

FROM THE FAMILY PRACTICE INQUIRIES NETWORK

First- or second-generation antihistamines: which are more effective at controlling pruritus?

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■ EVIDENCE-BASED ANSWER

For urticarial itch, first- and second-generation antihistamines have similar clinical benefit and are superior to placebo (strength of recommendation [SOR]: **A**, systematic review of randomized trials [RCT]). For itch related to atopic dermatitis, antihistamines are no better than placebo (SOR: **B**, small RCTs and other studies). Other categories of pruritus are best treated with non-antihistamine agents (SOR: **C**, based on expert opinion and disease-oriented research).

■ EVIDENCE SUMMARY

Based on the advantage of nocturnal sedation of first-generation antihistamines, clinicians frequently use these agents to treat pruritus. Evidence is lacking to support this intuitive approach. Furthermore, not all pruritus can be lumped into a single category, as distinct treatment recommendations exist for different categories.

The best evidence supporting antihistamines is for the treatment of urticarial pruritus. A Medline-based review found 7 double-blind, placebo-controlled trials that compared the benefit of first- and second-generation antihistamines in 720 patients with chronic idiopathic urticaria. Hydroxyzine was used in 682 patients, while the remainder took clemastine. Second-generation agents included cetirizine, loratadine, or acrivastine. The researchers qualitatively summarized outcomes and concluded that the treatment benefits were equivalent and superior to placebo.¹ The clinical practice of doubling the dose of second-generation agents for initial treatment failures was not recommended, due to absence of supporting data for this approach.

A recent review of therapies for urticarial itch concluded that second-generation antihistamines were preferred.² However, the methodology failed to use a systematic search technique. The conclusion was based upon a single double-blind placebo-controlled study of 188 patients at least 12 years of age. They received

cetirizine 10 mg daily, hydroxyzine 25 mg 3 times daily, or placebo. This study found both agents produced significant, and equivalent, pruritus reduction relative to placebo.³

In contrast to urticarial itch, pruritus from atopic dermatitis does not improve with antihistamines. An NHS Centre narrative review on relieving pruritus in atopic dermatitis concluded that there was little objective evidence to support the efficacy of first- or second-generation antihistamines; 803 participants from 16 case series and reports were included. There were no large RCTs. Results were not pooled or tested for heterogeneity, so they should be interpreted cautiously.^{4,5}

Another systematic review focusing on pediatric patients concluded oral antihistamines are not beneficial for pruritus from atopic dermatitis. A search of Cochrane and PubMed revealed only 2 relevant RCTs involving 177 children. Cetirizine and chlorpheniramine were each compared with placebo, and no statistically significant reduction in symptoms was found.⁶

Vigilance must be exercised when interpreting pruritus literature. Many studies are pharmacodynamic only, omit appropriate statistical information, and measure surrogate outcomes in healthy volunteers, such as wheal and flare suppression to injected histamine. Such disease-oriented evidence has filtered into clinical recommendations.

One recent nonsystematic, narrative review of pruritic dermatoses concluded second-generation antihistamines appear to be more effective.⁷ This conclusion was largely based on a study of 14 young, healthy, "light-skinned" Canadian men. No placebo control was used. Seven received fexofenadine 120 mg; the other 7 took diphenhydramine 50 mg. Primary outcomes were concentrations of drug in skin punch biopsies and plasma samples, plus degree of wheal and flare suppression to histamine. In this study, fexofenadine showed statistically significant disease-oriented results.⁸

■ RECOMMENDATIONS FROM OTHERS

No evidence-based guidelines or consensus statements were found that address antihistamine preference in the treatment of pruritus. Although use of non-antihistamine agents is beyond the scope of this inquiry, an excellent topical review of pruritus was recently published that comprehensively outlined the Twycross classification system and detailed the evidence for usual and nontraditional treatments.⁹ Since antihistamines do not benefit atopic-related pruritus, other options include emollients, counterirritants such as menthol/camphor or capsaicin, EMLA cream, topical pramoxine, topical corticosteroids, topical doxepin, topical immunomodulators such as pimecrolimus or tacrolimus, topical aspirin, and phototherapy with psoralen ultraviolet A-range (PUVA).

CLINICAL COMMENTARY

Antihistamines are not likely to remedy the itch for pruritus not due to urticaria

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Pruritus is a symptom; therefore, I must ask, "what is causing it?" For pruritus not due to urticaria, antihistamines are not likely to remedy the itch. For urticarial itch, I must consider the sedative, psychomotor, and anticholinergic effects of the first-generation antihistamines. In fact, the soporific effect may be their only useful property in nonurticarial pruritus—including atopic dermatitis—where it is considered a mainstay therapy. Yet in many situations, patients with urticaria cannot risk the significant CNS side effects of first-generation agents, which are comparable to alcohol and tranquilizers. Therefore, it is reassuring that the second-generation antihistamines seem equally efficacious.

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