Class Update: Cough & Cold Preparations

Date of Review: May 2016

Current Status of Preferred Drug List (PDL) Class:
See Appendix 1.

Purpose for Class Update: Four reviews\textsuperscript{1,2,3,4} that help to clarify the available evidence for cough treatments, new United States Food and Drug Administration (FDA) safety warnings on codeine in children,\textsuperscript{5,6} and new treatment guidelines\textsuperscript{7} were published since the last class update.

Research Questions:
1. What is the comparative evidence for available cough and cold treatments (including over-the-counter [OTC]) to reduce the severity or frequency of cough and cold?
2. What is the comparative evidence for available cough and cold treatments for safety?
3. Are there specific populations (e.g. children) where cough and cold treatments are safer or more effective?

Conclusions:
- The evidence is limited by few direct comparisons of the multiple combination products available, heterogeneous cough etiologies and small study sizes.
- There is insufficient evidence for efficacy of expectorants for cough\textsuperscript{1} and expectorants are not recommended for cough secondary to any cause.\textsuperscript{8}
- There is low quality evidence that various opioids (primarily codeine) and dextromethorphan reduce cough severity and cough frequency compared to placebo in patients with unexplained or refractory cough symptoms.\textsuperscript{1} Comparisons of opioids to dextromethorphan had mixed results.\textsuperscript{1} There was insufficient evidence of efficacy for benzonatate or antihistamines.\textsuperscript{1}
- There is low quality evidence that various combinations of antihistamines and decongestants have limited effect on “global effectiveness” for the common cold in adults and older children.\textsuperscript{9} There is no evidence of benefit in young children.\textsuperscript{9}
- There is insufficient comparative safety evidence.
- There is low quality evidence that OTC cough products provide no benefit in children with acute cough.\textsuperscript{2}
- There is low quality evidence of increased risk of death in young children associated with the use over-the-counter (OTC) cough and cold products\textsuperscript{3,10} and codeine cough remedies.\textsuperscript{5}

Recommendations:
- Prefer no expectorants and remove all guaifenesin single ingredient products (HSN = 000271) from the PDL.
- Ensure there is a minimum of 1 product with codeine and 1 with dextromethorphan preferred on the PDL for refractory cough as these have the strongest evidence of efficacy.
- After executive session, also make benzonatate products non-preferred.
Expand the pediatric restriction (children 13 years of age and older) to all cough and cold products (with or without codeine) (Appendix 4). Restrict codeine cough products to adults 19 years of age and older (Appendix 4).

Previous Conclusions:
- The level of comparative evidence of efficacy and safety is insufficient to identify differences between products.
- The overall evidence of efficacy of over-the-counter cough remedies to suppress cough was poor quality and showed conflicting results.
- The FDA recommended cough and cold preparations not be used to treat infants and children under 2 years old in 2008.
- The FDA issued a black box warning restricting the use of codeine in children under 13 for post-operative pain.\
- FDA warns about potential risk of serious side effects of using codeine-containing medicines to treat cough and colds in children under 18 years old.

Previous Recommendations:
- Create a PDL class for Cough & Cold Preparations (May 2013)
- Prefer: guaifenesin liquid 100 mg/5 mL, guaifenesin/dextromethorphan syrup, guaifenesin/codeine phosphate liquid, pseudoephedrine HCL tablets 30 mg and 60 mg, benzonatate capsules (May 2013)
- Mucinex™ made preferred (July 2015).
- Age restriction (<18 years) added to all codeine cough products (July 2015).

Background: Symptomatic treatment of common upper respiratory infections (URI) (Line 617) and rhinitis (Line 564) are not funded diagnoses on the Oregon Health Plan List of Prioritized Services. The Cough & Cold PDL class includes antitussives, expectorants, oral decongestants and combinations of all 3 with or without antihistamines. This class ranked 36 of 110 classes by number of prior authorization (PA) requests during Q1 2016. A total of 29 requests for non-preferred drugs were made (12 approved, 16 denied, 1 cancelled). The most commonly requested product was promethazine-codeine (9 requests) followed by hydrocodone-homatropine (8 requests). All other drugs had 2 or fewer requests. The Codeine Age Limit PA was not yet implemented in Q1-2016.

There is low quality evidence that various combinations of antihistamines and decongestants have limited effect on “global effectiveness” for the common cold in adults and older children. There is no evidence of benefit in young children.

The effectiveness of cough treatments is often evaluated for subjective severity rating and cough frequency. Cough can also be experimentally induced in patients using varying concentrations of inhaled capsaicin to cause 2 – 5 coughs (C2 – C5). This model has been called into question as to its predictive accuracy of disease. It is also recognized there is a significant placebo effect associated with cough treatments for young children.

The American College of Chest Physicians published evidence-based clinical practice guidelines for diagnosis and management of cough in 2006. The recommendations scale was as follows: A-strong; B-moderate; C-weak; D-negative. Acute cough (<3 week) is most frequently associated with the URI, acute bronchitis, allergic rhinitis or community-acquired pneumonia. Cough occurs sub-acutely (3-8 weeks) post-infectiously or with pertussis. Chronic cough (> 8 weeks) in adults is likely secondary to angiotensin-converting enzyme use, smoking, gastroesophageal reflux, asthma, chronic obstructive pulmonary disease, environmental irritant exposure, chronic sinusitis or allergic rhinitis. The primary cause of the cough should be addressed first in each case. Antitussives and expectorants have a very limited role. Antitussives, antihistamines or zinc containing products are not recommended for URI associated cough (Recommendation Grade D). Ipratropium is recommended for cough suppression for URI or chronic bronchitis (Recommendation Grade A). Hydrocodone, dihydrocodeine, codeine or dextromethorphan are recommended for short-term symptomatic relief of cough due to chronic bronchitis in adults.
Hypertonic saline is recommended to increase cough clearance for patients with bronchitis or cystic fibrosis. Expectorants are not recommended for chronic bronchitis (Recommendation Grade D).

Benzonatate is not mentioned in the guidelines.

**Methods:**
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo, was conducted. The Medline search strategy used for this review is available in Appendix 3, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials (RCTs) will be emphasized if evidence is lacking or insufficient from those preferred sources

**New Systematic Reviews:**
There have been 3 high quality systematic reviews or updates of cough treatments and 1 “short-cut review” of the safety of OTC cough and cold preparations published since the last scan in May 2013.

Yancey et al. compared treatments (pharmacologic and nonpharmacologic) for unexplained or refractory cough. The review was commissioned by the Agency for Health Research and Quality. It contained a meta-analysis of the English language medical literature through June 2012. The overall strength of evidence was limited by inconsistent and imprecise results, small numbers of direct comparisons and small studies. Forty-nine studies (n=3067) met inclusion criteria. There were 11 comparisons of opioids (primarily codeine) with placebo with 8 showing the opioid more effective for decreasing cough frequency and cough severity. Standardized mean differences for cough severity for opioids were 0.55 (95% CI, 0.38-0.72) and for rate ratios for cough frequency 0.57 (95% CI, 0.36-0.91). No one opioid was superior to another although codeine had a dose-response improvement. Comparisons of codeine to dextromethorphan were mixed. Six studies of dextromethorphan compared to placebo provided mean difference in cough severity of 0.37 (95% CI, 0.19-0.56) and rate ratios for cough frequency of 0.40 (95% CI, 0.18-0.85). Benzonatate effectiveness was mixed in 3 low quality studies; one placebo-controlled study was negative and 2 studies found it more effective than opioids. Two studies evaluated antihistamines (one of diphenhydramine and one of loratadine) but were limited by extremely small samples (<20). There were 6 negative studies comparing various expectorants (oral N-acetylcysteine, inhaled N-acetylcysteine, bromhexine, ambroxol, inhaled 2-mercaptoethanol sulfonate, narcotine-glycerol) to placebo. One good quality study (n=60) for guaifenesin showed improvement over placebo in a subgroup of patients who produced a high volume of sputum. Only 3 studies address cough in children and none of these evaluated antitussives or expectorants.

Cochrane published an updated review of OTC cough medications for acute cough in children and adults in 2014. The literature was searched through March 2014. The evidence was limited by few trials for each comparison as well as heterogeneous participants, interventions and outcomes such that pooling could not be done. There were 19 adult trials (n=3799) and 10 pediatric trials (n=1036) included. The adult placebo controlled trials included: 2 comparing codeine with non-significant results, 4 comparing dextromethorphan with mixed results, and 3 comparing guaifenesin with mixed results. In the pediatric studies, antitussives, antihistamines, antihistamine-decongestants and antitussive-bronchodilator combinations were no more effective than placebo. Adverse effects were reported in 21 studies with higher rates for those taking antihistamines or dextromethorphan.

Author: Ketchum

Date: May 2016
Cochrane published an updated review of honey for acute cough in children 1 to 18 years old. The search was current through November 2014 and identified 3 RCTs (n=568). The authors conclude honey was better than: no treatment in reducing the frequency of cough (mean difference [MD] -1.05; 95% confidence interval [CI] -1.48 to -0.62; I2 statistic 23%; two studies, 154 participants), placebo at reduction of cough frequency (MD -1.85; 95% CI -3.36 to -0.33; one study, 300 participants) and diphenhydramine in reducing cough frequency (MD -0.57; 95% CI -0.90 to -0.24; one study, 80 participants). Honey was no different than dextromethorphan at reducing cough frequency (MD -0.07; 95% CI -1.07 to 0.94; two studies, 149 participants). Honey should not be given to infants because of their poor immunity against Clostridium botulinum that may be present in honey.

A “short-cut review” identified 3 case-series (n=214) reporting deaths associated with OTC cough and cold preparations in children under the age of 12 years old from 1950 to 2007.

**New Treatment Guidelines:** The American College of Chest Physicians updated treatment guidelines for treatment of unexplained cough in January 2016. The guidelines were based upon a high quality systematic review evaluating the efficacy of treatments on cough severity and frequency for adults and adolescents 12 years or older with chronic cough of more than 8 weeks duration and unexplained after systematic workup. The review included the previously mentioned Yancy et al. The authors concluded the evidence was limited by the heterogeneity of therapeutic interventions with few studies available in each category, inconsistent outcome assessment tools and differing definitions of unexplained cough. The treatment algorithm adds empiric trials of speech therapy and gabapentin as last resort options.

**New FDA Safety Alerts:** The FDA is investigating the safety of codeine containing products to treat cough and cold in children under 18 years old. This was in reaction to the European Medicines Agency recommendation that codeine use is contraindicated in children under 12 years old and is not recommended in older children between 12 and 18 who have breathing problems.

**New FDA Drug Approvals:** No new molecular entities approved by the FDA for cough treatment were identified from 2013 to date.

**New Formulations:** Unable to report because of unclear tracking of over-the-counter formulations on the FDA website.

**Randomized Controlled Trials:**
A total of 30 citations were reviewed from the literature search (Appendix 3). After further review, 25 citations were excluded because the population, intervention or outcomes were not of interest. The search identified 4 recent reviews and 1 new treatment guideline that were included. No RCTs were included.

Author: Ketchum
Date: May 2016
References:


**Appendix 1: Preferred Alternatives:**

<table>
<thead>
<tr>
<th>HSN</th>
<th>Generic Drug Name</th>
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<tbody>
<tr>
<td>001929</td>
<td>Benzonatate</td>
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<tr>
<td>000271</td>
<td>Guaifenesin</td>
</tr>
<tr>
<td>000206</td>
<td>Guaifenesin/Codeine PHOS</td>
</tr>
<tr>
<td>000223</td>
<td>Guaifenesin/D-methorphan HB</td>
</tr>
<tr>
<td>002091</td>
<td>Pseudoephedrine HCL</td>
</tr>
</tbody>
</table>

**Appendix 2: Abstracts of Included Clinical Trials**

No RCTs included in this review
Appendix 3: Medline Search Strategy

Database: Ovid MEDLINE(R) <1946 to April Week 1 2016> Search Strategy:

1 exp Cough/ (13323)
2 exp Antitussive Agents/ (21643)
3 exp Expectorants/ (14917)
4 2 or 3 (36207)
5 1 and 4 (1458)
6 limit 5 to (English language and humans and yr="2013 -Current" and (clinical trial, all or controlled clinical trial or meta analysis or randomized controlled trial or systematic reviews))

30 text results returned

EXCLUDED: INTERVENTION NOT FDA APPROVED

EXCLUDED: INTERVENTION NOT FDA APPROVED

EXCLUDED: OUTCOME NOT OF INTEREST

EXCLUDED: OUTCOME/POPULATION NOT OF INTEREST

EXCLUDED: INTERVENTION NOT FDA APPROVED

EXCLUDED: OUTCOME NOT OF INTEREST
EXCLUDED: OUTCOME NOT OF INTEREST

EXCLUDED: POPULATION NOT OF INTEREST

INCLUDED

EXCLUDED: INTERVENTION NOT OF INTEREST

EXCLUDED: UPDATE WITH NO NEW TRIALS OR CONCLUSIONS

EXCLUDED: POPULATION NOT OF INTEREST

EXCLUDED: POPULATION NOT OF INTEREST

EXCLUDED: OUTCOME/POPULATION NOT OF INTEREST
EXCLUDED: OUTCOME NOT OF INTEREST

EXCLUDED: INTERVENTION NOT FDA APPROVED

EXCLUDED: INTERVENTION NOT FDA APPROVED

EXCLUDED: UPDATE OF PREVIOUS REVIEW- NO NEW STUDIES IDENTIFIED

EXCLUDED: INTERVENTION NOT OF INTEREST

INCLUDED

EXCLUDED: INTERVENTION NOT OF INTEREST

INCLUDED

EXCLUDED: NOT AVAILABLE (INCLUDED IN COCHRANE REVIEW OF OTC ANTITUSSIVES)

EXCLUDED: OUTCOME NOT OF INTEREST

Author: Ketchum  Date: May 2016
EXCLUDED: INTERVENTION NOT OF INTEREST

EXCLUDED: OUTCOME NOT OF INTEREST

EXCLUDED: POPULATION NOT OF INTEREST

EXCLUDED: INTERVENTION NOT OF INTEREST

EXCLUDED: OUTCOME NOT OF INTEREST

EXCLUDED: POPULATION NOT OF INTEREST
Appendix 4: Current Prior Authorization Criteria

Cough and Cold Preparations

Goal(s):
- Limit use of cough and cold preparations to OHP-funded diagnoses.
- Symptomatic treatment of upper respiratory tract infections is not funded by the OHP.

Length of Authorization:
Up to 12 months

Requires PA:
- All drugs (expectorants, antitussives, oral decongestants and combinations) in TC = 16, 17 except those listed below.
- All products for patients under 13 years of age.
- All codeine-containing products for patients under 19 years of age (see Codeine PA criteria).

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

<table>
<thead>
<tr>
<th>HSN</th>
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<tbody>
<tr>
<td>000206</td>
<td>Guaifenesin/codeine</td>
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<tr>
<td>000223</td>
<td>Guaifenesin/Dextromethorphan</td>
</tr>
<tr>
<td>002091</td>
<td>Pseudoephedrine</td>
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</tbody>
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Approval Criteria

1. What diagnosis is being treated? Record ICD10 code.

2. Is the diagnosis an OHP-funded diagnosis? All indications need to be evaluated to see if funded on the Oregon Health Plan list of prioritized services.
   - Yes: Go to #3
   - No: Pass to RPh. Deny; not funded by the OHP.

3. Has the patient tried and failed, or have contraindications to, one of the covered alternatives listed above?
   - Yes: document failure. Approve for up to 1 year.
   - No: Pass to RPh. Deny; cost-effectiveness

P&T Review: 5/16 (KK); 5/13; 2/06
Implementation: TBD; 1/10/08
Author: Ketchum
Date: May 2016
Codeine

**Goal(s):**
- Promote safe use of codeine in pediatric patients for analgesia or cough.

**Length of Authorization:**
Up to 3 days

**Requires PA:**
- All codeine products for patients under 19 years of age

**Covered Alternatives:**
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

## Approval Criteria

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<table>
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<tr>
<td>4. What diagnosis is being treated?</td>
<td>Record ICD10 code.</td>
</tr>
<tr>
<td>5. What is the age of the patient?</td>
<td><strong>Ages 0-12 years:</strong> Pass to RPh. Deny; medical appropriateness</td>
</tr>
<tr>
<td>6. Is the prescription for an OHP-funded condition?</td>
<td><strong>Yes:</strong> Go to #4</td>
</tr>
<tr>
<td>7. Has the patient recently undergone tonsillectomy or adenoidectomy?</td>
<td><strong>Yes:</strong> Pass to RPh. Deny; medical appropriateness</td>
</tr>
<tr>
<td>8. Does the dose exceed 240 mg per day?</td>
<td><strong>Yes:</strong> Pass to RPh. Deny; medical appropriateness</td>
</tr>
</tbody>
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P&T Review: 5/16; 9/15; 7/15
Implementation: TBD; 8/25/15

Author: Ketchum

Date: May 2016