Cochrane for Clinicians

Putting Evidence Into Practice

Oral Antihistamine/Analgesic/Decongestant Combinations for the Common Cold

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Author disclosure: No relevant financial relationships.

Clinical Question

Are over-the-counter formulas containing antihistamines, analgesics, and/or decongestants effective in treating symptoms of the common cold?

Evidence-Based Answer

Antihistamine/analgesic/decongestant combinations have some general benefit in adults and older children. However, these benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.[1] (Strength of Recommendation: B, inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

The common cold is an umbrella term for a wide range of noninfluenza viral respiratory tract infections characterized by nasal congestion, rhinorrhea, cough, sore throat, and sneezing. Although symptoms typically self-resolve within one to two weeks, patients seeking treatment account for approximately 110 million physician visits and 23.2 million physician telephone calls in the United States each year.[2] Although there is no cure, treatment options for cold symptoms are available, including combinations of analgesics for sore throat, decongestants for rhinorrhea, and antihistamines for coughing and sneezing. The authors of this review evaluated the effectiveness of these interventions.

This Cochrane review included 30 randomized trials involving 6,304 participants in the United States, Australia, Europe, and South America.[1] The control intervention was placebo in 26 trials and an active substance (acetaminophen, chlorphenindione plus phenylpropanolamine plus belladonna, or diphenhydramine [Benadryl]) in five trials. There were notable differences in study design, participants, interventions, and outcomes. Children participated in only nine of the trials. Three trials included children six months to five years of age, and six trials included children two years to 16 years of age. All four medication combinations demonstrated a general benefit in adults and children older than six years.

Six trials investigating oral antihistamine/decongestant combinations (n = 565) could be pooled into a meta-analysis; outcomes were usually physician or researcher judgments about treatment effectiveness. The authors concluded that this treatment combination had an overall beneficial effect (number needed to treat [NNT] for one additional participant to judge the intervention as beneficial = 4; 95% CI, 3 to 5; moderate-certainty evidence). On the final evaluation day (three to 10 days of follow-up), more patients in the treatment group were judged to have had a favorable response (70% vs. 55% in the placebo group); however, the antihistamine/decongestant group also experienced more adverse effects than the placebo group (31% vs. 24%).

Four trials evaluated antihistamine/analgesic combinations, including two that reported on global effectiveness; data could not be pooled because one of the trials used an active control. In the remaining trial that provided data on global effectiveness, the proportion of participants who were completely cured at the end of the trial (six days) was 70% with treatment vs. 43% with control (ascorbic acid), with an NNT of 7 (95% CI, 5 to 13; n = 582; moderate-certainty evidence). The antihistamine/analgesic group did not experience notably more adverse effects compared with placebo.

Seven trials evaluated analgesic/decongestant combinations; one trial (n = 181) demonstrated that treatment was beneficial in subjective global effectiveness (i.e., a patient's response to the question, "On the whole, do you think the tablets have helped you?"; odds ratio [OR] = 0.28; 95% CI, 0.15 to 0.52; moderate-certainty evidence). Six trials reported one or more adverse effects, with more patients who took an analgesic/decongestant combination experiencing dizziness or lightheadedness (number needed to harm = 18; 95% CI, 9 to 59; n = 1,797) compared with the control group.

Of the six trials that evaluated a combination of antihistamine, analgesic, and decongestant, five trials reported on global effectiveness; two studies in adults could be pooled (n = 548). More participants reported the treatment as beneficial when measured the morning after taking an evening dose (OR = 0.47; 95% CI, 0.33 to 0.67; NNT = 6; 95% CI, 4 to 10; low-certainty evidence). However, when asked on days 3 and 5, participants reported that treatment provided no notable benefit.

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, assistant medical editor.

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CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 241.

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This review included several studies from the 1980s and earlier; it was limited by a lack of trials investigating the effectiveness of individual monotherapies and instead focused on the potential benefit of combination products to treat the common cold. Additionally, it was unclear whether participants were recruited or sought care for common cold symptoms. Some trials did not report adverse effects, which raises concern that adverse effects were underestimated.

The U.S. Food and Drug Administration advises against the use of over-the-counter cough and cold medications in children younger than two years and recommends caution when using in children two years or older.[3] However, the American Academy of Pediatrics advises against the use of these medications in children younger than four years.[4] An American College of Chest Physicians consensus expert panel in 2017 recommended against the use of cough medications in adults and children until more convincing evidence is available.[5]

This review supports a modest benefit of combination medications for the common cold in older children and adults, but further high-quality studies are needed to provide additional support for their use. Physicians should counsel their patients on the self-limited nature of these illnesses and explain that, despite the over-the-counter availability of these medications, the modest potential for benefit must be balanced against the risk of adverse effects.

The practice recommendations in this activity are available at https://www.cochrane.org/CD004976.

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Lamotrigine in the Maintenance Treatment of Bipolar Disorder

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Clinical Question

Is lamotrigine (Lamictal) as effective and safe as lithium for the maintenance treatment of bipolar disorder?

Evidence-Based Answer

Compared with placebo, lamotrigine reduces the recurrence of manic symptoms at one year and the need for additional psychotropics necessitated by worsening clinical symptoms. (Strength of Recommendation [SOR]: B, inconsistent or limited-quality patient-oriented evidence.) The adverse effect profile of lamotrigine is similar to that of placebo.[1] (SOR: B, inconsistent or limited-quality patient-oriented evidence.)

Compared with lithium, lamotrigine is similarly effective at treating recurrences of depressive episodes and any episode requiring additional psychotropic therapy, but it is less effective at reducing the recurrence of manic episodes at one year. (SOR: B, inconsistent or limited-quality patient-oriented evidence.) Patients using lamotrigine have fewer reported adverse effects and withdrawals from treatment compared with those using lithium.[1] (SOR: A, consistent, good-quality patient-oriented evidence.)

Practice Pointers

Worldwide, the prevalence of bipolar disorder is 2.4%. People with bipolar disorder are at increased risk of suicide compared with individuals who have other types of mental illness.[2,3] Lithium has historically been the standard maintenance treatment for bipolar disorder. The authors of this review studied the effectiveness and adverse effect profile of lamotrigine compared with placebo or lithium.

This Cochrane review involved 11 randomized controlled trials and 2,314 participants.[1] Studies were included if lamotrigine was used as monotherapy, and daily dosages ranged from 100 mg to 500 mg. Among the studies that provided location, most occurred in the United States and other high-income countries. The primary outcomes were manic episodes (defined as a score of 15 or

more on the Young Mania Rating Scale), depressive episodes (defined as a score of 15 or more on the Montgomery-Åsberg Depression Rating Scale or 14 or more on the Hamilton Depression Rating Scale), worsening clinical symptoms requiring an additional psychiatric medication, active suicidal behavior, withdrawal from treatment for any reason, and adverse effects. The authors attempted to study hospitalizations for any mood episodes, but none of the studies reported this outcome.

Compared with placebo, lamotrigine was more effective at reducing the recurrence of manic episodes at one year (number needed to treat [NNT] = 8; 95% CI, 6 to 17). Lamotrigine was also more effective than placebo at reducing clinical symptoms requiring additional psychotropic medication (NNT = 11; 95% CI, 6 to 56). No differences were noted in the recurrence of depressive episodes at one year or in short-term (less than six months) or long-term (six to 12 months) adverse effects in patients treated with lamotrigine compared with placebo. Fewer study participants receiving lamotrigine stopped taking their medication after six to 12 months of treatment (relative risk = 0.88; 95% CI, 0.78 to 0.99).

Among the effectiveness outcomes studied, lamotrigine and lithium had a similar recurrence of depressive symptoms, recurrence of clinical symptoms requiring additional psychotropic therapy, recurrence of manic symptoms using the Young Mania Rating Scale, and active suicidal behavior. However, lamotrigine was less effective in reducing the recurrence of manic episodes at one year among studies using an assessor's judgment instead of a rating scale. Lamotrigine had lower rates of adverse effects after six to 12 months of treatment compared with lithium. Although the review did not describe which specific adverse effects were reported, common adverse effects of lithium include cognitive slowing, diabetes insipidus, diarrhea, hypothyroidism, nausea, polyuria, sedation, thirst, tremor, and weight gain. This review found that rates of adverse effects were similar between the lamotrigine and placebo groups; common adverse effects of lamotrigine included nausea, dizziness, skin rash, dry mouth, pancytopenia, leukopenia, and thrombocytopenia.[4]

Lamotrigine is an anticonvulsant approved by the U.S. Food and Drug Administration for the maintenance treatment of bipolar disorder. It is not effective for treating acute bipolar mania or hypomania. Given the reduced adverse effect profile compared with lithium, lamotrigine may be an appropriate monotherapy during the maintenance phase of bipolar disorder. When initiating lamotrigine, physicians should slowly increase the dosage to reduce the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. The recommended starting dosage is 25 mg by mouth daily; the dosage may be titrated up over six weeks to a maintenance dosage. If a rash develops, the patient should be advised to stop treatment immediately.[4]

Editor's Note: The NNTs and their corresponding CIs reported in this Cochrane for Clinicians were calculated by the author based on raw data provided in the original Cochrane review.

Dr. Salisbury-Afshar is a contributing editor for *AFP*.

The practice recommendations in this activity are available at https://www.cochrane.org/CD013575.

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