Antihistamines and the Common Cold
A Review and Critique of the Literature
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OBJECTIVE: To determine if antihistamines provided clinically significant relief from the symptoms of the common cold.

METHODS: Structured literature review following standardized guidelines of primary studies published after 1975.

MEASUREMENTS: Improvements in symptom scores for total symptoms and nasal symptoms over the first three days of a common cold.

RESULTS: Three of five studies reporting on sneezing found a statistically significant improvement in the antihistamine group; similarly, three of seven studies reporting on nasal discharge found a statistically significant improvement with therapy. No study reported improvement in total symptom score at the level of p < .05. The validity of these findings was weakened by several flaws in the literature such as inattention to clinical significance and functional impact, inappropriate use of statistical tests, and poorly described methodology. The clinical significance of these improvements was not demonstrated.

CONCLUSIONS: The primary literature offers little support for the use of antihistamines in the common cold.

KEY WORDS: antihistamines; common cold; literature review.

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Patients and clinicians want to know if antihistamines relieve the symptoms of the common cold. In 1975, West and colleagues reviewed 35 clinical studies examining this question and found that the majority lacked rigor in disease definition, research goals, and design. West concluded that there was little valid evidence for using antihistamines in the common cold. More recent work has shown that vasoactive peptides known as kinins, not histamine, contribute to the pathogenesis of symptoms in rhinovirus infections.

Despite this literature, the United States Food and Drug Administration has tentatively classified antihistamines as "effective" in the treatment of cold symptoms. This sanctions a pharmaceutical market in which antihistamines are nearly ubiquitous in the hundreds of cough and cold preparations available over the counter and by prescription.

Since the publication of the West review, the quality of clinical trials has improved considerably. Similarly, techniques for literature review have become more rigorous. The purpose of this review is to update the West review by examining studies of antihistamines and the common cold in both adults and children.

METHODS

We conducted two Medline searches for articles published after 1975. The first used the term "Common cold tx [limit to review articles]." These articles were culled for references to clinical trials. The second search used the term "Common cold & explode: histamine h1 receptor blockaders."

An article was reviewed if it met the following criteria: (1) it was a randomized, double-blind clinical trial; (2) at least one arm of the study compared antihistamines with placebo; (3) it was published after 1975 (the date of West's review); and (4) it involved healthy patients having either natural or experimentally induced colds. This strategy led us to 11 clinical trials.

We focused the review by asking the question: What are antihistamines expected to do? Sperber and Hayden proposed a number of potential roles for cold medications including alleviation of symptoms (antihistamines presumably act on nasal symptoms), improvement of function, prevention of complications, and prevention of spread. Symptom alleviation was the only outcome measured in these studies; therefore, we limited our review of the role of antihistamines to the alleviation of symptoms.

The methodologic evaluation of the studies involved nine areas: population studied, quality of cold diagnosis, success of randomization, validity of pharmaceutical intervention, report of relevant clinical outcomes, dropout rate, clinical similarity of groups, use of other medica-
tions, and side effects. Minimum criteria for acceptability were as follows: (1) The study had to enroll healthy (non-allergic) adults or children experiencing natural or experimentally induced colds. (2) The diagnosis of common cold had to be based on physician (or other practitioner) history and physical examination; an effort had to be made to exclude allergic conditions. (3) The authors needed to have evaluated the success of their randomization and found the two study groups comparable. (4) Antihistamines had to be given in doses similar to those used in the treatment of allergic rhinitis. (5) There had to be a patient (or parent) assessment of cold symptoms. (6) All patients needed to be accounted for. (7) The authors needed to compare the initial clinical severity in treatment and placebo groups and find no significant differences. (8) Patients could not use other antihistamines or anticholinergic agents during the study. (9) Patients had to be asked about drowsiness during the course of the study. Each area was evaluated as acceptable, not acceptable, or not reported. This evaluation was done independently by the two authors.

All published studies used some variation of the symptom scale developed by Jackson and colleagues. Individual symptoms (such as sneezing or headache) are rated as follows: 0 is absent; 1 is mild; 2 is moderate; and 3 is severe. Individual symptom scores are then summed into a total symptom score (TSS), which quantitates the severity of the cold. Studies often differed in the combination of symptoms used to determine the TSS, and as a result the maximal TSS varied from study to study.

A value of \( p < .05 \) is generally accepted as statistically significant. However, there is no such generally accepted criterion for clinical significance in studies on the common cold. Therefore, we postulated the following standard for evaluating clinical significance: we expected antihistamines either to reduce individual symptoms in the active treatment group by one point (on the 0 to 3 point scale) for a 24-hour period, or to reduce the TSS by 15% for a 24-hour period. Patients in the studies reviewed were enrolled with a TSS of approximately 10 (Fig. 1). Therefore a reduction in the TSS of 1.5 was considered clinically significant.

Because the symptoms of a cold improve dramatically over the first several days, we further required that any benefit from antihistamines be demonstrated during the first 3 days of therapy (i.e., within 72 hours of initiation of the drug).

In contrast to other authors, we accepted patients' (or parents') self-evaluation as a valid outcome measure based on a definition of symptoms as a "subjective indication of a disease or a change in condition as perceived by the patient." Because self-evaluation was the most valid indicator, we did not review data on physician assessment of symptoms or so-called objective measures of signs and symptoms (e.g., tissue counts, rhinometry, and dye-saccharin tests of nasal discharge).

The power of a study to detect a 15% decrease in the TSS was determined by the SPSS program, using a \( \beta \) error of 0.20 and information on the TSS for the first 3 days of illness derived from Figure 1.

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**FIGURE 1.** Total symptom scores for antihistamine and placebo groups in four studies.