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Original Investigation

Treatment of Uremic Pruritus: A Systematic Review

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Background: Uremic pruritus is a common and burdensome symptom afflicting patients with advanced chronic kidney disease (CKD) and has been declared a priority for CKD research by patients. The optimal treatments for uremic pruritus are not well defined.

Study Design: Systematic review.

Setting & Population: Adult patients with advanced CKD (stage ≥ 3) or receiving any form of dialysis.

Selection Criteria for Studies: PubMed, CINAHL, Embase, International Pharmaceutical Abstracts, Scopus, Cochrane Library, and ClinicalTrials.gov from their inception to March 6, 2017, were systematically searched for randomized controlled trials (RCTs) of uremic pruritus treatments in patients with advanced CKD (stage ≥ 3) or receiving any form of dialysis. 2 reviewers extracted data independently. Risk of bias was assessed using the Cochrane Collaboration risk-of-bias tool.

Intervention: Any intervention for the treatment of uremic pruritus was included.

Outcomes: A quantitative change in pruritus intensity on a visual analogue, verbal rating, or numerical rating scale.

Results: 44 RCTs examining 39 different treatments were included in the review. These treatments included gabapentin, pregabalin, mast cell stabilizers, phototherapy, hemodialysis modifications, and multiple other systemic and topical treatments. The largest body of evidence was found for the effectiveness of gabapentin. Due to the limited number of trials for the other treatments included, we are unable to comment on their efficacy. Risk of bias in most studies was high.

Limitations: Heterogeneity in design, treatments, and outcome measures rendered comparisons difficult and precluded meta-analysis.

Conclusions: Despite the acknowledged importance of uremic pruritus to patients, with the exception of gabapentin, the current evidence for treatments is weak. Large, simple, rigorous, multiarm RCTs of promising therapies are urgently needed.

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INDEX WORDS: Uremic pruritus; chronic kidney disease (CKD); gabapentin; systematic review; randomized control trials (RCTs); dialysis; end-stage renal disease (ESRD).

Uremic pruritus is a common and burdensome symptom for patients with kidney failure, affecting up to 46% of hemodialysis patients.[1-4] Uremic pruritus is most commonly described as a daily or near-daily occurrence of itch that spans large bilaterally symmetrical surface areas. It does not exhibit a dermatomal pattern and there is no associated primary skin lesion.[5-7] Uremic pruritus can vary from a generalized itch to a localized itch affecting the back, face, and arms.[5] Uremic pruritus intensity is associated with multiple health-related quality-of-life outcomes, such as sleep quality, mood, and social function,[2,7] and is independently associated with mortality.[8] Uremic pruritus has been identified as a key research priority by patients with kidney disease.[9]

The pathophysiology of uremic pruritus is not fully understood and likely is multifactorial. Subclinical or overt uremic neuropathy,[10,11] skin or nerve inflammation in the context of kidney failure–associated chronic systemic inflammation,[2,8,12] or an increase in activity of μ-opioid receptors due to kidney failure have all been implicated.[2,6,8,13,14]

Current therapies for pruritus, such as gabapentin,[15] a modulator of excitatory neurotransmitters; cromolyn

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sodium,[16] a mast cell stabilizer; and capsaicin,[17] a mediator of substance P release, generally target 1 or more of these mechanisms. Although several small studies have examined a variety of interventions, the efficacy of these interventions and the optimal treatments remain poorly defined. To address this important knowledge gap, we systematically reviewed the literature and summarized the evidence for the major interventions for the treatment of uremic pruritus.

METHODS

Data Sources and Searches

We sought to summarize results of all published randomized controlled trials (RCTs) of treatments for uremic pruritus. The search strategy was designed and implemented in collaboration with a medical librarian. The following databases were searched from their inception through March 6, 2017: PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase, International Pharmaceutical Abstracts, Scopus, Cochrane Library, and ClinicalTrials.gov. A combination of subject headings and MeSH terms was used as appropriate to cover the concepts of "chronic kidney disease," "hemodialysis," "peritoneal dialysis," "pruritus," and "treat." The search strategy was tailored for each database. No language restrictions were placed on the search. Retrieved citations were downloaded to EndNote, version X7.5 (Clarivate Analytics). The full search strategy is available in Item S1 (provided as online supplementary material).

Study Selection and Eligibility Criteria

Two reviewers (E.S. and B.L.) independently evaluated titles and abstracts of all citations. Any articles deemed potentially relevant by either reviewer were retrieved for full-text review. Any disagreements were resolved by consensus. If a consensus could not be reached, a third reviewer (C.R.) was consulted. Reference lists of relevant articles were manually searched for any additional relevant studies. We included prospective RCTs (parallel arm and crossover) of uremic pruritus treatments in adults (aged ≥18 years) with advanced chronic kidney disease (CKD; stage ≥ 3) or on dialysis therapy (peritoneal dialysis and hemodialysis). We included only studies using validated pruritus intensity measurement tools (visual analogue scale, verbal rating scale, and numerical rating scale).[18,19] Appropriate translators were used for non-English articles.

Data Extraction

Data extraction was done in Microsoft Excel and verified by 2 independent reviewers (E.S. and B.L.). The information gathered from each study included the following: title, first author, journal, year of publication, location, study population, study design, period of intervention, characteristics of intervention and control, pruritus intensity measurement tool, pruritus intensity results pre- and postintervention, and adverse drug reactions (Table S1).

Quality Assessment and Risk of Bias

The Cochrane Collaboration's tool for assessing risk of bias was used.[20] Each selected article was assessed and given a ranking of high, low, or unclear risk in the 7 different domains (sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues") as proposed by Cochrane. Two reviewers (E.S. and B.L.) performed the risk-of-bias assessment independently. Disputes were resolved by consensus.

Statistical Analysis

The data were summarized and tabulated. A formal meta-analysis was not possible due to between-study heterogeneity in treatments, outcome measures, and design.

RESULTS

Search Results and Study Selection

The search strategy recovered 823 unique records after deduplication, and 1 extra record was identified through a hand search. Of these, 114 were identified as potentially eligible for our systematic review, and full-text articles were retrieved. Forty-four met the inclusion criteria for our review[21-64] (Fig 1; Table S2).

Study Characteristics

Characteristics of included studies are summarized in Table 1. The 44 trials included a total of 2,293 patients and examined 39 different therapies. Sample sizes ranged from 10[46] to 339 patients,[36] with only 3 studies enrolling more than 100 participants.[27,36,56] Of the included studies, 17 originated in the Middle East; 16, East Asia; 5, Europe; 4, North America; and 2, South America. The included studies comprised a total of 14 randomized crossover trials and 30 randomized parallel-arm trials.

All studies included adults 18 years or older with the exception of 3 studies including patients 16 years and older.[48,56,60] All 44 studies included hemodialysis patients. Three studies included peritoneal dialysis patients[35,43,56] and 1 study included a cohort of patients with CKD stages 3 to 5.[29] Thirty-three studies measured uremic pruritus using a visual analogue scale; 11 studies, a verbal rating scale; and 1 study, a numerical rating scale. Length of treatment varied across studies, but in general was short (range, 1 week to 1 year).

Trials of Gabapentin or Pregabalin

Nine studies (total n = 527) explored the effects of gabapentin and/or pregabalin on uremic pruritus (Table 2). All but one[21] used a visual analogue scale to report the results. Of these, 6 studies were parallel-arm studies: 2 comparing gabapentin to placebo,[38,41] 1 comparing gabapentin to ketotifen,[21] 1 comparing pregabalin to doxepin,[60] 1 comparing pregabalin with both ondansetron and placebo,[56] and 1 group comparing gabapentin to usual care.[59] The remaining 3 studies were crossover studies: 2 compared gabapentin to placebo,[33,50] and the third compared gabapentin to pregabalin in a population with established neuropathy and/or neuropathic pain.[47] Overall, when gabapentin or pregabalin was compared to placebo, there was a statistically significant benefit in favor of