Effect of Dextromethorphan, Diphenhydramine, and Placebo on Nocturnal Cough and Sleep Quality for Coughing Children and Their Parents

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ABSTRACT. *Objectives.* **To determine whether the commonly used over-the-counter medications dextromethorphan and diphenhydramine are superior to placebo for the treatment of nocturnal cough and sleep difficulty associated with upper respiratory infections and to determine whether parents have improved sleep quality when their children receive the medications when compared with placebo.**

Methods. **Parents of 100 children with upper respiratory infections were questioned to assess the frequency, severity, and bothersome nature of the nocturnal cough. Their answers were recorded on 2 consecutive days, initially on the day of presentation, when no medication had been given the previous evening, and then again on the subsequent day, when either medication or placebo was given before bedtime. Sleep quality for both the child and the parent were also assessed for both nights.**

Results. **For the entire cohort, all outcomes were significantly improved on the second night of the study when either medication or placebo was given. However, neither diphenhydramine nor dextromethorphan produced a superior benefit when compared with placebo for any of the outcomes studied. Insomnia was reported more frequently in those who were given dextromethorphan, and drowsiness was reported more commonly in those who were given diphenhydramine.**

Conclusions. **Diphenhydramine and dextromethorphan are not superior to placebo in providing nocturnal symptom relief for children with cough and sleep difficulty as a result of an upper respiratory infection. Furthermore, the medications given to children do not result in improved quality of sleep for their parents when compared with placebo. Each clinician should consider these findings, the potential for adverse effects, and the individual and cumulative costs of the drugs before recommending them to families.** *Pediatrics* **2004;114:e85–e90. URL: http://www.pediatrics.org/cgi/content/full/114/1/e85;** ***cough, upper respiratory infection, dextromethorphan, diphenhydramine, placebo.***

ABBREVIATIONS. URI, upper respiratory tract infection; DM, dextromethorphan; OTC, over-the-counter; DPH, diphenhydramine; PL, placebo.

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Cough may be the most bothersome symptom for children with upper respiratory tract infections (URIs), and each year results in more ambulatory health care visits than any other symptom in the United States.[1] The use of codeine or dextromethorphan (DM), the most common over-the-counter (OTC) antitussive, for treatment of cough is not supported by the American Academy of Pediatrics, largely because there is a lack of proven benefit and some potential for toxicity and overdose.[2,3] Diphenhydramine (DPH), an OTC antihistamine, is also commonly administered for symptomatic relief in children with URIs.

Cough is particularly vexing at night because it often adversely affects sleep for both ill children and their parents with impact on subsequent daytime activities. Thus, giving their children medications that contain either DM or DPH before bed is often an attempt by parents to improve their own sleep and functioning during the subsequent day.

In this era when health care expenses continue to escalate, consumers spend billions of dollars per year on OTC medications for cough.[4,5] The desire to give or take a medicine commonly outweighs the paucity of sound research on the effect of these drugs or the conditions that require them. Unfortunately, there are no clearly proven therapeutic alternatives.

Although 2 older subjective investigations found DM to be an effective antitussive medication for children with URIs,[6,7] more recent studies have shown it to be no better than placebo (PL) in controlling acute cough.[8–13] Objective assessments of DM in adults with URI also have had conflicting results.[14–16] DPH is generally thought to be ineffective when compared with PL for the treatment of acute cough as a result of URIs,[17–19] but some reports contradict this belief.[20,21] DPH is widely accepted as an effective sedative.[18,22–28] This antihistamine was found to be significantly more sedating than PL in children with the common cold.[18]

The current lack of clarity regarding symptomatic care in children with cough as a result of URIs has created an environment in which many pediatricians prescribe,[29] many Internet sites recommend,[30] and therefore many parents administer cough suppressants or antihistamines to relieve these symptoms.[31] The objective of this trial was to determine whether DM or DPH administered to children with acute cough as a result of URIs subjectively improves noc-

turnal cough when compared with PL. The quality of sleep for both the child and the administering parent were also important outcomes of interest. It was hypothesized that parents would report a greater improvement in symptoms for those who received the active medications than those whose children received PL.

METHODS

From June 2002 through May 2003, patients were recruited from 2 university-affiliated pediatric practices in the Hershey, Pennsylvania, vicinity on presentation for an acute-care visit. Eligible patients were 2 through 18 years of age with cough attributed to URIs. URIs were characterized by the presence of rhinorrhea and cough for ≤7 days' duration. Other symptoms may have included but were not limited to congestion, fever, sore throat, myalgias, and headache. Patients were excluded when they had signs or symptoms of a more treatable disease (eg, asthma, pneumonia, laryngotracheobronchitis, sinusitis) or allergic rhinitis (sneezing, itchy and watery eyes). They also were ineligible when they had a history of reactive airway disease, asthma, chronic lung disease, or allergic rhinitis. Patients also were excluded when they had taken a medication that included an antihistamine or DM on the evening before enrollment or within 8 hours of bedtime on the day of enrollment. Concurrent use of drugs that are known to inhibit cytochrome P450 2D6, such as serotonin-selective reuptake inhibitors, was also a contraindication to enrollment. Children who had comorbid diagnoses of otitis media or streptococcal pharyngitis and were prescribed antibiotics were not excluded from the investigation. Patients were not excluded when analgesic medications such as acetaminophen or ibuprofen were administered on either night of the study.

Subjective parental assessments of cough and sleep difficulty were assessed after informed consent was obtained through questions using a 7-point Likert scale (Fig 1). Three trained study coordinators and the principal investigator were responsible for survey administration. The range of cough frequency ranged from "constant" (equal to 6 points) to "not at all" (equal to 0 points); questions related to impact on ability to sleep, severity of cough, and bothersome nature of the cough ranged from "extremely" (6 points) to "not at all" (0 points). In an effort to administer medication to a population that was likely to receive a therapeutic intervention by parents, minimum symptom severity criteria for enrollment were established. Only parents who answered at least "somewhat" (3 points) for a minimum of 2 of 3 questions related to nocturnal cough frequency, impact on the child's sleep, and impact on parental sleep were eligible.

After stratification for age (2–5 years, 6–11 years, 12–18 years), each child was randomly assigned in a double-masked manner to receive DM (Benylin; Parke Davis, Morris Plains, NJ), DPH (Diphen AF; Morton Grove Pharmaceuticals, Morton Grove, IL), or PL (Simple syrup NF; Humco, Texarkana, TX). Dosage for DM was based on the label recommendations with children 2 to 5 years of age receiving 7.5 mg/dose, children 6 to 11 years of age receiving 15 mg/dose, and children aged 12 to 18 years of age receiving 30 mg/dose. DPH was dosed by weight at 1.25 mg/kg/dose (maximum 50 mg/dose) as described by a standard pediatric reference.[32] The medications were distributed by the pharmacy in a brown paper bag to mask the investigators to the volume of medication. Parents were instructed to administer the medication 30 minutes before the child was to go to sleep. A second survey asking the same questions was then administered the following day to assess symptom severity for the night when treatment was given.

Sample size calculations indicated that a total of 105 subjects (35 in each treatment arm) would have 80% power to detect a 1-point difference between any 2 treatment groups based on a 2-sided Mann-Whitney test with $\alpha = .05$. The principle outcome measure of interest was frequency of cough. Change in cough severity, the impact of the cough on sleep for both child and parent, and the bothersome nature of the cough for the child and the parent all were secondary outcome measures of importance.

As distributional assumptions were satisfied, outcome measures were treated as interval data, providing a modest increase in power. Treatment group comparisons were conducted by 1-way analysis of variance. Fisher exact tests were used to compare adverse reaction rates between treatments. The between-night change in individual outcomes and the combined symptom score were evaluated using paired *t* tests for the entire cohort. The study was approved by the Penn State Milton S. Hershey Medical Center's Institutional Review Board.

RESULTS

One hundred children with URIs were enrolled and completed the single-night study. The median age of the patients was 4.50 years (range: 2.00–16.50 years) with no significant difference between treatment groups (Table 1). Thirty-three patients received diphenhydramine, 33 received dextromethorphan, and 34 received placebo. Fifty-eight percent of the children were female. The children were ill an average of 4.21 ± 1.57 days before participation without significant differences between the assigned treatment. In addition, there were no differences between measures of symptom severity at baseline.

Symptom scores were obtained for the night before enrollment when no medications were given and then compared with scores from the subsequent night when either medication or PL was given before bed (Table 2). All outcomes showed dramatic improvement. The scores for cough frequency, impact

1) How frequent was your child's cough last night?
o Constant o Very Much o A lot o Somewhat o A little o Occasional o Not at all

2) How much did last night's cough affect your child's ability to sleep?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

3) How much did last night's cough affect your ability to sleep?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

4) How severe was your child's cough last night?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

5) How bothersome was last night's cough to your child?
o Extremely o Very Much o A lot o Somewhat o A little o Occasional o Not at all

Fig 1. Survey questions to assess nocturnal cough and sleep difficulty.

TABLE 1. Demographics and Baseline Characteristics

	DPH (n = 33)	DM (n = 33)	PL (n = 34)	P
Age (y; median ± quartile range)	3.90 ± 4.20	4.90 ± 3.90	4.50 ± 4.70	.62
Race (n [%])				
White	25 (76)	27 (82)	27 (79)	.82
Black	1 (3)	0 (0)	1 (3)	
Asian	1 (3)	0 (0)	0 (0)	
Latino	1 (3)	1 (3)	3 (9)	
Other	5 (15)	5 (15)	3 (9)	
Gender (n [%])				
Female	21 (64)	19 (58)	18 (53)	.72
Male	12 (36)	14 (42)	16 (47)	
Duration of illness (d; mean ± SD)	4.00 ± 1.27	4.53 ± 1.80	4.12 ± 1.61	.77
Cough frequency score, mean ± SD	3.79 ± 1.27	3.88 ± 1.02	4.15 ± 0.70	.15
Cough impact on child sleep score, mean ± SD	4.00 ± 1.06	3.67 ± 1.29	3.97 ± 1.27	.93
Cough impact on parent sleep score, mean ± SD	4.12 ± 1.11	3.97 ± 1.29	4.21 ± 1.12	.76
Cough "bothersome" to child score, mean ± SD	4.06 ± 1.14	3.73 ± 1.44	3.94 ± 1.30	.71
Cough severity score, mean ± SD	4.09 ± 0.98	3.97 ± 0.88	3.94 ± 0.98	.52
Combined symptom score, mean ± SD	20.06 ± 3.97	19.21 ± 4.13	20.21 ± 4.21	.88

on child and parent sleep, "bothersome" nature of cough, and severity of cough all were scored significantly lower on the second night ($P < .0001$). The mean combined symptom score was reduced from 19.83 to 8.93 (95% confidence interval for reduction: 9.38–12.42; $P < .0001$).

However, when separated by treatment group, no significant differences were found for any of the outcome measures when comparing the effects of DPH, DM, and PL (Fig 2). For cough frequency, those who received DPH and DM had a mean 1.97-point improvement as rated by their parents compared with a mean 2.24-point change for the better in those who received PL ($P = .56$). Parents did rate their child's sleep quality as better for those who received DPH with a mean improvement of 2.64 points compared with 1.88 points for DM and 2.18 points for PL, but this result did not achieve statistical significance ($P = .28$). This trend did not have an impact on the quality of parental sleep as reflected by changes of 2.67 points for the DPH arm and 2.45 and 2.59 points for DM and PL, respectively ($P = .85$). In all treatment arms, parents believed that the cough was less bothersome to their children, with improvements of 2.45 points for those who took DPH, 1.91 points for those who got DM, and 1.97 points for those in the PL arm ($P = .29$). Parents also noted similar improvements in the severity of their child's cough regardless of treatment: 2.06 points with DPH, 1.85 points with DM, and 1.88 points with PL ($P = .70$). When the results for these 5 outcomes were combined, there was no significant difference between treatments. The children in the DPH treatment group improved by an average of 11.79 points compared with 10.06 for DM and 10.85 for PL ($P = .62$).

Adverse effects were limited in this investigation (Table 3). The most commonly reported reaction was hyperactivity, which was reported for 14 children (14%), but there was no significant difference between the treatment arms, including placebo. The only 2 adverse reactions that approached statistical significance were insomnia in the DM arm ($P = .07$) and drowsiness in the DPH group ($P = .07$). One patient in each of the DPH and DM arms subsequently received a diagnosis and treatment for bacterial pneumonia; 1 patient in the placebo arm was subsequently treated for bacterial sinusitis.

DISCUSSION

This investigation sought to determine whether 2 common OTC medications were superior to placebo for the treatment of nocturnal cough as a result of URI. Because sleep difficulty for children and their parents is also an important source of morbidity with a URI, the effect of the medications on these outcomes was also examined. Disappointing was that neither DM nor DPH was superior to PL for any of the outcomes studied in this trial. The medications failed to produce an improvement in the frequency, severity, or bothersome nature of the cough to a greater degree than PL. Important for parents, neither their child's sleep nor their own sleep was significantly better when their child received medication compared with PL. For the cohort as a whole, however, it should be noted that there was a significant improvement for all symptoms over the previ-

TABLE 2. Comparison Between First and Second Nights of the Study for the Entire Cohort (N = 100)

	First Night (No Medication)	Second Night (Medication or Placebo)	P
Cough frequency score, mean ± SD	3.94 ± 1.02	1.88 ± 1.54	<.0001
Cough impact on child sleep score, mean ± SD	3.88 ± 1.21	1.65 ± 1.58	<.0001
Cough impact on parent sleep score, mean ± SD	4.10 ± 1.17	1.53 ± 1.54	<.0001
Cough "bothersome" to child score, mean ± SD	3.91 ± 1.30	1.80 ± 1.60	<.0001
Cough severity score, mean ± SD	4.00 ± 0.94	2.07 ± 1.66	<.0001
Combined symptom score, mean ± SD	19.83 ± 4.09	8.93 ± 7.11	<.0001

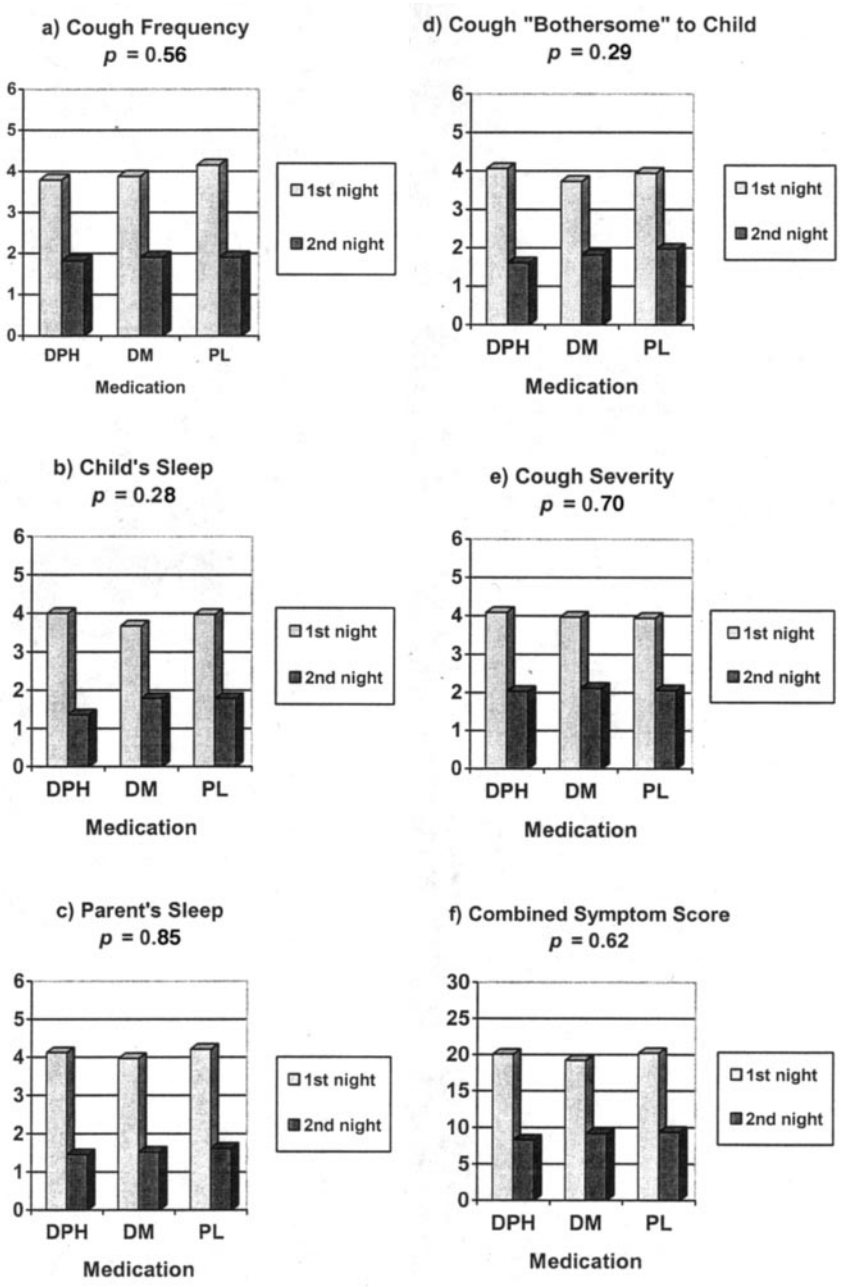

Fig 2. Comparison of the impact of DPH, DM, and PL on cough frequency (a), child's sleep (b), parent's sleep (c), cough "bothersome" to child (d), cough severity (e), and combined symptom score (f).

TABLE 3. Adverse Reactions

	DPH (n = 33)	DM (n = 33)	PL (n = 34)	P
Disorientation	0	0	1	1.00
Dizziness	0	1	0	.66
Drowsiness	3	0	0	.07
Headache	1	0	0	.66
Hyperactivity	3	6	5	.52
Insomnia	0	3	0	.07
Nervousness	1	1	0	.77
Stomachache/nausea	1	2	3	.87

ous night. This should reassure clinicians and parents that regardless of treatment, the natural history of a URI favors resolution of symptoms with time.

The questionnaire used in this study was designed in a manner that would be easily reproducible and takes into account the symptoms that generally cause parents to bring their children to medical attention with a URI. Because the severity of these complaints is subjectively assessed in clinical practice, objective criteria were not mandatory to determine the answers to these clinical questions, as has been stated previously.[9,18]

That noted, subjective reporting of cough by children and their parents has been shown to be imprecise.[33–38] These studies, however, were performed on children with chronic cough, asthma, or cystic fibrosis as opposed to the acute cough that was evaluated in this study. In addition, in this investigation, each parent served as his or her own control, because their answers were compared with their own responses from the previous night. Another limitation of the study was that compliance with medication administration could not be guaranteed. The only assur-

ance available was that by the parent during the follow-up telephone interview.

It is important to note that this study evaluated the effect of the medications versus placebo using 1 dose administered on a single evening. It is possible that an effect could have been demonstrated with DPH or DM if children were given either multiple doses throughout the day or repeated nocturnal doses for several consecutive evenings. Finally, a no-treatment arm was not included in this study. Eccles[39] detailed the placebo effect in studies that evaluated antitussives that may have been present in the current investigation.

We were interested in performing this study because cough can be an extremely frustrating symptom for children, parents, and physicians. Cough is the most common acute cause for an ambulatory health care visit in the United States and the second most common reason for visits during childhood.[1] Nocturnal cough can be particularly annoying because of its adverse impact on the ability of children and their parents to sleep. Schools and child care facilities often do not tolerate a significant cough, and therefore cough leads to missed school for children and/or missed work for parents. It is because of these factors that parents come to clinicians for assistance, seeking treatment for this common symptom. Despite the American Academy of Pediatrics policy statement,[2] the desire to lessen the symptoms for children and ease the frustration of parents leads clinicians to recommend OTC treatments for cough such as antitussives and antihistamines.

Given the results of this investigation and the results of other related investigations,[8,9] it is important to evaluate whether the OTC availability of these substances is benign. For example, whereas the efficacy of DM has been uncertain, its potential for toxicity has not. Described reactions and associations using standard doses include dystonia,[40] anaphylaxis,[41] and bullous mastocytosis.[42] Accidental ingestions and overdoses are not uncommon,[3,43] and dependence,[44] psychosis,[45] mania,[46,47] hallucinations,[48] ataxia,[49,50] somnolence,[50] insulin-dependent diabetes,[51] and death[52] have been reported from high doses, particularly when DM is combined with other OTC medications.[53,54] DM is also a drug of abuse among adolescents.[55–60]

First-generation antihistamines—DPH in particular—have also been shown to have adverse effects. This class of medications is known to produce somnolence but occasionally causes restlessness, nervousness, and insomnia with therapeutic doses.[61–63] Standard doses of DPH have also been associated with acute dystonia,[64] impaired driving ability,[65,66] and an increased risk of serious injury.[67] Chronic ingestion and overdose have been linked to dependence,[68] psychosis,[62,69,70] cardiac dysrhythmias and a prolonged QT interval,[62,71–74] rhabdomyolysis,[75,76] seizures,[62,70] and death.[77,78]

The desire to ease symptoms is strong for both parents and clinicians. This investigation supports the concept that URIs are self-limited illnesses that improve with time. It also questions whether common OTC medications have a place in the treatment of these illnesses for children. Each clinician should consider these findings, the potential for adverse effects, and the individual and cumulative costs of the drugs before recommending them to families.

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