Lung (2010) 188(Suppl 1):S47–S52
DOI 10.1007/s00408-009-9197-8

The Efficacy of a NOP1 Agonist (SCH486757) in Subacute Cough

Ashley Woodcock · Robbie L. McLeod · Jonathan Sadeh · Jaclyn A. Smith

Received: 25 October 2009 / Accepted: 26 October 2009 / Published online: 24 November 2009

Abstract Currently, opiates are widely used as antitussives but have substantial side effects. Recently, it has been proposed that NOP1 receptor agonists may be useful as a novel approach to cough suppression. Therefore, we compared the effect of NOP1 receptor agonist SCH486757 with matched placebo and codeine in a multicentre, double-blind, parallel-group study in patients with subacute cough. The primary outcome was change in cough severity scores, with the key secondary outcome change in objective daytime cough counts. We studied 91 subjects with subacute cough [59 (65%) female, median age = 41 (range = 18–64) years, and median cough duration = 33 (range = 16–99) days]. Subjects were randomised to receive either SCH486757 100 mg, codeine 30 mg, or matched placebo twice daily for 5 days. Cough severity was scored throughout using a diary card and objective cough frequency recorded for 8 h at baseline and on the first and last treatment days. There were no significant differences in changes in average cough severity scores from baseline to treatment between SCH486757 and placebo [mean change = −0.57 (−30.1%) vs. mean change = −0.49 (−19.7%); $P = 0.56$] or between codeine and placebo [mean change = −0.72 (−33.2%); $P = 0.07$ compared to placebo). Changes in objective cough counts also showed no differences between the three treatment groups. There were some hints of possible limited antitussive efficacy with SCH486757. Unfortunately, the maximum clinical dose is limited by its tendency to produce somnolence. If the therapeutic ratio of NOP1 agonists could be improved, these drugs may still prove to contain effective antitussives.

Keywords Antitussive · NOP1 · Subacute cough

A. Woodcock · J. A. Smith
Respiratory Research Group, The University of Manchester, Oxford Road, Manchester M13 9PL, UK

A. Woodcock
University Hospital of South Manchester NHS Foundation Trust, Manchester M23 9LT, UK

R. L. McLeod · J. Sadeh
Schering-Plough Research Institute, 2015 Galloping Hill Road, Kenilworth, NJ 07033, USA

J. A. Smith (✉)
Education and Research Centre, University Hospital of South Manchester, 2nd Floor, Southmoor Road, Wythenshawe, Manchester M23 9LT, UK
e-mail: jacky.smith@manchester.ac.uk

Introduction

There is a real need for effective and safe antitussive drugs. There are a number of possible reasons that no new effective antitussive drugs have been developed. First, we have little understanding of the mechanisms underlying increased cough in humans. For example, do acute cough and subacute cough have a similar pathophysiological basis to chronic cough and are they amenable to similar interventions? Second, how do we test for clinical efficacy in patients, and in which cough syndrome? Third, the efficacy predicted from animal models may not translate into human disease. Finally, the pharmaceutical industry, with few exceptions, has been reluctant to invest significant resources into this area, underestimating the clinical need and perceiving cough treatments as a high-risk area whilst the underlying mechanisms are poorly understood.

In the UK, there are an estimated 48 million episodes of acute cough (cough lasting <3 weeks) in the community

annually, resulting in 24 million episodes of self-medication using £100 million of nonprescription cough medicines, and about 12 million episodes result in a general practitioner consultation [1]. Cough is the commonest symptom presenting in primary care [2], but acute cough may be a difficult scenario in which to test an antitussive because of the potential for large placebo effects [3–5] that occur against a background of a rapidly declining cough rate over a short illness. Subacute cough [defined as cough persisting 3–8 weeks after an upper respiratory tract infection (URTI)] may be a more appropriate clinical model to study new antitussives since the rate of improvement is, by definition, slower and cough symptoms may have stabilized by that point.

Currently, opiates are widely used as antitussives, but drugs such as codeine that activate μ opioid (MOP) receptors have substantial side effects, including respiratory depression, constipation, sedation, and physical dependency. Recently, it has been proposed that an orally active selective NOP1 (nociceptin opioid 1) receptor agonist may be useful as a novel approach to cough suppression [6–10]. NOP1 is a G-protein-coupled receptor that was identified from a human cDNA library [11]. This receptor has been found to share significant homology with the classical opioid receptors μ (MOP), k (KOP), and d (DOP) [12]. The endogenous ligand for NOP is nociceptin/orphanin FQ (N/OFQ), a 17-amino-acid peptide [13–15]. SCH486757 [8-[bis(2-chlorophenyl)methyl]-3-(2-pyrimidinyl)-8-azabicyclo[3.2.1.]octan-3-ol] is a potent and highly selective NOP receptor agonist. For example, in human binding studies, SCH486757 displays high binding affinity for human NOP receptors relative to opioid MOP (226-fold difference), DOP (119-fold), and KOP (3076-fold) receptors. In addition, SCH486757 was found to produce comparable oral antitussive activity compared to codeine in a guinea pig capsaicin-evoked cough model.

We compared the effect of SCH486757 with matched placebo and codeine in a multicentre, double-blind, parallel-group study of patients with subacute cough. The primary end point was the change in cough severity scores for SCH486757 compared to placebo, with the key secondary outcome of change in objective daytime cough counts.

Methods

Study Design

We carried out a randomised, double-blind, placebo-controlled, parallel-group study. The study was conducted in 16 centres in the United Kingdom, Latin America, and South Africa. Subjects who qualified for inclusion were randomised (stratified by gender) to receive one of the following treatments for 5 days: (1) SCH486757 100 mg twice daily, (2) codeine 30 mg twice daily, (3) matched placebo twice daily. The dose of SCH486757 was selected based on studies in normal volunteers that showed that higher doses were associated with dizziness, fatigue, and somnolence.

Subjects

Both male and female subjects 18 to <65 years old were eligible for the study. All subjects gave a history of a persistent cough following symptoms indicative of a viral upper respiratory tract infection with an onset of a least 14 days, but no more than 90 days prior to the prescreening visit.

Subjects with a history of any active lung or other systemic disease and current or ex-smokers of more than 10 pack-years were excluded, as were those taking ACE inhibitors or opiates. Females who were pregnant or breastfeeding were excluded and those with childbearing potential were required to use adequate birth control. All patients were provided with written information prior to obtaining written consent. Approval for the study was obtained from the Medicines and Healthcare Products Regulatory Agency (MHRA) (SP protocol P03069; South Manchester Research and Ethics Committee) and the trial was registered at www.clinicaltrials.gov (NCT00230230).

Procedures

Subjects first attended for a prescreening visit (Day −7) where baseline safety measures (see below) were performed (Fig. 1). If safety measures were satisfactory, then a screening visit followed (Day −1) to collect baseline cough severity scores and 8 h of cough monitoring. Randomisation and first dosing (Day 1) took place only if the subject had been sufficiently clinically symptomatic since the screening visit, with an average cough severity score of at least 2 (moderate) in the diary card over the last three evaluations (i.e., morning and evening scores for the previous day and the morning score for the visit day). The allocated treatment was given for 5 days (Days 1–5), with cough severity scores recorded throughout and cough monitoring performed for 8 h on the first and final treatment days.

Efficacy Measures

Subjective Cough Scores Diary cards were completed twice daily, on waking in the morning and before going to sleep at night, reflecting the subjects' cough over the preceding 12 h. The severity of cough was rated on a scale of 0–3 (0 = none, no cough evident; 1 = mild, cough clearly

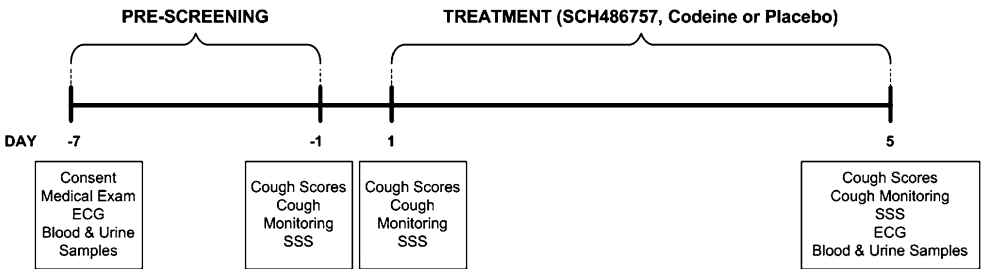

Fig. 1 Study design (*SSS* Stanford Sleepiness Scale)

present but minimal awareness, easily tolerated, did not interfere with normal activity; 2 = moderate, definite awareness of cough which is bothersome but tolerable, must stop activity during coughing episode; 3 = severe, cough is hard to tolerate, may interfere with activities of daily living and/or sleeping, stops activity for some time and is exhausting). Baseline cough severity was defined as the mean severity score of the three evaluations: on the screening day (a.m. and p.m.) and immediately before the first dose of randomised treatment (a.m.). Treatment cough severity was defined as the mean scores over the 5 treatment days.

Subjects also recorded cough frequency twice daily, lack of sleep (morning only), interference with daytime activities (evening only), and "how the cough has affected me" on a 10-cm visual analogue scale twice daily. Adverse events, additional medication taken, and timing of study medication also were recorded in the diary. The primary end point was the change in mean cough severity score from baseline to treatment for SCH486757 compared to placebo.

Cough Monitoring To monitor cough frequency, subjects wore a Lifeshirt^{TM} (VivoMetrics Inc., Ventura, CA) [16] for 8 h at screening and on treatment days 1 and 5 following dose administration. Coughing is identified from two signals: chest wall motion detected by inductive plethysmography and sound via a microphone worn around the throat. Data were recorded and explosive cough phases counted blind at a central site. Data were analysed for the key secondary end points of cough counts for 0–4 h and also for 0–8 h. The change from baseline in objective daytime cough count (from time zero to 4 h after dose) for SCH486757 compared to placebo was the key secondary efficacy outcome.

Safety Measures

Patients completed the Stanford Sleepiness Scale (SSS) [17], a 7-point numeric rating scale that describes current sleepiness from fully awake to fully asleep. Adverse events and physical examination were documented at each visit. Routine laboratory tests and ECGs were documented at baseline and at the start and end of each treatment period. Blood sampling was conducted for pharmacokinetic and pharmacogenetic analyses. Spirometry was performed according to American Thoracic Society (ATS) guidelines [18].

Statistical Analysis

The primary objective of this trial was to evaluate the effect of SCH486757 compared to placebo on cough severity score. With a sample size of 50 subjects per treatment group, a difference in cough severity score of 0.4 would provide 80% power at a 5% level of significance, assuming a pooled standard deviation of 0.7. Efficacy analyses and summaries of safety data were based on all randomised subjects with at least some follow-up information (intent-to-treat principle). Analysis of the primary efficacy outcome was performed using an analysis of variance, extracting sources of variation due to treatment, gender, and study centre. Treatment comparisons were based on the least-squares means from the model at the 5% two-tailed level of significance. For the key secondary outcome, cough frequency measures were highly skewed so median values are given and nonparametric analysis applied. Comparisons of cough severity were made first for SCH486757 versus placebo and then for codeine versus placebo. The data are described as an absolute change from baseline.

Results

Subjects

The study proved difficult in terms of patient enrolment. It was initiated during a mild winter cold season in the UK, continued during the southern hemisphere winter, and then back to the UK for a second winter. At the end of the study, 91 subjects had been enrolled [59 (65%) female, median age = 41 (range = 18–64) years and median cough duration = 33 (range = 16–99) days] against a target population of 150 subjects. Of these 91 subjects, 27 were randomised to SCH486757, 34 to codeine, and 30 to placebo. There was no significant difference in gender

Table 1 Characteristics of patients randomised to each treatment arm

	SCH486757 100 mg bd ($n = 27$)	Codeine 30 mg bd ($n = 34$)	Placebo ($n = 30$)
Sex			
Female	19 (70%)	21 (62%)	19 (65%)
Male	8 (30%)	13 (38%)	11 (37%)
Race			
White	25 (93%)	34 (100%)	27 (90%)
Nonwhite	2 (7%)	0	3 (10%)
Multiracial	2 (7%)	0	3 (10%)
Age (years) (range)	42.0 (18–64)	41.0 (18–62)	40.5 (19–61)
Weight (kg) (range)	75.0 (56.5–115.0)	77.5 (50–138.0)	73.0 (49.0–113.7)
Height (cm)	165.7 (9.6)	168.5 (11.8)	169.3 (10.6)

distribution, ethnicity, height, or weight between the three groups (Table 1). Two subjects dropped out of the study because of adverse events, one in each of the active treatments; therefore, 89 subjects completed the study.

Cough Severity Scores

There was no significant difference in the primary end point of change in average cough severity scores from baseline to treatment between SCH486757 and placebo [SCH486757 mean baseline = 1.98, mean change during treatment = –0.57 (−30.1%); placebo mean baseline = 2.01, mean change = −0.49 (−19.7%), $P = 0.56$]. Nor were there significant changes in cough severity score for codeine compared to placebo [codeine mean baseline = 2.15, mean change = −0.72 (−33.2%), $P = 0.07$ compared to placebo). As can be seen in Fig. 2, cough severity scores in all three groups declined gradually over the 5 days. Codeine had numerically lower scores throughout. There was no significant difference between groups for any of the other secondary diary card data (cough frequency, lack of sleep, interference with daytime activities, and overall impact of cough). There was a nonsignificant trend for increased Stanford sleepiness scores on SCH486757.

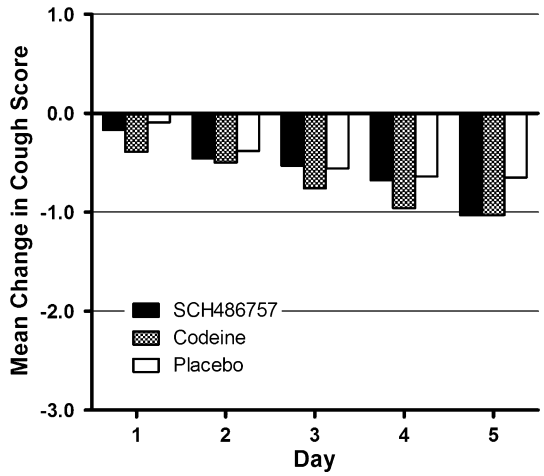

Fig. 2 Mean change from baseline cough severity score, average of morning and evening evaluations

Objective Cough Monitoring

Of the 91 randomised subjects, 74 (81.3%) had objective cough counts using the Lifeshirt at baseline and Days 1 and 5; 17 subjects had technical problems with the Lifeshirt recordings. Median cough counts per hour at baseline were 18.0 coughs/h (range = 11.5–25.0) for patients randomised to SCH486757, 25.3 coughs/h (17.5–28.5) for codeine, and 19.5 coughs/h (17.0–22.5) for placebo ($P = 0.02$).

The median changes in cough counts from baseline hour by hour are shown in Fig. 3. On Day 1, SCH486757 reduced cough counts by a median of 3.4 coughs/h, codeine by 0.1 coughs/h, and placebo by 2.8 coughs/h compared to

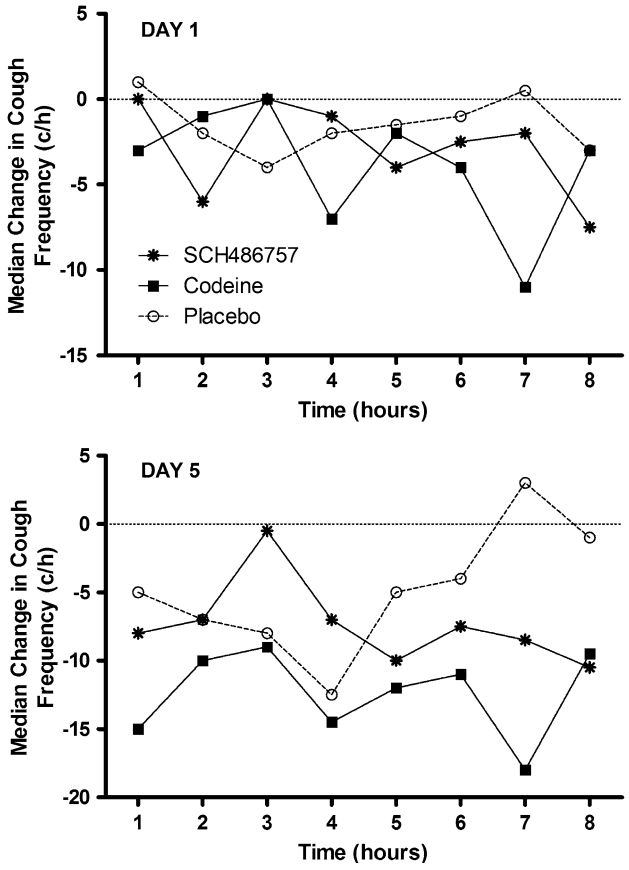

Fig. 3 Median changes in objective cough frequency from baseline with SCH486757, codeine, and placebo treatments on Day 1 and Day 5 of therapy

baseline over the first 4 h after dosing, with no significant differences for the key secondary end point of SCH486757 versus placebo ($P = 0.30$) or for codeine versus placebo ($P = 0.68$). Changes in cough counts also were not significantly different between treatment groups over the total 8-h monitoring period (SCH486757 reduced cough counts by a median of 2.5 coughs/h, codeine by 1.9 coughs/h, and placebo by 1.1 coughs/h; $P = 0.29$) (Fig. 3).

On Day 5, SCH486757 reduced cough counts by a median of 7.0 coughs/h, codeine reduced counts by 13.8 coughs/h, and placebo reduced counts by 7.8 coughs/h over the first 4 h. There was no significant difference in effect for the key secondary outcome of SCH486757 versus placebo ($P = 0.71$) or for codeine versus placebo ($P = 0.16$). Similarly, median changes in cough count from baseline were not statistically significant over the full 8 h of cough monitoring (SCH486757 reduced cough counts by a median of 8.1 coughs/h, codeine by 14.4 coughs/h, and placebo by 2.3 coughs/h; $P = 0.10$).

Somnolence was reported by seven patients on SCH486757, three patients on codeine, and four patients on placebo. Gastrointestinal complaints were reported in four patients on SCH486757, ten on codeine, and four on placebo.

Discussion

This is the first randomized placebo-controlled study of a NOP1 agonist to be reported. We believe this is also the first clinical trial published about a novel antitussive drug since dextromethorphan. We were not able to demonstrate statistically significant subjective or objective efficacy compared to placebo. Both SCH486757 and codeine reduced symptoms to a similar degree but not statistically different than placebo. There was no difference in cough counts for either drug compared to placebo. More patients on SCH486757 reported sedation, but fewer reported gastrointestinal side effects compared to codeine. This suggests a different profile compared to MOP agonists.

Subacute cough proved a difficult clinical syndrome in which to test a potential novel antitussive. The study was very slow to recruit, except for primary care. This presented difficulties with appropriate safety monitoring for a novel drug, and for quality control with complex technology for cough counting in the community. We studied subacute cough because we thought it might be more stable than acute cough. However, it is notable that even in this clinical setting, symptoms and objective cough rates declined substantially over the 5 days. Subacute cough may not be ideal for future studies of novel antitussives in light of these difficulties.

The Lifeshirt is the first licensed objective cough counter but the validation data are limited [16]. The Lifeshirt consists of a modified vest plethysmograph with a throat microphone. In practice, patients found it cumbersome, and whilst 8-h recordings were obtained in the majority of subjects, it may inhibit patients from carrying out their usual activities of daily living. The Lifeshirt cough rates in this study were similar to those we have observed previously in subjects complaining of chronic cough [19]. However, the accuracy of cough detection for this system for subacute cough is not known, and there may have been false positives (i.e., noncough sounds interpreted as cough), which could conceal clinical efficacy.

There has been no new antitussive agent introduced to the antitussive market since dextromethorphan in the late 1950s. In the current study, when codeine is critically assessed against objective end points in a blind study, it fails to demonstrate efficacy. The development of novel antitussive agents has critical limitations in its reliance on and interpretation of data from animal models. For the most part, much of the preclinical profiling of potential new antitussive agents has been conducted in healthy animals using mechanical or chemical irritants (e.g., capsaicin, citric acid) of the airways. In these models NOP1 agonists typically display impressive antitussive effects in the range of 50–60% inhibition of capsaicin-evoked cough and 70–90% inhibition of mechanically elicited cough in guinea pigs and cats, respectively [6, 8, 20]. Our new human data suggest that the current healthy animal models may have overpredicted the level of efficacy of this pharmacological class of drug. Novel models that better reflect human disease are needed to predict the potential efficacy in human cough. These may include new animal disease models [18], and models of animal cough reflex hypersensitivity [21].

In summary, there were some hints of limited antitussive efficacy with SCH486757. However, the statistical power of the study was limited by low recruitment of patients with subacute cough and by the substantial decline in symptom scores across the study, even on placebo. Unfortunately, the maximum clinical dose of SCH486757 is limited by its tendency to produce somnolence. If the therapeutic ratio of NOP1 agonists could be improved, this category of drugs may still ultimately prove to contain effective antitussives.

Acknowledgments The study sites were as follows: A.M. George, Cambridgeshire, UK; Philip Marazzi East Horsley, Surrey, UK; Lorcan McGarvey, Belfast, Northern Ireland, UK; Alyn Morice, Cottingham, UK; Moyra Anderson, Greenisland, Northern Ireland, UK; Thomas James Anthony Egerton, Bangor, County Down, Ireland; Anna M. E. Ker, Pretoria, South Africa; Fabian Galleguillos, Santiago, Chile; Monica Gutierrez, Vina Del Mar, Chile; Patricia Rivas, Rancagua, Chile; Tamara Soler, Santiago, Chile; Danelle C. Richter, Capetown South Africa; Nigel Gough, Wiltshire, UK.

References

1. Morice AH, McGarvey L, Pavord I (2006) Recommendations for the management of cough in adults. Thorax 61(Suppl 1):i1–i24
2. Schappert SM, Burt CW (2006) Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001–02. Vital Health Stat 13(159):1–66
3. Eccles R, Morris S, Jawad M (1992) Lack of effect of codeine in the treatment of cough associated with acute upper respiratory tract infection. J Clin Pharm Ther 17(3):175–180
4. Lee PCL, Jawad MS, Eccles R (2000) Antitussive efficacy of dextromethorphan in cough associated with acute upper respiratory tract infection. J Pharm Pharmacol 52(9):1137–1142
5. Lee PC, Jawad MS, Hull JD, West WH, Shaw K, Eccles R (2005) The antitussive effect of placebo treatment on cough associated with acute upper respiratory infection. Psychosom Med 67(2):314–317
6. McLeod RL, Parra LE, Mutter JC, Erickson CH, Carey GJ, Tulshian DB, Fawzi AB, Smith-Torhan A, Egan RW, Cuss FM, Hey JA (2001) Nociceptin inhibits cough in the guinea-pig by activation of ORL(1) receptors. Br J Pharmacol 132(6):1175–1178
7. McLeod RL, Tulshian DB, Hey JA (2003) Novel pharmacological targets and potential progression of new antitussive drugs. Expert Opin Therapeut Pat 13:1501–1512
8. McLeod RL, Tulshian DB, Ho GD, Fernandez X, Bolser DC, Parra LE, Zimmer JC, Erickson CH, Fawzi AB, Jayappa H, Lehr C, Erskine J, Smith-Torhan A, Zhang H, Hey JA (2009) Effect of a novel NOP receptor agonist (SCH 225288) on guinea pig irritant-evoked, feline mechanically induced and canine infectious tracheobronchitis cough. Pharmacology 84:153–161
9. Ho GD, Anthes J, Bercovici A, Caldwell JP, Cheng KC, Cui X, Fawzi A, Fernandez X, Greenlee WJ, Hey J, Korfmacher W, Lu SX, McLeod RL, Ng F, Torhan AS, Tan Z, Tulshian D, Varty GB, Xu X, Zhang H (2009) The discovery of tropane derivatives as nociceptin receptor ligands for the management of cough and anxiety. Bioorg Med Chem Lett 19(9):2519–2523
10. Yang SW, Ho G, Tulshian D, Greenlee WJ, Anthes J, Fernandez X, McLeod RL, Hey JA, Xu X (2009) Discovery of orally active 3-pyridinyl-tropane as a potent nociceptin receptor agonist for the management of cough. J Med Chem 52(17):5323–5329
11. Bunzow JR, Saez C, Mortrud M, Bouvier C, Williams JT, Low M, Grandy DK (1994) Molecular cloning and tissue distribution of a putative member of the rat opioid receptor gene family that is not a mu, delta or kappa opioid receptor type. FEBS Lett 347(2–3):284–288
12. Mollereau C, Parmentier M, Mailleux P, Butour JL, Moisand C, Chalon P, Caput D, Vassart G, Meunier JC (1994) ORL1, a novel member of the opioid receptor family. Cloning, functional expression and localization. FEBS Lett 341(1):33–38
13. Meunier JC, Mollereau C, Toll L, Suaudeau C, Moisand C, Alvinerie P, Butour JL, Guillemot JC, Ferrara P, Monsarrat B et al (1995) Isolation and structure of the endogenous agonist of opioid receptor-like ORL1 receptor. Nature 377(6549):532–535
14. Reinscheid RK, Nothacker HP, Bourson A, Ardati A, Henningsen RA, Bunzow JR, Grandy DK, Langen H, Monsma FJ Jr, Civelli O (1995) Orphanin FQ: a neuropeptide that activates an opioidlike G protein-coupled receptor. Science 270(5237):792–794
15. Calo G, Guerrini R, Rizzi A, Salvadori S, Regoli D (2000) Pharmacology of nociceptin and its receptor: a novel therapeutic target. Br J Pharmacol 129(7):1261–1283
16. Coyle MA, Keenan DB, Henderson LS, Watkins ML, Haumann BK, Mayleben DW, Wilson MG (2005) Evaluation of an ambulatory system for the quantification of cough frequency in patients with chronic obstructive pulmonary disease. Cough 1:3
17. Hoddes E, Zarcone V, Smythe H, Phillips R, Dement WC (1973) Quantification of sleepiness: a new approach. Psychophysiology 10(4):431–436
18. Nasra J, Belvisi MG (2009) Modulation of sensory nerve function and the cough reflex: understanding disease pathogenesis. Pharmacol Ther [Epub ahead of print]
19. Decalmer SC, Webster D, Kelsall AA, McGuinness K, Woodcock AA, Smith JA (2007) Chronic cough: how do cough reflex sensitivity and subjective assessments correlate with objective cough counts during ambulatory monitoring? Thorax 62(4):329–334
20. Bolser DC, McLeod RL, Tulshian DB, Hey JA (2001) Antitussive action of nociceptin in the cat. Eur J Pharmacol 430(1):107–111
21. Mazzone SB, Mori N, Canning BJ (2005) Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs. J Physiol 569(Pt 2):559–573

Financial Disclosure/Conflict of Interest Statement

The authors of this article have no commercial associations (e.g., consultancies, stock ownership, equity interests, patent-licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article, except as disclosed below. All funding sources supporting the work and all institutional or corporate affiliations of the authors are acknowledged.

Dr. Jaclyn Smith and Professor Ashley Woodcock have both acted as consultants for Schering Plough, and Dr. Jonathan Sadeh and Dr. Robbie McLeod are employees of Schering Plough Research Institute, Kenilworth, USA.