

Conclusions In healthy volunteers, Talnetant had no significant effect on cough reflex sensitivity to citric acid despite an adequately powered study and sufficient systemic drug exposure. Possible explanations for this lack of efficacy are (1) NK3 receptors do not play an appreciable role in the healthy human cough reflex or (2) the role of NK3 receptors may be limited to the central nervous system where Talnetant has limited penetrance and receptor occupancy. Whilst this study suggests predominantly peripherally acting NK3 receptor antagonists do not influence the cough reflex in healthy volunteers, a significant effect in patients with a hypersensitive cough reflex cannot be excluded and this class of drugs may yet prove to have anti-tussive properties, especially with improved central activity.

S115 MAGNITUDE OF COUGH RESPONSE TO INHALED CAPSAICIN DIFFERENTIATES BETWEEN HEALTH AND DISEASE

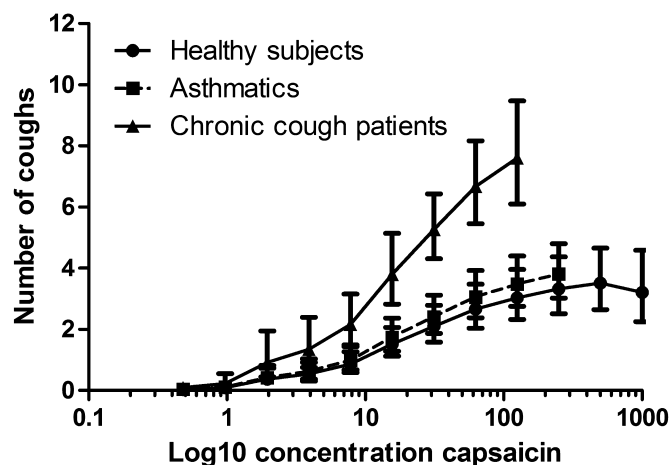
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Background Patients with chronic cough (CC) have substantially higher 24-h cough rates compared to patients with asthma (A) or healthy controls (HC). CC patients also have a more sensitive cough reflex, when measured as the 'threshold' dose of a tussive agent (eg, capsaicin) inducing at least two or five coughs (C2/C5), although there is substantial overlap between CC and HC. We aimed to investigate if the 'magnitude' of cough response to inhaled capsaicin would better differentiate CC patients from A and HC subjects.

Methods We devised a cough challenge technique, with increasing doubling concentrations of capsaicin (0.48–1000 µMol) extended beyond the C5 threshold, up to the maximum tolerated dose. At each capsaicin concentration four single-breath inhalations were administered from a dosimeter 30 s apart. After each inhalation, the number of coughs in the first 15 s was counted. Using Generalised Estimating Equations (GEE), we explored the effect of group and gender on average cough response to increasing concentrations of capsaicin.

Results We studied 20 treatment resistant CC, 18 stable mild/moderate A and 20 HC subjects, matched for age and gender; (M:F 10:10, 9:9,10:10, respectively), age [mean (±SD) 57.1 years (±15.7),



Abstract S115 Figure 1 Average cough frequency with increasing doubling doses of capsaicin (log 10 scale) according to group. Adjusted means and 95% CI from GEE model shown.

51.7 years (±13.5), 58.8 years (±13.5); $p=0.17$], and lung function [3.02L (±0.98), 2.96L (±1.10), 3.20L (±0.99); $p=0.72$]. CC (vs HC $p<0.001$) and females (vs males, $p<0.001$) cough significantly more after capsaicin (see Abstract S115 Figure 1). There was no significant difference between A and HC ($p=0.407$).

Conclusions Magnitude of cough responses to inhaled capsaicin, beyond the standard endpoints:

- ▶ clearly discriminates chronic cough from healthy controls,
- ▶ demonstrates gender differences,
- ▶ may be valuable for investigation of physiological mechanisms and anti-tussive agents.

In addition to a reduced cough threshold, these findings are consistent with a failure of inhibitory mechanisms to prevent coughing to repetitive and potent stimuli in chronic cough.

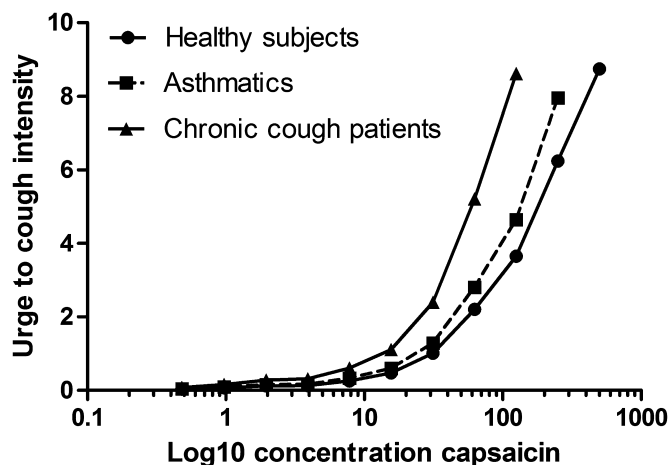
S116 URGE-TO-COUGH INTENSITY IN CHRONIC COUGH PATIENTS COMPARED TO ASTHMATICS AND HEALTHY CONTROLS

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Background Healthy subjects inhaling increasing doses of capsaicin perceive an urge-to-cough (UTC) prior to initiating coughing. We compared subjective ratings of UTC intensity following inhalation of capsaicin in patients with chronic cough (CC), asthma (A) and healthy controls (HC).

Methods A double-blind, randomised block design, capsaicin cough challenge was performed using single-breath inhalations, separated by 1 min, through a dosimeter (inspiratory flow rate limited). Seven individually pre-determined doses (0.48–1000 µMol; maximum dose inducing an average of at least five coughs) and one placebo dose were administered four times each, in four individually randomised blocks (Davenport *et al*), to reduce the bias associated with subjective UTC ratings. After each inhalation, UTC was rated on a modified Borg scale (0–10) and number of coughs in the first 15 s was recorded. Using Generalised Estimating Equations (GEE), we explored the effect of group and gender on average UTC intensity and average cough responses to increasing concentrations of capsaicin.



Abstract S116 Figure 1 Average urge to cough frequency with increasing doubling doses of capsaicin (log 10 scale) according to group. Adjusted means extracted from GEE model shown.

Results We studied 20 treatment resistant CC, 18 stable mild/moderate A and 20 HC subjects, matched for gender (M:F 10:10, 9:9,10:10, respectively), age [mean (\pm SD) 57.1 years (\pm 15.7), 51.7 years (\pm 13.5), 58.8 years (\pm 13.5); $p=0.17$], and lung function [3.02L (\pm 0.98), 2.96L (\pm 1.10), 3.20L (\pm 0.99); $p=0.72$]. CC had significantly greater UTC intensity ($p=0.006$, see Abstract S116 Figure 1) and cough responses ($p=0.002$) compared to HC. Females had significantly greater UTC ($p=0.001$) and cough responses ($p<0.001$) compared to males. There was no significant difference in UTC intensity ($p=0.449$) or cough responses ($p=0.997$) between A and HC.

Conclusions In a randomised double-blind capsaicin cough challenge:

- ▶ Chronic cough patients perceive a more intense UTC sensation and also demonstrate a greater magnitude of cough response than healthy controls.
- ▶ Females perceive a more intense UTC sensation than males. These findings suggest both a heightened sensory experience in addition to an excessive motor response in patients with chronic cough. This data could be explained by sensitisation of afferent pathways (ie, peripheral and/or central sensitisation) but also by impaired inhibitory control mechanisms.

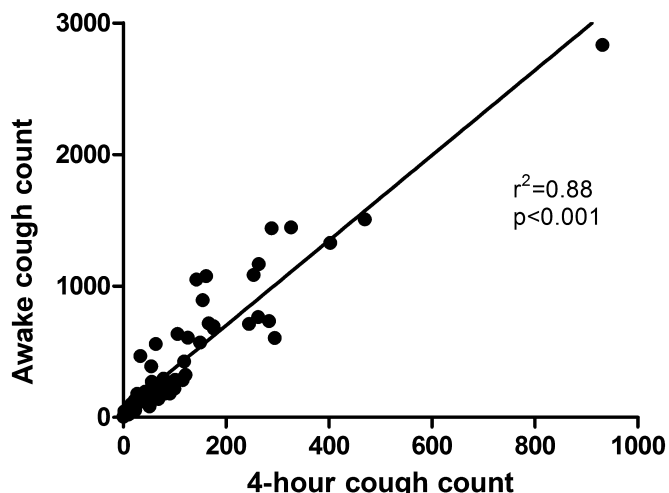
S117 4 H COUGH FREQUENCY MONITORING WITH THE LEICESTER COUGH MONITOR

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Introduction The Leicester Cough Monitor (LCM) is a validated 24-h automated cough frequency monitor. Shorter recordings are more convenient for patients and take less time to analyse but their validity for assessing cough is not known. We assessed the relationship between short duration and 24-h recordings.

Methods 100 patients (57 females) with chronic cough underwent 24-h ambulatory cough frequency monitoring with the LCM. Patients completed diaries to identify awake and sleep periods. Cough frequency was determined by automated analysis and presented as 24-h cough frequency (CF_{24}), awake cough frequency, sleep cough frequency, and short duration (1–6 h). Subjective cough severity was assessed by cough visual analogue scale and



Abstract S117 Figure 1 Relationship between 4-h cough counts and awake cough counts.

quality of life questionnaire (Leicester Cough Questionnaire, LCQ). The optimal short cough recording duration was determined by assessing its relationship with awake cough frequency and subjective cough severity. The responsiveness of short duration recordings was tested in 20 patients undergoing trials of therapy.

Results The median (IQR) 24-h cough frequency was 11.5 (5.8 to 26.6) coughs/h, awake cough frequency 13.2 (7.6 to 37.5) coughs/h and sleep cough frequency 4.2 (1.0 to 9.2) coughs/h. 4-h cough counts correlated strongly with both awake and 24-h cough counts; $r^2=0.88$ and $r^2=0.87$ respectively (Abstract S117 Figure 1). There was a moderate relationship between 4-h cough frequency (CF_4) and LCQ and cough VAS ($r=-0.48$, $p<0.001$ and 0.49 , $p<0.001$) which was comparable to that between awake cough frequency and LCQ and cough VAS. The effect size of change in CF_4 after therapeutic trials was 0.55.

Conclusions Shorter duration cough frequency recordings with the LCM accurately reflect daytime and 24-h cough frequency in patients with chronic cough. They can be used to assess daytime cough frequency and the response to trials of therapy.

S118 ACUTE HEMISPHERIC STROKE PATIENTS HAVE REDUCED FUNCTIONAL RESIDUAL CAPACITY AND COUGH FLOW RATES

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Introduction Cough is a complex manoeuvre, requiring coordinated action of the respiratory and upperairway musculature. The mechanisms of impaired cough following hemispheric stroke are unclear. Reduced functional residual capacity (FRC) may impair cough due to the effect of lung volume on the length and pressure generating capacity of the expiratory muscles. We compared FRC (primary outcome) and peak cough flowrate for voluntary cough (PCFR, secondary outcome) in stroke patients and healthy controls.

Methods 27 patients and 30 healthy controls were studied. Stroke patients were within 2 weeks of first-ever middle cerebral artery infarct. Stroke severity was scored by a clinician (NIHSS score, worst=31). FRC was measured by helium dilution using a dry rolling seal spirometre. To measure PCFR, subjects wore a tight-fitting facemask and were asked to cough forcefully into the spirometre. During these measurements, the volume inspired before the cough manoeuvre was also recorded. Measurements were performed in a chair with the back reclined to 45°, mimicking patient position in hospital. FRC and PCFR data were expressed as % predicted.¹

Results Patients' median NIHSS score was 4 (IQR 2–6) reflecting mild disability. FRC % predicted, the volume inspired before cough and PCFR were significantly reduced in patients. Both FRC and the volume inspired before cough were significant predictors of PCFR.

Conclusions FRC (% predicted), the volume inspired before cough and PCFR were significantly reduced in acute hemispheric stroke patients. Higher peak cough flow rates are associated with greater lung volume prior to cough. Interventions that increase FRC, for example, continuous positive airway pressure and upright sitting may improve cough function in stroke patients.