

**Use of Cough Suppressants in Children
Expert Roundtable Meeting
April 27, 2017, 10 AM – 1 PM
FDA White Oak Campus, Silver Spring, MD**

Meeting Purpose

Discuss the experience of health care professionals with the use of cough suppressants in children (<18 years of age), particularly opioid-containing antitussive (OCA) products.

Participants

FDA

John Alexander	Center for Drug Evaluation and Research (CDER)
Jason Bunting	CDER
Grace Chai	CDER
Susan McCune	Office of the Commissioner (OC)
Sally Seymour	CDER
Judy Staffa	CDER
Peter Starke	CDER
Shannon Thor	OC
Theresa Toigo	CDER
Scott Winiiecki	CDER
Lynne Yao	CDER
Rosemary Addy	CDER
George Greeley	CDER
Meshaun Payne	CDER
Denise Pica-Branco	CDER
Jacqueline Yancy	CDER

Health Professional Organizations

Jahn Avarello	American College of Emergency Physicians
Kathleen Brown	American College of Emergency Physicians

Tate Heuer	American Academy of PAs
Brian R. Wingrove	American Academy of PAs
Nick Schilligo	American Osteopathic Association
Scott Cyrus	American Osteopathic Association
Shawna Mudd	National Association Of Pediatric Nurse Practitioners
Millicent Collins	National Association Of Pediatric Nurse Practitioners
Hsiang (Shonna) Yin	NYU School of Medicine
Debra M Boyer	American Thoracic Society
Bridgette Jones (remote)	American Academy of Pediatrics
James Baumberger	American Academy of Pediatrics
Kathleen Neville	American Academy of Pediatrics
Kenneth Lin (remote)	American Academy of Family Physicians
Jan Towers	American Association of Nurse Practitioners
Sheila Heitzig	American Academy of Allergy Asthma and Immunology
Mandel Sher (remote)	American Academy of Allergy Asthma and Immunology
John Oppenheimer (remote)	American College of Chest Physicians (ACCP)

Summary of Discussion

FDA welcomed the representatives of health professional societies and briefly provided an overview of the purpose of the meeting: To obtain information on the use of cough suppressants, particularly opioid cough suppressants in children. FDA clarified that this meeting would not be used to make regulatory decisions, but to help inform a future advisory committee meeting.

FDA Question: What is your experience with the use of cough suppressants in children (<18 years of age), particularly opioid-containing antitussive (OCA) products, and do your organizations have any existing guidelines or recommendations on their use?

Participants distinguished among categories of cough, stating that it is important to distinguish between cough that is productive or non-productive (irritant-causing) and cough that is acute or chronic. Participants emphasized the importance of identifying the underlying cause of cough in determining the appropriate treatment, rather than focusing on cough suppression.

Participants noted that the use of cough suppressants depends on the clinical situation, but that cough should not be suppressed unless it is causing clinical consequences, including, for example:

1. Cough leading to consecutive nights of poor sleep and/or vomiting
2. Cough leading to rib fractures
3. Cough severe enough to lead to hypoxia

Acute and Chronic Cough Treatments

Participants first focused on treatment of acute cough. Overall, participants felt that in the acute setting, if the cough is productive, identification of the cause and treatment of the underlying condition is important. Cough suppressants should not be used, in general, for acute productive cough.

FDA Question: What might be a determining factor that would lead to treating an acute cough and how might they treat it?

Although the discussion at that point was focused on acute cough, the discussion also included treatments used in the setting of chronic cough. Participants included the following therapies for treatment of acute “irritant” cough:

1. Nasal saline
2. Increased humidification
3. Honey
4. Treatment of post-nasal drip (e.g., antihistamines and physical maneuvers)
5. Bronchodilators and both oral and/or inhaled corticosteroids
6. Dextromethorphan, guaifenesin, or benzonatate
7. Treatment of GERD when associated with cough

One expert noted that official guidelines from the American Academy of Chest Physicians recommend that acute cough not be suppressed and also noted that there are no interventions that have been evaluated in controlled studies that have demonstrated effectiveness.

Participants noted that treatment with bronchodilators and corticosteroids may be therapeutic and diagnostic. Participants acknowledged use of bronchodilators for cough, conveying the perception that the bronchodilators and other options listed were viewed as less likely to be harmful.

In addition, although not proven to be effective, some of the participants reported having used benzonatate and dextromethorphan and may treat with albuterol for bronchospasm or with another agent to minimize, but not suppress, the cough as some co-morbidities may be present.

One expert from the American Osteopathic Association described the use of osteopathic manipulative techniques for cough in pediatric patients.

Some of the participants stated that they might also treat acute cough with honey. Participants reiterated that the data indicate that there are no really good medications for treating acute cough with, perhaps, the exception of honey.

Overall, participants stated that for acute cough, the situations when a suppressant might be warranted would be in a setting of pretty significant consequences to the child (i.e. fractured ribs, consecutive nights of no sleep). Under no circumstance would participants treat with an opioid for acute cough.

FDA Request for Clarification: What would be the age cut-off for using codeine or hydrocodone? Specifically, do concerns about using these products apply mainly to younger children, or include adolescents?

Participants indicated that the concerns applied to the entire pediatric age range, and some participants who treat adults suggested that their views on the use of opioid drugs to treat cough extended to adults.

Some participants stated that with respect to adult patients, long-acting hydrocodone may be useful for suppression of chronic cough in some cases, but a new approach (still investigational) would be to use neuromodulators (off label) as they have been observed to work for chronic cough.

Other participants stated that there are few situations in adolescents when codeine might be used (e.g., end of life situations for pain mainly with reduction of cough as an added benefit). Overall, the participants did not see a role for the use hydrocodone or codeine for the use of cough in pediatric patients.

FDA Request for Clarification: Could you expand on the types of agents that could be used for suppression of cough in children, particularly for chronic cough?

Depending on the patient status (in-patient/out-patient) and the underlying cause, different treatments could be given. Some of those treatments include:

- Inhaled and oral corticosteroids
- Lansoprazole if the cough is due to a gastrointestinal issue like GERD
- Anti-histamines
- Warm saline
- Honey
- Camphor
- Vapor rub (except in asthmatics as it may exacerbate their condition)
- Nasal suctioning and clearing

For cases of behavioral or habit cough, participants suggested speech or behavioral therapy.

Participants stated that distinguishing between a wet or dry cough with respect to a chronic cough should be considered. Several participants stated that there are no standard definitions of *chronic cough*, but some have used cough duration of less than or greater than 4 weeks. This is partly based on expected resolution of a viral condition by week 2, or a bacterial condition, like bacterial bronchitis or sinusitis, that may take 3 to 4 weeks to clear.

FDA Request: Could you describe the types of neuromodulators or other products you might use to treat adults with chronic irritant cough?

Examples given included (off-label) use of gabapentin, amitriptyline, pregabalin, and slow-release morphine (available in Europe). One participant stated that the paradigm is switching from chronic coughers to cough hypersensitivities. Thus, the focus has changed to products used for treatment of post-nasal drip, allergic rhinitis, etc.

Overall, participants emphasized that in chronic cough situations, it is extremely important to differentiate between a cough that is productive and an irritant cough. The participants agreed that when the cough is productive, it is important to identify the underlying condition.

Participants discussed how treatment for chronic and acute cough changes based on the age of the patient. Children between 4 and 5 years of age can usually do a lung function test that will allow the physician to determine if asthma is contributing to cough. However, for the younger patient, a trial of albuterol may be given. For older kids (older than 2 years), participants said the treatment for acute or chronic cough includes steroids and albuterol, unless the underlying cause is bacterial, then the treatment would be antibiotics and rest.

The Role of Opioid Cough Suppressants in Children

Participants stated that in general pediatrician office visits, if an opioid is needed for treatment, it should be prescribed by a specialist. However, participants repeated that there is no role for the use of an opioid in treating or suppressing acute cough. Many participants stated that they had never prescribed an opioid for children under 18, except for the extreme conditions mentioned earlier.

FDA Request for Clarification: Are the reasons for not prescribing opioid treatment based on safety or efficacy?

Participants stated that they are concerned about both: the benefits for cough suppression are questionable, and there are concerns about harm from opioid use. Overall, participants agreed that treatment of cough with opioid-containing products was **not** appropriate and that alternative treatments for cough would differ depending on the age of the child.

Participants also expressed the concern that, although they do not prescribe opioids to pediatric patients, there are some practitioners who do prescribe them. Some participants

described pressures from caregivers to treat cough as well as indirect pressure from consumer reviews and ratings published on line.

General Comments and

- Participants agreed about the need for outreach to inform and educate practitioners that prescribing opioids for cough in children is not recommended.
- Some commented that removing the cough treatment indication for opioid products in labeling might help reduce pressure to treat, as described above. Participants noted that removal of the indication might shift the treatment to other cough suppressants like dextromethorphan. There was concern, however, about resistance from some practitioners to removing the cough treatment indication for opioids, even though there are other treatment options.
- Some participants suggested investigating the characteristics of those physicians who prescribe these drugs more often than others.
- Participants supported educating the public and families about the concerns related to using opioids to treat pediatric patients.
- Participants agreed that the availability of non-opioid, cough controlling products approved for children would be of benefit.
- The suggestion was made to review the adverse event profile of alternative agents for chronic cough for comparison to codeine-containing cough products.
- Participants encouraged FDA to include patient and family representatives, urgent care physicians, rural health prescribers, osteopathic practitioners, and representation from other practices in any future public meetings. One AAP representative suggested that the AAP could contact others about future public meetings.

Society/Organizational Recommendations/Guidelines on Treatment of Cough in Children

Participants provided a number of references and policy statements that specifically discuss (and typically discourage) opioid use for treating cough in pediatric patients. Although not exhaustive, the following list contains some of the references discussed during the meeting.

American Academy of Pediatrics. 1997 (Reaffirmed 2006). "Use of codeine- and dextromethorphan-containing cough remedies in children," in AAP Committee on Drugs Policy Statement., *Pediatr.*, 1997, 99:6, pp 918-920. Available at <http://pediatrics.aappublications.org/content/99/6/918.long>. Accessed June 2017.

Chang AB and Glomb WB. 2006. Guideline for evaluating chronic cough in pediatrics: ACCP evidence-based clinical practice guidelines. *Chest*, 2006; 129:260S–283S. Available at <http://journal.publications.chestnet.org/article.aspx?articleid=1084264>. Accessed June 2017.

Gardiner SJ, Chang AB, Marchant JM, and Petsky HL. 2016. Codeine versus placebo for chronic cough in children. Cochrane Database of Systematic Reviews. Published online. DOI: 10.1002/14651858.CD011914.pub2. Available at <http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD011914.pub2/full>. Accessed June 2017.

Green JL, Wang GS, Reynolds KM, Reynolds KM, Banner W, Bond GR et al. 2017. Safety profile of cough and cold medication use in pediatrics. *Pediatrics*. 2017. 139:e20163070. Available at <http://pediatrics.aappublications.org/content/early/2017/05/02/peds.2016-3070>. Accessed June 2017.

Paul IM, Reynolds KM, Kauffman RE, Banner W, et al. Adverse events associated with pediatric exposures to dextromethorphan. *Clin Toxicol (Phila)*. 2017 Jan; 55(1):25-32. doi: 10.1080/15563650.2016.1240803. Epub 2016 Oct 13.

Smith SM, Schroeder K, and Fahey T. 2014. Over-the-counter (OTC) medications for acute cough in children and adults in community settings. Cochrane Database of Systematic Reviews 2014, Issue 11. Available at http://www.cochrane.org/CD001831/ARI_over-the-counter-otc-medications-for-acute-cough-in-children-and-adults-in-community-settings. Accessed June 2017.

Tobias J, Green TP, and Coté CJ. 2016., “Codeine: Time to Say ‘No,’ AAP Clinical Report.,” in AAP Section on Anesthesiology and Pain Medicine, AAP Committee on Drugs, *Pediatr*. 2016;138(4): e20162396. Available At <http://pediatrics.aappublications.org/content/early/2016/09/15/peds.2016-2396.full>. Accessed June 2017.

Vertigan AE, Murad MH, Pringsheim T, Feinstein A, Chang AB, Newcombe PA, et al. 2015. “Somatic Cough Syndrome (Previously Referred to as Psychogenic Cough) and Tic Cough (Previously Referred to as Habit Cough) in Adults and Children,” in CHEST Guideline and Expert Panel Report. *Chest*, 2015; 148 (1): 24 - 31Jul;148(1):24-31. doi. Available at <https://www.ncbi.nlm.nih.gov/pubmed/25856777>. Accessed June 2017.

World Health Organization. Department of Child and Adolescent Health and Development. 2001. Cough and cold remedies for the treatment of acute respiratory infections in young children. Available at http://apps.who.int/iris/bitstream/10665/66856/1/WHO_FCH_CAH_01.02.pdf?ua=1&ua=1. Accessed June 2017.

Yancy WS, McCrory DC, Coeytaux RR, Schmit KM, Kemper AR, Goode A, et al. 2013. Efficacy and tolerability of treatments for chronic cough: a systematic review and meta-analysis. *Chest*, 2013; 144(6):1827–1838. Available at <https://www.ncbi.nlm.nih.gov/pubmed/23928798>. Accessed June 2017.