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Month/Year of Review: May 2013
PDL Classes: Cough and Cold

Date of Last Review: May 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Current Preferred Agents: NONE. Acute Upper Respiratory Infections and Common Cold are below the line on the OHP prioritized list.
- Current Non-Preferred Agents: DIPHENHYDRAMINE, PSEUDOEPHEDRINE, CODEINE, CHLORPHENIRAMINE, DOXYLAMINE, PROMETHAZINE, HYDROXYZINE, GUAIFENESIN, NAPHAZOLINE, OXYMETAZOLINE, PHENYLEPHRINE, BROMPHENIRAMINE, CLEMASTINE, DEXTROMETHORPHAN

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Do not cover

Methods:

A Medline OVID search was conducted with the following search terms: diphenhydramine, pseudoephedrine, codeine, chlorpheniramine, doxylamine, promethazine, hydroxyzine, guaifenesin, homatropine, scopolamine, phenylephrine, brompheniramine, clemastine, dextromethorphan, decongestant, expectorant, antihistamine, antitussive, cough, cold, rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, adenovirus, enterovirus, influenza, sore throat, congestion, sneezing, and fever. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week 2 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials:

A total of 67 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Shadkam[1] et al conducted a study comparing the effect of honey, diphenhydramine, dextromethorphan or placebo in relieving nighttime coughing and improving sleep quality in young children with an upper respiratory infection. One hundred-sixty children aged 2 to 5 years old were randomized to one of four treatment groups for a single night intervention. Parents filled out a questionnaire before and after the intervention scoring the severity and frequency of their child's cough, as well the quality of sleep. The mean score for all variables after all four interventions was significantly improved. There was no significant difference between diphenhydramine and dextromethorphan in cough and sleep improvement. This was a low quality study with very little information provided on baseline characteristics, randomization, blinding or allocation concealment.

Eskiizmir[2] et al compared oxymetazoline and xylometazoline to relieve nasal congestion. Relief was measured by airway resistance, nasal airflow, and cross-sectional area of the nasal cavity. Thirty adults were randomized to one of the nasal decongestants or a placebo saline solution. Patients administered a spray to each nostril. Improvement in resistance and airflow were measured after one hour by an analyst blinded to treatment selection. Both oxymetazoline and

xylometazoline significantly improved airway resistance and nasal airflow compared with placebo; however, compared with each other, there was no statistical difference between the two nasal decongestants.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
No new safety alerts were found, but safety labeling changes were added to codeine[3] and a safety warning was issued for over-the-counter ophthalmic and nasal decongestants[4]. In February 2013, the FDA added a Black Box Warning to codeine to restrict use in children for post-operative pain. Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine following a tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine causing fatal amounts of morphine in the body. The Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label were also updated with this information.

In October 2012, the FDA released a warning concerning the accidental swallowing by children of ophthalmic and nasal decongestants. The eye drops and nasal sprays involved contain the active ingredients tetrahydrozoline, oxymetazoline, or naphazoline and are sold under various brand, generic and store brand names. The children involved (all aged five or younger) experienced serious events requiring hospitalization such as coma, decreased heart rate, decreased breathing, and sedation after ingestion of less than five milliliters. Because these medications are usually not packaged as child-proof, the FDA advises consumers to keep any ophthalmic or nasal products out of reach of children. If ingested, the FDA advises parents contact the toll-free Poison Hotline and seek emergency medical attention immediately.

These warnings are following the 2008 FDA recommendation that these drugs not be used to treat infants and children under 2 years of age because serious and potentially life-threatening side effects can occur. The FDA has yet to complete its safety analysis of these medications in children age 2 to 11. However, many regulatory agencies in other countries such as Australia, New Zealand and the UK have made recommendations that they not be used to treat children under 6 years of age.

New Systematic Reviews:
Two new Cochrane Collaboration systematic reviews were identified. Please see Appendix 2 for the full abstracts.

De Sutter[5] et al reviewed over the counter cold medicine combinations. The trials included in the review were of poor quality with major differences in subjects, interventions, and outcomes making it difficult to pool all results. Combinations examined were antihistamine-analgesic, antihistamine-decongestant, decongestant-analgesic, and antihistamine-analgesic-decongestant. For all ingredient combinations, the reported outcome was global effectiveness described as the odds of treatment failure compared with placebo. For antihistamine-decongestant combinations, six trials were analyzed. The odds ratio of treatment failure was 0.27 (95% CI 0.15 to 0.50), with a number needed to treat (NNT) for an additional benefit of 4. For the antihistamine-analgesic combination medications, one trial was included (N=582); the odds ratio was 0.33 (95% CI 0.23 to 0.46) and the NNT was 6.67. One decongestant-analgesic combination trial was included (OR 0.28; 95% CI 0.15 to 0.52) with a NNT of 4. Two trials pooled with antihistamine-analgesic-decongestant combinations had an OR of 0.47 (95% CI 0.33 to 0.67) and NNT of 5.6.

Smith[6] et al examined the effectiveness of over-the-counter medications in suppressing cough due to upper respiratory infections for adults and children. Twenty-six trials of antitussives, expectorants, mucolytics, antihistamine-decongestants, and antihistamines were included. Relief or reduction in cough was the reported outcome with all results compared to placebo. Results were not pooled and quantified due to the limited number of trials in each group. Overall, the studies were of poor quality and showed conflicting evidence. In total, 11 of the 26 trials showed a positive result, while the other 15 showed no difference between active treatment and placebo. For children: studies showed

antitussives, antihistamines, and antihistamine-decongestant combinations were no more effective than placebo. For adults: antitussives, expectorants, and antihistamine-decongestant combination trials had variable results. A single mucolytic trial showed reduced cough frequency and symptom scores.

Guidelines:
No new or updated guidelines were identified.

Recommendations:

- No further research or review needed at this time.
- Make this a PDL class.
- Prefer these GSN's: Guaifenesin liquid 100mg/5ml, guafenesin/dextromethorphan syrump, guafenesin/codeine phosphate liquid, psedoephedrine HCL tablets 30mg and 60mg
- Make benzoate capsules as a preferred alternative to Mucinex tablets.

References:

1. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A Comparison of the Effect of Honey, Dextromethorphan, and Diphenhydramine on Nightly Cough and Sleep Quality in Children and Their Parents. *The Journal of Alternative and Complementary Medicine*. 2010;16(7):787–793.

2. Eskiizmir G, Hirçin Z, Özyurt B, Ünlü H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. *European Journal of Clinical Pharmacology*. 2010;67(1):19–23.

3. Drug Safety and Availability > FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm. Accessed March 5, 2013.

4. Drug Safety and Availability > FDA Drug Safety Communication: Serious adverse events from accidental ingestion by children of over-the-counter eye drops and nasal sprays. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm325257.htm. Accessed March 5, 2013.

5. De Sutter AI, Van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. In: The Cochrane Collaboration, De Sutter AI, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD004976.pub3. Accessed March 11, 2013.

6. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. In: The Cochrane Collaboration, Smith SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD001831.pub4. Accessed March 17, 2013.

Appendix 1
Randomized Control Trials

Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A Comparison of the Effect of Honey, Dextromethorphan, and Diphenhydramine on Nightly Cough and Sleep Quality in Children and Their Parents. *The Journal of Alternative and Complementary Medicine*. 2010;16(7):787–793.

OBJECTIVES: Coughing is a prevalent symptom of upper respiratory infections (URIs) that cause disturbance in the sleep of children and their parents. There is as yet no reliable treatment to control URIs and their related cough; however, drugs such as dextromethorphan (DM) and diphenhydramine (DPH) are now mainly used in the world. The aim of this study is to compare the effect of honey, DM, and DPH on the nightly cough and sleep quality of children and their parents. DESIGN: This was a clinical trial study in which 139 children aged 24-60 months suffering from coughing due to URIs were selected and assigned randomly to 4 groups. The first group received honey (HG), the second one DM (DMG), the third DPH (DPHG), but the fourth group or control group (CG) was assigned to a supportive treatment. OUTCOME MEASURES: After approximately a 24-hour intervention, the 4 groups were reexamined and their cough frequency, cough severity, and sleep quality in children and their parents were recorded by using the questionnaire with Likert-type questions. RESULTS: The mean of cough frequency score HG is 4.09 +/- 0.72 and 1.93 +/- 0.65 before and after the intervention, respectively, while these figures for the CG are 4.11 +/- 0.78 and 3.11 +/- 0.57, respectively. After the intervention, the difference of the mean score of the variables in all groups became statistically significant. The mean score of all variables in HG has stood significantly higher than those in other groups. There is also a significant relationship between the DMG and CG groups, even though there is no statistically difference between DMG and DPHG groups. CONCLUSIONS: The result of the study demonstrated that receiving a 2.5-mL dose of honey before sleep has a more alleviating effect on URIs-induced cough compared with DM and DPH doses.

Eskiizmir G, Hirçin Z, Özyurt B, Ünlü H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. *European Journal of Clinical Pharmacology*. 2010;67(1):19–23.

BACKGROUND: Oxymetazoline and xylometazoline are locally effective and direct acting drugs that relieve nasal congestion. The aim of this study was to objectively determine and compare the decongestive effects of oxymetazoline and xylometazoline in healthy subjects. METHODS: The study population comprised thirty healthy adults. All subjects underwent active anterior rhinomanometry (AARhm) and acoustic rhinometry (AR) tests following the application of oxymetazoline, xylometazoline, or placebo (physiological saline). The change in nasal resistance, nasal airflow, and different cross-sectional areas (CSAs) of the nasal cavity in the subjects were examined for each solution separately. The measurements were obtained over a 1-h period (baseline and 1, 15, 30, and 60 min post-dosing). All results were analyzed using the Kruskal-Wallis test and the Mann-Whitney U test. RESULTS: A total of 6,300 measurements of AARhm and AR were obtained. The application of placebo did not cause a statistically significant change in nasal resistance, nasal airflow, and CSAs (CSA1, 2, and 3, respectively) of the nasal cavity. In contrast, statistically significant changes in nasal resistance (inspiration $p = 0.000$ and $p = 0.004$; expiration $p = 0.000$ and $p = 0.000$), nasal airflow (inspiration $p = 0.000$ and $p = 0.004$; expiration $p = 0.000$ and $p = 0.000$), and CSAs of the nasal cavity (CSA2 $p = 0.000$ and $p = 0.000$, CSA3 $p = 0.000$ and $p = 0.00$), with the exception of CSA1 ($p = 0.982$ and $p = 0.994$), were obtained after the application of oxymetazoline and xylometazoline. A comparison of oxymetazoline and xylometazoline based on nasal resistance, nasal airflow, and CSAs of the nasal cavity demonstrated no statistically significant difference, except for CSA3. CONCLUSION: Oxymetazoline and xylometazoline are fast-acting and potent topical decongestants that have similar decongestive effects.

Appendix 2
Systematic Reviews

De Sutter AI, Van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. In: The Cochrane Collaboration, De Sutter AI, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD004976.pub3. Accessed March 11, 2013.

BACKGROUND: Although combination formulas containing antihistamines, decongestants and/or analgesics are sold over-the-counter (OTC) in large quantities for the common cold, the evidence of effectiveness is limited. OBJECTIVES: To assess the effectiveness of antihistamine-decongestant-analgesic combinations in reducing the duration and alleviating the symptoms of the common cold in adults and children.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, OLDMEDLINE (1953 to 1965), MEDLINE (1966 to November Week 3, 2011) and EMBASE (1990 to December 2011).

SELECTION CRITERIA: Randomised controlled trials (RCTs) investigating the effectiveness of antihistamine-decongestant-analgesic combinations compared with placebo, other active treatment (excluding antibiotics) or no treatment in children and adults with the common cold.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted and summarised data on general recovery, nasal obstruction, rhinorrhoea, sneezing, cough and side effects. We categorised the trials according to the active ingredients.

MAIN RESULTS: We included 27 trials (5117 participants) of common cold treatments. Fourteen trials studied antihistamine-decongestant combinations; two antihistamine-analgesic; six analgesic-decongestant; and five antihistamine-analgesic-decongestant combinations. In 21 trials the control intervention was placebo and in six trials an active substance. Reporting of methods in most trials was poor and there were large differences in design, participants, interventions and outcomes. Pooling was only possible for a limited number of studies and outcomes.Antihistamine-decongestant: 12 trials. Eight trials report on global effectiveness, six could be pooled; n = 309 on active treatment, n = 312 placebo) the odds ratio (OR) of treatment failure was 0.27 (95% confidence interval (CI) 0.15 to 0.50); the number needed to treat for an additional beneficial outcome (NNTB) was four (95% CI 3 to 5.6). On the final evaluation day 41% of participants in the placebo group had a favourable response compared to 66% on active treatment. Of the two trials that were not included in the pooling, one showed some global effect, the other showed no effect.Antihistamine-analgesic: three trials. Two reported on global effectiveness, data from one study was presented. (n = 290 on active treatment, n = 292 ascorbic acid). The OR of treatment failure was 0.33 (95% CI 0.23 to 0.46) and the NNTB was 6.67 (95% CI 4.76 to 12.5). After six days of treatment 43% were cured in the control group and 70% in the active treatment group. The second study also showed an effect in favour of active treatment.Analgesic-decongestant: six trials. One trial reported on global effectiveness: 73% benefited compared with 52% in the control group (paracetamol) (OR 0.28, 95% CI 0.15 to 0.52).Antihistamine-analgesic-decongestant: Five trials. Four trials reported on global effectiveness, two could be pooled: global effect reported (less than one severity point on a four or five-point scale) with active treatment (52%) and placebo (34%); the OR of treatment failure was 0.47 (95% CI 0.33 to 0.67) and the NNTB was 5.6 (95% CI 3.8 to 10.2). Two other trials found no beneficial effect. Two other studies did not show any effect.Two studies with antihistamine-decongestant (113 children) could not be pooled. There was no significant effect of the active treatment.Adverse effects: the combination of antihistamine-decongestant had more adverse effects than the control intervention but the difference was not significant: 157/810 (19%) versus 60/477 (13%) participants suffered one or more adverse effects (OR 1.58, 95% CI 0.78 to 3.21). Analgesic-decongestant combinations had significantly more adverse effects than control (OR 1.71, 95% CI 1.23 to 2.37); the number needed to treat for an additional harmful outcome (NNTH) was 14. None of the other two combinations caused significantly more adverse effects. Antihistamine-analgesic: 11/90 with combination suffered one or more adverse effects (12%) versus 9/91 (10%) with control (OR 1.27, 95% CI 0.50 to 3.23). Antihistamine-analgesic-decongestant: in one study 5/224 (2%) suffered adverse effects with active

treatment versus 9/208 (4%) with placebo. Two other trials reported no differences between treatment groups but numbers were not reported.
AUTHORS' CONCLUSIONS: Current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.

Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. In: The Cochrane Collaboration, Smith SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD001831.pub4. Accessed March 17, 2013

BACKGROUND: Acute cough due to upper respiratory tract infection (URTI) is a common symptom. Non-prescription, over-the-counter (OTC) medicines are frequently recommended as a first-line treatment, but there is little evidence as to whether these drugs are effective. OBJECTIVES: To assess the effects of oral OTC cough preparations for acute cough in children and adults.
SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012 Issue 3 which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to March week 1 2012), EMBASE (January 1974 to March 2012), CINAHL (January 2010 to March 2012), LILACS (January 2010 to March 2012), Web of Science (January 2010 to March 2012) and the UK Department of Health National Research Register (March 2010).
SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in ambulatory settings. We considered all cough outcomes and secondary outcomes of interest were adverse effects.
DATA COLLECTION AND ANALYSIS: Two review authors independently screened potentially relevant citations, extracted data and assessed study quality. We performed quantitative analysis where appropriate. MAIN RESULTS: Twenty-six trials (18 in adults, eight in children) involving 4037 people (3421 adults and 616 children) were included. In the adult studies six trials compared antitussives with placebo and had variable results. Two trials compared the expectorant guaifenesin with placebo; one indicated significant benefit whereas the other did not. One trial found that a mucolytic reduced cough frequency and symptom scores. Two studies examined antihistamine-decongestant combinations and found conflicting results. Four studies compared other combinations of drugs with placebo and indicated some benefit in reducing cough symptoms. Three trials found antihistamines were no more effective than placebo in relieving cough symptoms. In the children studies antitussives (two studies), antihistamines (two studies), antihistamine decongestants (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. No studies using expectorants met our inclusion criteria. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group.A minority of studies reported adverse effects and described a low incidence of mainly minor side effects such as nausea, vomiting, headache and drowsiness.
AUTHORS' CONCLUSIONS: There is no good evidence for or against the effectiveness of OTC medicines in acute cough. The results of this review have to be interpreted with caution due to differences in study characteristics and quality. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self care treatments for acute cough.