment of UP [15]. In a case series, the VAS scores of two UP patients treated with amitriptyline, a tricyclic antidepressant, decreased from 7 to 3 and 7-0, respectively [36]. Seventy-four HD patients with pruritus were included in an RCT comparing the antipruritic effects of pregabalin and doxepin; both drugs had a good antipruritic effect, but pregabalin reduced the patients' 5-D itch scale (5-DIS) and Dermatology Life Quality Index scores more than doxepin did [37]. Recently, in an RCT that enrolled 50 UP patients, the reduction in VAS scores in the sertraline group was greater than that in the placebo group [38]. Neurological side effects of oral antidepressants, such as mild fatigue and drowsiness, were noticed, and the soporific effect might correspond to the antipruritic effect. Therefore, oral antidepressants are suggested for UP patients who are unresponsive to conventional treatment [15]. Gabapentin and

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pregabalin are the antidepressants most often used in the treatment of neuropathic pain, but there are many reports of their use for UP with good results. Recently, a pooled meta-analysis of 4 RCTs found that gabapentin decreased UP severity significantly more than placebo. Although adverse effects of gabapentin, such as dizziness, drowsiness, and somnolence, were noted in each RCT, the results of the meta-analysis showed no statistically significant differences compared to comparators and placebo [39]. The antipruritic effects of gabapentin were better than those of antihistamines, such as hydroxyzine and ketotifen [40,41]. In an RCT that included 179 UP patients separated into three groups-pregabalin, ondansetron, and placebo – found that in the pregabalin group, pruritus was apparently mitigated and VAS scores declined from 8 to 1.4, but the antipruritic effects of ondansetron and placebo were negligible. However, side effects of somnolence, severe dizziness and loss of balance occurred in 5 cases in the pregabalin group [42]. Another RCT reported that the pregabalin group showed greater reduction of pruritis than the doxepin group [37]. Thalidomide, an immunomodulator and neuromodulator, alleviated UP severity by approximately 81% in an early RCT study [43]. While thalidomide improved chronic refractory pruritus, it caused many adverse effects, such as teratogenesis, peripheral neuropathy, sedation, dizziness, and thromboembolism [44]. Pentoxifylline (PTX) is mainly used to treat vascular disease and has shown the ability to suppress inflammation. In a pilot study of PTX that included 7 UP patients, 4 patients stopped the treatment due to side effects; only 3 patients finished the study, and the best reduction of VAS scores was a decrease from 6 to 1 [45]. Granisetron is a selective inhibitor of 5-HT3 receptors. In 14 HD patients with moderate to severe pruritus who received granisetron, pruritus disappeared in 7 patients, and in 3 patients, the pruritus severity was reduced to mild [46]. Cholestyramine is a bile acid sequestrant that was used to treat 10 HD patients with UP in an early study. In 4 out of 5 patients in the treatment group, pruritis improved considerably, but adverse effects of constipation and nausea were observed [47]. Oral and intravenous nicergoline was effective in 13 out of 15 patients with severe UP during the treatment period, but itching reappeared soon after nicergoline was terminated. Hypotension was observed during nicergoline administration [48]. Some early RCTs for UP treatments such as cholestyramine, nicergoline, and thalidomide showed good pruritus improvement, but new and large-scale trials are lacking [43,47,48]. An anti-itching effect for UP was also noticed in some small-scale trials of such medications as PTX and granisetron. Among the medicines for immune system dysregulation, CS showed an antipruritic effect superior that of montelukast and hydroxyzine [30]. Although antidepressants and opioid receptor modulators showed better antipruritic ability than antihistamines in some reports, they had a higher occurrence of adverse effects [15,33]. Gabapentin showed a better antipruritic effect than antihistamines such as hydroxyzine and ketotifen and had fewer side effects [40,41] [Table 1].

Topical treatments

Topical therapy is considered the baseline treatment for UP because it is effective, efficient, safe, and easily applied. Natural emollients can rehydrate the skin to maintain moisture. Furthermore, some essential oils and emollients with chemical additives have both hydrating and anti-inflammatory effects. An open-label study in which topical Vitamin D or vehicle was applied to 20 patients with UP revealed significantly lower VAS scores in the group that used topical Vitamin D than in the vehicle group [50]. Baby oil soothed itching briefly and improved sleep quality and quality of life in an RCT of 70 HD patients with pruritus [51]. *Avena sativa* lotion and vinegar can be used to soothe itching by producing a protective moisturizing barrier; moreover, vinegar can reduce the pH of the skin's surface to limit the effects of serine proteases on skin nerve fibers. Both products can effectively decrease pruritus in HD patients [52]. Sericin cream reduces pruritus in HD patients from severe to mild, although skin pigmentation was reported in an RCT study [53]. Essential oils rich in linoleic acid (LA), such as sweet almond oil and chia seed oil, can soothe itching [54]. In a study in which topical 2.2% γ-linolenic acid cream was applied to patients with refractory UP, the treatment alleviated pruritus more than a placebo-based cream did [55]. Furthermore, another study found that topical sweet almond oil significantly improved the itch-related quality of life of patients with UP [56]. Chia seed oils contain LA along with flavonol, which has antioxidant and anti-inflammatory effects. In a controlled study of UP patients that compared the effects of 4% chia seed oil lotion with moisturizers only, itching and skin disorders such as skin hydration and lichen simplex chronicus were all improved in the treatment side [57]. Clove oil is an essential oil with topical anesthetic effects that is used in dentistry. In a study in which topical clove oil was applied for renal pruritus, all parameters of the 5-DIS showed improvement compared to the results for the petrolatum group [58]. Pramoxine, a topical analgesic agent, showed the ability to relieve the itch intensity of 61% of the treatment group [59]. Topical capsaicin application can remove substance *P* from peripheral neurons and may inhibit conduction in pruritis. Topical capsaicin 0.025% cream has been successful in the treatment of UP, but treatment-related side effects of local burning and cutaneous erythema were observed [60]. In a study of 21 HD patients with pruritus, a cream with structured physiological lipids and endogenous cannabinoids alleviated itching. Pruritus was completely eliminated in 8 patients, and xerosis was completely reduced in 17 patients [61]. CS 4% cream improved itching severity considerably compared to placebo [62]. Topical therapy is simple, safe, and effective for reducing itching. Basic emollients can maintain moisture in dry skin, but moisturizers with additional additives such as essential oils or analgesic or anesthetic medicines show better curative effects for UP[54] [Table 2].

Other and complementary and alternative medicine treatments

Phototherapy has shown the ability to inhibit UP by modulating the immune mechanism. Narrowband ultraviolet B (NBUVB) phototherapy has good antipruritic effects for UP patients and is safer than broadband UVB (BB-UVB) [63]. Although NBUVB is safer and less erythemogenic than BB-UVB [63], UVB carries the risk of carcinogenesis and is not suitable for patients receiving immunosuppressive

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Table 1: Systemic treatments for uremic pruritus

Author/year	Intervention/medication	Mechanism/usage	Study design	Number of patients	Duration	Result
Kalili *et al*., 2006 [29]	Hydroxyzine 25 mg, TID	Mast cell stabilizer	Controlled	30	2 weeks	PSS↘ 33%
Vessal *et al*., 2010 [30]	Cromolyn sodium 135 mg, TID	Mast cell stabilizer	RCT	40	8 weeks	VAS↘ (8.48±2.2→0.9±1.8)
Mahmudpour *et al*., 2017 [31]	Montelukast 10 mg, QD	LTRA	RCT	80	30 days	VAS↘ (6.43±2.36→2.73±2.03) DPS↘ (8.89±4.78→3.24±2.20) CRP↘ (5.48±3.86→3.81±3.58)
Legroux-Crespel *et al*. 2004 [32]	Naltrexone 50 mg, QD	Opioid agonist and antagonist	RCT	52	2 weeks	VAS↘ (Delta >3/10) in 7/26 patients
Jaiswal *et al*., 2016[33]	Nalfurafine 2.5 μg QD or 5 μg IV 3 times per week		MA Case report	422 1	2 weeks 2 months	VAS↘ (9.5 mm over placebo in 100-mm VAS)
Forouzandeh *et al*., 2019 [34]	Butorphanol intranasal spray 1mg, QD					VAS↘ (10→0, intranasal spray)
To *et al*., 2012 [35]	Ondancetron 8 mg, TID	5-HT3 antagonists	SR	34	2 weeks	No pruritus↘ (negligible effect)
Layegh *et al*., 2007 [46]	Granisetron 1 mg, BID		Case series	14	1 month	PS↘ (31.5±8.1→8 ± 11)
Yong *et al*., 2013 [36]	Amitriptyline	Antidepressants	Case series	2	1~2 weeks	VAS↘ (7→3, 7→0)
Foroutan *et al*., 2017 [37]	25 mg or 10 mg, QD		RCT	72	4 weeks	VAS↘ (7.1±1.3→4.2±2.6)
Shakiba *et al*., 2018 [49]	Doxepin 10 mg, QD Sertraline 50 mg, QD		RCT	19	4 month	Pruritus severity↘
Eusebio-Alpapara *et al*. 2019 [39]	Gabapentin 100-300 mg, QD, 3-4 times weekly	Anticonvulsants	MA RCT	171 179	2-4 weeks 4 weeks	RR=0.18 (VS placebo) VAS↘ (7.5±1.4→2.1±2.6)
Foroutan *et al*., 2017 [37]	Pregabalin 50 mg, every other day					
Silva *et al*., 1994 [43]	Thalidomide 100 mg, TID	Immunosuppressant	RCT	18	1 weeks	VAS↘ 81%
Mettang *et al*., 2007 [45]	Pentoxifylline 600 mg iv, 3 times weekly	Hemorrheologic agents	Case series	3	5 weeks	VAS↘ (6→1)
Silverberg *et al*., 1977 [47]	Cholestyramine 5 g, BID	Bile acid sequestrant	RCT	10	1 month	Pruritus↘ (80% improved)
Bousquet *et al*., 1989 [48]	Nicergoline 30 mg, QD and 5 mg iv, 3 times weekly	α-adrenergic receptor antagonist	Controlled	15	6 months	Pruritus↘ (86% improved)

↘: This symbol represents improvement. RCT: Randomized controlled trial, PSS: Pruritus severity score, VAS: Visual analog scale, LTRA: Leukotriene receptor antagonist, DPS: Detailed pruritus score, CRP: C-reactive protein, MA: Meta-analysis, 5-HT3: 5-hydroxytryptamine type 3, SR: Systemic review, RR: Risk ratio, MDPS: Modified Duo pruritus score

Table 2: Topical treatments for uremic pruritus

Author/year	Intervention/ medication	Mechanism/ usage	Study design	Number of patients	Duration	Result
Jung *et al*., 2015 [50]	Vitamin D agent, BID	Emollients	Controlled	23	1 month	VAS↘ (70% improved)
Karadag *et al*., 2014 [51]	Baby oil, TID		Controlled	70	1 month	VAS↘ (5.68±1.82→3.17±1.67)
Nakhaee *et al*., 2015 [52]	*Avena sativa*, BID		RCT	23	2 weeks	VAS↘ (5.21±1.69→4.10±2.34)
Nakhaee *et al*., 2015 [52]	Vinegar, BID		RCT	23	2 weeks	VAS↘ (5.19±1.88→3.73±2.41)
Aramwit *et al*., 2012 [53]	Sericin cream, BID		RCT	47	6 weeks	VAS↘ (7.05±2.17→2.23±1.73)
Chen *et al*., 2006 [55]	GLA, QID	Essential oil	RCT	17	2 weeks	VAS↘ (75→30 in 100-mm VAS)
Mehri *et al*., 2018 [56]	Sweet almond oil, QD		RCT	42	2 weeks	ItchyQoL↘ (50.3±16.7→31.6 8.9)
Jeong *et al*., 2010 [57]	Chia seed oil, PRN		Controlled	5	8 weeks	Some improvement of pruritus
Ibrahim *et al*., 2017 [58]	Clove oil, BID		Controlled	50	2 weeks	5-DIS↘ (27.8±5.84→16.1±4.09)
Young *et al*., 2009 [59]	Pramoxine, BID	Analgesics and anesthetic	RCT	28	4 weeks	Pruritus↘ (61% improved)
Tarng *et al*., 1997 [60]	Capsaicin, QID		Controlled	19	4 weeks	Pruritus↘ (86% improved)
Szepietowski *et al*., 2005 [61]	Endocannabinoids, BID		Case series	21	3 weeks	VAS↘ (6.24±2.19→1.29±1.41)
Feily *et al*., 2012 [62]	Cromolyn sodium, BID		RCT	60	4 weeks	VAS↘ (2.5±1.1→0.3±1.3)

↘: This symbol represents improvement. VAS: Visual analog scale, RCT: Randomized controlled trial, GLA: γ-linolenic acid, ItchyQoL: Itch-related quality of life, 5-DIS: 5-D itchy scale

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treatment [64]. A case report in which dupilumab combined with phototherapy and gabapentin was used to treat UP found that VAS scores decreased from 8 to 1 for 6 months and hypothesized that the mechanism for this effect was the targeting of T helper 2 cells to decrease IL-31 [65]. Although dupilumab seems to offer new hope for UP treatment, it costs more than other available methods [66]. Omega-3 supplementation was reported to relieve UP in an RCT study of 64 patients [67]. Fatty acid abnormalities often occur in ESRD patients and are an etiology related to UP. Essential fatty acid supplements such as omega-3 and omega-6 offer benefits for alleviating pruritus, but omega-3 showed greater reductions in pruritis scores than omega-6 did [68,69]. Pruritus and skin dryness showed meaningful improvement in HD patients who received evening primrose oil [70]. Oral activated charcoal is used as a uremic detoxifier. After taking oral activated powdered charcoal, 10 out of 23 HD patients with severe pruritus achieved complete or partial mitigation. The antipruritic effect lasted for several weeks, even after treatment was stopped [71,72]. Oral zinc sulfate not only improved UP but also lowered serum histamine in a study conducted in 1987 [73]. Two other RCTs showed that zinc supplementation was more effective at reducing itching than placebo or hydroxyzine [74-76]. Zinc deficiencies and high serum histamine levels have also been observed in itching patients with ESRD. Oral zinc sulfate supplementation lowers serum histamine and has minimal adverse reactions [76]. CAM has become popular, and methods such as acupuncture, CHBT, Chinese herbal ointments, and oral herbal medicines have been successfully used to treat UP with few side effects. Forty UP patients were randomized to two groups: Acupuncture at the Quchi (LI11) acupoint and at a nonacupoint 2 cm from the Quchi acupoint three times per week for 3 months. Acupuncture at the acupoint reduced the detailed pruritus far more than sham acupuncture did [77]. The first meta-analysis using acupressure for UP pooled 3 RCT articles and suggested that there is insufficient evidence supporting the use of acupressure combined with routine medication [78]. An RCT in which auricular acupressure with vaccaria seed was applied to UP patients found that this treatment could decrease VAS scores and serum histamine levels and showed a significant difference compared to sham tape. Possible antipruritic mechanisms of acupuncture or acupressure are that it stimulates the release of endogenous opiate-like substances to blunt pruritus sensations [79]. In an RCT with 80 UP patients, a Chinese herb-based cream (CHBC) showed a better ability to relieve itching than lotion without active ingredients because CHBC possesses anti-inflammatory abilities and accelerates blood circulation [80]. A meta-analysis that included 17 eligible RCTs showed that CHBT could alleviate UP better than sham therapy did because CHBT accelerated blood circulation and promoted sweating to eliminate metabolic toxins [81]. Oral *Fumaria parviflora* Lam not only significantly decreases the severity of UP in HD patients but also lowers interferon-γ and elevates serum IL-4 [82]. Attenuation of UP and high-sensitivity CRP in ESRD patients were also noted in an RCT study of oral turmeric, which has anti-inflammatory abilities and no adverse effects [83]. Xiao Feng San (XFS), a traditional Chinese formula containing 13 herbs, is widely used to treat dermatologic diseases by inhibiting inflammation, allergies, and oxidation reactions. The effective rate was much higher in the XFS group than in the group that received dialysis only. Interestingly, the PTH clearance rate was higher in the XFS group. XFS could accelerate blood circulation and anti-inflammation[84] [Table 3].

Comparison of Western and complementary alternative medicine treatments

For UP, both CAM and Western medicine (WM) offer internal and external treatment methods, but CAM includes acupuncture and CHBT. The evidence levels of CAM and WM studies are the same; both are supported by case reports, RCTs and meta-analyses, but the WM research design is more rigorous. CAM studies are poor in experimental scale and experimental design, such as random allocation and blinding. However, CAM has fewer side effects [Table 4].

Treatment algorithm for uremic pruritus

To the therapeutic algorithm for UP proposed by Dr. Mettang [3], we add the abovementioned therapies for UP according to their strength of evidence to create a UP treatment algorithm for the selection of therapeutic modality depending on pruritus severity [Figure 2] [85]. Pruritus assessments include unidimensional and multidimensional scales. Both the numerical rating scale (NRS) and 5-DIS are useful for grading the pruritus severity of patients receiving HD. The NRS is a broadly used unidimensional scale that assesses pruritic severity on a scale from 0 to 10 (0 = no itching, 10 = maximal itching). The 5-DIS is a multidimensional scale that includes

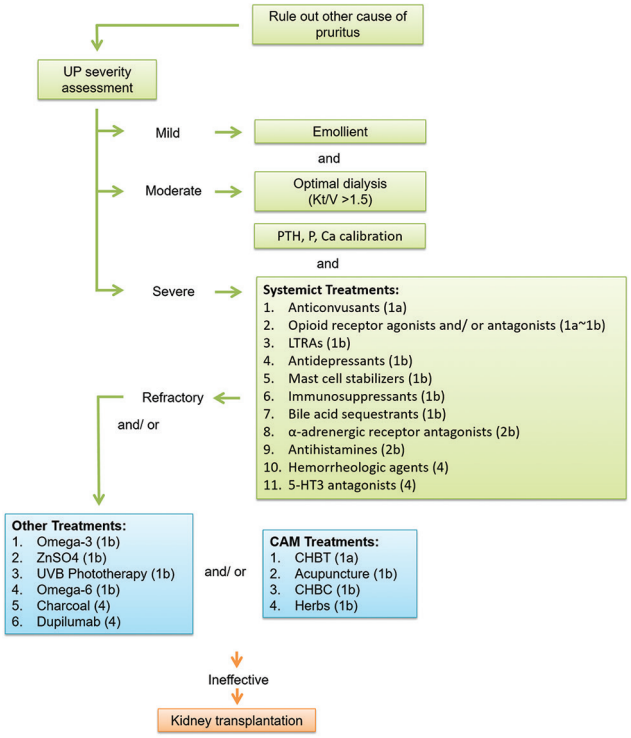

Figure 2: Therapeutic algorithm in uremic pruritus arranged via pruritus severity and evidence level

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Table 3: Other and complementary alternative medicine treatments for uremic pruritus

Author/year	Intervention/medication	Mechanism/usage	Study design	Number of patients	Duration	Result
Other treatments						
Ko *et al*., 2011 [63]	Phototherapy 210 mg/cm^{2†}, 3 times per week	Immune modulator	RCT	21	6 weeks	VAS↘ (7.83→3.92)
Silverberg *et al*., 2019 [65]	Dupilumab 600 mg then 300 mg every other week	Immune modulator	Case report	1	6 months	VAS↘ (8→1)
Shayanpour *et al*., 2019 [67]	Omega-3-2 g, QD	EFA supplement	RCT	64	3 weeks	5-DIS degree↘ (3.56±0.66→1.72±0.63)
Yoshimoto-Furuie *et al*., 1999 [70]	Omega-6-2 g, QD	EFA supplement	RCT	16	6 weeks	Pruritus↘ (skin scores improved)
Giovannetti *et al*., 1995 [71]	Charcoal - 6 g, QD	Uremic detoxifiers	Case series	23	6 weeks	PGS↘ (5.4±0.5→1.6±1.0)
Najafabadi *et al*., 2012 [76]	$ZnSO_4$-440 mg, QD	Mast cell regulator	RCT	40	3 month	VAS↘ (7.3±1.92→3.8±2.73)
CAM treatments						
Chou *et al*., 2005 [77]	Acupuncture LI11 acupoint, 3 times weekly	Acupuncture, endogenous opiate like substances production	RCT	40	1 month	PS↘ (38.3±4.3→16.5±4.9)
Badiee *et al*., 2018 [78]	Acupressure LI11 or SP6, ST36, SP10 and LI11 or CO10, CO14, CO15, TF4, CO18 and AT4, 3 times weekly		MA	190	4-6 weeks	Insufficient evidence
Yan *et al*., 2015 [79]	Auricular acupressure CO10, CO14, CO15, TF4, CO18 and AT4, 3 times weekly		RCT	62	6 weeks	VAS↘ (5.75±2.03→3.84±1.68)
Xue *et al*., 2019 [81]	CHBT average 11 Chinese herbs, 30-40 min, QD	CHBT, antipruritic, accelerate blood circulation and promote sweating	MA	111	2-4 weeks	VAS↘ (MD=−2.38)
Bai *et al*., 2002 [80]	Lifu paste, BID	CHBC, emollients, anti-inflammation and accelerate blood circulation	RCT	80	2 weeks	VAS↘ (82.35%)
Akrami *et al*., 2016 [82]	*Fumaria parviflora* 1 g, TID	Herbs, anti-inflammation	RCT	79	8 weeks	VAS↘ (7.03±2.07→0.88±0.70)
Pakfetrat *et al*., 2014 [83]	Turmeric 500 mg, BID		RCT	100	8 weeks	Duo sore↘ (25.13±9.46→3.09±2.55)
Wang *et al*., 2010 [84]	Xiao Feng San 200 mL, BID		RCT	50	4 weeks	Duo sore↘ (23.9±2.6→10.3±1.6)
						Pruritus↘ (effective rate=90%)

↘: This symbol represents improvement. †210 mJ/cm^2 and was increased by 10% each time. RCT: Randomized controlled trial, VAS: Visual analog scale, EFA: Essential fatty acid, 5-DIS: 5-D itchy scale, PGS: Pruritus grading scale, MA: Meta-analysis, PS: Pruritus score, CAM: Complementary alternative medicine, CHBT: Chinese herbal bath therapy, CHBC: Chinese herbal-based cream

Table 4: Comparison of western medicine and complementary alternative medicine treatments

Category	WM	CAM
Therapeutic modalities	Systemic and topical treatments, surgeries	Systemic and topical treatments, acupuncture, CHBT
Evidence level	Case report, RCT and MA	
Study scale (patients)	10-179	40-100
Study design	Rigorous	Poor
ADR	Some	Less

WM: Western medicine, CAM: Complementary alternative medicine, CHBT: Chinese herbal bath therapy, RCT: Randomized controlled trial, MA: Meta-analysis, ADR: Adverse drug reaction

five dimensions: degree, duration, direction, disability, and distribution. The severity of distribution is assessed according to the number of itchy places, and the severity of the other four dimensions is measured on a scale from 0 to 5 (0 = none, 5 = most severe) [86].

Lai *et al*. reported the categories for the 5-DIS and the transformation between the 5-DIS and the NRS. There are five categories of the NRS and the 5-DIS: none, mild, moderate, severe, and very severe [Table 5] [87]. For mild itching, the use of emollients with or without additives is suggested first. Moisturizers with additional functions have a better curative effect. Moisturizing is the basic treatment for uric itchiness, and it is recommended at any stage. If the itching is moderate, modification of the dose of dialysis and adjusting the electrolyte balance are recommended. Severe pruritus can also be defined as itching that does not improve despite the use of emollients, dialysis modification, and electrolyte adjustments; in such cases, treatment should begin with oral drugs with fewer side effects. When the above treatments are not effective, the addition of other therapies or CAM therapies can be considered. Omega-3 and zinc sulfate supplements with minimal adverse effects can be used first; external treatments without side effects, such as acupuncture, CHBT,

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Table 5: Severity grade of pruritus assessments for uremic pruritus

Severity grade	NRS	5-DIS
No	0	≤8
Mild	1-3	9-11
Moderate	4-6	12-17
Severe	7-8	18-21
Very severe	≥9	≥22

NRS: Numerical rating scale, 5-DIS: 5-D itchy scale

and Chinese herbal-based cream, can then be considered. Oral internal medicines or herbs with less support from clinical evidence should be the last consideration. If all treatments are ineffective for refractory pruritus, KTx is the final recourse.

Advantages and limitations

This article differs from previous research in that we considered both Western and CAM treatments for UP patients receiving dialysis and those with ESRD. In addition, we included meta-analyses, RCTs, and the most recent clinical cases. Only gabapentin, nalfurafine, acupressure, and CHBT showed evidence-based antipruritic effects according to the meta-analysis. Furthermore, we classified the abovementioned therapies into three tables and arranged them according to the strength of evidence to produce a treatment algorithm based on pruritus severity. There are some limitations to our brief review. First, different articles used different itching scales to assess severity, making it difficult to evaluate them as a group and compare them. Second, some nonrandom, small-scale successful treatments for UP offer patients new hope, but evidence is still insufficient. Finally, due to the lack of strong evidence for most treatments, the proposed algorithm is still flawed.

Conclusion

Effective treatment guidelines are still lacking for UP, a truly disturbing symptom that affects quality of life. Studies with a large sample size and a methodologically rigorous design are urgently needed.

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Conflicts of interest

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