Nonprescription medications for respiratory symptoms: Facts and marketing fictions

Miles Weinberger, M.D.[1,2] and Leslie Hendeles, Pharm.D.[3]

ABSTRACT

Background: *There are many nonprescription (over-the-counter [OTC]) medications available on pharmacy shelves marketed for relief of respiratory symptoms. The number of such medications has been increasing.*

Objective: *This review provides an evidence-based examination of OTC products used for respiratory symptoms.*

Methods: *Antihistamines, decongestants, mucolytics, antitussives, and intranasal steroids were selected as the most common OTC medications taken by adults and children for various respiratory symptoms. Controlled clinical trials of efficacy were identified by searching a medical literature data base. Those trials and key publications related to the pharmacokinetics and pharmacodynamics of the products were reviewed.*

Results: *Comparisons of the various OTC antihistamines' ability to suppress the effects of histamine were related to their clinical benefit. Intranasal corticosteroids are the preferred agents for maintenance therapy of persistent nasal congestion and are highly effective for symptoms of inhalant allergy other than allergic conjunctivitis. The disconnect between marketing claims and evidence was demonstrated for antihistamines and oral alpha-1 adrenergic agonist decongestants. Data for OTC mucolytics and antitussives were insufficient to justify their use based on the evidence.*

Conclusion: *There was little relationship between marketing claims and evidence regarding OTC medications used for respiratory symptoms. Analysis of data supported cetirizine, levocetirizine, and fexofenadine as the most effective of the OTC antihistamines. There were no data that supported the use of oral phenylephrine as a decongestant. Neither OTC mucolytics or antitussives provided sufficient evidence to justify their use.*

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Antihistamines, decongestants, mucolytics, antitussives, and intranasal corticosteroids are among the most common nonprescription (over-the-counter [OTC]) medications taken by adults and children. Many OTC medications are prescribed or recommended by physicians. Although most patients, parents of patients, and physicians are aware of the extensive advertising and marketing claims for these medications, few are familiar with the data related to the efficacy of these agents, let alone the pharmacodynamics and pharmacokinetics of these ubiquitous medications. Let us consider first what is expected from the medications to be reviewed by category of anticipated therapeutic effect and then examine data for the products in a medical literature data base (Pubmed):

- Antihistamines—competitive antagonist of histamine at H_1 receptor
  - Influences sneezing, rhinorrhea, conjunctivitis from allergens but not infections
  - No direct effect on nasal congestion
- Decongestants—decrease nasal congestion and nasal airway resistance, thereby increasing nasal air flow
- Mucolytics—loosen and clear the mucus from the airways by decreasing viscosity and increasing volume
- Antitussives—suppress cough
- Ophthalmic products for allergic conjunctivitis—decrease conjunctival injection and itching
- Mast cell stabilizer—prevents release of mediators, such as histamine, with relief of nasal symptoms
- Intranasal corticosteroids—decrease inflammation of the nasal mucosa, thereby decreasing mediator release and nasal congestion
- Chicken soup—transient decrease in respiratory symptoms
- There are multiple medications within some of these functional categories (Table 1).

From the [1]Pediatric Allergy & Pulmonary Division, University of Iowa, Iowa City, Iowa, [2]Rady Children's Hospital, University of California San Diego, San Diego, California, and [3]Pharmacy and Pediatrics, University of Florida, Gainesville, Florida
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Address correspondence to Miles Weinberger, M.D., 450 Sandalwood Court Encinitas CA 92024
E-mail address: miles-weinberger@uiowa.edu

Antihistamines

Antihistamines have long been used most commonly by individuals who experience nasal symptoms of inhalant allergy. Some individuals may also have attempted to use them for somewhat similar symptoms of a common cold, for which these medications are not

Table 1 **Common nonprescription medications for respiratory and allergic eye symptoms (common brand name are in parentheses)***

Antihistamines
Cetirizine (Zyrtec, McNeil, Fort Washington, PA)
Chlorpheniramine
Diphenhydramine (Benadryl, Mcneil, Fort Washington, PA)
Fexofenadine (Allegra, Sanofi-aventis, Bridgewater, NJ)
Levocetirizine (Xyzal, sanofi-aventis, Bridgewater, NJ)
Loratadine (Claritin, Schering-Plough, Kenilworth, NJ)
Pheniramine
α-1 Adrenergic decongestants
Oxymetazoline (Afrin, Bayer, Whippany, NJ)
Pseudoephedrine (Sudafed, Mcneil, Fort Washington, PA)
Phenylephrine (Sudafed PE, McNeil, Fort Washington, PA)
Topical nasal corticosteroid decongestants
Triamcinolone (Nasacort, Sanofi-aventis, Bridgewater, NJ)
Budesonide (Rhinocort, McNeil, Fort Washington, PA)
Fluticasone propionate (Flonase, GSK, Triangle Park, North Carolina)
Fluticasone furoate (Flonase Sensimist, GSK, Triangle Park, North Carolina)
Mucolytic
Guaifenesin (Robitussin, Pfizer, New York, NY; Mucinex, Reckitt Benckiser, Parsippany, NJ)
Antitussive
Dextromethorphan (Robitussin DM, Pfizer, New York, NY; Delsym, Reckitt Benckise, Richmond, VA)
Mast cell stabilizer for nasal respiratory symptoms
Cromolyn (Teva, North Wales, PA)
Ophthalmics for allergic rhinitis
Ketotifen (Zyrtec McNeil, Fort Washington, PA, Zaditor Alcon, Fort Worth, TX)
Naphazoline and pheniramine (Naphcon A, Alcon, Fort Worth, TX; Opcon A, Bausch & Lomb, Bridgewater Township, NJ)
Tetrahydrozoline and pheniramine (Visine A, Johnson & Johnson, Fort Worth, TX)

**Some are marketed in various combinations; most are also available as generic preparations.*

clinically useful.[1] Chlorpheniramine was common before the development of agents with little or none of the sedation common to older antihistamines. Diphenhydramine (Benadryl, McNeil, Fort Washington, PA)

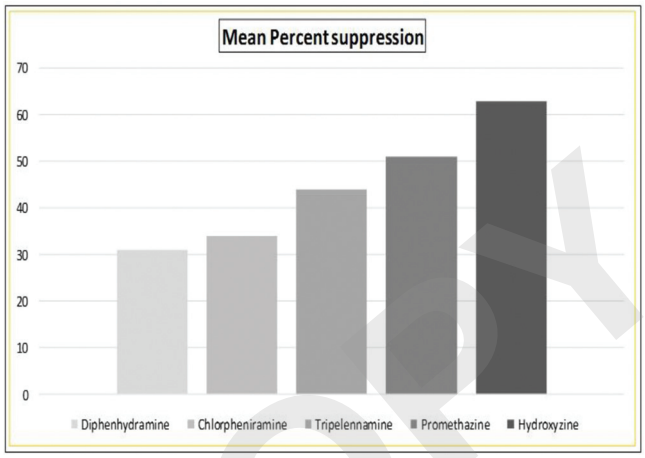

Figure 1. *Degree of skin test suppression of histamine-induced wheal from five classic antihistamines (from Ref. 2).*

continues in common use, sometimes as a mild hypnotic to induce sleep. This category of OTC medication has the largest number of agents and is the best studied. At one time, it was popular to classify these medications by their chemical structure: alkylamines (*e.g.,* chlorpheniramine), ethanolamines (*e.g.,* diphenhydramine), ethylenediamines (*e.g.,* pyrilamine), phenothiazines (*e.g.,* promethazine), piperidines (*e.g.,* loratadine), and piperazines (*e.g.,* cetirizine): the first four of these are older antihistamines and are currently called first generation, and the last two are currently termed second generation. The presumption was that specific agents within each structural grouping would have some similarities. However, there were few data to select either a class or the agents within a class.

The first attempt to assess the relative antihistaminic effect examined the ability of five common antihistamines, one from each structural class, in conventional doses in a bioassay of H_1 receptor potency in 18 human volunteers. Before and after 3 days of dosing (based on the manufacturer's recommendation in the package insert), the allergen was placed before the first dose, after the final dose, and daily thereafter for a week. Differences in both the maximal suppression and duration of suppression of an allergen-induced wheal were identified, with hydroxyzine producing the greatest and diphenhydramine the least suppression (Fig. 1).[2] In the study, diphenhydramine and hydroxyzine produced the same degree of sedation, which demonstrated that the antihistaminic effect and sedation were independent characteristics.[2]

A second study by the same senior author, Heinz Wittig, examined the relative efficacy of three antihistamines from different chemical groups in preventing pruritus from intradermal histamine.[3] Each of the three antihistamines was given 8 hours and 1 hour before testing. There was a 1-week washout between

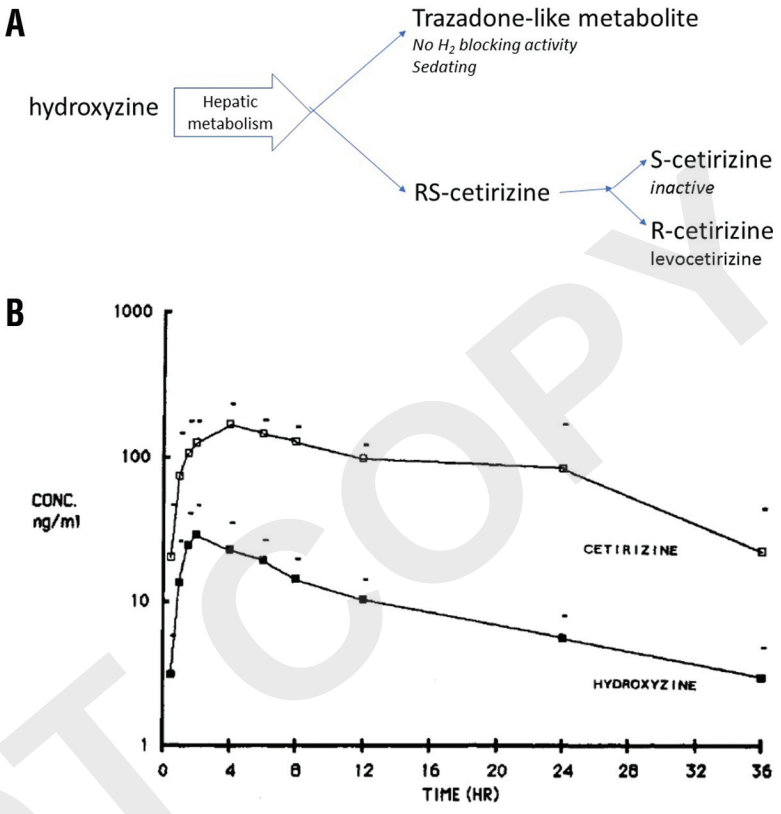

Figure 2. (A) Metabolism of hydroxyzine to racemic cetirizine (RS-cetirizine) and a metabolite with sedation but no antihistaminic effect; racemic cetirizine can be separated into the individual enantiomers, the inactive S-cetirizine and the active R-cetirizine, also known as levocetirizine (Xyzal); (B) The mean cetirizine and hydroxyzine serum concentrations after administration of 25 mg of hydroxyzine to 25 adult male volunteers (from Ref. 10).

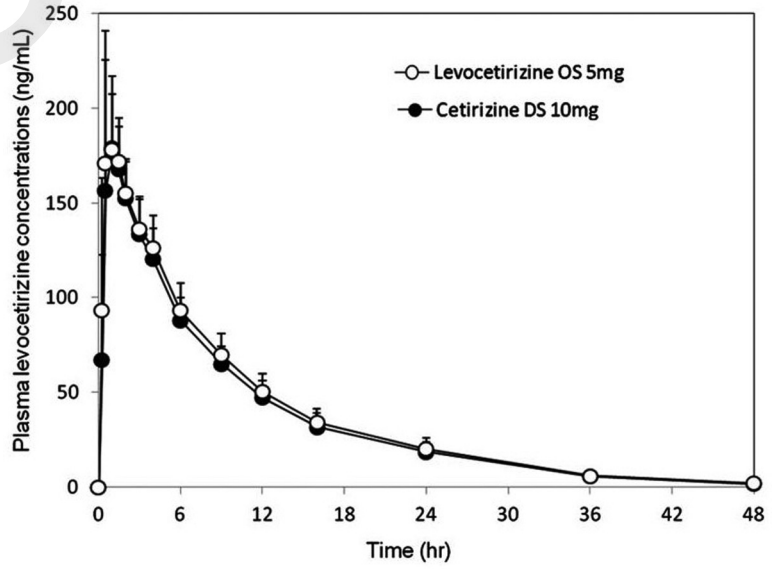

Figure 3. Cetirizine, a racemate, contains levocetirizine, the pharmacologically active optical isomer (enantiomer); equimolar amounts of levocetirizine, whether as the single enantiomer or as racemic cetirizine produce the same blood level (from Ref. 11).

the treatments. As with the intensity and duration of allergen-induced wheal suppression, suppression of pruritus was much greater with hydroxyzine than with diphenhydramine or cyproheptadine (another older antihistamine).[3] By using an analogous approach after single doses of hydroxyzine and two newer antihistamines, desloratadine and fexofenadine, hydroxyzine was substantially more effective in suppressing a histamine-induced wheal than were the other two.[4]

Based on the efficacy of hydroxyzine in suppressing histamine-induced wheal and pruritus, we hypothesized that it would be effective for allergic rhinitis, although hydroxyzine, as Vistaril (Roerig, Hoffman Estates, IL), was marketed "for symptomatic relief of anxiety and tension associated with

psychoneurosis and as an adjunct in organic disease states in which anxiety is manifested" (from the Vistaril package insert). Hydroxyzine was also marketed at the time as Atarax (Roerig, Hoffman Estates, IL) for treatment of urticaria. Double-blind, randomized, placebo controlled trials were performed in two consecutive Midwest ragweed seasons by using maximally tolerated doses of hydroxyzine 75 mg twice a day compared in the second study with chlorpheniramine, 12 mg twice a day, the leading OTC antihistamine at the time.[5,6] Of interest was the observation that the sedation adverse effects of both hydroxyzine and chlorpheniramine were transient, even at the high doses used in the study. This is in contrast to initial sedative effects described for those antihistamines, which is the basis for disallowing all but nonsedating antihistamines use in active pilots.[7–9] The current relevance of greater potency of hydroxyzine to nonprescription antihistamines is that hydroxyzine essentially acts as a prodrug for the second-generation H_1 blocker, cetirizine (Zyrtec, McNeil, Fort Washington, PA), its active metabolite (Fig. 2).[10]

Although antihistamines have generally had an excellent safety record, fexofenadine (Allegra, Sanofi-aventis, Bridgewater, NJ) was the safe active metabolite of terfenadine, a popular previous prescription-only product marketed as Seldane (Hoechst Marion Roussel, Kansas City, MO). Terfenadine was withdrawn from the market when cases of life-threatening cardiac arrhythmias caused by QT interval prolongation were reported. Two newer antihistamines, desloratadine and levocetirizine, are active forms of their parent drug. Desloratadine (Clarinex, Schering-Plough, Kenilworth, NJ), not yet nonprescription, is the active metabolite of loratadine. Levocetirizine, the R-enantiomer of racemic cetirizine, available nonprescription as Xyzal (Sanofi-aventis, Bridgewater, NJ), is the active optical isomer (enantiomer) of racemic cetirizine (Fig. 3).[11] When compared with the racemic cetirizine, no clinical advantage over the parent drug based on suppression of a histamine-induced wheal is apparent; the S-enantiomer had no clinical effect.[12]

The dose-response of antihistamines has been studied. It has been common practice to increase the dose of antihistamines to four times the usual dosage for chronic urticaria. An examination of that practice by using levocetirizine, the active enantiomer of cetirizine, 5–20 mg, compared with desloratadine, 5–20 mg, demonstrated a progressive dose-response effect of the levocetirizine over that fourfold range but a lesser effect from the same dose range and no progressive increase beyond 10 mg for desloratadine, the active metabolite of loratadine.[13] This is consistent with the lesser effect of U.S Food and Drug Administration (FDA) approved doses of loratadine compared with cetirizine[14] and fexofenadine.[15] The minimal clinical effect of loratadine and the controversy surrounding its approval was extensively described in 2001 by a writer for *The New York Times* in a lengthy article in the Sunday magazine section.[16] Fexofenadine has an initial effect similar to cetirizine in suppressing a histamine-induced wheal for the first 4 hours, but cetirizine maintains the same degree of suppression for 24 hours, whereas the suppressive effect of fexofenadine, at both the 120- and 180-mg doses, decreases by 24 hours,[17] which indicates that twice daily administration of fexofenadine may be more effective than once daily for some patients as it was initially approved.

Based on the evidence, cetirizine (whether as the racemate or its active enantiomer alone, levocetirizine) is the antihistamine most likely to be effective for common problems, such as allergic rhinitis and chronic urticaria. For the occasional patient who experiences persistent drowsiness or other adverse effect from cetirizine, fexofenadine provides an agent with no apparent central nervous system (CNS) effect. It is noteworthy that fexofenadine is transported into the systemic circulation by organic anion–transporting polypeptides. Fexofenadine is removed from the CNS by the same mechanism, which explains why it has no CNS effect, even at higher doses. In contrast, diphenhydramine, the least potent antihistamine is available in nonprescription medications as an aid to sleep because of its sedative effect. A single 50-mg dose of diphenhydramine and the legal limit of alcohol had effects similar to alcohol in performance when using a driving simulator.[18] However, diphenhydramine had no measurable effect on 8–10-year-old school children who were given two 25-mg doses before performance testing compared with loratadine or placebo.[19]

Because the anticholinergic effect of many antihistamines can be demonstrated, it is speculated that the anticholinergic effect provides clinical benefit by drying nasal secretions. *In vitro* and *in vivo* anticholinergic effects for various antihistamines have been examined.[20] Some degree of anticholinergic effect, although much less than from atropine, was seen for the antihistamines, cyproheptadine, promethazine, desloratadine, diphenhydramine, loratadine, chlorpheniramine, hydroxyzine, and pyrilamine. Cetirizine and fexofenadine had no detectable anticholinergic effect. It is not apparent that the presence of measurable anticholinergic effect in some antihistamines has any important clinical benefit or concerning clinical adverse effect.

An anticholinergic product, ipratropium, is not an OTC medication but is uniquely effective at stopping nasal secretions. First described for the chronic rhinorrhea of "skier's nose,"[21] it is useful for chronic rhinorrhea that can persist after a common cold or for chronic nonspecific rhinorrhea. It does not improve nasal con-

gestion or sneezing, or increase nasal air flow. Adverse effects can be cessation of salivation if overused.

Decongestants

The purpose of a decongestant is to decrease nasal congestion and decrease nasal airway resistance to improve air flow through the nose. There are two classes of medications that decrease nasal airway congestion. The α-1 adrenergic agonists cause vasoconstriction of the capillaries in the nasal mucosa. Such vasoconstriction decreases blood flow through the nasal mucosa and results in shrinkage of the tissue. Topical corticosteroids may have a topical vasoconstrictor effect as well as decrease inflammation in the nasal mucosa, which results in shrinking of the swollen congested nasal mucosa. Topical corticosteroids also decrease mediator release.

Oxymetazoline is an α-1 adrenergic agonist that, when applied topically in the nose, causes rapid vasoconstriction and, consequently, decreases the volume of the nasal mucosa, thereby decreasing nasal congestion and increasing air flow. It is marketed as Afrin (Bayer, Whippany, NJ) but is readily available generically from multiple sources. When used regularly, it eventually causes rebound nasal congestion, which results in severe nasal congestion until it is used again. This is known as rhinitis medicamentosa, the avoidance of which requires that oxymetazoline be limited to no more than ~3 days of continuous usage.[22] Phenylephrine applied topically to the nose has a similar decongestant effect but with a much shorter duration of action. It can be useful for diagnostic purposes to quickly assess whether nasal obstruction is due to mucosal congestion. If there is no improvement of nasal congestion within 10–15 minutes, then an anatomic obstruction, such as choanal stenosis or adenoidal hypertrophy, should be suspected and evaluated. The use of topical decongestants should be avoided in patients with chronic rhinitis because the long-term use has a substantial risk of causing rhinitis medicamentosa. However, safe and effective treatment is possible for nasal congestion due to a viral respiratory infection. There then is little risk of rhinitis medicamentosa when used for the short term due to a cold.

Pseudoephedrine and phenylephrine are α-1 adrenergic agonists marketed as oral decongestants. Oral pseudoephedrine has a measurable but modest effect in decreasing nasal airway resistance and is sold without a prescription but behind the pharmacy counter as a single ingredient and in combination products.[23] Phenylephrine was eventually substituted for pseudoephedrine in oral OTC preparations sold in front of the counter of pharmacies, convenience stores, and grocery stores because of the illicit production of methamphetamine from pseudoephedrine. Unlike pseudoephedrine, which is well absorbed orally, oral phenylephrine is inactivated in the gut and during the first pass through the liver, and, consequently, is poorly bioavailable.[24] A small statistically significant effect on nasal airway resistance was calculated in one meta-analysis of a single dose of phenylephrine in patients with nasal congestion from a common cold[25] but not in a second study that used a more appropriate statistical analysis.[26] No clinical decongestant effect was seen during multiple daily doses in patients with nasal congestion from seasonal allergic rhinitis, even in doses up to 40 mg, four times the FDA-approved OTC dose.[27]

Nasal corticosteroid sprays (also known as intranasal corticosteroids) are highly effective at decreasing inflammation in the nasal mucosa, thereby decreasing congestion and improving nasal air flow. Also, they decrease the release of mediators that cause sneezing, nasal itching, and rhinorrhea. They are the preferred agents for maintenance therapy of persistent nasal congestion and are highly effective for allergic rhinitis.[28] Their maximum effect can be slow, so sometimes initial treatment with oxymetazoline is of value to rapidly shrink severely congested and swollen mucous membrane for the topical corticosteroids to be effectively delivered. Multiple liquid sprays, including triamcinolone (Nasacort, Sanofi-aventis, Bridgewater, NJ), budesonide (Rhinocort, McNeil, Fort Washington, PA), fluticasone propionate (Flonase, Sanofi-aventis, Bridgewater, NJ), and fluticasone furoate (Flonase Sensimist, GSK, Triangle Park, North Carolina) have become available OTC without prescription. Careful instruction for delivery of the liquid nasal spray is important because intuitive use tends not to deliver medication throughout the nasal cavity (Fig. 4). Two dry powder sprays that contain beclomethasone and ciclesonide remain prescription items; some patients may prefer that delivery over the liquid sprays. For some patients, administering the dose of any of these products twice rather than once daily may provide greater efficacy at the initiation of therapy or even later if needed.[29]

Mucolytics

Guaifenesin, formerly known as glyceryl guaiacolate, is in OTC preparations as an alleged mucolytic, with such common names as Robitussin (Pfizer, New York, NY) and Mucinex (Reckitt Benckiser, Parsippany, NJ). In the FDA-approved OTC dose, this drug neither thins sputum nor decreases sputum volume.[30] In a randomized, double-blind study, patients were dosed with either 1200 mg of extended-release guaifenesin ($n = 188$) or placebo ($n = 190$) every 12 hours for 7 days. Efficacy was assessed by using subjective measures, including the Daily Cough and Phlegm Diary, the Spontaneous Symptom Severity Assessment, and

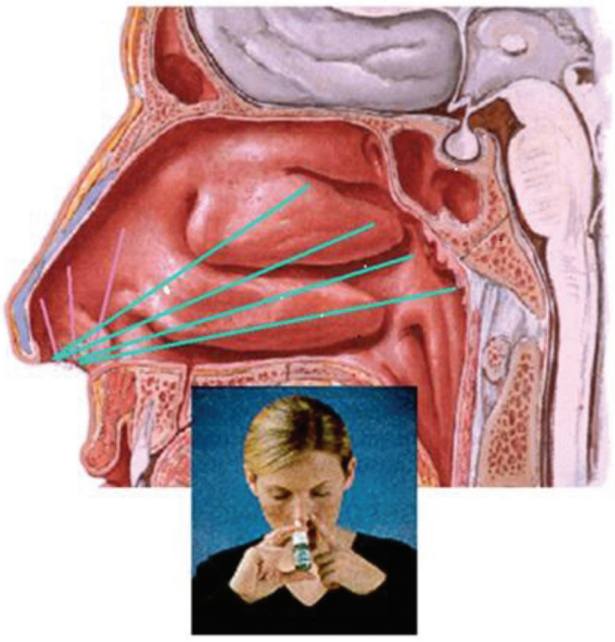

Figure 4. *A lateral view of the nasal cavity, illustrating that the delivery of aerosol to the nasal cavity should be directed so that the whole nasal cavity is reached; intuitive delivery up the nose reaches little of the area where swelling and congestion and occur.*

the Wisconsin Upper Respiratory Symptom Survey. No statistically significant difference was seen between use of guaifenesin and placebo.[31] No other study seems to have demonstrated clinical benefit from guaifenesin, although one small study of adults with sputum-producing cough reported a significantly greater number of respondents who perceived thinning of mucous than those who received a placebo but without any decrease in mucus content and no effect on cough.[32]

Antitussives

Dextromethorphan is in nonprescription preparations as an antitussive. Its efficacy has been compared with placebo and honey in children ages 2 to 18 years.[33] The honey and dextromethorphan were blinded.[33] Dextromethorphan was little better than placebo, whereas honey provided the greatest benefit (Fig. 5).[33,34] Data on the various products that combine dextromethorphan with guaifenesin or an antihistamine are unlikely to have significantly more antitussive effect than dextromethorphan alone. Whether higher doses might have more antitussive effect is not likely to be examined because CNS toxicity occurs at high doses of dextromethorphan, especially in poor metabolizers, because of a deficiency in cytochrome P_{450}2D6.[35] Skepticism regarding the value of nonprescription OTC medications for acute cough has also been published in a Cochrane Review.[36]

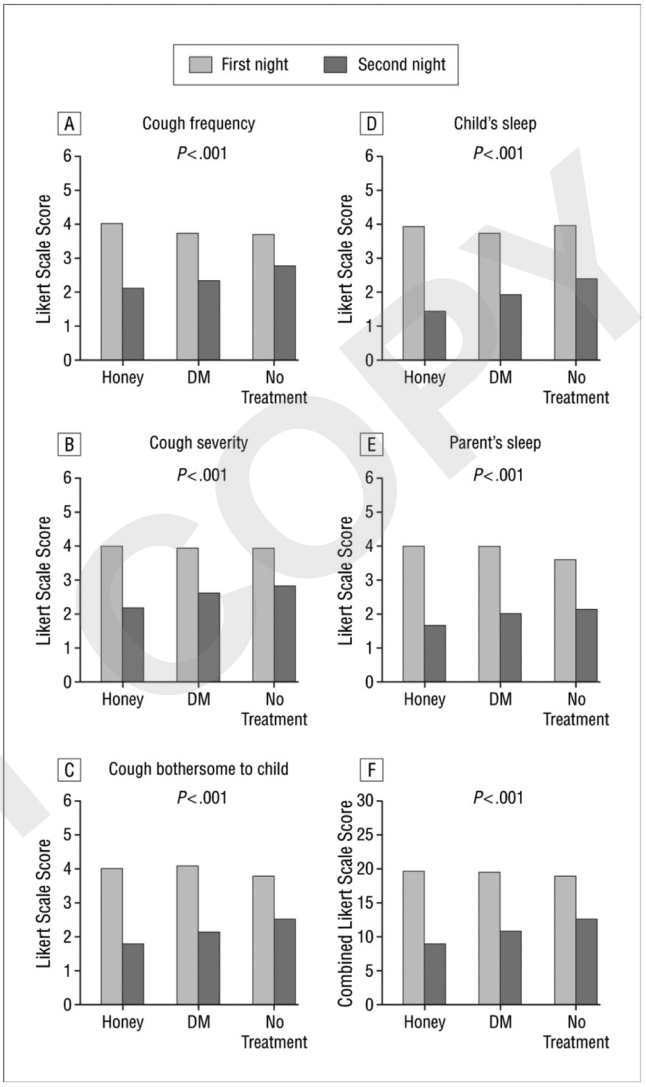

Figure 5. *A comparison of the effect of honey, dextromethorphan (DM), and no treatment on (A) cough frequency, (B) cough severity, (C) the cough being bothersome to the child, (D) the child's sleep, (E) the parent's sleep, and (F) the combined symptom score (from Ref. 33).*

Ophthalmic Products for Allergic Conjunctivitis

Red itchy eyes are commonly associated with nasal allergy. Although oral antihistamines and nasal corticosteroids may provide some benefit for allergic conjunctivitis, they may not be sufficient during the peak of a pollen season or other environmental situations in which allergic exposure is increased. Eye drops that contain an α-1 adrenergic agonist vasoconstrictor, naphazoline or tetrahydrozoline, with and without the antihistamine, pheniramine (*e.g.,* Visine, Visine A, Johnson & Johnson, Fort Worth, TX; Naphcon, Naphcon A, Alcon, Fort Worth, TX; Opcon A, Bausch & Lomb, Bridgewater Township, NJ), have long been available OTC. The rationale for the adrenergic vasoconstrictor is to provide rapid treatment for conjuncti-

val vascular injection. Ketotifen (*e.g.*, Zyrtec or Zaditor, Alcon, Fort Worth, TX) is an antihistamine with mast cell stabilizing properties available OTC for allergic conjunctivitis. Some products may be more comfortable to use, and some may be longer acting than others. Although all topical antihistamines may relieve symptoms of allergic conjunctivitis, there are few data that compare these alternatives.[37]

Mast Cell Stabilizer

Intranasal cromolyn (NasalCrom, Teva, North Wales, PA) is available OTC for the treatment of seasonal allergic rhinitis. It requires administration 3–4 times a day and is less effective than nasal corticosteroids.[38]

Chicken Soup

Chicken soup has been a traditional treatment for the respiratory symptoms of viral colds. When studied, it transiently increased nasal mucus velocity[39] and inhibits its neutrophil chemotaxis *in vitro*.[40] Beyond subjective impressions and traditional feel-better belief, there is no documentation of clinical benefit.

CONCLUSION

OTC medications of value include antihistamines for allergic rhinitis and hives, with cetirizine and fexofenadine preferred because of their efficacy and minimal risk of adverse effects. Diphenhydramine has the least relative potency. Topical nasal corticosteroids are the most effective OTC agents for persistent nasal congestion and other symptoms of allergic rhinitis, with oxymetazoline effective for short-term quick relief for nasal congestion. There were no evidence-based OTC mucolytics, (also commonly called "expectorants") or antitussives likely to be of clinical value.

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