ORIGINAL ARTICLE

Aprepitant for Cough in Lung Cancer

A Randomized Placebo-controlled Trial and Mechanistic Insights

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Abstract

Rationale: Effective cough treatments are a significant unmet need in patients with lung cancer. Aprepitant is a licensed treatment for nausea and vomiting, which blocks substance P activation of NK-1 (neurokinin 1) receptors, a mechanism also implicated in cough.

Objectives: To assess aprepitant in patients with lung cancer with cough and evaluate mechanisms in vagal nerve tissue.

Methods: Randomized double-blind crossover trial of patients with lung cancer and bothersome cough. They received 3 days of aprepitant or matched placebo; after a 3-day washout, patients crossed to the alternative treatment. The primary endpoint was awake cough frequency measured at screening and Day 3 of each treatment; secondary endpoints included patient-reported outcomes. *In vitro*, the depolarization of isolated guinea pig and human vagus nerve sections in grease-gap recording chambers, indicative of sensory nerve activation, was measured to evaluate the mechanism.

Measurements and Main Results: Twenty patients with lung cancer enrolled, with a mean age 66 years (±7.7); 60% were female and 80% had non–small cell cancer, 50% had advanced stage, and 55% had World Health Organization performance status 1. Cough frequency improved with aprepitant, reducing by 22.2% (95% confidence interval [CI], 2.8–37.7%) over placebo while awake ($P = 0.03$), 30.3% (95% CI, 12.7–44.3) over 24 hours ($P = 0.002$), and 59.8% (95% CI, 15.1–86.0) during sleep ($P = 0.081$). Patient-reported outcomes all significantly improved. Substance P depolarized both guinea pig and human vagus nerve. Aprepitant significantly inhibited substance P–induced depolarization by 78% in guinea pig ($P = 0.0145$) and 94% in human vagus ($P = 0.0145$).

Conclusions: Substance P activation of NK-1 receptors appears to be an important mechanism driving cough in lung cancer, and NK-1 antagonists show promise as antitussive therapies.

Keywords: neurokinin 1; substance P; cough monitoring

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At a Glance Commentary

Scientific Knowledge on the Subject: NK-1 (neurokinin 1) antagonists are established therapies for the treatment of chemotherapy-induced nausea and vomiting, acting in the central nervous system; however, this receptor and its natural ligand, substance P, have also been implicated in the cough reflex. Effective treatments for cough associated with lung cancer are a significant unmet need.

What This Study Adds to the Field: An NK-1 antagonist (aprepitant) significantly reduced cough frequency in a randomized controlled trial of patients with lung cancer, and it also inhibited substance P activation of vagal tissue. Substance P activation of NK-1 receptors may be an important mechanism driving cough in lung cancer, and NK-1 antagonists show promise as antitussive therapies.

Lung cancer is the leading cause of death from cancer in the United Kingdom, accounting for 35,300 deaths annually in 2015–2017 (1). Until recently, the morbidity associated with chronic coughing in patients with lung cancer was underestimated, and hence the treatment of cough in such patients remains an important unmet need. In an unselected UK lung cancer population attending oncology outpatient clinics, over half of patients reported cough, and two-thirds of these believed it was severe enough to warrant treatment (2). Chronic coughing is known to impact physical, psychological, and social aspects of daily living, but in lung cancer, cough also contributes to pain, fatigue, dyspnea, social isolation, and anxiety (3). Effective cough therapies are lacking, in part because of our limited understanding of the underlying pathophysiology but also because of the lack of well-designed trials incorporating validated endpoints (4). Moreover, it is often assumed that symptoms will improve with anticancer therapy; yet, despite the development of more effective treatments, cough often persists (5).

Cough is mediated by vagal afferent nerve fibers innervating the larynx and airways, synapsing in the nucleus tractus solitarius and paratrigeminal nucleus of the brainstem (6). Preclinical experiments show vagal airway C fibers are capable of manufacturing substance P (SP), a neuropeptide active at NK-1 (neurokinin 1) receptor. Although SP is primarily a neurotransmitter, it is also produced by inflammatory cells, including mast cells, macrophages, eosinophils, lymphocytes, and dendritic cells (7). In the central nervous system, the nucleus tractus solitarius is enriched with SP immunoreactive nerve terminals, and microinjection of SP into this region enhances cough responses via the NK-1 receptor (8). Furthermore, exposures such as cigarette smoke increase SP synthesis in vagal airway fibers, enhancing synaptic transmission and cough responses, which are both blocked by NK-1 receptor antagonism (9). In animal models, NK-1 antagonists inhibit cough responses to inhaled irritant agents in five different species (10).

Although two previous clinical trials failed to demonstrate antitussive effects of NK-1 antagonism (11, 12), progress has since been made in cough assessment tools, including validated quality of life questionnaires and objective cough monitoring systems. Given the limitations of previous study endpoints and the poor central nervous system penetrance of some clinically tested compounds, the potential for a centrally acting NK-1 antagonist to be an effective antitussive treatment has never been ruled out. This study therefore aimed to provide proof of concept that NK-1 antagonism improves cough associated with lung cancer and to offer some insights into the possible mechanism of action. To do this, we assessed the antitussive effect of aprepitant, a potent, centrally active NK-1 receptor antagonist developed and licensed to treat chemotherapy-induced nausea and vomiting. We conducted a placebo-controlled study measuring objective cough frequency and validated patient-reported outcome measures in patients with troublesome cough associated with lung cancer. In addition, we assessed a possible peripheral mechanism of action by performing *in vitro* mechanistic studies to assess the activity of aprepitant on vagal nerve depolarization. Some of the results of these studies have been previously reported in the form of abstracts (13, 14).

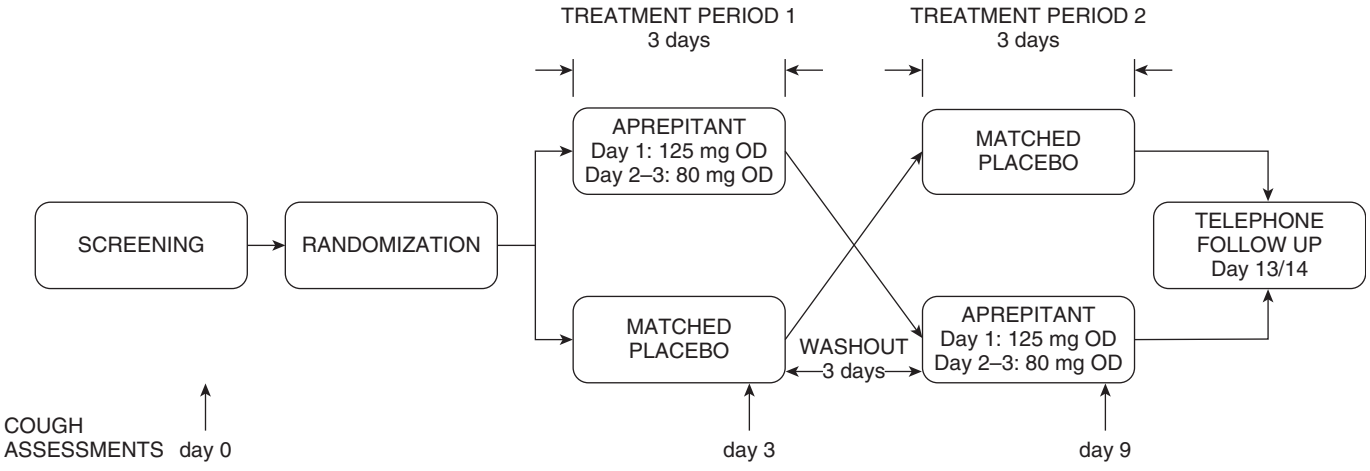

Figure 1. Study design of double-blind, randomized, placebo-controlled crossover trial assessing aprepitant for the treatment. OD = once daily.

Methods

Clinical Study

Study design. We performed a randomized, double-blind, placebo-controlled crossover trial in patients with cough associated with lung cancer attending oncology outpatient clinics at the Christie National Health Service Foundation Trust in Manchester, United Kingdom (Figure 1). Patients received a standard antiemetic course of aprepitant therapy (3 d duration; 125 mg once daily on Day 1 and 80 mg once daily on Days 2 and 3) or matched placebos; for randomization details, *see* online supplement. After a 3-day washout period, patients crossed over to the alternative treatment (placebo or aprepitant) for a further 3 days of treatment. Cough was assessed at screening and on Day 3 of each treatment using an ambulatory cough monitoring system and patient-reported outcomes, including a cough severity visual analog scale (VAS), cough impact questionnaire (Manchester Cough in Lung Cancer Scale [MCLCS]) (15), and global rating of change scale. A final follow-up evaluation was performed over the telephone at Day 13/14.

Patients. Adult patients with histologically confirmed non–small cell or small cell lung cancer and a bothersome cough (≥4 wk duration) were enrolled. Patients with a World Health Organization performance status score of 0–2 who were willing and able to comply with the study protocol were eligible. The main exclusion criteria were subjects due to commence anticancer therapy during the trial, those within 6 weeks of commencement of chemotherapy, those within 8 weeks of starting a tyrosine kinase inhibitor, and those receiving/within 12 weeks of completion of thoracic radiotherapy. Patients receiving other treatments that may modulate cough, such as steroids, opiates, pregabalin, or gabapentin, were included as long as the cough was still troublesome, they had been on the treatment for at least 4 weeks, and the dose remained stable for the duration of the study. Patients on antibiotics were excluded from the trial, as were those reporting a respiratory tract infection within 4 weeks of enrollment. Ethical approval for the study was obtained from the local research ethics committee (13/NW/0084), and all patients provided written informed consent.

Procedures. Data on patient demographics, cancer characteristics, anticancer treatment, and comorbidities were collected at screening. Subjects underwent efficacy

Table 1. Baseline Clinical and Demographic Characteristics

Characteristics (*n* = *20*)	*n* (%)*
Sex	
F	12 (60)
M	8 (40)
Age, yr, mean (±SD)	66 (± 6.74)
Performance status (WHO)	
0	4 (20)
1	11 (55)
2	5 (25)
Smoking history	
Never	1 (5)
Former	14 (70)
Current	5 (25)
Smoking history, pack-years, median (IQR)	37 (20–47)
Duration of cough, mo, median (IQR)	17.5 (9.3–31.3)
Comorbidities (self-reported)	
GERD	9 (45)
Asthma	0 (0)
COPD	6 (30)
Other	13 (65)
Reflux according to BRI score	
No	13 (65)
Yes	7 (35)
Type of cough	
Dry	9 (45)
Productive	11 (55)
Concurrent medications	
Opiates	9 (45)
Proton pump inhibitors	10 (50)
ACE inhibitor	1 (5)
Steroids	3 (15)
Other (anticholinergics/salbutamol)	4 (20)
Histology	
NSCLC	16 (80)
SCLC	4 (20)
NSCLC histological subtype	
Squamous	7 (44)
Adenocarcinoma	5 (32)
Large	1 (6)
Mixed	1(6)
Not otherwise specified	1(6)
Bronchoalveolar	1 (6)
Stage†	
ES SCLC	0 (0)
LS SCLC	4 (20)
IIIA NSCLC	6 (30)
IIIB NSCLC	4 (20)
IV NSCLC	6 (30)
Tumor location	
Central	13 (65)
Peripheral	7 (35)
Anticancer therapy	
On treatment	4 (20)
Off treatment	16 (80)
Prior anticancer therapy	
Chemotherapy	12 (60)
Tyrosine kinase inhibitor	3 (15)
Radiotherapy (thoracic)	12 (60)
Radiotherapy (brain)	3 (15)
Radiotherapy (bones)	1 (5)
Thoracic surgery	0 (0)

Definition of abbreviations: ACE = angiotensin-converting enzyme; BRI = Brief Reflux Inventory; COPD = chronic obstructive pulmonary disease; ES = extensive stage; GERD = gastroesophageal reflux disease; IQR = interquartile range; LS = limited stage; NSCLC = non-SCLC; SCLC = small cell lung cancer; WHO = World Health Organization.

*Unless otherwise indicated.

†Cancer staged according to seventh edition of Tumor, Node, Metastasis in Lung Cancer of the International Association for the Study of Lung Cancer Staging Committee in 2009.

assessments at screening and during the last 24 hours of each 3-day treatment period. Safety was assessed through monitoring of adverse events, physical examinations, and vital signs. Concomitant medications were monitored throughout the study.

The primary endpoint was awake objective cough frequency collected using a cough monitoring device (VitaloJAK; Vitalograph Ltd.); sleep and 24-hour cough frequency were also determined (16). Secondary endpoints included changes in a 100-mm cough severity VAS, cough-specific quality of life (MCLCS) (15), and 15-point global rating of change scales for both cough severity and cough frequency at the end of each treatment period. Subjects also completed the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Core Questionnaire and Lung Cancer Module. Researchers rated the patients' cough using the Common Terminology Criteria for Adverse Events (CTCAE version 4). For additional details of procedures, *see* online supplement.

Statistical analyses. The effect of treatment (aprepitant vs. placebo) on awake cough frequency was assessed using general estimating equations modeling of log transformed data (SPSS version 22; IBM Corp). The model was adjusted for the effect of baseline cough frequency and assessed for any influence of treatment sequence and period. Similar models were used to assess the effect of treatment on 24-hour cough frequency, sleep cough frequency, cough severity VAS, MCLCS, global rating of change scales, CTCAE score, and EORTC item 31 responses.

The sample size calculation used data from patients with refractory chronic cough (17). Based on a paired t test, 18 participants were needed to detect a difference in cough frequency of 30% between aprepitant and placebo at 5% significance and 90% power, assuming the change in 24-hour cough frequency was normally distributed with a SD of 36.5%. Data in participants with refractory chronic cough suggest that a 20–30% decrease in cough frequency from baseline is likely to be the minimal clinically important difference (18). Allowing for 10% attrition, the recruitment target was 20 patients to obtain complete data on 18.

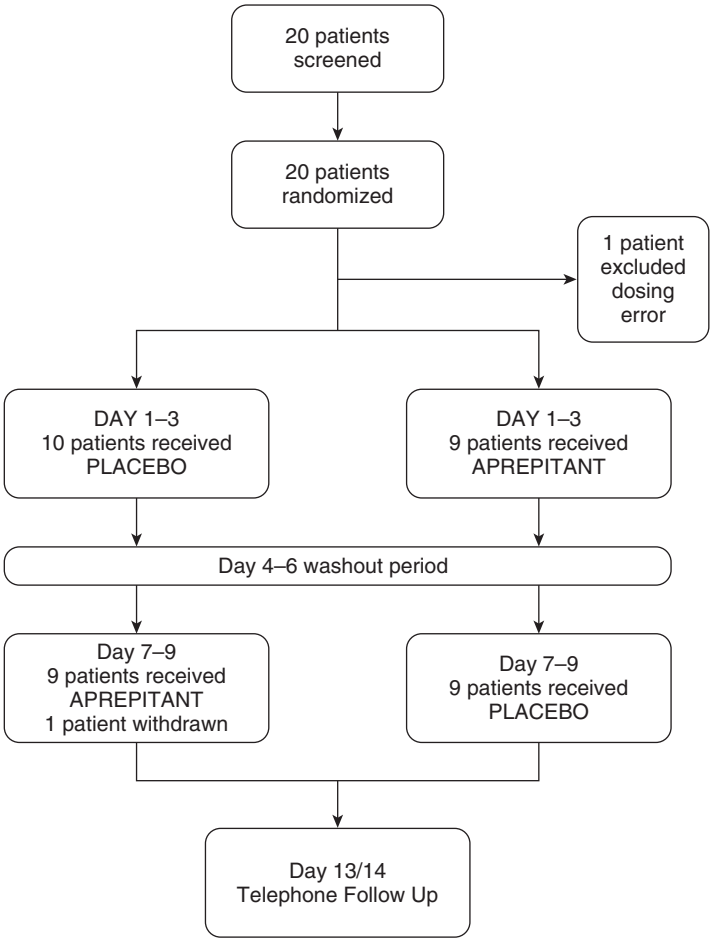

Figure 2. Consort diagram showing study patient flow through trial. Only one patient withdrew because of development of a respiratory tract infection.

Preclinical Studies

Animals. Male guinea pigs (Dunkin-Hartley) weighing 300–500 g were housed in temperature-controlled (21°C) facilities for at least 1 week before any procedures. Experiments were performed in accordance with the UK Home Office guidelines for animal welfare based on the Animals (Scientific Procedures) Act of 1986 and the Animal Research: Reporting of *In Vivo* Experiments guidelines (19).

Human tissue. Vagal nerve tissue, which is surplus to donor requirements, was acquired and consent for use was obtained by the International Institute for the Advancement of Medicine. Approvals for use in scientific research and ethics were obtained from the Royal Brompton and Harefield Trust (09/H0708/72).

Collection of isolated vagus nerve. Guinea pigs were killed by overdose of pentobarbitone (200 mg/kg i.p.); vagus nerve trunks were dissected as described previously (20). Human vagus nerve trunks were placed into Krebs-Heinseleit solution, which was gassed with 95% O_2/5% CO_2 at room temperature until use.

Recording of isolated vagus nerve depolarization. Segments (~15 mm) of guinea pig or human vagus nerve were mounted in a "grease-gap" recording system (21). The nerve segments were perfused constantly with Krebs-Heinseleit solution (at 37°C, bubbled with 95% O_2/5% CO_2), and after each stimulus, depolarization was recorded on a Lectromed 2 (Digitimer) chart recorder with DAM50 differential amplifier (World Precision Instruments).

Stock solutions of SP (Sigma) were prepared using 0.1% bovine serum albumin in distilled H_2O whereas stock solutions of aprepitant (Cayman Chemical) were prepared in neat DMSO. Stock solutions were aliquoted and kept at −20°C until use on the day of the experiment, when they were diluted to working concentrations with

modified Krebs-Henseliet solution (Krebs: 118 mM NaCl, 5.9 mM KCl; 1.2 mM $MgSO_4$, 1.2 mM NaH_2PO_4, 2.5 mM $CaCl_2$; 6.6 mM glucose; and 25.5 mM $NaHCO_3$).

Two repeatable baseline responses to SP (1 μM; concentration chosen from response curves) were first obtained before pretreatment with the NK-1 antagonist aprepitant (10 μM) for 10 minutes before a 2-minute application of the SP in the presence of the aprepitant. After a 10-minute washout, a recovery response to SP was then obtained to confirm nerve viability at the end of the experiment. If a recovery response could not be obtained, the data were disregarded.

Results

Patient Characteristics

Twenty patients were recruited between October 2013 and November 2014. Baseline demographics and clinical characteristics are shown in Table 1, and patient study flow is shown in Figure 2. One patient was withdrawn after the first treatment because of a respiratory tract infection and a second was withdrawn after starting the treatment at screening in error. Otherwise, there was very high compliance with the study schedule and no missing data, as seen in Table 2.

Efficacy Assessments

After 3 days of aprepitant treatment, awake cough frequency was significantly improved compared with placebo treatment, with a reduction of 22.2% (95% confidence interval [CI], 2.8–37.7) over placebo ($P = 0.03$); *see* Table 2 and Figure 3A. Of note, the reduction in awake cough frequency with placebo treatment in this study was extremely small (0.0%; 95% CI, 0.4 to −1.8). There was no significant effect of treatment sequence or period and no significant interaction between baseline awake cough frequency and the efficacy of aprepitant, suggesting the treatment effect was independent of screening cough frequency. Age and sex also had no significant influence on efficacy. Of note, an intention-to-treat analysis (including the patient who received the study treatment at screening in error) produced almost identical results, with a reduction of 22.7% in awake cough frequency ($P = 0.03$). Cough frequency also improved over the whole 24-hour recording period (mean reduction, 30.3%; 95% CI, 12.7–44.3; $P = 0.002$) and during sleep (59.8%; 95% CI, 15.1–86.0; $P = 0.081$); however, cough frequency during sleep is highly variable over time, and therefore the effects did not quite reach statistical significance (Figures 3B and 3C).

Importantly, all patient-reported cough measures also significantly improved. The mean cough severity VAS score improved by 9.5 mm (95% CI, 3.5–15.4) over placebo treatment ($P = 0.002$). Improvements were also seen in the MCLCS cough-specific quality of life score, EORTC Quality of Life Core Questionnaire and Lung Cancer Module (Table 2), and in the global rating of

Table 2. Efficacy Endpoint Data Comparing Screening with Aprepitant and Placebo

	Screening	Aprepitant	Placebo	Placebo-adjusted Effect of Aprepitant	*P* Value
Awake cough frequency					
Geometric mean (95% CI), c/h	16.3 (9.7 to 27.1)	12.1 (7.9 to 18.4)	16.1 (11.3 to 23.0)	−22.2% (−37.7 to −2.8)	0.026
Patients in analysis	19	18	19	—	
Sleep cough frequency					
Median (IQR), c/h	4.6 (1.9 to 10.0)	2.2 (0.5 to 5.4)	5.3 (1.8 to 13.0)	−59.8% (−86.0 to 15.1)	0.081
Patients in analysis	19	18	19	—	
24 h cough frequency					
Geometric mean (95% CI), c/h	12.6 (7.8 to 20.4)	9.1 (6.0 to 13.9)	13.4 (9.6 to 18.7)	−30.3% (−44.3 to −12.7)	0.002
Patients in analysis	19	18	19	—	
Cough severity VAS					
Mean score (95% CI), mm	54.5 (45.3 to 63.7)	39.6 (32.3 to 46.8)	49.6 (43.6 to 55.7)	−9.5 (−15.4 to −3.5)	0.002
Patients in analysis	19	18	19	—	
Cough impact MCLCS					
Mean score (95% CI)	24.8 (22.1 to 27.5)	19.1 (17.1 to 21.1)	21.3 (19.6 to 23.0)	−2.0 (−3.2 to −0.9)	0.001
Patients in analysis	19	18	19	—	
Item 31 EORTC QLQ-C30 + LC13					
Mean score (95% CI)	2.8 (2.6 to 3.1)	2.4 (2.1 to 2.6)	2.6 (2.3 to 2.8)	0.2 (0.0 to 0.4)	0.016
Patients in analysis	19	18	19	—	
CTCAE v4.0					
Mean score (95% CI)	2.0 (1.7 to 2.3)	1.7 (1.4 to 1.9)	1.9 (1.7 to 2.1)	0.2 (0.0 to 0.4)	0.019
Patients in analysis	19	18	19	—	
Global rating of change scales					
Cough frequency					
Mean score (95% CI)	n/a	2.4 (1.4 to 2.3)	0.3 (−0.9 to 1.5)	2.1 (0.8 to 3.3)	0.001
Cough severity					
Mean score (95% CI)	n/a	1.6 (0.4 to 2.8)	−0.8 (−1.2 to 1.0)	1.7 (0.2 to 3.2)	0.028
Patients in analysis	n/a	18	19	—	

Definition of abbreviations: c/h = coughs per hour; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; EORTC = European Organization for the Research and Treatment of Cancer; IQR = interquartile range; MCLCS = Manchester Cough in Lung Cancer Scale; n/a = not applicable; QLQ-C30+LC13 = Quality of Life Core Questionnaire and Lung Cancer Module; VAS = visual analog scale.

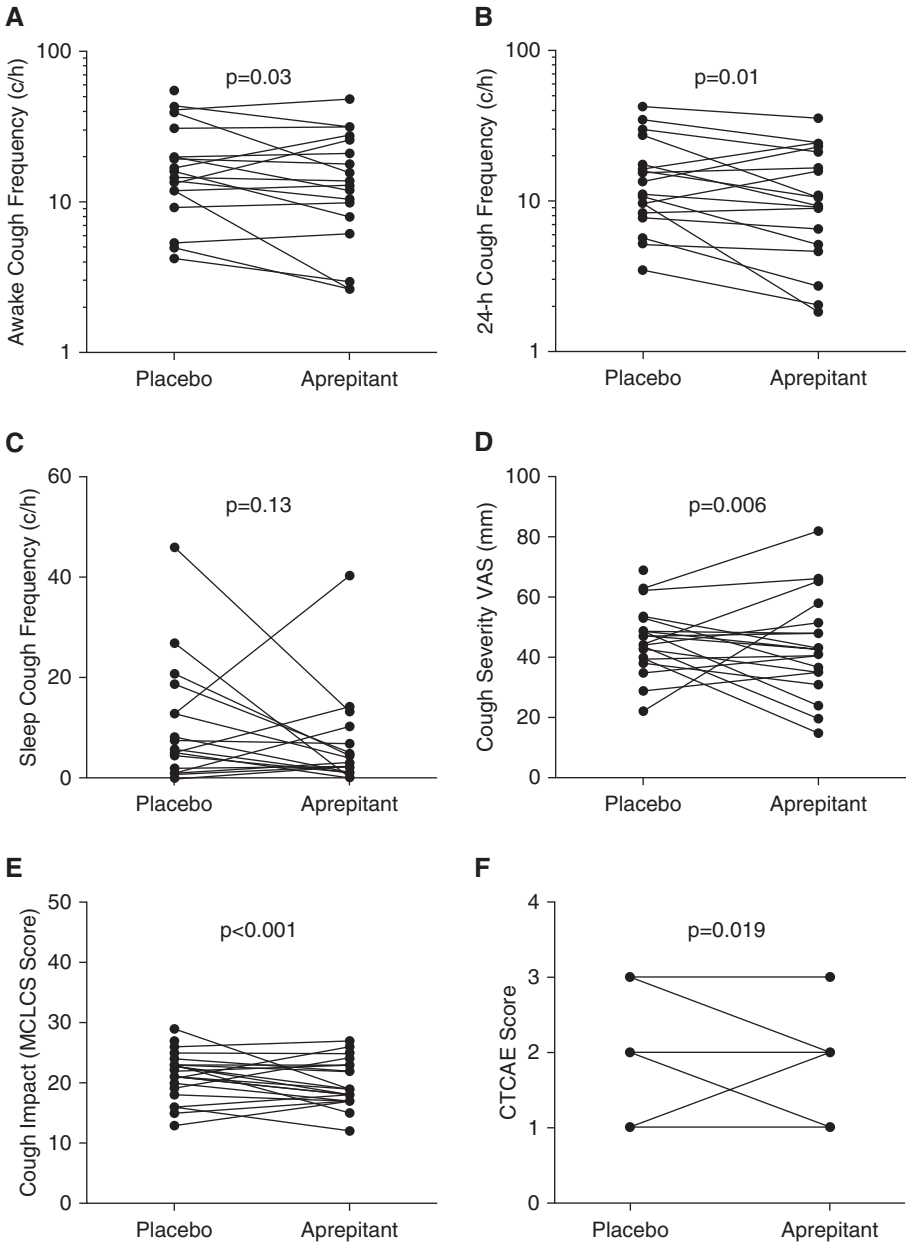

Figure 3. Efficacy measures for aprepitant and placebo treatments. Note logarithmic scale on *y*-axes for (*A*) awake and (*B*) 24-hour cough frequency data. (*C–F*) Sleep cough frequency (*C*) is displayed on a linear scale, as are patient-reported outcomes (*D–F*). c/h = coughs per hour; CTCAE = Common Terminology Criteria for Adverse Events (grade 3 = worse cough severity); MCLCS = Manchester Cough in Lung Cancer Scale (50 = worse cough impact); VAS = visual analog scale (100 mm = worse cough severity).

change scales for both cough frequency ($P = 0.001$) and cough severity ($P = 0.028$). Researchers also rated the patients' cough with the CTCAE as improved with aprepitant compared with placebo (Table 2).

Safety

Aprepitant was well tolerated, with only mild adverse events reported. There were no serious adverse events and no grade 3 or 4 toxicities (severe/life-threatening); however, there was a greater number of adverse events on aprepitant compared with placebo (Table 3).

Preclinical Studies

Isolated vagus nerve responses to SP. *In vitro*, SP depolarized the guinea pig vagus nerve in a concentration-dependent manner (Figure 4A). SP (1 μM) was selected for further antagonist studies. In the isolated guinea pig vagus, pretreatment with aprepitant (10 μM; 0.1% DMSO) significantly inhibited responses to SP (1 μM) from 0.083 mV ± 0.007 to 0.0180 mV ± 0.008, a reduction of 78% ($P = 0.003$; $n = 5$; Figure 4B). Pretreatment with vehicle (0.1% DMSO) had no effect on SP (1 μM) responses ($P = 0.882$; $n = 4$). These results were mirrored in human tissue ($n = 3$ women, 67–73 yr old), in which aprepitant (10 μM; 0.1% DMSO) significantly inhibited responses to SP (1 μM) from 0.087 mV ± 0.013 to 0.003 mV ± 0.003, a reduction of 97% ($P = 0.0145$; $n = 3$; Figure 4C).

Discussion

To the best of our knowledge, this is the first placebo-controlled study to objectively demonstrate the antitussive efficacy of a NK-1 antagonist in humans and also the first trial in patients with lung cancer to employ acoustic cough monitoring. The improvements in cough frequency, with reductions over placebo of 22% during awaking hours and 30% over the whole 24-hour period, were sufficient to be appreciated by study participants, who recorded significant improvements on all patient-reported outcomes, which is striking given the very short (3 d) duration of treatment. Furthermore, our preclinical data provide mechanistic insights, suggesting that the inhibition of peripheral vagal nerves may contribute to the influence of aprepitant on coughing in addition to an effect in the central nervous system that might be predicted on the basis of the antiemetic mode of action.

The control of cancer symptoms is a key component of palliative care, which, when delivered early to patients with metastatic, incurable non–small cell lung cancer, has been shown to not only improve quality of life and mood but also prolong survival (22). Yet effective therapies to address the main symptom cluster in lung cancer—breathlessness, cough, and fatigue—are lacking. Indeed, efficacious agents for cough in any clinical condition are needed. Recent progress in the development of treatments for refractory chronic cough has suggested that therapies specifically targeting neuronal function via P2X3 antagonism may be

Table 3. Adverse Events Reported during the Trial

Adverse Events	Placebo (*n* = 19)	Aprepitant (*n* = 19)
Constipation	0 (0)	1 (5.5)
Vomiting	1 (5.2)	0 (0)
Fatigue	0 (0)	2 (11)
Vertigo	1 (5.2)	2 (11.0)
Headaches	1 (5.2)	0 (0)
Dyspnea	0 (0)	1 (5.5)
Gastroesophageal reflux disease	1 (5.2)	0 (0)
Chest infection	0 (0)	1 (5.5)
Vaginal pruritus	0 (0)	1 (5.5)
Conjunctivitis	1 (5.2)	0 (0)
Diarrhea	0 (0)	1 (5.5)
Malaise	0 (0)	1 (5.5)

All were grade 1, and there were no serious adverse events; only three were believed to possibly relate to aprepitant. Data are presented as *n* (%).

effective (23–25). This study provides the first objective evidence that a similar approach may also be valuable in cough associated with lung cancer. However, it should not be assumed that treatments targeting specific neuronal mechanisms will implicitly be effective for cough across a range of respiratory diseases. Recent evidence suggests changes in airway nerve function are likely to be disease specific, and therefore treatments may need to be tailored to particular neurophenotypes in respiratory disorders (26). Indeed, two recent phase 2b studies of other centrally acting NK-1 antagonists (serlopitant and orvepitant) in patients with refractory chronic cough rather than lung cancer both failed to achieve their primary endpoints (27, 28).

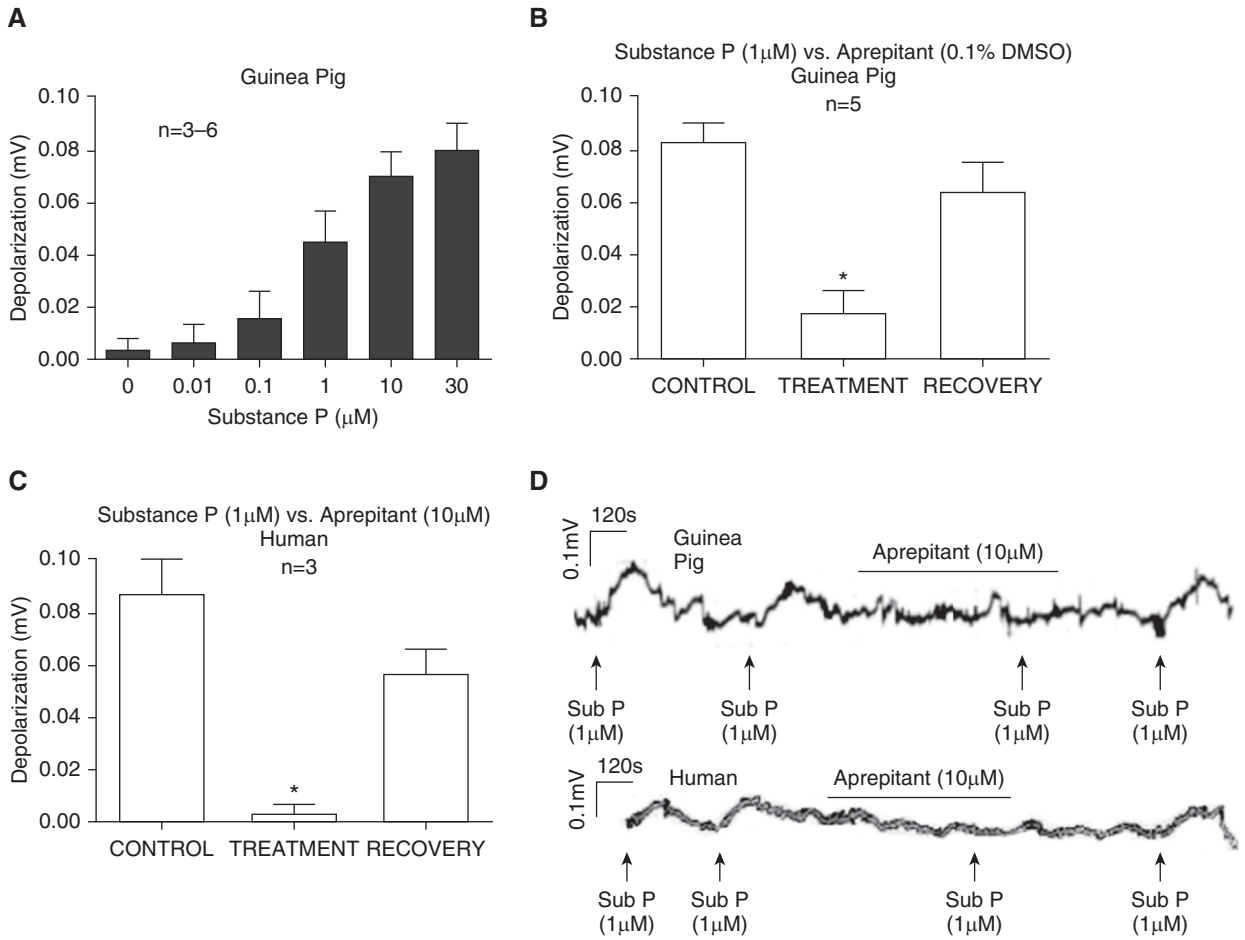

Figure 4. Concentration-dependent depolarization of guinea pig vagus with (*A*) substance P was blocked by (*B*) aprepitant, a reduction of 78% ($P = 0.003$, $n = 5$). Substance P depolarization of human vagus was also blocked by aprepitant, a reduction of 97% ($P = 0.0145$; $n = 3$). (*C*) Example tracings from vagus nerve preparations showing two control depolarization responses before the addition of aprepitant (10 μM) and then (*D*) showing the response to substance P (1 μM) recovered after washout. Data are mean (± SEM). *$P < 0.05$. Sub P = substance P.

Although the improvements achieved with aprepitant could be considered modest compared with those seen with P2X3 antagonism in refractory cough (37–75% reductions over placebo over treatment periods of up to 12 wk), the duration of treatment in this study was much shorter by comparison. Nonetheless, the improvement in the cough severity VAS after 3 days of aprepitant treatment reported in this study approached that seen with 10 weeks of gabapentin treatment (12 mm over placebo) in refractory chronic cough (29), and the reduction in the MCLCS is comparable to that reported in a 12-week feasibility study of a nonpharmacological intervention to address a respiratory distress symptom cluster in lung cancer (30). Further work is needed to evaluate whether NK-1 antagonism will deliver antitussive benefits with longer treatment durations, but the involvement of SP and NK-1 receptors in neuroplastic changes at synapses in the brainstem would suggest greater benefits might be expected from long-term therapy. Consistent with this notion, an unblinded trial, which was inspired by this study, recently randomized 128 patients with advanced lung cancer to receive aprepitant or standard antitussive therapy for 7 days (31). Although objective cough monitoring was not used and the study was not placebo controlled, significant improvements in cough severity VAS and MCLCS were found at Day 9 over standard antitussive care, and the absolute changes were increased compared with those seen in this study.

The participants in this study were typical of a lung cancer outpatient population. The greater proportion of female patients may be a consequence of selecting those with troublesome cough. Women are overrepresented in specialist clinics treating chronic cough (32), and even in health, women exhibit heightened cough reflex responses compared with men (33). It is notable that at enrollment to this study, almost half of patients were receiving opioid treatments and the majority had completed anticancer therapy, yet all still suffered from bothersome coughing with cough frequencies comparable with those of patients presenting with chronic cough as their main complaint (34).

Aprepitant and fosaprepitant, the intravenously administered prodrug of aprepitant, are currently the only licensed NK-1 antagonists in the United Kingdom, with rolapitant also available in the United States. Used in the prevention of chemotherapy-induced and postoperative nausea and vomiting, the antiemetic effects of NK-1 antagonists are believed to occur in the brainstem, where they prevent activation of the area postrema and nucleus tractus solitarius by afferent vagal inputs from the gastrointestinal tract and circulating emetic agents. Apart from their role in emesis, SP and the NK-1 receptor have been implicated in the regulation of a number of physiological and pathophysiological processes, including pain, inflammation, anxiety/depression, and itch, and thus newer NK-1 antagonists have been explored as antidepressants and antipruritics. NK-1 receptors are believed to play an important role in inducing and maintaining pruritus through both peripheral inflammatory mechanisms operating in the skin and processes in the central nervous system. In the skin, SP released by activation of a subgroup of C fibers plays a major role in the induction of "neurogenic inflammation," producing vasodilation and inflammatory cell recruitment. In rodents, a similar effect can be observed in the airways, with tachykinin release also producing bronchoconstriction and mucus hypersecretion. The reporting of airway neurogenic inflammation in rodent models previously led to considerable efforts to develop a variety of NK antagonists as novel asthma therapies; however, disappointing results in phase II clinical trials questioned the relevance of such mechanisms in asthma and in humans (35). Although it is impossible to determine from our studies whether the main antitussive effects of aprepitant are located in the airways or the central nervous system, our study does provide evidence of a possible inhibitory effect on peripheral nerves contributing to the mode of action of aprepitant. However, rather than C fibers releasing tachykinins such as SP to evoke neurogenic inflammation and cause cough, our studies suggest that SP activates airway C-fiber afferents to evoke cough.

This study has some limitations. The clinical study sample size was small, as this proof of concept study was only powered to assess the effect of aprepitant on objective cough frequency. This limits the conclusions about the general applicability of aprepitant for the treatment of cough in patients with lung cancer and also restricts the analysis of predictors of response. Nonetheless, we were able to demonstrate significant improvements in a range of cough measurements, including patient-reported outcomes, therefore suggesting the improvements in objective cough frequency observed were clinically meaningful. In addition, the dose level and duration were determined by the licensed doses optimized to treat nausea and vomiting, and therefore the relevance of these to antitussive effects needs further exploration with studies including a range of doses and longer duration.

Conclusions

These data suggest that the SP/NK-1 pathway plays a significant role in cough associated with lung cancer. Larger trials are warranted to evaluate this effect further, especially over longer treatment durations to determine whether antitussive effects are sustained or even enhanced. Antitussive efficacy, together with the established effects on nausea and vomiting and potential benefits for mood (36) and sleep quality (37), make the NK-1 receptor an attractive target for the development of treatment to palliate lung cancer symptoms. ■

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