Management of Pruritus in Patients with Chronic Kidney Disease

BCRenal
Provincial Health Services Authority

Generalized Pruritus

Assessment

- Generalized pruritus, duration & character (e.g., paroxysmal vs continuous)
- Exacerbating (e.g., new soap or detergent) and relieving factors
- Detailed drug history
- Treatments tried (prescription/over the counter, topical, oral etc.)

Primary lesion apresent? — **Yes** → **Refer to dermatologist** for diagnosis and management

No

Consider non-renal potential cause(s) of pruritus - treat as appropriate.

- Liver disease/cholestatic pruritus
- Hematologic pruritus (Iron deficiency anemia, Polycythemia vera)
- Endocrine pruritus (thyroid disease, uncontrolled diabetes)
- Malignancy (leukemia, Hodgkin and Non-Hodgkin lymphoma)

Implement general treatment measures for dry skin

1. Bathing recommendations:
   - Fragrance-free sensitive skin bar soap (i.e., Dove sensitive skin® bar soap)
   - Limit use of soap to axillae and groin/perineum
   - Avoid excessive bathing or bathing with hot water
2. Avoid wearing rough clothing, such as wool, over itchy areas.
3. Use mild detergent for clothes/sheets and rinse well.
4. Keep fingernails short and clean. Try not to rub or scratch the itchy areas.
5. Keep your house cool and humid, especially in the winter.
6. Topical emollients:
   - Fragrance-free emollient[1] BID to TID and especially after bathing; OR
   - Baby oil BID to TID; OR
   - Menthol 0.25%/camphor 0.25% in emollient[1] BID to TID
   - For localized pruritus
     - Consider Capsaicin 0.025% cream, apply sparingly BID-QID (onset in 2-4 weeks)
     - Pramoxine 1% in emollient BID-TID PRN
7. Consider acupuncture

[1] Suggested Fragrance-free emollients:

- Cerave® cream
- Cetaphil® cream
- Lipikar® Baume AP & cream
- Aveeno® cream
- Glaxal base® cream
- Cliniderm® soothing cream
- Aquaphor® ointment
- Vaseline® ointment

Additional considerations for HD patients:

- Assess phosphate and PTH, treat as needed
- Consider heparin allergy, discontinue & reassess
- Consider allergy to dialyzer, change & reassess
- Ensure tubing is BPA and DEHP free
- Assess dialysis adequacy

Offer 1st line medications. Try at least one month, then reassess:

- Oral antihistamine: Hydroxyzine, 10-25mg po QID PRN or Diphenhydramine 25 mg po QID PRN (watch for sedation)
- Gabapentin 100mg po HS, titrate by 100mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance – see drug monograph. Consider 50mg (compounded capsule) po HS as a starting dose in frail elderly &/or if eGFR < 15mL/min.

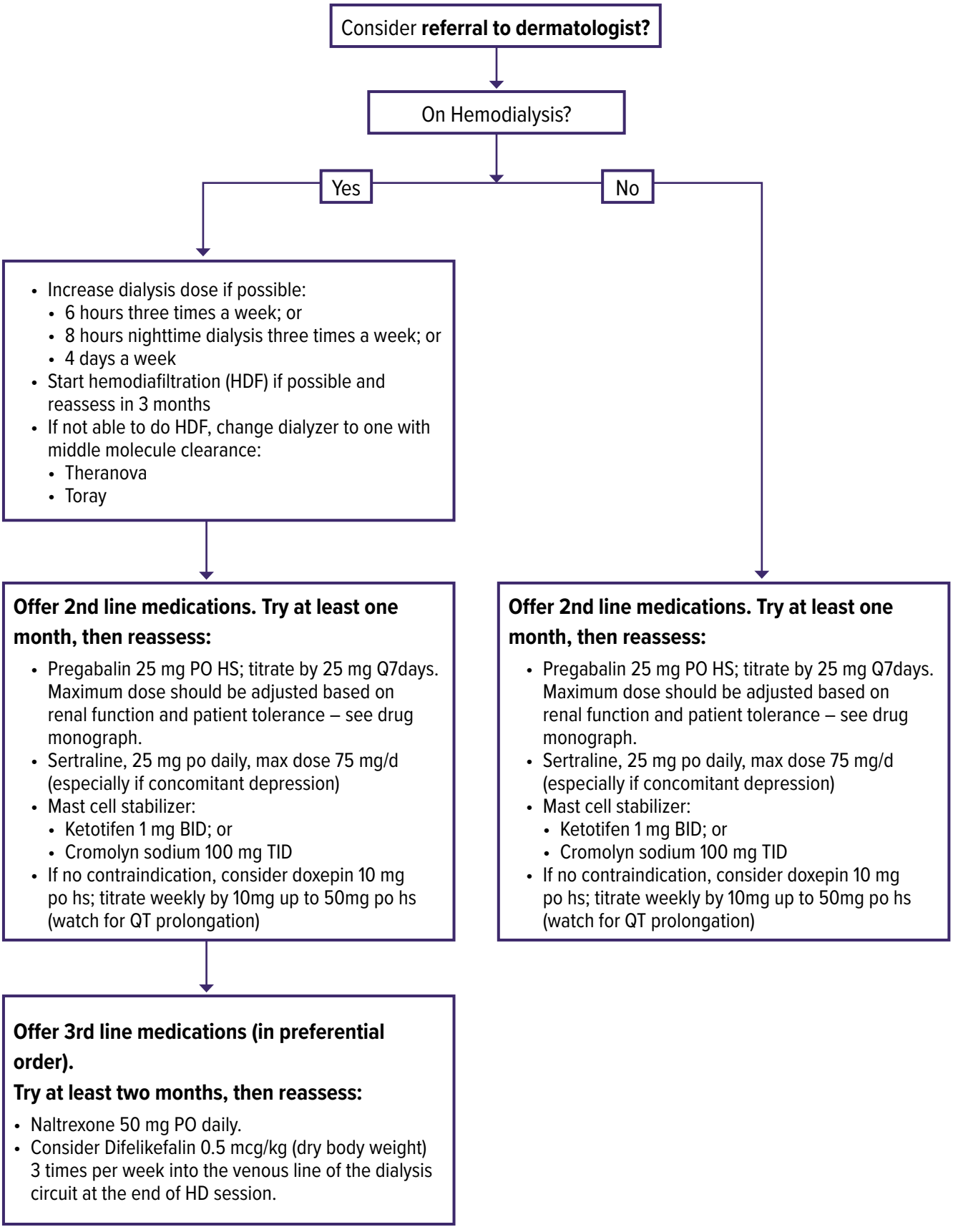
Consider **referral to dermatologist?**
On Hemodialysis?
Yes
No
• Increase dialysis dose if possible:
• 6 hours three times a week; or
• 8 hours nighttime dialysis three times a week; or
• 4 days a week
• Start hemodiafiltration (HDF) if possible and reassess in 3 months
• If not able to do HDF, change dialyzer to one with middle molecule clearance:
• Theranova
• Toray
Offer 2nd line medications. Try at least one month, then reassess:
• Pregabalin 25 mg PO HS; titrate by 25 mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance – see drug monograph.
• Sertraline, 25 mg po daily, max dose 75 mg/d (especially if concomitant depression)
• Mast cell stabilizer:
• Ketotifen 1 mg BID; or
• Cromolyn sodium 100 mg TID
• If no contraindication, consider doxepin 10 mg po hs; titrate weekly by 10mg up to 50mg po hs (watch for QT prolongation)
Offer 3rd line medications (in preferential order).
Try at least two months, then reassess:
• Naltrexone 50 mg PO daily.
• Consider Difelikefalin 0.5 mcg/kg (dry body weight) 3 times per week into the venous line of the dialysis circuit at the end of HD session.
Offer 2nd line medications. Try at least one month, then reassess:
• Pregabalin 25 mg PO HS; titrate by 25 mg Q7days. Maximum dose should be adjusted based on renal function and patient tolerance – see drug monograph.
• Sertraline, 25 mg po daily, max dose 75 mg/d (especially if concomitant depression)
• Mast cell stabilizer:
• Ketotifen 1 mg BID; or
• Cromolyn sodium 100 mg TID
• If no contraindication, consider doxepin 10 mg po hs; titrate weekly by 10mg up to 50mg po hs (watch for QT prolongation)

Table 1: Funding Information for Medications Used for Pruritis (i.e., medications identified on the algorithm)

	On BCR Formulary (funded by BCR)?	May be funded by BC PharmaCare (see note below)	PharmaCare Special Authority required?
Hydroxyzine	Yes	Yes	No
Diphenhydramine	Yes	Yes (also available without a prescription)	No
Gabapentin	Yes	Yes	No
Pregabalin	No	Yes	No
Sertraline	No	Yes	No
Ketotifen	No	Yes	No
Cromolyn sodium	No	Yes	No
Doxepin	No	Yes	No
Naltrexone	No	Yes	No
Difelikefalin	No	No	Not funded

Note: PharmaCare coverage depends on the PharmaCare plan, the maximum funded per tablet/capsule and the "Fair PharmaCare" deductible for each patient. Generic medications are typically preferred by Pharmacare and BC Renal.

Supplemental Evidence for Treatment Options

In terms of non-pharmacological therapies: Moisturizing cream should be considered for all chronic kidney disease (CKD) patients as xerosis is prevalent in this population.

- Lotions are not recommended (the higher concentrations of emulsifiers and stabilizers and the lower concentration of lipid in lotions can further worsen dry skin)
- Other non-drug measures, e.g., minimizing the use of soap and hot bath, should also be considered.

The successful use of behavioral therapy or habit reversal techniques has been reported in patients with chronic pruritus; however, their utility in the CKD population has not been studied. We are not recommending steroid based cream or ointment for uremic pruritus unless the patient has an inflammatory skin condition. Patients with renal pruritus typically have intense pruritus with no primary lesions. If the patient has primary lesions, a dermatology consultation should be considered for diagnosis and appropriate management. A dermatology consultation should be considered early for narrow band ultraviolet B (NB-UVB) phototherapy in severe or difficult-to-treat cases. Several locations in British Columbia are available with phototherapy units.

In terms of pharmacotherapies, available literature in CKD non-dialysis patients is limited, with only 4 publications on the topic.[1–4] Most of the pharmacotherapy options suggested in the algorithm have been trialed in hemodialysis patients. Published studies for both populations are of small sample size, from single centres, and have significant drop-out rates or crossover design with a short washout period.

Although there are no studies confirming the efficacy of sedating antihistamines in the treatment of pruritus in CKD non-dialysis patients, they have historically been used as first-line agents for this indication. Efficacy data regarding non-sedating antihistamines are scarce and contradictory. A

negative study comparing loratadine to naltrexone reported loratadine to decrease VAS (visual analogue scale) score pruritus likely not clinically significant and none of the patients had a decrease in the VAS score > 3 points while receiving this medication.[5] Another study compared desloratadine to gabapentin during a cross-over trial in 22 hemodialysis patients. While being on desloratadine 5 mg po 3 times/ week, patients' VAS score decreased to similar extent then while on gabapentin 300 mg po 3 times/ week therapy, with less adverse reactions reported in the desloratadine group.[6] Most experts do not recommend non-sedating antihistamine in alleviating pruritus in CKD patients as they do not cross the blood brain barrier, and therefore may be unable to affect the perception of itch.

Due to the lack of confirmatory studies, the agents listed under limited evidence are not included in the treatment algorithm but could be considered if other typical more cost-effective agents fail.

Positive Studies

Narrow band UVB

A prospective study of 42 HD patients with renal pruritus compared with a matched control group (n=21 in each group) to test the efficacy of NB-UVB was conducted in a hospital in Taipei, Taiwan. The intervention group received NB-UVB 3x/week for 2 weeks and control group was maintained on their prior pruritus treatment. Pruritus intensity was measured with a numerical rating scale at baseline and on alternating days for seven times. The intervention group had significantly lower pruritus intensity than the control group: 3.14 ($p<0.001$) at time seven, 1.71 ($p< 0.001$) at time six and 1.24 at time five ($p< 0.001$).[7]

Another study investigated whether or not NB-UVB phototherapy is an effective treatment for uremic pruritus. A single-blind, randomized (1:1), controlled trial for patients (n=21; 14 HD and 3 PD) with refractory uremic pruritus was conducted where the treatment group received NB-UVB 3x/week for 6 weeks and control group received time-matched exposures to long-wave UVA radiation for 12 weeks. The characteristics of pruritus were assessed at baseline and after 6 weeks of phototherapy. NB-UVB and control group had improvement in pruritus intensity. Compared to the control group, the NB-UVB group showed a significant improvement in the involved body surface area affected by pruritus ($p=0.006$) but not in sleep quality. Patients in the NB-UVB group have lower pruritus intensity scores at week 6, 10 and 12 which may indicate a beneficial difference at certain time points, but the effect was marginal overall. This study concludes that NB-UVB phototherapy does not show a significant effect in reducing pruritus intensity compared with the control group.[8]

A pilot study of NB-UVB phototherapy was conducted for the treatment of 20 patients (n=20) with uremic pruritus. Ten patients (10 patients left the study) completed the 6-week study period with treatment 3x/week. Eight patients were responders. Of the 10 patients that did not complete the study, 6 were satisfied with the response. In the follow-up period at 6 months post-treatment, 7 responders were assessed and 3 were in remission, however pruritus recurred in the remaining 4. NB-UVB may be an effective treatment but recurrence of pruritus is a problem.[9]

A meta-analysis of UVB trials for uremic pruritus was conducted using only randomized control trials available on MEDLINE from 1966 to March 1991. Clinically significant outcomes were obtained for 2 of 3 whole-body UVB trials. Meta-analysis of the UVB trials retained the significant effect in analysis of proportions (pooled odds ratio 18; 95% confidence interval). Trials of lidocaine, charcoal and nicergoline demonstrated either statistically significant

improvement in pruritus score or in proportions, but not both. UVB phototherapy was found to be the treatment of choice in moderate to severe uremic pruritus.[10]

Another study evaluated the effect of UV phototherapy on uremic pruritus in 56 patients with chronic kidney disease (52 on HD, 4 PD). Seven patients (n=7) were treated 2x/week for 4 weeks with UVB to ½ of the body and placebo phototherapy (UVA) to the other half. All patients noted generalized improvement without localization of benefit to the UVB side. Patients treated more frequently (3x/weekly) improved faster. Overall, 32 of 38 patients improved after a course of 6 or 8 UVB exposures. Pruritus recurred in 15 patients after a mean remission of 3 months. Sixteen patients remained in remission for 10.6 months after the 1st or 2nd course of treatment.[11]

Baby oil (topical)

A prospective study of 35 hemodialysis patients with pruritus compared with a matched control group (n=35) looked at the efficacy of cool baby oil (10-15) applied on the affected area for 15-20 minutes 3 times/week prior to hemodialysis for 1 month.[12] Baby oil improved VAS pruritus score, the Pittsburgh sleep quality index as well as the SF-36 Quality of life Physical and Mental component scores.

Another prospective study looked at the effect of chilled baby oil (n=30), vs. room temperature baby oil (n=31), vs. routine care (n=32) on the pruritus score of hemodialysis patients.[13] Pruritus improved in both baby oil groups, with no differences were found in the baby oil temperature.

Capsaicin (topical)

In a double-blind, placebo-controlled, crossover trial[14] of 34 hemodialysis patients with uremic pruritus, capsaicin 0.03% was compared to placebo x 4 weeks with a 2-week washout. The mean pruritus score (maximum 18 points) was significantly reduced from 15.9 + 6.3 to 2.5 + 2.5 in the capsaicin treatment period vs 15 + 6.0 to 7.2 + 5.5 in the placebo treatment period.

In another double-blind, placebo-controlled, crossover study[15], capsaicin 0.025% cream was compared to placebo in 17 hemodialysis patients with moderate to severe pruritus. Fourteen had marked relief, of whom 5 had complete remission, with prolonged antipruritic effect 8 weeks post capsaicin treatment. No serious adverse reactions were noted.

In an open-label uncontrolled trial and a double-blind, vehicle-controlled trial[16] evaluating capsaicin 0.025% cream in hemodialysis patients. Eight of 9 evaluable patients in the open label trials reported marked relief or complete resolution; 12 patients were not evaluable. In the double-blind trial, 2 of 5 evaluable patients reported complete resolution and 2 were not evaluable. No serious adverse reactions were noted.

In a systematic review, six RCTs were assessed in which 3/6 were in HD patients. Due to the poor quality of the HD patient studies, the reviewers were unable to assess the efficacy of capsaicin.[17]

Pramoxine (topical)

A double-blind randomized placebo control trial looked at the use of pramoxine 1% lotion in reducing pruritus in hemodialysis patients. VAS mean score decreased by 61% in the pramoxine group (n=13) vs. a 12% decrease in the placebo group (n=14). No adverse effects were reported.[18]

Gabapentin (1st line medication) and pregabalin (2nd line medication)

In a retrospective single centre study, gabapentin efficacy and safety was compared between 34 CKD non-dialysis patients and 15 hemodialysis patients for restless legs syndrome and/or pruritus[1]. Median

gabapentin dosage needed to control pruritus in CKD patients was 100 mg/day. Adverse drug reactions were reported In 47.1% of patients with 17% of patients discontinuing therapy. Conservatively managed CKD patients were found to be at higher risk of experiencing drug adverse effects (47.1% vs. 14.3%).

Another prospective longitudinal study, used gabapentin or pregabalin in 25 CKD patients stage 4 and 5, 40 hemodialysis patients and 6 peritoneal dialysis patients.2 We will concentrate here on the results in the CKD population. 13 of 25 CKD patients had a significant reduction in their pruritus, 10 patients stopped gabapentin because of side effects and 2 patients stopped because of lack of pruritus improvement. Median length of follow-up was 1 month and the median gabapentin daily dosage was 100 mg/day. Patients who didn't tolerate or improve with gabapentin (n=6), were offered pregabalin. 4 patients reported having their itch improved with pregabalin, 1 patient stopped therapy because of a lack of efficacy and 1 patient stopped because of side effects.

Another prospective study collected data on the use of pregabalin in 10 hemodialysis patients and 2 CKD stage 4 patients with severe intractable pruritus.3 The average pruritus score prior to treatment was 9.7 ± 0.9 and decrease to 3.7 ± 2.35, 3.2 ± 1.75 and 3 ± 1.5 after 1, 4 and 24 weeks of treatment respectively ($p< 0.05$). 6 patients reported improvement in their symptoms during the first week of treatment. 2 patients developed dizziness and somnolence. These patients restarted pregabalin therapy after pruritus relapse a few days after stopping the treatment. Median pregabalin daily dosage was 25 mg (range from 25 mg 3 times/week, 50 mg/day).

A systematic review was recently published reviewing the efficacy of gabapentin in hemodialysis patients. Seven studies with a total of 179 patients were included. Most of the patients included had pruritus refractory to antihistamine and topical emollients. Six studies found improvement in pruritus with gabapentin, with a decrease in the VAS score between 5.7 to 9.4 points from baseline by 3 to 8 weeks. Common adverse drug reactions reported were somnolence, dizziness and fatigue with 4/179 patients needing to discontinue treatment.[19]

An open-label series[20] evaluated pregabalin 25mg po HS in 16 hemodialysis patients refractory to antihistamine for 2 months (hydroxyzine or desloratadine + levocetirizine). There was a statistically significant difference between the 10-point visual analogue scores before and one month after treatment, 7.44 + 2.01 vs. 1.7 + 1.31, respectively. Four patients discontinued treatment due to side effects.

Randomized, cross-over study comparing gabapentin 300mg post-hemodialysis and pregabalin 75mg daily in 40 HD patients with a history of neuropathic pain in 6 week treatment blocks. The investigators measured pruritus using a VAS (10cm). There was no statistical difference between these two treatments.[21]

Sertraline (2nd line medication)

A retrospective study in 17 conservative CKD Stage 5 patients with pruritus refractory to antihistamines looked at the efficacy of sertraline. Median used daily dosage was 25 mg (range from 25 to 75 mg/day) and the onset of action was 5 weeks.[4]

In another prospective study, 19 hemodialysis patients with severe chronic pruritus were randomly selected. Prior to treatment, 9 patients had moderate pruritus and 10 patients had severe pruritus. After taking Sertraline 50 mg/day for 4 months, pruritus score decrease to weak in 11 patients 6 patients had moderate pruritus score and 2 patients had severe pruritus.[22]

Mast cell stabilizers (2nd line medications)

Study	Design	Country	Population	N=	Treatment duration (wks)	Treatment	Pruritus assessment	Results
Mahmudpour et al., 2017[23]	Parallel	Iran	HD	80	4	Montelukast vs. placebo	VAS, QPS	A greater reduction of VAS in the montelukast group (2.73 +/- 2.03) compared to the placebo group (5.47+/-2.37, P<.001).
Feily 2012[24]	Parallel	Iran	HD	60	4	Topical cromolyn sodium 4% vs placebo	0-5 VAS	Greater reduction in VAS in cromolyn sodium group (2.5 ± 1.1 to 0.3 ± 1.3) than the placebo group (p <0.04) in the third and 4th week.
Vessal G et al., 2010[25]	Parallel	Iran	HD	62	8	Cromolyn sodium 135 mg TID vs. placebo	VAS	A greater reduction of VAS in the cromolyn sodium group (–7.78) than the placebo group (–2.90) (p < 0.001).
Rosner MH. 2006[26]	Case report	US	HD	2	12	Cromolyn sodium 100mg QID	VAS 1-10	Stopped after 12wks and symptoms returned within 4 weeks. Reintroduction had symptom improvement again. Pt 1 (8 → 3 (12 wks) → 9 (stopped med) → 5 (restart) Pt 2 (10 -> 2.5 (12wks) -> 7 (stopped med) -> 4 (restart).
Francos GC et al., 1991[27]	OL	US	HD	5	10	Ketotifen 1 mg BID then 2mg BID (after 4 wks)	Non -standardized Scale 1-6	Significant reduction from mean pruritus scores of 5.9 to 2.3 (p <0.01). Plasma histamine, histaminase activity and skin histamine content had no change.
Amirkhanlou S et al., 2016[28]	RCT DB	Iran	HD	52	2 wks	Ketotifen 1mg BID VS gabapentin 100mg daily	Shiratori's severity score (0 to 4)	23% had no response, 27% had partial and 50% complete response. No difference between two groups for response (p=0.481).

Note: PharmaCare coverage depends on the PharmaCare plan, the maximum funded per tablet/capsule and the "Fair PharmaCare" deductible for each patient. Generic medications are typically preferred by Pharmacare and BC Renal.

Doxepin (2nd line medication)

In a randomized, placebo-controlled, crossover trial[29], doxepin 10mg po BID x 1 week was compared to placebo in 24 patients with pruritus resistant to conventional treatment. There was a 1-week washout between treatment periods. Mean age was 48 years. Complete resolution was reported in 58.3% patients with doxepin vs 8.3% with placebo ($p<0.001$) with relative improvement in 29.2% vs 16.7%, respectively. Drowsiness was reported in 50% of patients, which resolved in about 2 days. One patient refused doxepin.

Although there is only one study conducted with doxepin in the treatment of pruritus in hemodialysis patients, it has been successfully used in the treatment of intractable pruritus due to its strong anti-H1 histaminic activity. If there is no contraindication to tricyclic antidepressants, doxepin may be tried after other treatments failed.

Naltrexone (3rd line medication)

Three randomized, double-blind crossover studies have been performed thus far. Peer et al performed a randomized, double-blind, placebo-controlled crossover trial with naltrexone 50mg po daily for 7 days in 15 hemodialysis patients with severe resistant pruritus. Their median pruritus scores reduced from 9.9 (out of 10) to 2.1 for the naltrexone-placebo sequence and 1.0 for the placebo-naltrexone sequence at the end of the naltrexone treatment.[30]

Another randomized, double blind cross over study done by Pauli-Magnus et al compared naltrexone 50mg po daily for 4 weeks to placebo in 23 hemodialysis and peritoneal dialysis patients. Seven patients did not complete the study. Their baseline visual analog score (VAS) was 5.5 (out of 10) and scores reduced by 29.2% in naltrexone group and 16.9% in placebo ($p=0.095$). Nine patients had GI issues including poor appetite and nausea.[31]

The most recent randomized study compared naltrexone 50mg daily to loratadine 10mg daily over 2 weeks in 52 hemodialysis patients. By day 7, the mean VAS scores reduced from baseline significantly in both groups. Seven patients had a dramatic regression of pruritus with >3 unit reduction in VAS scores with naltrexone. Adverse events were seen in 10 of the patients in the naltrexone group with a total of 30 recorded events including nausea and vertigo.[5]

Difelikefalin (3rd line medication)

Study	Design	Country	Population	N=	Treatment duration (wks)	Treatment	Pruritus assessment	Results
Peer et al., 1996[30]	RCT, DB, crossover	Israel	HD	15	1	Naltrexone 50mg daily vs. placebo	VAS (0-10)	More reduction of VAS in the naltrexone group (–8.3) than the placebo group (–1.1).
Pauli-Magnus et al., 2000[31]	RCT, DB, crossover	Germany	HD, PD	23	4	Naltrexone 50mg daily vs. placebo	VAS (0-10), QPS	Percentage of reduction in VAS was not different between the naltrexone (29.2%) and placebo groups (16.9%) (p = 0.095) and p=0.6 for the detailed score 9/23 had GI issues (poor appetite and nausea) Dialysis adequacy concern: 6/23 iPTH >18 and 12/23 PO4 >1.7 Baseline VAS 5.5/6.5
Legroux-crespel 2004[5]	RCT	France	HD	52	2	Naltrexone 50mg daily VS loratadine 10mg daily	VAS (0-10)	Naltrexone VAS >3/10 decrease in 7 pt @ baseline VAS 4.85 mm. By day 7: 4.54mm (N) and 3.96mm (L) (p< <0.01 for both to baseline) Naltrexone ADE – nausea and sleep disturbance
KALM-1 fishbane et al 2020[32]	MC, RCT, DB	US	HD	378	12	Difelikefalin 0.5mcg/kg IV vs placebo 3x/wk post HD	WI-NRS (3 point improvement) Baseline WI-NRS 6.8	At week 12, 52% and 31% randomized to difelikefalin and placebo achieved primary outcome from baseline to week 12 OR 2.72 (95% CI, 1.72 to 4.3; p<0.001) 50% of pt remained on antihistamines while on active drug ADE – diarrhea, dizziness, vomiting
KALM-2 Wooldridge et al 2020[33]	MC, RCT, DB	Global (EU, US, Asia, Canada)	HD	473	12	Difelikefalin 0.5mcg/kg IV vs placebo 3x/wk post HD	WI-NRS (3 point improvement)	At week 12, 50% and 37% randomized to difelikefalin and placebo achieved primary outcome from baseline to week 12 OR 1.61 (95% CI, 1.08 to 2.41; p=0.02) ADE- diarrhea, vomiting, falls, nausea
Narita 2022[34]	RCT, DB	Japan	HD	247	8	Difelikefalin 0.25, 0.5 or 1mcg/kg IV vs placebo 3x/wk post HD	WI-NRS Baseline WI-NRS 6.5	Change from baseline were -2.86 (0.29) in placebo, -2.97 (0.29) in the 0.25mcg/kg difelikefalin, -3.65 (p=0.04, CI-1.55 to -0.04) in the 0.5mcg/kg and -3.64 (p=0.04, CI -1.54 to -0.03) in the 1mcg/kg difelikefalin group AE: somnolence, dizziness more frequent in 1mcg/kg group
Yosipovitch G et al. 2023[35]	RCT, DB Phase 2	USA	CKD 3-5 (80%) and	52	2 wks	Difelikefalin 0.25, 0.5 or 1mg po daily Taken ≥ 2hrs before or after a meal vs placebo	WI-NRS (3 point improvement) Baseline WI-NRS 7.1	At week 12, 72.1% vs 57.9% randomized to difelikefalin 1mg po daily achieved primary outcome 38.6% achieved complete response (WI-NRS 0-1) vs 14.4% ADE – dizziness, fall, constipation, diarrhea, GERD

KALM-1 and 1 were the largest phase II clinical trials to compare difelikefalin with placebo in hemodialysis patients experiencing moderate-to-severe pruritus. Randomization was stratified based on use of concomitant medications to treat itch during the week before randomization (yes or no), and specific medical conditions. Using the Worst Itch Intensity Numerical Rating scale, the primary efficacy end point was percentage of patients at week 12 who achieved at least 3 point improvement from baseline in their weekly mean score. There is uncertainty regarding the most appropriate minimally important difference for the WI-NRS score; whether 3 point or 4 point improvement would be most clinically relevant. Secondary end points were change of itch-related quality of life measured by 5D itch scale total score and Skindex-10 scale total score. At baseline, 39.8% of patients and 36.5% in KALM-1 and 2 trials respectively were using anti-itch medications with median duration of CKD associated pruritus was 2.5 and 2.3 years respectively.

When using a 3 point improvement in the WI-NRS scale, both studies showed an improvement from baseline to week 12 favoring difelikefalin. When using a 4 point improvement, KALM-1 had proportion of 41% and 21% of patients in difelikefalin and placebo respectively resulting in odds ratio of 2.89 (95% CI, 1.75 to 4.76; p<0.001); KALM-2 trial, WI-NRS score had a proportion of 38% and 25% of patients in difelikefalin and placebo corresponding to odds ratio of 1.77 (95% CI, 1.14 to 2.74 p=0.01). Notably, odds ratios can give inflated impression of treatment effects compared with relative risks. Difelikefalin showed improvement at 12 weeks from baseline in the WI-NRS that was clinically meaningful based on both 3 and 4 point improvements in the score. Secondary end points for WI-NRS improvement at week 4 and 8 were reported in KALM-2 which showed at week 4 (35% versus 22%) and week 8 (45% versus 33%) for proportion of patients with 3 point improvement from baseline.

Discontinuation rates were higher in treatment groups with 14.3% versus 9.6% for difelikefalin group for KALM-1 and 12.3% versus 5.5% in KALM-2 also higher for difelikefalin group. Reason was due to side effects such as diarrhea, dizziness, nausea and falls. There was also a higher rate of missing data in the difelikefalin group than in placebo which may introduce attrition bias compared to the placebo groups. The placebo group in both studies had a notable response and may be due to optimization of hemodialysis treatment associated with thrice weekly dialysis.

Another limitation was the choice of concomitant antiitch medications. In KALM-1, of the 45% of patients who continued their anti-itch medications, 33% of patients were on diphenhydramine and 10% on hydroxyzine and no patient was on gabapentin or pregabalin. Other anti-itch treatments such as phototherapy or topical therapies were not commented on either.

Limited evidence

Activated Charcoal

In an open-label case series[36], 23 hemodialysis patients were treated with activated charcoal 6g po daily (30 x 200mg capsules) x 6 weeks. Ten single-blinded patients received placebo treatment prior to charcoal. Ten patients' pruritus completely resolved, ten patients had partial response while 3 were unresponsive. Four patients complained of nausea, weight gain or difficulty with pill burden.

In a double-blind, placebo controlled, crossover study[37], activated charcoal 6g po daily x 8 weeks was shown to relieve pruritus in 10/11 hemodialysis

patients with idiopathic generalized pruritus (p=0.01). Four patients were non-compliant. No adverse effects were noted.

Although there is some limited evidence suggesting the efficacy of activated charcoal, the product is commercially available as 260mg capsules and may be compounded as 360mg capsules by compounding pharmacies. Therefore, it requires 17 to 23 capsules per day to make up a 6 g daily dose. In addition, activated charcoal may bind to and needs to be spaced apart from other medications during administration. Due to the significant pill burden and potential drug interactions, this option is not listed in the algorithm but may be used as a last resort.

Gamma-linolenic acid (topical)

A randomized, double-blind, placebo-controlled, crossover study[38] compared gamma-linolenic acid 2.2% cream vs. placebo for 2 weeks with a 2-week washout in 16 dialysis patients with refractory uremic pruritus. Gamma-linolenic acid cream shows statistically significant change in visual analogue scale and pruritus score compared to placebo.

Tumeric

In a double-blind randomized control trial conducted on 100 HD patients with pruritus[39], treatment with tumeric 500 mg po 3 times/day for 8 weeks reduced pruritus score greater than placebo 13.6 ±2.6 vs. 7.2 ± 2.6, p=0.001. No adverse reactions were observed during this trial.

Omega-3 fatty acids

A double-blind, cross-over randomized trial in 4 hemodialysis centres looked at the efficacy of Omega-3 1g 3 times/day for 20 days vs. placebo in 22 patients with drug resistant pruritus[40]. The pruritus score in the Omega-3 group decreased from 20.3 95% CI: 16.7-23.8) to 6.4 (95% CI: 2.9-9.8) vs. 17.0 (95% CI: 12.4-21.6) to 14.4 (95% CI: 10.5-18.2) (p=0.0001) in the placebo group. No adverse reactions were reported. Recent evidence, however, suggests Omega-3 may increase the risk of developing atrial fibrillation.[41]

Calcipotriol

23 hemodialysis patients were enrolled in an open-label study looking at calcipotriol vs. vehicule solution twice daily for 1 month[42]. Calcipotriol improved the validated modified pruritus assessment score and the VAS pruritus score after 2 and 4 weeks of treatment. Ski dryness was also improved with calcipotriol. No side effects were reported.

Zinc Sulfate

A randomized, double-blind, placebo controlled trial comparing zinc sulfate 440mg po daily in 40 HD patients for 8 weeks. VAS (0-10) was used to assess efficacy and found that both groups had decreased VAS scores after treatment. However, the difference after treatment was higher with zinc sulfate group and statistically significant (3.8 vs. 2.05). Given that this was a single study and modest effect this treatment has been classified as limited evidence.[43]

Negative Studies

Ondansetron/Granisetron

A randomized, double-blind, placebo-controlled study[44] failed to demonstrate ondansetron 8mg po TID x 2 weeks to be more effective than placebo in 24 hemodialysis patients.

A prospective, placebo-controlled, double-blind, crossover study[45] compared ondansetron 8mg po TID vs placebo x 2 weeks in 16 hemodialysis patients with persistent pruritus. No statistically significant difference in daily pruritus score was reported between both treatment periods.

A randomized, double-blind study compared pregabalin 75mg po twice weekly vs ondansetron 8mg po daily vs. placebo over 12 weeks in 179 patients on dialysis with uremic pruritus. Pregabalin was found to be more effective than placebo and ondansetron (Mean VAS change from baseline = -4.6cm). Ondansetron had a non-statistically significant change from baseline VAS of -0.5cm.[46]

14 HD patients with moderate to severe pruritus were treated with granisetron 1mg po BID for 1 month. Efficacy was evaluated using modified Duo pruritus score at the 1st, 2nd and 4th week. Patients at 4 weeks showed a statistically significant difference in pruritus score.[47]

Tacrolimus 0.1% Ointment

A randomized, double-blind, vehicle-controlled study[48] failed to demonstrate tacrolimus 0.1% ointment (n=12) to be more effective than vehicle (n=8) in relieving uremic pruritus.

Two consecutive treatment periods of 3 weeks segments using 0.1% and 0.03% tacrolimus was conducted in 25 dialysis patients over the course of 6 weeks. Efficacy was assessed by a modified pruritus assessment score and a VAS. Pruritus was reduced by 81.8% after 6 weeks of treatment on the modified pruritus assessment score (median baseline was 11, decreased to median of 2 at week 6; $P < 0.05$). VAS decreased from median of 7 to median of 4 ($P < 0.05$).[49]

Oral nicotinamide

50 hemodialysis patients with refractory uremic pruritus were enrolled in a prospective randomized trial looking at the efficacy of oral nicotinamide vs. placebo.[50] Nicotinamide didn't improve the VAS pruritus score after 4 weeks of therapy in comparison to placebo.

Ergocalciferol

50 hemodialysis patients with refractory uremic pruritus were enrolled in a prospective randomized trial looking at the efficacy of ergocalciferol 50,000 units/week vs. placebo for 12 weeks.[51] Ergocalciferol didn't improve the VAS pruritus score in comparison to placebo.

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