Chronic Cough: How Do Cough Reflex Sensitivity And Subjective Assessments Correlate With Objective Cough Counts During Ambulatory Monitoring?

Samantha Decalmer, Deborah Webster, Angela Kelsall, Kevin McGuinness, Ashley Woodcock and Jaclyn Smith
University of Manchester, North West Lung Centre, South Manchester University Hospitals Trust, Manchester, UK

Correspondence:

Dr Samantha Decalmer,
North West Lung Research Centre,
Wythenshawe Hospital, Southmoor Rd,
Wythenshawe, Manchester M23 9LT,
United Kingdom

Telephone +44 161 291 5031
Fax +44 161 291 5057
Email samdecalmer@hotmail.com

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Abstract

Background: Cough reflex sensitivity, subjective estimates of cough frequency and cough related quality of life have been used to assess cough and monitor treatment responses. The relationships between these measures and objective cough monitoring remains unclear and the usefulness of subjective assessments, questionable.

Subjects: 62 patients with chronic cough (39 female) were studied. Mean age of subjects was 54.9 years (±12.2), with a median duration of cough of 5.5 years (range 1-30).

Methods: Cough reflex sensitivity testing (C5; citric acid) was performed in all subjects prior to fully ambulatory day and night-time cough recordings. Patients scored the frequency and severity of their cough (visual analogue scales and 0-5 score) for each recording period and completed a cough related quality of life questionnaire, Leicester Cough Questionnaire (LCQ). Ambulatory cough recordings were manually counted and reported in terms of cough seconds per hour (cs/hr). Cough rates were Log10 transformed for analysis.

Results: The median time spent coughing was 11.36cs/hr (range 1.06-46) with median day rates of 15.59cs/hr (range 2-74.8) and median night rates of 2.94cs/hr (range 0-26.67). An inverse relationship was seen between day cough rates and Log10 C5 (r=-0.452 p=<0.001). Subjective cough scores and visual analogue scales were only moderately associated with objective time spent coughing, with night-time scores more strongly associated than day. The strongest correlation with objective cough frequency was cough related quality of life (LCQ), (r=-0.622, p=<0.001), mediated via the psychological domain.

Conclusions: Subjective measures of cough and cough reflex sensitivity are only moderately related to objective time spent coughing, so cannot be used as surrogate markers for objective cough frequency measurements. Cough related quality of life (LCQ) is most strongly related to objectively counted cough, and may be a useful adjunct to objective measures in the assessment of cough.
**Key Words**
Ambulatory monitoring of cough
Cough challenge
Citric acid
Chronic Cough
<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description</th>
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<tbody>
<tr>
<td>LCQ</td>
<td>Leicester Cough Questionnaire</td>
</tr>
<tr>
<td>Log C&lt;sub&gt;5&lt;/sub&gt;</td>
<td>Logarithmic transformation of concentration causing 5 coughs</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>cs/hr</td>
<td>Cough Seconds per hour</td>
</tr>
</tbody>
</table>
Introduction

Cough is the most common respiratory complaint for which medical attention is sought, and its impact is reflected in the £93 million spent on over the counter anti-tussives each year in the UK. Most cough is acute and self-limiting, secondary to respiratory tract infection, but when cough becomes chronic (>8 weeks duration) it can account for up to one third of all referrals to chest physicians.

Chronic cough has a major impact on quality of life and patients consume substantial healthcare resources, often seeing several specialists over many years. It may prove diagnostically difficult, requiring multiple investigations and treatment trials with diagnostic success quoted as ranging from 100% within a general respiratory clinic setting, to 58% within the specialist cough clinic setting.

Assessment of cough and its response to treatment has mainly been based on subjective symptom perception using cough diary scores and cough visual analogue scales (VAS). However, the lack of an objective gold standard in terms of objectively counted cough has meant that it has been impossible to assess the relative value of these different subjective measures. Cough reflex sensitivity testing has also been employed as a surrogate index of disease severity, although it is not disease specific. The dose of an inhaled tussogenic substance such as citric acid or capsaicin (usually which induces 5 coughs in the minute after inhalation – C5) is reduced amongst patients with chronic cough and increases following successful treatment. A study of 7 patients found a strong correlation with objective cough monitoring in adults with chronic cough when monitored for a short period (6 hours) during the day, but whether this relationship holds for prolonged ambulatory, and especially home monitoring, is not known.

Cough specific quality of life questionnaires have been developed, psychometrically tested and found to be reproducible and valid when compared to other quality of life measures. These have been used to monitor treatment responses and the Leicester Cough Questionnaire (LCQ) correlates with short daytime recordings of objective cough counts. This relationship has not been explored with 24 hour monitoring at home, where a quality of life measurement is most relevant.

An objective measure of cough would be very valuable in the assessment of frequency, diurnal variation and treatment responses. The ideal cough monitor would be robust, unobtrusive and portable, and allow recording over at least 24 hours. It would be operator friendly, and able to identify all coughs, distinguishing them from all speech, sneezing, laughter and background noise, automatically. To date, an automated monitor has been used to study cough in COPD in a controlled, non ambulatory setting. This has been validated against video data but sensitivity is low. Ambulatory monitors with manual counting have been used in chronic cough patients but for short periods only (6 hours).
We have developed a method for fully ambulatory cough recording, validated against manual cough counts from video recordings\textsuperscript{17-19} which is responsive to change\textsuperscript{20}. Currently coughs are counted manually and quantified in terms of cough seconds per hour, defined as the number of seconds containing at least one explosive cough sound\textsuperscript{17 21}, with excellent inter and intra-observer agreement\textsuperscript{17 21}.

The aim of this study was to explore the relationships between subjective cough scores, cough quality of life, cough reflex sensitivity, and objective time spent coughing derived from ambulatory home recordings in patients with chronic cough.

**Methods and Materials**

Consecutive patients with chronic cough (> 8 weeks duration), who were referred to the tertiary referral cough clinic at the North West Lung Centre, were studied. Current smokers, ex-smoker of less than 6 months duration, those with a respiratory tract infection in the preceding month and subjects taking ACE inhibitors or opiates were excluded. Diagnosis of the underlying cause of chronic cough was established from the history, investigations and trials of treatment. Investigations in addition to those reported here included 24 hour pH monitoring, bronchoscopy, CT scanning and ENT examination. Diagnoses were established when resolution or significant improvement of the cough occurred with specific therapy. Those patients without significant findings on investigation and no response to treatment were considered idiopathic. All measures of cough were performed prior to investigation or trials of treatment.

The study was approved by the Local Research Ethics Committee and all subjects gave written, informed consent. A sample size of 62 subjects would have 80\% power to detect correlation coefficients of 0.35 and above. In a previous study in patients with Chronic Obstructive Pulmonary Disease\textsuperscript{22} we found that the weakest correlation was between objective cough rate and cough scores (0.37), hence we powered this study to detect correlations of this order and above.

**Cough Reflex Sensitivity**

A citric acid cough challenge test was performed to assess the sensitivity of the cough reflex\textsuperscript{23}. Six ascending concentrations (doubling doses from 0.03M to 1M) were delivered as 12\textmu l single breath inhalations (Mefar dosimeter, Italy or KoKo dosimeter, Pds Instrumentation, USA). Three placebo inhalations of normal saline were randomly interspersed, with both operator and subject blinded to their position. Following each inhalation, the number of coughs in the subsequent minute was counted by an experienced observer. The challenge was terminated at the concentration of citric acid which resulted in 5 consecutive coughs (C5).
Objective Time spent coughing

Ambulatory cough recording was commenced immediately after the cough challenge was completed; we have previously found that cough reflex testing does not significantly alter objective cough frequency in the subsequent 24 hours. Patients were discharged from hospital with the cough monitor in place and instructed to return to their normal daily routine. Digital sound recordings were made during the day and overnight as described previously (16 KHz, 16 bit wav format). Cough recordings were transferred from the digital recorders to a personal computer and archived on compact disc. For each recording, coughs were counted manually in “cough seconds” i.e. the number of seconds per hour in which at least one explosive cough sound was present (cs/hr). If coughs occurred as a ‘peel’, that is several cough sounds occurring after one inspiration, the total number of seconds in which these sounds were heard was recorded. We present objective cough data as time spent coughing per hour (cs/hr) for which we have demonstrated a very high level of agreement between observers.

In 10 subjects cough monitoring was repeated after 14 days in order to measure the repeatability of cough seconds.

Subjective Measures of Cough

Patients were asked to subjectively assess their cough severity for the day and night recording periods by means of a visual analogue scale (100mm linear scale marked with a horizontal line by the patient, with 0mm representing “no cough” and 100mm “worst cough”). Subjective scores of cough frequency were measured by a patient completed cough scoring system (Table 1).

Table 1 Cough Scoring system adapted from Hsu et al

<table>
<thead>
<tr>
<th>Score</th>
<th>Daytime</th>
<th>Score</th>
<th>Night-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No cough during the day</td>
<td>0</td>
<td>No cough during the night</td>
</tr>
<tr>
<td>1</td>
<td>Cough for one short period</td>
<td>1</td>
<td>Cough on waking only</td>
</tr>
<tr>
<td>2</td>
<td>Cough for more than two short periods</td>
<td>2</td>
<td>Wake once or early due to cough</td>
</tr>
<tr>
<td>3</td>
<td>Frequent coughing which did not interfere with usual daytime activities</td>
<td>3</td>
<td>Frequent waking due to coughs</td>
</tr>
<tr>
<td>4</td>
<td>Frequent coughing which did interfere with usual daytime activities</td>
<td>4</td>
<td>Frequent coughs most of the night</td>
</tr>
<tr>
<td>5</td>
<td>Distressing cough most of the day</td>
<td>5</td>
<td>Distressing cough most of the night</td>
</tr>
</tbody>
</table>
Cough Related Quality of Life

All patients completed the Leicester Cough Questionnaire (LCQ), a cough specific quality of life measure. This is a nineteen item validated, repeatable and responsive questionnaire which contains physical, social and psychological domains. Answers are graded on a seven point Likert scale giving a total score ranging from 3-21, a higher score indicating a better health status\textsuperscript{14}.

Statistical Analysis

Day, night and total cough rates were positively skewed, logarithmic transformation normalized the distribution of total and daytime rates but not night-time rates. Night-time VAS and night-time cough scores were also positively skewed and were not normalised by logarithmic transformation. All other variables were normally distributed.

To examine correlations between objective and subjective measures, the appropriate parametric and non parametric tests were performed using SPSS version 11.0 (SPSS Inc, Chicago). The relationships between the domains of the LCQ and objective cough rates were examined using a multiple linear regression analysis.
Results

Subjects

From 111 subjects assessed in the cough clinic, 79 met the inclusion criteria for the study. Of these, 66 agreed to participate in the study but 4 patients failed to complete. Data is presented on 62 patients (39 female, 62.9%) with a mean age of 54.9 years (standard deviation ±12.2), mean FEV₁ 101.8 (±16.2) percentage of predicted and mean FVC 107.0 (±15.5) percentage of predicted. The median duration of coughing was 5.5 years (range 1-30). At initial presentation to clinic, 29% (n=18) of patients were taking inhaled steroid, 1.6% (n=1) oral steroid, 1.6% (n=1) nasal steroid, 9.7% (n=6) antihistamine and 35.5% (n=22) PPI. 23 patients were ex-smokers, with a median period of abstinence of 15 years (range 3-35 years).

Based on history, investigation and response to treatment trials diagnosis was established in 64.5% of patients (n=40), the remainder were classed as idiopathic (n=22). One diagnosis was identified in 74.2% of patients, two in 21% and three in 4.8%. The most common diagnosis was gastro-oesophageal reflux disease (GORD) (n=33), followed by post nasal drip (n=8), asthma (n=6), eosinophilic bronchitis (n=2), bronchiectasis (n=2) and tracheopathia osteochondroplastica (n=2). Isolated cases of tracheomalacia, extrinsic allergic alveolitis, endobronchial amyloidosis, emphysema and respiratory bronchiolitis were also identified.
Objective Cough Monitoring
All 62 patients had successful daytime recordings, with 58 having successful overnight recordings (4 patients were unable to initiate overnight recordings in spite of repeated attempts). The median total time spent coughing was 11.36 cough seconds per hour, with a wide range noted (range 1.06-46). Median daytime cough rates of 15.59cs/hr (range 2-74.8) were substantially higher than median night-time rates of 2.94cs/hr (range 0-26.67) (Wilcoxon Signed Rank Test, p=<0.001) (Table 2 and Figure 1).

Table 2 Summary statistics for objective and subjective measures of cough during the day and night (†median (range), *mean (± standard deviation))

<table>
<thead>
<tr>
<th></th>
<th>Day</th>
<th>Night</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Cough Rate cs/hr</td>
<td>15.59 (2-74.8)</td>
<td>2.94 (0-26.7)</td>
<td>p=&lt;0.001*</td>
</tr>
<tr>
<td>Cough Score</td>
<td>2.81 (±0.85)*</td>
<td>1 (0-4)†</td>
<td>p=&lt;0.001*</td>
</tr>
<tr>
<td>Cough VAS in mm</td>
<td>40.6 (±23.7)*</td>
<td>18 (0-87)†</td>
<td>p=&lt;0.001*</td>
</tr>
<tr>
<td>Median C5 (M)</td>
<td>0.25 (0.03-4)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean LogC5 (M)</td>
<td>-0.52 (±0.58)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Wilcoxon Signed Rank Test,

Repeatability of cough monitoring was excellent. Daytime cough rates were similar for both visits [mean/range day 1 and day 14: 13.3cs/hr (2.0 – 22.8) and 12.0 (0.9 - 27.0) respectively, p=0.56] with a mean difference of 1.24 cs/hr (95% limits of agreement -11.3 to 13.8 cs/hr). Overnight cough rates were also reproducible between visits [mean/range day 1 and day 14: 3.7cs/hr (0.0 to 17.2) and 2.67cs/hr (0.51 to 12.64) respectively, p = 0.14], with a mean difference of 1.91cs/hr (95% limits of agreement -5.40 to 9.21cs/hr).

Relationship between Objective Cough Monitoring and Cough Reflex Sensitivity
One patient coughed on a placebo inhalation of normal saline and therefore did not achieve a measurable C5. In the remaining 61 patients the median concentration of citric acid inducing 5 coughs was 0.25M (range 0.03-4). As cough reflex sensitivity was measured during the daytime, we investigated relationships with daytime cough counts only. There was a significant inverse correlation between log10 daytime cough rates and log C5 (Pearson’s r=-0.45, p=<0.001) (Figure2).
Relationship between Objective and Subjective Cough Measures

Subjective cough measures tended to correlate more strongly with objective cough rates for overnight than daytime recordings and the VAS correlated more strongly than cough scores. (Table 3)

Table 3 Correlations between objective and subjective measures of cough in patients with chronic cough; †non parametric correlations.

<table>
<thead>
<tr>
<th></th>
<th>Log Total Time Spent Coughing</th>
<th>Log Day Time Spent Coughing</th>
<th>Log Night Time Spent Coughing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cough Score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day</td>
<td>N/A</td>
<td>r=0.50</td>
<td>N/A</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>night</td>
<td>N/A</td>
<td>N/A</td>
<td>r=0.55†</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td></td>
<td>p=&lt;0.001</td>
</tr>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day</td>
<td>N/A</td>
<td>r= 0.46</td>
<td>N/A</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>night</td>
<td>N/A</td>
<td>N/A</td>
<td>r=0.61†</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td></td>
<td>p=&lt;0.001</td>
</tr>
<tr>
<td><strong>Log_{10} C5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day</td>
<td>N/A</td>
<td>r= - 0.45</td>
<td>N/A</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LCQ</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>r= -0.62</td>
<td>r= -0.54</td>
</tr>
<tr>
<td>p= &lt;0.001</td>
<td></td>
<td>p= &lt;0.001</td>
<td>p= &lt;0.001</td>
</tr>
<tr>
<td>physical</td>
<td></td>
<td>r= -0.55</td>
<td>r= -0.43</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td>p= 0.001</td>
<td>p= &lt;0.001</td>
</tr>
<tr>
<td>psycho</td>
<td></td>
<td>r= -0.59</td>
<td>r= -0.54</td>
</tr>
<tr>
<td>p=&lt;0.001</td>
<td></td>
<td>P= &lt;0.001</td>
<td>p= &lt;0.001</td>
</tr>
<tr>
<td>social</td>
<td></td>
<td>r= -0.55</td>
<td>r= -0.49</td>
</tr>
<tr>
<td>p= &lt;0.001</td>
<td></td>
<td>p= &lt;0.001</td>
<td>p= 0.053</td>
</tr>
</tbody>
</table>
**Cough Score**
Mean daytime scores were 2.82 (SD±0.85) and median night-time scores 1 (range 0-4). Day and night cough scores showed moderate positive correlation with logarithmically transformed objective time spent coughing during the day and night respectively. (Pearson’s, day $r=0.50$, $p<0.001$ and Spearman’s night $r=0.55$, $p<0.001$)

**VAS Scores**
A mean daytime VAS of 40.5 (SD ±23.7) and median night-time VAS of 18 (range 0-87) was seen. These positively correlated with Log$_{10}$ day and night cough rates respectively (Pearson’s, day $r=0.46$, $p<0.001$, Spearman’s night $r=0.61$, $p<0.001$). (Figure 3)

**Cough related Quality of Life (Leicester Cough Questionnaire LCQ)**
All 62 patients completed the LCQ. The median total LCQ score was 12.8 (SD ±3.7); scores for the physical, psychological and social domains were 4.4 (SD ±1.1), 4.3 (SD ±1.5) and 4.1 (SD ±1.5), respectively. A moderately strong negative correlation was seen between Log$_{10}$ total cough rates and total LCQ score (Pearson’s $r=-0.62$, $p<0.001$, (Figure 4 and Table 3). Similar correlations were seen in the physical, psychological and social domains when examined separately (Table 3).

As the LCQ correlated most strongly with total objective cough frequency, a multiple linear regression was used to examine the relative contribution of the sub-domains to this relationship. In this analysis only the psychological domain remained statistically significantly related to objective cough frequency ($B=-0.13$ (95%CI -0.19 to -0.07), $p<0.001$, adjusted for age and gender).

The LCQ also correlated with both day and night cough frequency separately (Table 3). Regression analysis found for daytime, objective cough frequency the psychological sub-domain again was significantly associated ($B=-0.12$ [95% CI -0.20 to -0.03], $p<0.001$). For overnight cough frequency however the physical domain alone was significant ($B=-0.38$ [95% CI -0.57 to -0.20], $p<0.001$). Both analyses were also adjusted for age and gender.
Discussion

This is the first study to examine the relationships between subjective measures of cough severity, cough related quality of life, cough reflex sensitivity and objective cough rates monitored over 24 hours in fully ambulatory adults with chronic cough. Most previous studies have only used either subjective measures of cough, or cough related quality of life questionnaires to assess frequency and severity of cough, and monitor treatment responses. However, it has been impossible to assess their validity in the absence of an objective measure of cough frequency.

We appreciate that the use of cough seconds as a measure of cough frequency is somewhat different from other investigators who report cough sounds. However a strong linear relationship has been demonstrated between cough sounds and cough seconds and excellent inter observer agreement has been noted, making this a comparable measure, giving an indication of overall time spent coughing.17

Cough rates measured in the home environment, with ambulatory monitoring over a 24-hour period, seem lower than those reported previously in the shorter studies in fewer patients, mainly under hospital surveillance. For example, Birring et al recorded mean cough rates of 43 coughs per hour in studies over six hours13. There are a number of possible explanations for the discrepancy; firstly the methods for quantifying cough are different. Cough seconds will always be less than the number of explosive cough phases17. Secondly it is our experience and that of others that cough rate data is positively skewed22,25. The scatter plot of the Birring et al data suggests this data may also be positively skewed and hence the mean would be an inappropriate summary statistic; the median appears to be about 17, i.e. in agreement with our data. Finally the subjects were only monitored for a short period of time (6 hrs) and it is possible that the subjects paid more attention to their urge to cough as they were aware of the cough monitor and hence coughed more. Over longer time periods subjects are more likely to be distracted and be less influenced by the presence of the monitor.

Both cough scores and VAS showed a moderate correlation with cough frequency. The relationship between overnight cough frequency and subjective measures appears to be stronger than for daytime data, in contrast to a previous small study suggesting that night-time cough scores and observed rates failed to correlate7. We speculate that the stronger correlations, seen in our larger data set, between objective night-time cough rates and subjective evaluation may result from sleep disturbance and fatigue. This interpretation tends to be supported by the cough quality of life data which suggested nocturnal coughing was independently related to cough related quality of life, in particular the physical domain.

A post hoc analysis suggested that the strongest relationship existed with the psychological domain of the LCQ. In a recent study, over 50% of patients attending a specialist chronic cough clinic met the criteria on the CES-D (Center for Epidemiologic Studies Depression Scale) for clinical depression.
Furthermore depression scores dramatically improved in patients whose cough was successfully treated. It is possible that psychological problems increase the cough frequency but it would seem more plausible that the patients with the highest cough rates suffer the greatest psychological consequences.

There is limited data on the relationship between cough reflex sensitivity and cough frequency. All the patients in the current study had a measurable cough reflex sensitivity to citric acid. However, many normal volunteers also have a measurable cough reflex sensitivity in the absence of symptoms. We found only a moderate inverse correlation for the sensitivity of the cough reflex (log_{10} C5) with observed cough frequency, suggesting that higher cough rates are only moderately associated with a more sensitive cough reflex. Cough reflex sensitivity testing is probably of most use in gaining insights into the mechanisms by which coughing occurs and treatments have their action, rather than assessing severity of cough or response to treatment.

Manually counting coughs, from ambulatory recordings remains extremely laborious. In spite of this we have found excellent inter and intra-observer agreement and excellent agreement between cough rates over a two-week period. Customised computer software is only now becoming available to allow automated counting of cough. This has proved a technical challenge, especially for daytime recordings where extraneous noise, particularly speech and background coughs may provide false positives. All recordings used in this study were manually counted in their entirety.

Whilst assessment of objective cough rates represents a significant improvement in quantifying coughing, frequency may not be the only parameter that is significant in a patient’s perception of the severity of cough and its impact on quality of life. The intensity or effort of each cough may be important particularly in predicting the physical consequences of coughing. This should be possible in the future and it will be interesting to see whether cough intensity accounts for the remaining variance in subjective measures of cough not explained by cough frequency.

In summary, subjective measures of cough, cough related quality of life, and cough reflex sensitivity correlate modestly with objective measures of cough frequency in chronic cough subjects. Cough frequency seems to relate best to the psychological sub-domain of cough related quality of life rather than social or physical sub-domains. We suggest that currently a combination of objective cough frequency and cough related quality of life is the optimal combination for assessing cough.
Acknowledgements

We would like to thank all the patients who took part in the study. We are grateful to Dr Surinder Birring for his permission to use the Leicester Cough Questionnaire (LCQ) and to the Moulton Charitable Trust for their financial support.

Legends

Figure 1 Time spent coughing during the day and night in individuals with chronic dry cough
Figure 2 Correlation between cough reflex sensitivity and daytime cough rates
Figure 3 Correlation between objective cough frequency and VAS
Figure 4 Correlation between total cough rates and total LCQ score
References

1. UK OTC Market Summary, 2004: www.pagb.co.uk.

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