Study objective: The purpose of the meta-analysis was to understand the antitussive effect of treatment with dextromethorphan hydrobromide, 30 mg, vs placebo over a 3-h treatment period in patients with cough due to uncomplicated upper respiratory tract infection (URTI), and to show that the computerized system for acquisition and analysis of cough sound was consistent and reproducible across the individual studies.

Study design: The six studies used for the meta-analysis were randomized, double-blind, parallel-group, single-dose, placebo-controlled studies with a 3-h postdose cough evaluation period.

Setting: One study was conducted in Durban, South Africa, and five studies were conducted in Bombay, India. Four studies took place in clinics, and two studies were in-home studies.

Patients: Seven hundred ten adult patients with cough due to uncomplicated URTI who were otherwise healthy and who satisfied the inclusion/exclusion criteria for the meta-analysis.

Measurements and results: For each patient, a standard baseline was calculated pretreatment, then a 3-h continuous cough recording was made after treatment was initiated. Five efficacy variables were measured in 30-min intervals: cough bouts, cough components, cough effort, cough intensity, and cough latency. The meta-analysis showed consistent results across most of the studies for each of the efficacy variables. It demonstrated significantly greater overall reductions in cough bouts, cough components, and cough effort, and an increase in cough latency for patients treated with dextromethorphan hydrobromide, 30 mg, vs those treated with placebo.

Conclusion: The results of a meta-analysis of the six clinical studies show that the antitussive effect of a single dose of dextromethorphan hydrobromide, 30 mg, has been established. The consistent nature of the results shows that the computerized cough acquisition and analysis system is a valid and reproducible methodology for evaluating cough associated with URTI.

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Key words: acute cough; antitussive; computerized objective measure; cough effort; cough frequency; cough intensity; cough latency; dextromethorphan; meta-analysis

Abbreviations: AUC = area under the curve; CAT = computerized audio timed; OTC = over-the-counter; URTI = upper respiratory tract infection

Dextromethorphan hydrobromide, hereafter referred to as dextromethorphan, has a long history as an effective antitussive agent,\(^1,2\) with cough associated with uncomplicated upper respiratory tract infection (URTI) being the most common indication for its use. This is illustrated by the fact that in the United Kingdom alone, there are 16 different over-the-counter (OTC) cough products containing dextromethorphan,\(^3\) and in the United States, dextromethorphan has been reported to account for 75% of OTC sales of antitussives.\(^4\)

Although cough associated with URTI is not a serious medical condition, treatment is important because it may reduce discomfort and other complications that might impair daily living\(^5\) or even lead to...
time off from work. However, relatively little research has been carried out on cough in this context\(^6\) and in particular on dextromethorphan as a treatment. This may be due partly to acute cough itself being difficult to measure, because of the high variability (both within and between patients) and the voluntary control aspect of the condition. Also, it is logistically more difficult to recruit patients with this acute form of cough into studies. Another factor is that there have been only limited objective methods for evaluating the efficacy of antitussives in treating patients with natural cough to date, and these methods have also been limited in terms of what they can measure.\(^7\) Finally, because antitussives, which are licensed for OTC use, are not expected to show large percentage treatment differences, sensitive evaluation methods are required.

We have spent the last decade developing our computerized cough acquisition and analysis system for acquisition and multidimensional analysis of the cough sound. This is now a carefully validated methodology\(^8\) and has been upgraded and made portable.

In this article, we present an overview of this innovative methodology and the results of a meta-analysis of six clinical trials using the system to investigate the antitussive effect of dextromethorphan vs placebo in subjects with cough due to uncomplicated URTI. We show that the antitussive effect of a single, oral, 30-mg dose of dextromethorphan vs placebo has been reproducibly established in these studies, in a 3-h postdose evaluation.

**MATERIALS AND METHODS**

**Computerized System**

Our original computerized cough acquisition and analysis system has been described previously.\(^8\) The system was further made portable to record cough signals from human volunteers who stay at home during clinical studies. This new computerized audio timed (CAT) recorder is portable, uses a telemetric method, and operates for a long duration to enable in-home monitoring of cough for > 24 h.

The main components of the recorder are shown in Figure 1. A contact microphone (or accelerometer), attached with a special adhesive tape against the subject’s suprasternal notch, picks up cough audio vibration signals. The audio signals picked up by the microphone are fed into a frequency modulation transmitter, a small device worn in a belt pouch. The transmitter modulates the audio signal with radio frequency electromagnetic waves, which can be sent without the need for a direct wire connection. This telemetric arrangement ensures that the volunteer participating in the study is mobile and free to carry out normal activities during the course of the study. The transmitted signals have a range of 100-m radius in the normal domestic environment. Hence, the volunteers can move anywhere within their homes, including different floor levels, during the recording.

The hardware is enclosed in a locked box and is kept in the volunteer’s home. The cough acoustic signals are digitized and stored on the hard disk of the computer in a compressed form, along with the time of occurrence. The timing information is used to reconstruct the data and to evaluate the treatment effect with respect to time. From the objective multidimensional analysis of the data, the antitussive/expectorant action of a cough medicine is evaluated. The key parameters are the following: cough counts measured as components and bouts, cough effort or the energy spent during coughing, average cough intensity (severity per bout), and average cough latency or rest period between coughs. Cough wetness is graded during the analysis and is used as an additional parameter. Finally, the software analyzes the patterns of various coughs. The parameters and their definitions are shown in Table 1. Figure 2 further illustrates how cough effort is measured.

The CAT system is a comprehensive tool to measure objectively multiple parameters for the evaluation of cough medicines. Its key features are as follows:

1. It is a calibrated system and provides a meaningful cough effort measure. The calibration ensures the stability of the equipment and also the comparability of the data acquired by different CATs.
2. The portability means that data can be recorded in a natural environment in which subjects are uninhibited and the “white coat effect” is minimized.
3. The telemetric monitoring keeps the subject ambulatory and free to carry out daily activities.
4. Long-duration recording, day and night, is possible. This enables evaluation of the effect of multiple doses and controlled release formulations.
5. The complete CAT hardware is validated along with the controlling software, in both acute and chronic cough models in clinical studies, and has been reviewed by an external quality assurance agency.

![Figure 1. Components of the CAT system.](attachment:image.png)
Parvez et al: methorphan, 30-mg, group and 354 in the placebo group. The subjects were equally distributed between the studies, and the demographic characteristics were comparable across the studies. On average, there were at least 50 subjects per treatment leg in each study, and the demographic characteristics were comparable across the studies (Table 3). The subjects were predominantly young (average age, 30 years), there were approximately equal numbers of male and female subjects, and they were predominantly nonsmokers. The subjects were equally distributed between the two treatment groups: 356 subjects in the dextromethorphan, 30-mg, group and 354 in the placebo group. The subjects for the meta-analysis met the following key inclusion criteria. These selection criteria are detailed fully by Parvez et al:

- Keys for inclusion: Healthy male and female subjects, between 18 years and 70 years of age, who were experiencing acute cough due to uncomplicated URTI, and who were reporting the onset of cough not later than the first 10 to 15 days of symptoms of URTI were included in this study. The subjects also exceeded a minimum number (15) of cough bouts during the 1-h baseline qualifying period.

- Keys for exclusion: Subjects with positive identification of Streptococcus pyogenes from a throat swab or those with complicated URTI, a history of asthma or chronic bronchopulmonary disease, or any other medical condition that may have interfered with the results of the study were excluded. Also, those who had consumed disallowed medication (ie, any medicinal products other than paracetamol) within appropriate designated time periods prior to screening were excluded. Only paracetamol was allowed during the studies, provided it was taken at least 6 h prior to the recording period.

The meta-analysis was conducted rigorously and followed a standard published process. All six studies were conducted by Procter and Gamble (Mumbai, India). They were all parallel-group, placebo-controlled studies with the same inclusion and exclusion criteria and identical study procedures, therefore representing an ideal situation in which to carry out a meta-analysis. The results of each study were pooled, and a test for treatment by study interactions, which were at the 0.2 level.

### Methods

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The efficacy of each of the five parameters was analyzed using the area under the curve (AUC) [calculated using the trapezoidal rule], cumulated total (ie, the cumulated sum of the 30-min intervals), and individual time point analyses (ie, at each half-hour interval). The results from the meta-analysis are based on an analysis of the covariance model of the pooled data, in which the baseline score was used as the covariate and study and treatment were used as factors. For the individual studies, the results are based on an analysis of the covariance model, in which the baseline score was used as a covariate, and treatment was used as a factor.

Subgroup analyses were undertaken to evaluate treatment effects in subgroups of the subject population using the following variables: the type of cough (dry or nondry—scored subjectively but blindly on an average wetness scale based on the audible nature of the cough sound and its waveform); gender; smoking habit (smokers or nonsmokers); and the type of cough signal pick-up device used (accelerometer or microphone). All responses were log-transformed, which helped to stabilize variances and to normalize the data. All statistical analyses were at the two-sided 0.05 level of significance, with the exception of interactions, which were at the 0.2 level.

### Results

The meta-analysis was based on a total of 710 subjects, comprising all evaluable subjects who received 30 mg dextromethorphan (n = 356) vs all evaluable subjects who received placebo (n = 354).

#### AUC Analysis

The majority of the individual studies showed consistent results for AUC for each of the five efficacy variables. Although these differences were directionally in favor of dextromethorphan and were considered clinically relevant, the individual studies were not

### Table 1—Parameters Measured by the Computerized Cough Acquisition and Analysis System

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough counts</td>
<td>Individual cough episode occurring in a single breath</td>
</tr>
<tr>
<td>Bout</td>
<td>Sounds within each bout, ie, individual tussive blasts</td>
</tr>
<tr>
<td>Components</td>
<td>Rest periods between bouts</td>
</tr>
<tr>
<td>Cough latency</td>
<td>AUC of cough acoustic power spectrum (measure of cough energy) (see Fig 2)</td>
</tr>
<tr>
<td>Cough effort</td>
<td>Average intensity of cough = cough effort/total cough count*</td>
</tr>
<tr>
<td>Wetness grading</td>
<td>Graded by cough analyst based on cough sound and waveform</td>
</tr>
<tr>
<td>Others</td>
<td>Duration of each cough event, study of cough patterns, etc</td>
</tr>
</tbody>
</table>

*Normalized with respect to the calibration signal.

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powered to show statistical significance. Statistically significant results were seen in two studies at the 0.01 level for total cough bouts, in one study at the 0.05 level for cough components, in two studies at the 0.05 level for cough effort, and in one study at the 0.1 level for cough latency.

The meta-analysis showed differences in the same region as the individual studies and was statistically significant for dextromethorphan, 30 mg, vs placebo for the efficacy variables, cough bouts, cough components, cough effort, and cough latency, but not for cough intensity (see “Discussion” section). The average differences in these values for dextromethorphan vs placebo are detailed in Table 4.

**Cumulated Total**

Again, the meta-analysis showed statistically significant treatment differences between placebo and dextromethorphan, 30 mg, for total cough bouts, total cough components, total cough effort, and total cough latency, but not for total cough intensity.

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**Table 2—Practical Differences Among the Six Clinical Studies Used for the Meta-analysis**

<table>
<thead>
<tr>
<th>Study Environments</th>
<th>Dextromethorphan Forms</th>
<th>Type of Sensor Used To Record Cough</th>
<th>Locations</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-clinic (4)</td>
<td>Liquid (3)</td>
<td>Accelerometer (2)</td>
<td>Bombay, India (5)</td>
</tr>
<tr>
<td>In-home (2)</td>
<td>Capsule (3)</td>
<td>Microphone (4)</td>
<td>Durban, South Africa (1)</td>
</tr>
</tbody>
</table>

*Numbers in parentheses indicate the number of studies of that type.*
Therefore, as expected, the results were similar for the AUC and cumulated total methods of data analysis.

**Individual Time Point Analysis**

The results from the meta-analysis showed that the largest reduction in cough bouts and components for those subjects receiving dextromethorphan, 30 mg, compared with placebo occurred between 90 min and 120 min after receiving the drug, on average. This result was the same for cough latency. This is consistent with published data for dextromethorphan, which state time to peak concentration as 120 to 150 min.\(^{11,12}\) The individual time point analysis showed an interaction between treatment and dose form. Subgroup analysis showed that the liquid-dose form produced greater treatment differences between dextromethorphan and placebo than the capsule during the first 60 min postdose. This is demonstrated by, for example, Figure 3, which shows the effect of the dose form on cough effort at the 30-min time point. This treatment difference is addressed in the "Discussion" section.

Although some trends were evident, overall the individual time point analysis did not show the consistency seen with the summary parameters AUC and the cumulated total. We believed this was largely due to the fact that patients experiencing acute cough demonstrate a large variability in their tussive profile over time, probably as a result of disease fluctuations and external factors.\(^6,13\)

**Subgroup Analysis**

The results showed a generally greater treatment effect for dextromethorphan, 30 mg, vs placebo in subjects with dry cough, compared with those with nondry cough for each of the efficacy variables. For example, Figure 4 shows the effect of dry cough vs nondry cough on AUC for cough effort. The meta-analysis showed that the effect of the treatment was slightly greater in men, though not statistically significantly different due to gender, and that the age of subjects made no statistically significant difference overall. Also there were no statistically significant differences between smokers and nonsmokers; however, this result was not based on a large base size because the number of smokers in the Indian study population was very small. Finally, the type of device used to record the subject’s cough (microphone or accelerometer taped against the suprasternal notch) gave no statistically significant differences in treatment effect.

It was also found that the percentage difference between the effect of dextromethorphan, 30 mg, vs placebo does not generally increase as the severity of cough recorded at baseline increases. This indicates that dextromethorphan has a consistent antitussive effect whether the cough is mild, moderate, or severe.

**Discussion**

This meta-analysis of six studies provides new objective evidence for the known antitussive effect of dextromethorphan using a computerized system to acquire and analyze cough sounds. The consistent nature of the results shows that the computerized cough acquisition and analysis system is reproducible and is a valid methodology to evaluate cough objectively.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Log Least-Squared Means (SE)</th>
<th>p Value</th>
<th>Percentage Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough bouts</td>
<td>Placebo 3.47 (0.03)</td>
<td>Dextromethorphan, 30 mg 3.34 (0.03)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Cough components</td>
<td>Placebo 3.90 (0.04)</td>
<td>Dextromethorphan, 30 mg 3.75 (0.03)</td>
<td>0.0032</td>
</tr>
<tr>
<td>Cough effort</td>
<td>Placebo 5.15 (0.04)</td>
<td>Dextromethorphan, 30 mg 4.96 (0.04)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Cough latency</td>
<td>Placebo 6.65 (0.04)</td>
<td>Dextromethorphan, 30 mg 6.84 (0.04)</td>
<td>0.0024</td>
</tr>
<tr>
<td>Cough intensity</td>
<td>Placebo 2.77 (0.03)</td>
<td>Dextromethorphan, 30 mg 2.71 (0.03)</td>
<td>0.1510</td>
</tr>
</tbody>
</table>

*Values given as mean (SE), unless otherwise indicated.
The methodology was consistent across different environments; the results of the in-clinic studies were similar to those carried out in subjects’ homes, and the studies located in India were comparable to those in the South African study. Our computerized methodology is noninvasive, portable, and easy to use, allowing us to carry out clinical studies in unattended ambulatory real-life settings within the patients’ home environments. The in-home studies are clearly more relevant than in-clinic studies for studying the effects of OTC drugs. In addition, the methodology was sensitive enough to pick up treatment differences for OTC medications in which the percentage differences are not expected to be large.

Figure 3. Results of the subgroup analysis, showing a plot of cough effort vs capsule/liquid dose form by treatment, at 30-min assessment; showing least-squared means ± 1 SE.

Figure 4. Results of the subgroup analysis, demonstrating a plot of AUC for cough effort vs dry or nondry cough, by treatment. Values are given as least-squared mean ± SE. See Figure 3 legend for expansion of abbreviations.
The meta-analysis showed consistent results across most of the studies for each of the cough efficacy variables. It demonstrated significantly greater overall reductions in cough bouts, cough components, and cough effort, and an increase in cough latency when a subject received a single dose of dextromethorphan, 30 mg, compared with placebo (with respect to AUC and cumulated total) in subjects with acute cough due to uncomplicated URTI. Although consistent directional differences were seen in our six individual efficacy studies in favor of dextromethorphan (changes being close to those reported in Table 3), the differences were not usually statistically significant due to the small study size. Therefore, it can be seen that studies need to be adequately powered with a large number of subjects (see example below).

The average treatment difference for dextromethorphan, 30 mg, vs placebo was 12 to 17% for our efficacy parameters, which is generally in line with previous research on dextromethorphan as an antitussive. Clearly, this treatment effect is relatively small, and we have shown that a large cohort of subjects is required because of this, as well as the fact, well-recognized among researchers, that there are inherent difficulties in this kind of study due to the variability of cough as a condition. Data from our meta-analysis for cough bouts show that detection of a 17% difference at the one-sided (α = 0.1) level of significance and 80% power would require 101 subjects per group.

Because the research we have presented concerns acute cough associated with uncomplicated URTI using objective measurements, we have extended previous work carried out on dextromethorphan. Although there are a number of published studies describing the effect of dextromethorphan on chronic pathologic cough and artificially induced cough, there seem to be only three studies that address acute cough in URTI. Of these, just one used objective, in addition to subjective, methods to assess cough. This study showed changes quantitatively similar to those in our study for dextromethorphan, 30 mg, vs placebo, but there was seldom a significant difference between the two treatments—presumably because, as with our individual studies, their cohort was small (43 subjects). However, as we have shown above, data presented herein suggest that, to be confident in seeing statistically significant differences, a higher number of subjects is needed. Our individual studies were designed with treatment groups of dextromethorphan, 30 mg, vs placebo, using a minimum number of subjects to validate the methodology and not to show the efficacy of dextromethorphan. When the meta-analysis was carried out, the results emerged as powerful and new objective evidence of the antitussive effect of dextromethorphan, even though this effect was relatively small.

Another observation was that segmenting on the basis of the severity of baseline cough did not generally show treatment differences. This indicates that dextromethorphan has a consistent antitussive effect whether the cough is mild, moderate, or severe, which is appropriate for its use as an OTC medication for acute cough associated with the common cold.

We also studied the effects of other potentially confounding variables, in particular dry vs nondry cough and the dose form of dextromethorphan (liquid vs capsule). We found that the treatment differences tended to be greater in subjects with dry cough, compared with those with nondry cough and that the liquid dose was consistently faster acting than the capsule dose. It should be noted that this treatment difference between liquid and capsule dose form may have been partly due to the fact that the liquid formulation contained coolants, such as menthol, which the capsule form did not.

Cough intensity was not consistent between studies. However, this is to be expected in an acute cough model because intensity is an indication of the effectiveness of a cough, which is more relevant in chronic cough where sputum is expectorated (and an effective expectorant will cause the objective measure of cough intensity to decrease). In subjects with acute cough, the effectiveness of the cough would not be expected to alter, because there is little or no sputum associated with it, and antitussives that control the frequency of coughing are appropriate.

We have shown that the important parameters of cough in which significant differences were seen for dextromethorphan vs placebo were cough bouts, cough components, and cough latency, all measures relating to the frequency of cough, and also to cough effort. However, unlike other methods, our computerized cough acquisition system has the advantage, because it can reliably measure other parameters, like cough intensity; therefore, the system has the capability to evaluate comprehensively other antitussive and expectorant agents in the future.

In these studies, the methodology was applied, by means of the meta-analysis, to provide new objective support for the known antitussive effectiveness of dextromethorphan, and, given that placebo is generally believed to show some degree of treatment benefit itself, it can be noted that the 12 to 17% measured difference really constitutes the activity of dextromethorphan over and above that of the placebo effect.
CONCLUSION

We have developed a reliable, noninvasive computerized methodology that is calibrated and validated for objectively assessing the efficacy of antitussives by measuring a comprehensive range of parameters. We have presented the results of a meta-analysis of six clinical trials using this methodology and have shown that the antitussive effect of a single, oral 30-mg dose of dextromethorphan has been reproducibly established in these studies in acute cough due to uncomplicated URTI. We have also shown that studies should be appropriately powered to show significant results in this context.

This work has clearly demonstrated the small but genuine efficacy of dextromethorphan, over and above any beneficial effect of placebo itself, using simple presentations of dextromethorphan and placebos. Future work is required to determine whether this method is universally applicable to other product forms or formulations.

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