Canadian Society of Nephrology/
Société canadienne de néphrologie
CSN/SCN

CANADIAN JOURNAL OF
KIDNEY HEALTH AND DISEASE
Journal canadien de la santé et de la maladie rénale

Article

Targeting the Opioid Pathway for Uremic Pruritus: A Systematic Review and Meta-analysis

Canadian Journal of Kidney Health and Disease
Volume 3: 1–9

DOI: 10.1177/2054358116675345
cjk.sagepub.com
SAGE

Deep Jaiswal[1], Drea Uzans[1], Jill Hayden[2], Bryce A. Kiberd[1,3], and Karthik K. Tennankore[1,3]

Abstract

Background: Patients undergoing hemodialysis or peritoneal dialysis often experience pruritus which is associated with morbidity and mortality. One proposed treatment approach is to target the opioid pathway using either μ-opioid antagonists or κ-opioid agonists.
Objective: To review the efficacy of targeting the opioid pathway for pruritus among dialysis patients (uremic pruritus).
Design: Systematic review and meta-analysis.
Setting/Methods: The systematic review included randomized controlled and randomized crossover trials identified in the MEDLINE, EMBASE, and Cochrane databases (1990 to June 2014) evaluating the efficacy of μ-opioid antagonists or κ-opioid agonists in the treatment of uremic pruritus.
Patients: Adult (≥18 years) chronic dialysis patients.
Measurements: The primary outcome being evaluated was reduction in itch severity measured on a patient-reported visual analog scale (VAS).
Results: Five studies out of 3587 screened articles met the inclusion criteria. Three studies evaluated the efficacy of naltrexone, a μ-opioid antagonist, and 2 studies evaluated the efficacy of nalfurafine, a κ-opioid agonist. Duration of included studies was short, ranging from 2 to 9 weeks.
Limitations: Due to the heterogeneity in reporting of outcomes, data from the studies evaluating naltrexone could not be pooled. Pooled analysis, using a random effects model, found that use of nalfurafine resulted in a 9.50 mm (95% confidence interval [CI], 6.27-12.74, $P < .001$) greater reduction of itch severity (measured on a 100-mm VAS) than placebo in the treatment of uremic pruritus.
Conclusions: Nalfurafine holds some promise with respect to the treatment of uremic pruritus among dialysis patients. However, more long-term randomized controlled trials evaluating the efficacy of therapies targeting the opioid pathway for uremic pruritus are required.

Abrégé

Mise en contexte: Les patients sous hémodialyse ou traités par dialyse péritonéale éprouvent souvent du prurit et ce dernier est associé au taux de morbidité et de mortalité. Une approche proposée pour le traitement de cette affection est de cibler la voie métabolique des opioïdes par l'administration d'opioïdes-μ antagonistes ou d'opioïdes-κ agonistes.
Objectif de l'étude: On a voulu examiner l'efficacité d'un traitement ayant pour cible la voie métabolique des opioïdes dans le soulagement du prurit urémique chez les patients sous dialyse.
Schéma de l'étude/Méthodologie: L'étude a consisté en une méta-analyse et une revue systématique des bases de données de MEDLINE, EMBASE et Cochrane. On y a répertorié tous les essais randomisés contrôlés ainsi que les essais croisés randomisés qui évaluaient l'efficacité des opioïdes-μ antagonistes ou des opioïdes-κ agonistes dans le traitement du prurit urémique.
Patients: L'étude a porté sur des adultes sous dialyse chronique.
Mesures: Le principal paramètre évalué était la réduction de la sévérité des démangeaisons que l'on a mesurée sur une échelle visuelle analogue d'après un compte rendu du patient.
Résultats: Seulement cinq études, parmi les 3587 articles passés en revue, satisfaisaient le critère d'exclusion. Trois études avaient évalué l'efficacité de la naltrexone, un opioïde-μ antagoniste, et deux autres avaient évalué l'efficacité de la nalfurafine, un opioïde-κ agoniste. La durée des études retenues était relativement courte, soit de deux à neuf semaines.
Limites de l'étude: Les données concernant la naltrexone n'ont pu être regroupées en raison d'un manque d'homogénéité dans la façon de présenter les résultats. L'analyse par regroupement, effectuée à l'aide d'un modèle à effets aléatoires, a permis d'observer que l'administration de nalfurafine a entrainé une diminution de la sévérité des démangeaisons (mesurée sur une échelle visuelle analogue de 100 mm) de 9,50 mm (IC à 95% entre 6,27 et 12,74; $P < 0,001$) de plus qu'un placebo lors du à traitement du prurit urémique.

Conclusions: La nalfurafine offre de bonnes perspectives pour le traitement du prurit urémique chez les patients sous dialyse. Par contre, un plus grand nombre d'essais randomisés contrôlés, évaluant à long terme l'efficacité des thérapies ciblant la voie métabolique des opioïdes pour le traitement du prurit urémique, sont souhaités.

Keywords
dialysis, κ-opioid agonist, nalfurafine, uremic pruritus

Received August 16, 2016. Accepted for publication September 7, 2016.

What Was Known Before?

Uremic pruritus is a debilitating condition affecting dialysis patients. Individual studies have evaluated the effectiveness of opioid-pathway modifiers of uremic pruritus, but pooled effects have not been evaluated.

What Does This Add?

This study enhances our understanding of the efficacy of a μ-opioid antagonist (naltrexone) and κ-opioid agonist (nalfurafine) in the management of uremic pruritus. This study also identifies an important area of research that needs more randomized controlled trials to be conducted.

Background

Patients with chronic kidney disease often experience persistent itch termed "uremic pruritus."[1,2] Uremic pruritus (chronic persistent itch that is an associated complication of kidney disease) is a common symptom of patients undergoing hemodialysis and peritoneal dialysis.[1,2]

The prevalence of uremic pruritus among dialysis has been reported as being close to 50% to 90% in some studies.[3-7] Consequences of uremic pruritus are not insignificant; studies have reported that uremic pruritus is associated with an impaired quality of life, depressed mood, and disturbed sleep.[2,5-7] Furthermore, the degree of quality-of-life impairment and sleep disturbance increases with itch severity.[2,5,6] One study also found that moderate-to-extreme pruritus was associated with a 17% higher mortality risk among hemodialysis patients.[6]

The pathophysiological mechanism underlying uremic pruritus is not well understood.[1,8] Furthermore, multiple complex mechanisms may play a role in causing pruritus associated with end-stage renal disease.[1,3,4,8] One proposed mechanism involves endogenous opioid peptides and the opioid system.[1,3,4,8] Activation of the μ-opioid system has been suggested to induce pruritus; this is supported by reports of morphine, an agonist of the μ-opioid system, triggering itch.[1,4,8,9] In addition, studies also suggest that activation of the κ-opioid system modulates pruritus by reducing itch.[1,3,4,8] Moreover, studies utilizing mouse models report that antagonism of μ-opioid receptors and activation of κ-opioid receptors inhibit substance P-induced itch.[9,10]

Interventions targeting the opioid itch pathway have the potential to reduce itch severity in patients experiencing uremic pruritus. To our knowledge, a systematic review evaluating the efficacy of such interventions has not been carried out. To study this, we conducted a systematic review and meta-analysis of randomized controlled trials involving drugs that target μ- and κ-opioid receptors for the treatment of uremic pruritus in dialysis patients.

Methods

Search Strategy and Study Selection Process

We initially searched for studies in the following electronic databases: MEDLINE, EMBASE, and the Cochrane Library (all years to June 2014). We developed our search strategy with the assistance of a medical librarian including keywords and controlled subject language for 2 concepts and then combined the sets of terms. The first category pertained to the symptom of interest and included the terms such as "pruritus," "itch," and "scratch." The second category pertained to the disease state of interest and included the terms such as "chronic kidney disease," "chronic kidney failure," "uremic," and "end stage renal disease." Terms related to the interventions were not included to avoid narrowing our search results and potentially excluding citations that would have warranted screening. Search results from each database were combined, and duplicate citations were removed. The full search strategy for Medline is available as a supplemental file (Supplement 1); we did not limit searches by language of publication and we included conference proceedings.

[1]Dalhousie University, Halifax, Nova Scotia, Canada
[2]Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada
[3]Division of Nephrology, Department of Medicine, Nova Scotia Health, Halifax, Canada

Corresponding Author:
Karthik K. Tennankore, Dalhousie University, 5820 University Avenue, Halifax, Nova Scotia, Canada B3H 1V8.
Email: karthikk.tennankore@nshealth.ca

Eligibility and Exclusion Criteria

We included randomized controlled or randomized crossover trials comparing either a μ-opioid antagonist or κ-opioid agonist to placebo or another drug among dialysis patients 18 years or older. Our primary outcome of interest was pruritus severity measured using a 10-point, 10-cm or 100-mm visual analog scale (VAS), or numerical rating system. We did not limit the inclusion of any studies on the basis of treatment duration.

Exclusion criteria were as follows:

1. Not randomized controlled or crossover trials.
2. Study did not utilize opioid antagonists or opioid agonists in the treatment of uremic pruritus.
3. Study did not evaluate the efficacy of treatments in adult hemodialysis or peritoneal dialysis patients.
4. Study did not evaluate pruritus severity.

Two reviewers (D.J. and D.U.) independently screened citations generated from the first search by applying selection criteria. Articles meeting criteria or for which there was uncertainty were selected for inclusion after both reviewers assessed the full text of the article. Any disagreement pertaining to the final inclusion of a study was resolved by consensus or via input from a third reviewer (K.K.T.).

Data Collection Process

Characteristics and outcome data for included studies were recorded in a standardized spreadsheet by D.J. and checked by D.U.; any discrepancies were resolved by consensus. Study characteristics extracted included study design, geographic jurisdiction, participant characteristics, inclusion and exclusion criteria, intervention characteristics, primary outcome data, and secondary outcome data such as the intervention's impact on itch duration and sleep. We attempted to contact all authors of included studies with missing or unclear data.

Two reviewers (D.J. and D.U.) independently assessed included studies using the Cochrane Risk of Bias tool.[11] Risk of bias across 6 domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting), as outlined in the Cochrane Handbook, were given a rating of high, uncertain, or low.[11] The formatting of our article was consistent with the guidelines set out by the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[12]

Data Analysis

When there was sufficient homogeneous data available, we pooled the weighted mean differences in pruritus severity reduction with a generic inverse-variance approach and random effects model.[13] We compared the mean difference in pruritus severity reduction over 2 weeks between patients receiving a κ-opioid agonist versus placebo. We appropriately calculated standard errors (SEs) from reported 95% confidence interval (CI) data as described in the Cochrane Handbook[14] and rescaled individual trial outcomes on the VAS itch score to 0 to 100 points for consistent presentation. In addition, we used methods described in the Cochrane Handbook to combine mean differences from 2 intervention groups that investigated the same therapy at different doses[14]; this was done to avoid double counting the placebo comparison group. We describe the percentage variability in effect estimates (I^2) to quantify heterogeneity across pooled data.[13] We used the Review Manager 5.3 software package to conduct quantitative analyses.[15] Furthermore, we also conducted a narrative synthesis of all included studies and described the overall quality of evidence available. The need for ethics approval was waived by our local research ethics board (The Nova Scotia Health Authority Research Ethics Board).

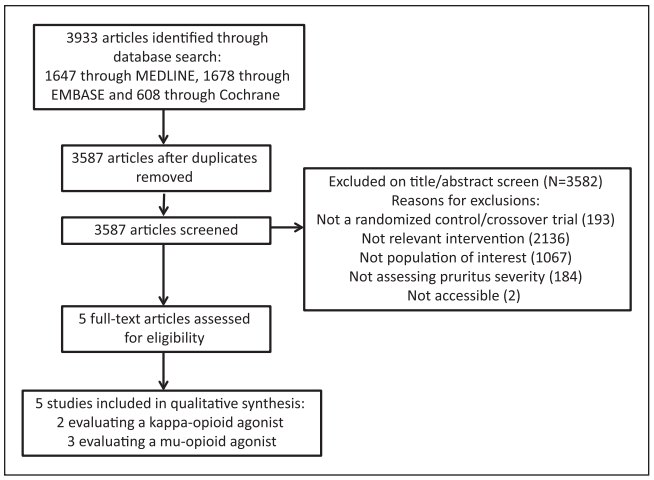

Figure 1. Study selection flowchart.
Note. RCT = randomized controlled trial.

Results

Study Selection and Study Characteristics

We identified 3587 independent citations in our electronic search strategy; 3057 were excluded after the title screen (kappa = 0.48), and an additional 525 were excluded after the abstract screen (no disagreement between reviewers). Overall, 3582 were excluded based on a title and abstract screen (Figure 1); reasons for exclusion were as follows: Study was not a randomized controlled or randomized crossover trial (n = 193), study did not involve the intervention being reviewed (n = 2136), study did not examine pruritus or pruritus severity (n = 184), or the population of interest (n = 1067). Two abstracts were excluded because, despite contacting publishers and organizers of conference proceedings, we were unable to access them.[16,17] Five articles were selected for full text review, and none were excluded during this phase.[18-22]

Three studies[19-21] utilized naltrexone (μ-opioid antagonist) and 2 studies[18,22] utilized nalfurafine (κ-opioid agonist) as the intervention (Table 1). Of the 3 studies that utilized naltrexone,

Table 1. Characteristics of Included Studies Evaluating the Efficacy of Either a μ-Opioid Antagonist or κ-Opioid Agonist in the Treatment of Uremic Pruritus.

Study	Study design	Location	Duration	Patient population	Intervention (n)	Control (n)	N	Concurrent treatment	Study inclusion criteria
Kumagai et al[18,20]	Multicenter, randomized controlled trial	JPN	2 weeks	HD, ≥20 yo	Group 1 = NLF HCL 2.5 μg PO daily (112) Group 2 = NLF HCL 5 μg PO daily (114)	Group 3 = Placebo (111)	337	Yes	Eligible patients experiencing uremic pruritus refractory to systemic or local treatment
Legroux-Crespel et al[19]	Multicenter, randomized controlled trial	FRA	2 weeks	HD, ≥18 yo	Group 1 = NTX 50 mg daily (26)	Group 2 = LRD 10 mg daily (26)	52	No	Eligible patients experiencing uremic pruritus for ≥1 month
Pauli-Magnus et al[20]	Randomized crossover trial	GER	9 weeks	HD and PD, ≥20 and ≤85 yo	Group 1 = NTX HCL 50 mg daily for 4 weeks followed by 7-day washout and placebo for 4 weeks (NA)	Group 2 = Placebo for 4 weeks followed by 7-day washout and NTX HCL 50 mg daily for 4 weeks (NA)	23 (18 HD, 5 PD)	No	Eligible patients experiencing persistent, treatment-resistant uremic pruritus that impaired sleep or daytime activity for ≥6 months
Peer et al[21]	Randomized crossover trial	NA	2 weeks	HD, age NA	Group 1 = NTX HCL 50 mg daily for 7 days followed by placebo for 7 days (8)	Group 2 = Placebo for 7 days, then 50 mg NTX and 50 mg HCL daily for 7 days (7)	15	No	Eligible patients had persistent treatment-resistant pruritus and were examined to exclude other causes of pruritus
Wikstrom et al[22]	Multicenter, randomized controlled trial	Center 1: SWE Center 2: POL	2 weeks	HD, ≥18 yo	Group 1 = NLF 5 μg IV 3 times per week after HD session (42)	Group 2 = Placebo (43)	85	All except for neutral topical agents discontinued	Eligible patients had severe uncontrolled pruritus caused only by ESRD

Note. JPN = Japan; HD = hemodialysis; yo = years old; NLF = nalfurafine; HCL = hydrochloride; PO = oral; FRA = France; NTX = naltrexone; LRD = loratadine; GER = Germany; PD = peritoneal dialysis; NA = not available; SWE = Sweden; IV = intravenous; ESRD = end-stage renal disease; POL = Poland.

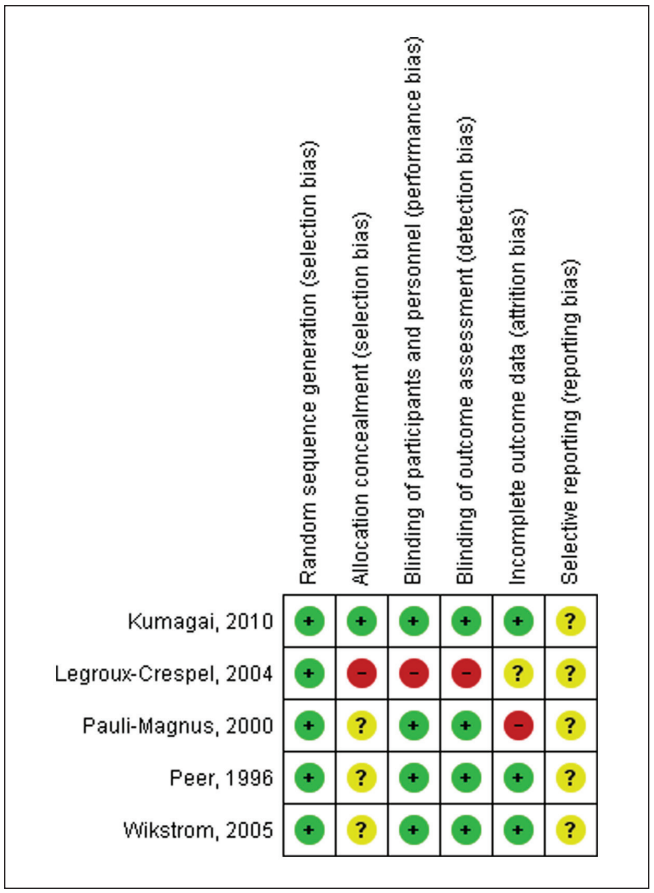

Figure 2. Summary of risk of bias assessment.
Note. + = low risk of bias; − = high risk of bias; ? = uncertain risk of bias.

2[20,21] compared with placebo and 1[19] compared with loratadine. Both studies of nalfurafine compared our treatment of interest with a placebo group. Two studies[20,21] were randomized crossover trials, and the remaining 3 studies[18,19,22] were 2-arm randomized controlled trials. Four studies reported locations where the trials were conducted (Japan,[18] France,[19] Germany,[20] Sweden,[22] and Poland[22]).

Risk of Bias

All studies[18-22] had a low risk of the random sequence generation component of selection bias (Figure 2). One study[18] had a low risk of the allocation concealment component of selection bias, 4 studies[18,20-22] had a low risk of performance and detection bias, and 3 studies[18,21,22] had a low risk of attrition bias. Selective reporting bias could not be determined for any of the studies.[18-22]

Study Outcomes: μ-Opioid Antagonists and Uremic Pruritus

Studies utilizing naltrexone as the intervention were not synthesized using meta-analysis because of the heterogeneity resulting from inadequate reporting of outcome data. Two studies[19,21] (Tables 1 and 2) reported that administration of 50 mg of daily naltrexone reduced pruritus score measured on a 10 cm VAS. Legroux-Crespel et al[19] identified a reduction in mean pruritus score (rescaled on a 100-point scale) from 48.50 mm at baseline to 45.40 mm on day 7 ($P < .01$); however, there were no significant differences in scores between patients receiving naltrexone or loratadine. In the crossover study by Peer et al,[21] a decrease in rescaled VAS scores was observed at day 7—99.00 mm (interquartile range [IQR], 98.50-99.50 mm]) to 21.00 mm (IQR, 15.00-21.50 mm)—in the group that received naltrexone as first treatment. A decrease in rescaled VAS scores (99.00 mm [IQR, 93.00-100.00 mm] to 10.00 mm [IQR, 4.00-11.50 mm]) was also observed at day 7 post naltrexone treatment in the group that first received placebo.[21] In contrast, Pauli-Magnus et al[20] reported no significant decline in mean pruritus score measured on a rescaled 100-point VAS with the administration of 50 mg of daily naltrexone for 4 weeks (Tables 1 and 2; change in mean pruritus score from 55 [95% CI, 42-68] to 41 [95% CI, 26-56]).[20]

Study Outcomes: κ-Opioid Agonists and Uremic Pruritus

The 2 included studies[18,22] that evaluated nalfurafine reported a significantly greater reduction in mean pruritus score measured on a 100-mm VAS over 2 weeks compared with control. After pooling the data of both studies (n = 422), as shown in Figure 3, the pooled difference in mean pruritus score reduction over 2 weeks was 9.50 mm (95% CI, 6.27-12.74) between nalfurafine treatment and placebo ($P < .001$). No significant heterogeneity among the pooled results was identified (I^2 of 0%).

Kumagai et al[18] reported a mean pruritus score reduction difference of 10 mm (95% CI, 4-14) between the intervention group receiving nalfurafine 2.5 μg daily and the placebo group. The same study also reported a mean pruritus score reduction difference over 2 weeks of 9 mm (95% CI, 4-14) between the intervention group receiving nalfurafine 5 μg daily and the placebo group.[18] Wikstrom et al[22] reported a weighted mean pruritus score reduction difference over 2 weeks of 9.53 mm (95% CI, 1.42-17.64) between the intervention receiving nalfurafine 5 μg thrice weekly and placebo.

Impact of Interventions on Secondary Outcomes

Only 2 studies[20,22] reported relevant secondary outcomes (Tables 1 and 2). Pauli-Magnus et al[20] reported a detailed score that was a composite of reported itch severity/distribution and frequency of pruritus-related sleep disturbance. No significant reduction in the detailed score (from 17.7 [95% CI, 12.9-22.5] to 14.2 [95% CI, 8.9-19.6]) was reported after 4 weeks of naltrexone.[20] Wikstrom et al[22] identified an

Table 2. Individual Study Results.

Study	Primary outcome measured	Results
Kumagai et al[18]	Mean difference of pruritus severity reduction on a 100-mm VAS over 2 weeks between treatment groups (NLF HCL 2.5 µg PO and NLF HCL 5 µg PO daily) combined and placebo group	Calculated mean difference between treatment groups combined and placebo group = 9.50 mm (calculated SE = 1.80)
Legroux-Crespel et al[19]	Pruritus severity on a 100-mm rescaled VAS. Mean VAS score on day 0 was 48.50 mm for both groups	On day 7, mean VAS score was 45.40 mm for Group 1 (NTX 50 mg) and 39.60 mm for Group 2 (LRD 10 mg) ($P < .01$ for both groups)
Pauli-Magnus et al[20]	Itch intensity on 100-point rescaled VAS. At study entry, mean VAS score; Group 1 (NTX-placebo) = 55 (95% CI, 42-68), Group 2 (placebo-NTX) = 65 (95% CI, 53-76)	At week 4, mean VAS score; Group 1 = 41 (95% CI, 26-56), Group 2 = 54 (95% CI, 40-69)
Peer et al[21]	Pruritus severity on a 100-mm rescaled VAS. Before receiving NTX HCL mean VAS score; Group 1 (NTX-placebo) = 99.00 mm (IQR, 98.50-99.50 mm), Group 2 (placebo-NTX) = 99.00 mm (IQR, 93.00-100.00 mm)	Mean VAS score after receiving NTX HCL for 7 days; Group 1 = 21.00 mm (IQR, 15.00-21.50 mm), Group 2 = 10.00 mm (IQR, 4.00-11.50 mm)
Wikstrom et al[22]	Weighted mean difference in reduction of pruritus severity over 2 weeks between Group 1 (NLF 5µg IV) and Group 2 (placebo) on a 100-mm VAS	Point estimate = 9.53 mm (calculated SE = 4.14)

Note. VAS = visual analog scale; NLF = nalfurafine; HCL = hydrochloride; PO = oral; SE = standard error; NTX = naltrexone; LRD = loratadine; CI = confidence interval; IQR = interquartile range; IV = intravenous.

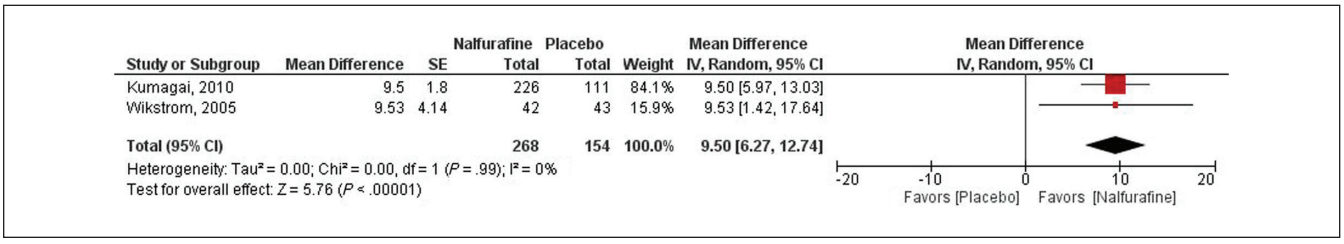

Figure 3. Mean difference in reduction of pruritus severity over 2 weeks between nalfurafine treatment and placebo on the 100-mm visual analog scale.
Note. SE = standard error; IV = intravenous; CI = confidence interval.

increase in the number of nights with sound sleep from 1.7 to 4.3 nights/week (at week 2) in the group receiving nalfurafine hydrochloride. The study also reported an increase in the number of days with nondisturbing itch from 0.6 to 2.8 days/week (at week 2).[22]

Adverse Events or Reactions

Four studies[18,19,21,22] reported incidence of adverse events or reactions (Table 3). Kumagai et al[18] reported event rates (in the intervention groups receiving nalfurafine hydrochloride 2.5 and 5 µg) of 25% and 35% versus 16% in the placebo group.[18] Common adverse drug reactions included insomnia, somnolence, and constipation.[18] The incidence of adverse drug events in the study by Wikstrom et al[22] was 45% in those receiving nalfurafine and 34% in the placebo group, but types of events were not included. Event incidence rates in studies of naltrexone were 33%[21] and 58%.[19] Reported events included vomiting, nausea, anorexia, abdominal distention, malaise, cramps, sleep disturbance, vertigos, headaches, somnolence, paresthesia, heartburn, and upper abdominal discomfort.

Discussion

Our systematic review and meta-analysis aimed to evaluate the efficacy of µ-opioid antagonists and κ-opioid agonists in the treatment of uremic pruritus experienced by patients undergoing dialysis. We found that nalfurafine led to a significantly greater reduction in pruritus severity over 2 weeks compared with placebo. Although 2 out of 3 studies reported a significant reduction in pruritus severity using naltrexone, data could not be pooled due to heterogeneity of data, intervention and outcome.

How might these findings inform practice? Although it is difficult to recommend the use of the µ-opioid antagonist naltrexone for management of uremic pruritus based on limited data, our meta-analysis suggests that nalfurafine is a

Table 3. Adverse Events and Drug Reactions Reported by Individual Studies.

Study	Incidence of adverse events/drug reactions	Most common adverse events/reactions
Kumagai et al[18]	Group 1 (NLF HCL 2.5 µg) = 25%; Group 2 (NLF HCL 5 µg) = 35%; Group 3 (placebo) = 16%	Insomnia, somnolence, and constipation
Legroux-Crespel et al[19]	Group 1 (NTX 50 mg) = 58%; Group 2 (LRD 10 mg) = 8%	Vomiting, nausea, anorexia, abdominal distention, malaise, cramps, sleep disturbances, vertigos, headaches, somnolence, and paresthesia
Pauli-Magnus et al[20]	NA	NA
Peer et al[21]	Adverse reaction incidence associated with naltrexone hydrochloride administration = 33%	Heartburn and upper abdominal discomfort
Wikstrom et al[22]	Incidence in Group 1 (NLF 5 µg IV) = 45%; Group 2 (placebo) = 34%	Headache, nausea, insomnia, vertigo, vomiting, and elevation of liver enzymes (association with intervention or placebo not specified)

Note. NLF = nalfurafine; HCL = hydrochloride; NTX = naltrexone; LRD = loratadine; NA = not applicable; IV = intravenous.

potential treatment for uremic pruritus. Acknowledging that uremic pruritus is a debilitating symptom with multiple negative consequences,[2,5-7] identifying therapies that may provide benefit is crucial. However, despite the signal for benefit, there are also important limitations of the current body of literature surrounding nalfurafine. Studies have only been of short duration (2 weeks), and the majority of the weight in our pooled analysis is derived from 1 study.[18,22] Inconsistency with adverse event reporting makes it difficult to determine whether the benefits outweigh the risks and side effects of therapy. A lack of homogeneity prevented the evaluation of changes in mood, sleep, or quality of life with treatment. Finally, it is difficult to put a reduction in itch severity of 9.50 mm more than placebo for those receiving nalfurafine treatment in clinical context. Although a minimal clinically important difference (MCID) has not been definitively established for pruritus, Reich and colleagues[23] have suggested that it may be 3 points (2.6-3.5 cm) if pruritus is improved. As the pooled reduction was less than the suggested MCID, our results should be interpreted cautiously. Therefore, although there is promise with this treatment, it is difficult to recommend it for long-term therapy of uremic pruritus based on the available data. Rather, more extensive, longer term evaluations of the relative efficacy of nalfurafine are required.

The need for longer follow-up is further highlighted by the results of observational studies. In an open label, single arm, prospective study of 145 patients, nalfurafine hydrochloride (5 µg orally daily) was administered over 52 weeks.[24] There was a significant reduction in mean pruritus score on the 100-mm VAS from 75.2 mm (95% CI, 73.5-76.9) to 30.9 mm (95% CI, 26.6-35.1) by week 52, and statistically significant improvements in nighttime symptom severity.[24] However, the incidence of adverse drug reactions (including insomnia and constipation) was 48.8%.[24] Moreover, anemia was a common adverse drug reaction that was reported to occur between weeks 3 and 52.[24] Nevertheless, it appears as though reductions in pruritus severity may be sustained with continued use of nalfurafine, acknowledging the side effects that may accompany treatment. It is unclear (outside of inferences from treatment discontinuation) whether patients are able to better tolerate side effects if concurrently experiencing marked benefits. Once again, confirmation in a longer term randomized controlled trial would be an important consideration, as would evaluation of a combined endpoint that incorporates side effects with relative benefits of pruritus reduction. Furthermore, the recently demonstrated efficacy of nalbuphine hydrochloride extended release (HCL ER), a mixed µ-antagonist/κ-agonist, may add further support to the potential benefit of opioid-pathway modifiers for uremic pruritus.[25]

This meta-analysis highlights the relative deficiency of literature surrounding optimal opioid-pathway modifying management strategies for uremic pruritus. This deficiency is made more apparent when considering patient perspectives. A recent survey (conducted by the Canadian Kidney Knowledge Translation and Generation Network) identified that management of dialysis-associated itch was a priority area for patients and their care providers.[26] Additional evaluation of pharmacological therapies[1,27] (including topical treatments) and nonpharmacological treatments of uremic pruritus[1,27] should be considered. As well, because none of the studies were conducted in North America and included very few peritoneal dialysis patients, threats to external validity in future studies could be mitigated by involving peritoneal dialysis patients and extending trials to North American centers.

A major strength of our study is that a comprehensive search strategy was utilized to identify randomized controlled and randomized crossover trials that evaluated naltrexone and nalfurafine treatment for uremic pruritus. Our study also pooled data and established short-term efficacy of nalfurafine. Furthermore, we were able to identify important considerations for future research projects that aim to evaluate nalfurafine or naltrexone for the treatment of uremic pruritus.

There are limitations to this study. In terms of bias, although most studies demonstrated a low risk of selection bias and blinding of participants further strengthened the results, we were not able to evaluate bias for selective reporting within the included studies. Furthermore, because of the small number of eligible studies, we were not able to assess for publication bias. We were unable to compare different opioid pathways (in terms of efficacy in reducing pruritus) due to data heterogeneity and the limited total number of studies. Furthermore, while we did manage to evaluate efficacy in itch reduction for nalfurafine, we were not able to comprehensively evaluate the effect of the studied treatments on quality of life, an important secondary outcome.

Conclusions

Although nalfurafine is a promising treatment for uremic pruritus, additional long-term randomized controlled trials are needed to establish its efficacy. Future studies of therapies for uremic pruritus should additionally evaluate the impact of nalfurafine on factors such as sleep quality, adverse events, and quality of life.

List of Abbreviations

VAS, visual analog scale.

Ethics Approval

Waived by Nova Scotia Health Authority Research Ethics Board

Consent for Publication

Not applicable.

Availability of Data and Supporting Materials

The search strategy is attached in a supplemental file.

Authors' Note

The results presented in this article have not been published previously in whole or part, except in abstract format.

Author Contributions

All Authors contributed to the design of this study. DJ and DU performed the initial article review. Any disagreements were resolved with consensus review by KKT. Data analysis was performed with assistance from JH. DJ drafted the original article. All authors provided manuscript revisions for scientific content. All authors approved the final version of the manuscript for publication.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Karthik Tennankore has received unrestricted grant funding for quality improvement projects from Amgen, Canada.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Deep Jaiswal received a Dalhousie Medical Research Foundation E.J. Gordon Studentship through the Research in Medicine program at Dalhousie University as part of funding for this project.

References

1. Urbonas A, Schwartz RA, Szepietwoski JC. Uremic pruritus—an update. *Am J Nephrol*. 2001;21(5):343-350.
2. Susel J, Batycka-Baran A, Reich A, Szepietowski JC. Uraemic pruritus markedly affects the quality of life and depressive symptoms in haemodialysis patients with end-stage renal disease. *Acta Derm Venereol*. 2014;94:276-281.
3. Lugon JR. Uremic pruritus: a review. *Hemodial Int*. 2005;9:180-188.
4. Manenti L, Tansinda P, Vaglio A. Uraemic pruritus: clinical characteristics, pathophysiology and treatment. *Drugs*. 2009;69:251-263.
5. Mathur VS, Lindberg J, Germain M, et al. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5:1410-1419.
6. Pisoni RL, Wikstrom B, Elder SJ, et al. Pruritus in haemodialysis patients: international results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2006;21:3495-3505.
7. Zucker I, Yosipovitch G, David M, Gafter U, Boner G. Prevalence and characterization of uremic pruritus in patients undergoing hemodialysis: uremic pruritus is still a major problem for patients with end-stage renal disease. *J Am Acad Dermatol*. 2003;49:842-846.
8. Narita I, Iguchi S, Omori K, Gejyo F. Uremic pruritus in chronic hemodialysis patients. *J Nephrol*. 2008;21:161-165.
9. Umeuchi H, Togashi Y, Honda T, et al. Involvement of central μ-opioid system in the scratching behavior in mice, and the suppression of it by the activation of κ-opioid system. *Eur J Pharmacol*. 2003;477:29-35.
10. Togashi Y, Umeuchi H, Okano K, et al. Antipruritic activity of the κ-opioid receptor antagonist, TRK-820. *Eur J Pharmacol*. 2002;435:259-264.
11. Higgins JPT, Altman DG, Sterne JAC, eds. Chapter 8: assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Updated March 2011). The Cochrane Collaboration. http://www.handbook.cochrane.org/. Published 2011. Accessed March 22, 2015.
12. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med*. 2009;6:e1000097.
13. Deeks JJ, Higgins JPT, Altman DG, eds. Chapter 9: analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0* (Updated March 2011). The Cochrane Collaboration. http://www.handbook.cochrane.org/. Published 2011. Accessed March 22, 2015.
14. Higgins JPT, Deeks JJ, eds. Chapter 7: selecting studies and collecting data. In: Higgins JPT, Green S, eds. *Cochrane*

Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). The Cochrane Collaboration. http://www.handbook.cochrane.org/. Published 2011. Accessed March 22, 2015.
15. *Review Manager (RevMan)* [Computer program]. Version 5.3. Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014.
16. Ghura HS, Patterson I, Carmichael AI. Naltrexone in the treatment of renal itch (abstract). *Br J Dermatol*. 1998; 139(S51):64.
17. Peer G, Silverberg DS, Blum M, Kaplan E, Iaina A. Naltrexone an opiate antagonist relieves pruritus in dialysis patients. ISN XIII International Congress of Nephrology; July 2-6, 1995; *Madrid, Spain*.
18. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 haemodialysis patients: a phase III, randomized, double-blind, placebo-controlled study. *Nephrol Dial Transplant*. 2010;25:1251-1257.
19. Legroux-Crespel E, Cledes J, Misery L. A comparative study on the effects of naltrexone and loratadine on uremic pruritus. *Dermatology*. 2004;208:326-330.
20. Pauli-Magnus C, Mikus G, Alscher DM, et al. Naltrexone does not relieve uremic pruritus: results of a randomized, double-blind, placebo-controlled crossover study. *J Am Soc Nephrol*. 2000;11:514-519.
21. Peer G, Kivity S, Agami O, et al. Randomised crossover trial of naltrexone in uraemic pruritus. *Lancet*. 1996;348:1552-1554.
22. Wikstrom B, Gellert R, Ladefoged SD, et al. κ-opioid system in uremic pruritus: multicenter, randomized, double-blind, placebo-controlled clinical studies. *J Am Soc Nephrol*. 2005;16:3742-3747.
23. Reich A, Halupczok J, Ramus M, Ständer S, Szepietowski J. New data on the validation of VAS and NRS in pruritus assessment: minimal clinically important difference and itch frequency measurement. Abstract (PP39). 6th International Workshop for the Study of Itch. Brest, France: Medical Journals Limited Journal Source; 2011.
24. Kumagai H, Ebata T, Takamori K, et al. Efficacy and safety of a novel κ-agonist for managing intractable pruritus in dialysis patients. *Am J Nephrol*. 2012;36:175-183.
25. Mathur VS, Kumar J, Crawford PW, et al. Randomized, double-blind, placebo-controlled, parallel, 3-arm study of the safety and anti-pruritic efficacy of nalbuphine HCl ER tablets in hemodialysis patients with uremic pruritus. Abstract (HI-OR07). American Society of Nephrology Annual Meeting. CA, USA: American Society of Nephrology; 2015.
26. CANN.NET: Canadian Kidney Knowledge Translation and Generation Network. Research priorities-survey. http://www.cann-net.ca/patient-information/dialysis-research-priorities-survey#results. Accessed August 30, 2015.
27. Schwartz IF, Iaina A. Management of uremic pruritus. *Semin Dial*. 2000;13(3):177-180.