Gabapentin for refractory chronic cough: a randomised, double-blind, placebo-controlled trial

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Summary

Background **Refractory chronic cough causes substantial symptoms and quality-of-life impairment. Similarities between central reflex sensitisation in refractory chronic cough and neuropathic pain suggest that neuromodulators such as gabapentin might be effective for refractory chronic cough. We established the efficacy of gabapentin in patients with refractory chronic cough.**

Methods **This randomised, double-blind, placebo-controlled trial was undertaken at an outpatient clinic in Australia. Adults with refractory chronic cough (>8 weeks' duration) without active respiratory disease or infection were randomly assigned to receive gabapentin (maximum tolerable daily dose of 1800 mg) or matching placebo for 10 weeks. Block randomisation was done with randomisation generator software, stratified by sex. Patients and investigators were masked to assigned treatment. The primary endpoint was change in cough-specific quality of life (Leicester cough questionnaire [LCQ] score) from baseline to 8 weeks of treatment, analysed by intention to treat. This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12608000248369.**

Findings **62 patients were randomly assigned to gabepentin (n=32) or placebo (n=30) and ten patients withdrew before the study end. Gabapentin significantly improved cough-specific quality of life compared with placebo (between-group difference in LCQ score during treatment period 1·80, 95% CI 0·56–3·04; p=0·004; number needed to treat of 3·58). Side-effects occurred in ten patients (31%) given gabapentin (the most common being nausea and fatigue) and three (10%) given placebo.**

Interpretation **The treatment of refractory chronic cough with gabapentin is both effective and well tolerated. These positive effects suggest that central reflex sensitisation is a relevant mechanism in refractory chronic cough.**

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See **Online** for a video interview with Surinder Birring

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Introduction

Chronic cough is a common clinical problem for 11–16% of the population,[1] affecting physical, psychological, and social domains of health.[2] Although many patients are treated successfully,[3] cough can persist even after extensive investigation or treatment trials in 20–42% of outpatient referrals. These patients have refractory chronic cough.[4,5]

The sensitivity of the cough reflex is increased in chronic cough.[4,6] Hypersensitivity to tussive stimuli such as capsaicin is caused by both peripheral and central mechanisms. Non-tussive stimuli can also trigger cough, which suggests that additional central neuronal mechanisms or central reflex sensitisation are implicated. Peripheral sensitisation (cough reflex hypersensitivity in peripheral nerves) has been shown with enhanced cough responses to inhaled capsaicin[4,6] and increased neural expression of transient receptor potential receptors. The role of central sensitisation in refractory cough has received little attention; however, refractory cough shares similarities with other disorders associated with central sensitisation, such as neuropathic pain.[7]

The clinical features that indicate central sensitisation in chronic pain, such as paraesthesia (abnormal sensation in the absence of a stimulus), hyperalgesia (pain triggered by a low exposure to a known painful stimulus), and allodynia (pain triggered by a non-painful stimulus), show similarities with the clinical features of refractory chronic cough, such as an abnormal throat sensation or tickle (laryngeal paraesthesia), increased cough sensitivity in response to known tussigens (hypertussia), and cough triggered in response to non-tussive stimuli such as talking or cold air (allotussia).[8]

The neuromodulator gabapentin is effective for neuropathic pain with central sensitisation, and findings from two case series have shown success with gabapentin in chronic cough.[9,10] We aimed to test whether gabapentin, given to patients with refractory chronic cough, improves cough-specific quality of life and decreases cough severity and frequency.

Methods

Study design and participants

In this randomised, double-blind, placebo-controlled trial, we recruited adults with chronic cough lasting longer than 8 weeks from the John Hunter Hospital respiratory outpatient clinic (New Lambton, NSW, Australia), which receives referrals from primary and

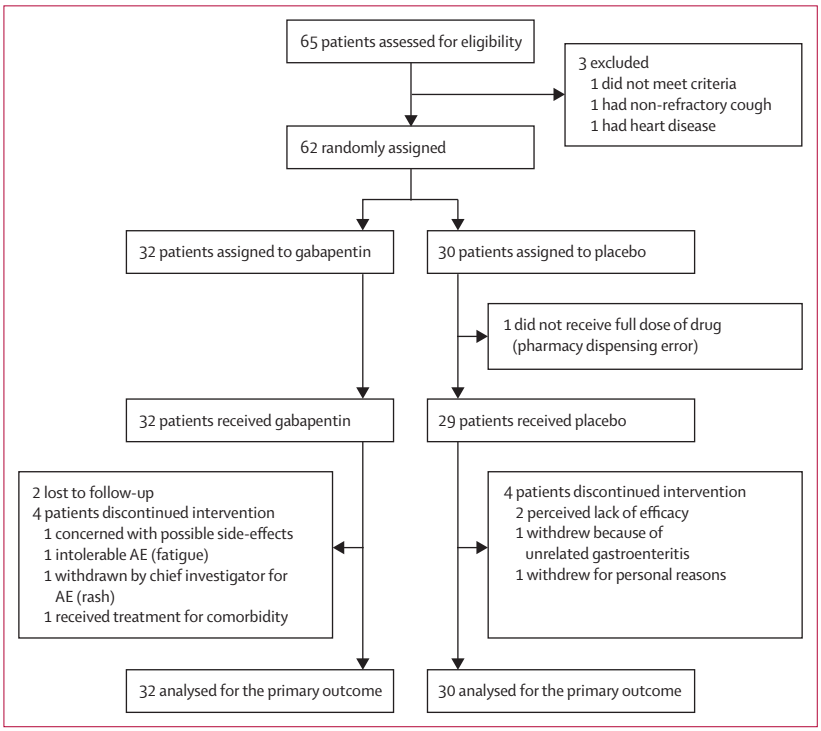

Figure 1: **Trial profile**
AE=adverse event.

secondary care. Recruitment took place between October, 2008, and September, 2010. All participants had negative responses to previous investigations or trials of treatments for asthma, gastro-oesophageal reflux disease, and rhinitis (inhaled or oral corticosteroids, nasal corticosteroids or antihistamines, or proton-pump-inhibitor therapy).

We excluded patients who smoked, had active respiratory disease (such as chronic obstructive pulmonary disease or untreated asthma), had a respiratory tract infection in the month before randomisation, were taking an angiotensin-converting enzyme inhibitor, had a cough that was producing purulent sputum, were pregnant or breastfeeding, or had impaired liver function. We obtained written consent from each participant and the study was approved by The University of Newcastle and the Hunter New England Human Research Ethics committees.

After a screening assessment, participants entered the study and a randomisation visit was scheduled. Participants attended five visits over 16 weeks. At visit 1 (the randomisation and treatment initiation visit) we did a cough assessment and recorded clinical history, drug use, and the results of a visual analogue scale (VAS) of cough severity (0–100 mm),[11] a laryngeal dysfunction questionnaire, a generic quality-of-life questionnaire (short-form 36 health survey, SF-36), and a cough-specific quality-of-life questionnaire (Leicester cough questionnaire, LCQ).[2] We then measured fractional exhaled nitric oxide (FeNO) and did a hypertonic saline challenge to test for bronchial hyper-responsiveness (≥15% fall in forced expiratory volume in 1 s, FEV_1) and extrathoracic airway hyper-responsiveness (≥20% fall in forced inspiratory flow at 50% of vital capacity, $FIF_{50\%}$).[12] We used the Leicester cough monitor with external microphone[13] to measure the frequency of patients' coughs during the visit. We measured capsaicin cough reflex sensitivity with the single-dose method.[14] Participants were then randomly assigned to a treatment group (gabapentin or matching placebo) and began their assigned treatment.

Random allocation was done by a data manager with randomisation generator software that used permuted blocks of six and stratification by sex. Bottles of 300 mg gabapentin capsules and bottles of matching placebo (lactose with 0·5% alum potassium sulphate) capsules (Stenlake Compounding Chemist, NSW, Australia) were dispensed by the John Hunter Hospital pharmacy according to a randomisation schedule retained by the clinical trials pharmacist. The participants and the research staff were masked to treatment allocation. Investigators assessing the outcomes were not masked.

Procedures

Patients undertook treatment visits 4 weeks (visit 2) and 8 weeks (visit 3) after initiation of treatment, during which we gave patients more study drug, repeated many of the study measurements, and reviewed adverse events. Visit 3 was the outcome (efficacy) visit at which we assessed the primary outcome. At this visit participants were instructed in a 6-day dose-reduction schedule beginning at the start of week 12, resulting in drug cessation by the end of week 12 (visit 4). Visit 5 was undertaken 4 weeks after completed drug cessation with the same study measurements.

Patients followed a 6-day dose escalation schedule at start of treatment and a 6-day dose reduction schedule at the end of treatment, corresponding to a 10-week prescribed maximum daily dose of 1800 mg (six capsules). Each participant was instructed to take one capsule on day 1 and then take one extra capsule daily, unless their cough symptoms completely stopped or they could not tolerate the side-effects, until they reached a maximum of six capsules per day. Maximum tolerable daily doses were 1800 mg (6 capsules per day) from day 6 to day 77. Patients reduced their dose by 50% on day 78 and again by 67% (ie, from three capsules to one) 3 days later, before stopping completely on day 84.

Participants kept a cough diary recording their daily drug intake. At each visit we checked the participant's diary with the participant present, and discussed any dose variation from the maximum prescribed daily dose. Patients returned drug bottles at each visit and we counted and recorded the contents. We recorded instances of dose violation and the reasons for it in the study database.

Study outcomes

We measured FeNO with NIOX (Aerocrine AB, Solna, Sweden) in accordance with published guidelines from the European Respiratory Society and American Thoracic Society.[15] We measured inspiratory–expiratory flow-volume loops with KoKo K323200 Spirometer (Technipro, North Parramatta, NSW, Australia). For the hypertonic saline challenge, which measured greatest fall in FEV_1 and $FIF_{50\%}$,[16] we regarded a greater than 20% fall in $FIF_{50\%}$ as positive for extrathoracic airway hyper-responsiveness, a result associated with laryngeal dysfunction.[16,17]

We diagnosed central sensitisation of the cough reflex on the basis of cough reflex hypersensitivity (defined in patients for whom a concentration of <134·8 μM/L of capsaicin stimulated five coughs [C5])[18] and a history of each of the following cough characteristics: cough triggered by laryngeal paraesthesia (throat irritation/sensation), non-tussive triggers such as talking on the phone or air conditioning (allotussia), and tussive triggers such as smoke and fumes (hypertussia).[8]

We used capsaicin cough reflex sensitivity to investigate mechanisms of action of gabapentin according to previously reported methods.[12] Serial doubling concentrations ranging from 0·98 μM to 500 μM were freshly prepared on each test day. Participants inhaled one breath of capsaicin aerosol interspersed with 0·9% saline solution from a compressed air-driven nebuliser controlled by a dosimeter. The inspiratory flow was standardised at 0·5 L/s with an inspiratory flow regulator valve. We counted coughs for 30 s after exposure to each dose, during which the participant's rated their urge to cough. The test ended when the participant coughed five or more times in response to one dose, or received a dose of the highest concentration.

We used the Leicester cough monitor, which consists of a recording device and an external free-field microphone,[13] to objectively monitor cough frequency. We attached it to each participant at the beginning of their assessment visit for 1 h. We controlled measurement bias by ensuring that cough monitoring was started at the same time of day as each previous cough monitoring assessment and was done in conjunction with the cough severity VAS assessment for each participant. We downloaded the recording onto a computer and analysed it with automated cough detection software. We regarded coughs as one event irrespective of whether the cough occurred singly or in bouts, and reported the number of coughs per h.

The primary outcome was a change in LCQ score from baseline to week 8. Secondary endpoints were changes in cough frequency, cough severity (VAS score), urge-to-cough score, and laryngeal dysfunction score. We used cough reflex sensitivity testing to assess treatment mechanism.

Statistical analysis

We assessed baseline characteristics for distribution and rechecked the distribution after transformation if it was not normal. We presented normally distributed partici-

	Gabapentin (n=32)	Placebo (n=30)
Age (years)	62·7 (14·0)	60·9 (12·9)
Sex		
Male	12 (38%)	10 (33%)
Female	20 (63%)	20 (67%)
Smoking history		
Never smoked	20 (63%)	16 (53%)
Ex-smoker	12 (38%)	14 (47%)
Pack years*	4 (0–5)	5 (2–15)
Cough duration (months)	36 (18–150)	48 (18–156)
BMI (kg/m²)	28·9 (22·7–31·6)	27·1 (24·6–30·5)
Previous drug trials		
Over-the-counter cough suppressants	23 (72%)	22 (73%)
Oral corticosteroid course	12 (38%)	6 (20%)
Antibiotics	19 (59%)	14 (47%)
Codeine or opiates	5 (16%)	7 (23%)
Inhaled drugs	25 (78%)	23 (77%)
PPIs and/or H_2 antagonists	23 (72%)	20 (67%)
Nasal corticosteroids	20 (63%)	21 (70%)
Drugs at time of study		
Short-acting β2 agonist	4 (13%)	11 (37%)
Leukotriene modifier	1 (4%)	0
Short-acting anticholinergic	1 (4%)	0
Non-steroidal anti-inflammatory	0	2 (7%)
Inhaled corticosteroids	2 (6%)	2 (7%)
Inhaled corticosteroids and LABA	4 (13%)	6 (20%)
Antihistamines	4 (13%)	2 (7%)
Nasal steroids	4 (13%)	8 (27%)
PPIs and/or H_2 antagonists	16 (50%)	15 (50%)
Spirometry		
FEV_1 (predicted)	89·4% (18·8)	94·7% (18·8)
FVC (predicted)	89·1% (19·1)	93·4% (14·1)
FEV_1 (fall)	5·0% (2·0–8·7)	5·2% (3·0–10·5)
$FIF_{50\%}$ (predicted)	92·4% (29·7)	100·3% (30·0)
$FIF_{50\%}$ (fall)	18·1% (13·7–28·9)	21·7% (12·0–36·7)
EAHR (n)	12 (42·9%)	17 (58·6%)
FeNO (ppb)	12·4 (9·3–19·4)	14·0 (9·2–21·0)
SF-36 total score	521·9(160·9)	522·8 (196·2)
Efficacy variables		
LCQ score†	13·3 (3·1)	12·1 (3·9)
Cough severity (VAS score, mm)	43·6 (29·6)	44·2 (21·3)
CRS C5 (μM)‡	6·31 (0·6)	4·31 (0·49)
LDQ score	4·7 (2·3)	4·5 (2·3)
Urge-to-cough score	4·0 (1·8)	4·3 (2·8)
Cough frequency (coughs/h)‡	45·3 (1·9)	68·8 (1·9)

Data are mean (SD), n (%), or median (IQR). BMI=body-mass index. PPI=proton-pump inhibitor. H_2=histamine 2. LABA=long-acting β agonist. FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. $FIF_{50\%}$=forced inspiratory flow at 50% of vital capacity. EAHR=extrathoracic airway hyper-responsiveness. FeNO=fraction of exhaled nitric oxide. ppb=parts per billion. SF-36=short-form (36) health survey. LCQ=Leicester cough questionnaire. VAS=visual analogue scale. CRS C5=cough reflex sensitivity defined by quantity of capsaicin needed to induce five coughs. LDQ=laryngeal dysfunction questionnaire. *Value takes into account participants who have never smoked (ie, pack year 0) and ex-smokers. †A higher score indicates a better health status. ‡Data are geometric mean (logSD).

Table 1: **Participant characteristics at baseline**

pant characteristics as mean (SD) or geometric mean (logSD), whereas we presented variables that remained non-normal after transformation as median (IQR).

We used an ANCOVA-type model to examine differences between groups during treatment (visits 2 and 3), with adjustment for baseline differences, and after treatment (visits 4 and 5), also after adjustment for baseline differences. We fitted the ANCOVA model into a generalised linear mixed model framework to allow for repeated measurements on the outcome side of the equation. This model then used a generalised linear mixed model to assess the change in outcomes between the treatment and post-treatment periods.

The target sample size was 28 patients per treatment group, giving greater than 80% power (significance level α=0·05, two-sided test) for LCQ score, cough reflex sensitivity, and cough frequency outcomes. This calculation was based on our previous data showing a mean change in logC5 of 1·64 and a within-patient logSD of 1·91.[12] For LCQ score, a mean change of 4·99 and within-patient SD of 4·23 meant 12 patients were needed per treatment group—a far more conservative measure than for C5. We did statistical analysis with STATA (version 11) by intention to treat. We analysed cough VAS score post hoc because of its importance as an outcome measure in cough research.[19]

This study is registered with the Australian New Zealand Clinical Trials Registry, number ACTRN12608000248369.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. NR and PG had full access to all the data in the study and PG had final responsibility for the decision to submit for publication.

Results

We recruited 65 patients diagnosed with refractory chronic cough. We excluded three patients and randomly assigned the remaining 62 to either gabapentin (n=32) or placebo (n=30). Ten participants withdrew from the study and 52 completed it (gabapentin, n=26; placebo, n=26; figure 1), although one in the placebo group did not receive the full dose of the study drug due to a pharmacy dispensing error.

All patients had received several treatment trials before study entry and their cough was refractory to these therapies (table 1). Drugs for concomitant disorders or cough were still taken throughout the trial. At baseline, 25 (78%) of 32 patients assigned to gabapentin presented with voice changes compared with 22 (73%) of 30 patients assigned to placebo, 19 (59%) of 32 patients assigned to gabapentin had symptoms of central reflex sensitisation compared with 20 (67%) of 30 patients assigned to placebo, and 15 (47%) of 32 patients assigned to gabapentin had laryngeal hypersensitivity compared with 16 (53%) of

	Gabapentin (n=17)	Placebo (n=6)
Blurred vision	1 (6%)	0
Depression	0	1* (17%)
Disorientation, confusion	2 (12%)	0
Dizziness	3 (18%)	1 (17%)
Dry or very dry mouth	2 (12%)	1 (17%)
Fatigue	3 (18%)	1 (17%)
Headache	1 (6%)	0
Memory loss	1 (6%)	0
Nausea, stomach pain	4 (24%)	2 (33%)

Data are number of events (%). n=total number of events associated with study drug. *Possible comorbidity (present before study).

Table 2: **Adverse effects**

	Mean change from baseline to treatment period				Mean change from baseline to post-treatment period				Between-group difference in change from treatment period to post-treatment period* (95% CI)	p for interaction
	Gabapentin	Placebo	Difference* (95% CI)	p value	Gabapentin	Placebo	Difference* (95% CI)	p value		
Mean LCQ score†	+2·5	+1·1	1·80 (0·56 to 3·04)	0·004	+1·7	+1·4	0·85 (−0·75 to 2·44)	0·30	−1·22 (−2·35 to −0·09)	0·034
Cough frequency (coughs/h)	−22·5	−4·3	−27·31 (−51·75 to −2·88)	0·028	−9·7	−8·9	−3·10 (−43·31 to 37·11)	0·88	26·49 (0·49 to 52·48)	0·046
Mean cough severity (VAS score, mm)	−11·1	+0·8	−12·23 (−23·22 to −1·25)	0·029	+2·0	−4·8	5·57 (−4·93 to 16·07)	0·29	18·92 (7·71 to 30·13)	0·001
Cough reflex sensitivity at C5 (μM)	+15·1	+5·1	3·12 (−13·59 to 19·82)	0·72	+30·5	+8·6	13·15 (−14·67 to 40·97)	0·35	10·06 (−12·35 to 32·46)	0·38
Mean urge-to-cough score	−0·7	−1·4	0·59 (−0·52 to 1·70)	0·30	−0·9	−1·1	0·021 (−1·29 to 1·34)	0·98	−0·21 (−1·35 to 0·93)	0·72
Mean LDQ score	−1·6	−1·5	0·048 (−0·82 to 0·92)	0·91	−1·6	−1·8	0·44 (−0·45 to 1·33)	0·33	0·27 (−0·62 to 1·15)	0·56

Baseline refers to visit 1 (before treatment). Treatment period refers to visit 2 and visit 3 (on treatment). To calculate mean change between baseline and treatment period, an average of the score at visit 2 and visit 3 was taken away from the score at baseline. Post-treatment period refers to visit 4 and visit 5 (off treatment). To calculate mean change between baseline and post-treatment period, an average of the score of visit 4 and visit 5 was taken away from the score at baseline. LCQ=Leicester cough questionnaire. VAS=visual analogue score. C5=concentration of capsaicin needed to induce five coughs. LDQ=laryngeal dysfunction questionnaire. *Baseline differences adjusted for. †A higher score indicates a better health status.

Table 3: **Efficacy analysis for gabapentin versus placebo in the treatment of refractory chronic cough**

30 patients assigned to placebo. Central reflex sensitisation symptoms included abnormal laryngeal sensations consistent with laryngeal paraesthesia, such as sensations of throat irritation, tickle, tightness, presence of mucus, and the sensation of something sticking in the throat (data not shown). Triggers causing cough were mainly non-tussive (allotussia) and included an abnormal sensation in the throat, talking, laughing, singing, air conditioning, cold air, and eating or drinking (data not shown). Some participants described a tussive cough triggered by low-level stimuli such as smoke or aerosols that mainly occurred in association with non-tussive triggers.

24 (92%) of 26 patients assigned gabapentin and 24 (92%) of 26 assigned placebo who completed the study showed greater than 90% compliance with the treatment and prescribed dose. Ten (31%) of 32 patients assigned gabapentin had one or more adverse effects compared with three (10%) of 30 assigned placebo (p=0·059; table 2). We managed adverse effects by temporarily reducing the dose (in six [19%] in the gabapentin group *vs* three [10%] in the placebo group), or by withdrawing patients from the study (one [3%] *vs* one [3%]).

Gabapentin led to a greater improvement in LCQ score than did placebo during the treatment period (table 3, figure 2). Significantly more participants in the gabapentin group still in the study at week 8 had a clinical improvement in LCQ score of greater than 1·3 (the smallest change in score regarded as clinically meaningful[20]) after 8 weeks of treatment than did those in the placebo group (20 [74·1%] of 27 *vs* 12 [46·2%] of 26; p=0·038), giving a number needed to treat of 3·58. Reduction in cough frequency during the treatment period was statistically significantly greater in patients assigned gabapentin than in those assigned placebo (table 3, figure 2). Patients assigned gabapentin had significant improvement in cough severity (VAS score) compared with those assigned placebo (table 3, figure 2). However, these positive effects were not maintained after cessation of treatment, with cough severity (VAS score) significantly increasing to greater than baseline values (table 3, figure 2). We noted no difference between gabapentin and placebo during the treatment period for cough reflex sensitivity (table 3, figure 2), urge to cough, and laryngeal dysfunction questionnaire score (table 3).

Participants with central sensitisation had an enhanced response to gabapentin compared with those without central sensitisation (table 4). Mean SF-36 score after treatment was significantly lower in the gabapentin group than in the placebo group (481·8 [SD 197·9] *vs* 581·8 [160·2]; p=0·013).

Discussion

Findings from this trial have shown that gabapentin significantly improved cough-specific quality of life compared with placebo. These results suggest that gabapentin might be an effective therapy for refractory chronic cough (panel).

The onset of action of gabapentin was within 4 weeks, and the effect was maintained during maximal dosing at 8 weeks. However, the improvement in cough-specific

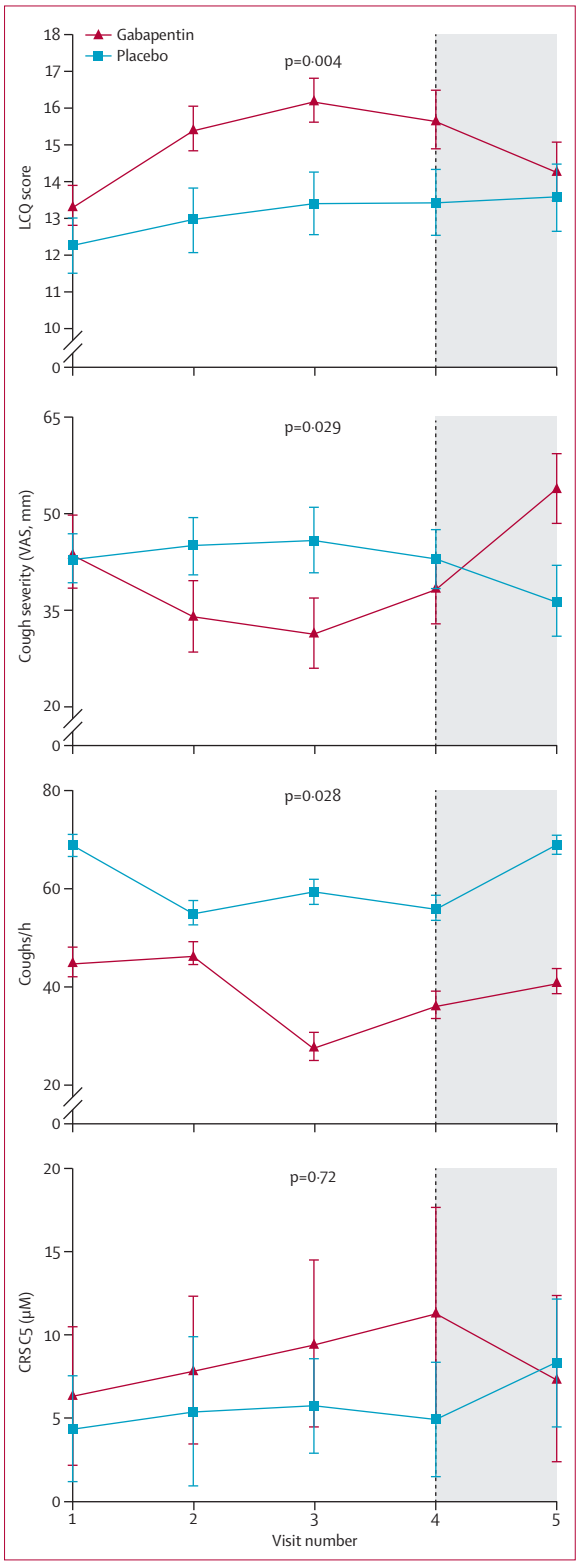

Figure 2: **Mean efficacy variable scores for gabapentin versus placebo, during and after treatment**
Dose was escalated from days 1–6 and reduced from days 78–83. Treatment was stopped completely by visit 4 (dotted line). p values represent the significance of the between-group difference in the change in efficacy outcomes from baseline to treatment period (average score from visits 2 and 3). LCQ=Leicester cough questionnaire. VAS=visual analogue scale. CRS C5=cough reflex sensitivity defined by quantity of capsaicin needed to induce five coughs. Error bars show SE.

	Gabapentin (n=32)		Placebo (n=30)		p value
	No CS (n=13)	CS (n=19)	No CS (n=10)	CS (n=20)	
Baseline	13·9 (9·5)	13·5 (8·6)	12·2 (9·9)	12·9 (9·5)	..
Week 4	15·0 (9·5)	16·2 (10·1)	14·1 (11·5)	13·6 (10·7)	0·240
Week 8	15·3 (8·7)	17·1 (10·6)*	13·7 (12·2)	14·2 (10·4)	0·001

Data are mean score (SD). Adjusted p value for significance=0·0042. LCQ= Leicester cough questionnaire. *Gabapentin without CS *vs* placebo without CS, p=0·0006. Gabapentin without CS *vs* placebo with CS, p=0·0003. Gabapentin without CS *vs* gabapentin with CS, p=0·021. CS=central sensitisation.

Table 4: **LCQ score according to presence of central sensitisation of the cough reflex**

Panel: **Research in context**

Systematic review

We searched PubMed, Medline, and Google Scholar for articles published in English with the terms "gabapentin in chronic cough", "central sensitization", "neuropathic pain", and "laryngeal sensory neuropathy" up to August, 2011. We did not apply publication date restrictions. We also searched the reference lists of relevant articles, case studies, and non-randomised studies that examined gabapentin in chronic cough, sensory neuropathy, or neuropathic pain. The use of gabapentin in chronic cough is restricted to case studies that do not include objective outcome measures for cough. We did not identify any previous randomised trials using gabapentin in the treatment of refractory chronic cough.

Interpretation

This study is the first randomised placebo-controlled trial to investigate gabapentin for the treatment of refractory chronic cough. Gabapentin resulted in a significant improvement in cough-specific quality of life, cough severity, and cough frequency and was well tolerated; therefore, it could be considered a viable alternative to current chronic cough treatment, especially for refractory chronic cough. The addition of gabapentin to chronic cough standard practice guidelines should be considered, although replication studies are necessary before this happens.

quality of life (LCQ score) was not sustained after treatment withdrawal and LCQ score returned to baseline values. Reduction in cough frequency and cough severity (VAS score) were also not sustained. The reduction in efficacy of gabapentin after withdrawal further supports its antitussive effect. The treatment was generally well tolerated, apart from a low frequency of expected side-effects that were managed by dose reduction.

Peripheral cough reflex sensitivity to capsaicin did not change significantly, suggesting that gabapentin did not act by reducing peripheral sensitisation.

Gabapentin is a lipophilic structural analogue of the neurotransmitter γ-aminobutyric acid with known central action. Central sites of pharmacological action include calcium channels (which inhibit the release of excitatory neurotransmitters such as substance P, a potent tussigen) and possibly *N*-methyl-D-aspartate receptors.[21] The cerebral cortex might both modulate and initiate cough by acting on the respiratory area of the brainstem or at the spinal level.[22] Cough might be reduced or abolished by inhibition within the cerebral cortex that suppresses the urge to cough.

Opioids are also centrally acting agents that suppress cough via stimulation of μ-opioid receptors within the cough centres of the brain. Patients given slow-release morphine sulphate had a significant improvement in cough-related quality of life compared with those given placebo,[23] and cough reflex sensitivity was not affected, which is consistent with the central action of morphine. We report similar effects with gabapentin, supporting a central mode of action for refractory chronic cough; however, we would need to do pharmokinetic studies to show this mechanism. Side-effects and dependence are obvious concerns with opiate therapy for what is a disabling but non-life-threatening disorder. The advantages of gabapentin are that it is well tolerated and has few drug interactions.

Patients with refractory chronic cough are predominantly middle-age women with a longstanding chronic dry cough that often follows a respiratory tract infection. Our study population was similar to those in other studies[24,25] of refractory chronic cough. All our study participants had been investigated and had not responded to standard treatment, including inhaled asthma drugs, antibiotics, nasal corticosteroids or antihistamines, and antireflux drugs, and had cough reflex hypersensitivity to capsaicin.[4] Refractory chronic cough could be caused by many disorders, including organ-specific autoimmune disease of the airways,[24] neurogenic airway inflammation, non-acid gastro-oesophageal reflux,[26] cough secondary to irritation or injury of the airway from prolonged coughing,[27] a laryngeal sensory neuropathy,[10,28] or irritability of the throat. These mechanisms are not mutually exclusive, and central reflex sensitisation might be a common accompanying component. Different initiating mechanisms (eg, inflammation or injury from chemical or mechanical causes)[29] might injure airway epithelial surfaces and induce central neuronal sensitisation, and because gabapentin acts centrally, it might be useful in all these situations.

Otolaryngology studies[10,28] have supported the idea that refractory chronic cough is associated with central sensitisation.[8] Similarities have been identified between refractory chronic cough and chronic neuropathic pain syndromes with central sensitisation.[8] A positive response to neuromodulatory therapies such as gabapentin suggests similarities between refractory cough and chronic pain syndromes. In one case study,[9] five of six patients with intractable idiopathic chronic cough responded to gabapentin treatment with either complete resolution or

substantial improvement in cough symptoms. In a second study,[10] 19 (68%) patients who had chronic cough or throat clearing as a manifestation of sensory neuropathy responded to gabapentin. Although these case studies were uncontrolled and did not use objective measurement techniques to assess improvement, they describe refractory chronic cough as a sensory neuropathy that responds to gabapentin treatment. Our study used both a placebo control and objective assessment to show the efficacy of gabapentin in refractory chronic cough.

The known CNS effects of gabapentin might have affected the success of masking, but we used a matching placebo and dose escalation to minimise this effect. Additionally, we used objective measures of cough to further substantiate the effects of the therapy. Future studies should consider an active placebo. The randomisation process successfully achieved balance between the groups of key variables. Cough frequency at baseline differed, although not significantly. Future work could minimise this difference by use of stratified randomisation. Although 24 h cough recording is most frequently used in studies of this type, emerging data suggest that short-duration cough frequency recording, as used in this study, relates well to 24 h recording.[30] We did not specifically assess non-acid reflux, and our results do not preclude the efficacy of other therapies in refractory chronic cough. Rather they identify that a gabapentin-responsive pathway is a relevant feature of refractory chronic cough and warrants consideration in further treatment programmes. Gabapentin should also be investigated in studies of explained cough.

Contributors

NMR searched for published work, designed the study, and analysed and interpreted the data. SSB was responsible for outcome assessment development, and analysed and interpreted the data. PGG conceived and designed the study and interpreted the data. All authors wrote and edited the report.

Conflicts of interest

We declare that they we have no conflicts of interest.

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