From the Cochrane Library: Interventions for chronic pruritus of unknown origin

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Abstract

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Conflict of Interest: Dr. Dellavalle is a Joint Coordinating Editor for *Cochrane Skin*, a dermatology section editor for *UpToDate*, a Social Media Editor for the *Journal of the American Academy of Dermatology* (JAAD), a Podcast Editor for the *Journal of Investigative Dermatology* (JID), Editor-in-Chief of the *Journal of Medical Internet Research* (JMIR) *Dermatology* and is a coordinating editor representative on *Cochrane* Council.

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To The Editor: Chronic pruritus of unknown origin (CPUO) is characterized by pruritus lasting longer than 6 weeks and is a diagnosis of exclusion with no identifiable cause; the estimated prevalence ranges between 7–45.9%, and is highest in the elderly.[1] Affected individuals experience a significant disruption to quality of life, including sleep disturbances and psychological concerns, which can further contribute to itching.[2] Treatment of patients with CPUO is particularly challenging, due to its unknown pathophysiology.[3] No FDA-approved treatment for CPUO currently exists. First-line treatment consists of antihistamines and topical steroids; unfortunately, treatments for CPUO are only variably responsive.[4] Research on interventions for CPUO is sparse, including assessments of safety and efficacy. A Cochrane systematic review, "Interventions for chronic pruritus of unknown origin," assessed interventions for CPUO in adults and children by examining available evidence from randomized controlled trials (RCT) and quasi-RCTs for the efficacy of CPUO interventions.[2] 7,148 records published up until July 2019 were analyzed in the literature search with only one eligible trial meeting inclusion criteria which consisted of a 6 week minimum complaint of pruritus unresponsive to first-line treatment and ≥7 cm on the visual analogue scale (VAS) at baseline, considered severe chronic pruritus. Exclusion criteria were based on serum creatinine, aspartate aminotransferase, or alanine aminotransferase levels >2x upper limit of normal or previous diagnoses suggestive of secondary pruritus causes.

The primary endpoint of the included RCT (N=257) was evaluation of itch severity and adverse events (AEs). Secondary endpoints included 'Health-related quality of life', 'Sleep disturbances', 'Depression', and 'Patient satisfaction'. The GRADE approach was applied to interpret the certainty of the findings.[5] The RCT quantified the therapeutic impact via percentage change in VAS at three different dosing levels of serlopitant, a novel NK1 receptor antagonist downregulating the NK1 itch signaling pathway. Compared to placebo, patients who received serlopitant, 5 mg orally once daily for 6 weeks showed significant improvements in VAS (Risk Ratio RR = 2.06, 95% Confidence Interval (CI)1.27–3.35]) and reduced patient-reported Numerical Rating Scale (NRS) itch intensity (Mean Difference (MD): -10.30%, 95% CI-20.01 to -0.59); number needed to treat (NNT) was approximately 4. Increased risk of adverse events was unclear (RR 1.48, 95% CI:0.87–2.50). Certainty of evidence was low to very low, with risk-of-bias concerns due to missing outcome data and presence of potential underlying diagnoses in many RCT participants.

Findings from smaller-scale studies conducted after the Cochrane review's publication suggest that new therapeutic approaches including pregabalin and dupilumab may be more effective at reducing VAS and NRS scores in treatment-resistant CPUO.[3,4] Pregabalin is thought to alleviate CPUO through modulating thresholds of the C-fibers shown to transmit itch signals by suppressing the release of several neurotransmitters such as substance P, which may be chronically elevated in patients with CPUO.[3] Dupilumab, a JAK inhibitor, in addition to anti-inflammatory properties, may alleviate CPUO through cytokine-neural interactions.[4] Pregabalin decreased VAS scores for 70% of patients with CPUO refractory to antihistamine therapy in one study.[4] Likewise, treatment with dupilumab resulted in a substantial mean decrease in NRS itch score by 7.[3] These findings suggest potential alternative treatment approaches for patients who have treatment-refractory CPUO, which remains a diagnosis of exclusion with unclear etiology. Current treatments including emollient creams, cooling lotions, topical corticosteroids, topical antidepressants, systemic antihistamines, systemic antidepressants, systemic anticonvulsants, and phototherapy lack extensive study, especially

in RCTs.[2] These studies taken together, suggest that after current treatment approaches failed, treatment of CPUO with serlopitant, 5 mg orally once daily for 6 weeks, or alternatively pregabalin, 150 mg daily for 2 weeks or Dupilumab 600 mg subcutaneous injection (SC) followed by 300 mg SC biweekly, are potential treatment options (Figure 1).

Poorly understood pruritic cutaneous manifestations related to COVID-19 disease, frequent handwashing, personal protective equipment use, and psychosocial stress during the pandemic have presented difficulties in determining root causes of itch in many patients, likely exacerbated by reduced access to healthcare and heightened fear of infection.[6] Post-pandemic recovery may require further research to reconsider ideal CPUO management approaches given interruptions to care; ultimately, additional investigation is needed to characterize the various molecular underpinnings of CPUO and may aid in more effective and targeted therapeutics.

Table 1: Summary of study primary and secondary endpoint findings of different doses of Serlopitant for chronic pruritus

Group	Dose	Total Participants	Reduction in VAS [a] (RR, 95% CI) Compared to placebo n=total participants used for analysis	Adverse Events[b] (RR, 95% CI) Compared to placebo n=total participants used for analysis	Quality of Life[c] (MD with serlopitant, 95% CI) Compared to placebo n=total participants used for analysis	Sleep Disturbance[d] (RR, 95% CI) Compared to placebo n=total participants used for analysis
Placebo n=64	1x/day x 6 weeks	64	-	-	-	-
Serlopitant 0.25 mg n=64	0.25 mg, 1x/day x 6 weeks	127	RR 1.66 (1.00 to 2.77) n=127	RR 1.29 (0.75 to 2.24) n=127	MD 5.70 lower (13.18 lower to 1.78 higher) n=127	RR 0.60 (0.31 to 1.17) n=127
Serlopitant 1 mg n=65	1.0 mg, 1x/day x 6 weeks	126-128	RR 1.50 (0.89 to 2.54) n=126	RR 1.45 (0.86 to 2.47) n=128	MD 6.90 lower (14.38 lower to 0.58 higher)	RR 0.38 (0.17 to 0.84) n=128

					n=128		
Serlopitant 5 mg n=64	5 mg, 1x/day x 6 weeks	126-128	RR 2.06 (1.27 to 3.35) n=126	RR 1.48 (0.87 to 2.50) n=127	MD 4.20 lower (11.68 lower to 3.28 higher) n=127	RR 0.49 (0.24 to 1.01) n=128	

a: Reduction in visual analogue (VAS) was defined as ≥ 4cm reduction in VAS (range: 0 to 10 cm).

b: Adverse events (AE) were defined as the number of participants with any AE

c: Health-related quality of life was assessed with the Dermatology Life Quality Index (DLQI) score (range 0 to 30)

d: Sleep disturbances were defined as number of participants with insomnia (Assessed with Pittsburgh Sleep Symptom Questionnaire)

Abbreviations: VAS: visual analogue scale; RR: risk ratio; CI= confidence interval; MD= mean difference

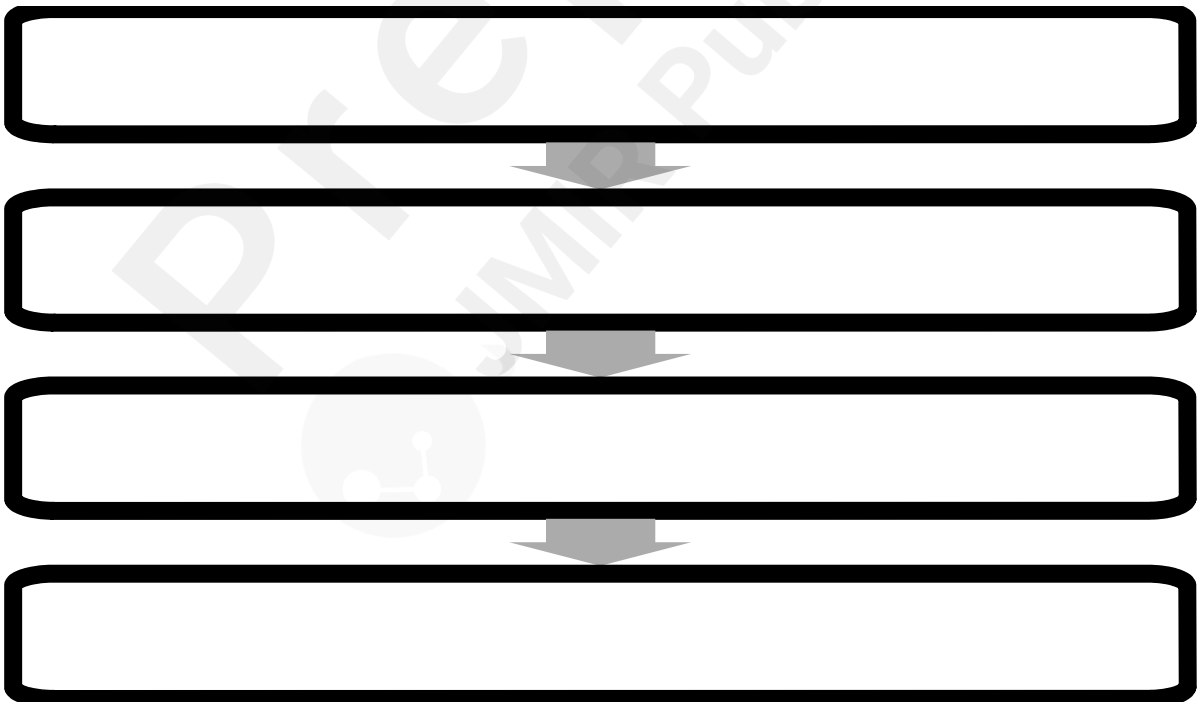

Figure 1: Practical algorithmic treatment options once chronic itch is identified in a patient, based on current treatment approaches and the 3 studies included.

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