EVALUATION OF PATIENTS’ SELF-RATED PERCEPTIONS OF EFFECTIVENESS AND DOSING PATTERNS OF AN UNBRANDED OTC COUGH SUPPRESSANT UNDER “IN HOME” USE CONDITIONS: A MULTI-CENTER OPEN-LABEL STUDY

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ABSTRACT

BACKGROUND AND OBJECTIVES: Dextromethorphan is the most commonly used ingredient in U.S. over-the-counter (OTC) cough preparations. The present study examined dosing patterns and patients’ perception of effectiveness from an unbranded dextromethorphan product in the OTC setting.

METHODS: The study used a prospective, open-label, single-arm design and was conducted at eleven geographically-dispersed U.S. consumer research centers. Of 431 adults screened, 421 completed the study (mean age 41, range 18–66 years old). All had cough due to a cold or influenza, which began ≤ 72 hours before a study visit where dextromethorphan syrup was dispensed. Data were gathered via telephone following a 3-day use period. Participants were asked to follow the dosing instructions of the product’s labeling and dosing information was collected to evaluate dose amount and frequency of daily intakes. Participants’ perceptions of effectiveness (defined as cough symptom relief) and overall satisfaction with the medicine were scored on a 5-point scale. Adverse events were collected to assess tolerability.

RESULTS: Dextromethorphan syrup was used a median of twice daily for a median daily dose of 60 mg. Of 421 participants, 386 (92 %) reported good to excellent cough symptom relief, and 381 (90%) were somewhat to extremely satisfied with the medication. No serious or severe adverse events were reported.

CONCLUSION: While these results provide valuable consumer insights under “in home” use conditions, they cannot be seen as evidence for dextromethorphan’s clinical efficacy since the study had neither a placebo nor a no-treatment arm.

Key words: Cough, common cold, cough suppressant, antitussive, dextromethorphan, OTC medicine
INTRODUCTION

A cough is often one of the most burdensome symptoms of the common cold, which itself is the most frequent acute illness throughout the industrialized world. It is estimated that adults in the United States suffer on average 2 to 4 colds each year; that number is higher in children. Cough is also the most frequent reason individuals visit a physician’s office due to illness or injury.

Preceding the present study, the Consumer Healthcare Products Association (CHPA), the national trade association representing U.S. manufacturers and distributors of over-the-counter (OTC) medicines and dietary supplements, conducted a nationwide survey on OTC cough medicine use of over 3,000 adults 18 years of age and older in the United States. Forty-one percent of survey respondents reported they had experienced cough in the past 3 months, and 39% sought medical attention for cough. Among individuals 65 years or older, however, 56% said they talked with a physician about treating their cough. Of the individuals who had cough in the previous 3 months, 66% had used an OTC cough medicine. The latter result is consistent with findings in a nationwide survey of U.S. households conducted between November 2000 and February 2001 by researchers at the University of Michigan. In this study, more than two-thirds (69%) of survey participants with colds had self-medicated with an OTC product.

The most commonly used OTC cough medicines contain dextromethorphan as the antitussive active ingredient. In the United States, dextromethorphan is used in more than 140 OTC cough and cold medicines, and since its approval by the Food and Drug Administration (FDA) in 1958, dextromethorphan has gradually replaced codeine as the most widely used cough suppressant.

In the 1970s, FDA initiated a review process to determine which OTC drugs could be considered “generally recognized as safe and effective” (GRASE). After reviewing all available data in experimentally induced cough, controlled studies in pathologic cough with both subjective and objective efficacy endpoints, and uncontrolled studies in a variety of disease states, FDA published the report of the advisory panel, which deemed dextromethorphan as GRASE in 1976. In 1987, the agency issued the Final Monograph for OTC Antitussive Drug Products, indicating that dextromethorphan was a safe and effective (GRASE) cough suppressant when administered at 10-20 mg orally every 4 hours or 30 mg every 6 to 8 hours in adults and children over 12 years of age.

More recently, placebo-controlled clinical studies have examined dextromethorphan in induced cough and acute cough due to acute upper respiratory infection. With the exception of a study with a smaller sample size (n=43) by Lee et al., these newer studies have shown significantly greater efficacy for dextromethorphan versus placebo, as determined by objective cough measurements and subjective visual analog scales. In 2001, Pavesi et al. conducted a meta-analysis of efficacy studies with single 30-mg dextromethorphan doses in acute cough due to acute upper respiratory infection. This meta-analysis of six placebo-controlled clinical
studies, all of which used objective cough recording, showed significantly greater increases in the rest periods between cough bouts (on average +17.3%) and significantly greater reductions in cough bouts (-12.7%), cough components (-13.4%), and cough effort (-17.3%) for dextromethorphan compared to placebo, but not significantly reduced cough intensity (-5.8%).

The objectives of the present study were to evaluate users’ perceptions of effectiveness and satisfaction, daily intake, and adverse events with OTC dextromethorphan syrup for cough symptom relief under conditions of use without medical supervision. We are not aware of research aimed at these outcome measures under “in home” use conditions rather than in a controlled, physician-monitored, clinical trial setting. By having participants use the medication in their homes, under conditions as close as possible to the natural setting (i.e., without explicit verbal directions for use given by the investigators other than the printed label, without questionnaires to complete at the time of dosing), the investigators sought to mimic the subjective effects patients would experience during in OTC use.

MATERIALS AND METHODS

STUDY DESIGN

CHPA member companies formed a task group, which funded the present study and commissioned Concentrics Research LLC, a specialty contract research organization, to conduct an effectiveness and satisfaction study with dextromethorphan. The member companies of the CHPA task group were Adams Respiratory Therapeutics, McNeil Consumer Healthcare, Novartis Consumer Health, Inc., Perrigo Company, Schering-Plough HealthCare Products, Inc., The Procter & Gamble Company, and Wyeth Consumer Healthcare. This was a prospective, open-label, single-arm study in adults with cough symptoms related to a cold or influenza and whose cough symptoms began less than 72 hours earlier.

STUDY PARTICIPANTS

The study population consisted of adults actively experiencing cough due to a cold or influenza. Persons were eligible for the study if they were 18 to 65 years of age; had used an OTC cough product in the past 12 months (to obtain a sample of likely future OTC antitussant users); were within the first 72 hours of actively experiencing cough at the recruitment visit. This time period was chosen because it has been observed that patients with coughs due to rhinovirus colds begin recovering 5 days after onset of illness but may continue to cough for at least 10 days. Participants had not taken any OTC cough or cold medication for at least 24 hours (to allow for a washout period) and voluntarily signed an informed consent document. Exclusion criteria included cough due to smoking; bronchitis, asthma, chronic obstructive pulmonary disease (COPD), or emphysema; currently treated by a physician with a prescription medication that in the opinion of the investigator would interfere with the OTC cough medicine; participation in another clinical study or received an investigational drug within the previous 30 days; had previously participated in this study; employed by a pharmaceutical, health care, or market research company; currently pregnant or breastfeeding; or had a medical condition that was...
contraindicated for dextromethorphan use according to the “Drug Facts” label.

STUDY ORGANIZATION

Study activities were managed by Concentrics Research, LLC under a central Institutional Review Board (IRB) and in compliance with Good Clinical Practices (GCP). The principal investigator, a physician from Concentrics Research LLC, coordinated and supervised the study. Trained nurses performed recruitment and follow-up contacts with participants at 11 geographically dispersed, U.S. consumer research sites, which specialize in understanding the preferences, attitudes, and behaviors of consumers to marketed products. The sites were located in Baltimore, MD; Buffalo, NY; Cleveland, OH; Denver, CO; Houston, TX; Louisville, KY; St. Paul, MN; Tampa, FL; Charleston, WV; Detroit, MI; and Indianapolis, IN. The study was conducted under a common protocol, and care was taken to promote consistency in study execution across sites. This was accomplished through uniform training of study personnel, central communications, and common procedures for corrective and preventive actions.

STUDY MEDICATION AND DOSAGE

The study drug was a dextromethorphan-containing cough syrup (15 mg/5 mL) supplied as an unbranded, generically labeled 118-mL bottle with “Drug Facts” labeling. An accompanying measuring cup showed the appropriate dose. Participants were instructed to use the product for 3 consecutive days according to “Drug Facts” labeling (see Figure 1).

FIGURE 1: REPRESENTATIVE LABELLING OF THE STUDY MEDICATION

<table>
<thead>
<tr>
<th>Drug Facts</th>
<th>Drug Facts (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Ingredient</strong> (in each 5 mL teaspoonful)</td>
<td><strong>Purpose</strong></td>
</tr>
<tr>
<td>Dextromethorphan HBr, USP 15 mg</td>
<td>Cough suppressant</td>
</tr>
</tbody>
</table>

**Use**
-temporarily relieves cough due to minor throat and bronchial irritation as may occur with a cold

**Warnings**
-Do not use if you are now taking a prescription monoamine oxidase inhibitor (MAOI) (certain drugs for depression, psychiatric or emotional conditions, or Parkinson’s disease), or for 2 weeks after stopping the MAOI drug. If you do not know if your prescription drug contains an MAOI, ask a doctor or pharmacist before taking this product.

**Stop and ask a doctor if**
- cough lasts for more than 7 days, comes back, or occurs with fever, rash or persistent headache.
- a persistent cough may be a sign of a serious condition.

**If pregnant or breast-feeding, ask a health professional**
- Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

**Directions**
- dose may be repeated every 6-8 hours
- do not exceed 4 doses in a 24-hour period

adults and children 12 years and over: 2 teaspoonfuls (5 mL) every 6-8 hours

under 12: ask a doctor

**Other Information**
- store at room temperature
- 59°-86°F

**Inactive ingredients**
- alcohol 1.4%, citric acid, FD&C red no. 40, flavors, glucose, glycerin, high fructose corn syrup, sucralose, sodium benzoate, water.

**Sealed with printed neckband for your protection**

**Subject #: __________________**

**Dispense:** __________________

**Date:** __________________

**For Investigational Use Only**
- Protocol #72008
- Emergency Contact #: 1-888-250-6141
STUDY PLAN

Study participants were recruited via print and radio advertisements and flyers to ensure a minimum of 400 participants completed the study. The advertising directed potential participants to a toll-free telephone number for more information and preliminary screening. Persons who passed the preliminary screening and were interested in participating were directed to a local consumer research location. During the research center visit, the potential participant received a brief study overview, including the timing and activities involved. The person was then asked if he or she was willing to take the cough product home to use for a 3-day period. Those agreeing to participate in the study read and signed an informed consent form. A nurse then took a brief medical and medication history and confirmed the inclusion/exclusion criteria. If the person was eligible, the nurse approved dispensing the product and the participant was given a 118-mL bottle of dextromethorphan cough syrup. Participants were prohibited from using other cough medications during the 3-day treatment period. Participants were given a diary to record the time, frequency, and dose of product used over the next 3 days in an unsupervised environment. Diaries were used to facilitate recall of events when talking to the nurse during the post-use follow-up call. They were designed to be brief to avoid interfering with the participant’s experience in the home environment. Participants were given a telephone number for reporting adverse events or changes in their health to a study nurse. A study nurse called each participant 3 days after the study period to obtain feedback on participant-perceived effectiveness and satisfaction with the medication. Information on the number of doses and frequency of dosing was also gathered. Participants were compensated for their time and expenses related to study participation.

OUTCOME MEASURES AND DATA ANALYSES

The primary outcome measure was participant-reported effectiveness, defined as cough symptom relief after dosing with dextromethorphan syrup, as scored on a 5-point scale. The following question was asked by the nurse during the post-dose follow-up: “Overall, how would you rate the product you used for relief of cough symptoms—excellent, very good, good, fair, or poor?” The secondary outcome measure was overall satisfaction with the medicine as scored on a 5-point scale. The following question was asked during the follow-up call: “Overall, how would you rate your satisfaction with the product you used—extremely satisfied, somewhat satisfied, neither satisfied nor dissatisfied, somewhat dissatisfied, or extremely dissatisfied?”

To evaluate dosage patterns, participants were asked how often they took the medication each day and which amount they took at each dose. Volunteers were provided with a 24-hour telephone number that they could call to report any adverse event or change in their health during study participation. The telephone line was staffed by nurses and available until 3 days after the final participant had completed the nurse-led efficacy interview.

All adverse events reported during the study were recorded and classified using MedDRA coding. All reported adverse events were summarized by the number of subjects reporting them, body system, severity, seriousness, and relationship to study medication. A serious
adverse event was defined as any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization, resulted in disability or incapacity. An adverse event was considered severe if it was incapacitating or prevented normal everyday activity.

Data from the 11 study sites were pooled for analyses. The primary analysis was done on a modified intent-to-treat population and included all participants who used at least two doses of study medication and completed the post-use interview with a nurse. This was also the definition of a completed participant. Safety endpoints were evaluated for all participants who used at least one dose of study medication and provided safety information, regardless of evaluability for efficacy. For demographic variables, means and standard deviations for continuous variables and counts and proportions for categorical variables were calculated. Descriptive statistics calculated for dosing frequency included mean, standard deviation, median, and minimum to maximum counts for each day of use. Finally, participant perceptions of effectiveness and satisfaction were evaluated via proportions endorsing each alternative with 95% confidence intervals. To assess site differences in perceived effectiveness and satisfaction, Cochrane-Mantel-Haenszel tests were conducted using only the highest enrolling sites, Sites 6, 7 and 9 (n=110, 68, and 85, respectively), given the small sample sizes at the other sites (n=22, 36, 30, 18, 9, 10, 7, and 26). All analyses were conducted using SAS software, Version 9.1.

RESULTS

Of the 431 persons screened, 421 completed the study. The first participant’s visit was on February 27, 2007, and the last participant’s follow-up call was on April 3, 2007. Six of the persons screened did not meet the inclusion and exclusion criteria (2 with cough due to smoking, and 1 each with cough due to bronchitis, asthma, COPD or emphysema; previous study participation; worked for pharmaceutical, healthcare or market research company; and currently pregnant or breastfeeding). Only four participants were lost to follow-up after being dispensed the product and did not provide any information about dosing, effectiveness, or safety. They were not included in the analyses.

The age of the completed participants ranged from 18 to 66, with a mean of 41 years (Standard Deviation (SD) 11.4). More than 70% were Caucasian, and almost two-thirds were female. Most had a high school education or above (see Table 1). The median number of times the product was taken during the 3 days of medicine use was two times per day (see Table 2). Overall 413 participants (98%) took the recommended amount of two teaspoons (corresponding to 30 mg dextromethorphan) at each dose. Only one subject took four teaspoons at one occasion. The remaining subjects who did not follow the labeled dosing instructions used half or one tablespoon at one or more occasions. Tables 3 and 4 show the results of the primary and secondary outcome measures, i.e. relief of cough symptoms and overall satisfaction with the dextromethorphan syrup. Of 421 participants, 386 (92%) rated their relief of cough symptoms as “excellent,” “very good,” or “good.” A total of 381 (90%) were “extremely satisfied”
or “somewhat satisfied” with the product. No significant site differences were found in relief (p=0.642) or satisfaction (p=0.184) for the three highest enrolling sites.

No serious or severe adverse events were reported. The most commonly reported adverse event was somnolence (4%; 16/421), followed by headache (2%; 9/421), dizziness (1%; 6/421), and nausea (1%, 4/421). Diarrhea, flatulence, fatigue, laryngitis, and rhinorrhea were reported by two participants each. Additionally palpitations, conjunctival hemorrhage, dyspepsia, stomach discomfort, pain, nasopharyngitis, ageusia, sinus headache, insomnia, cough, throat irritation, and pruritus were reported by one participant each.

### Table 1: Subject demographics (Intent-to-Treat subjects)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>N 421</th>
<th>Mean 41.1</th>
<th>SD 11.42</th>
<th>Median 41.0</th>
<th>Min. - Max 18 to 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 150 (36%)</td>
<td>Female 271 (64%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian 298 (71%)</td>
<td>Black 119 (28%)</td>
<td>Native American 0 (0%)</td>
<td>Asian/Pacific Islander 1 (&lt;1%)</td>
<td>Other a 3 (1%)</td>
</tr>
<tr>
<td>Ethnicity (Hispanic origin)</td>
<td>Yes 10 (2%)</td>
<td>No 411 (98%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education level b</td>
<td>Some high school 17 (4%)</td>
<td>High school degree or GED 141 (33%)</td>
<td>Some college 128 (30%)</td>
<td>Vocational/technical school 20 (5%)</td>
<td>College degree 80 (19%)</td>
</tr>
</tbody>
</table>

a Black and Asian/Pacific Islander (1), Native American/Caucasian (1), Lebanese/American (1)

b Two subjects checked two levels: one subject checked some college and vocational/technical school and one subject checked college degree and post graduate degree.

### Table 2: Summary of extent of exposure for Days 1, 2 and 3 and overall (Intent-to-Treat subjects)

<table>
<thead>
<tr>
<th>Number of times medication taken</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>421</td>
<td>420</td>
<td>416</td>
<td>421</td>
</tr>
<tr>
<td>Mean</td>
<td>1.8</td>
<td>2.4</td>
<td>2.1</td>
<td>6.3</td>
</tr>
<tr>
<td>SD</td>
<td>0.71</td>
<td>0.81</td>
<td>0.88</td>
<td>1.94</td>
</tr>
<tr>
<td>Median</td>
<td>2.0</td>
<td>2.0</td>
<td>2.0</td>
<td>6.0</td>
</tr>
<tr>
<td>Min. - Max</td>
<td>0 to 4</td>
<td>0 to 4</td>
<td>0 to 4</td>
<td>2 to 12</td>
</tr>
</tbody>
</table>

### Table 3: Summary of relief of cough symptoms with dextromethorphan syrup (modified Intent-to-Treat subjects) (N=421)

<table>
<thead>
<tr>
<th>Cough Relief</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>101 (24%)</td>
<td>(20%, 28%)</td>
</tr>
<tr>
<td>Very Good</td>
<td>192 (46%)</td>
<td>(41%, 50%)</td>
</tr>
<tr>
<td>Good</td>
<td>93 (22%)</td>
<td>(18%, 26%)</td>
</tr>
<tr>
<td>Fair</td>
<td>26 (6%)</td>
<td>(4%, 8%)</td>
</tr>
<tr>
<td>Poor</td>
<td>9 (2%)</td>
<td>(1%, 4%)</td>
</tr>
</tbody>
</table>

### Table 4: Summary of overall satisfaction with dextromethorphan syrup (modified Intent-to-Treat subjects) (N=421)

<table>
<thead>
<tr>
<th>Overall satisfaction with medication</th>
<th>n (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extremely satisfied</td>
<td>194 (46%)</td>
<td>(41%, 51%)</td>
</tr>
<tr>
<td>Somewhat satisfied</td>
<td>187 (44%)</td>
<td>(40%, 49%)</td>
</tr>
<tr>
<td>Neither satisfied nor dissatisfied</td>
<td>21 (5%)</td>
<td>(3%, 7%)</td>
</tr>
<tr>
<td>Somewhat dissatisfied</td>
<td>13 (3%)</td>
<td>(1%, 5%)</td>
</tr>
<tr>
<td>Extremely dissatisfied</td>
<td>6 (1%)</td>
<td>(0%, 3%)</td>
</tr>
</tbody>
</table>
DISCUSSION

The present study aimed to evaluate patients’ self-rated perceptions of effectiveness of an unbranded generically labeled dextromethorphan cough syrup under conditions of in-home use. The study had neither a placebo nor a no-treatment arm that would have allowed assessment of the contribution of the placebo effect or the natural progress of the condition. Also, it is not possible to verify absolutely that participants’ administered medication according to all label directions or that they refrained from using any prohibited cough medicines during their study participation. However, the design does have the benefit of reflecting more closely how the medicine is used in a real world setting than in a more controlled trial design. Study participants received no instructions for use other than those provided in the Drug Facts label, and inclusion/exclusion criteria were kept relatively broad to reflect the population of patients likely to purchase a cough syrup for relief of acute cough due to cold or influenza.

The study population represented adults from 18 to 66 years old and was predominantly Caucasian (71%) and African-American (28%) with 2% of Hispanic or Latino origin. Compared to 2000 U.S. Census data, individuals of African-American origin were overrepresented and individuals of Hispanic origin were underrepresented in the study population (2000 US census: 12% African-American, 12.5% were of Hispanic or Latino origin). Participants used a median of two dextromethorphan doses per day, less than the four doses allowable. Ninety-eight (98)% of participants used the label-recommended amount of two teaspoons of the cough syrup at each dose.

Overall, 386 of 421 subjects (92%) using the dextromethorphan syrup reported excellent, very good, or good relief of their cough symptoms, and 381 of 421 subjects (90%) reported they were satisfied with the medication. Reviews of placebo-controlled studies with dextromethorphan conducted by the Cochrane Collaboration and the American College of Chest Physicians question whether dextromethorphan’s effects are clinically meaningful in acute cough due to upper respiratory infections. Due to its open label design, the present study does not add new evidence to the discussion on the treatment difference between dextromethorphan and placebo. According to Eccles, the total effectiveness of a cough syrup should be attributed to: a marked placebo effect based on a psychobiological response, the demulcent properties of the syrup, and such nonspecific effects as natural recovery from the common cold. Additional factors influencing the perception of effectiveness in this study may include desire for and expectations of a therapeutic effect, previous experience with OTC cough medicines or medications in general, recommendations from family members or friends, brand awareness, and drug advertising. An unbranded, generically labeled product was chosen to minimize the influence of the latter two factors. The study medication was, however, labeled as “cough suppressant” to inform participants of the product’s intended use. In addition, the influence of selection bias must also be considered. Persons who had used OTC cough products in the prior 12 months were selected for the study, as this population represents OTC medicine users.

In this study almost all participants complied well with dosing instructions during unsupervised
use and a high proportion expressed satisfaction with their treatment outcome. The complex nature of the relief persons report, the influence of the psychobiological placebo response, the demulcent properties of the syrup, and other nonspecific effects should be investigated further. This study suggests that such investigations could be conducted satisfactorily in natural “in home” settings.

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Authors’ Contributions: MDH, SEC, AD, and HS participated in the design of the study. MDH, LMS and HS collated the data from the study and drafted the manuscript. All authors reviewed and approved the manuscript.

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Authors’ declaration of personal interest: MDH and HS are employed by the Consumer Healthcare Products Association, a national trade organization representing U.S. manufacturers and distributors of OTC medicines, including OTC cough syrup. SEC, AD, and EHF are employed by US manufacturers of OTC cough syrup. LMS is employed by contract research organization.

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REFERENCES


