

Effect of codeine on objective measurement of cough in chronic obstructive pulmonary disease

Jaclyn Smith, MD, PhD,^a Emily Owen, MPhil,^a John Earis, MD,^b and Ashley Woodcock, MD^a

Manchester and Liverpool, United Kingdom

Background: Codeine is the standard antitussive treatment to which novel agents are compared. Little is known about the objective effect of any treatments on cough in chronic obstructive pulmonary disease (COPD).

Objective: To quantify the effect of codeine on objective cough frequency (quantified as time spent coughing: cough seconds, cs/h), citric acid cough threshold, and subjective measures in a double-blind, placebo-controlled crossover study in COPD.

Methods: We studied 21 patients with physician-diagnosed, stable disease who complained of cough (76.9% male; mean age, 67.7 years; mean predicted FEV₁, 53.4%; median smoking history, 43.5 pack-years). Each subject performed a cough challenge (single breath, citric acid), 10-hour daytime ambulatory and overnight cough recordings, subjective cough scores, and visual analog scales at baseline and on 2 study days, 1 week apart. Codeine phosphate 60 mg or matched placebo were given, in random order, at the start of each cough recording (0 and 12 hours).

Results: Median time spent coughing at baseline was 8.27 cs/h (interquartile range [IQR], 5.94-11.67); after placebo treatment, 7.22 cs/h (IQR 4.42-10.40); and after codeine treatment, 6.41 cs/h (IQR 3.86-9.10). Codeine treatment had a significant effect on time spent coughing compared with baseline ($P = .02$) but not compared with placebo ($P = .52$).

There were no significant differences in cough challenge thresholds (log concentration of tussive agent causing 2 coughs or log concentration of tussive agent causing 5 coughs) or subjective cough measures for codeine compared with placebo. **Conclusion:** In this study, codeine was no more effective than placebo in patients with COPD complaining of cough.

Clinical implications: Codeine is the antitussive agent to which we compare new treatments; however, in a group of stable patients with COPD, it had no effect on cough frequency over placebo. (J Allergy Clin Immunol 2006;117:831-5.)

Key words: Antitussives, chronic bronchitis, placebo, chronic obstructive pulmonary disease, cough, cough monitoring

Abbreviations used

C2: Concentration of tussive agent causing 2 coughs

C5: Concentration of tussive agent causing 5 coughs

COPD: Chronic obstructive pulmonary disease

cs: Cough seconds

IQR: Interquartile range

VAS: Visual analog scale

Cough is the most common symptom reported by patients with chronic obstructive pulmonary disease (COPD).¹ A study comparing 2 specific cough quality of life questionnaires (Leicester Cough Questionnaire² and Cough Quality of Life Questionnaire³) found that patients with COPD have similar cough-related quality of life impairment to patients presenting with chronic cough.⁴ Ambulatory cough monitoring has been technically challenging and laborious. Hence we know very little about the efficacy of antitussives or current standard treatments on cough in COPD. In 1 study of cough reflex sensitivity in COPD, anticholinergic therapy was associated with a more sensitive cough reflex.⁵ We have recently shown that the assessment of cough by challenge thresholds and symptom scores is a poor predictor of cough frequency during ambulatory monitoring in stable COPD.⁶ Their value in predicting objective response to an antitussive treatment is unknown.

Codeine is widely prescribed as an antitussive agent and is accepted as the standard treatment against which other antitussive agents should be compared. However, only a small number of trials have objectively examined the efficacy of codeine for cough, and none specifically in COPD. Laboratory-based trials, with important limitations, have suggested a significant antitussive effect for codeine using objective cough monitoring in patients with cough of mixed etiology.⁷⁻¹¹ Studies of codeine on cough reflex sensitivity have produced inconsistent results.¹²⁻¹⁴ Several studies in healthy subjects with upper respiratory tract infections have included some objective cough monitoring for short periods and have failed to show any effect above placebo.¹⁵⁻¹⁷

Over-the-counter treatments for cough have recently been the subject of a Cochrane review^{18,19} concluding that there was no good evidence for the effectiveness of these treatments because of a lack of good quality research. The measurement of the efficacy of any antitussive drug is currently hampered by the lack of objective measures of

From ^athe North West Lung Centre, South Manchester University Hospitals Trust, Manchester; and ^bthe Aintree Chest Centre, University Hospital Aintree, Liverpool.

Supported by an educational grant from GlaxoSmithKline Ltd.

Disclosure of potential conflict of interest: The authors have declared they have no conflict of interest.

Received for publication August 2, 2005; revised September 14, 2005; accepted for publication September 16, 2005.

Available online February 7, 2006.

Reprint requests: Jaclyn Smith, PhD, North West Lung Research Centre, Wythenshawe Hospital, Southmoor Rd, Wythenshawe, Manchester M23 9LT, United Kingdom. E-mail: jackyannsmith@hotmail.com.

0091-6749/\$32.00

© 2006 American Academy of Allergy, Asthma and Immunology

doi:10.1016/j.jaci.2005.09.055

TABLE I. Subjective cough scoring system for daytime and overnight cough

Score	Daytime	Score	Nighttime
0	No cough during the day	0	No cough during the night
1	Cough for 1 short period	1	Cough on waking only
2	Cough for more than 2 short periods	2	Wake once or early because of cough
3	Frequent coughing which did not interfere with usual daytime activities	3	Frequent waking because of coughs
4	Frequent coughing which did interfere with usual daytime activities	4	Frequent coughs most of the night
5	Distressing cough most of the day	5	Distressing cough most of the night

Reprinted with permission from Hsu et al.²⁶

cough and a lack of clarity in the meaning of subjective measures and cough challenge models.

We have developed an ambulatory digital recording system by adapting a portable mp3 (Moving Picture Experts Group 1 layer 3) player/recorder. This allows cough sounds to be recorded and quantified manually with the assistance of custom-written software. We hypothesized that codeine would produce a greater than 30% reduction in time spent coughing (cough seconds, cs) over placebo, using our cough recording system. We describe a randomized, double-blind, placebo-controlled crossover study of codeine in patients with stable COPD and chronic cough. Cough was assessed by 4 different measures: (1) ambulatory cough monitoring, (2) cough reflex sensitivity, (3) subjective scores, and (4) visual analog scales.

METHODS

Subjects

Patients with stable COPD (FEV₁ 30-75% predicted) who complained of cough (subjective cough score of 2 or more; Table I) were invited for screening. Patients with exacerbations in the last month, previous acute hypercapnic ventilatory failure, or low transcutaneous oxygen saturation (<92%) were excluded. Current smokers and patients who reported a history of gastroesophageal reflux disease, postnasal drip, and asthma were ineligible. The study was approved by the Local Research Ethics Committee, and all subjects gave written, informed consent.

A sample size calculation and a minimum cough rate for inclusion were based on existing data.⁷ Twenty subjects would have 80% power to detect a reduction of 20% in cough for codeine compared with placebo (assuming an average of 80 cs and SD for the change of 30 cs) using a paired *t* test and the conventional 5% significance level.

Screening

Patients attended at 0900 hours, and spirometry (Vitalograph Ltd, Buckingham, United Kingdom), arterial oxygen saturation (Pulsox-3, Konica Minolta Holdings Inc, Tokyo, Japan), and exhaled carbon monoxide (Bedfont Scientific Ltd, Rochester, United Kingdom) were measured.

TABLE II. Demographics and baseline characteristics of randomized patients

	Mean ± SD (unless otherwise stated)
Age	68.0 y (±6.86)
Sex	M:F 14:5
FEV ₁ % predicted	53.83% (±13.25)
FEV ₁ /FVC ratio	59.47% (±8.46)
Smoking history	Median 52.49 pack-years (17-135)
Duration of cough	Median 9.0 y (3-72)
Productive cough	73.7%

FVC, Forced vital capacity.

A citric acid cough challenge test was performed.²⁰ Briefly, 6 ascending concentrations of citric acid (0.03 mol/L to 1 mol/L) were delivered as a series of single breath inhalations (Mefar Dosimeter, Brescia, Italy). Three inhalations of normal saline were randomly interspersed; the operator and subject were blind to their position. After each inhalation, coughs in the subsequent minute were counted by 2 experienced observers. The concentration of citric acid inducing 2 and 5 coughs (C2 and C5) was noted.

Daytime ambulatory cough recording commenced after the cough challenge was completed. Cough sounds were recorded digitally at home for 10 hours (Nomad Jukebox 3; Creative Technology Ltd, Singapore) from a lapel microphone (AOI, ECM-1025) positioned 30 cm from the mouth. Overnight recordings (10 hours) were set up at the bedside by a technician who visited the patient at home. Cough recordings were transferred to a personal computer and archived on compact disc. Recordings were compressed with custom written software removing silences and low amplitude sounds. For each recording period coughs were counted manually in cough seconds, the number of seconds in which explosive cough sounds were present.

Subjective cough was assessed by using a cough symptom score²¹ (Table I) and a 100-mm visual analog scale (VAS), from “no cough” (0 mm) to “worst cough” (100 mm).^{2,21}

Randomized study

Patients with more than 80 cs on 20 hours ambulatory monitoring entered the randomized study and attended on 2 further occasions at intervals of 7 to 10 days. Randomization of the treatment order for codeine and placebo was performed independently by the hospital pharmacy. Allocation was concealed by the use of numbered containers for study medication.

Patients attended at 0800 h on both study days. They received overencapsulated codeine 60 mg or matched placebo in random order and again after 12 hours (2000 h)—that is, 1 hour before the day and night recording. Codeine and placebo capsules were identical in appearance. A dissolution test was performed on the overencapsulated codeine, showing the capsule dissolved in less than 15 minutes. Dosing and monitoring times were based on codeine pharmacokinetics.¹¹

The daytime cough recording commenced at 0900 h and overnight recording at 2100 h. Monitoring was suspended during the citric acid cough challenge (1000 h). Subjective cough scores were performed the next day. Between visits, patients took only their routine therapy. The procedures performed on each study day were identical. All data were analyzed blind.

Statistical analyses

Cough rates were log₁₀-transformed for analysis and comparisons made among baseline, placebo, and codeine using a repeat-measures

TABLE III. Summary of measures of cough at baseline and after treatment with codeine and placebo, for day and night*

	Baseline	Placebo	Codeine
Cough frequency (cs/h), median (IQR)			
Day	13.8 (10.5-17.4)	11.1 (7.7-16.4)	10.7 (6.2-14.6)
Night	2.1 (1.0-4.3)	2.0 (0.9-3.5)	1.9 (1.1-3.6)
Cough score, mean ($\pm$ SD)			
Day	2.8 ($\pm$ 0.7)	2.7 ($\pm$ 0.6)	2.8 ($\pm$ 1.0)
Night	1.7 ($\pm$ 1.0)	1.7 ($\pm$ 1.2)	1.4 ($\pm$ 0.9)
VAS (mm), median (IQR)			
Day	44 (32-66)	27 (11-61)	24 (11-63)
Night	12 (8-38)	17 (12-47)	7 (6-19)
Log C5 median (IQR)	-1.20 (-1.50 to -0.9)	-0.60 (-1.21 to -1.05)	-0.90 (-1.2 to -0.6)
Log C2 median (IQR)	-1.21 (-1.50 to -1.20)	-1.05 (-1.50 to -0.88)	-1.21 (-1.5 to -0.9)

*Cough frequency is quantified as time spent coughing in cs/h, cough score is as per Table I, and cough challenge result as $\log_{10}$ of molar concentration of citric acid inducing 2 coughs (C2) and 5 coughs (C5), respectively.

ANOVA (SPSS Inc, Chicago, Ill). Cough challenges and VAS results were analyzed by using the Friedman test.

RESULTS

Twenty-six patients were screened, 21 patients met the inclusion criteria and were enrolled in the randomized study, and 19 patients completed the study. Fourteen were male subjects, and subjects had a mean age of 68.0 ± 6.86 years (Table II). One patient did not complete both treatment days because of an episode of gastroenteritis, and 1 patient had an exacerbation related to paint fumes and was excluded. Complete data on 19 subjects are presented (Table III) and were analyzed. Two subjects complained of drowsiness, one on both study days, the other on the codeine study day. No other adverse reactions were reported.

Ambulatory cough monitoring

Median baseline cough rate was 8.27 cs/h (interquartile range [IQR], 5.94-11.67, cumulative for day and night), placebo rate was 7.22 cs/h (IQR, 4.42-10.40), and codeine rate was 6.41 cs/h (IQR, 3.86-9.10; Fig 1). For $\log_{10}$ -transformed cough rates, there were significant differences among baseline, placebo, and codeine cough rates (repeat-measures ANOVA, $F = 4.97$, $df = 2$, $P = .02$). These were a result of significant differences between baseline and both codeine and placebo rates (t test $P = .02$ and $P = .03$, respectively). There was no significant difference in time spent coughing between codeine treatment and placebo ($P = .52$). No significant period effect was found.

On the basis of the within-subject variation in the difference between log-transformed cough rates on placebo and codeine, the study ($n = 19$) would have 80% power to detect a 25% reduction in cough rate. In fact, only a 4% reduction in cough rate (geometric mean difference of 1.1 cs/h; 95% CI, 0.89-1.25 cs/h) was observed for codeine compared with placebo treatment.

When the day and nighttime cough rates are considered separately, the differences among baseline, codeine, and placebo treatments is seen by day ($F = 3.72$; $df = 2$; $P =$

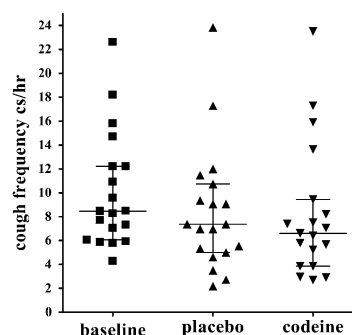


FIG 1. Time spent coughing on baseline study day and after treatment with codeine and placebo. Horizontal lines represent median time spent coughing and error bars the IQR.

.05) but not by night ($F = 0.56$; $df = 2$; $P = .48$). This may be a result of the much lower cough rates overnight.

The temporal distribution of cough at baseline with codeine and placebo treatment was examined to identify any short-lived effects (Fig 2). Cough varied substantially during the day, with different patterns in different individuals. The median hourly data conceal the degree of individual variability. In patients with stable COPD, cough effectively stops throughout the night. Cough was highest in the morning of the screening day; this may represent patient's unfamiliarity with the equipment and their awareness of having their cough monitored.

Citric acid cough threshold

There was no significant difference among codeine, placebo, and baseline for cough reflex sensitivity as measured by log C5 or log C2 (Friedman test; $P = .12$ and $P = .46$, respectively).

Subjective cough measures

Mean subjective cough scores showed little change throughout the study. There was no significant difference between subjective cough scores at baseline, with codeine or placebo treatment, for both day and night ($F = 0.453$, $df = 2$, $P = .59$; and $F = 0.68$, $df = 2$, $P = .50$, respectively). For daytime VAS, there was a trend toward a

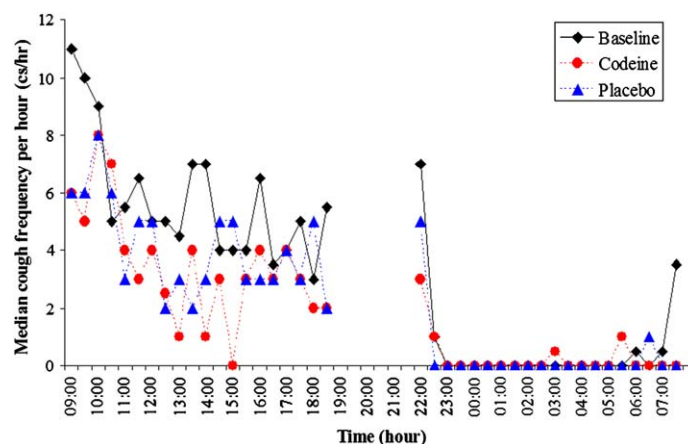


FIG 2. Temporal distribution of cough on each study day. The median cough rate is plotted for each 30-minute time interval for day and night on each study day.

significance between the scores ($P = .11$), but no significant difference between codeine and placebo ($P = .96$). For overnight VAS, there was no significant difference between the 3 measurements ($P = .25$).

There were no significant correlations between the change in time spent coughing and the change in cough threshold ($r = -0.27$; $P = .30$), change in cough score (day $r = -0.07$, $P = .78$; night $r = 0.17$, $P = .48$), or change in VAS (day $r = -0.07$, $P = .79$; night $r = 0.30$, $P = .24$).

DISCUSSION

This is the first double-blind, randomized, placebo-controlled study to use a range of outcomes, including ambulatory cough monitoring, to assess the efficacy of an antitussive agent in COPD. It shows that codeine has no additional antitussive effect above that of placebo in patients with stable COPD who complained of cough. However, both codeine and placebo showed substantial reductions in time spent coughing during the day compared with baseline, underlining the necessity for appropriately designed placebo-controlled studies for the assessment of antitussives. Unlike postviral cough, cough rates in stable COPD are not likely to improve over time. We tested for a significant change in cough rate in relation to the order of treatment and found none.

Because there is no difference between codeine and placebo for the gold standard measure of ambulatory cough rate, it is not possible to compare the validity of the other cough measures to detect change. However, the change in C5 and C2 thresholds, symptom scores, and visual analog scores did not correlate with the change in cough between baseline and the randomized treatments. This suggests that these measures are less related to cough rates and more influenced by how patients perceive cough.

Post hoc repeat of the power calculation, based on the actual within-subject variation in the difference between log-transformed cough rates, shows that the power of our

study was still adequate. The nonsignificant numerical difference between codeine and placebo in time spent coughing was unlikely to be of any clinical importance, although the size of antitussive effect that is clinically important or appreciated by the patient remains unknown. Further work is needed because this value may not be the same in the different conditions that cause cough.

Ambulatory cough monitoring with digital recording of cough sounds is feasible, but manual counting (even with computer assistance) is time-consuming and laborious. Automated cough analysis is under development, and current computer algorithms do provide reasonable sensitivity and specificity for quiet nighttime recordings.²² However, daytime recordings with extraneous noise and substantial amounts of speech have proved technically challenging, with many false positives. The recognition that the sound signal of cough varies widely between different individuals²³ and different diseases^{24,25} may necessitate an individually optimized algorithm rather than a single generic cough monitor.

The advantage of ambulatory cough monitoring is that patients can be monitored in their own environment. The symptom of cough is under substantial voluntary control. It is noticeable that cough rates are highest during the first hour of recording and may be prone to the Hawthorn effect—that cough rates are affected by the subjects' knowledge that their cough has been monitored. This is a particular problem for laboratory-based cough studies and may in part account for the very stable cough rates seen in some studies,⁷ which contrast with the widely varying cough rates seen in ambulatory studies.²⁶ Adaptation of commercial recording equipment meant it was not possible to make continuous 24-hour recordings in this study; increases in the memory capacity of devices should soon make this possible.

The quantification of cough is problematic. Previous studies have apparently counted single explosive cough sounds, but, for example, should a peel of coughs in 1 breath constitute 1 cough epoch or several individual coughs? Cough monitors identifying epochs of coughing

are likely to underestimate any benefit from an antitussive that shortens these epochs.^{26,27} In our study, the primary endpoint was time spent coughing (cs), a parameter that overcomes these difficulties. This may still miss an effect on cough intensity; it is possible to derive an estimate of this from the sound recordings, but further work is needed.

The dose of codeine used here far exceeds that in over-the-counter cough remedies and is in excess of that used in many previous studies.^{7,14,15,17} This study examines chronic cough in patients with stable COPD. Cough in COPD may be valuable in clearing small amounts of sputum, and may not respond well to an antitussive. Also, the effect of more prolonged treatment with multiple doses may have been different. Recent studies of cough in upper respiratory tract infections have also failed to demonstrate an antitussive effect of codeine¹⁵⁻¹⁷ and dextromethorphan.²⁸ The only studies to suggest a significant effect on cough studied subjects in laboratory conditions.⁷⁻¹¹ In these studies, patients may have been able to detect codeine from placebo because of its bitter taste; in the current study, this was avoided by using overencapsulated tablets. In the current study, subjects who reported symptoms of gastrointestinal reflux and postnasal drip were excluded, but it is impossible to be certain that COPD was the sole cause of their cough. Nevertheless, this study is consistent with the view that any antitussive effect of codeine is attributable to a placebo effect.^{29,30} When several studies of dextromethorphan in upper respiratory tract infection were combined for more than 700 subjects, only a 17% reduction in cough could be detected over placebo.³¹ Whether this is of clinical value is questionable. Further appropriately placebo-controlled studies of cough in other clinical situations are urgently needed if the widely prescribed antitussive remedies are to be continued to be used.

We thank all of the patients who agreed to take part in the study; Kevin McGuiness for adapting and maintaining the recording equipment; Yen Ha Hiew, David Tait, and Barry Cheetham for software to assist in cough counting; and GlaxoSmithKline for the educational grant that funded this study.

REFERENCES

1. Rennard S, Decramer M, Calverley PM, Pride NB, Soriano JB, Vermeire PA, et al. Impact of COPD in North America and Europe in 2000: subjects' perspective of Confronting COPD International Survey. *Eur Respir J* 2002;20:799-805.
2. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;58:339-43.
3. French CT, Irwin RS, Fletcher KE, Adams TM. Evaluation of a cough-specific quality-of-life questionnaire. *Chest* 2002;121:1123-31.
4. Yaman MN, Patterson N, Heaney LG, McGarvey LP. A cross-sectional comparison of two cough specific health related quality of life questionnaires. *Thorax* 2003;58(suppl 3):iii43.
5. Doherty MJ, Mister R, Pearson MG, Calverley PM. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. *Thorax* 2000;55:643-9.
6. Smith JA, Hambleton EC, Earis JE, Woodcock AA. Measurements of cough in chronic obstructive pulmonary disease. *Thorax* 2003;58(suppl 3):iii48.
7. Matthys H, Bleicher B, Bleicher U. Dextromethorphan and codeine: objective assessment of antitussive activity in patients with chronic cough. *J Int Med Res* 1983;11:92-100.
8. Sevelius H, McCoy JF, Colmore JP. Dose response to codeine in patients with chronic cough. *Clin Pharmacol Ther* 1971;12:449-55.
9. Woolf CR, Rosenberg A. Objective assessment of cough suppressants under clinical conditions using a tape recorder system. *Thorax* 1964;19:125-30.
10. Sevelius H, Colmore JP. Objective assessment of antitussive agents in patients with chronic cough. *J New Drugs* 1966;6:216-23.
11. Aylward M, Maddock J, Davies DE, Protheroe DA, Leideman T. Dextromethorphan and codeine: comparison of plasma kinetics and antitussive effects. *Eur J Respir Dis* 1984;65:283-91.
12. Cox ID, Wallis PJ, Apps MC, Hughes DT, Empey DW, Osman RC, et al. An electromyographic method of objectively assessing cough intensity and use of the method to assess effects of codeine on the dose-response curve to citric acid. *Br J Clin Pharmacol* 1984;18:377-82.
13. Dilworth JP, Pounsford JC, White RJ. Cough threshold after upper abdominal surgery. *Thorax* 1990;45:207-9.
14. Empey DW, Laitinen LA, Young GA, Bye CE, Hughes DT. Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscaphine 30 mg using citric acid-induced cough in normal subjects. *Eur J Clin Pharmacol* 1979;16:393-7.
15. Eccles R, Morris S, Jawad M. Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. *J Clin Pharm Ther* 1992;17:175-80.
16. Freestone C, Eccles R. Assessment of the antitussive efficacy of codeine in cough associated with common cold. *J Pharm Pharmacol* 1997;49:1045-9.
17. Freestone C, Eccles R, Morris S, Jawad MS. Assessment of the antitussive efficacy of codeine using cough sound pressure levels as a means of measuring cough. *Pulm Pharmacol* 1997;9:365.
18. Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev* 2004;4:CD001831.
19. Schroeder K, Fahey T. Systematic review of randomised controlled trials of over the counter cough medicines for acute cough in adults. *BMJ* 2002;324:329-31.
20. Morice AH, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol* 2001;52:365-75.
21. Chang AB, Newman RG, Carlin JB, Phelan PD, Robertson CF. Subjective scoring of cough in children: parent-completed vs child-completed diary cards vs an objective method. *Eur Respir J* 1998;11:462-6.
22. Hiew Y, Smith JA, Tait D, Cheetham BMG, Earis JE, Woodcock AA. DSP algorithm for cough identification and counting. *IEEE International Conference on Acoustics, Speech, and Signal Processing, Proceedings 2002;Volume 4:IV-3888-91.*
23. Olia PM, Sestini P, Vagliasindi M. Acoustic parameters of voluntary cough in healthy non-smoking subjects. *Respirology* 2000;5:271-5.
24. Thorpe CW, Toop LJ, Dawson KP. Towards a quantitative description of asthmatic cough sounds. *Eur Respir J* 1992;5:685-92.
25. Smith JA, Earis A, Woodcock AA, Earis JE. Acoustic properties of spontaneous coughs in common respiratory diseases. *Am J Respir Crit Care Med* 2004;169:A200.
26. Hsu JY, Stone RA, Logan-Sinclair RB, Worsdell M, Busst CM, Chung KF. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. *Eur Respir J* 1994;7:1246-53.
27. Hamutcu R, Francis J, Karakoc F, Bush A. Objective monitoring of cough in children with cystic fibrosis. *Pediatr Pulmonol* 2002;34:331-5.
28. Paul IM, Yoder KE, Crowell KR, Shaffer ML, McMillan HS, Carlson LC, et al. Effect of dextromethorphan, diphenhydramine, and placebo on nocturnal cough and sleep quality for coughing children and their parents. *Pediatrics* 2004;114:e85-90.
29. Eccles R. The powerful placebo in cough studies? *Pulm Pharmacol Ther* 2002;15:303-8.
30. Lee PCL, Jawad MS, Eccles R. Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory tract infection. *J Pharm Pharmacol* 2000;52:1137-42.
31. Pavesi L, Subburaj S, Porter-Shaw K. Application and validation of a computerized cough acquisition system for objective monitoring of acute cough: a meta-analysis. *Chest* 2001;120:1121-8.