CLINICAL STUDY PROTOCOL

A DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THREE DOSES OF ORVEPITANT IN SUBJECTS WITH CHRONIC REFRACTORY COUGH

IND No:	132343
EudraCT No:	2016-004979-49
ClinicalTrials.gov No:	NCT02993822
Protocol No.:	VOLCANO-2
Version No:	Final 5.0
Date of Protocol:	21 February 2018

Sponsor: NeRRe Therapeutics Ltd,
SBC, Incubator Building,
Gunnels Wood Rd.,
Stevenage,
SG1 2FX
United Kingdom

This study will be conducted in compliance with Good Clinical Practice (GCP), the General Principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

1. PROTOCOL SYNOPSIS

PROTOCOL TITLE	A DOUBLE-BLIND, RANDOMIZED, PLACEBO CONTROLLED STUDY OF THE EFFICACY AND SAFETY OF THREE DOSES OF ORVEPITANT IN SUBJECTS WITH CHRONIC REFRACTORY COUGH
PROTOCOL No.	VOLCANO-2
CHIEF INVESTIGATOR	Professor Jaclyn Smith MB ChB PhD FRCP
SPONSOR	NeRRe Therapeutics Ltd
INVESTIGATIONAL MEDICINAL PRODUCT	Orvepitant and placebo
PHASE OF DEVELOPMENT	Phase 2
INDICATION AND RATIONALE	Chronic Refractory Cough
STUDY DESIGN	A multi-center, double-blind, randomized, parallel group, placebo-controlled dose range study in subjects with chronic refractory cough (CRC). Doses of orvepitant (10 mg/day, 20 mg/day and 30 mg/day) and placebo will be investigated in four parallel groups. Subjects will be randomized 1:1:1:1 to each of the groups. All subjects will enter a three-week Screening period to determine eligibility. Eligible subjects will be randomized at the Baseline/Day 1 visit and enter a 12-week double-blind dosing period. During this period there will be four visits at Weeks 2, 4, 8 and 12. There will be a final safety follow-up visit at Week 14.

STUDY OBJECTIVES

Primary

- To evaluate the efficacy of once daily doses of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in reducing awake objective cough frequency

Secondary

- To evaluate the efficacy of once daily dosing of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in:
  - Reducing 24-hour objective cough frequency
  - Reducing night-time (non-waking time) objective cough frequency
  - Reducing subject assessed cough severity and Urge-to-Cough
  - Improving Quality-of-Life and subject perception of change
- To evaluate the dose-response relationship of 10 mg, 20 mg, and 30 mg orvepitant
- To assess the safety and tolerability of 10 mg, 20 mg, and 30 mg orvepitant versus placebo over 12 weeks dosing

Pharmacokinetics

- To evaluate the exposure-response relationship of orvepitant using population pharmacokinetics (PK) with sparse sampling

STUDY ENDPOINTS

Primary

- Change from Baseline to Week 12 in awake objective cough frequency measured with an automated cough monitor (ACM), [redacted]

Secondary

- Change in awake objective cough frequency at Weeks 2, and 4 compared to Baseline
- Change in 24-hour objective cough frequency at Weeks 2, 4 and 12 compared to Baseline
- Change in night-time (non-waking time) objective cough frequency at Weeks 2, 4 and 12 compared to Baseline
- Change in the Cough Severity visual analogue scale (VAS) at Weeks 2, 4, 8, and 12 compared to Baseline

	• Change in the Urge-to-Cough VAS at Weeks 2, 4, 8, and 12 compared to Baseline • Change in the Leicester Cough Questionnaire (LCQ) score (total and three domain scores) at Weeks 2, 4, 8, and 12 compared to Baseline • Global Rating of Change in Cough Frequency and Severity at Weeks 2, 4, 8, and 12
Safety	• Change from Baseline in clinical laboratory assessments (hematology, clinical chemistry, urinalysis) • Change from Baseline in vital signs (temperature, sitting/standing Blood Pressure (BP), pulse, respiration rate, weight) • Change from Baseline in 12-lead Electrocardiogram (ECG) variables (heart rate and rhythm and RR, PR, QRS, QT, QTcF and QTcB intervals) • Nature and severity of Adverse Events (AE) • Withdrawals due to an AE • Use of concomitant medications
Pharmacokinetics	• PK exposure-response relationship for the orvepitant groups (10 mg, 20 mg, and 30 mg) will be carried out to examine the possible relationship over time between clinical efficacy and plasma levels of the drug
PLANNED SAMPLE SIZE AND STATISTICAL CONSIDERATIONS	The initial planned sample size for this study was 55 subjects per treatment group (220 subjects in total). As a result of the planned sample size re-estimation the sample size is increased to 65 subjects per group (260 in total) The sample size calculation is based on pairwise comparisons of the primary endpoint for each active dose versus placebo. Objective cough frequency will be analyzed on a log scale. A two-sided type I error of 0.05, not adjusted for multiple comparisons against placebo, will be used for this exploratory study. Assuming a revised standard deviation of change from Baseline (after taking logs) of 0.285 (based on the sample size re-estimate and increased from the original assumption of 0.261), a reduction in the placebo group of 10% and a reduction in the orvepitant group of 35%, 65 subjects per arm will provide a power of 80%. This new standard deviation estimate has been obtained (at the first sample size review) by considering the revised full analysis set of

subjects.

After at least 100 subjects have completed the Week 12 ACM assessment (and in addition to the now completed first sample size re-estimate) the cough frequency data will be reviewed to check the estimate of variability assumed for the primary efficacy variable. This sample-size re-estimation will be done on a blinded basis and may result in an increase in the sample size.

Assuming no further changes to the sample size estimate, approximately 292 subjects will be randomized to ensure at least 260 completers (assuming approximately 10% drop out rate). The sample size may be adjusted again after the second re-estimate and provided no more than 320 subjects (approximately 80 per group) are required the precise number will be documented in a non-substantial (administrative) amendment to the protocol.

SUBJECT POPULATION

Inclusion Criteria

1. Male and female subjects ≥18 years of age
2. Able to understand and comply with the requirements of the study and sign Informed Consent forms
3. Diagnosis of CRC or unexplained cough for at least 1 year prior to Screening (see American College Chest Physicians/British Thoracic Society [ACCP/BTS] guidelines Section 17)
4. An awake average cough frequency of ≥10 coughs/hour, as assessed using an ACM during the Screening period (note, the ACM will be worn for a 24-hour period and the average waking cough frequency determined)
5. Females must be non-pregnant and non-lactating with no intention of pregnancy during study treatment
6. Women of child-bearing potential (WOCP) (i.e. not surgically sterilised or post-menopausal*) must have a negative blood serum pregnancy test performed at the Screening visit and agree to use two methods of birth control, one of which must be a barrier method (note: the double barrier method is not considered acceptable) for the duration of participation in the study.
   ** Post-menopausal is defined as >1 year since the last menstrual period for women >55 years of age or >1 year since their last menstrual period and have an*

FSH level in the menopausal range for women <55years of age.

Acceptable methods of birth control are:

a. Surgical sterilization of the subject's male partner (vasectomy with documented azoospermia) if he is the sole partner of that subject

b. Established hormonal contraception (implantable, patch, oral or intramuscular [IM]) administered for at least one month prior to IMP administration and to continue for at least 4 weeks after the last dose of IMP

c. An intrauterine device (IUD) or intrauterine system (IUS) with failure rate of less than 1% per year inserted by qualified physician at least one month prior to IMP administration and to remain in place for at least 4 weeks after the last dose of IMP

d. Barrier methods such as male condom or cap, diaphragm or sponge with spermicide

7. Male subjects and their partners of child-bearing potential must use two methods of acceptable birth control, one of which must be a barrier method; male subjects must make no donation of sperm from Screening until 90 days after the last dose of IMP

Exclusion Criteria

1. Subjects with recent respiratory tract infection (<4 weeks prior to Screening)
2. Females who are breast feeding or pregnant
3. Current smokers or ex-smokers with <6 months' abstinence prior to Screening
4. Treatment with Angiotensin Converting Enzyme (ACE) inhibitors within 3 months of Screening
5. A history of drug or alcohol abuse within 12 months of Screening
6. Both FEV_1 <80% predicted and FEV_1/FVC ratio < 0.7, measured at Screening using spirometry
7. History of cystic fibrosis, idiopathic pulmonary fibrosis, clinically significant bronchiectasis, moderate to severe asthma, chronic obstructive pulmonary disease (COPD)

8. Evidence of uncontrolled hypertension at Screening or Baseline[1]
9. Recent myocardial infarction (within 1 year prior to Screening), or history of congestive cardiac failure
10. Any clinically significant abnormalities on 12-lead ECG at Screening or Baseline/Day 1
11. Subjects with prior renal transplant, current renal dialysis, or history of renal tubular acidosis
12. Any clinically significant neurological disorder
13. Any clinically significant or unstable medical or psychiatric condition that would interfere with the subject's ability to participate in the study
14. Subjects with a prior medical history of or an increased risk of seizures (except febrile seizures in infancy), or who have a history of recent head trauma (within the last 6 months prior to Screening) that resulted in a loss of consciousness or concussion
15. Any malignancy in the past 5 years unless non-invasive and in remission (disease-free for >5 years prior to Screening) and written approval has been obtained from Sponsor, with the exception of skin cancers not including malignant melanoma
16. Any clinically significant abnormal laboratory test result(s), measured at Screening[2]
17. Inability to comply with the use of prohibited and allowed medications as described below:
    a. The use of opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines or tricyclic antidepressants (e.g. amitriptyline) for treatment of cough is not allowed throughout the study. Subjects must have discontinued these drugs at least 1 month prior to Screening. Subjects may, however, be permitted to continue to use these drugs if they have been prescribed solely for the management of another disorder (e.g. neuropathic pain, depression).
    b. The use of other drugs taken solely for the treatment of cough (including those used on an as needed basis) is also prohibited from at least 1

[1] as guidance, systolic >160 mm Hg or diastolic >90 mmHg should result in further evaluation which may include repeat measurements after a period of rest

[2] The investigator should judge the clinical relevance of any abnormal laboratory parameters in the context of the subject's current and past medical history and any know contributing factors (e.g., strenuous exercise resulting in elevated AST or CK)

month prior to Screening.

c. Concomitant respiratory medication (other than for management of cough) is allowed, but subjects must be stable on such medication and take it for the duration of the study

d. Use of digoxin is not allowed from Screening until 1 week after the last dose of IMP

e. Use of known CYP3A4 substrates with a narrow therapeutic range is not allowed from Screening until 1 week after the last dose of IMP (including but not limited to alfentanil. cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus)

f. Use of strong or moderate inhibitors of CYP3A4 is not allowed from Screening until 1 week after the last dose of IMP (including but not limited to clarithromycin, erythromycin, grapefruit juice, indinavir, lopinavir, ritonavir, saquinavir, atazanavir, itraconazole, ketoconazole, voriconazole, fluconazole, posaconazole, cimetidine, cyclosporine, diltiazem, fluvoxamine, imatinib, verapamil, troleandomycin and ciprofloxacin)

g. Use of inducers of CYP3A4 is not allowed from Screening until 1 week after the last dose of IMP (including but not limited to rifampicin, carbamazepine, efavirenz, bosentan, modafinil, St. John's Wort)

h. Use of known P-glycoprotein inhibitors is not allowed from Screening until 1 week after the last dose of IMP (including but not limited to amiodarone, azithromycin, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quinidine, ranolazine, verapamil)

18. Participation in any clinical research study evaluating another investigational drug or therapy within 30 days or within 5 half-lives (whichever is longer) of the investigational drug prior to Screening. If the subject is in an observational clinical study no washout is required

19. Subjects receiving aprepitant (Emend®) or fosaprepitant (Ivemend®), NK-1 antagonists licensed as anti-emetics <4 weeks before the Screening visit

20. Subjects who have previously received orvepitant at

	any time 21. Known allergy to any of the excipients (see Section 9.2) used in the investigational medicinal product (IMP) (orvepitant or placebo tablets) 22. Subjects who, in the opinion of the Investigator, should not participate in the study for any other reason
ORVEPITANT FORMULATION/DOSE	Orvepitant 10 mg, 20 mg, 30 mg tablets
REFERENCE FORMULATION/DOSE	Matching placebo
ROUTE OF ADMINISTRATION	Oral
DURATION/FREQUENCY OF TREATMENT	Once daily dosing for 12 weeks
EFFICACY ASSESSMENTS	• Subjects will be fitted with an ACM [redacted] to record objective cough frequency over 24 hours at Screening, Weeks 2, 4, and 12 • Subjects will complete the LCQ at the clinic at Baseline/Day 1 and Weeks 2 ,4 ,8, and 12 • Subjects will complete the Global Rating of Change for Cough Frequency & Severity Scale at the clinic at Weeks 2, 4, 8, and 12 • Subjects will complete both the Cough Severity VAS and Urge-to-Cough VAS at the clinic at Baseline/Day 1 and Weeks 2, 4, 8, and 12
SAFETY ASSESSMENTS	Safety and tolerability will be assessed by the following: • Physical Examinations • Change from Baseline in ECG variables (heart rate and rhythm and RR, PR, QRS, QT, QTcF and QTcB intervals) • Change from Baseline in clinical laboratory assessments (hematology, clinical chemistry, urinalysis) • Change from Baseline in vital signs • Adverse events • Use of concomitant medications

PHARMACOKINETICS	Plasma levels of orvepitant will be measured by analysis of samples collected at the clinic visits on Weeks 2, 4, 8 and 12.
STATISTICAL METHODS	Relevant Screening and Baseline data (i.e. data collected prior to the treatment administration) and demographic characteristics will be summarized descriptively for each treatment group. Efficacy and safety endpoints will be summarized by descriptive statistics for each treatment group and for each time point. All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0.05. No adjustment for multiple comparisons will be used for this study. The primary analysis of log transformed awake objective cough frequency will be conducted via a mixed model for repeated measures (MMRM) with the model including terms for region, baseline log-transformed awake objective cough frequency, treatment group, week, week*region, week*baseline and week*treatment interactions. Subject will be included as a random effect. Dose response analyses will be conducted. The other secondary endpoints will be analyzed using a MMRM except for the global rating of change in cough frequency and in severity which will be analyzed using Mantel-Haenszel methodology. The safety and tolerability profile will be assessed versus Baseline conditions and differences between treatment groups and descriptive statistics will be produced, where applicable. Plasma concentrations of orvepitant will be summarized descriptively; possible exposure-response relationships will be explored.
PLANNED DATE OF FIRST SUBJECT ENROLLED	01-Apr-2017

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACM	Ambulatory Cough Monitor
AE	Adverse Event
ADR	Adverse Drug Reaction
ALT	Alanine amino transferase
ACE	Angiotensin Converting Enzyme
AST	Aspartate amino transferase
BP	Blood Pressure
BTS	British Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
eCRF	Electronic Case Report Form
CRC	Chronic Refractory Cough
CSR	Clinical Study Report
CQLQ	Cough specific Quality-of-Life Questionnaire
CRO	Contract Research Organization
cVRG	caudal Ventral Respiratory Group
DAP	Data Analysis Plan
ECG	Electro cardiogram
EGFRi	Epidermal Growth Factor Receptor inhibitor
ERS	European Respiratory Society
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma Glutamyl Transferase
H0	Null Hypothesis
H1	Alternative Hypothesis
IB	Investigators Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IM	Intramuscular
IUD	Intrauterine Device
IUS	Intrauterine System
IWRS	Interactive Web Response Services
LCQ	Leicester Cough Questionnaire
MCV	Mean Corpuscular Volume
MDD	Major Depressive Disorder
MeDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MMRM	Mixed model for repeated measures
NK	Neurokinin
NONMEM®	Nonlinear mixed effects modeling
NTS	Nucleus Tractus Solitarius
PET	Positron Emission Tomography
PIS	Participant Information Sheet
PK	Pharmacokinetic
Pop PK	Population PK
PTSD	Post-Traumatic Stress Disorder
QD	One a day
RBC	Red Blood Cell
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment Emergent Adverse Events
TMF	Trial Master File
VAS	Visual Analogue Scale
WBC	White Blood Cell
WOCP	Women of Child-bearing Potential

4. INVESTIGATORS AND ADMINISTRATIVE STRUCTURE

Chief Investigator

Prof Jaclyn Smith MB ChB PhD FRCP
Professor of Respiratory Medicine and Honorary Consultant
Division of Infection, Immunity and Respiratory Medicine, University of Manchester,
Director, South Manchester Respiratory and Allergy Clinical Research Facility,
[redacted]

Medical Expert (Sponsor)

Stephen Pawsey MBBS FRCA FFPM
NeRRe Therapeutics Ltd
SBC, Incubator Building,
Gunnels Wood Rd.,
Stevenage, SG1 2FX, UK
[redacted]

Contract Research Organization / Monitors

[redacted]

Statistical Consultants

[redacted]

GENERAL INFORMATION (continued)

Central Clinical Laboratories

[redacted]

Pharmacokinetic Laboratory

[redacted]

Ambulatory Cough Monitor Provision and Reading Centre

[redacted]

5. BACKGROUND INFORMATION

5.1 Orvepitant

NeRRe is developing orvepitant as a treatment for Chronic Refractory Cough (CRC), also known as chronic idiopathic cough or unexplained chronic cough (Irwin et al., 1998; Gibson et al., 2016). Cough in these subjects is a difficult symptom to manage and there remains a substantial need for new and effective treatments (Gibson & Vertigan, 2015). It is hypothesized that chronic cough results from hypersensitivity of peripheral airway sensory afferent neurones and neurones centrally in the brainstem that together govern the cough reflex, resulting in enhanced cough in either response to otherwise trivial stimuli or in the absence of an initiating event (reviewed in Canning et al., 2014; Gibson & Vertigan, 2015). Substance P and its cognate neurokinin (NK)-1 receptor have been implicated as having a role in induction and maintenance of the peripheral and central cough reflex hypersensitivity; thus NK-1 antagonism has the potential to provide a novel and effective approach to address the CRC subject population (Canning, 2009; Lavinka & Dong, 2013; Harle et al., 2016).

Therefore, the overall anticipated benefits of orvepitant as a centrally penetrant, potent and selective NK-1 receptor antagonist include rapid and sustained control of CRC together with associated enhanced general Quality-of-Life.

Refer to the Investigator's Brochure (IB) for additional information related to the physical, chemical and pharmaceutical properties and formulation of orvepitant.

5.2 Pre-clinical research

[redacted]

5.3 Clinical experience

[redacted]

[redacted]

5.4 Chronic Cough background and rationale for this study

Cough is a defensive reflex action of the respiratory system that is activated to clear the upper airways (Chung & Pavord, 2008). Excessive coughing is the leading reason for ambulatory care visits by subjects in the US (Hsiao et al., 2010) and has a significant impact on subject Quality-of-Life (French et al., 1998; Chamberlain et al., 2015). Chronic coughing has been shown to have significant physical, social and psychological consequences (Birring et al., 2003; French et al., 2002, Dicpinigaitis et al., 2006). Subjects often suffer complications such as chest and abdominal pains, retching and vomiting, urinary incontinence and even cough syncope. Many are embarrassed and stigmatized by this symptom and therefore avoid public places and social gatherings. Guidelines from the American College of Chest Physicians (ACCP) define chronic cough as being of duration ≥8 weeks (Irwin et al., 2006). A recent meta-analysis found the worldwide epidemiological prevalence of chronic cough to be 7.9% (Song et al., 2015) and was significantly more frequent in Europe (12.7%) and America (11.0%). Chronic cough afflicts women more often than men and generally has an onset from middle age (Irwin et al., 1981; Janson et al., 2001; Ford et al., 2006; Irwin et al., 2006; Everett et al., 2007).

CRC represents a particular problem to physicians as the management is difficult with symptoms persisting despite guideline based treatment (Gibson & Vertigan, 2015). For example, in a community based chronic cough survey, 60% of respondents reported that their symptoms had not improved despite treatment (Everett et al., 2007).

The cough pathway is complex; it is activated by sensory afferent nerve fibers in the airways that converge into vagus nerves to a central cough-reflex centre in the brain stem called the Nucleus

Tractus Solitarius (NTS). The NTS is connected in turn to respiratory related neurones that are involved in coordinating the cough response; higher cortical centers also provide a controlling influence enabling either voluntary production or inhibition of cough. A cough activating reflex event may occur as a result of inflammatory or mechanical changes or be triggered due to the inhalation of irritants. It is hypothesized that the pathological basis of chronic cough is plastic changes in peripheral airway sensory afferent neurones and neurones centrally in the brainstem that hypersensitizes the cough reflex resulting in enhanced cough in either response to otherwise trivial stimuli or in the absence of an initiating event (reviewed in Canning et al., 2014; Gibson & Vertigan, 2015). Current thinking is that a mechanism that can target both peripheral and central cough reflex hypersensitivity could therefore provide an optimum approach to address the CRC subject population.

One such potential mechanism that could be targeted is the NK-1 receptor and its cognate ligand Substance P. Peripherally in the airways, hypersensitivity could result by activation of lung mast cells that degranulate, releasing mediators which in turn stimulate unmyelinated C-fibers to release Substance P creating a neuro-inflammatory state (Lavinka & Dong, 2013). Such a mechanism is consistent with emerging data that has shown that in isolated vagal nerves from both guinea-pig and humans, Substance P can cause depolarization that is blocked by the NK-1 antagonist aprepitant (Harle et al., 2016). Centrally the hypersensitization could be due to the key role that the NK-1 receptor system plays as a controlling excitatory transmitter regulator in the cough reflex centre in the NTS (Joad et al., 2004; Mazzone et al., 2005; Mutulo et al., 2007; Canning, 2009; Chen et al., 2009; Sekizawa et al., 2011). Recently NK-1 receptors have been shown to be implicated in the cough reflex pathway in another brainstem location, the caudal Ventral Respiratory Group (cVRG) (Mutolo et al., 2010). In vivo in animal models, NK-1 receptor antagonists have demonstrated to be effective anti-tussive agents in five different species, namely: guinea pigs (Bolser et al., 1997; El-Hashim et al., 2004; Mazzone et al., 2005), rabbits (Mutolo et al., 2008; Mutolo et al., 2010), cats (Bolser et al., 1997; Bolser et al., 1999), dogs (Chapman et al., 2004) and pigs (Moreaux et al., 2000). In these experiments, the NK-1 antagonists were administered by different routes: systemically, by intracerebroventricular injection, via the central artery or by direct injection into both the NTS and cVRG. In canine chronic bronchitis, which is a self-perpetuating, inflammatory disease of airways, characterized by cough >2 months in duration, treatment with the NK-1 antagonist maropitant in a small 14-day study, significantly decreased cough frequency ($p < 0.001$) and cough VAS scores ($p = 0.005$) (Grobman & Reinero, 2016).

Clinically, raised plasma levels of Substance P have been reported in humans suffering with both asthmatic and non-asthmatic persistent cough (Otsuka et al., 2011). Substance P was also elevated in induced sputum from cough subjects with acid reflux (Patterson et al., 2007), and chronic cough subjects with non-acid gastro-esophageal reflux (Qiu et al., 2011). Substance P has also been reported to be increased in nasal secretions from subjects with chronic cough (Lim et al., 2011) and those whose cough has been demonstrated to be hypersensitive to capsaicin challenge (Bae et al., 2012). Subjects with idiopathic pulmonary fibrosis (Hope-Gill et al., 2003)

and acute cough (Katsumata et al., 1989) also appear to have increased sensitivity to Substance P cough challenge.

Recent clinical trial data further supports the notion that centrally penetrant NK-1 antagonists could be effective anti-tussive agents. Firstly, a randomized, double-blind, placebo-controlled, crossover trial in 20 lung cancer subjects with cough demonstrated that the marketed NK-1 antagonist aprepitant (EMEND®, that is approved as an acute treatment for nausea and vomiting) showed a statistically significant improvement in all primary (awake cough frequency) and secondary endpoints versus placebo (Harle et al., 2016). [redacted]

Taken together these data support the notion that NK-1 receptor antagonists generally, and more specifically orvepitant with its combined peripheral and central mechanisms of action, may prove of benefit in the treatment of CRC.

The anticipated benefits of orvepitant as a centrally penetrant, potent and selective NK-1 receptor antagonist include rapid and sustained control of cough together with associated enhanced general Quality-of-Life.

[redacted]

The objective of this study is to evaluate the efficacy and safety of orvepitant in adult subjects suffering from CRC and to identify a suitable dose of this NK-1 antagonist with which to initiate a pivotal Phase 3 registration program.

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), the General Principles of the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

5.5 Rationale for endpoints

A combination of objective and subjective tools will be used to assess the impact of orvepitant on subjects' CRC.

The primary endpoint will be change from Baseline to Week 12 in awake objective cough frequency measured with an automated cough monitor (ACM), [redacted] The use of acoustic cough counting to objectively assess cough frequency is recognized as a valid and increasingly preferred tool for primary endpoint determination in cough clinical studies (Spinou & Birring, 2014; Boulet et al., 2015).

Secondary endpoint measures to be utilized that will aim to further characterize the CRC treatment outcomes will include awake objective cough frequency changes at other clinic visits and the validated Quality-of-Life assessment tool the Leicester Cough Questionnaire (LCQ) (Birring et al., 2003; Spinou & Birring, 2014; Boulet et al., 2015). Other patient-reported outcome instruments that will be deployed are the Cough Severity visual analogue scale (VAS), a simple to use tool that is widely utilized in cough clinical studies (Morice et al., 2007), the Urge-to-Cough VAS (Spinou & Birring, 2014) and the Global Rating of Change for Cough Frequency and Severity. Safety and tolerability will be evaluated through conventional assessments used in the evaluation of investigational medicinal products (IMP).

The pharmacokinetic (PK) profile of orvepitant in the target population will be characterized through collection of sparse samples from all subjects. Sparse sampling is a well-established method of collecting PK data that avoids the need for multiple blood draws and extended clinic visits.

6. STUDY OBJECTIVES AND PURPOSE

6.1 Primary objectives

- To evaluate the efficacy of once daily doses of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in reducing awake objective cough frequency.

6.2 Secondary objectives

- To evaluate the efficacy of once daily dosing of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in:
    - Reducing 24-hour objective cough frequency
    - Reducing night-time (non-waking time) objective cough frequency
    - Reducing subject assessed cough severity and Urge-to-Cough
    - Improving Quality-of-Life and subject perception of change
- To evaluate the dose-response relationship of 10 mg, 20 mg, and 30 mg orvepitant

- To assess the safety and tolerability of 10 mg, 20 mg, and 30 mg orvepitant versus placebo over 12 weeks dosing

6.3 Pharmacokinetic objectives

- To evaluate the exposure-response relationship of orvepitant using population PK with sparse sampling

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Subject numbers

Participants in the clinical investigation shall be referred to as "subjects".

It is anticipated that approximately 292 subjects will be enrolled to ensure approximately 260 completers (~ 65 subjects per group; assuming approximately 10% drop out rate). The number of subjects enrolled may, however, be increased to a maximum of 320 in the event that the interim sample size re-estimation indicates that 292 is insufficient (see Section 11.1).

Subjects will be enrolled at approximately 50 sites across North America and Europe. Additional sites and regions may be added.

7.2 Inclusion criteria

The following inclusion criteria will apply to all subjects:

1. Male and female subjects ≥18 years of age
2. Able to understand and comply with the requirements of the study and sign Informed Consent forms
3. Diagnosis of CRC or unexplained cough for at least 1 year prior to Screening (see ACCP/BTS guidelines in section 17)
4. An awake average cough frequency of ≥10 coughs/ hour, as assessed using an ACM during the Screening period (note, the ACM will be worn for a 24-hour period and the average waking cough frequency determined)
5. Females must be non-pregnant and non-lactating with no intention of pregnancy during study treatment
6. Women of child-bearing potential (WOCP) (i.e. not surgically sterilised or post-menopausal*) must have a negative blood serum pregnancy test performed at the Screening visit and agree to use two methods of birth control, one of which must be a barrier method (note: the double barrier method is not considered acceptable) for the duration of participation in the study
   ** Post-menopausal is defined as >1 year since the last menstrual period for women >55 years of age or >1 year since their last menstrual period and have an FSH level in the menopausal range for women <55years of age.*
   Acceptable methods of birth control are:

a. Surgical sterilization of the subject's male partner (vasectomy with documented azoospermia) if he is the sole partner of that subject
b. Established hormonal contraception (implantable, patch, oral or intramuscular [IM]) administered for at least one month prior to IMP administration and to continue for at least 4 weeks after the last dose of IMP
c. An intrauterine device (IUD) or intrauterine system (IUS) with failure rate of less than 1% per year inserted by qualified physician at least one month prior to IMP administration and to remain in place for at least 4 weeks after the last dose of IMP
d. Barrier methods such as male condom or cap, diaphragm or sponge with spermicide

7. Male subjects and their partners of child-bearing potential must use two methods of acceptable birth control, one of which must be a barrier method; male subjects must make no donation of sperm from Screening until 90 days after the last dose of IMP

7.3 Exclusion criteria

The following exclusion criteria will apply to all subjects:

1. Subjects with respiratory tract infection (<4 weeks prior to Screening)
2. Females who are breast feeding or pregnant
3. Current smokers or ex-smokers with <6 months' abstinence prior to Screening
4. Treatment with Angiotensin Converting Enzyme (ACE) inhibitors within 3 months of Screening
5. A history of drug or alcohol abuse within 12 months of Screening
6. Both FEV_1 <80% predicted and FEV_1/FVC ratio < 0.7, measured at Screening using spirometry
7. History of cystic fibrosis, idiopathic pulmonary fibrosis, clinically significant bronchiectasis, moderate to severe asthma, chronic obstructive pulmonary disease (COPD)
8. Evidence of uncontrolled hypertension at Screening or Baseline[3]
9. Recent myocardial infarction (within 1 year prior to screening), or history of congestive cardiac failure
10. Any clinically significant abnormalities on 12-lead ECG at Screening or Baseline/Day 1
11. Subjects with prior renal transplant, current renal dialysis, or history of renal tubular acidosis.
12. Any clinically significant neurological disorder
13. Any clinically significant or unstable medical or psychiatric condition that would interfere with the subject's ability to participate in the study

[3] As guidance, systolic >160 mm Hg or diastolic >90 mmHg should result in further evaluation which may include repeat measurements after a period of rest

14. Subjects with a prior medical history of or an increased risk of seizures (except febrile seizures in infancy), or who have a history of recent head trauma (within the last 6 months prior to Screening) that resulted in a loss of consciousness or concussion
15. Any malignancy in the past 5 years unless non-invasive and in remission (disease-free for >5 years prior to Screening) and written approval has been obtained from Sponsor, with the exception of skin cancers not including malignant melanoma
16. Any clinically significant abnormal laboratory test result(s) measured at Screening[4]
17. Inability to comply with the use of prohibited and allowed medications as described below:
    a. The use of opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines or tricyclic antidepressants (e.g. amitriptyline) for treatment of cough is not allowed throughout the study. Subjects must have discontinued these drugs at least 1 month prior to Screening. Subjects may, however, be permitted to continue to use these drugs if they have been prescribed solely for the management of another disorder (e.g. neuropathic pain, depression).
    b. The use of other drugs taken solely for the treatment of cough (including those used on an as needed basis) is also prohibited from at least 1 month prior to Screening.
    c. Concomitant respiratory medication (other than for management of cough) is allowed, but subjects must be stable on such medication and take it for the duration of the study
    d. [redacted]
    e. [redacted]

[4] The investigator should judge the clinical relevance of any abnormal laboratory parameters in the context of the subject's current and past medical history and any know contributing factors (e.g., strenuous exercise resulting in elevated AST or CK)

[redacted]

18. Participation in any clinical research study evaluating another investigational drug or therapy within 30 days or within 5 half-lives (whichever is longer) of the investigational drug prior to Screening. If the subject is in an observational clinical study no washout is required
19. Subjects receiving aprepitant (Emend®) or fosaprepitant (Ivemend®), NK-1 antagonists licensed as anti-emetics <4 weeks before the Screening visit
20. Subjects who have previously received orvepitant at any time
21. Known allergy to any of the excipients used in the IMP (orvepitant or placebo tablets), see Section 9.2
22. Subjects who, in the opinion of the Investigator, should not participate in the study for any other reason

7.4 Withdrawal criteria

The subjects will be informed that they have the right to withdraw from the study at any time without stating a reason and without prejudice to further treatment.

The Investigator may withdraw subjects from the study or may discontinue study treatment at any time.

Withdrawal from the study or early discontinuation from the IMP is to be registered in the Interactive Web Response Service (IWRS).

Early withdrawal or early discontinuation from the IMP of any subject who has given informed consent to participate will be recorded including the reason for withdrawal. The primary reason will be selected from the following standard categories of early discontinuations or withdrawals:

- **Failed to meet randomization criteria (screen failure)**

- **Adverse Event**: Clinical events occurred or laboratory results are reported that in the medical judgment of the investigator are grounds for discontinuation from participation in the best interests of the subject

- **Withdrawal of Consent**: The subject desired to withdraw from further participation in the study. The subject is not obliged to provide any reason for withdrawal of consent, but where a reason is given this will be recorded on the electronic Case Report Form (eCRF)

- **Protocol Violation**: The subject failed to adhere to the protocol requirements, at the investigator's discretion e.g. the subject requires to start taking a medication from the prohibited medications list (Section 9.9)

- **Lost to Follow-Up**: The subject stopped coming for visits and study personnel were unable to contact the subject

- **Pregnancy**: Any subject becoming pregnant during the study will be withdrawn from dosing.

- **Other:** The subject was terminated for a reason other than those listed above, such as theft or loss of study drugs or termination of study by Sponsor

Subjects who withdraw or are withdrawn from participation in the study should attend an Early Termination visit at which the procedures scheduled for the Week 14 Follow Up visit will be undertaken. If the subject withdraws due to an adverse event (AE), the event should be followed until resolution or care is transferred to the subject's general practitioner or primary care physician.

Subjects who are withdrawn after randomization will not be replaced.

In some circumstances, the Investigator may discontinue study treatment without the need to withdraw the subject from participation in the study. When subjects permanently discontinue IMP, effort should be made to continue following the subject through to the end of scheduled visits for safety and to obtain efficacy assessments that can be assigned to the originally randomized treatment.

7.5 Criteria for Stopping the Study

The Sponsor may terminate the study for safety or administrative reasons at any time. If, in the opinion of an Investigator in consultation with the Sponsor, the clinical safety observations in the study suggest that it may be unwise to continue, the study may be terminated either at that Investigator's site or overall.

8. STUDY DESIGN

8.1 Primary endpoint

The primary endpoint will be change from Baseline to Week 12 in awake objective cough frequency measured with an ACM, [redacted]

8.2 Secondary efficacy endpoints

The secondary efficacy endpoints include:

Objective awake cough frequency changes:

- Change in awake objective cough frequency at Weeks 2, and 4 compared to Baseline
- Change in 24-hour objective cough frequency at Weeks 2, 4, and 12 compared to Baseline
- Change in night-time (non-waking time) objective cough frequency at Weeks 2, 4 and 12 compared to Baseline

The validated Quality-of-Life assessment tool the LCQ.

- Change in the LCQ score (total and three domain scores) at Weeks 2, 4, 8, and 12 compared to Baseline

The Cough Severity VAS, the Urge-to-Cough VAS and the Global Rating of Change for Cough Frequency and Severity.

- Change in the Cough Severity VAS at Weeks 2, 4, 8, and 12 compared to Baseline
- Change in the Urge-to-Cough VAS at Weeks 2, 4, 8, and 12 compared to Baseline
- Global Rating of Change in Cough Frequency and Severity at Weeks 2, 4, 8, and 12

8.3 Pharmacokinetic endpoints

PK exposure-response relationship for the orvepitant groups (10 mg, 20 mg, and 30 mg) will be carried out to examine the possible relationship over time between clinical efficacy and plasma levels of the drug.

8.4 Safety endpoints

- Change from Baseline in clinical laboratory assessments (hematology, clinical chemistry, urinalysis)
- Change from Baseline in vital signs (temperature, sitting/standing BP, heart rate, respiration rate, weight)
- Change from Baseline in 12-lead ECG variables (heart rate and rhythm, and RR, PR, QRS, QT, QTcF and QTcB intervals)
- Nature and severity of AEs
- Withdrawals due to an AE
- Use of concomitant medications

8.5 Study design

This is a multi-center, double blind, randomized, parallel group, placebo-controlled dose range study in subjects with CRC.

Subjects will be recruited into four parallel groups, 10 mg once per day orvepitant, 20 mg once per day orvepitant, 30 mg once per day orvepitant, and placebo once per day. See Figure 1 for study design schematic.

Subjects will enter a Screening period of up to three weeks to determine eligibility.

Subjects will be provided the Participant Information Sheet (PIS) and Informed Consent Form (ICF) for their prior review. Informed consent to participation in the study will be obtained for all subjects before any study related procedures are performed (subjects must personally sign and date the approved ICF and, where applicable, privacy statement).

8.5.1 Screening

The Screening visit will include the following assessments to determine the subject's eligibility for inclusion into the study:

- Full physical examination, 12 lead ECG, vital signs and spirometry (FEV_1 and FVC)
- Recording of the subject's medical history, and prior and concomitant medication use, in particular other concomitant respiratory medications, both prescribed and/or over the counter medications
- Blood sampling and urine sample collection for both Clinical Safety labs and serum pregnancy test (WOCP only)
- Subjects will be fitted with an ACM, which will be initiated prior to the subject leaving the clinic to monitor cough frequency over the next 24 hours. Immediately after the end of this period the subjects will either return the ACM to the clinic or collection of the ACM from the subjects will be organised

The digital recording data from the ACM will be uploaded and read centrally by [redacted] and the cough frequency determined.

If the ACM fails during the Screening assessment and no useable recording is generated, the 24hr Screening ACM may be repeated provided this is done at least 10 days prior to the planned Baseline/Day 1 visit and under these circumstances the Screening period may be extended by up to one week (so a maximum of 28 days).

8.5.2 Baseline Visit / Day 1

At the Baseline visit a physician must assess the Baseline eligibility criteria then sign and date supportive documentation at the time of the subject's visit.

Limited data will be collected for subjects who withdraw from the study after providing informed consent but prior to randomization onto the study (Screen Failures).

Eligibility for randomization will be reviewed based on the results of the 24-hour cough frequency measured using the ACM following the Screening visit. To be eligible for inclusion, subjects must have an awake average cough frequency of ≥10 coughs/ hour.

The Baseline visit will be Day 1. Prior to dosing on Day 1, the following assessments will be completed:

- Symptom directed physical examination
- Vital signs (after resting for ≥ 5 mins per Section 10.3.8)
- 12-lead ECG
- Safety labs: blood samples for clinical chemistry and hematology and urine sample for urinalysis

- Opiate drug screen
- Urine pregnancy test for WOCP
- Subjects will be asked to complete the LCQ, Cough Severity VAS and Urge-to-Cough VAS

Eligible subjects will be randomized on Day 1 in a 1:1:1:1 ratio to orvepitant (10 mg/day, 20 mg/day, 30 mg/day) or placebo. Randomization will be performed centrally via an IWRS.

Subjects will be given their first dose of IMP in the clinic and take all subsequent doses every day in the morning for a total of 12 weeks.

8.5.3 Interim and Final Study Visits

During the double-blind treatment phase, subjects will return to the Clinic on Weeks, 2 4, 8 and 12. All clinic visits must occur in the morning. The Weeks 2 and 4 visits should be scheduled within ±3 days of the target visit day and the Weeks 8 and 12 visits within ±5 days of the target visit day.

Subjects will be instructed to attend these visits not having taken their dose of IMP. At the start of each visit a blood sample will be taken for determination of plasma levels of orvepitant. At the same time, if required per the Schedule of Events in Section 10, blood samples for safety laboratory assessments will be taken. Subjects will be asked to provide the time they took their morning dose on the previous day. After this sample subjects will take their dose of IMP in the clinic. At all these visits subjects will complete LCQ, Cough Severity VAS, Urge-to-Cough VAS, and Global Rating of Change and safety assessments will be performed.

All assessments will be performed according to the Schedule of Events in Section 10. The order of assessments at these visits should be as follows:

- Blood sampling (PK, safety labs, as applicable)
- Dosing
- Vital signs (after resting for ≥ 5 mins per Section 10.3.8)
- 12-lead ECG (after resting semi-recumbent for 5 mins)
- Questionnaires (LCQ, VAS assessments, Global Rating of Change)

The urine sample for urinalysis, pregnancy testing and opiate drug screen can be provided at any time.

At the end of the Weeks 2, 4 and 12 visits they will be fitted with an ACM, which will be initiated prior to the subject leaving the clinic to monitor cough frequency over the next 24 hours. Immediately after the end of this period the subjects will either return the ACM to the clinic or it will be collected from the subjects. The digital recording data from the ACM will be uploaded and read centrally by [redacted] and the cough frequency determined.

At Week 14 a safety follow-up visit will be performed.

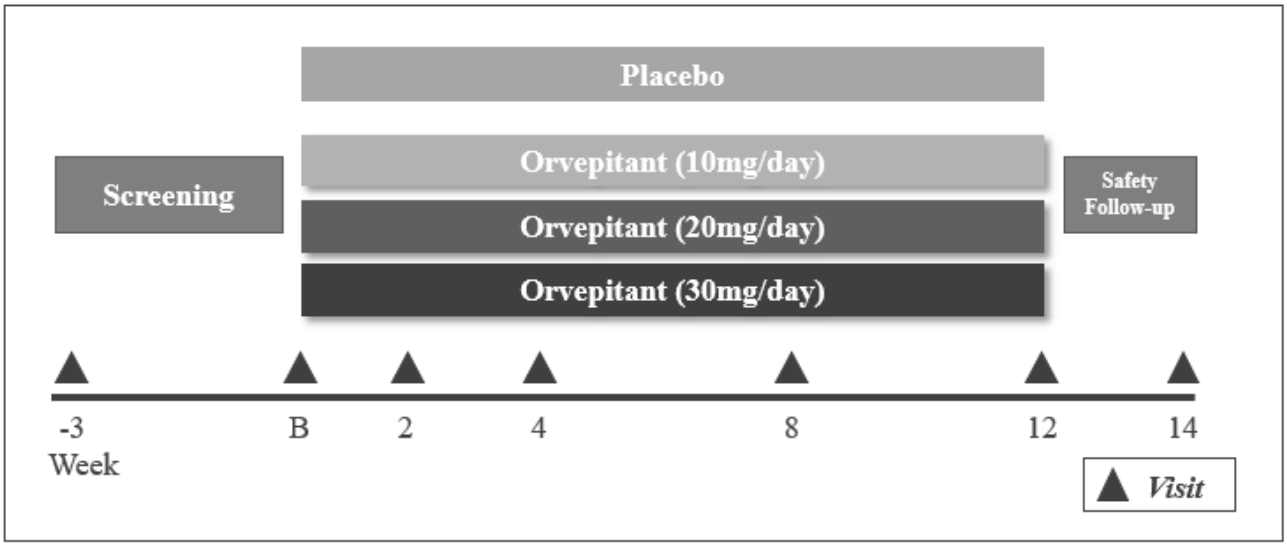
All Week 14 assessments will be performed according to the Schedule of Events in Section 10. The following assessments will be completed:

- Symptom directed physical examination
- Vital signs (after resting for ≥ 5 mins per Section 10.3.8)
- 12-lead ECG
- Safety labs
- Urine pregnancy test for WOCP

Throughout the study, subjects will be monitored for safety including assessments of AEs and concomitant medication recordings.

Please see Section 10 for the complete list of assessments.

Figure 1: Study schematic



9. INVESTIGATIONAL PRODUCT AND ADMINISTRATION

9.1 Selection of doses in the study

[redacted]

[redacted]

[redacted]

[redacted]

9.2 Investigational medicinal product

The IMP will consist of orvepitant 10 mg, 20 mg and 30 mg tablets or matching placebo. The tablets are white film-coated round tablets containing orvepitant as the maleate salt or matching placebo to be taken orally once-daily.

Excipients in the tablets are as follows:

Orvepitant 10 mg, 20 mg and 30 mg tablets:

- [redacted]
- [redacted]

Placebo tablets:

- [redacted]
- [redacted]

The physical, chemical, pharmaceutical formulation properties and characteristics of the IMP are described in the IB.

IMP (i.e. orvepitant 10 mg. orvepitant 20 mg, orvepitant 30 mg or placebo) will be provided in white, opaque, high density polyethylene bottles with white opaque, plastic, child-resistant closures that include induction seal liners. A desiccant is also utilized for the IMP. Each bottle will contain 36 tablets (enough for a 4-week dosing period plus overage).

The IMP bottles will be labelled according to Annex 13, Volume 4 of EudraLex and will be in accordance with US regulatory requirements.

All IMP must be stored in a secure area with access limited to the Investigator and authorized site staff. The IMP is to be stored at ambient room temperature up to a maximum of 30ºC.

Only authorized investigational site study staff members are to dispense the IMP.

9.3 Allocation to Treatment

The study will be conducted in a double-blind manner, with the subjects, Investigators and Sponsor all blinded to the treatment allocated. Both orvepitant (10 mg, 20 mg, and 30 mg) and placebo will be presented as white tablets, identical in size and shape.

Following the Screening period and confirmation of eligibility, subjects in each cohort will be randomized in a 1:1:1:1 ratio to receive either orvepitant 10 mg/day, 20 mg/day 30 mg/day or placebo. Randomization will be stratified by region, namely North America and Europe.

The IMP each subject will receive will be allocated by an IWRS tool provided by [redacted] on behalf of the Sponsor.

9.4 Study Treatment and Administration

IMP will be taken once daily during the 12-week double-blind treatment phase (i.e. Day 1 through Week 12). IMP doses are fixed and will not be adjusted for individual subjects during the study.

At each visit subjects will be dispensed IMP for self-administration for daily dosing until the subsequent visit, with overage included to allow for visit windows.

Subjects will be required to take one tablet of IMP once-daily in the morning upon waking with or without food.

Subjects will receive their first dose (Day 1) whilst at the clinic and will also take the daily dose at the clinic at each of the Week 2, 4, 8 and 12 visits.

At Day 1 subjects will be dispensed sufficient supply to cover the period from Day 2 to Week 4. An interim check of compliance will be made during the Week 2 visit (subjects will be instructed to bring their IMP bottle with them to this visit).

At Week 4 subjects will be dispensed sufficient supply to cover the period from Week 4 to Week 8.

At Week 8 subjects will be dispensed sufficient supply from Week 8 to Week 12.

At each visit an overage will be included to allow for visit windows.

On the days of clinic visits (Weeks 2, 4, 8, and 12) subjects will be instructed to attend the clinic not having taken their morning dose. The dose on these days will be taken in the clinic after a blood sample for analysis of blood levels of orvepitant is taken. At each clinic visit subjects will be asked to provide the time that they took their dose the previous morning and this will be documented in the eCRF; after the PK sample has been taken subjects will take their dose of IMP and the time recorded in the eCRF.

All doses are to be taken at approximately the same time each morning. In the event that a subject forgets to take a dose in the morning then the dose can be taken at any time up until 6:00pm. After this time, the dose should not be taken and will be considered a missed dose. Subjects will return any unused medication at each clinic visit.

9.5 Duration of Subject Participation

The planned duration of participation in the study for an individual subject is up to 18 weeks, which includes the following:

- Initial Screening phase of up to three weeks (can be extended to up to four weeks in the event that the ACM fails and the 24-hour cough monitoring must be repeated)
- 12-week double blind treatment phase
- Two-week safety follow-up

9.6 Treatment Accountability and Compliance Checks

In accordance with regulatory requirements, the Investigator or designated site staff must document the amount of IMP dispensed and/or administered to study subjects, the amount returned by study subjects, and the amount received from and returned to the Sponsor (or representative) when applicable. IMP accountability records must be maintained throughout the course of the study. The accountability unit for this study is a tablet. Discrepancies are to be reconciled or resolved. Procedures for final disposition of unused IMP will be provided in the Pharmacy Manual.

The Investigator has overall responsibility in ensuring that the study treatment is received and managed at the study site in accordance with GCP.

Limited responsibility may be delegated to a nominated study site representative and this delegation must be documented. Study treatment will be dispensed by a nominated person at each study site.

The Sponsor will be permitted upon request to audit supplies, storage and dispensing records and procedures.

Every effort should be made to encourage subject compliance with the dosage regimen as per the protocol. All subjects will be instructed to return their medication bottle with any unused tablets at each visit (at the Week 2 visit the same bottle will be given back to the subject for continuation

of dosing up to Week 4). A record of the tablets dispensed, taken, and returned will be recorded at each visit and compliance calculated.

9.7 Treatment Blinding Code

Study investigators will be given access to the IWRS system for the purposes of emergency unblinding. Investigators are permitted to unblind treatment for a subject if it is deemed that knowledge of the subject's treatment will impact subject's future medical care. If possible, the medical monitor or Sponsor medical expert should be notified prior to the blind being broken. If this is not possible, the medical monitor or Sponsor medical expert must be notified as soon as possible if a code break was performed.

If a suspected unexpected serious adverse reaction (SUSAR) occurs that requires expedited reporting to the relevant regulatory agency/Institutional Review Board (IRB) /Independent Ethics Committee (IEC), then the blind will be broken for the relevant subject by the [redacted] safety group, in order to provide the Regulators the knowledge of the event and the causal agent. This is in agreement with ICH E2A and a blinded copy of the report will be provided to the investigators and the relevant IRB/IEC.

If unblinding occurs accidentally this will be considered a protocol deviation, this must be documented in the subject's medical notes and in the trial master file (TMF), and the Sponsor must be informed.

9.8 Permitted Concomitant Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

Concomitant respiratory medication is allowed, but subjects must have been on a stable dose/regimen for the three months prior to Screening and must continue to take the same dose/regimen for the duration of the study.

9.9 Prohibited Concomitant Medication

Due to their potential effect on cough reflex sensitivity, the use of opioids, dextromethorphan, gabapentin, pregabalin, baclofen, antihistamines or tricyclic antidepressants (e.g. amitriptyline) for treatment of cough is not allowed throughout the study. Subjects must have discontinued these drugs at least 1 month prior to Screening and should not have them started during the study. Subjects may, however, be permitted to continue to use these drugs if they have been prescribed solely for the management of another disorder (eg neuropathic pain, depression).

The use of other drugs taken solely for the treatment of cough (including those used on an as needed basis) is also prohibited from at least 1 month prior to Screening.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.10 Other Study Restrictions

[redacted]

10. STUDY SCHEDULE

Table 1: Schedule of Events

	Screening Day -21 to 1[j]	Baseline / Day 1	Wk 2 (± 3 days)[k]	Wk 4 (± 3 days)[k]	Wk 8 (± 5 days)[k]	Wk 12 (± 5 days)[k]	Early Termination	Wk 14 follow-up (± 5 days[k])
Informed Consent	X							
Medical History	X							
Physical Examination[i]	X	X[c]					X	X
Spirometry	X							
Incl/Excl Criteria	X	X[c]						
Randomization		X						
Vital Signs[a]	X	X[c]	X	X	X	X	X	X
12-lead ECG	X	X[c]	X	X	X	X	X	X
Ambulatory cough monitoring[b]	X[g]		X	X		X		
LCQ		X[c]	X	X	X	X		
Global Rating of Change			X	X	X	X		
Cough Severity VAS		X[c]	X	X	X	X		
Urge-to-Cough VAS		X[c]	X	X	X	X		
PK sample			X[h]	X[h]	X[h]	X[h]		
Safety labs[e]	X	X[c]		X[h]	X[h]	X[h]	X	X
Opiate drug screen		X[c]	X[h]	X[h]	X[h]	X[h]		
Pregnancy test[f]	X	X[c]		X	X	X	X	X
Dosing[d]		X ----------				X		
AE recording	X ----------							X
Con Med recording	X ----------							X

a Vital signs: systolic and diastolic blood pressure, pulse, temperature; weight (weight at Baseline/Day 1, Week 12 and Follow-up only)
b ACM [redacted] to be fitted during the visit and initiated prior to the subject leaving the clinic, monitoring will be continuous for 24hrs and device switched off after this period. Subjects will either return the ACM to the clinic (during Screening this must be done the following day) or collection from the subjects will be organized
c Performed prior to start of dosing
d Subjects are given their first dose of IMP in the clinic. All doses to be taken at approximately the same time each day; on clinic visits subjects will take their dose in the clinic after the pre-dose PK and safety samples, as applicable, have been taken. All other assessments can be performed post-dose
e Safety labs include blood samples and urine samples
f Pregnancy test in women of child-bearing potential only; serum pregnancy test at Screening, urine pregnancy at Baseline/Day 1, Wks 4, 8, and 12

g If the ACM fails during the Screening assessment and no useable recording is generated, the 24hr Screening ACM may be repeated and in this circumstance the Screening period may be extended by up to 1 week (to a maximum of 28 days)
h All blood and urine samples are taken immediately prior to the dose
i Full physical examination at Screening; symptom directed physical examination at subsequent visits
j Screening period may be extended for up to 1 week should the original ACM fail and this need to be repeated
k All visits and visit windows relate to Day 1

10.1 Volume of Blood sampling

Approximate blood sample volumes are detailed below. The volumes for individual samples may vary accordingly to laboratory requirements and the number of samples taken may increase due to unscheduled visits, lost or damaged samples where additional blood draws are needed, however, the total volume is not expected to exceed 150 mL per subject

Clinical chemistry	5 mL
Hematology	3 mL
PK	6 mL

10.2 Efficacy assessments

10.2.1 Ambulatory Cough Monitor

Subjects will be fitted with an ACM [redacted] to record objective cough frequency over 24 hours at the Screening, Weeks 2, 4, and 12 Visits.

The ACM will be initiated prior to the subject leaving the clinic to monitor cough frequency over 24 hours. After this period, the subjects will either return the ACM to the clinic (during Screening this must be done the following day) or collection from the subjects will be organized; and the cough frequency will be determined.

The digitally recorded data from the ACM will be forwarded to [redacted] who will undertake cough counting for all subjects using a standardised process.

The awake period is considered to be the time between subjects rising from their beds in the morning and retiring to their beds in the evening. This can be determined from the 24-hour acoustic recordings and approximates to waking hours when cough rates are highest. Analysed data will be transferred to [redacted] for statistical analysis. [redacted] will be provided with subject identifier information but will not have access to the randomisation code.

10.2.2 Leicester Cough Questionnaire

The LCQ is a 19-item questionnaire that assesses cough-related Quality-of-Life. It has three domains (physical, psychological and social). The total score range is 3-21 and domain scores each range from 1-7; a higher score indicates a better Quality-of-Life.

Subjects will complete the LCQ whilst in the clinic at Baseline/Day 1 (pre-dose), Weeks 2, 4, 8, and 12.

10.2.3 Cough Severity Visual Analogue Scale

The cough VAS is a 100-mm scale on which subjects indicate the severity of cough in the previous 24 hours, both during the daytime (awake time) and during night-time (non-awake time) separately. The VAS ranges from "no cough" on the left to "worst cough" on the right.

Subjects will complete the cough severity VAS at Baseline/Day 1, Weeks 2, 4, 8, and 12.

10.2.4 Urge-to-Cough

The Urge-to-Cough VAS is a 100-mm scale on which subjects indicate their Urge-to-Cough over the previous 24 hours (day/awake time and night time combined). The VAS ranges from "no Urge-to-Cough" on the left to "severe Urge-to-Cough" on the right.

Subjects will complete the Urge-to-Cough VAS at Baseline/Day 1, Weeks 2, 4, 8, and 12.

10.2.5 Global Rating of Change Questionnaire for Cough Frequency and Severity

In the Global Rating of Change Scale subjects will indicate if there has been a change in their symptoms (cough frequency and, separately, cough severity) since starting the IMP. They will respond with "worse", "about the same" or "better". If they indicate a change (either "worse" or "better") they will then further indicate on a 7-point scale the degree of change ranging from 1 (almost the same, hardly any change) to 7 (a very great deal changed).

Subjects will document their Global Rating of Change in Cough Frequency and Cough Severity at Weeks 2, 4, 8, and 12.

10.3 Safety Assessments

10.3.1 Medical history and concomitant diseases

A review of medical and medication history will be performed at Screening to confirm subject eligibility. This must be confirmed by an investigator.

- The investigator must record all medically and clinical relevant information regardless of the time since the date of diagnosis

History should include (but is not limited to):

- All current and past medications taken during three months before the Screening Visit
- Relevant history of respiratory, cardiovascular, renal, gastro-intestinal, hepatic, endocrine, hematological, neurological, psychiatric and any other diseases
- The specific history related to diagnosis of CRC according to either the ACCP guidelines (for subjects at US sites) or the BTS guidelines (for subjects at UK sites). Evidence of diagnosis (i.e. exclusion of other etiology) will be documented in the source data.

10.3.2 Physical examinations

A full physical examination will be conducted at the Screening visit and a symptom directed physical examination at the time points indicated in the Study Schedule in Table 1: Schedule of Events. This will be completed by a physician or an appropriately qualified delegate.

A full physical examination is composed of a review of the following body systems:

- General appearance
- Skin
- Head, eyes, ears, nose and throat
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Musculoskeletal
- Neurological

Any abnormalities that are identified at the Screening Visit will be documented on the medical history eCRF page. Any changes (including new and worsening findings) between the Screening Visit and Final study visit should be captured as AEs on the AE eCRF page, as determined by the Investigator and documented in the subject's notes.

If an improvement/resolution of a physical examination finding documented in the subject's medical history occurs during the study, it should be recorded in the source document. If there is resolution of a physical examination finding previously noted as an AE, then the event resolution and stop date should be recorded on the AE eCRF page and documented in the subject's notes.

10.3.3 Spirometry

Spirometry measurements will be conducted in accordance to local practice, adjusting for race, gender and age. For patients of mixed race, the "predominant race" as self-reported by the patient will be used and if this is not possible to determine, the predicted values for Caucasians will be used.

Spirometry will be performed at the Screening visit. The highest values (FEV_1 and FVC) from three technically satisfactory attempts will be recorded and used for the purpose of eligibility.

10.3.4 12-Lead ECGs

Resting 12-lead ECG data will be captured at all study visits, as indicated in Table 1: Schedule of Events.

All ECGs will be performed after the patient has rested for five minutes in a semi-recumbent position. The same model of ECG recorder will be used throughout the study for any given subject.

All ECG reports must be reviewed, signed and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal findings and determine whether they are clinically significant. These assessments will be recorded in the eCRF and clinically significant findings must also be reported as AEs in the eCRF.

10.3.5 Clinical chemistry

Blood for clinical chemistry assessments will be collected as indicated in the Study Schedule in Table 1: Schedule of Events and sent to a central laboratory for analysis. The following clinical chemistry parameters will be assessed: sodium, potassium, glucose, urea, creatinine, creatine kinase, albumin, calcium, phosphate, bilirubin (total), alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), gamma glutamyl transferase (GGT), bicarbonate, magnesium, chloride, total protein. Subjects do not need to fast before clinical chemistry samples are taken.

All clinical chemistry test reports must be reviewed, signed and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

10.3.6 Hematology

Blood for hematology assessments will be collected as indicated in in the Study Schedule inn Table 1: Schedule of Events and sent to a central laboratory for analysis. The following hematology parameters will be assessed: red blood cell (RBC) count, white blood cell (WBC) count, hematocrit, hemoglobin, MCV, platelet count and WBC differentials.

All hematology test reports must be reviewed, signed and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

10.3.7 Urinalysis

Urine for urinalysis assessments will be collected as indicated in the Study Schedule in Table 1: Schedule of Events and sent to a central laboratory for analysis. Urinalysis will include glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrites, leucocyte esterase, sedimentation.

All urinalysis test reports must be reviewed, signed and dated by the Investigator or delegated physician. Reports will then be filed with the subject's medical record. The Investigator will comment on all abnormal results and determine whether they are clinically significant. Clinically significant findings must also be reported as adverse events in the eCRF.

A urine sample will also be collected to perform the opiate drug screen.

10.3.8 Vital signs

Vital signs will be measured at the time points indicated in Table 1: Schedule of Events and will include systolic and diastolic BP, pulse, temperature and weight. Weight will be measured at Baseline/Day 1, Week 12 and Follow-up only.

Blood pressure will be measured using a standardized process:

- Subject should sit for ≥5 minutes with feet flat on the floor and measurement arm supported so that the midpoint of the manometer cuff is at heart level
- Use an automatic blood pressure device with an appropriately sized cuff with the bladder centered over the brachial artery
- Measure and record the blood pressure using the same arm throughout the study

All measurements are to be recorded on the Vital Signs eCRF.

All vital signs must be reviewed by the Investigator or delegated physician. The Investigator will comment on all abnormal results and determine whether they are clinically significant. These assessments will be recorded in the eCRF and clinically significant findings must also be reported as adverse events in the eCRF.

10.3.9 Pregnancy Testing, Contraception and Pregnancy

10.3.9.1 Pregnancy Testing

Female subjects of childbearing potential (WOCP) will have a serum pregnancy test at initial Screening to confirm a negative result for subject eligibility, and a dipstick urine pregnancy test will be performed at Baseline/Day1 and must be negative for the subject to remain eligible. A dipstick urine pregnancy test will be performed at Weeks 4, 8 12, and 14. Tests must be negative for the subject to continue with dosing.

10.3.9.2 Contraception

Female subjects of childbearing potential and male subjects with female partners of childbearing potential must follow the permitted contraceptive methods outlined in Section 7.2 for the duration of their participation in the study.

Male subjects will also be reminded to continue to use the permitted contraception methods for 90 days following discontinuation of IMP.

10.3.9.3 Pregnancy

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study and for up to 30 days after the last dose of IMP. The Investigator will record pregnancy information on the appropriate form and submit it to the Medical Monitor within 24-hours of learning of a subject's pregnancy through the same process as reporting an SAE. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Medical Monitor. Generally, follow-up will be no longer than six to eight weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

Female subjects will be instructed that if they become pregnant during the study or up to 30 days after their last dose of IMP, this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study.

Any female subject reporting a pregnancy during the study will be withdrawn from the study.

If the partner of a male study subject becomes pregnant during the subject's participation in the study and for up to 90 days after the last dose of IMP, this should be reported to the investigator. Consent will be sought from the partner and, if granted, any pregnancy will be followed and the status of mother and/or child will be reported to the sponsor after delivery.

10.4 Pharmacokinetics

Blood samples for analysis of plasma orvepitant concentrations will be collected at the clinic visits at Weeks 2, 4, 8 and 12, immediately prior (<15 mins) to the dose to be taken in the clinic.

The actual date and time of each blood sample collection will be recorded, together with the date and time of the most recent dose of IMP.

Approximately 6 mL of blood will be collected at each time point. Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures will be provided in the Study Manual.

10.5 Adverse events

10.5.1 Definitions

Adverse Event (AE)

Any untoward medical occurrence in a subject or clinical trial subject administered a IMP and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a IMP, whether or not considered related to the IMP.

Adverse Drug Reaction (ADR)

All AEs considered to be untoward and unintended responses to a IMP related to any dose should be considered ADRs. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The phrase "responses to a IMP" means that a causal relationship between a IMP and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Serious Adverse Event (SAE)

An adverse event that:

- Results in death
- Is life-threatening (i.e. the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Requires in-subject hospitalization or prolongation of existing hospitalization (see explanation below)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is considered to be an important medical event

Based upon medical and scientific judgment, important medical events that may not be immediately life-threatening, or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above may be considered a SAE.

Hospitalizations are defined as initial or prolonged admissions that include an overnight stay. Hospitalization or prolonged hospitalization for technical, practical or social reasons, in the absence of an adverse event is not an SAE and neither is attendance at an Emergency Room / Accident and Emergency Department that takes place in the evening or night and does not result in admission to the hospital.

Pregnancy

Pregnancy itself is not considered an AE. However, any pregnancy complication, spontaneous or elective abortion (for medical reasons), still birth, neonatal death, or congenital anomaly will be recorded as an AE or SAE.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with applicable product information (e.g., IB for an unapproved IMP).

Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse event that is suspected to be related to the administered medicinal product and the nature or severity of which is not consistent with applicable product information.

10.5.2 Assessment of Severity

The severity (intensity) of each adverse event will be classified as:

- **Mild** Awareness of sign or symptom, but easily tolerated
- **Moderate** Sign or symptom causes discomfort, but does not interfere with normal activities
- **Severe** Sign or symptom of sufficient intensity to interfere with normal activities

10.5.3 Assessment of Causality

A determination will be made of the relationship (if any) between an AE and the study drug. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug or study procedure. AEs will be classified as either related or unrelated.

10.5.4 Adverse Event Reporting

Adverse events may be volunteered spontaneously by the subject, or discovered as a result of general, non-leading questioning. Adverse events occurring from the time of consent up to the final study visit will be recorded. All AEs should be recorded in the eCRF and in the subjects' source notes.

Any SAE occurring from the time the subject signs informed consent until 30 days after the last dose of IMP must be reported immediately (within 24 hours of the investigator becoming aware of it) and recorded on the SAE Form. Detailed instructions for the reporting of SAEs can be found in the Study Manual. All patients with a SAE must be followed up and the outcomes reported. The investigator must supply the Sponsor and the relevant agency/IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports). Any follow-up information on a previously reported SAE will also be reported within 24 hours of awareness.

If the Investigator does not have all information regarding an SAE, he/ she will not wait to receive additional information before reporting the event and completing the appropriate data collection form. The Investigator will always provide a preliminary assessment of causality at the time of the initial report as described in Section 10.5.3.

The primary mechanism for reporting SAEs will be a paper collection form.

Fax transmission or 'scan & email' of the SAE form is the preferred method to transmit this information to the project contact for SAE receipt. In rare circumstances and in the absence of fax equipment, notification by telephone is acceptable, with a copy of the SAE data collection form

sent by overnight mail. Initial notification via the telephone does not replace the need for the Investigator to complete and sign the SAE data collection form within the designated reporting periods.

NeRRe is required to expedite to worldwide regulatory authorities reports of SUSARs in line with the relevant legislation. Fatal or life-threatening SUSARs must be reported within 7 calendar days and other SUSARs within 15 calendar days.

In accordance with the European Commission Directive 2001/20/EC, NeRRe will notify the relevant Ethics Committees in concerned Member states of applicable SUSARs as individual notifications or through a periodic line listing.

NeRRe will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

All investigators will receive a safety letter notifying them of relevant SUSAR reports. Each Investigator must then notify his or her relevant agency/IRB/IEC of the SAE as required by local regulatory authorities and in accordance with IRB/IEC policy. NeRRe will submit to the regulatory authorities all safety updates and periodic reports, as required by applicable regulatory requirements.

11. STATISTICAL CONSIDERATIONS

The primary objective of the study is to evaluate the efficacy of 10 mg, 20 mg, and 30 mg orvepitant versus placebo in reducing awake objective cough frequency. The corresponding primary endpoint is the change in objective awake cough frequency at Week 12 compared to Baseline and will be analyzed after taking logs (to base 10).

The primary objective will be assessed by testing the following hypotheses for each orvepitant group separately:

Null hypothesis (H0): There is no difference in the mean change in log transformed objective awake cough frequency at Week 12 compared to Baseline for the orvepitant treatment group compared to placebo.

$$H0: \mu (active) = \mu (placebo)$$

Alternative hypothesis (H1): There is a difference in the mean change in log transformed objective awake cough frequency at Week 12 compared to Baseline for the orvepitant treatment group compared to placebo.

$$H1: \mu (active) \neq \mu (placebo)$$

Each comparison will be carried out at the two-sided 5% level of statistical significance. No adjustment will be made for the multiple orvepitant versus placebo group comparisons in this

phase 2 study (three in total: 10 mg versus placebo, 20 mg versus placebo and 30 mg versus placebo) with the understanding that this increases the overall type I error rate of the study.

11.1 Estimated Sample Size

The initial planned sample size for this study was 55 subjects per treatment group (220 subjects in total). As a result of the planned sample size re-estimation the sample size is increased to 65 subjects per group (260 in total). The sample size calculation is based on pairwise comparisons of the primary endpoint for each active dose versus placebo. Objective cough frequency will be analysed on a log scale. A two-sided type I error of 0.05, not adjusted for multiple comparisons against placebo, will be used for this exploratory study. Assuming a revised standard deviation of change from Baseline (after taking logs) of 0.285 (based on the sample size re-estimate and increased from the original assumption of 0.261) a reduction in the placebo group of 10% and a reduction in the orvepitant group of 35%, 65 subjects per arm will provide a power of 80%. This new standard deviation estimate has been obtained (at the first sample size review) by considering the full analysis set subjects (as revised, See Section 11.2).

After at least 100 subjects have completed the Week 12 ACM assessment (and in addition to the now completed first sample size re-estimate) the cough frequency data will be reviewed to check the estimate of variability assumed for the primary efficacy variable. This interim sample-size re-estimation will be done on a fully blinded basis using an overall pooled estimate of standard deviation and may result in an increase in the sample size (Kieser and Friede, 2000). Only the awake cough frequency data will be reviewed.

Assuming no further changes to the sample size estimate, approximately 292 subjects will be randomized to ensure at least 260 completers (assuming approximately 10% drop out rate). The sample size may be adjusted again after the second re-estimate and provided no more than 320 subjects (approximately 80 per group) are required the precise number will be documented in a non-substantial (administrative) amendment to the protocol. Any possible impact on the type I error due to this blinded sample size re-assessment procedure is believed to be negligible (Kieser and Friede, 2003).

11.2 Analysis Sets

The following data sets will be used for the statistical analysis.

1. **Safety Set**: All subjects who receive at least one dose of double-blind study drug irrespective of treatment received. Subjects will be analyzed according to treatment received

2. **Full Analysis Set (FAS):** All randomized subjects who received at least one dose of double-blind study drug, irrespective of treatment received, satisfy inclusion criterion number 4 (awake cough frequency of >=10 coughs/hour during the Screening period), and have awake cough frequency data from the ACM for at least one post-treatment assessment. Subjects will be analyzed according to randomized treatment. This is the primary efficacy analysis set for the study.

3. **Per Protocol (PP) Set**: All subjects in the FAS excluding those identified as relevant protocol violators.

4. **Exposure-Response (ER) Set:** all subjects who received at least one dose of double-blind study drug and for whom the PK data are considered sufficient.

Analysis Sets will be identified prior to the unblinding of the study data.

11.3 Data Analysis

More details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and finalized prior to the breaking of the blind.

For continuous data and for ordered categorical data, if appropriate, the number of non-missing observations, mean, standard deviation, median, first and third quartiles, minimum and maximum will be calculated. For ordered categorical data and nominal data, absolute counts and relative frequencies (in %) will be calculated.

All statistical hypothesis tests and confidence intervals will be two sided, using a type I error rate of 0.05. No adjustment for multiple comparisons will be used for this study.

Raw data will be listed.

11.4 Demographics and Baseline Characteristics

Relevant Screening and Baseline data (i.e. data collected prior to the treatment administration) and demographic characteristics will be summarized descriptively for each treatment group. There will be no formal comparison of Baseline data, that is, no statistical hypothesis testing.

11.5 Statistical Methods for Efficacy Parameters

11.5.1 Primary Efficacy Analysis

Awake objective cough frequency at Baseline and Weeks 2, 4 and 12, along with change from Baseline, will be summarized for each treatment group and for each time point on the original scale (including percent change from Baseline) and after log (base 10) transformation. NB: The Baseline for objective cough frequency outcomes is the measurement obtained during the Screening period.

The primary analysis of log transformed awake objective cough frequency will be conducted via a mixed model for repeated measures (MMRM) with the model including terms for region, baseline log-transformed awake objective cough frequency, treatment group, week, week*region, week*baseline and week*treatment interactions. Subject will be included as a random effect. The estimated treatment means and differences (orvepitant versus placebo) at Week 12 (primary endpoint) will be reported as part of this analysis, along with 95% confidence intervals and associated p-values. Dose response analyses will be conducted.

11.5.2 Secondary Efficacy Analysis

The analysis of change from Baseline in awake objective cough frequency at Weeks 2 and 4 will be conducted as part of the analysis model for the primary endpoint. The analysis of change from Baseline in both 24 hour and night-time (non-waking time) objective cough frequency will be analyzed in the same way as for the primary endpoint. The other secondary endpoints will be also be analyzed using the MMRM except for the global rating of change in cough frequency and in severity. These shall be summarized as categorical endpoints ("worse", "about the same" and "better") and analyzed using Mantel-Haenszel methodology. The 7-point scale for degree of change (if they indicate a change) will also be summarized.

11.6 Statistical Methods for Safety Parameters

Safety data will be summarised descriptively for each treatment group. No formal inferential tests will be performed on safety data.

The number of treatment emergent AEs (TEAEs), and subjects with TEAEs, will be compared between groups. TEAEs are defined as AEs that first occurred or worsened in severity after the first dose of IMP.

TEAEs will be summarised for all causality AEs and for treatment-related AEs (those with related relationship to IMP and missing). TEAEs will be summarised by MeDRA body system and preferred term. TEAEs will also be reported by severity.

Any deaths, SAEs and AEs leading to discontinuation of IMP administration will also be summarised by treatment group.

SAEs will be presented in a similar way to AEs.

Vital signs will be summarised for each treatment group by visit. Summary statistics will be presented for absolute values and the change from Baseline.

ECGs will be assessed by the Investigator for abnormal findings. These will be categorised and summarised as normal, abnormal-not clinically significant or abnormal-clinically significant. ECG intervals will be recorded and summarised as absolute values and changes from Baseline.

Clinical laboratory data for individual subjects will be listed and any out of range values will be highlighted. Laboratory data will be summarised for each treatment group by visit. Summary statistics will be presented for absolute values and change from Baseline, as well as an analysis of shifts from Baseline.

Extent of exposure and compliance will be evaluated.

11.7 Pharmacokinetics Analysis

The plasma orvepitant concentrations will be analyzed using a population pharmacokinetic (Pop PK) approach by nonlinear mixed effects modeling (NONMEM®). The Pop PK model will be used to evaluate the relationship between orvepitant exposure and clinical endpoints. The details of the analysis will be described in a Pop PK Data Analysis Plan (DAP).

11.8 Missing Data

Summary statistics will be based primarily on non-missing values. For hypothesis tests, estimates and confidence intervals, missing values for continuous efficacy endpoints analyzed via likelihood methods (e.g. repeated measures mixed models) will not be directly imputed as they are handled within the analysis itself, under the assumption that the model specification is correct and that the data is missing at random. Sensitivity analyses may be conducted to check the robustness of the analysis results under alternative assumptions with regards to missing data. Further details on the handling of missing values, including rules applied to incomplete questionnaires and any planned sensitivity analyses will be defined in the SAP.

12. END OF THE STUDY

The end of the study will be defined as the last subject's last visit.

13. ETHICS COMMITTEE REVIEW/INFORMED CONSENT

13.1 Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and Relevant Authorities

The final study protocol, the subject information and consent form and any other subject facing materials (e.g. questionnaires, advertisements) will be approved by an appropriately constituted IRB/IEC. Approval will be received in writing before initiation of the study.

Clinical Study Authorization will be obtained prior to initiation of the study from the relevant Regulatory Authority.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with the local regulations, the principals of Good Clinical Practice (GCP) as described by the International Council for Harmonization (ICH), and the ethical principles that have their origins in the Declaration of Helsinki.

13.3 Informed Consent

For each study subject, written informed consent will be obtained prior to any protocol-related activities. As part of this procedure, the principal investigator or one of his/her associates will explain orally and in writing the nature, duration, purpose of the study, and the action of the study drug in such a manner that the subject is aware of the potential risks, inconveniences, or adverse

effects that may occur. They will be informed that their medical records may be reviewed by appropriately qualified monitors of the Sponsor or Sponsor Representative, and by auditors or regulatory authorities to ensure the accuracy of the details recorded as part of the study. They will be informed that they may withdraw from the study at any time without prejudice to further treatment. They will receive all information that is required by local regulations and ICH guidelines.

14. STUDY AND DATA MANAGEMENT

14.1 Protocol Amendments

Once approved by the applicable Regulatory Authorities and IRBs/IECs, the protocol must not be amended without approval by NeRRe. Unless an amendment is required to be implemented urgently in the interests of safety, or is deemed administrative by NeRRe, any amendments to the protocol must be authorized by the applicable Regulatory Authorities and IRB/IEC prior to implementation.

14.2 Monitoring

In accordance with applicable regulations including GCP and NeRRe or delegated CRO's Standard Operating Procedures (SOP), approved clinical research monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and NeRRe requirements. When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which the eCRF will serve as the source document. A list of what is to be classed as 'source documentation' will be documented in the Study Monitoring Manual.

NeRRe will monitor the study and sites to verify:

- Data are authentic, accurate and complete
- Safety and right of the subjects are being protected
- IMP accountability
- SAE reporting
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP and all applicable regulatory requirements

The investigator[s]/institution[s] will permit study-related monitoring, providing direct access to source data/documents.

14.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, the investigator[s]/institution[s] will permit study-related audits, IRB/IEC review, and regulatory inspection[s], providing direct access to source data/documents.

14.4 Data Recording

14.4.1 Data to be Considered as Source Data

An eCRF will be used to capture subject data into a secure, validated database. Access to enter data in the eCRF will be limited to delegated and trained investigator site staff only. ACM, PK and safety laboratory data will be transferred electronically into the database periodically during the study.

Source data may be defined as information from an original record or certified copy of the original record containing patient information for use in the trial. The information may include, but is not limited, to clinical findings, observations, or other activities necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies) (ICH E2A Guideline). Examples of source data include subject identification and randomization identification.

14.5 Confidentiality

The Investigator must assure that the subjects' anonymity will be maintained. On all study documentation, with the exception of the consent form and subject ID logs, subjects will only be identified by their unique identification code and initials and will not be referred to by name.

Study data will be handled with utmost discretion within the context of physician's confidentiality. On the eCRFs and other study specific documents, subjects are not identified by their names, but by a unique subject number. Names of participating subjects and data generated as a result of this study will not be passed on to unauthorized persons.

The Investigator must assure that the subjects are properly anonymized throughout the study. On all study documentation which is supposed to leave the site (i.e., to be transmitted to NeRRe, CRO or third parties), subjects will only be identified by their unique identification code and will not be referred to by name.

NeRRe may transfer some data collected during the study to a different company or regulatory authority outside of the US or EU for the purpose of processing, review, analysis or storage. Whenever the subject's personal data is transferred, it will be kept confidential and secure, and will used only for the purpose for which it was collected.

Safety analysis samples collected during the study will be analyzed at a central laboratory. Samples will be identified by the subjects' unique identification code. All safety samples will be destroyed after the assays have been completed.

Blood samples for analysis of orvepitant concentrations will be shipped to Aptuit Srl, Italy for analysis. Samples will be identified by the subjects' unique identification code. Following completion of the analysis, all samples will be destroyed.

14.6 Retention of Study Data

Following closure of the study, the Investigator must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/ regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The Investigator must assure that all reproductions are legible and are a true and accurate copy of the originals, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the Investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

NeRRe will inform the Investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or NeRRe, or delegated CRO's SOPs; otherwise, the retention period will default to 15 years.

The Investigator must notify NeRRe of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the Investigator leaves the site. The Investigator may not dispose of any records without prior approval from NeRRe.

14.7 Communication and Publication of Results

Where required by applicable regulatory requirements, an Investigator signatory will be identified for the approval of the clinical study report (CSR). The Investigator will be provided appropriate access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at NeRRe or another mutually agreeable location.

The original eCRFs and all data generated during the study under this protocol will become the property of the Sponsor.

Upon completion of the CSR, NeRRe will ensure public disclosure of the clinical trial research results according to the NeRRe's SOP and provide the Investigator with the full summary of the study results. The Investigator is encouraged to share the summary results with the study subjects, as appropriate.

It is the intent of all parties that the results of the study be published in a timely manner consistent with academic standards and with due consideration given to the protection of intellectual property rights. The Principal Investigator and NeRRe will be responsible for assembling the proposed publication; this must happen with due diligence and with minimal delay.

Any proposed publication or presentation (including a manuscript, abstract or poster) for submission to a journal or scientific meeting should be sent to the Sponsor for review at least sixty (60) days prior to submission. The Sponsor's comments on the proposed publication shall be considered in good faith by the authors. Sponsor may delay such submission by a maximum of six months if it reasonably believes that publication of results may compromise its intellectual property rights or else insist that such information or data is removed from the proposed publication. Publication of the results will not include confidential information without the permission of the Sponsor.

14.8 Indemnification

In the event of study-related damage or injuries, the clinical trial insurance of the Sponsor provides compensation for claims that arise in accordance with the regulatory requirements of the countries involved, except for claims that arise from willful misconduct or gross negligence. A copy of the country-specific insurance certificates will be held in the TMF and in the Investigator Site File.

15. REFERENCES

Bae YJ, Moon KA, Kim TB, Jang YJ, Lee YS, Park CS, Lee KY, Moon HB, Cho YS.
The role of nitrosative stress in the pathogenesis of unexplained chronic cough with cough hypersensitivity.
Am J Rhinol Allergy. 2012 Jan-Feb;26(1)

Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID.
Development of a symptom specific health status measure for subjects with chronic cough: Leicester Cough Questionnaire (LCQ).
Thorax 2003; 58(4):339-43.

Bolser DC, DeGennaro FC, O'Reilly S, McLeod RL, Hey JA.
Central antitussive activity of the NK1 and NK2 tachykinin receptor antagonists, CP-99,994 and SR 48968, in the guinea-pig and cat.
Br J Pharmacol. 1997 May; 121(2):165-70.

Bolser DC, Hey JA, Chapman RW.
Influence of central antitussive drugs on the cough motor pattern.
J Appl Physiol (1985). 1999 Mar; 86(3):1017-24.

Boulet LP, Coeytaux RR, McCrory DC, French CT, Chang AB, Birring SS, Smith J, Diekemper RL, Rubin B, Irwin RS; CHEST Expert Cough Panel.
Tools for assessing outcomes in studies of chronic cough: CHEST guideline and expert panel report.
Chest. 2015 Mar;147(3):804-14.

Canning BJ.
Central regulation of the cough reflex: therapeutic implications.
Pulm Pharmacol Ther. 2009 Apr; 22 (2):75-81.

Canning BJ, Chang AB, Bolser DC, Smith JA, Mazzone SB, McGarvey L; CHEST Expert Cough
Anatomy and neurophysiology of cough: CHEST Guideline and Expert Panel report.
Panel; CHEST Expert Cough Panel.
Chest. 2014 Dec;146(6):1633-48.

Chamberlain SA, Garrod R, Douiri A, Masefield S, Powell P, Bücher C, Pandyan A, Morice AH, Birring SS.
The impact of chronic cough: a cross-sectional European survey.
Lung. 2015 Jun;193(3):401-8.

Chapman RW, House A, Liu F, Celly C, Mei H, Hey JA.
Antitussive activity of the tachykinin NK1 receptor antagonist, CP-99994, in dogs.
Eur J Pharmacol. 2004 Feb 6; 485(1-3):329-32.

Chen CY, Joad JP, Bric J, Bonham AC.
Central mechanisms I: plasticity of central pathways.
Handb Exp Pharmacol. 2009;(187):187-201.

Chung KF, Pavord ID.
Prevalence, pathogenesis, and causes of chronic cough.
Lancet. 2008 Apr 19;371(9621):1364-74.

Dicpinigaitis PV, Tso R, Banauch G.
Prevalence of depressive symptoms among subjects with chronic cough.
Chest 2006; 130(6):1839-43.

Di Fabio R, Alvaro G, Braggio S, Carletti R, Gerrard PA, Griffante C, Marchioro C, Pozzan A, Melotto S, Poffe A, Piccoli L, Ratti E, Tranquillini E, Trower M, Spada S, Corsi M.
Identification, biological characterization and pharmacophoric analysis of a new potent and selective NK1 receptor antagonist clinical candidate.
Bioorg Med Chem. 2013 Nov 1;21(21):6264-73.

El-Hashim AZ, Wyss D, Lewis C.
Effect of a novel NK1 receptor selective antagonist (NKP608) on citric acid induced cough and airway obstruction.
Pulm Pharmacol Ther. 2004; 17(1):11-8

Everett CF, Kastelik JA, Thompson RH, Morice AH.
Chronic persistent cough in the community: a questionnaire survey.
Cough. 2007 Mar 23;3:5.

Ford AC, Forman D, Moayyedi P, Morice AH.
Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. Thorax 2006;61(11):975-9.

French CL, Irwin RS, Curley FJ, Krikorian CJ.
Impact of chronic cough on Quality-of-Life.
Arch Intern Med. 1998 Aug 10-24;158(15):1657-61.

French CT, Irwin RS, Fletcher KE, Adams TM.
Evaluation of a cough-specific quality-of-life questionnaire.
Chest 2002; 121(4):1123-31.

Gibson PG, Vertigan AE.
Management of chronic refractory cough.
BMJ. 2015 Dec 14;351:h5590.

Gibson P, Wang G, McGarvey L, Vertigan AE, Altman KW, Birring SS; CHEST Expert Cough Panel.
Treatment of Unexplained Chronic Cough: CHEST Guideline and Expert Panel Report.
Chest. 2016 Jan;149(1):27-44.

Grobman M, Reinero C.
Investigation of Neurokinin-1 Receptor Antagonism as a Novel Treatment for Chronic Bronchitis in Dogs.

J Vet Intern Med. 2016 May;30(3):847-52.

GSK Study No. NKG10002. An open label positron emission tomography study in healthy male subjects to investigate brain neurokinin-1 receptor occupancy kinetics, pharmacokinetics and safety of single oral doses of GW823296, using the specific PET ligand [11C]- GR205171 as tracer (2005).

GSK Study No. NKG10004. A Parallel Group, Single-Blind, Randomised, Placebo-Controlled Study to Evaluate the Safety, Tolerability and Pharmacokinetics of GW823296 and its Effect on the Pharmacokinetics of Midazolam after Once Daily Repeated Oral Doses in Healthy Subjects (2008).

GSK Study No. NKG111733. A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Fixed Dose Study Evaluating the Efficacy and Safety of Orvepitant in Subjects with Major Depressive Disorder (MDD) (2010)

GSK Study No. NKG110833. A Randomised, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Orvepitant in Subjects with Major Depressive Disorder (2010).

GSK Study No. NKG113211. A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Fixed-Dose Study Evaluating the Efficacy and Safety of the Neurokinin-1 Receptor Antagonist Orvepitant (GW823296) in Posttraumatic Stress Disorder (PTSD) (2010).

Harle M, Blackhall F, Molassiotis A, Holt K, Dockry R, Russell P, Burns K, Robinson R, Birrell M, Belvisi, Smith J.
Neurokinin-1 receptor antagonism for the treatment of cough in lung cancer
ERS International Congress 2016, Abstract PA5060

Hope-Gill BD, Hilldrup S, Davies C, Newton RP, Harrison NK.
A study of the cough reflex in idiopathic pulmonary fibrosis.
Am J Respir Crit Care Med. 2003 Oct 15;168(8):995-1002.

Hsiao C-J, Cherry DK, Beatty PC, Rechtsteiner EA.
National Ambulatory Medical Care Survey: 2007 Summary
National Health Statistics Reports 2010 Nov 3;(27):1-32.

Irwin RS, Corrao WM, Pratter MR.
Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy.
The American review of respiratory disease 1981; 123(4 Pt 1):413-7.

Irwin RS, Boulet LP, Cloutier MM, Fuller R, Gold PM, Hoffstein V, Ing AJ, McCool FD, O'Byrne P, Poe RH, Prakash UB, Pratter MR, Rubin BK.
Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians.
Chest. 1998 Aug;114(2 Suppl Managing):133S-181S.

Irwin RS, Baumann MH, Bolser DC, Boulet LP, Braman SS, Brightling CE, Brown KK, Canning BJ, Chang AB, Dicpinigaitis PV, Eccles R, Glomb WB, Goldstein LB, Graham LM, Hargreave FE, Kvale PA, Lewis SZ, McCool FD, McCrory DC, Prakash UB, Pratter MR, Rosen MJ,

Schulman E, Shannon JJ, Smith Hammond C, Tarlo SM; American College of Chest Physicians (ACCP).
Diagnosis and management of cough executive summary: ACCP evidence-based clinical practice guidelines.
Chest. 2006 Jan;129(1 Suppl):1S-23S.

Janson C, Chinn S, Jarvis D, Burney P.
Determinants of cough in young adults participating in the European Community Respiratory Health Survey.
The European respiratory journal: official journal of the European Society for Clinical Respiratory Physiology 2001; 18(4):647-54.

Joad JP, Munch PA, Bric JM, Evans SJ, Pinkerton KE, Chen CY, Bonham AC
Passive smoke effects on cough and airways in young guinea pigs: role of brainstem substance P.
Am J Respir Crit Care Med. 2004 Feb 15;169(4):499-504.

Katsumata U, Sekizawa K, Inoue H, Sasaki H, Takishima T.
Inhibitory actions of procaterol, a beta-2 stimulant, on substance P-induced cough in normal subjects during upper respiratory tract infection.
Tohoku J Exp Med. 1989 May;158(1):105-6.

Kieser M, Friede T.
Blinded sample size re-estimation in multi-armed clinical trials.
Drug Information Journal 2000; 34:455– 460.

Kieser M, Friede T
Simple procedures for blinded sample size adjustment that do not affect the type 1 error rate.
Statist. Med 2003; 22:3571-3581

Lavinka PC, Dong X.
Molecular signaling and targets from itch: lessons for cough.
Cough. 2013 Mar 6; 9(1):8.

Lim KG, Rank MA, Kita H, Patel A, Moore E.
Neuropeptide levels in nasal secretions from subjects with and without chronic cough.
Ann Allergy Asthma Immunol. 2011 Oct; 107(4): 360-3.

Mazzone SB, Mori N, Canning BJ.
Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea-pigs.
J Physiol. 2005 Dec 1;569(Pt 2):559-73.

Moreaux B, Nemmar A, Vincke G, Halloy D, Beerens D, Advenier C, Gustin P.
Role of substance P and tachykinin receptor antagonists in citric acid-induced cough in pigs.
Eur J Pharmacol. 2000 Nov 24; 408(3):305-12.

Morice AH, McGarvey L, Pavord I, on behalf of the British Thoracic Society Cough Guideline Group
Recommendations for the management of cough in adults.
Thorax 2006;61(Suppl I):i1–i24.

Morice AH, Fontana GA, Belvisi MG, Birring SS, Chung KF, Dicpinigaitis PV, Kastelik JA, McGarvey LP, Smith JA, Tatar M, Widdicombe J; European Respiratory Society (ERS).
ERS guidelines on the assessment of cough.
Eur Respir J. 2007 Jun;29(6):1256-76.

Mutolo D, Bongianni F, Fontana GA, Pantaleo T.
The role of excitatory amino acids and substance P in the mediation of the cough reflex within the nucleus tractus solitarii of the rabbit.
Brain Res Bull. 2007 Sep 28;74(4):284-93.

Mutolo D, Bongianni F, Cinelli E, Fontana GA, Pantaleo T.
Modulation of the cough reflex by antitussive agents within the caudal aspect of the nucleus tractus solitarii in the rabbit.
Am J Physiol Regul Integr Comp Physiol. 2008 Jul; 295(1):R243-51.

Mutolo D, Bongianni F, Cinelli E, Pantaleo T.
Depression of cough reflex by microinjections of antitussive agents into caudal ventral respiratory group of the rabbit.
J Appl Physiol (1985). 2010 Oct; 109(4):1002-10.

NeRRe Study No: NT2014/Orv/Prot001 (RELIEVE-1)
A randomised, double-blind, placebo-controlled study to evaluate the efficacy of orvepitant compared with placebo on EGFRi-induced intense pruritus in oncology subjects (2016).

NeRRe Study No: NT2014/Orv/Prot001 (VOLCANO-1)
Evaluation of orvepitant in an exploratory open-label clinical study in
chronic treatment-refractory cough (2016).

Otsuka K, Niimi A, Matsumoto H, Ito I, Yamaguchi M, Matsuoka H, Jinnai M, Oguma T, Takeda T, Nakaji H, Chin K, Sasaki K, Aoyama N, Mishima M.
Plasma substance P levels in subjects with persistent cough.
Respiration. 2011; 82(5):431-8.

Parexel Study No: 228126. Pharmacokinetic predictions for Orvepitant (GW823296) based on GSK Clinical Study Report VM2008/00003/01(Study NKG10004) (2016).

Patterson RN, Johnston BT, Ardill JE, Heaney LG, McGarvey LP.
Increased tachykinin levels in induced sputum from asthmatic and cough subjects with acid reflux. Thorax. 2007 Jun; 62(6):491-5.

Qiu Z, Yu L, Xu S, Liu B, Zhao T, Lü H, Qiu Z.
Cough reflex sensitivity and airway inflammation in subjects with chronic cough due to non-acid gastro-oesophageal reflux.
Respirology. 2011 May; 16(4):645-52.

Sekizawa S, Joad JP, Pinkerton KE, Bonham AC.
Distinct tachykinin NK(1) receptor function in primate nucleus tractus solitarius neurons is dysregulated after second-hand tobacco smoke exposure.
Br J Pharmacol. 2011 Jun;163(4):782-91.

Song WJ, Chang YS, Faruqi S, Kim JY, Kang MG, Kim S, Jo EJ, Kim MH, Plevkova J, Park HW, Cho SH, Morice AH.
The global epidemiology of chronic cough in adults: a systematic review and meta-analysis.
Eur Respir J. 2015 May;45(5):1479-81.

Spinou A, Birring SS.
An update on measurement and monitoring of cough: what are the important study endpoints?
J Thorac Dis. 2014 Oct; 6(Suppl 7): S728–S734.

Trower MK, Fisher A, Upton N, Ratti E.
Neurokinin-1 receptor antagonist orvepitant is an effective inhibitor of itch-associated response in a Mongolian gerbil model of scratching behaviour.
Exp Dermatol. 2014 Nov;23(11):858-60.

16. SIGNATURES AND AGREEMENT WITH THE PROTOCOL

Sponsor Approval

I have reviewed and approved the protocol and confirm that the protocol follows GCP.

Signature:  Date: 21 Feb 2018

Stephen Pawsey MBBS FRCA FFPM
Chief Medical Officer, NeRRe Therapeutics Ltd.

Principal Investigator Agreement

I agree to conduct the study according to the terms and conditions of this protocol, current Good Clinical Practice and with applicable regulatory requirements. All information pertaining to the study shall be treated in a confidential manner.

Signature: _____

Name of Principal Investigator:
Title:

Date:

17. APPENDICES

Appendix A: ACCP Guidelines (Irwin et al 2006)

Appendix B: BTS Guidelines (Morice et al 2006)

Diagnosis and Management of Cough Executive Summary

ACCP Evidence-Based Clinical Practice Guidelines

Richard S. Irwin, MD, FCCP, Chair;
Michael H. Baumann, MD, FCCP (HSP Liaison); Donald C. Bolser, PhD;
Louis-Philippe Boulet, MD, FCCP (CTS Representative);
Sidney S. Braman, MD, FCCP; Christopher E. Brightling, MBBS, FCCP;
Kevin K. Brown, MD, FCCP; Brendan J. Canning, PhD;
Anne B. Chang, MBBS, PhD; Peter V. Dicpinigaitis, MD, FCCP;
Ron Eccles, DSc; W. Brendle Glomb, MD, FCCP; Larry B. Goldstein, MD;
LeRoy M. Graham, MD, FCCP; Frederick E. Hargreave, MD;
Paul A. Kvale, MD, FCCP; Sandra Zelman Lewis, PhD;
F. Dennis McCool, MD, FCCP; Douglas C. McCrory, MD, MHSc;
Udaya B.S. Prakash, MD, FCCP; Melvin R. Pratter, MD, FCCP;
Mark J. Rosen, MD, FCCP;
Edward Schulman, MD, FCCP (ATS Representative);
John Jay Shannon, MD, FCCP (ACP Representative);
Carol Smith Hammond, PhD; and Susan M. Tarlo, MBBS, FCCP

(CHEST 2006; 129:1S–23S)

Abbreviations: ACE = angiotensin-converting enzyme; ACP = American College of Physicians; A/D = antihistamine/decongestant; ATS = American Thoracic Society; BPC = bronchoprovocation challenge; CTS = Canadian Thoracic Society; DPB = diffuse panbronchiolitis; dTap = acellular pertussis; FEES = fiberoptic endoscopic evaluation of swallowing; GERD = gastroesophageal reflux disease; HRCT = high-resolution CT; HSP = Health and Science Policy Committee; IBD = inflammatory bowel disease; ICS = inhaled corticosteroid; ILD = interstitial lung disease; NAEB = nonasthmatic eosinophilic bronchitis; NSCLC = non-small cell lung cancer; SLP = speech-language pathologist; TB = tuberculosis; UACS = upper airway cough syndrome; URI = upper respiratory infection; VC = voluntary cough; VSE = videofluoroscopic swallow evaluation

Recognition of the importance of cough in clinical medicine was the impetus for the original evidence-based consensus panel report on "Managing Cough as a Defense Mechanism and as a Symptom," published in 1998,[1] and this updated revision. Compared to the original cough consensus statement, this revision (1) more narrowly focuses the guidelines on the diagnosis and treatment of cough, the symptom, in adult and pediatric populations, and minimizes the discussion of cough as a defense mechanism; (2) improves on the rigor of the evidence-based review and describes the methodology in a separate section; (3) updates and expands, when appropriate, all previous sections; and (4) adds new sections with topics that were not previously covered. These new sections include nonasthmatic eosinophilic bronchitis (NAEB); acute bronchitis; nonbronchiectatic suppurative airway diseases; cough due to aspiration secondary to oral/pharyngeal dysphagia; environmental/occupational causes of cough; tuberculosis (TB) and other infections; cough in the dialysis patient; uncommon causes of cough; unexplained cough, previously referred to as idiopathic cough; an empiric integrative approach to the management of cough; assessing cough severity and efficacy of therapy in clinical research; potential future therapies; and future directions for research.

To mitigate future diagnostic confusion, two new diagnostic terms have been introduced to replace two

Correspondence to: Richard S. Irwin, MD, FCCP, University of Massachusetts Medical School, Room S6-842, 55 Lake Ave North, Worcester, MA 01655; e-mail address: Irwinr@ummhc.org

older terms that may represent misnomers. The committee unanimously recommends that the term *upper airway cough syndrome* (UACS) be used in preference to *postnasal drip syndrome* (PNDS) when discussing cough that is associated with upper airway conditions because it is unclear whether the mechanism of cough is postnasal drip, direct irritation, or inflammation of the cough receptors in the upper airway. The committee also recommends using the term *unexplained cough* rather than *idiopathic cough* because it is likely that more than one unknown cause of chronic cough will be discovered. The term *idiopathic* implies that one is dealing with only one disease.

For managing adult patients with cough, the committee recommends an empiric, integrative diagnostic approach, which is presented in the section entitled "An Empiric Integrative Approach to the Management of Cough".[3] Guidelines for managing acute, subacute, and chronic cough are presented in algorithmic form (Fig 1–3). Guidelines with algorithms for evaluating chronic cough in pediatric patients < 15 years of age are presented in the section entitled "Guidelines for Evaluating Chronic Cough in Pediatrics"[2,4] [Fig 4, 5]. For a full discussion on how to use the algorithms, please refer to these sections.

Summary and Recommendations

Recommendations for each section of these guidelines are listed under their respective section titles. For an in-depth discussion or clarification of each recommendation, readers are encouraged to read the specific section in question in its entirety.

Methodology and Grading of the Evidence for the Diagnosis and Management of Cough[5]

- The recommendations were graded, by consensus by the panel, using the American College of Chest Physicians Health and Science Policy Grading System, which is based on the following two components: quality of evidence; and the net benefit of the diagnostic and therapeutic procedure.
- The quality of evidence is rated according to the study design and strength of other methodologies used in the included studies.
- The net benefit of the recommendations is based on the estimated benefit to the specific patient population described in each recommendation and not for an individual patient. Usually, the net benefit is a clinical benefit to the population of patients defined in the first phrase of the recommendation, but, in recommendations for future research or other nonclinical recommendations, it may be a societal benefit.
- Both the quality of evidence and the net benefit components are listed after each recommendation; their interaction defines the strength of the recommendations.
- The recommendations scale is as follows: A, strong; B, moderate; C, weak; D, negative; I, inconclusive (no recommendation possible); E/A,

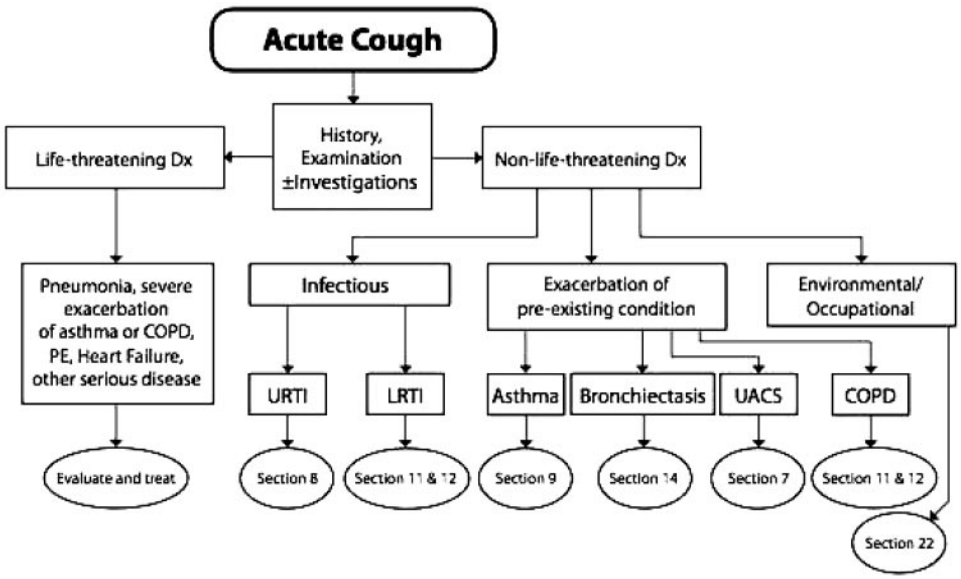


FIGURE 1. Acute cough algorithm for the management of patients ≥ 15 years of age with cough lasting < 3 weeks. For diagnosis and treatment recommendations refer to the section indicated in the algorithm. PE = pulmonary embolism; Dx = diagnosis; Rx = treatment; URTI = upper respiratory tract infection; LRTI = lower respiratory tract infection. Section 7 = Irwin[8]; Section 8 = Pratter[9]; Section 9 = Pratter[10]; Section 10 = Pratter[11]; Section 11 = Dicpinigaitis[12]; Section 12 = Irwin[13]; Section 13 = Braman[14]; Section 14 = Braman[15]; Section 16 = Rosen[17]; Section 22 = Irwin et al.[23]

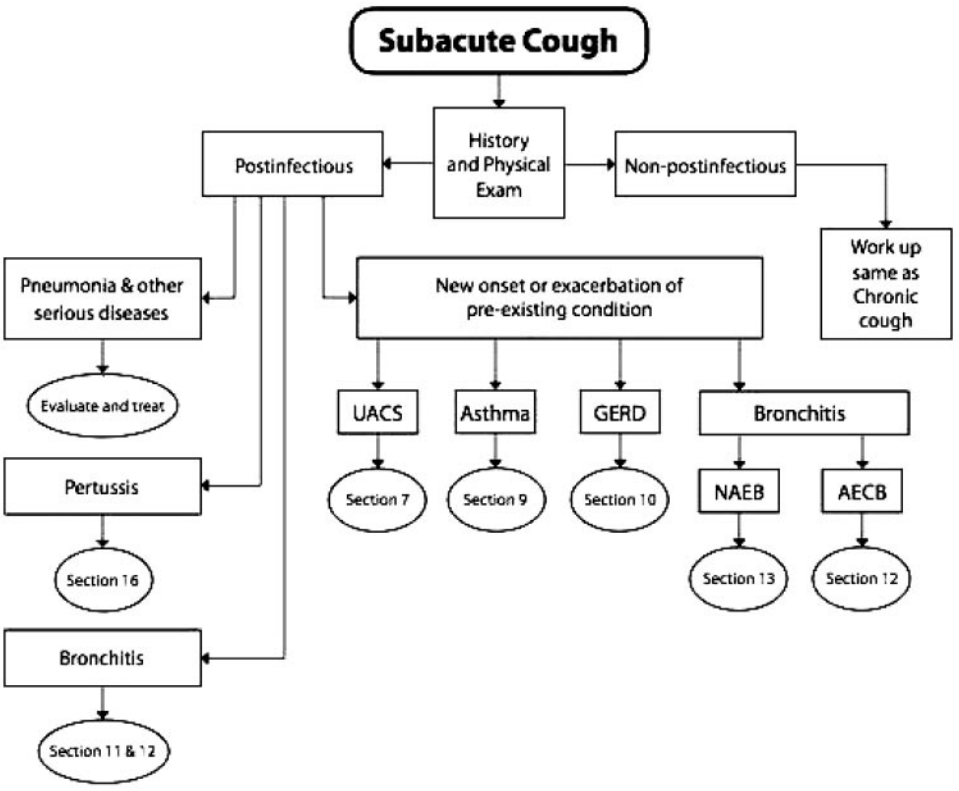


FIGURE 2. Subacute cough algorithm for the management of patients ≥ 15 years of age with cough lasting 3 to 8 weeks. For diagnosis and treatment recommendations refer to the section indicated in the algorithm. AECB = acute exacerbation of chronic bronchitis. See the legend of Figure 1 for abbreviations not used in the text. See Figure 1 for references to Sections.

strong recommendation based on expert opinion only; E/B, moderate recommendation based on expert opinion only; E/C, weak recommendation based on expert opinion only; and E/D, negative recommendation based on expert opinion only

Anatomy and Neurophysiology of the Cough Reflex[6]

- There is clear evidence that vagal afferent nerves regulate involuntary coughing.
- Coughing, like swallowing, belching, urinating, and defecating, is unique because there is higher cortical control of this visceral reflex.
- Cortical control can manifest as cough inhibition or voluntary cough. The implications of this are several-fold: because placebos can have a profound effect on coughing, treatment studies must be placebo-controlled. Because cough can be an affective behavior, psychological issues must be considered as a cause or effect of coughing.
- There is a need to study the roles of consciousness and perception in coughing.

Global Physiology and Pathophysiology of Cough[7]

1. In patients with endotracheal tubes, tracheostomy need not be performed to improve cough effectiveness. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

2. Individuals with neuromuscular weakness and no concomitant airway obstruction may benefit from mechanical aids to improve cough. Level of evidence, low; net benefit, intermediate; grade of recommendation, C

3. In patients with ineffective cough, the clinician should be aware of and monitor for possible complications, such as pneumonia, atelectasis, and/or respiratory failure. Level of evidence, low; net benefit, substantial; grade of recommendation, B

Complications of Cough[8]

1. In patients complaining of cough, evaluate for a variety of complications associated with coughing (*eg*, cardiovascular, constitutional, GI, genitourinary, musculoskeletal, neurologic, ophthalmologic, psychosocial, and skin complications), which can lead to a decrease in a patient's health-related quality of life. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. Patients with cough should have a thor-

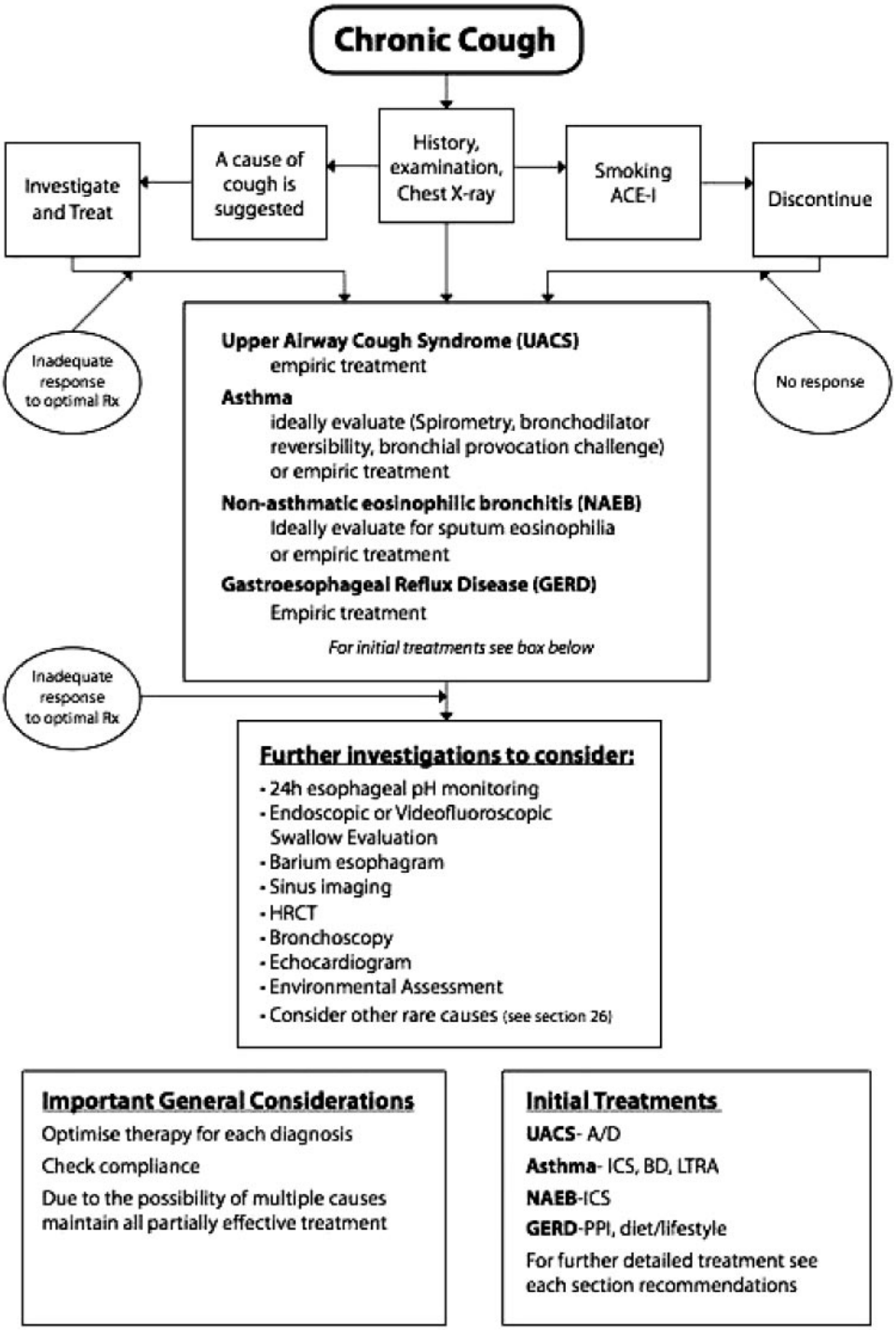


FIGURE 3. Chronic cough algorithm for the management of patients ≥ 15 years of age with cough lasting > 8 weeks. ACE-I = ACE inhibitor; BD = bronchodilator; LTRA = leukotriene receptor antagonist; PPI = proton pump inhibitor. See the legend of Figure 1 for abbreviations not used in the text.

ough diagnostic evaluation, according to the guidelines set forth in this document, to mitigate or prevent these complications. Level of evidence, low; net benefit, substantial; grade of recommendation, B

Overview of Common Causes of Chronic Cough[9]

1. In patients with chronic cough and a normal chest roentgenogram finding who are nonsmokers and are not receiving therapy with an

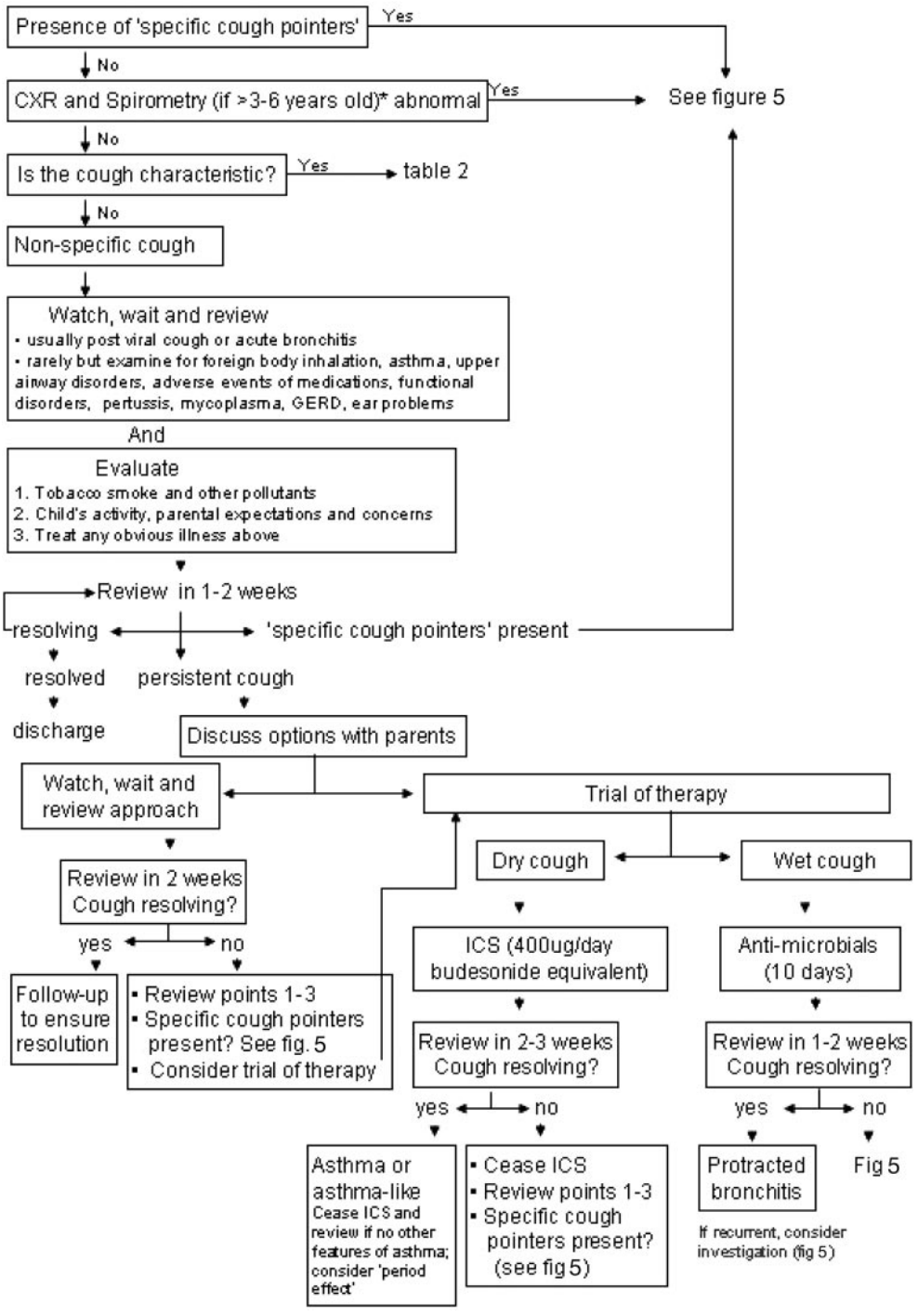


FIGURE 4. Approach to a child < 15 years of age with chronic cough. There are limitations of the algorithm, which should be read with the accompanying text. Spirometry can usually be reliably performed in children > 6 years of age and in some children > 3 years of age if trained pediatric personnel are present. CXR = chest radiograph.[2]

angiotensin-converting enzyme (ACE) inhibitor, the diagnostic approach should focus on the detection and treatment of UACS (formerly called *PNDS*), asthma, NAEB, or GERD, alone or in combination. This approach is most likely to result in a high rate of success in achieving cough resolution. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. In all patients with chronic cough, regardless of clinical signs or symptoms, because

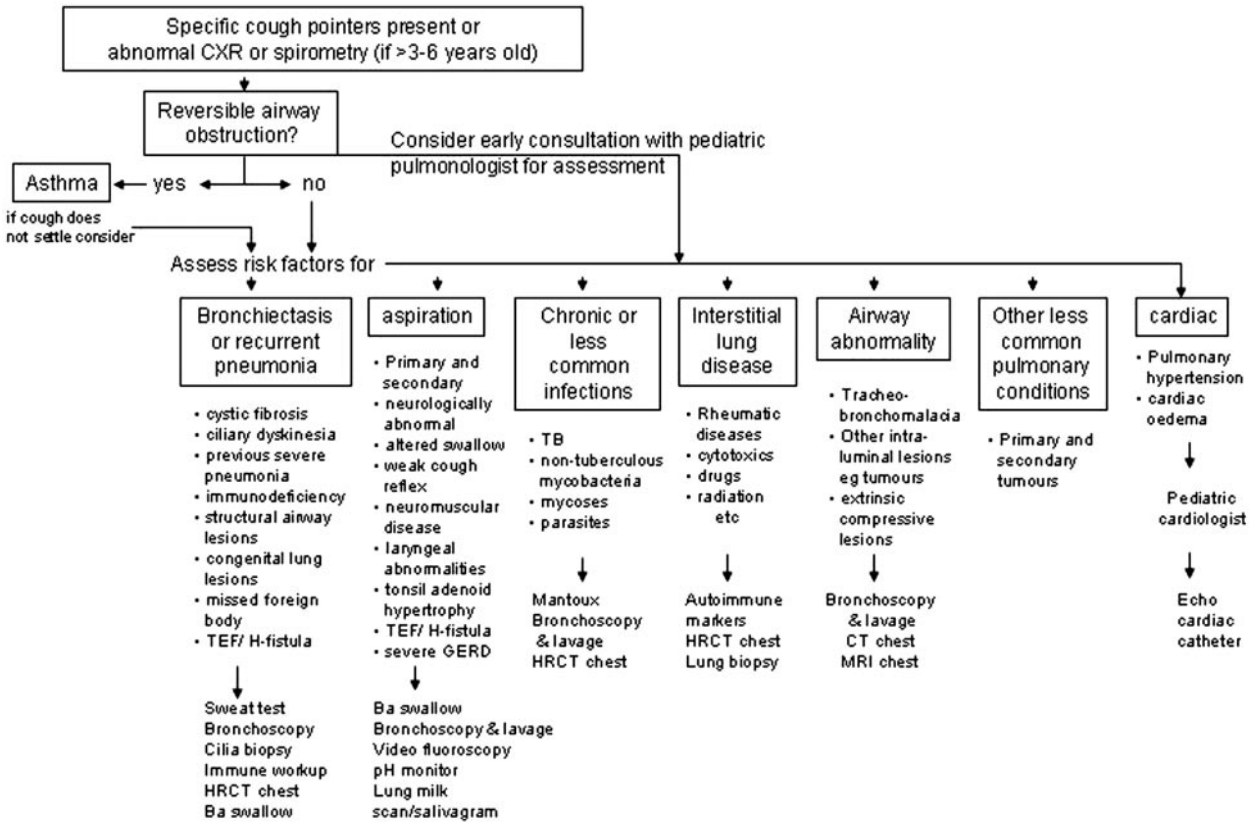


FIGURE 5. Approach to a child ≤ 14 years of age with chronic specific cough (*ie*, cough associated with other features suggestive of an underlying pulmonary and/or systemic abnormality). Children > 14 years of age should be managed as outlined in adult guidelines but there is no good evidence where the age cutoff should be. TEF = tracheal esophageal fistula. See the legend of Figure 4 for abbreviation not used in the text.

UACS (formerly called *PNDS*), asthma, and GERD each may present only as cough with no other associated clinical findings (*ie*, "silent PNDS," "cough variant asthma," and "silent GERD"), each of these diagnoses must be considered. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with chronic cough, neither the patient's description of his or her cough in terms of its character or timing, nor the presence or absence of sputum production, should be used to rule in or rule out a diagnosis or to determine the clinical approach. Level of evidence, low; benefit, substantial; grade of recommendation, B

Chronic Upper Airway Cough Syndrome Secondary to Rhinosinus Diseases (Previously Referred to as Postnasal Drip Syndrome)[10]

1. In patients with chronic cough that is related to upper airway abnormalities, the committee considers the term *UACS* to be more accurate, and it should therefore be used instead of the term *PNDS*. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough, the diagnosis of UACS-induced cough should be determined by considering a combination of criteria, including symptoms, physical examination findings, radiographic findings, and, ultimately, the response to specific therapy. Because it is a syndrome, no pathognomonic findings exist. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients in whom the cause of the UACS-induced cough is apparent, specific therapy directed at this condition should be instituted. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. For patients with chronic cough, an empiric trial of therapy for UACS should be administered because the improvement or resolution of cough in response to specific treatment is the

pivotal factor in confirming the diagnosis of UACS as a cause of cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. A patient suspected of having UACS-induced cough who does not respond to empiric antihistamine/decongestant (A/D) therapy with a first-generation antihistamine should next undergo sinus imaging. Although chronic sinusitis may cause a productive cough, it may also be clinically silent, in that the cough can be relatively or even completely nonproductive and none of the typical findings associated with acute sinusitis may be present. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In patients for whom a specific etiology of chronic cough is not apparent, empiric therapy for UACS in the form of a first-generation A/D preparation should be prescribed before beginning an extensive diagnostic workup. Level of evidence, low; benefit, intermediate; grade of recommendation, C

Cough and the Common Cold[11]

1. Patients with acute cough (as well as PND and throat clearing) associated with the common cold can be treated with a first-generation A/D preparation (brompheniramine and sustained-release pseudoephedrine). Naproxen can also be administered to help decrease cough in this setting. Level of evidence, fair; benefit, substantial; grade of recommendation, A

2. In patients with the common cold, newer generation nonsedating antihistamines are ineffective for reducing cough and should not be used. Level of evidence, fair; benefit, none; grade of recommendation, D

3. In patients with cough and acute URTI, because symptoms, signs, and even sinus-imaging abnormalities may be indistinguishable from acute bacterial sinusitis, the diagnosis of bacterial sinusitis should not be made during the first week of symptoms. (Clinical judgment is required to decide whether to institute antibiotic therapy.) Level of evidence, fair; benefit, none; grade of recommendation, D

Chronic Cough Due to Asthma[12]

1. In a patient with chronic cough, asthma should always be considered as a potential etiology because asthma is a common condition with which cough is commonly associated. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

2. In a patient suspected of having CVA but in whom physical examination and spirometry findings are nondiagnostic, MIC testing should be performed to confirm the presence of asthma. However, a diagnosis of CVA as the cause of cough is established only after the resolution of cough with specific antiasthmatic therapy. If MIC testing cannot be performed, empiric therapy should be administered; however, a response to steroid therapy will not exclude NAEB as an etiology of the patient's cough. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

3. Patients with cough due to asthma should initially be treated with a standard antiasthmatic regimen of inhaled bronchodilators and inhaled corticosteroids (ICSs). Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

4. In patients whose cough is refractory to treatment with ICSs, an assessment of airway inflammation should be performed whenever available and feasible. The demonstration of persistent airway eosinophilia during such an assessment will identify those patients who may benefit from more aggressive antiinflammatory therapy. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

5a. For patients with asthmatic cough that is refractory to treatment with ICSs and bronchodilators, in whom poor compliance or another contributing condition has been excluded, a leukotriene receptor antagonist may be added to the therapeutic regimen before the escalation of therapy to systemic corticosteroids. Quality of evidence, fair; net benefit, intermediate; grade of recommendation, B

5b. Patients with severe and/or refractory cough due to asthma should receive a short course (1 to 2 weeks) of systemic (oral) corticosteroids followed by ICSs. Quality of evidence, low; net benefit,: substantial; grade of recommendation, B

Chronic Cough Due to Gastroesophageal Reflux Disease[13]

1. In patients with chronic cough due to gastroesophageal reflux disease (GERD), the term *acid reflux disease*, unless it can be definitively shown to apply, should be replaced by the more general term *reflux disease* so as not to mislead the clinicians into thinking that all patients with cough due to GERD should improve with acid-suppression therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough who also

complain of typical and frequent GI complaints such as daily heartburn and regurgitation, especially when the findings of chest-imaging studies and/or clinical syndrome are consistent with an aspiration syndrome, the diagnostic evaluation should always include GERD as a possible cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. Patients with chronic cough who have GI symptoms that are consistent with GERD or who fit the clinical profile described in Table 1 in Irwin[13], should be considered to have a high likelihood of having GERD and should be prescribed antireflux treatment even when they have no GI symptoms. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. In patients with chronic cough, it should not be assumed that GERD has been definitively ruled out as a cause of cough simply because there is a history of antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with chronic cough, while tests that link GERD with cough suggest a potential cause-effect relationship, a definitive diagnosis of cough due to GERD requires that cough nearly or completely disappear with antireflux treatment. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In patients with chronic cough being evaluated for GERD, the 24-h esophageal pH-monitoring test is the most sensitive and specific test; however, it is recommended that the test results be interpreted as normal only when conventional indices for acid reflux are within the normal range and no reflux-induced coughs appear during the monitoring study. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients with cough who are undergoing 24-h monitoring, a low percentage of coughs associated with (or induced by) reflux does not exclude a diagnosis of cough due to GERD. Level of evidence, low; benefit, substantial; grade of recommendation, B

8. In patients with cough due to GERD, the degree of abnormality noted in the esophageal pH-monitoring variables, such as the frequency and duration of reflux events, does not directly correlate with the severity of the patients' cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

9. In diagnosing nonacid GERD as the cause of cough, barium esophagography may be the only available test to reveal GER of potential pathologic significance in this setting (see the "Discussion" section regarding esophageal impedance monitoring). When this is the case, barium esophagography is the test of choice to reveal GER of potential pathologic significance. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients with cough due to GERD, a normal esophagoscopy finding does not rule out GERD as the cause of cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

11. For patients fitting the clinical profile for cough due to GERD, it is recommended that treatment be initially started in lieu of testing. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. For patients fitting the clinical profile for cough due to GERD, the performance of 24-h esophageal pH monitoring is recommended on therapy when cough does not improve or resolve to assist in determining whether the therapy needs to be intensified or if medical therapy has failed. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. For patients with chronic cough, the following tests are not routinely recommended to link cough with GERD: (a) assessing for lipid-laden macrophages in BAL fluid and induced sputum, because this test has not been studied in patients with chronic cough and because a positive test result is not specific for aspiration; (b) exhaled nitric oxide measurements, because they do not appear to be helpful in diagnosing cough due to GERD; (c) a Bernstein test, because a negative Bernstein test result cannot be used to exclude the diagnosis of cough due to GERD; and (d) inhaled tussigenic challenges with capsaicin, because they are not specific for coughs due to GERD and because the test result can be positive in patients with GERD without cough. Level of evidence, low; benefit, conflicting; grade of recommendation, I

14. In patients who meet the clinical profile predicting that silent GERD is the likely cause of chronic cough or in patients with chronic cough who also have prominent upper GI symptoms consistent with GERD, an empiric trial of medical antireflux therapy is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B

15. For treating the majority of patients with chronic cough due to GERD, the following medical therapies are recommended: (a) dietary and lifestyle modifications; (b) acid suppression therapy; and (c) the addition of prokinetic therapy either initially or if there is no response to the first two therapies. The re-

sponse to these therapies should be assessed within 1 to 3 months. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

16. In patients in which this empiric treatment fails, it cannot be assumed that GERD has been ruled out as a cause of chronic cough; rather, the objective investigation for GERD is then recommended because the empiric therapy may not have been intensive enough or medical therapy may have failed. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

17. In some patients, cough due to GERD will favorably respond to acid suppression therapy alone; proton pump inhibition may be effective when H_2-antagonism has been ineffective; prokinetic therapy and diet, when added to proton pump inhibition, may be effective when proton pump inhibition alone has been ineffective. Level of evidence, low; benefit, substantial; grade of recommendation, B

18. Patients requiring an intensive medical treatment regimen should be treated with the following: (a) antireflux diet that includes no > 45 g of fat in 24 h and no coffee, tea, soda, chocolate, mints, citrus products, including tomatoes, or alcohol, no smoking, and limiting vigorous exercise that will increase intraabdominal pressure; (b) acid suppression with a proton pump inhibitor; (c) prokinetic therapy; and (d) efforts to mitigate the influences of comorbid diseases such as obstructive sleep apnea or therapy for comorbid conditions (*eg*, nitrates, progesterone, and calcium channel blockers) whenever possible. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

19. In patients with chronic cough due to GERD that has failed to improve with the most maximal medical therapy, which includes an intensive antireflux diet and lifestyle modification, maximum acid suppression, and prokinetic therapy, and the rest of the spectrum of treatment options in Table 3 in Irwin,[13] cough may only improve or be eliminated with antireflux surgery. Level of evidence, low; benefit, substantial; grade of recommendation, B

20. In patients who meet the following criteria, antireflux surgery is the recommended treatment: (a) findings of a 24-h esophageal pH-monitoring study before treatment is positive, as defined above; (b) patients fit the clinical profile suggesting that GERD is the likely cause of their cough (Table 1 in Irwin[13]); (c) cough has not improved after a minimum of 3 months of intensive therapy (Table 3 in Irwin[13]), and serial esophageal pH-monitoring studies or other objective studies (*eg*, barium esophagography, esophagoscopy, and gastric-emptying study with solids) performed while the patient receives therapy show that intensive medical therapy has failed to control the reflux disease and that GERD is still the likely cause of cough; and (d) patients express the opinion that their persisting cough does not allow them a satisfactory quality of life. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Chronic Cough Due to Acute Bronchitis[14]

1. In a patient with an acute respiratory infection manifested predominantly by cough, with or without sputum production, lasting no more than 3 weeks, a diagnosis of acute bronchitis should not be made unless there is no clinical or radiographic evidence of pneumonia, and the common cold, acute asthma, or an exacerbation of COPD have been ruled out as the cause of cough. Quality of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with the presumed diagnosis of acute bronchitis, viral cultures, serologic assays, and sputum analyses should not be routinely performed because the responsible organism is rarely identified in clinical practice. Quality of evidence, low; benefit, intermediate; grade of recommendation, C

3. In patients with acute cough and sputum production suggestive of acute bronchitis, the absence of the following findings reduces the likelihood of pneumonia sufficiently to eliminate the need for a chest radiograph: (1) heart rate > 100 beats/min; (2) respiratory rate > 24 breaths/min; (3) oral body temperature of > 38°C; and (4) chest examination findings of focal consolidation, egophony, or fremitus. Quality of evidence, low; benefit, substantial; grade of recommendation, B

4a. For patients with the putative diagnosis of acute bronchitis, routine treatment with antibiotics is not justified and should not be offered. Quality of evidence, good; benefit, none; grade of recommendation, D

4b. For these patients, the decision not to use an antibiotic should be addressed individually and explanations should be offered because many patients expect to receive an antibiotic based on previous experiences and public expectation. Quality of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

5. Children and adult patients with confirmed and probable whooping cough should receive a macrolide antibiotic and should be isolated for 5 days from the start of treatment; early treatment within the first few weeks will diminish the coughing paroxysms and prevent spread of the disease; the patient is unlikely to respond to treatment beyond this period. Level of evidence, good; net benefit, substantial; grade of evidence, A

6a. In most patients with a diagnosis of acute bronchitis, β_2-agonist bronchodilators should not be routinely used to alleviate cough. Quality of evidence, fair; benefit, none; grade of recommendation, D

6b. In select adult patients with a diagnosis of acute bronchitis and wheezing accompanying the cough, treatment with β_2-agonist bronchodilators may be useful. Quality of evidence, fair; benefit, small/weak; grade of recommendation, C

7. In patients with a diagnosis of acute bronchitis, antitussive agents are occasionally useful and can be offered for short-term symptomatic relief of coughing. Quality of evidence, fair; benefit, small/weak; grade of recommendation, C

8. In patients with a diagnosis of acute bronchitis, because there is no consistent favorable effect of mucokinetic agents on cough, they are not recommended. Quality of evidence, fair; benefit, conflicting; grade of recommendation, I

Chronic Cough Due to Chronic Bronchitis[15]

1. Adults who have a history of chronic cough and sputum expectoration occurring on most days for at least 3 months and for at least 2 consecutive years should be given a diagnosis of chronic bronchitis when other respiratory or cardiac causes of chronic productive cough are ruled out. Level of evidence, low; net benefit, substantial; grade of recommendation, B

2. The evaluation of patients with chronic cough should include a complete history regarding exposures to respiratory irritants including cigarette, cigar, and pipe smoke; passive smoke exposures; and hazardous environments in the home and workplace. All are predisposing factors of chronic bronchitis. Level of evidence, low; net benefit, substantial; grade of recommendation, B

3. Smoke-free workplace and public place laws should be enacted in all communities. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

4. Stable patients with chronic bronchitis who have a sudden deterioration of symptoms with increased cough, sputum production, sputum purulence, and/or shortness of breath, which are often preceded by symptoms of an upper respiratory tract infection, should be considered to have an acute exacerbation of chronic bronchitis, as long as conditions other than acute tracheobronchitis are ruled out or are considered unlikely. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

5. In patients with chronic cough who have chronic exposure to respiratory irritants, such as personal tobacco use, passive smoke exposure, and workplace hazards, avoidance should always be recommended. It is the most effective means to improve or eliminate the cough of chronic bronchitis. Ninety percent of patients will have resolution of their cough after smoking cessation. Level of evidence, good; net benefit, substantial; grade of recommendation, A

6. In stable patients with chronic bronchitis, there is no role for long-term prophylactic therapy with antibiotics. Level of evidence, low; benefit, none; grade of recommendation, I

7. In patients with acute exacerbations of chronic bronchitis, the use of antibiotics is recommended; patients with severe exacerbations and those with more severe airflow obstruction at baseline are the most likely to benefit. Level of evidence, fair; net benefit, substantial; grade of recommendation, A

8. In stable patients with chronic bronchitis, the clinical benefits of postural drainage and chest percussion have not been proven, and they are not recommended. Level of evidence, fair; net benefit, conflicting; grade of recommendation, I

9. In patients with an acute exacerbation of chronic bronchitis, the clinical benefits of postural drainage and chest percussion have not been proven, and they are not recommended. Level of evidence, fair; net benefit, conflicting; grade of recommendation, I

10a. In stable patients with chronic bronchitis, therapy with short-acting β-agonists should be used to control bronchospasm and relieve dyspnea; in some patients, it may also reduce chronic cough. Level of evidence, good; net benefit, substantial; grade of recommendation, A

10b. In stable patients with chronic bronchitis, therapy with ipratropium bromide should be offered to improve cough. Level of evidence, fair; net benefit, substantial; grade of recommendation, A

10c. In stable patients with chronic bronchi-

tis, treatment with theophylline should be considered to control chronic cough; careful monitoring for complications is necessary. Level of evidence, fair; net benefit, substantial; grade of recommendation, A

11. For patients with an acute exacerbation of chronic bronchitis, therapy with short-acting β-agonists or anticholinergic bronchodilators should be administered during the acute exacerbation. If the patient does not show a prompt response, the other agent should be added after the first is administered at the maximal dose. Level of evidence, good; net benefit, substantial; grade of recommendation, A

12. For patients with an acute exacerbation of chronic bronchitis, theophylline should not be used for treatment. Level of evidence, good; net benefit, none; grade of recommendation, D

13. For stable patients with chronic bronchitis, there is no evidence that the currently available expectorants are effective and therefore they should not be used. Level of evidence, low; net benefit, none; grade of recommendation, I

14. In stable patients with chronic bronchitis, treatment with a long-acting β-agonist when coupled with an ICS should be offered to control chronic cough. Level of evidence, good; net benefit, substantial; grade of recommendation, A

15. For stable patients with chronic bronchitis and an FEV_1 of < 50% predicted or for those patients with frequent exacerbations of chronic bronchitis, ICS therapy should be offered. Level of evidence, good; net benefit, substantial; grade of recommendation, A

16. For stable patients with chronic bronchitis, long-term maintenance therapy with oral corticosteroids such as prednisone should not be used; there is no evidence that it improves cough and sputum production, and the risks of serious side effects are high. Level of evidence, expert opinion; net benefit, negative; grade of recommendation, E/D

17. For patients with an acute exacerbation of chronic bronchitis, there is no evidence that the currently available expectorants are effective, and therefore they should not be used. Level of evidence, low; net benefit, none; grade of recommendation, I

18. For patients with an acute exacerbation of chronic bronchitis, a short course (10 to 15 days) of systemic corticosteroid therapy should be given; IV therapy in hospitalized patients and oral therapy for ambulatory patients have both proven to be effective. Level of evidence, good; net benefit, substantial; grade of recommendation, A

19. In patients with chronic bronchitis, central cough suppressants such as codeine and dextromethorphan are recommended for short-term symptomatic relief of coughing. Level of evidence, fair; benefit, intermediate; grade of evidence, B

Chronic Cough Due to Nonasthmatic Eosinophilic Bronchitis[16]

1. In patients with chronic cough who have normal chest radiograph findings, normal spirometry findings, and no evidence of variable airflow obstruction or airway hyperresponsiveness, the diagnosis of NAEB should be considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough with normal chest radiograph findings, normal spirometry findings, and no evidence of variable airflow obstruction or airway hyperresponsiveness, the diagnosis of NAEB as the cause of the chronic cough is confirmed by the presence of airway eosinophilia, either by sputum induction or bronchial wash fluid obtained by bronchoscopy, and an improvement in the cough following corticosteroid therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

3. In patients with chronic cough due to NAEB, the possibility of an occupation-related cause needs to be considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. For patients with chronic cough due to NAEB, the first-line treatment is ICSs (except when a causal allergen or sensitizer is identified [see recommendation 5]). Level of evidence, low; benefit, substantial; grade of recommendation, B

5. For patients with chronic cough due to NAEB, when a causal allergen or occupational sensitizer is identified, avoidance is the best treatment. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. For patients with chronic cough due to NAEB, if symptoms are persistently troublesome and/or the natural history of eosinophilic airway inflammation progresses despite treatment with high-dose ICSs, oral corticosteroids should be given. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Chronic Cough Due to Bronchiectasis[17]

1. In patients with suspected bronchiectasis without a characteristic chest radiograph finding, an high-resolution CT (HRCT) scan of the

chest should be ordered because it is the diagnostic procedure of choice to confirm the diagnosis. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. In patients for whom there is no obvious cause, a diagnostic evaluation for an underlying disorder causing bronchiectasis should be performed, because the results may lead to treatment that may slow or halt the progression of disease. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with bronchiectasis with airflow obstruction and/or bronchial hyperreactivity, therapy with bronchodilators may be of benefit. Level of evidence, expert opinion; benefit, small; grade of recommendation, E/C

4. In patients with bronchiectasis caused by cystic fibrosis (CF), rhDNase should be used to improve spirometry. Level of evidence, low; benefit, small; grade of recommendation, C

5. In patients with CF, prolonged treatment with systemic corticosteroids should not be offered to most patients because of significant side effects. Level of evidence, low; benefit, conflicting; grade of recommendation, I

6. In patients with CF, prolonged courses of ibuprofen should not be used. Level of evidence, low; benefit, conflicting; grade of recommendation, I

7. In patients with idiopathic bronchiectasis, the prolonged systemic administration of antibiotics may produce small benefits in reducing sputum volume and purulence, but may also be associated with intolerable side effects. Level of evidence, low; benefit, conflicting, grade of recommendation, I

8. In patients with CF, therapy with aerosolized antipseudomonal antibiotics are recommended. Level of evidence, low; benefit, intermediate; grade of recommendation, C

9. In patients with idiopathic bronchiectasis, aerosolized antibiotics should not be used. Level of evidence, low; benefit, negative; recommendation, D

10. In patients with conditions associated with the hypersecretion of mucus and the inability to expectorate effectively, chest physiotherapy should be used and patients should be monitored for symptom improvement. Level of evidence, expert opinion; benefit, small/weak; grade of recommendation, E/C

11. In selected patients with localized bronchiectasis that causes intolerable symptoms despite maximal medical therapy, surgery should be offered. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. In patients with exacerbations of bronchiectasis, antibiotics should be used, with the selection of agents depending on the likely pathogens. Level of evidence, low; benefit, substantial; grade of recommendation, B

Chronic Cough Due to Nonbronchiectatic Suppurative Airway Disease (Bronchiolitis)[18]

1. In patients with cough and incomplete or irreversible airflow limitation, direct or indirect signs of small airways disease seen on HRCT scan, or purulent secretions seen on bronchoscopy, nonbronchiectatic suppurative airways disease (bronchiolitis) should be suspected as the primary cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with cough in whom more common causes have been excluded, because bacterial suppurative airways disease may be present and clinically unsuspected, bronchoscopy is required before excluding it as a cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients in whom bronchiolitis is suspected, a surgical lung biopsy should be performed when the combination of the clinical syndrome, physiology, and HRCT findings do not provide a confident diagnosis. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. In patients with bacterial bronchiolitis, prolonged antibiotic therapy improves cough and is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with toxic/antigenic exposure or drug-related bronchiolitis, cessation of the exposure or medication plus corticosteroid therapy for those with physiologic impairment is appropriate. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. In the inflammatory bowel disease (IBD) patient with cough, bronchiolitis should be suspected as a potential cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients in whom IBD-related bronchiolitis is suspected, both adverse drug reaction and infection should be specifically considered. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

8. In patients with IBD, therapy with both oral corticosteroids and ICSs may improve cough, and a trial of therapy is suggested. Level of evidence, low; benefit, substantial; grade of recommendation, B

9. In patients with chronic cough who have recently lived in Japan, Korea, or China, diffuse

panbronchiolitis (DPB) should be considered in the evaluations of the cause. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients with suspected DPB, an appropriate clinical setting and characteristic HRCT scan findings may obviate the need for invasive testing and a trial of macrolide therapy (erythromycin or other 14-member ring macrolides such as clarithromycin and roxithromycin) is appropriate. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

11. In patients with DPB, prolonged treatment (≥ 2 to 6 months) with erythromycin (or other 14-member ring macrolides such as clarithromycin and roxithromycin) is recommended. Level of evidence, low; benefit, substantial; grade of recommendation, B

Postinfectious Cough[19]

1. When a patient complains of cough that has been present following symptoms of an acute respiratory infection for at least 3 weeks, but not more than 8 weeks, consider a diagnosis of postinfectious cough. Quality of evidence, expert opinion; net benefit, intermediate; strength of recommendation, E/B

2. In patients with subacute postinfectious cough, because there are multiple pathogenetic factors that may contribute to the cause of cough (including postviral airway inflammation with its attendant complications such as bronchial hyperresponsiveness, mucus hypersecretion and impaired mucociliary clearance, upper airway cough syndrome [UACS], asthma, and gastroesophageal reflux disease), judge which factors are most likely provoking cough before considering therapy. Quality of evidence, expert opinion; net benefit, intermediate; strength of recommendation, E/B

3. In children and adult patients with cough following an acute respiratory tract infection, if cough has persisted for > 8 weeks, consider diagnoses other than postinfectious cough. Quality of evidence, low; net benefit, intermediate; strength of recommendation, C

4. For adult patients with postinfectious cough, not due to bacterial sinusitis or early on in a *Bordetella pertussis* infection, while the optimal treatment is not known:

4a. Therapy with antibiotics has no role, as the cause is not bacterial infection. Level of evidence, expert opinion; net benefit, none; grade of evidence, I

4b. Consider a trial of inhaled ipratropium as it may attenuate the cough. Level of evidence, fair; net benefit, intermediate; grade of evidence, B

4c. In patients with postinfectious cough, when the cough adversely affects the patient's quality of life and when cough persists despite use of inhaled ipratropinin, consider the use of inhaled corticosteroids. Level of evidence, expert opinion; net benefit, intermediate; grade of evidence, E/B

4d. For severe paroxysms of postinfectious cough, consider prescribing 30 to 40 mg of prednisone per day for a short, finite period of time when other common causes of cough (*eg*, UACS due to rhinosinus diseases, asthma, or gastroesophageal reflux disease) have been ruled out. Level of evidence, low; net benefit, intermediate; grade of evidence, C

4e. Central acting antitussive agents such as codeine and dextromethorphan should be considered when other measures fail. Level of evidence, expert opinion; net benefit, intermediate; grade of evidence, E/B

5. When a patient has a cough lasting for ≥ 2 weeks without another apparent cause and it is accompanied by paroxysms of coughing, posttussive vomiting, and/or an inspiratory whooping sound, the diagnosis of a *B pertussis* infection should be made unless another diagnosis is proven. Level of evidence, low; net benefit, substantial; grade of evidence, B

6a. For all patients who are suspected of having whooping cough, to make a definitive diagnosis order a nasopharyngeal aspirate or polymer (Dacron; INVISTA; Wichita, KS) swab of the nasopharynx for culture to confirm the presence of *B pertussis*. Isolation of the bacteria is the only certain way to make the diagnosis. Level of evidence, low; net benefit, substantial; grade of evidence, B

6b. PCR confirmation is available but is not recommended as there is no universally accepted, validated technique for routine clinical testing. Level of evidence, low; net benefit, conflicting; grade of evidence, I

7. In patients with suspected pertussis infection, to make a presumptive diagnosis of this infection, order paired acute and convalescent sera in a reference laboratory. A fourfold increase in IgG or IgA antibodies to PT or FHA is consistent with the presence of a recent *B pertussis* infection. Level of evidence, low; net benefit, intermediate; grade of evidence, C

8. A confirmed diagnosis of pertussis infection should be made when a patient with cough has *B pertussis* isolated from a nasopharyngeal culture or has a compatible clinical picture with

an epidemiologic linkage to a confirmed case. Level of evidence, low; net benefit, substantial; grade of evidence, B

9. Children and adult patients with confirmed or probable whooping cough should receive a macrolide antibiotic and should be isolated for 5 days from the start of treatment because early treatment within the first few weeks will diminish the coughing paroxysms and prevent spread of the disease; treatment beyond this period may be offered but it is unlikely the patient will respond. Level of evidence, good; net benefit, substantial; grade of evidence, A

10. Long-acting β-agonists, antihistamines, corticosteroids, and pertussis Ig should not be offered to patients with whooping cough because there is no evidence that they benefit these patients. Level of evidence, good; net benefit, none; grade of evidence, D

11. All children should receive prevention against pertussis infection as part of a complete diphtheria, tetanus, acellular pertussis (DTap) primary vaccination series. This should be followed by a single dose DTap booster vaccination early in adolescence. Level of evidence, good; net benefit, substantial; grade of evidence, A

12. For all adults up to the age of 65, vaccination with the stronger formulation of TDap vaccine should be administered according to CDC guidelines. Level of evidence, expert opinion; net benefit, substantial; grade of evidence, E/A

Chronic Cough Due to Lung Tumors[20]

1. In a patient with cough who has risk factors for lung cancer or a known or suspected cancer in another site that may metastasize to the lungs, a chest radiograph should be obtained. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with a suspicion of airway involvement by a malignancy (*eg*, smokers with hemoptysis), even when the chest radiograph findings are normal, bronchoscopy is indicated. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. For patients with stage I and II non-small cell lung cancer (NSCLC), surgery to remove the NSCLC is the treatment of choice. If cough was caused by a NSCLC that can be surgically removed, the cough will typically cease. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. For patients with more advanced NSCLC (stages III and IV), external beam radiation and/or chemotherapy should usually be offered. Level of evidence, good; benefit, intermediate; grade of recommendation, A

5. For patients with dyspnea or hemoptysis due to endobronchial tumors, cough may also be present. Endobronchial methods should be considered for the palliation of these symptoms, but cough alone is seldom a reason to offer such treatment. Level of evidence, fair; benefit, small; grade of recommendation, C

6. For patients with cough and lung cancer, the use of centrally acting cough suppressants such as dihydrocodeine and hydrocodone is recommended. Level of evidence, low; benefit, intermediate; grade of recommendation, C

Cough and Aspiration of Food and Liquids Due to Oral-Pharyngeal Dysphagia[21]

1. In patients with cough, a medical history particularly directed at identifying conditions increasing the likelihood of oral-pharyngeal dysphagia and aspiration (as indicated in Table 1 in Smith Hammond and Goldstein[21]) should be obtained. Patients with high-risk conditions should be referred for an oral-pharyngeal swallowing evaluation. Level of evidence, low; benefit, substantial; grade of recommendation, B

2a. Patients with cough and their caregivers should be questioned regarding perceived swallowing problems, including an association of cough while eating or drinking and a fear of choking while eating and drinking. If a patient with cough reports swallowing problems, further evaluation for oral-pharyngeal dysphagia is indicated. Level of evidence, low; benefit, substantial; grade of recommendation, B

2b. Further evaluation, including a chest radiograph and a nutritional assessment, should be considered in patients with cough or conditions associated with aspiration. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. Patients with oral-pharyngeal dysphagia and cough should be referred, ideally to a speech-language pathologist (SLP), for an oral-pharyngeal swallow evaluation. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. Patients with cough related to pneumonia and bronchitis who have received medical diagnoses and conditions associated with aspiration (Table 1 in Smith Hammond and Goldstein[21]) should be referred, ideally to an SLP, for an

oral-pharyngeal swallow evaluation. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. Patients with a reduced level of consciousness are at high risk for aspiration and should not be fed orally until the level of consciousness has improved. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. Alert patients with cough who are in high-risk groups for aspiration (Table 1 in Smith Hammond and Goldstein[21]) should be observed drinking small amounts of water (3 oz). If the patient coughs or shows clinical signs that are associated with aspiration (Tables 2, 3 in Smith Hammond and Goldstein[21]), the patient should be referred for a detailed swallowing evaluation, preferably to an SLP. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients with cough, the value of the subjective assessment of voluntary cough (VC) as the sole predictor of aspiration is uncertain because of poor reliability and an unclear association with evaluation. Level of evidence, low; benefit, conflicting; grade of evidence, I

8. The assessment of the reflexive cough response to inhaled irritants as a predictor of aspiration risk and subsequent pneumonia is not recommended due to a lack of adequate supportive studies. Level of evidence, low; benefit, conflicting; grade of evidence, I

9. In acute stroke patients, the expulsive phase rise time of VC may predict aspiration. The use of this test has not been validated in other patient groups, and further studies comparing the accuracy of objective measures of VC to the clinical swallow evaluation to identify aspiration risk are needed. Level of evidence, low; benefit, small; grade of recommendation, C

10. Patients with dysphagia should undergo videofluoroscopic swallow evaluation (VSE) or fiberoptic endoscopic evaluation of swallowing (FEES) to identify appropriate treatment. Level of evidence, low; benefit, substantial; grade of recommendation, B

11. Patients with dysphagia should be managed by organized multidisciplinary teams that may include a physician, a nurse, an SLP, a dietitian, and physical and occupational therapists. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. In patients with dysphagia, VSE or FEES can be useful for determining compensatory strategies enabling patients with dysphagia to safely swallow. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. In patients with dysphagia, dietary recommendations should be prescribed when indicated, and can be refined by testing with foods and liquids simulating those in a normal diet during the VSE or FEES. Level of evidence, low; benefit, substantial; grade of recommendation, B

14. For patients with muscular weakness during swallowing, muscle strength training, with or without electromyographic biofeedback, and electrical stimulation treatment of the swallowing musculature are promising techniques but cannot be recommended at this time until further work in larger populations is performed. Level of evidence, low; benefit, conflicting; grade of evidence, I

15. Patients with intractable aspiration may be considered for surgical intervention. Level of evidence, low; benefit, substantial; grade of recommendation, B

Angiotensin-Converting Enzyme Inhibitor-Induced Cough[22]

1. In patients presenting with chronic cough, in order to determine that the angiotensin-converting enzyme (ACE) inhibitor is the cause of the cough, therapy with ACE inhibitors should be discontinued regardless of the temporal relation between the onset of cough and the initiation of ACE inhibitor therapy. The diagnosis is confirmed by the resolution of cough, usually within 1 to 4 weeks of the cessation of the offending agent; however, the resolution of cough may be delayed in a subgroup of patients for up to 3 months. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

2. In patients presenting with chronic ACE inhibitor-induced cough, discontinue therapy with the drug because it is the only uniformly effective treatment. Quality of evidence, low; net benefit, substantial; grade of recommendation, B

3. In patients whose cough resolves after the cessation of therapy with ACE inhibitors, and for whom there is a compelling reason to treat with these agents, a repeat trial of ACE inhibitor therapy may be attempted. Quality of evidence, fair; net benefit, substantial; grade of recommendation, A

4. In patients for whom the cessation of ACE inhibitor therapy is not an option, pharmacologic therapy, including that with sodium cromoglycate, theophylline, sulindac, indomethacin, amlodipine, nifedipine, ferrous sulfate, and picotamide that is aimed at suppressing cough should be attempted. Quality of evidence, fair; net benefit, intermediate; grade of recommendation, B

5. In patients in whom persistent or intolerable ACE inhibitor-induced cough occurs, therapy should be switched, when indicated, to an angiotensin receptor blocker, with which the incidence of associated cough appears to be similar to that for the control drug, or to an appropriate agent of another drug class. Quality of evidence, good; net benefit, substantial; grade of recommendation, A

Habit Cough, Tic Cough, and Psychogenic Cough in Adult and Pediatric Populations[23]

1a. In adult patients with chronic cough, the diagnoses of habit cough or psychogenic cough can only be made after an extensive evaluation has been performed that includes ruling out tic disorders and uncommon causes (as described in the section "Uncommon Causes of Cough"), and cough improves with specific therapy such as behavior modification or psychiatric therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

1b. In adult patients with chronic cough that remains persistently troublesome despite an extensive and thorough evidence-based evaluation, and after behavior modification and/or psychiatric therapy have failed, unexplained cough should be diagnosed rather than a habit cough or psychogenic cough. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

1c. In children with chronic cough, the diagnoses of habit cough or psychogenic cough can only be made after tic disorders and Tourette syndrome have been evaluated and cough improves with specific therapy such as behavior modification or psychiatric therapy. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In adult patients with cough, the diagnosis of habit cough should not be made unless biological and genetic tic disorders associated with coughing such as Tourette syndrome have been ruled out. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

3. In adults with chronic cough, the presence or absence of nighttime cough or cough with a barking or honking character should not be used to diagnose or exclude a diagnosis of psychogenic cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. In children with chronic cough, the characteristics of the cough may be suggestive of, but are not diagnostic of, psychogenic cough. The presence or absence of nighttime cough should not be used to diagnose or exclude psychogenic cough. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

5. In adult and pediatric patients with chronic unexplained cough, common psychosocial problems such as anxiety, depression, domestic violence, and child abuse/neglect that are often associated with somatization disorders should be evaluated. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. In adult and pediatric patients with chronic cough associated with troublesome psychological manifestations, psychological counseling or psychiatric intervention should be encouraged, after other causes have been ruled out. Level of evidence, expert opinion; benefit, small/weak; grade of recommendation, E/C

Chronic Cough Due to Chronic Interstitial Pulmonary Diseases[24]

1. In patients with chronic cough, before diagnosing interstitial lung disease (ILD) as the sole cause, common etiologies such as UACS, which was previously referred to as *PNDS*, asthma, and GERD should be considered. As these common causes may also share clinical features with specific ILDs, a diagnosis of ILD as the cause of cough should be considered a diagnosis of exclusion. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with cough secondary to an ILD, because of the prognostic implications, primary treatment should be dictated by the specific disorder. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with cough secondary to idiopathic pulmonary fibrosis, corticosteroids may lead to symptomatic improvement; however, as they have been shown to neither prolong survival nor improve quality of life and may be associated with significant side effects, their use requires an individualized analysis of the overall benefits and risks. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

4. In patients with cough and characteristic clinical and radiographic features, sarcoidosis should be considered as a cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

5. In patients with cough secondary to sarcoidosis, although therapy with oral corticosteroids may lead to symptomatic improvement, as they have not been proven to have a durable benefit

and are associated with significant side effects, an individualized analysis of the overall benefit and risk is necessary. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

6. In patients with cough secondary to sarcoidosis, therapy with oral corticosteroids followed by ICSs may improve symptoms. Level of evidence, fair; benefit, conflicting; grade of recommendation, I

7. In patients with cough, ILD, and a concerning environmental, occupational, or avocational exposure, hypersensitivity pneumonitis should be considered as a potential cause. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

8. In patients with cough due to hypersensitivity pneumonitis, treatment should include the removal of the offending exposure and systemic corticosteroid therapy in those with evidence of physiologic impairment. Level of evidence, low; benefit, substantial; grade of recommendation, B

Cough: Occupational and Environmental Considerations[25]

1. In every patient with cough, when taking a medical history, ask about occupational and environmental causes. Level of evidence, expert opinion; benefit, substantial; grade of recommendations, E/A

2. In every patient with cough who has potentially significant exposures to suspicious environmental or occupational causes, determine the relationship of these occupational and environmental factors to confirm or refute their role in cough and to modify or eliminate exposure to the relevant agents. Level of evidence, expert opinion; benefit, substantial; grade of recommendations, E/A

3. Because outdoor environmental pollution and occupational exposures can be important factors in causing cough, physicians should play a role in developing and supporting enforceable standards for safe workplace and outdoor air pollution exposure limits. Level of evidence, expert opinion; benefit, substantial; grade of recommendations, E/A

4. In patients with a high suspicion of cough due to environmental or occupational exposures, consider referring the patient to a specialist in this area or consult evidence-based guidelines. Level of evidence, expert opinion; net benefit, substantial; grade of recommendation, E/A

Chronic Cough Due to Tuberculosis and Other Infections[26]

1. In areas where there is a high prevalence of TB, chronic cough should be defined as it is in the World Health Organization Practical Approach to Lung Health program as being 2 to 3 weeks in duration. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. In patients with chronic cough who live in areas with a high prevalence of TB, this diagnosis should be considered, but not to the exclusion of the more common etiologies. Sputum smears and cultures for acid-fast bacilli and a chest radiograph should be obtained whenever possible. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. In patients with suspected TB, future investigations are needed to refine the criteria for suspecting TB and initiating a diagnostic evaluation, to utilize resources in a cost-effective manner and to improve patient and caregiver adherence to diagnostic recommendations. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4. In populations at increased risk of becoming infected with TB and transmitting it to others by cough (*eg*, those persons in prisons and nursing homes), special measures to prevent outbreaks must be made by public health agencies to screen for new cases, maintain surveillance of existing populations, and establish effective diagnostic and treatment programs early in the evaluation. Level of evidence, good; benefit, substantial; grade of recommendation, A

5. In patients with unexplained chronic cough who have resided in areas of endemic infection with fungi or parasites, a diagnostic evaluation for these pathogens should be undertaken when more common causes of cough have been ruled out. Level of evidence, low; benefit, substantial; grade of recommendation, B

Peritoneal Dialysis and Cough[27]

1. In patients receiving long-term peritoneal dialysis with cough, evaluate the patient for the potential causes with increased prevalence in this population such as GERD, ACE inhibitors, pulmonary edema, asthma that may be exacerbated by β-adrenergic-blocking medications, and infection. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Cough in the Immunocompromised Host[28]

1. In patients with immune deficiency, the initial diagnostic algorithm for patients with

acute, subacute, and chronic cough is the same as that for immunocompetent persons, taking into account an expanded list of differential diagnoses that considers the type and severity of immune defect and geographic factors. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In HIV-infected patients, CD4+ lymphocyte counts should be used in constructing the list of differential diagnostic possibilities potentially causing cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. HIV-infected patients with CD4+ lymphocyte counts of < 200 cells/μL or those patients with counts of > 200 cells/μL with unexplained fever, weight loss, or thrush who have unexplained cough should be suspected of having Pneumocystis pneumonia, tuberculosis, and other opportunistic infections, and should be evaluated accordingly. Level of evidence, low; benefit, substantial; grade of recommendation, B

Uncommon Causes of Cough[29]

1. In patients with chronic cough, uncommon causes should be considered when cough persists after evaluation for common causes and when the diagnostic evaluation suggests that an uncommon cause, pulmonary as well as extrapulmonary (see Table 1 in section 28), may be contributing. Level of evidence, low; benefit, substantial; grade of recommendation, B

2. In patients with chronic cough, until uncommon causes that potentially may be contributing to the patient's cough have been ruled out, the diagnosis of unexplained cough should not be made. Level of evidence, low; benefit, substantial; grade of recommendation, B

3. If cough persists after consideration of the most common causes, perform a chest CT scan and, if necessary, a bronchoscopic evaluation. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. In patients who present with abrupt onset of cough, consider the possibility of an airway foreign body. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In patients with unexplained cough, evaluate the possibility of drug-induced cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In patients with unexplained cough, consider a therapeutic trial of withdrawing the drug that is suspected to cause the cough. Level of evidence, low; benefit, substantial; grade of recommendation, B

Unexplained (Idiopathic) Cough[30]

1. The diagnosis of unexplained (idiopathic) cough is a diagnosis of exclusion. It should not be made until a thorough diagnostic evaluation is performed, specific and appropriate treatment (according to the management protocols that have performed the best in the literature) has been tried and has failed, and uncommon causes have been ruled out. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

An Empiric Integrative Approach to the Management of Cough[3]

1. In patients with cough, the starting point is the medical history and physical examination. Although the timing and characteristics of the cough are of little diagnostic value, the medical history is important to determine whether the patient is receiving an ACE inhibitor, is a smoker, or has evidence of a serious life-threatening or systemic disease. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with an acute cough, first determine whether the acute cough is a reflection of a serious illness such as pneumonia or pulmonary embolism, or, as is usually the case, a manifestation of a non-life-threatening disease such as a respiratory tract infection (*eg*, common cold or lower respiratory tract infection), an exacerbation of a preexisting condition (*eg*, COPD, UACS, asthma, or bronchiectasis), or an environmental or occupational exposure to some noxious or irritating agent (*eg*, allergic or irritant-induced rhinitis). Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

3. In patients with a subacute cough, first determine whether it is a postinfectious cough or not. If it is postinfectious, determine whether it is a result of UACS, transient bronchial hyperresponsiveness, asthma, pertussis, or an acute exacerbation of chronic bronchitis. If it is noninfectious, manage the cough the same way as chronic cough. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

4a. In patients with chronic cough, systematically direct empiric treatment at the most common causes of cough (*ie*, UACS, asthma, NAEB, and GERD). Level of evidence, low; benefit, substantial; grade of recommendation, B

4b. In patients with chronic cough, therapy should be given in sequential and additive steps

because more than one cause of cough may be present. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. Patients with a chronic cough who smoke should be counseled and assisted with smoking cessation. Level of evidence, low; benefit, substantial; grade of recommendation, B

6. In a patient with cough who is receiving an ACE inhibitor, therapy with the drug should be stopped and the drug should be replaced. Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In patients with chronic cough, initial empiric treatment should begin with an oral first-generation A/D. Level of evidence, low; benefit, substantial; grade of recommendation, B

8a. In patients whose chronic cough persists after treatment for UACS, the possibility that asthma is the cause of cough should be worked up next. The medical history is sometimes suggestive, but is not reliable in either ruling in or ruling out asthma. Therefore, ideally, bronchoprovocation challenge (BPC), if spirometry does not indicate reversible airflow obstruction, should be performed in the evaluation for asthma as a cause of cough. In the absence of the availability of BPC, an empiric trial of antiasthma therapy should be administered (see section on the treatment of asthma in this guideline). Level of evidence, low; benefit, substantial; grade of recommendation, B

8b. In patients with chronic cough, in whom the diagnoses of UACS and asthma have been eliminated or treated without the elimination of cough, NAEB should be considered next with a properly performed induced sputum test for eosinophils. If a properly performed induced sputum test to determine whether eosinophilic bronchitis is present cannot be performed, an empiric trial of corticosteroids should be the next step. Level of evidence, low; benefit, substantial; grade of recommendation, B

9. In the majority of patients with suspected cough due to asthma, ideally, before starting an oral corticosteroid regimen, a BPC should be performed and, if the result is positive, some combination therapy of ICSs, inhaled β-agonists, or oral leukotriene inhibitors should be administered. A limited trial of oral corticosteroids, however, should be administered in some patients who are suspected of having asthma-induced cough before eliminating the diagnosis from further consideration. Level of evidence, low; benefit, substantial; grade of recommendation, B

10. In patients whose cough responds only partially or not at all to interventions for UACS and asthma or NAEB, treatment for GERD should be instituted next. Level of evidence, low; benefit, substantial; grade of recommendation, B

11. In patients with cough whose condition remains undiagnosed after all of the above has been done, referral to a cough specialist is indicated. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Assessing Cough Severity and Efficacy of Therapy in Clinical Research[31]

1. In patients with chronic cough, to optimally evaluate the efficacy of cough-modifying agents, investigators should use both subjective and objective methods because they have the potential to measure different things. A patient's subjective response is likely to be the only one that measures the impact of the intensity of cough. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with chronic cough, with respect to subjective methods, it is recommended that a valid and reliable cough-specific health-related quality-of-life instrument be utilized. Level of evidence, fair; benefit, substantial; grade of recommendation, A

3. When assessing patients with chronic cough, even though visual analog scales have not been psychometrically tested, they are recommended because they are commonly used and valid, and they are likely to yield different but complementary results to cough-specific health-related quality-of-life instruments. Level of evidence, low; benefit, intermediate; grade of recommendation, C

4. When assessing patients with chronic cough, because health-related quality-of-life instruments have been psychometrically tested and visual analog scales have not, the cough-specific health-related quality-of-life instruments are recommended as the primary subjective outcome measure. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

5. In patients with chronic cough, with respect to objective methods, tussigenic challenges should be used before and after the intervention to assess the effect of therapy on cough sensitivity only in disease states in which cough reflex sensitivity is known to be heightened. Level of evidence, low; benefit, small/weak; grade of recommendation, C

6. In patients with chronic cough, because the act of coughing has the potential to traumatize the upper airway (*eg*, the vocal cords), assessing the presence of upper airway edema

before and after therapy with flow-volume loops is useful. Level of evidence, low; benefit, intermediate; grade of recommendation, C

7. In patients undergoing treatment for chronic cough, cough counting over 24 h is recommended with a computerized methodology that is reliable and accurate, noninvasive and portable, and easy to use in unattended, ambulatory, real-life settings within a patient's home environment. Level of evidence, low; benefit, intermediate; grade of recommendation, C

Cough Suppressant and Pharmacologic Protussive Therapy[32]

1. In patients with chronic bronchitis, agents that have been shown to alter mucus characteristics are not recommended for cough suppression. Level of evidence, good; benefit, none; grade of recommendation, D

2. In patients with cough due to upper respiratory infection (URI) or chronic bronchitis, the only inhaled anticholinergic agent that is recommended for cough suppression is ipratropium bromide. Level of evidence, fair; benefit, substantial; grade of recommendation, A

3. In patients with chronic or acute bronchitis, peripheral cough suppressants, such as levodropropizine and moguisteine, are recommended for the short-term symptomatic relief of coughing. Level of evidence, good; benefit, substantial; grade of recommendation, A

4. In patients with cough due to URI, peripheral cough suppressants have limited efficacy and are not recommended for this use. Level of evidence, good; benefit, none; grade of recommendation, D

5. In patients with chronic bronchitis, central cough suppressants, such as codeine and dextromethorphan, are recommended for the short-term symptomatic relief of coughing. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

6. In patients with cough due to URI, central cough suppressants have limited efficacy for symptomatic relief and are not recommended for this use. Level of evidence, good; benefit, none; grade of recommendation, D

7. In patients with chronic or acute cough requiring symptomatic relief, drugs that affect the efferent limb of the cough reflex are not recommended. Level of evidence, low; benefit, none; grade of recommendation, D

8. In patients requiring intubation during general anesthesia, the use of neuromuscular blocking agents is recommended to suppress coughing. Level of evidence, good; benefit, substantial; grade of recommendation, A

9. In patients with acute cough due to the common cold, preparations containing zinc are not recommended. Level of evidence, good; benefit, none; grade of recommendation, D

10. In patients with acute cough due to the common cold, over the counter combination cold medications, with the exception of an older antihistamine-decongestant, are not recommended until randomized controlled trials prove they are effective cough suppressants. Level of evidence, fair; benefit, none; grade of recommendation, D

11. In patients with acute or chronic cough not due to asthma, albuterol is not recommended. Level of evidence, good; benefit, none; grade of recommendation, D

12. In patients with neuromuscular impairment, protussive pharmacologic agents are ineffective and should not be prescribed. Level of evidence, good; benefit, none; grade of recommendation, D

13. In patients with bronchitis, hypertonic saline solution and erdosteine are recommended on a short-term basis to increase cough clearance. Level of evidence, good; benefit, substantial; grade of recommendation, A

14. In adult patients with CF, amiloride is recommended to increase cough clearance. Level of evidence, good; benefit, substantial; grade of recommendation, A

15. In adult patients with CF, while recombinant DNase does improve spirometry it is not recommended to increase cough clearance. Level of evidence, good; benefit, none; grade of recommendation, D

Nonpharmacologic Airway Clearance Therapies[33]

1. In patients with CF, chest physiotherapy is recommended as an effective technique to increase mucus clearance, but the effects of each treatment are relatively modest and the long-term benefits unproven. Level of evidence, fair; benefit, small; grade of recommendation, C

2. In patients with expiratory muscle weakness, manually assisted cough should be considered to reduce the incidence of respiratory complications. Level of evidence, low; benefit, small; grade of recommendation, C

3. In persons with airflow obstruction caused by disorders like COPD, manually assisted cough may be detrimental and should not be used. Level of evidence, low; benefit, negative; grade of recommendation, D

4. In patients with COPD and CF, huffing should be taught as an adjunct to other methods of sputum clearance. Level of evidence, low; benefit, small; grade of recommendation, C

5. In patients with CF, autogenic drainage should be taught as an adjunct to postural drainage as a method to clear sputum because it has the advantage of being performed without assistance and in one position. Level of evidence, low; benefit, small; grade of recommendation, C

6. In patients with neuromuscular weakness and impaired cough, expiratory muscle training is recommended to improve peak expiratory pressure, which may have a beneficial effect on cough. Level of evidence, expert opinion; benefit, small; grade of recommendation, E/C

7. In patients with CF, positive expiratory pressure is recommended over conventional chest physiotherapy because it is approximately as effective as chest physiotherapy, and is inexpensive, safe, and can be self-administered. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

8. In patients with CF, devices designed to oscillate gas in the airway, either directly or by compressing the chest wall, can be considered as an alternative to chest physiotherapy. Level of evidence, low; benefit, conflicting; grade of recommendation, I

9. In patients with neuromuscular disease with impaired cough, mechanical cough assist devices are recommended to prevent respiratory complications. Level of evidence, low; benefit, intermediate; grade of recommendation, C

10. The effect of nonpharmacologic airway clearance techniques on long-term outcomes such as health-related quality of life and rates of exacerbations, hospitalizations, and mortality is not known at this time. The committee recommends that future investigations measure these outcomes in patients with CF, and in other populations with bronchiectasis, COPD, and neuromuscular diseases. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

Guidelines for Evaluating Cough in Pediatrics[4]

1. Children with chronic cough require careful and systematic evaluation for the presence of specific diagnostic indicators. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. Children with chronic cough should undergo, as a minimum, a chest radiograph and spirometry (if age appropriate). Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

3. In children with specific cough, further investigations may be warranted, except when asthma is the etiologic factor. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

4. Children with chronic productive purulent cough should always be investigated to document the presence or absence of bronchiectasis and to identify underlying and treatable causes such as cystic fibrosis and immune deficiency. Level of evidence, low; benefit, substantial; grade of recommendation, B

5. In children with chronic cough, the etiology should be defined and treatment should be etiologically based. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

6. In children with nonspecific cough, cough may spontaneously resolve, but children should be reevaluated for the emergence of specific etiologic pointers (see Table 1 in Chang and Glomb[4]). Level of evidence, low; benefit, substantial; grade of recommendation, B

7. In children with nonspecific cough and risk factors for asthma, a short trial (*ie*, 2 to 4 weeks) of beclomethasone, 400 μg/d, or the equivalent dosage with budesonide may be warranted. However, most children with nonspecific cough do not have asthma. In any case, these children should always be reevaluated in 2 to 4 weeks. Level of evidence, fair; benefit, intermediate; grade of recommendation, B

8. In children who have started therapy with a medication, if the cough does not resolve during the medication trial within the expected response time, the medication should be withdrawn and other diagnoses considered. Level of evidence, low; benefit, intermediate; grade of recommendation, C

9. In children with cough, cough suppressants and other over-the-counter cough medicines should not be used as patients, especially young children, may experience significant morbidity and mortality. Level of evidence, good; benefit, none; grade of recommendation, D

10. In children with nonspecific cough, parental expectations should be determined, and the specific concerns of the parents should be sought and addressed. Level of evidence, low; benefit, intermediate; grade of recommendation, E/B

11. In all children with cough, exacerbating factors such as exposure to tobacco smoke should be determined and interventional options for the ces-

sation of exposure advised or initiated. Level of evidence, low; benefit, substantial; grade of recommendation, B

12. Children should be managed according to the studies and guidelines for children (when available), because etiologic factors and treatments in children are sometimes different from those in adults. Level of evidence, low; benefit, substantial; grade of recommendation, B

13. In children ≤ 14 years of age with chronic cough, when pediatric-specific cough recommendations are unavailable, adult recommendations should be used with caution. Level of evidence, expert opinion; benefit, intermediate; grade of recommendation, E/B

Potential Future Therapies for the Management of Cough[34]

- Currently available cough-suppressant therapy is severely limited by a dearth of effective agents and their unacceptable side affects. Several classes of pharmacologic agents are currently under investigation in an attempt to develop clinically useful cough suppression.

Future Directions in the Clinical Management of Cough[35]

1. As suggested in the various sections of this guideline, further research should be conducted to elucidate the mechanisms of the production of cough in various diseases and conditions, the optimal methods of assessment, and treatment, specific to the suspected cause. Level of evidence, expert opinion; benefit, substantial; strength of recommendation, E/A

2. Research is particularly needed in areas such as the treatment of postinfectious cough, the characterization of psychogenic cough, the methods of assessment of cough, and pharmacotherapy. Level of evidence, expert opinion; benefit, substantial; strength of recommendation, E/A

ACKNOWLEDGMENT: This clinical practice guideline received the endorsements of the ATS and the CTS.

References

1 Irwin RS, Boulet LP, Cloutier MM, et al. Managing cough as a defense mechanism and as a symptom: a consensus panel report of the American College of Chest Physicians. Chest 1998; 114(suppl):133S–181S
2 Rudolph C, Mazur L, Liptak G, et al. Guidelines for evaluation and treatment of gastroesophageal reflux in infants and children: recommendations of the North American Society for Pediatric Gastroenterology and Nutrition. J Pediatr Gastroenterol Nutr 2001; 32(suppl):S1–S31
3 Pratter MR, Brightling CE, Boulet LP, et al. An empiric integrative approach to the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):222S–231S
4 Chang AB, Glomb WB. Guidelines for evaluating cough in pediatrics: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):260S–283S
5 McCrory DC, Zelman Lewis S. Methodology and grading of the evidence for the diagnosis and management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):28S–32S
6 Canning BJ. Anatomy and neurophysiology of the cough reflex: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):33S–47S
7 McCool FD. Global physiology and pathophysiology of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):48S–53S
8 Irwin RS. Complications of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):54S–58S
9 Pratter MR. Overview of common causes of chronic cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):59S–62S
10 Pratter MR. Chronic upper airway cough syndrome secondary to rhinosinus diseases (previously referred to as postnasal drip syndrome): ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):63S–71S
11 Pratter MR. Cough and the common cold: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl): 72S–74S
12 Dicpinigaitis PV. Chronic cough due to asthma: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):75S–79S
13 Irwin RS. Chronic cough due to gastroesophageal reflux disease: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):80S–94S
14 Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):95S–103S
15 Braman SS. Chronic cough due to chronic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):104S–115S
16 Brightling CE. Chronic cough due to nonasthmatic eosinophilic bronchitis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):116S–121S
17 Rosen MJ. Chronic cough due to bronchiectasis: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):122S–131S
18 Brown KK. Chronic cough due to nonbronchiectatic suppurative airway disease (bronchiolitis): ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):132S–137S
19 Braman SS. Postinfectious cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):138S–146S
20 Kvale PA. Chronic cough due to lung tumors: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):147S–153S
21 Smith Hammond CA, Goldstein LB. Cough and aspiration of food and liquids due to oral-pharyngeal dysphagia: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):154S–168S
22 Dicpinigaitis PV. Angiotensin-converting enzyme inhibitor-induced cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):169S–173S
23 Irwin RS, Glomb WB, Chang AB. Habit cough, tic cough, and psychogenic cough in adult and pediatric populations: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):174S–179S

24 Brown KK. Chronic cough due to chronic interstitial pulmonary diseases: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):180S–185S
25 Tarlo SM. Cough: occupational and environmental considerations: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):186S–196S
26 Rosen MJ. Chronic cough due to tuberculosis and other infections: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):197S–201S
27 Tarlo SM. Peritoneal dialysis and cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl): 202S–203S
28 Rosen MJ. Cough in the immunocompromised host: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):204S–205S
29 Prakash UBS. Uncommon causes of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl): 206S–219S
30 Pratter MR. Unexplained (idiopathic) cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):220S–221S
31 Irwin RS. Assessing cough severity and efficacy of therapy in clinical research: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):232S–237S
32 Bolser DC. Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):238S–249S
33 McCool FD, Rosen MJ. Nonpharmacologic airway clearance therapies: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):250S–259S
34 Dicpinigaitis PV. Potential future therapies for the management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):284S–286S
35 Boulet LP. Future directions in the clinical management of cough: ACCP evidence-based clinical practice guidelines. Chest 2006; 129(suppl):287S–292S

BTS GUIDELINES

Recommendations for the management of cough in adults

A H Morice, L McGarvey, I Pavord, on behalf of the British Thoracic Society Cough Guideline Group

Thorax 2006;**61**(Suppl I):i1–i24. doi: 10.1136/thx.2006.065144

1. INTRODUCTION

1.1 Background

Patients with cough frequently present to clinicians working in both primary and secondary care.[1 2] Acute cough, which often follows an upper respiratory tract infection, may be initially disruptive but is usually self limiting and rarely needs significant medical intervention. Chronic cough is often the key symptom of many important chronic respiratory diseases but may be the sole presenting feature of a number of extrapulmonary conditions, in particular upper airway and gastrointestinal disease. Even with a clear diagnosis, cough can be difficult to control and, for the patient, can be associated with impaired quality of life.[3 4] Sessions dedicated to cough at respiratory meetings are popular, suggesting that the pathophysiology, evaluation, and successful treatment of cough remain topics of keen interest to many medical practitioners.

1.2 Need and purpose of BTS recommendations on the management of cough

The American College of Chest Physicians (ACCP) and the European Respiratory Society (ERS)[5 6] have each endorsed their own set of guidelines on the management of cough; however, criticism[7] of their content and breadth suggest the need for further concise recommendations. The British Thoracic Society guidelines cover not only chronic cough but also acute cough and the organisational issues of cough clinics. International differences in delivery of respiratory health care and management strategies support the notion that such guidelines would be desirable. The British Thoracic Society Standards of Care Committee agreed to the development of a Working Group tasked with the job of producing a set of guidelines for the management of cough with the following key objectives:

- To produce guidelines that are relevant to the clinical management of cough in both primary and secondary care.
- To produce a critical review of the available literature.
- To highlight cough as a clinical and research area of considerable importance.
- To encourage extended cooperation between clinicians, scientists, and the pharmaceutical industry with the core aim of developing effective cough therapies.

1.3 Structure of the guidelines

The guidelines are prefaced with the key points and recommendations summarised as a table of abstracted bullet points. The subsequent section begins with concise definitions for the key terms: *cough*, *acute cough* and *chronic cough*. Individual sections detailing guidelines for the management of acute and chronic cough with additional recommendations for specialist cough clinics follow. Each of these sections includes separate recommendations for management of cough in adults. The final section contains appendices which include a recommended cough management algorithm for adults (available online only at http://www.thoraxjnl.com/supplemental), together with a patient information sheet designed for primary care.

1.4 Methodology for generation of the guidelines

The members of the guideline group initially met to discuss content, format and purpose of the document and to consider the most appropriate methodology for the critical review of available literature and the generation of recommendations. Consensus was obtained on these points and members of the Guideline Group were allocated to one of three subgroups concerned with acute cough, chronic cough, or specialist cough clinics. These three clinical areas were further divided into sections and individuals were identified to conduct an independent literature search for each of these and to produce a discussion document based on their literature appraisal. The search engines recommended were Medline (1966 onwards), EMBASE, and the Cochrane Library database. These were applied to locate all English language studies relevant to the aetiology, diagnosis, severity staging, investigation, prognosis, complications, or treatment of chronic cough in adults over 16 years.

At a subsequent meeting of the Guideline Group these documents were presented, discussed, and recommendations agreed upon. The existing lack of evidence made the formulation of evidence based guidelines difficult. A striking example of this is that a search of the Cochrane Library database to 2005 for systematic reviews of treatment of cough in adults generated one article. Consequently, recommendations have been made based on the available reliability of evidence and, where indicated, on the clinical experience of the members of the Guideline Group.

Because of the generally poor level of evidence and the consequent arbitrary nature of the recommendations, a grading system was thought to be inappropriate.

Once the individual sections were complete, an initial document was drafted which was then circulated to the BTS Standards of Care Committee.

See end of article for authors' affiliations

Correspondence to: Professor A H Morice, University of Hull, Castle Hill Hospital, Cottingham, East Yorkshire HU16 5JQ, UK; a.h.morice@hull.ac.uk

Summary of key points and recommendations

Introduction

Key points

- Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound.
- Cough frequently presents as a troublesome symptom to clinicians working in both primary and secondary care.

Acute cough

Key points

- Acute cough is defined as one lasting less than 3 weeks.
- Acute cough is the commonest new presentation in primary care and is most commonly associated with viral upper respiratory tract infection.
- In the absence of significant co morbidity, an acute cough is normally benign and self limiting.
- It is the commonest symptom associated with acute exacerbations and hospitalisations with asthma and COPD.
- The cost of acute cough to the UK economy is estimated to be at least £979 million. This comprises £875 million to loss of productivity and £104 million cost to the healthcare system and the purchase of non prescription medicines.

Recommendations

- Indications for further investigation include haemoptysis, prominent systemic illness, suspicion of inhaled foreign body, suspicion of lung cancer.
- Patients report benefit from various over the counter preparations; there is little evidence of a specific pharmacological effect.

Chronic cough

Key points

- Chronic cough is defined as one lasting more than 8 weeks.
- It is reported by 10 20% of adults, commoner in females and obese.
- Cough accounts for 10% of respiratory referrals to secondary care.
- Most patients present with a dry or minimally productive cough.
- Decrement in quality of life is comparable with severe COPD.
- The presence of significant sputum production usually indicates primary lung pathology.
- In chronic cough a heightened cough reflex is the primary abnormality.

Clinical evaluation of chronic cough

Recommendations

- A detailed history including a thorough occupational history should be performed in all patients.
- Physical examination should concentrate on the afferent sites identified as most commonly associated with cough.
- The evaluation of patients with chronic cough should include an assessment of health status and cough severity. Cough visual analogue scores are an alternative to cough specific quality of life questionnaires but are less well validated. (Audit)
- Chest radiograph and spirometry are mandatory. (Audit)
- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometry.
- Bronchoscopy should be undertaken in all patients with chronic cough in whom inhalation of a foreign body is suspected.
- High resolution computed tomography may be of use in patients with chronic cough in whom other more targeted investigations are normal.
- Optimal management should comprise a combination of diagnostic testing and treatment trials based on the most probable aggravant(s).
- Treatment effects should be formally quantified. (Audit)

A recommended diagnostic algorithm for the evaluation of an adult with chronic cough is displayed in Appendix 2 (Parts 1 and 2) available online at http://www.thoraxjnl.com/supplemental.

Management of specific aggravants

Key point

- Most cases of troublesome cough reflect the presence of an aggravant (asthma, drugs, environmental, gastro oesophageal reflux, upper airway pathology) in a susceptible individual.

Asthma/eosinophic bronchitis

Key points

- Cough may be the only manifestation of these syndromes.
- No currently available tests of airway function can reliably exclude a corticosteroid responsive cough.

Recommendation

- Cough is unlikely to be due to eosinophilic airway inflammation if there is no response to a two week oral steroid trial. (Audit)

Drugs

Recommendation

- No patient with a troublesome cough should continue on ACE inhibitors.

Environment

Key point

- One of the commonest causes of persistent cough is smoking and appears to be dose related.

Recommendation

- Smoking cessation should be encouraged as it is accompanied by significant remission in cough symptoms.

Gastro-oesophageal reflux disease (GORD)

Key points

- Failure to consider GORD as a cause for cough is a common reason for treatment failure.
- Reflux associated cough may occur in the absence of gastrointestinal symptoms.

Recommendations

- Intensive acid suppression with proton pump inhibitors and alginates should be undertaken for a minimum of 3 months. (Audit)
- Antireflux therapy may be effective in treating cough in carefully selected cases.

Upper airway pathology

Key points

- Rhinosinusitis is commonly associated with chronic cough.
- There is an association between upper airway disease and cough but a poor association between the various symptoms and cough.
- There is disparity in the reported efficacy of antihistamines.

Recommendations

- In the presence of prominent upper airway symptoms a trial of topical corticosteroid is recommended.

Undiagnosed or idiopathic cough

Key points

- Chronic cough should only be considered idiopathic following thorough assessment at a specialist cough clinic.
- The clinical history of reflux cough is often present in patients with idiopathic cough.
- A typical lymphocytic airways inflammation is seen in idiopathic cough.

Treatment of cough due to other common respiratory diseases

Key point

- Cough can be a debilitating symptom in many common acute and chronic respiratory diseases.

Recommendation

- Suppression may be relatively contraindicated especially when cough clearance is important.

Specialist cough clinics

Key points

- A systematic approach to diagnosis and treatment remains the most effective way to manage chronic cough.
- Important questions remain as to the complexity and cost effectiveness of existing diagnostic algorithms.

Recommendations

- No single existing diagnostic protocol can be recommended.
- A combination of selected diagnostic testing and empirical trials of treatment is likely to be most cost effective.
- Referral to a specialist cough clinic should be encouraged and a directory of specialist centres should be made available.

Specialist investigations

Key point

- Debate remains as to the interpretation and clinical utility of more complex investigations.

Bronchial provocation testing

Recommendations

- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometry.
- A negative test excludes asthma but does not rule out a steroid responsive cough.

Oesophageal studies

Recommendations

- Empirical treatment should be offered to patients with cough and typical reflux symptoms before oesophageal testing.
- No current test of oesophageal function predicts treatment response.

Upper airway investigations

Recommendations

- Examination of ear, nose and throat should be performed in preference to sinus imaging in patients suspected of having rhinosinusitis, but with persisting cough despite an adequate trial of treatment directed at the upper airway.
- Specialist cough clinics should have access to fibreoptic laryngoscopy, preferably within the clinic setting.

Cough provocation testing

Recommendations

- There is no current evidence to support the routine use of cough challenge testing in the management of chronic cough.
- For research purposes, standardisation of methodology is required and accurate data on the distribution of cough responsiveness within the population are needed.

Measurement and monitoring of cough

Recommendations

- Accurate measurement of cough helps determine cough severity, assess treatment efficacy, and may provide diagnostic information.
- Ambulatory cough recording currently offers most promise in the objective assessment of cough, although further technical refinement is required if it is to be broadly accessible to physicians.

Assessing airway inflammation

Recommendations

- The demonstration of sputum eosinophilia has important treatment implications and should be available in cough clinics.
- Induced sputum should be requested after exclusion of the other common causes.
- There is insufficient evidence to recommend the routine use of exhaled breath measurements in the clinical evaluation of chronic cough.

Potential new treatments for cough

Key point

- There are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio.

Recommendation

- There is a need for multicentre clinical trials on new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indexes.

1.5 Updating of recommendations
It is envisaged that the Executive Committee of the Guideline Group will meet every two years to review any new published evidence obtained from a subsequent structured literature search. An additional purpose of these update meetings will be to formulate key clinical and research priorities.

1.6 Audit
A number of quality indicators were chosen from recommendations made in this document against which the quality of management of cough could be measured. The key indicators were:

- Chest radiography and spirometry are mandatory in the evaluation of chronic cough.
- The severity of the cough should be quantified.
- Treatment effects should be formally quantified.
- Intensive acid suppression with proton pump inhibitors should be undertaken for a minimum of 2 months.
- Decision to continue steroids made on the basis of a 2 week trial of oral corticosteroids.

2. DEFINITIONS
2.1. Cough
Debate exists as to the most appropriate clinical definition of a cough event.[8] For the purposes of this document, the members of the Task Force agreed the following definition: ''*Cough is a forced expulsive manoeuvre, usually against a closed glottis and which is associated with a characteristic sound*.''

2.2 Acute and chronic cough
Recommendations
- Acute cough is defined as one lasting less than 3 weeks.
- Chronic cough is defined as one lasting more than 8 weeks.

Classification of cough based on symptom duration is somewhat arbitrary. A cough lasting less than 3 weeks is termed *acute* and one lasting longer than 8 weeks is defined as *chronic*. Acute cough is usually a result of a viral upper respiratory tract infection as almost all such coughs resolve within this time period.[9] A post infective cough may, however, persist for a considerable period of time. An upper respiratory tract infection (URTI) cough lingering for more than 3 weeks is usually termed ''post viral cough''. The grey area between 3 and 8 weeks of cough is difficult to define aetiologically since all chronic cough will have started as an acute cough, but the clear diagnostic groups of chronic cough are diluted by those patients with post viral cough.

3. ACUTE COUGH
3.1 Epidemiology
Key points
- Acute cough is the commonest new presentation in primary care.
- It is most commonly associated with viral upper respiratory tract infection.
- In the absence of significant co morbidity, it is normally benign and self limiting.
- It is one of the commonest symptoms associated with acute exacerbations and hospitalisations with asthma and chronic obstructive pulmonary disease (COPD).

Acute cough is usually caused by a viral URTI but may arise from other aetiologies such as pneumonia or aspiration of a foreign body. The duration of a single episode of URTI associated cough varies but is rarely more than 2 weeks. A cut off of 2 months for chronic cough has been arbitrarily agreed in both American[10] and European guidelines.[6] The economic impact of acute cough may be usefully thought of in terms of a series of patient thresholds that trigger interventions such as the purchase of a cough medicine or consultation with a general practitioner (GP).

3.1.1 Incidence of URTI
Symptomatic URTI occur at rates of 2–5 per adult person per year, with school children suffering 7–10 episodes per year.[11] If one accepts the lowest rate of URTI of two episodes per person per year, then this translates into a conservative estimate of an incidence of 120 million episodes of URTI per year in the UK (fig 1).

3.1.2 Incidence of acute cough
Only a proportion of cases of URTI are associated with cough as a symptom. In naturally acquired URTI, cough was present in 40–50% of patients.[12 13] This translates into an incidence of approximately 48 million cases of acute cough per year in the UK. The severity and duration of acute cough will vary widely but many will reach a threshold of severity that precipitates self medication.

3.1.3 Incidence of self medication
The sale of non prescription liquid cough medicines grossed £96.5 millions in 2001 in the UK.[14] This sales figure is an underestimate of total sales as it is for sales from pharmacy and grocery outlets only, and does not include sales from outlets such as supermarkets and convenience stores. With cough medicines averaging £3–4 per unit, this represents at least 24 million episodes per year in the UK.

3.1.4 Consultations with a general practitioner
Morbidity statistics from general practice for the period 1991–2 reported that more people consulted for respiratory illnesses (31%) than for any other single disease category.[15] With 20% of patients consulting for URTI, this translates into 12 million consultations per year, with acute cough representing ''the largest single cause of consultation in primary care''.[16]

3.1.5 Hospital admissions
In normal subjects acute cough associated with URTI is not usually a cause of hospital admission. However, in patients with co morbidity such as asthma[11] and COPD,[17] viral URTI is the commonest cause of admission. Cough is a common symptom in this group of patients as well as those admitted

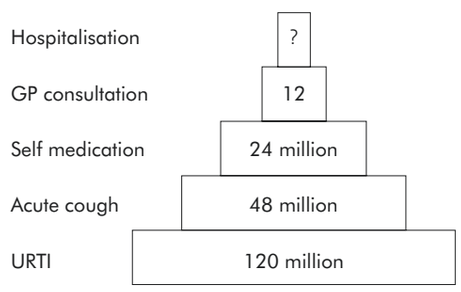


Figure 1 Pyramid of incidence of acute cough. The base represents the population with an upper respiratory tract infection (URTI), some of whom will suffer from acute cough. Level 2 represents all those suffering from acute cough. Level 3 is the proportion of those suffering from acute cough who reach the threshold of severity of cough to trigger the purchase of a cough medicine. Level 4 is the proportion of those suffering from acute cough who reach the threshold of severity of cough to trigger a GP consultation. Level 5 is the proportion of those suffering from acute cough who are admitted to hospital. It is not possible to estimate the number of this latter group (see text).

to hospital for complications associated with infection with influenza or respiratory syncytial virus (RSV).

3.1.6 Sex differences

Between 16 and 64 years of age women are almost twice as likely as men to consult their GP for URTI,[15] and this may relate to a sex difference in the sensitivity of the cough reflex.

3.1.7 Age

The incidence of URTI is much greater in infants and children than in adults. The GP consultation rate for URTI for the age group 0 4 years is about four times greater than the adult rate of consultation.[15]

3.1.8 Seasonality

Acute viral URTIs exhibit seasonality, and this causes seasonality in the incidence of acute cough and sales of cough medicines[18] as well as hospital admissions with co morbidity. Cough is a common symptom associated with influenza and influenza like illness, with 93% of patients suffering from influenza having cough as a symptom.[19] Influenza activity in the population shows a clear seasonality that usually peaks at the turn of the year around week 52.[20] The seasonality of influenza like illness will contribute to seasonality of cough as a common seasonal symptom in the general population.

3.2 Economic impact of acute cough

Key point

- The cost of acute cough to the UK economy is estimated to be at least £979 million. This comprises £875 million in loss of productivity and £104 million cost to the healthcare system and the purchase of non prescription medicines. More accurate estimates specific to the UK are required.

The economic cost of cough is a combination of at least the following six factors:

- ''on the job'' productivity reduction;
- absenteeism from work;
- absenteeism due to care giving for others (mainly children) with URTI;
- physician consultation cost;
- prescription medication cost;
- non prescription medication cost.

The economic burden of acute cough in the UK is not well characterised, so the figures quoted are extrapolations from US data where this subject appears to receive more attention.[21 22] In the US it is estimated that $25 000 million is lost due to the common cold (excluding influenza related URTIs), of which $16 600 million is ''on the job'' productiv ity loss, $8000 million is due to absenteeism, and $230 million is due to caregiver absenteeism.

Assuming that the rate of viral URTI is the same in the UK as the US, adjustment for population differences (UK population estimates (2001) from www.statistics.gov.uk/census2000/profiles/uk.asp), US population estimates (2000) from www.census.gov) suggests a total loss of £3500 million, of which £2300 million is due to on the job productivity loss, £1100 million is due to absenteeism, and £32 million is due to care giving. Using UK figures which suggest up to 25% of URTI sufferers report cough as the main reason they consulted a healthcare professional, this trans lates into a loss of productivity of £875 million due to URTI associated cough.

The cost of medical consultation and non prescription treatment for acute cough is estimated to be at least £104 million.[14]

Table 1 Common serious conditions presenting with isolated cough

- Neoplasm
- Infection, e.g. tuberculosis
- Foreign body inhalation
- Acute allergy anaphylaxis
- Interstitial lung disease

Table 2 Symptoms associated with acute cough prompting a chest radiograph

- Haemoptysis
- Breathlessness
- Fever
- Chest pain
- Weight loss

3.3 Management of acute cough

Recommendation

- Indications for further investigation include haemoptysis, prominent systemic illness, suspicion of inhaled foreign body, suspicion of lung cancer.

3.3.1 General

In the large majority of cases, acute cough is unlikely to need any investigation. General advice may be sufficient and a patient information sheet (see Appendix 1) may be helpful.

3.3.2 Taking a history

At risk groups and danger signs

Although cough is very common and usually self limiting, it is sometimes the first indication of a serious condition (table 1).

For most of these patients cough is not the only symptom and the presence of a number of others should prompt a chest radiograph (see tables 2 and 3). These features as well as a history of foreign body inhalation should always be ruled out by direct questions.

Specialist referral for consideration of bronchoscopy is mandatory when there is a history of significant haemoptysis or possible foreign body inhalation. A change in the voice may indicate vocal cord palsy.

Acute cough with increasing breathlessness while usually due to acute bronchitis should be assessed for asthma or anaphylaxis and treated appropriately.

Acute cough with fever, malaise, purulent sputum, or history of recent infection should be assessed for possible serious acute lung infection.

Table 3 Causes of acute cough with a normal chest radiograph

- Viral respiratory tract infection
  - Respiratory syncytial virus
  - Rhinovirus
  - Influenza
  - Parainfluenza
  - Adenovirus
  - Respiratory corona virus
  - Metapneumovirus
- Bacterial infection (acute bronchitis)
- Inhaled foreign body
- Inhaled toxic fume

3.3.3 Physical examination

At the outset of the common cold there may be clinical evidence of a rhinitis and pharyngitis with inflamed nasal mucosa and posterior pharynx with adherent or draining secretions. Inspection of the ears may reveal serious otitis. A computed tomographic (CT) study of the nasal passages and sinuses in the common cold has shown that widespread rhinosinusitis, which clears on resolution of the infection, is most typical.[23]

The findings on high resolution computed tomography (HRCT) scanning of the lung have been reported in a group of 76 young adults with a common cold.[24] No important pulmonary changes were reported which is consistent with the normal findings usually reported on examination of the lower respiratory tract.

Acute cough is common in any patient presenting with pneumonia. Physical findings on examination of the chest are often very helpful and include dullness on percussion, bronchial breathing, and crackles on auscultation.

3.3.4 Treatment

Recommendations

- Acute viral cough is almost invariably benign and prescribed treatment can be regarded as unnecessary.
- Acute viral cough can be distressing and cause significant morbidity.
- Patients report benefit from various over the counter preparations but there is little evidence of a specific pharmacological effect.
- The simplest and cheapest advice may be to provide a ''home remedy'' such as honey and lemon.
- Central modulation of the cough reflex is common; simple voluntary suppression of cough may be sufficient to reduce cough frequency.[25]
- This may be the mechanism for the effect of simple drinks and linctuses.
- Opiate antitussives have a significant adverse side effect profile and are not recommended.

Because of the variable and episodic nature of acute cough, little firm evidence has been obtained in clinical studies. Cough challenge methodologies have, however, shown suppression of the cough reflex and active agents include:

- dextromethorphan;
- menthol;
- sedative antihistamines;
- codeine or pholcodine.

Dextromethorphan

This non sedating opiate is a component of many over the counter cough remedies and has been shown to suppress acute cough in a single meta analysis.[26] The generally recommended dosage is probably subtherapeutic. There is a dose response, and maximum cough reflex suppression occurs at 60 mg and can be prolonged.[27] Care must be taken in recommending dextromethorphan at higher doses since some combined preparations contain other ingredients such as paracetamol.

Menthol

Menthol by inhalation suppresses the cough reflex[28] and may be prescribed as menthol crystals BPC or in the form of proprietary capsules. Cough suppression is acute and short lived.

Table 4 Over the counter antitussive preparations contining dextromethorphan or menthol

Adult Meltus® Expectorant with Decongestant (guaifenesin, pseudoephedrine, menthol)
Benylin Chesty Coughs® Original (diphenhydramine, menthol)
Benylin Cough and Congestion® (dextromethorphan, diphenhydramine, menthol, pseudoephedrine)
Benylin Dry Cough® (dextromethorphan, diphenhydramine, menthol)
Benylin Non drowsy for Chesty Coughs® (guaifenesin, menthol)
Benylin Non drowsy for Dry Coughs® (dextromethorphan)
Buttercup Syrup Honey and Lemon Flavour® (ipecacuanha, menthol)
Cabdrivers® (dextromethorphan, menthol)
Covonia Bronchial Balsam® (dextromethorphan, menthol)
Covonia Mentholated Cough Mixture® (liquorice, menthol, squill)
Covonia Night Time Formula® (dextromethorphan, diphenhydramine)
Expulin® (chlorphenamine, menthol, pholcodine, pseudoephedrine)
Histalix® (ammonium chloride, diphenhydramine, menthol)
Junior Meltus Dry Cough® (dextromethorphan, pseudoephedrine)
Meltus Dry Cough® (dextromethorphan, pseudoephedrine)
Multi action Actifed Dry Coughs® (dextromethorphan, pseudoephedrine, triprolidine)
Night Nurse® (dextromethorphan, paracetamol, promethazine)
Nirolex for Dry Coughs with Decongestant® (dextromethorphan, pseudoephedrine)
Non Drowsy Sudafed Linctus® (dextromethorphan, pseudoephedrine)
Robitussin Dry Cough® (dextromethorphan)
Robitussin Soft Pastilles For Dry Cough® (dextromethorphan)
Vicks Medinite® (dextromethorphan, doxylamine, ephedrine, paracetamol)
Vicks Vaposyrup for Tickly Coughs® (menthol)
Vicks Vaposyrup Dry Cough® (dextromethorphan)

Sedative antihistamines

First generation antihistamines with sedative properties suppress cough but also cause drowsiness. They may be a suitable treatment for nocturnal cough.

Codeine or pholcodine

These opiate antitussives have no greater efficacy than dextromethorphan but have a much greater adverse side effect profile and are not recommended.

Currently available over the counter cough treatments which contain dextromethorphan and/or menthol are listed in table 4.

4. CHRONIC COUGH

4.1 Epidemiology

In a European survey of young patients, which presumably included both acute and chronic cough, about 20% reported a non productive or productive cough during the winter months.[29] In epidemiological surveys of the general popula tion, persistent cough is reported in 18% of the US population, in up to 16% of a population in south east England, and in 11% of the Swedish population.[30 32] The only study to grade cough severity found 7% of a general population had cough sufficient to interfere with activities of daily living on at least a weekly basis.[33] A higher prevalence of nocturnal and non productive cough was reported in women than in men.[34 35] Most studies show a preponderance of females. This may be related to the increased sensitivity of cough reflex in women.[36 37] Cough is associated with a diagnosis of asthma, tobacco smoking in a dose related fashion, symptoms of reflux, irritable bowel syndrome, and obesity.[33 38] In the survey in south east England, up to 16% of 9077 responders had cough every day on half the days of the year, and up to 13.2% had sputum every day or on half the days of the year; 54% of this cohort were current cigarette smokers.[31]

Exposure to pollutants or environmental irritants is an important aggravating factor. In adults and school children, productive cough or chronic nocturnal dry cough has been

associated with levels of the particulates, PM_{10}.[39 40] Increases in levels of PM_{10} are related to increased reporting of cough, sputum production, and sore throat in children with or without asthma.[41] Living close to heavy traffic may be associated with asthma symptoms and longstanding cough compared with those not living close to heavy traffic.[42] In the Italian Po Valley district, the increase in air pollution has been associated with an increase in cough incidence among females but not males.[43] Nocturnal cough in relation to indoor exposure to cat allergens was observed not only in sensitised but also in non sensitised subjects.[44] There are no epidemiological data on the frequency of gastro oesophageal reflux and rhinosinusitis with postnasal drip associated with chronic cough.

4.2 Impact of cough on health status

Recommendations

- Chronic cough has wide ranging and potentially profound effects of cough on health status.
- The evaluation of a patient with chronic cough should include an assessment of health status in clinical practice and research.
- The Leicester Cough Questionnaire is a well validated cough specific quality of life questionnaire that can be used to assess longitudinal changes in patients with chronic cough.
- Cough visual analogue scores are an alternative to cough specific quality of life questionnaires but are less well validated.

4.2.1 Background

In acute cough, adverse effects on health status result from physical symptoms and are transient. In contrast, chronic cough is often perceived as a trivial problem but can be a disabling symptom associated with significantly impaired quality of life.[3 4] The impact on health status is varied, being minimal in some patients who do not seek medical attention to disabling in others, associated with impairment of quality of life comparable to other chronic respiratory disorders such as chronic obstructive pulmonary disease.[45] Physical, psychological, and social domains of health are commonly affected.[3] Patients with chronic cough frequently report musculoskeletal chest pains, sleep disturbance, and hoarse voice. More marked symptoms such as blackouts, stress incontinence, and vomiting can occur. The psychological impact of cough includes a high prevalence of depressive symptoms and worry about serious underlying diseases such as cancer and tuberculosis.[46] The impact of cough on social well being depends on individual circumstances and may result in difficulty in relationships, avoidance of public places, and disruption of employment.

Two recently developed self completed cough specific quality of life questionnaires for acute and chronic cough can be used to facilitate communication with patients and establish information on the range of problems affecting them.[3 4] Both are well validated, repeatable, and have good responsiveness. The Leicester Cough Questionnaire (LCQ) is brief, easy to administer, and comprises 19 items divided into three domains: physical, psychological and social.[3] The standard deviation of the 2 week repeatability within subject difference for the LCQ is 0.9 and a change of twice this is considered significant for an individual[3](available at http://thorax.bmjjournals.com/cgi/content/full/58/4/339 please seek permission from authors for use). The Cough Specific Quality of Life Questionnaire (CQLQ) is a 28 item questionnaire that has been developed and tested in North America.[4] The items are divided into six domains: physical complaints, extreme physical complaints, psychosocial issues, emotional well being, personal safety fears, and functional abilities. Studies to determine the minimal important clinical difference for both questionnaires are underway. Preliminary data suggest a good relationship between cough health status scores and cough visual analogue severity scores, but the relationship with cough diary scores has not been studied.[3]

Table 5 Causes of chronic cough in patients with a normal chest radiograph

- Reflux disease
  - Gastro oesophageal reflux
  - Laryngopharyngeal reflux
  - Oesophageal dysmotility
- Asthma syndromes
  - Cough variant asthma
  - Eosinophilic bronchitis
- Rhinitis

Published evidence

Preliminary data from studies using cough specific quality of life questionnaires afford an insight into the effects of cough on health status. Quality of life is significantly impaired in acute cough; this impairment affects men and women equally.[47] In patients with chronic cough, quality of life is impaired and is worse in women than in men.[48] The psychological aspects of health status are particularly affected in patients with chronic cough.[48 49] There is good evidence that health status improves significantly after specific treatment for the cough.[3 4]

4.3 Evaluation and management of chronic cough

4.3.1 Taking a history

There is little evidence in the existing literature to determine the best questions to ask when taking a history from a patient with chronic cough. The same is true for clinical examination. Much of what is currently done derives from consensus as a result of individual physicians' experience. The aim is to exclude structural disease as a cause for cough. Non specific associations also occur as a result of an abnormal cough reflex, itself associated with a number of factors. A detailed history will often suggest a likely association or trigger for chronic cough and should include a number of key components (table 5).

(a) Age and sex

- Chronic cough is more likely to occur in middle aged women.

Published evidence

Observational studies have shown a significant female preponderance.[50] The cough reflex is more sensitive in women with cough.[37]

(b) Smoking

- One of the commonest causes of persistent cough is smoking, which appears to be dose related. Patients often state that their cough changes in character with smoking cessation.

Published evidence

The prevalence of chronic cough is increased in smokers.[29] In a case control study of almost 2000 subjects, Jansen *et al* reported an increased prevalence of chronic cough among smokers.[51] Smoking cessation leads to a short term increase in cough reflex sensitivity.[52]

(c) Characteristics of the cough

- Interpretation of the diagnostic characteristics of the cough should be done with caution.

Published evidence

One study has suggested that the character and timing of a cough are not diagnostically helpful.[53] However, others have suggested a characteristic pattern in reflux cough.[54]

Important areas of inquiry may establish that the cough is associated with frequent throat clearing or the sensation of post nasal drip, occurs mainly at night or after meals, or is made worse with exercise or cold air. However, the symptoms of post nasal drip in a patient may reflect only coexistent rhinitis and the absence of dyspepsia does not rule out reflux as the cause of cough. In one study the predictive values for cough characteristics and associated symptoms were calcu lated.[55]

A cough with a ''honking'' or ''barking'' quality and which disappears with sleep has been suggested as typical of a psychogenic or habit cough. Such characteristics have been frequently reported in the paediatric literature and may represent a tic cough.[56]

Consensus would suggest the following areas should be covered in the history in relation to the cough. It may be easier to ask the patients to complete a history questionnaire around which to structure the consultation (see Appendix 3 for suggested questionnaire framework).

(i) Onset

- Did coughing begin gradually or suddenly?

Published evidence

Cough of sudden onset may be clinically associated with foreign body aspiration.

(ii) Duration

- When did the cough start? How long have you had your cough?

Published evidence

There is no evidence linking the duration of cough to a particular association.

(iii) Relation to infection

- Did coughing begin after an initial upper respiratory tract infection for example, a cold or sore throat?

Published evidence

Although patients commonly describe their persistent cough as starting after an infection, there are no data specifically linking ongoing viral infection to persistent cough. Viral infection enhances the cough reflex sensitivity[57] and may make subclinical bronchial hyperresponsiveness or reflux clinically apparent.

(iv) Sputum

- Is the cough dry/productive?
- Significant sputum production suggests primary pulmon ary pathology

Published evidence

Numerous studies link chronic cough and sputum produc tion. In a cross sectional study in 18 000 Italian adults there was a 11.9% prevalence of cough and phlegm for a minimum of 3 months per year.[58] Primary pulmonary disease is more likely in patients attending a specialist cough clinic with a productive cough.

(v) Diurnal variation in cough

- Patients cough less at night.
- A cough which abates overnight may be due to reflux (closure of the lower oesophageal sphincter).
- Asthma, infection, or heart failure can cause coughing which wakes patients.

Published evidence

Sleep is known to suppress the cough reflex. In a series of patients with lung disease and nocturnal cough, spontaneous cough was almost abolished during sleep stages 3 and 4.[59]

In an observational study in coughers, asthmatics and non coughers, ambulatory recordings have shown a marked reduction in cough overnight.[60]

(vi) Severe coughing spasms/paroxysms

- Severe coughing paroxysms may be associated with syncope.
- The Driver and Vehicle Licensing Agency (DVLA) stipu lates that those at risk of syncope should not be driving.

Published evidence

www.dvla.gov.uk

(vii) Incontinence

- Women with cough are often troubled by stress incon tinence and this may be one of their major concerns.

Published evidence

In a questionnaire survey 55% of women reported urinary incontinence in association with chronic cough.[54]

(viii) Origin of sensation

- It is unlikely to be of diagnostic value to enquire where the sensation that leads to cough arises.
- Whatever the aetiology, the irritation leading to cough is usually localised to the throat or upper chest.

Published evidence

The site where cough sensations arise in the thorax tends to be poorly localised. One case study reported cough and tickly throat occurring during ventricular pacing.[61 62] These C fibre sensations can be reproduced by systemic injections in both the throat and chest.

(ix) Cough triggers and aggravants

- Persistent cough may be perpetuated because the cough reflex is abnormally sensitive.
- A sensitised cough reflex is suggested if there is triggering of cough with change in air temperature, scent, sprays, aerosols, exercise.

Published evidence

Cough reflex sensitivity may vary from time to time, particularly when intercurrent respiratory infection occurs.[57] Other known cough aggravants have been shown to alter the sensitivity of the cough reflex for example, angiotensin converting enzyme (ACE) inhibitors[63] and diseases includ ing asthma and gastro oesophageal reflux disease (GORD).[55] The effect of air temperature, scent, sprays, aerosols, and exercise has not been studied.

(x) Posture

- Reflux is known to be related to posture, e.g. bending or lying down. However, there is no evidence demonstrating a connection between posture and reflux related cough.

Published evidence
See Bonnet *et al*.[64]

(xi) Food

- Cough on eating and postprandially may indicate reflux cough.

Published evidence
Maximum stimulation for transient opening of the lower oesophageal sphincter is gastric distention which typically occurs 10 minutes postprandially.[65] In a retrospective review of patients with proven reflux cough, three quarters had cough with food or postprandial cough.[66]

(xii) Cough on phonation

- Cough on phonation such as talking on the telephone, laughing, or singing may indicate reflux because of lack of diaphragmatic closure of the lower oesophageal sphincter (LOS).

Published evidence
A retrospective review again showed that 90% of patients with reflux cough associated the symptom with phonation.[66]

(d) Medications

- Note all medications, particularly ACE inhibitors, and consider which might be causing or potentiating the cough. The cough may take some months to settle following withdrawal of ACE inhibitors.

Published evidence
Cough associated with ACE inhibitors was first reported with captopril in 1985.[67] It is a class effect, but the reported incidence variable may be as high as 16%. It is not dose related and time to onset is variable, occurring within hours or more than a year after start of treatment.[68] Studies identifying predisposing factors for the development of cough associated with ACE inhibitors have been largely inconclusive. A recent large retrospective cohort study has identified smoking, East Asian ethnicity, and previous ACE inhibitor associated cough as risk factors.[69] ACE inhibitors are associated with an increased sensitivity of the cough reflex, so they may aggravate cough due to other causes.[63] The cough invariably resolves on cessation of the drug. The median time to resolution is 26 days although it may be longer (up to 40 weeks) in some patients.[68 70] Most patients with ACE inhibitor associated cough can tolerate angiotensin II receptor blockers.[71]

There are only occasional reports of cough as a troublesome side effect of other drug treatments. One case report has attributed chronic cough to antiretroviral therapy in an HIV positive woman.[72] Dry cough has also been reported as a rare complication of interferon alpha treatment in chronic viral gastroenteritis.[73]

(e) Occupation/hobbies/pets

- A thorough occupational history should be sought as work place sensitisers can lead to chronic cough. The same is true of dust/chemical exposure at home.

Published evidence
Numerous studies and case reports provide accounts of persistent cough as a presenting feature of occupational sensitisation of the airways.[74] Significant excess cough was reported in workers exposed to hot acidic conditions in a bottle factory[75] and in workers exposed to hot chilli peppers.[76]

(f) Past medical history and the association of cough with underlying disease

(i) Respiratory disease

- Chronic cough is a common association of respiratory diseases and a thorough respiratory history should be sought.

Persistent cough is commonly associated with asthma including eosinophilic bronchitis and upper airway disease. These will be detailed in subsequent sections of this document. Common respiratory diseases which are readily appreciated as being associated with chronic cough will be addressed below.

(ii) COPD
Although patients with COPD commonly report cough, it is usually in association with production of phlegm and breathlessness.

Published evidence
Smokers with persistent cough may be at risk of developing COPD (GOLD).[77] A productive cough in patients with established airflow obstruction is predictive of lung function decline.

(iii) Bronchiectasis
Although usually associated with sputum production, ''dry'' bronchiectasis can cause persistent cough and a history of past respiratory insult as a potential trigger should be sought.

Published evidence
Patients with productive cough may have the same range of aetiologies as those with dry cough. The prevalence of bronchiectasis among patients attending specialist cough clinics is low, estimated at 4%.[78]

(iv) Lung cancer
Cough may arise as a consequence of the cancer itself, the treatment, or other co existent disease.

Published evidence
Cough is the fourth commonest presenting feature of lung cancer.[79] Persistent cough contributes significantly to impaired quality of life. In one study, 39% of patients with inoperable non small cell lung cancer scored cough prominently.[80]

(v) Pertussis infection

- Persistent pertussis infection can lead to chronic cough.

Published evidence
An increasing body of circumstantial evidence implicates pertussis as a cause of persistent cough. In a series of 180 prospective cases of chronic cough, 10% had nasal swabs positive for *Bordetella*.[81] In a case control study of 201 patients with cough lasting up to 3 months, a significant increase in positive serology was reported for *Bordetella* in the patient group.[82]

(vi) Atopic disease

- There is an increase in respiratory symptoms in atopic individuals.

Published evidence
In a longitudinal comparative study in 620 adults, atopy was associated with bronchial hyperresponsiveness in sympto matic patients.[83] In Japan a separate syndrome of atopic cough is described,[84] although whether this is indeed a separate syndrome has been called into doubt.[85]

(vii) Cardiovascular disease

- Patients with heart disease can develop chronic cough and are at risk of myocardial infarction.

Published evidence
Analysis of the Framingham Heart Study data identified both chronic non productive cough and productive cough as independent risk factors for myocardial infarction.[86]

(viii) Organ-specific autoimmune disease

- An association between chronic cough and organ specific autoimmunity has been reported.

Published evidence
An association between organ specific autoimmune dis ease in particular thyroid disease has been reported.[87] In a case control study, there was more autoimmune disease and a higher proportion of organ specific autoantibodies in patients with cough than in age and sex matched controls.[87]

(f) Family history

- Chronic cough may be familial, suggesting either an inherited anatomical abnormality or neurological condi tion.

Published evidence
A kinship of autonomic sensory neuropathy prevalence with reflux cough (possibly vagal) followed by peripheral sensory neuropathy was recently described.[88]

4.3.2 Physical examination

Recommendation

- Physical examination should concentrate on the afferent sites of the vagus nerve most commonly associated with the irritation leading to chronic cough.

The physical examination of the patient with chronic cough may demonstrate clinical signs of obstructive lung disease, lung cancer, bronchiectasis, pulmonary fibrosis, or cardiac failure. However, more often the examination reveals less specific findings.

Physical examination should concentrate on the afferent sites identified as most commonly associated with chronic cough.

An ear, nose and throat (ENT) examination may reveal evidence of nasal obstruction due to inflamed turbinates or the presence of polyps. The appearance of secretions draining in the posterior pharynx may be apparent. A ''cobblestone'' appearance of the oropharyngeal mucosa has been suggested but is an uncommon finding in the routine examination of patients with chronic cough.[89] Tonsillar enlargement is seen in some patients with chronic cough. Tonsillectomy can improve cough reflex sensitivity.[90]

Evidence of irritation of the larynx and pharynx on indirect laryngoscopy could suggest proximal gastro oesophageal reflux.[91]

Examination of the chest is not useful in differentiating reversible airflow obstruction from fixed or partially rever sible airflow limitation. Likewise, there are no features which easily distinguish cough variant asthma. Asking the patient to inhale may trigger paroxysms of coughing. Chest auscultation may reveal wheezes and a prolonged expiratory phase on auscultation. Coarse crackles may be a prominent finding on examination of a patient with bronchiectasis, while widespread fine late inspiratory crackles are typical of diffuse parenchymal lung disease.

The presence of finger clubbing in a smoker together with evidence of a pleural effusion or lobar collapse on examina tion almost certainly points to a diagnosis of bronchogenic carcinoma.

In patients with a family history of chronic cough, neurological examination of the legs should be performed to look for signs of familial neuropathy.[88]

4.3.3 Baseline investigations: primary care

Cough is one of the most common symptoms of patients presenting to primary care, yet there are few studies investigating its management. One descriptive study found that 46% of patients presenting with a cough of more than 2 weeks' duration (28% of whom had a cough of more than 3 months' duration) had a diagnosis of asthma or chronic obstructive pulmonary disease.[92] This contrasts markedly with studies in secondary care and specialist cough clinics in which gastro oesophageal reflux, cough predominant asthma, and rhinitis are the main causes. A number of reviews outlining the diagnosis and management of chronic cough in primary care have been published.[93–95] However, the evidence for these is predominately based on descriptive cohort studies and case studies/clinical experience from specialist centres.

(a) Chest radiography

Recommendations

- A chest radiograph should be undertaken in all patients with chronic cough and those with acute cough demon strating atypical symptoms (see table 2).

Published evidence
There are numerous causes of chronic cough, many of which can be diagnosed from abnormalities on the chest radio graph. A study from a general respiratory clinic found that 31% of chest radiographs requested for the diagnosis of persistent cough were abnormal or yielded a diagnosis.[2] Studies using algorithms for the diagnosis of chronic cough have been validated in patients with normal chest radio graphs.[55 78 96 100] If the patient has an abnormality on the chest radiograph that would account for his/her symptoms, this should be investigated appropriately and use of a diagnostic algorithm for chronic cough is not appropriate.

(b) Assessment of pulmonary function

Recommendation

- Spirometry should be performed in all patients with chronic cough.
- Patients with normal spirometry and bronchodilator response in whom the diagnoses of cough predominant asthma or eosinophilic bronchitis are being considered should be offered a therapeutic trial of prednisolone.

Published evidence
Spirometry is helpful in identifying cough caused by chronic airways obstruction.[101] If an obstructive pattern is identified on spirometry, forced expiratory volume in 1 second (FEV_1) should be measured before and after inhalation of a short acting β_2 agonist (for example, salbutamol 400 μg by metered dose inhaler and spacer or 2.5 mg by nebuliser).[102] Normal

spirometry does not exclude asthma as a cause of chronic cough. In addition, many patients with asthma may not have spirometric reversibility sufficient to be defined as having asthma for the purpose of clinical studies.[103]

Single peak expiratory flow (PEF) measurements and, in particular, PEF to assess bronchodilator response are not as accurate as FEV_1 in diagnosing airflow obstruction as a cause of cough in primary care and should be avoided.[104] The role of serial PEF has not been studied in patients with persistent cough. Patients with ''cough variant'' or ''cough predominant'' asthma may not exhibit airways obstruction.[99 105] In addition, patients with cough due to eosinophilic bronchitis exhibit neither bronchial obstruction nor bronchial hyperresponsiveness.[106] Patients in whom the diagnosis is in doubt should be referred to a specialist centre.[107]

4.3.4 Baseline investigations: secondary care

Studies from general respiratory clinics have reported poor diagnostic and treatment outcomes compared with specialist cough clinics that use comprehensive management algorithms.[2 108 110] Extrapulmonary causes, particularly gastro oesophageal reflux, are frequently overlooked. The investigation of these conditions is dealt with under the specialist clinic section.

(a) Bronchoscopy

Recommendation

- Bronchoscopy should be undertaken in all patients in whom inhalation of a foreign body is suspected.
- Bronchoscopy may be useful in patients in whom other more targeted investigations are normal.

Published evidence

Bronchoscopy should be undertaken as an initial investigation in all patients suspected of having cough as a result of inhalation of a foreign body or aspiration. A retrospective study of 15 420 patients undergoing bronchoscopy without a history of inhalation of a foreign body, 91% of whom had a persistent cough and 63% of whom had normal chest radiographs, found that a foreign body was identified in only 0.3%.[111]

Descriptive studies have shown its diagnostic yield as part of a diagnostic algorithm for chronic cough is low (1 6%),[78 98 100 112] although in carefully selected cases the yield may be higher.[113 114] In addition, bronchoscopy allows inspection of the larynx for signs of chronic inflammation that may be a result of gastro oesophageal reflux.[91 115]

(b) High resolution computed tomographic (HRCT) scanning of the thorax

Recommendation

- High resolution computed tomographic (HRCT) scanning may be of use in patients with persistent atypical cough in whom other more targeted investigations are normal.

Published evidence

The role of HRCT scanning of the thorax in the diagnosis of cough has not been properly evaluated. In a prospective study of patients with chronic cough and normal radiographs who had undergone a complex diagnostic protocol, HRCT scanning was claimed to be diagnostic in 24% of patients; however, multiple diagnoses were frequently reported in this study.[100] In carefully selected patients the diagnostic rate may be higher.[116 117] HRCT scanning is more sensitive and specific than plain chest radiography in diagnosing bronchiectasis and diffuse pulmonary diseases that may present with chronic cough. Studies have shown abnormalities on HRCT scans in up to 42% of patients thought to have had a normal chest radiograph.[118 120]

4.4 Diganosis and management of specific cough syndromes

4.4.1 Cough variant asthma and eosinophilic bronchitis

(a) Definition

An isolated cough in a patient without objective evidence of asthma that is, variable airflow obstruction and evidence of eosinophilic inflammation. In cough variant asthma bronchial hyperresponsiveness is present, whereas in eosinophilic bronchitis it is absent.

These syndromes are a common cause of isolated cough, accounting for around 30% of cough referrals to cough clinics.[50 121] Clinical indicators of cough variant asthma include cough occurring nocturnally, after exercise, or after allergen exposure, although how reliable these features are is unclear. Some studies have highlighted overdiagnosis of cough variant asthma in children.[122]

(b) Diagnosis of cough variant asthma

Recommendations

Current methodology for measurement of airway hyperresponsiveness is well standardised and widely accepted. A negative test excludes asthma but does not rule out a steroid responsive cough.

Published evidence

This requires the demonstration of variable airflow obstruction and/or airway hyperresponsiveness. In patients with normal or near normal spirometric values (that is, FEV_1 >70% predicted), tests of airway responsiveness are more sensitive and specific than bronchodilator reversibility studies and PEF records.[107 123]

(c) Asthma syndromes and cough

Key points

- The presence of non asthmatic corticosteroid responsive cough syndromes emphasises the importance of assessment of airway inflammation or, if this is not available, a trial of corticosteroids in all patients with chronic cough, irrespective of the results of tests of variable airflow obstruction and airway hyperresponsiveness.
- The test box provides clear guidance on interpretation of the results of treatment trials.
- The type of corticosteroid used in a trial and the duration of treatment is unclear; expert opinion is that cough is unlikely to be due to eosinophilic airway inflammation if there is no response to treatment with prednisolone 30 mg/day for 2 weeks.
- In patients with apparently corticosteroid resistant cough variant asthma, an alternative diagnosis should be considered.

Published evidence

Eosinophilic bronchitis is a common cause of cough.[124] It presents as an isolated chronic cough and is characterised by eosinophilic airway inflammation associated with increased Th2 cytokine expression[125] in the absence of airway hyperresponsiveness or variable airflow obstruction. It is unclear whether eosinophilic bronchitis represents a distinct clinical entity. Some patients with cough and asthma have non eosinophilic airway inflammation.[126] This pattern of airway inflammation has been associated with corticosteroid

resistance;[126 127] theoretically it might be associated with a bronchodilator responsive but corticosteroid resistant cough. The prevalence of non eosinophilic asthma in patients presenting with cough variant asthma is unclear.

(d) Management

Recommendation

- Management of cough variant asthma should follow national guidelines, except at step 3 where there is no evidence for use of a long acting β agonist.
- At step 3, evidence exists for the use of leukotriene receptor antagonists. Eosinophilic bronchitis and atopic cough respond to inhaled corticosteroids.
- There is insufficient evidence to give guidance on dose, preparation, and duration of inhaled corticosteroid ther apy but use of the BTS asthma guidelines is recommended.
- There is some evidence to support the role of antihista mines and anti leukotrienes in cough due to asthma and its variants, but larger scale studies are required.

Published evidence

Cough variant asthma responds to treatment with cortico steroids.[128] Leukotriene receptor antagonists have also been reported to be effective in reducing cough in this condition.[129] High dose antihistamines have been shown to dramatically reduce cough in seasonal asthma[130] but have not been specifically investigated in cough variant asthma. Eosinophilic bronchitis is characteristically resistant to treatment with inhaled bronchodilators but responds to inhaled steroids.[131]

Longitudinal studies have shown that up to one third of patients who present with cough variant asthma later develop the typical wheezing of classical asthma.[84 132 133] In contrast, the development of wheezing or airway hyper responsiveness is extremely uncommon in eosinophilic bronchitis.[134]

4.4.2 Gastro oesophageal reflux disease (GORD)

(a) Background

Chronic cough due to gastro oesophageal disorders has been reported in prospective studies in 5 41% of cases.[97 100 110] Confusion between different diagnostic criteria, symptoms of dyspepsia, extra oesophageal reflux, and pH monitoring make quantification of cough due to GORD difficult.

Patients with GORD have an increased cough reflex sensitivity which improves with antireflux therapy.[135 137] GORD related cough may be induced by microaspiration of gastric content into the larynx and tracheobronchial tree.[138 140] A second proposed mechanism is through a vagally mediated oesophageal reflex stimulated by acid or non acid volume reflux.[141 143] Oesophageal motor dysfunction[144 148] and reduced oesophageal clearance[149] but not delayed gastric emptying[150] can contribute to both of these mechanisms. The presence of a self perpetuating cough reflux cycle has also been suggested.[143 151]

(b) Does antireflux therapy improve cough associated with GORD?

Recommendations

- Proton pump inhibitors (PPIs) such as omeprazole 20 40 mg twice daily or equivalent taken before meals for at least 8 weeks.
- Prokinetic agents such as metoclopramide 10 mg three times daily may be required in a proportion of patients.
- Elimination of medications that potentially can worsen GORD should be considered.

Published evidence

A number of uncontrolled studies have reported that antireflux therapy produces an improvement in chronic reflux cough in 75 100% of cases.[98 99 135] In contrast, randomised controlled trials suggest that proton pump inhibitors (PPIs) twice daily improve cough in 36 57% of patients with gastro oesophageal reflux related cough when given for 8 weeks.[152 153] Ranitidine 300 mg daily for 2 weeks improved cough in 54% of patients.[154] However, PPIs may be superior to H_2 antagonists.[99 155] Twice daily dosing and dosing before meals may be more appropriate.[156 157] Full acid suppression may only be achieved by a combination of twice daily PPIs and nocturnal H_2 antagonists.[158] A trial of treatment should be at least 8 weeks.[96 98 152 153 159] Prokinetic agents may be helpful in a proportion of patients.[78 96 98 160] Elimination of medications potentially worsening reflux (bisphosphonates, nitrates, calcium channel blockers, theo phylline, progesterones) may also help.[160]

The GABA agonist baclofen increases lower oesophageal tone and decreases lower oesophageal opening and, in an open study, decreased the incidence of GORD related cough resistant to other treatment.[161] A non specific effect on the cough reflex has also been demonstrated.[162]

(c) What is the role of antireflux surgery?

Recommendation

- Antireflux surgery may be effective in treating cough in carefully selected cases.

Published evidence

Some patients with GORD related cough may benefit from surgical intervention such as fundoplication.[160 163 164] However, the timing and indications for surgery remain undefined. Prior to surgery a careful evaluation should be undertaken including exclusion of other causes of cough, oesophageal ambulatory 24 hour pH measurement (measur ing acid and alkaline reflux and the temporal association between cough and reflux events), oesophageal manometry, barium meal, gastric emptying studies, Bernstein acid infusion tests, trial of PPI treatment, and elimination of medications potentially worsening reflux.[160 164 165] Abnormal oesophageal motility may be associated with a less satisfac tory outcome following surgery.[145]

4.4.3 Upper airway disease and cough

(a) Definition

Upper airway disease causes a cough commonly accompanied by nasal stuffiness, sinusitis, and the sensation of secretions draining into the posterior pharynx from the nose or sinuses, sometimes termed post nasal drip.

Key points

- There is an association between upper airway disease and cough but a poor association between the various symptoms and cough.
- There is disparity in the reported efficacy of antihista mines.
- In the presence of prominent upper airway symptoms, a 1 month trial of topical corticosteroid is recommended.

Published evidence

Post nasal drip syndrome (PNDS) has been reported in the American literature as the most common cause of chronic

cough,[97 99] although this is not a universal finding.[110] A broad range of diseases of the upper airway are associated with post nasal drip and cough. In contrast, many patients with observable post nasal secretion do not cough. Whether PNDS is a distinct syndrome or merely a symptom has been debated.[166]

Symptoms[89] and clinical findings[99] are not reliable discriminators in establishing post nasal drip upper airways disease as a cause of cough. A successful response to treatment directed at the upper airway is one recommended diagnostic approach.[5]

In the USA, recommended treatment involves a first line approach with a sedating antihistamine/decongestant combination.[5] The first generation antihistamines recommended in this document are not available in the UK and there is conflicting evidence as to the efficacy of second generation (less sedating) antihistamines in the treatment of cough.[167 168] There have been no randomised controlled studies evaluating the role of topical steroids in chronic cough, although one randomised placebo controlled trial has suggested that intranasal steroids given for 2 weeks are effective in the treatment of cough due to allergic rhinitis.[169] Intranasal steroids appear to be ineffective in the treatment of common cold symptoms including cough.[170] A number of prospective studies suggest that topical nasal steroids given for 2–8 weeks to patients with cough and post nasal drip are effective.[55 171]

4.4.4 Undiagnosed or idiopathic chronic cough

Key points

- Chronic cough should only be considered idiopathic following thorough assessment at a specialist cough clinic.
- The clinical history of reflux cough is often present in patients with idiopathic cough.
- A typical lymphocytic airways inflammation is seen in idiopathic cough.

Published evidence

In up to 20% of referrals to cough clinics[55 87 172 173] the cause of cough remains unclear after extensive investigations and treatment trials. It has been suggested that these patients represent a separate subgroup that should be labelled as idiopathic chronic cough. However, the clinical history usually suggests non acid reflux and opinion is divided as to whether, in the absence of a definitive diagnostic or therapeutic intervention, this represents the underlying aetiology. If reflux is the underlying cause, then the airway changes seen in these patients represent the response to the refluxate. The alternative view that there is a separate syndrome is discussed below.

Patients with idiopathic cough are predominantly middle aged women who typically present with a long standing chronic dry cough which starts around the time of the menopause[87 172 174] and often appears to follow a viral respiratory tract infection.[173] Organ specific autoimmune disease is present in up to 30%; autoimmune hypothyroidism is particularly common.[87 172] Patients have objective evidence of abnormal airways with a heightened cough reflex,[175] evidence of lymphocytic airway inflammation,[87 174 176 177] increased numbers of mast cells in bronchoalveolar lavage fluid,[178 179] and increased concentrations of tussive mediators such as histamine, prostaglandin (PG)D_2 and PGE_2 in induced sputum.[180] A plausible explanation for the development of cough is amplification of previously subclinical airway inflammation at the time of the menopause.[174 181 182] In some cases this airway inflammation may be as a result of aberrant homing of inflammatory cells to the lungs from a primary site of autoimmune inflammation.[87 183 185]

When evaluating a patient with idiopathic cough, it is important to recognise common pitfalls in managing chronic cough. Treatment for idiopathic chronic cough is disappointing and is largely limited to non specific antitussive therapy such as dextromethorphan and drugs with weak evidence of benefit such as baclofen and nebulised local anaesthetics (lidocaine, mepivicaine).[186] Low dose morphine has recently been shown to be helpful.[187]

4.4.5 Treatment of cough due to other common respiratory diseases

Cough may be a prominent and debilitating symptom in a number of common respiratory diseases including lower respiratory tract infections (acute tracheobronchitis and pneumonia) COPD, lung cancer, diffuse parenchymal lung disease, and bronchiectasis.

Key points

- Cough can be a debilitating symptom in many common acute and chronic respiratory diseases.
- Suppression may be relatively contraindicated, especially when cough clearance is important.

Published evidence

In some conditions, in particular pneumonia and bronchiectasis, cough clearance is important and its suppression would be undesirable. The treatment of COPD is mainly directed at the control of symptoms and reduction of exacerbations, but no studies have evaluated the effectiveness of a particular treatment on the cough itself.[188] The majority of lung cancer patients experience cough.[189] Radiotherapy and both opioid and non opioid antitussives have been recommended (www.rcseng.ac.uk). Breathlessness is usually the most distressing symptom for patients with diffuse parenchymal lung disease. However, cough is frequently reported and can be debilitating;[190] only limited information is available on its treatment.[191] There are no randomised trials evaluating the benefit of treatment directed solely at cough. The treatment of diffuse parenchymal lung disease is outside the scope of this document and the reader is referred to the appropriate BTS guidelines on this topic (www.brit thoracic.org.uk).

5. GUIDELINES FOR SPECIALIST COUGH CLINICS

General recommendation

- A systematic approach to diagnosis and treatment remains the most effective way to manage chronic cough. Important questions remain as to the complexity and cost effectiveness of existing diagnostic algorithms.

5.1 Introduction

The evaluation and management of cough in specialist clinics has been widely reported in the literature. Patients attending specialist cough clinics generally comprise non smokers with a female preponderance of approximately 2:1.[50] They have often had a combination of baseline investigations and trials of empirical treatment before referral.

Studies in the primary literature from specialist cough clinics consist mainly of descriptive cohort studies and reports of clinical experience from centres with recognised expertise in cough evaluation and management. There have been no comparative studies of diagnostic methodology within or between specialty clinics. The recommendations for specialist clinics in this document will therefore comprise a review of the published evidence and the clinical experience of the Guideline Development Group.

5.2 Do specialist cough clinics offer superior diagnostic/management outcomes?

Recommendations

- All clinics managing patients with chronic cough should ensure management protocols consider pulmonary and extrapulmonary causes of cough.

Published evidence

Three studies have reported poor diagnostic and treatment outcomes in hospital based clinics where no established management algorithm for cough existed.[2 108 109] The experience in such clinics markedly contrasts with the generally high treatment success attributed to the specialist approach.[55 98 99 171 192] In non specialist clinics extrapulmonary causes, particularly GORD, appears to be overlooked.

5.2.1 Comparison of specialist cough clinic protocols and outcomes

Recommendation

- Specialist protocols should continue to evaluate pulmonary and extrapulmonary causes for cough. Comparative studies of cough algorithms are required. No single existing diagnostic protocol can be recommended. A combination of therapeutic trials and targeted investigation is recommended when diagnostic doubt exists.

Published evidence

No direct comparisons of management protocols between specialty clinics have been published. However, treatment success reported from specialist clinics ranges from 68% to 100%.[55 97 100 171 192] Thus, despite the specialist evaluation of cough, a significant number of patients remain undiagnosed. It is not clear whether this variance reflects differences in referral population.

5.2.2 Cost effectiveness of diagnostic cough algorithms employed by specialist cough clinics

Recommendation

- A combination approach of selected diagnostic testing and empirical trials of treatment is likely to be most cost effective.

Published evidence

Algorithms for cough evaluation typically used in specialist clinics range from sequential trials of empirical treatment[99] to exhaustive diagnostic testing in all cases before any trial of treatment.[100] Only one study has explored the cost efficacy of such diagnostic cough algorithms.[193] The ''investigate all then treat'' approach was the most expensive, but with the shortest time to success compared with sequential trials of empirical treatment.

5.2.3 Is there a specific role for specialist cough clinics and when to refer?

Recommendation

- Referral to a specialist cough clinic should be encouraged when there has been a failure of empirical treatment.
- A directory of specialist centres should be made available.

The specialist cough clinics from Europe,[55 124 148 194] Asia Pacific,[84 192 195] and the Americas[98 100] broadly report successful outcomes when comprehensive diagnostic protocols are implemented. It would be desirable if all physicians were able to refer to a specialist cough clinic. Advice on how to set up a specialist cough clinic is given in Appendix 4. Appropriate referral criteria are:

- lack of availability of relevant diagnostic testing in primary or secondary care;
- failed trials of empirical treatment directed at asthma, GORD, and rhinosinusitis;
- a history suggestive of serious cough complication such as syncope or chest wall trauma;
- patient preference; and
- recruitment and participation in clinical trials of antitussive therapy.

5.3 Specialist investigations

5.3.1 Background

Mandatory investigations in patients with chronic cough are chest radiography and spirometry. This section will deal with more complex diagnostic tests where the interpretation remains open to debate, tests with largely research implications, and new innovations.

5.3.2 Bronchial provocation testing

Key points

- Current methodology for measurement of airway hyperresponsiveness is standardised and widely accepted. A negative test excludes asthma but does not rule out a steroid responsive cough.

Recommendations

- Bronchial provocation testing should be performed in patients without a clinically obvious aetiology referred to a respiratory physician with chronic cough and normal spirometric values.

Published evidence

Most of the published accounts from specialist cough clinics have described their experience with bronchial provocation testing. The methods of measurement of airway hyperresponsiveness have been well standardised. In cough clinics, direct methods using methacholine or histamine are most commonly employed,[55 98 171] although indirect methods have been described.[196] There is broad agreement between cough centres that a positive test is suggestive of asthma and should prompt treatment with inhaled steroids.[55 98 192] The positive predictive value of this test ranges from 78% to 88%.[55 98] While a negative test in a patient with cough rules out asthma, it does not eliminate a cough which may respond to steroids. A number of independent centres have reported steroid responsive cough in patients with no evidence of airway hyperresponsiveness.[124 195 196]

Extrathoracic airway responsiveness can be assessed by recording the maximal inspiratory flow/volume curve during conventional bronchial challenge testing. Three groups have used this method in the assessment of cough.[192 197 198] There is no wide agreement as to the interpretation of this test.

5.3.3 Oesophageal testing

Key point

- Failure to consider GORD as a cause of cough is a common reason for treatment failure.

Recommendation

- Empirical treatment should be offered to patients with cough and typical reflux symptoms before oesophageal testing.
- 24 hour pH monitoring poorly predicts the therapeutic response but may be indicated in cases of diagnostic doubt and in patients thought to require fundoplication.

Published evidence

Objective investigation for GORD including barium studies,[96 100] upper gastrointestinal endoscopy,[141] and ambulatory oesophageal pH testing[55 84 98 100 141 149] have been described. Ambulatory oesophageal pH monitoring is often regarded as the most sensitive and specific investigation for the diagnosis of GORD. A long term follow up study (median 30 months) has recently reported that less than 30% of patients with a ''positive'' oesophageal pH study respond to antireflux therapy, and no features on pH monitoring accurately predict the response.[199] One study has described a high prevalence of motility disorders in cough patients using oesophageal manometry testing.[148] As cough may arise as a consequence of non acid reflux, impedance testing may offer new insights into GORD related cough.[200] No published reports of its application in cough currently exist. One study has advocated the use of empirical therapy in place of oesophageal testing.[152]

5.3.4 Sinus imaging

Key point

- Rhinosinusitis is commonly associated with chronic cough.

Recommendation

- Examination of ear, nose and throat should be performed in preference to sinus imaging in patients suspected of having rhinosinusitis but with persisting cough, despite an adequate trial of treatment directed at the upper airway.

Published evidence

Existing cough guidelines make few recommendations on the role of sinus imaging, preferring to observe the response to a course of specific treatment for nasal disease.[10] In selected patients (chronic cough and excess sputum production) a sinus radiograph has a reported positive predictive value of 81% and negative predictive value of 95%.[78] However, sinus radiographs are less sensitive than CT imaging of the sinuses.[201] In a prospective study, routine CT sinus scanning was no better than an ENT examination in accurately identifying upper airway disease as a cause of the cough.[55]

5.3.5 Fibreoptic laryngoscopy

Recommendation

- Specialist cough clinics should have access to fibreoptic laryngoscopy, preferably within the clinic setting.

Published evidence

Pernasal fibreoptic laryngoscopy provides a quick and simple method of viewing the laryngeal apparatus without sedation. The presence of laryngopharyngeal reflux may be determined by the characteristic changes associated with laryngeal inflammation and oedema.[202] These include pseudosulcus (subglottic oedema), obliteration of the laryngeal ventricle, erythema of the arytenoids, oedema of the posterior laryngeal wall, and laryngeal mucus.

5.3.6 Cough provocation testing

Recommendations

- There is no current evidence to support the routine use of cough challenge testing in the management of chronic cough.
- For research purposes, standardisation of methodology is required and accurate data on the distribution of cough responsiveness within the population are needed.

Published evidence

A variety of methods to measure cough reflex sensitivity have been described in the specialist cough clinic setting. These include tidal breathing challenge with low chloride solutions, and single breath challenges with capsaicin[55 171 203] and citric acid.[37] Although safe and relatively simple to perform, a review of cough provocation testing has highlighted the need for consensus on methodology.[204]

Unlike bronchial hyperresponsiveness, cough challenge reveals a wide range of normal cough reflex sensitivity. Cough provocation testing therefore has no clear diagnostic applications and is likely to be confined to the clinical research of cough.

5.4 Measurement and monitoring of cough

Key points

- Accurate measurement of cough helps determine cough severity, assess treatment efficacy, and may provide diagnostic information.
- Ambulatory cough recording currently offers most promise in the objective assessment of cough, although further technical refinement is required if it is to be broadly accessible to physicians.

Published evidence

A number of methods to measure cough frequency, intensity and severity have been described. Visual analogue scales and self report cough diary cards have been used but do not consistently correlate with objective methods such as ambulatory cough monitoring.[205] The use of a series of different ambulatory cough recording monitors has been reported in both adult[60 206] and paediatric[207 209] literature. Although some technical limitations currently exist, they offer the best objective means of recording cough. Differences in the characteristics of the cough sound and flow pattern between asthma, bronchitis, and interstitial fibrosis have been reported.[210] Recently, analysis of overnight cough recording determined differences in character and intensity of cough sounds between patients with cystic fibrosis and those with cryptogenic fibrosing alveolitis.[211] These observations open the diagnostic possibilities for cough monitoring.

5.5 Assessing airway inflammation

5.5.1 Induced sputum

Recommendations

- The demonstration of sputum eosinophilia has important treatment implications and should be available in cough clinics.
- Induced sputum should be requested after exclusion of other common causes.

Published evidence

A number of independent groups have adapted conventional diagnostic strategies for chronic cough to include induced sputum.[84 124 195] The demonstration of airway eosinophilia (>3% sputum eosinophil count) in patients without the

functional abnormalities (particularly bronchial hyperreac tivity) associated with asthma has helped define eosinophilic bronchitis as a distinct cause for chronic cough. Eosinophilic bronchitis may account for up to 15% of cases of cough referred for specialist attention,[124] although debate remains as to whether eosinophilic bronchitis exists as a separate diagnostic entity.[212]

5.5.2 Exhaled breath

Recommendations

- There is insufficient evidence to recommend the routine use of exhaled breath measurements in the clinical evaluation of chronic cough.

Published evidence

Exhaled nitric oxide (NO) levels appear to be lower in non asthmatic coughers, allowing some differentiation from asthmatic patients with cough.[213] Exhaled NO may represent a simpler alternative to induced sputum tests but currently it has no clear diagnostic role in the management of chronic cough. An increase in nitrite levels has been reported in exhaled breath condensate from asthmatic children with cough but not from non asthmatic children with cough.[214] Measurement of many different inflammatory molecules in breath condensate, although currently a research procedure, may have a place in the future diagnosis of chronic cough.

5.6 Recommended diagnostic protocol (see Appendix 2, Parts 1 and 2)

The evaluation and management of cough in an adult should comprise two phases. The approach suggested in phase 1 is applicable to all physicians (primary and secondary care) encountering the patient for the first time. Treatment failure should prompt phase 2 of the evaluation algorithm. The algorithm is available online only at http://www.thoraxjnl.com/supplemental.

6. POTENTIAL NEW TREATMENTS FOR COUGH

Recommendations

- There is an urgent need for multicentre phase II trials on new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indices.

6.1 Background

Chronic cough is associated with many inflammatory airways diseases such as asthma, COPD, post viral infections, pulmonary fibrosis, and bronchiectasis.[10] In some cases certain drugs can be used to inhibit the underlying inflammatory process that, under certain conditions, cause cough for example, corticosteroids for the treatment of asthma or COPD, or PPIs as treatment for gastro oesophageal reflux. However, there are patients who cough who do not respond to treatments directed at the cause of the cough, and there are patients in whom there is no identifiable cause to treat. Therefore, there is also a requirement to develop compounds that are targeted to inhibit sensory nerve activity directly (by inhibition of peripheral or central mechanisms), which should in theory inhibit cough of any aetiology.

6.2 New treatments under investigation

6.2.1 Opioids

Attempts have been made to improve the therapeutic index by topical administration of a peripherally acting polar enkephalin analogue, BW443C81, which was shown to inhibit citric acid induced cough in guinea pigs.[215] However, in humans there was no effect on capsaicin induced cough in normal volunteers.[215] A novel opioid peptide, nociceptin, which binds to the opioid receptor like 1 receptor (NOP) has been shown to suppress capsaicin induced cough in guinea pigs and mechanically induced cough in the cat, but so far no data exist in humans.[216 217]

6.2.2 Neurokinin receptor (NK) antagonists

The NK_2 receptor antagonist SR 48968 has been shown to inhibit citric acid induced cough in conscious guinea pigs,[218 219] and an antitussive effect of NK_1 receptor antago nists is still under debate. Although there is a report suggesting an antitussive effect of a dual NK_1/NK_2 receptor antagonist (FK224) on bradykinin induced cough in asth matics,[220] other studies have failed to demonstrate any antitussive action of compounds of this type.[221] Recent data have implicated a role for NK_3 receptor activation in evoking a tussive response possibly via a peripheral mechanism of action,[222 223] even though there have been no reports of the presence of functional NK_3 receptor antagonists in the human lung.

6.2.3 Gamma aminobutyric acid ($GABA_B$) receptor agonists

$GABA_B$ agonists (such as baclofen) have been shown to inhibit capsaicin induced cough in the conscious guinea pig[224 225] and in normal volunteers,[226] and provided some benefit in patients with chronic cough.[227]

6.2.4 Cannabinoid CB_2 receptor agonists

CB_2 receptor agonists inhibit guinea pig and human sensory nerve activation in vitro and the cough reflex in guinea pigs, which suggests that the development of CB_2 agonists, devoid of CB_1 mediated central effects, will provide a new and safe antitussive treatment for chronic cough.[228] No clinical data exist in humans.

6.2.5 Local anaesthetics

Local anaesthetics such as lignocaine are delivered locally to the airways and have been shown to attenuate capsaicin induced cough in man.[229] However, the effect is transient and the antitussive effect is accompanied by oropharyngeal anaesthesia leading to an increased risk of aspiration of airway secretions and food.

6.2.6 Transient receptor potential (TRP) channels

The cold and menthol sensitive receptor (CMR1) has recently been characterised and cloned.[230] Interestingly, menthol has been proposed as an antitussive therapy and has been shown to inhibit citric acid induced cough in normal volunteers.[28] The heat sensitive channel TRPV1 is activated by capsaicin, the main pungent ingredient in hot chilli peppers,[231 232] and capsazepine, a blocker of this channel, inhibits capsaicin and citric acid induced cough in the guinea pig.[233] An increase in epithelial nerve profiles expressing TRPV1 has been reported in patients with non asthmatic chronic cough.[234] Compounds of this type are currently in clinical development.

6.2.7 Potassium channel openers

NS1619, an opener of large conductance calcium activated potassium (BKCa) channels, has been shown to inhibit sensory nerve function and cough induced by citric acid in the guinea pig.[235] ATP sensitive potassium channels may also be a good target.

6.3 Conclusions

Treatment of the causes of cough can often be an effective treatment strategy. However, at the moment there are no effective treatments controlling the cough response per se with an acceptable therapeutic ratio. The future looks promising with several novel mechanisms identified;

however, most of these studies have been carried out in animal models and these may not be predictive of effects in man as evidenced by the compound attrition rate from preclinical to clinical studies of antitussives tested in the past. Furthermore, there have been no large scale clinical trials of antitussive drugs as most of the studies illustrated have investigated drug efficacy in simple capsaicin challenge protocols in normal volunteers. There is therefore an urgent need for multicentre phase II trials of new drugs carried out across specialist centres using objective methods of cough counting as well as subjective quality of life and symptom indices in these patients with chronic cough.

7. RESEARCH DIRECTIONS

- Determining the best methodology for investigation of antitussive therapy.
- Simple diagnostic test, particularly for gastro oesophageal reflux.
- Causes of familial cough (genetic basis?).
- Relationship between cough/reflux/asthma.
- Fundoplication versus medical treatment.

The algorithm for the evaluation of chronic cough in adults is shown in Appendix 2 (Parts 1 and 2) available online at http://www.thoraxjnl.com/supplemental.

Authors' affiliations

A H Morice (Chairman), University of Hull, Castle Hill Hospital, Cottingham, UK
L McGarvey (Co-Chair), The Queen's University of Belfast, Belfast, UK
I Pavord (Co-Chair), University Hospitals of Leicester, Glenfield Hospital, Leicester, UK

Contributors: Professor M Belvisi, National Heart & Lung Institute, London, UK; Dr S S Birring, King's College Hospital, London, UK; Professor R Eccles, Cardiff University, Cardiff, UK; Professor K F Chung, National Heart & Lung Institute, London, UK; Professor D Geddes, The Royal Brompton Hospital, London, UK; Dr J Haughney, Aberdeen University, Alison Lea Medical Centre, Aberdeen, UK; Dr J A Kastelik, University of Hull, Castle Hill Hospital, Cottingham, UK; Dr J A McGlashan, University of Nottingham, Queen's Medical Centre, Nottingham, UK; Dr S Packham, Singleton Hospital, Swansea, UK; Dr R Stone, Taunton & Somerset Hospital, Somerset, UK

Conflicts of interest: Professor A H Morice has received research monies from Profile Respiratory Systems Ltd, Altana Pharma, AstraZeneca, GlaxoSmithKline (GSK), Schering Plough Research, Novartis; speaker honoraria from AstraZeneca, Altana Pharma, IVAX Pharmaceuticals, GSK, ReckittBenckiser Healthcare, and Novartis; advisory committee honoraria from Proctor and Gamble Healthcare and GSK; and sponsorship to attend international meetings from IVAX Pharmaceuticals and Boehringer Ingelheim. Dr L McGarvey has received speaker honoraria from GSK, AstraZeneca and Boehringer Ingelheim and consultancy honoraria from GSK. Professor I Pavord has received speakers' fees, research grants and funding to attend international meetings from GSK and AstraZeneca. Professor M Belvisi has received honoraria for consultancy work from GSK; grants from GSK and Novartis; and advisory committee honoraria for Biolipox and Euroscreen. Dr S S Birring has no conflict of interest in relation to this publication. Professor E Eccles has received consultancy fees from Proctor & Gamble and GSK. Professor K F Chung has received speakers' fees and educational grants from GSK, Novartis, Altana and Boehringer Ingelheim; consultancy honoraria from Scios, GSK, AstraZeneca, Novartis and Pfizer; and research grants from Novartis and GSK. Professor D Geddes has no conflicts of interest. Dr J Haughney has received speaker honoraria from AstraZeneca, Boehringer Ingelheim, Merck Sharp and Dohme, and consultancy honoraria from GSK, Merck Sharp & Dohme, Novartis and Schering Plough. Dr J A Kastelik has received speaker honoraria from AstraZeneca, GSK, Pfizer, Boehringer Ingelheim, Schering Plough and an educational grant from Altana Pharma. Mr J McGlashan discloses research funding, consultancy work and sponsorship to attend international meetings from Reckitt Benckiser, and an educational grant from Laryngograph Ltd. Dr S Packham has received speaker honoraria from AstraZeneca, GSK, and Boehringer Ingelheim and sponsorship to attend scientific meetings from AstraZeneca and GSK. Dr R Stone has received funds for lectures and travel from GSK, Boehringer Ingelheim, and AstraZeneca.

REFERENCES

1 **Schappert SM**. National ambulatory medical care survey: 1991 summary. *Adv Data* 1993;**230**:1–16.
2 **McGarvey LPA**, Heaney LG, MacMahon J. A retrospective survey of diagnosis and management of patients presenting with chronic cough to a general chest clinic. *Int J Clin Pract* 1998;**52**:158–61.
3 **Birring SS**, Prudon B, Carr AJ, *et al*. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003;**58**:339–43.
4 **French CT**, Irwin RS, Fletcher KE, *et al*. Evaluation of cough specific quality of life questionnaire. *Chest* 2002;**121**:1123–31.
5 **Irwin RS**, *et al*. Diagnosis and management of cough: ACCP evidence based clinical practice guidelines. *Chest* 2006;**129**:1–292s.
6 **Morice AH**, Fontana GA, Sovijarvi ARA, *et al*. The diagnosis and management of chronic cough. *Eur Respir J* 2004;**24**:481–92.
7 **Anon**. Cough guidelines choke on evidence. *Lancet* 2006;**367**:276.
8 **Widdicombe J**, Fontana G. Cough: what's in a name? *Eur Respir J* 2006;**28**:10–5.
9 **Curley FJ**, Irwin RS, Pratter MR, *et al*. Cough and the common cold. *Am Rev Respir Dis* 1988;**138**:305–11.
10 **Irwin RS**, Boulet LP, Cloutier MM, *et al*. Managing cough as a defense mechanism and as a symptom. A consensus panel report of the American College of Chest Physicians. *Chest* 1998;**114**:133–81S.
11 **Johnston SL**, Holgate ST. Epidemiology of respiratory tract infections. In: Myint S, Taylor Robinson D, eds. *Viral other infections of the human respiratory tract*. London: Chapman & Hall, 1996.
12 **Reid DD**, Williams RE, Hirch A. Colds among office workers, an epidemiological study. *Lancet* 1953;**265**:1303–6.
13 **Eccles R**, Loose I, Jawad M, *et al*. Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. *Pain Med* 2003;**4**:118–24.
14 **Proprietary Association of Great Britain (PAGB)**. *Annual review and report 2002*. London: Proprietary Association of Great Britain, 2002:1–30.
15 **Office of Population Censuses and Surveys**. *Morbidity statistics from general practice: 4th national study 1991–1992*, Series MB5,3. London: HMSO, 1995.
16 **Morice AH**. Epidemiology of cough. *Pulm Pharmacol Ther* 2002;**15**:253–9.
17 **Schaberg T**, Gialdroni Grassi G, Huchon G, *et al*. An analysis of decisions by European general practitioners to admit to hospital patients with lower respiratory tract infections. The European Study Group of Community Acquired Pneumonia (ESOCAP) of the European Respiratory Society. *Thorax* 1996;**51**:1017–22.
18 **Loudon RG**. Weather and cough. *Am Rev Respir Dis* 1964;**89**:352–9.
19 **Monto AS**, Gravenstein S, Elliott M, *et al*. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med* 2000;**160**:3243–7.
20 **Fleming D**, Harcourt S, Smith G. Influenza and adult hospital admissions for respiratory conditions in England 1989–2001. *Commun Dis Public Health* 2003;**6**:231–7.
21 **Fendrick AM**, Monto AS, Nightengale B, *et al*. The economic burden of non influenza related viral respiratory tract infection in the United States. *Arch Intern Med* 2003;**163**:487–94.
22 **Bramley TJ**, Lerner D, Sames M. Productivity losses related to the common cold. *J Occup Environ Med* 2002;**44**:822–9.
23 **Gwaltney JM Jr**, Phillips CD, Miller RD, *et al*. Computed tomographic study of the common cold. *N Engl J Med* 1994;**330**:25–30.
24 **Puhakka T**, Lavonius M, Varpula M, *et al*. Pulmonary imaging and function in the common cold. *Scand J Infect Dis* 2001;**33**:211–4.
25 **Hutchings HA**, Eccles R, Smith AP, *et al*. Voluntary cough suppression as an indication of symptom severity in upper respiratory tract infections. *Eur Respir J* 1993;**6**:1449–54.
26 **Parvez L**, Vaidya M, Sakhardande A, *et al*. Evaluation of antitussive agents in man. *Pulm Pharmacol* 1996;**9**:299–308.
27 **Manap RA**, Wright CE, Gregory A, *et al*. The antitussive effect of dextromethorphan in relation to CYP2D6 activity. *Br J Clin Pharmacol* 1999;**48**:382–7.
28 **Morice AH**, Marshall AE, Higgins KS, *et al*. Effect of inhaled menthol on citric acid induced cough in normal subjects. *Thorax* 1994;**49**:1024–6.
29 **Janson C**, Chinn S, Jarvis D, *et al*. Determinants of cough in young adults participating in the European Community Respiratory Health Survey. *Eur Respir J* 2001;**18**:647–54.
30 **Barbee RA**, Halonen M, Kaltenborn WT, *et al*. A longitudinal study of respiratory symptoms in a community population sample. Correlations with smoking, allergen skin test reactivity, and serum IgE. *Chest* 1991;**99**:20–6.
31 **Cullinan P**. Persistent cough and sputum: prevalence and clinical characteristics in south east England. *Respir Med* 1992;**86**:143–9.
32 **Lundback B**, Nystrom L, Rosenhall L, *et al*. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Respir J* 1991;**4**:257–66.

33 **Ford AC**, Forman D, Moayyedi P, *et al*. Cough in the community: a cross sectional survey and the relationship to gastrointestinal symptoms. *Thorax*, 2006 (epub ahead of print).
34 **Bjornsson E**, Plaschke P, Norrman E, *et al*. Symptoms related to asthma and chronic bronchitis in three areas of Sweden. *Eur Respir J* 1994;**7**:2146–53.
35 **Ludviksdottir D**, Bjornsson E, Janson C, *et al*. Habitual coughing and its associations with asthma, anxiety, and gastroesophageal reflux. *Chest* 1996;**109**:1262–8.
36 **Fujimura M**, Kasahara K, Kamio Y, *et al*. Female gender as a determinant of cough threshold to inhaled capsaicin. *Eur Respir J* 1996;**9**:1624–6.
37 **Kastelik JA**, Thompson RH, Aziz I, *et al*. Sex related differences in cough reflex sensitivity in patients with chronic cough. *Am J Respir Crit Care Med* 2002;**166**:961–4.
38 **Turner D**, Wailoo A, Nicholson K, *et al*. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technol Assess* 2003;**7**:iii–xiii.
39 **Zemp E**, Elsasser S, Schindler C, *et al*. Long term ambient air pollution and respiratory symptoms in adults (SAPALDIA study). The SAPALDIA Team. *Am J Respir Crit Care Med* 1999;**159**:1257–66.
40 **Braun-Fahrlander C**, Wuthrich B, Gassner M, *et al*. Validation of a rhinitis symptom questionnaire (ISAAC core questions) in a population of Swiss school children visiting the school health services. SCARPOL team. Swiss Study on Childhood Allergy and Respiratory Symptom with respect to Air Pollution and Climate. International Study of Asthma and Allergies in Childhood. *Pediatr Allergy Immunol* 1997;**8**:75–82.
41 **Vedal S**, Petkau J, White R, *et al*. Acute effects of ambient inhalable particles in asthmatic and nonasthmatic children. *Am J Respir Crit Care Med* 1998;**157**:1034–43.
42 **Montnemery P**, Bengtsson P, Elliot A, *et al*. Prevalence of obstructive lung diseases and respiratory symptoms in relation to living environment and socio economic group. *Respir Med* 2001;**95**:744–52.
43 **Viegi G**, Pedreschi M, Baldacci S, *et al*. Prevalence rates of respiratory symptoms and diseases in general population samples of North and Central Italy. *Int J Tuberc Lung Dis* 1999;**3**:1034–42.
44 **Gehring U**, Heinrich J, Jacob B, *et al*. Respiratory symptoms in relation to indoor exposure to mite and cat allergens and endotoxins. Indoor Factors and Genetics in Asthma (INGA) Study Group. *Eur Respir J* 2001;**18**:555–63.
45 **French CL**, Irwin RS, Curley FJ, *et al*. Impact of chronic cough on quality of life. *Arch Intern Med* 1998;**158**:1657–61.
46 **Dicpinigaitis PV**, Tso R. Prevalence of depressive symptoms in patients with chronic cough (abstract). *Proceedings of the American Thoracic Society* 2005;**2**:A520.
47 **French CT**, Fletcher KE, Irwin RS. A comparison of gender differences in health related quality of life in acute and chronic coughers. *Chest* 2005;**127**:1991–8.
48 **French CT**, Fletcher KE, Irwin RS. Gender differences in health related quality of life in patients complaining of chronic cough. *Chest* 2004;**125**:482–8.
49 **Birring SS**, Patel RB, Prudon B, *et al*. Quality of life in chronic cough (abstract). *Am J Respir Crit Care Med* 2003;**167**:A135.
50 **Morice AH**, Kastelik JA. Cough 1: Chronic cough in adults. *Thorax* 2003;**58**:901–7.
51 **Jansen DF**, Schouten JP, Vonk JM, *et al*. Smoking and airway hyperresponsiveness especially in the presence of blood eosinophilia increase the risk to develop respiratory symptoms: a 25 year follow up study in the general adult population. *Am J Respir Crit Care Med* 1999;**160**:259–64.
52 **Dicpinigaitis PV**. Cough reflex sensitivity in cigarette smokers. *Chest* 2003;**123**:685–8.
53 **Mello CJ**, Irwin RS, Curley FJ. Predictive values of the character, timing, and complications of chronic cough in diagnosing its cause. *Arch Intern Med* 1996;**156**:997–1003.
54 **Everett CF**, Ojoo JC, Thompson RH, *et al*. A questionnaire survey of individuals complaining of chronic cough (abstract). *Am J Respir Crit Care Med* 2003;**167**(Suppl):A316.
55 **McGarvey LP**, Heaney LG, Lawson JT, *et al*. Evaluation and outcome of patients with chronic non productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;**53**:738–43.
56 **Ojoo JC**, Kastelik JA, Morice AH. A boy with a disabling cough. *Lancet* 2003;**361**:674.
57 **O'Connell F**, Thomas VE, Studham JM, *et al*. Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med* 1996;**90**:279–86.
58 **Cerveri I**, Accordini S, Corsico A, *et al*. Chronic cough and phlegm in young adults. *Eur Respir J* 2003;**22**:413–7.
59 **Power JT**, Stewart IC, Connaughton JJ, *et al*. Nocturnal cough in patients with chronic bronchitis and emphysema. *Am Rev Respir Dis* 1984;**130**:999–1001.
60 **Hsu JY**, Stone RA, Logan Sinclair RB, *et al*. Coughing frequency in patients with persistent cough: assessment using a 24 hour ambulatory recorder. *Eur Respir J* 1994;**7**:1246–53.
61 **Hargreaves M**, Channon K. Mechanism of pacemaker induced cough. *Br Heart J* 1994;**71**:484–6.
62 **Raj H**, Singh VK, Anand A, *et al*. Sensory origin of lobeline induced sensations: a correlative study in man and cat. *J Physiol* 1995;**482**:235–46.
63 **Morice AH**, Lowry R, Brown MJ, *et al*. Angiotensin converting enzyme and the cough reflex. *Lancet* 1987;**2**:1116–8.
64 **Bonnet R**, Jorres R, Downey R, *et al*. Intractable cough associated with the supine body position. Effective therapy with nasal CPAP. *Chest* 1995;**108**:581–5.
65 **Mittal RK**, Balaban DH. The esophagogastric junction. *N Engl J Med* 1997;**336**:924–32.
66 **Everett CF**, Morice AH. Clinical history in gastroesophageal cough. *Respir Med*, 2006 (epub ahead of print).
67 **Sesoko S**, Kaneko Y. Cough associated with the use of captopril. *Arch Intern Med* 1985;**145**:1524.
68 **Yeo WW**, Foster G, Ramsay LE. Prevalence of persistent cough during long term enalapril treatment: controlled study versus nifedipine. *Q J Med* 1991;**80**:763–70.
69 **Morimoto T**, Gandhi TK, Fiskio JM, *et al*. An evaluation of risk factors for adverse drug events associated with angiotensin converting enzyme inhibitors. *J Eval Clin Pract* 2004;**10**:499–509.
70 **Ojoo JC**, Kastelik JA, Morice AH. Duration of angiotensin converting enzyme inhibitor (ACEI) induced cough (abstract). *Thorax* 2001;**56**(Suppl III):iii72.
71 **Pitt B**, Segal R, Martinez FA, *et al*. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet* 1997;**349**:747–52.
72 **Peyriere H**, Mauboussin JM, Arnaud A, *et al*. Chronic cough induced by abacavir apart from a context of hypersensitivity. *Allerg Immunol (Paris)* 2002;**34**:359–60.
73 **Isler M**, Akhan G, Bardak Y, *et al*. Dry cough and optic neuritis: two rare complications of interferon alpha treatment in chronic viral hepatitis. *Am J Gastroenterol* 2001;**96**:1303–4.
74 **Kern J**, Mustajbegovic J, Schachter EN, *et al*. Respiratory findings in farmworkers. *J Occup Environ Med* 2001;**43**:905–13.
75 **Gordon SB**, Curran AD, Wong CH, *et al*. Chronic respiratory symptom excess in bottle factory workers. *Eur Respir J* 1996;**9**:23s.
76 **Blanc P**, Liu D, Juarez C, *et al*. Cough in hot pepper workers. *Chest* 1991;**99**:27–32.
77 **Pauwels RA**, Buist AS, Ma P, *et al*. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. *Respir Care* 2001;**46**:798–825.
78 **Smyrnios NA**, Irwin RS, Curley FJ. Chronic cough with a history of excessive sputum production. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Chest* 1995;**108**:991–7.
79 **Hopwood P**, Stephens RJ. Symptoms at presentation for treatment in patients with lung cancer: implications for the evaluation of palliative treatment. The Medical Research Council (MRC) Lung Cancer Working Party. *Br J Cancer* 1995;**71**:633–6.
80 **Bergman B**, Aaronson NK, Ahmedzai S, *et al*. The EORTC QLQ LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur J Cancer* 1994;**30A**:635–42.
81 **Galdi E**, Moscato G. Pertussis in the aetiology of chronic cough in adults. *Monaldi Arch Chest Dis* 2002;**57**:229–30.
82 **Birkebaek NH**, Kristiansen M, Seefeldt T, *et al*. Bordetella pertussis and chronic cough in adults. *Clin Infect Dis* 1999;**29**:1239–42.
83 **Jansen DF**, Rijcken B, Schouten JP, *et al*. The relationship of skin test positivity, high serum total IgE levels, and peripheral blood eosinophilia to symptomatic and asymptomatic airway hyperresponsiveness. *Am J Respir Crit Care Med* 1999;**159**:924–31.
84 **Fujimura M**, Ogawa H, Nishizawa Y, *et al*. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax* 2003;**58**:14–8.
85 **McGarvey L**, Morice AH. Atopic cough: little evidence to support a new clinical entity. *Thorax* 2003;**58**:736–7.
86 **Haider AW**, Larson MG, O'Donnell CJ, *et al*. The association of chronic cough with the risk of myocardial infarction: the Framingham Heart Study. *Am J Med* 1999;**106**:279–84.
87 **Birring SS**, Brightling CE, Symon FA, *et al*. Idiopathic chronic cough: association with organ specific autoimmune disease and bronchoalveolar lymphocytosis. *Thorax* 2003;**58**:1066–70.
88 **Kok C**, Kennerson ML, Spring PJ, *et al*. A locus for hereditary sensory neuropathy with cough and gastroesophageal reflux on chromosome 3p22 p24. *Am J Hum Genet* 2003;**73**:632–7.
89 **McGarvey LP**, Heaney LG, Lawson JT, *et al*. Evaluation and outcome of patients with chronic non productive cough using a comprehensive diagnostic protocol. *Thorax* 1998;**53**:738–43.
90 **Birring SS**, Passant C, Patel RB, *et al*. Chronic tonsillar enlargement and cough: preliminary evidence of a novel and treatable cause of chronic cough. *Eur Respir J* 2004;**23**:199–201.
91 **Koufman JA**. The otolaryngologic manifestations of gastroesophageal reflux disease (GERD): a clinical investigation of 225 patients using ambulatory 24 hour pH monitoring and an experimental investigation of the role of acid and pepsin in the development of laryngeal injury. *Laryngoscope* 1991;**101**:1–78.
92 **Thiadens HA**, De Bock GH, Dekker FW, *et al*. Identifying asthma and chronic obstructive pulmonary disease in patients with persistent cough presenting to general practitioners: descriptive study. *BMJ* 1998;**316**:1286–90.
93 **Yu ML**, Ryu JH. Assessment of the patient with chronic cough (see comment). *Mayo Clin Proc* 1997;**72**:957–9.
94 **Lawler WR**. An office approach to the diagnosis of chronic cough. *Am Fam Physician* 1998;**58**:2015–22.
95 **D'Urzo A**, Jugovic P. Chronic cough. Three most common causes. *Can Fam Physician* 2002;**48**:1311–6.
96 **Irwin RS**, Corrao WM, Pratter MR. Chronic persistent cough in the adult: the spectrum and frequency of causes and successful outcome of specific therapy. *Am Rev Respir Dis* 1981;**123**:413–7.

97 **Poe RH**, Harder RV, Israel RH, *et al*. Chronic persistent cough. Experience in diagnosis and outcome using an anatomic diagnostic protocol. *Chest* 1989;**95**:723–8.
98 **Irwin RS**, Curley FJ, French CL. Chronic cough. The spectrum and frequency of causes, key components of the diagnostic evaluation, and outcome of specific therapy. *Am Rev Respir Dis* 1990;**141**:640–7.
99 **Pratter MR**, Bartter T, Akers S, *et al*. An algorithmic approach to chronic cough. *Ann Intern Med* 1993;**119**:977–83.
100 **Palombini BC**, Villanova CA, Araujo E, *et al*. A pathogenic triad in chronic cough: asthma, postnasal drip syndrome, and gastroesophageal reflux disease. *Chest* 1999;**116**:279–84.
101 **Celli BR**, MacNee W. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004;**23**:932–46.
102 **British Thoracic Society/Scottish Intercollegiate Guidelines Network**. British guideline on the management of asthma. *Thorax* 2003;**58**(Suppl I):i1–94.
103 **Cockcroft DW**, Jokic R, Marciniuk DD, *et al*. The current dilemma with spirometric inclusion criteria for asthma drug trials. *Ann Allergy Asthma Immunol* 1997;**79**:226–8.
104 **Thiadens HA**, De Bock GH, Van Houwelingen JC, *et al*. Can peak expiratory flow measurements reliably identify the presence of airway obstruction and bronchodilator response as assessed by FEV_1 in primary care patients presenting with a persistent cough? *Thorax* 1999;**54**:1055–60.
105 **Corrao WM**, Braman SS, Irwin RS. Chronic cough as the sole presenting manifestation of bronchial asthma. *N Engl J Med* 1979;**300**:633–7.
106 **Gibson PG**, Dolovich J, Denburg J, *et al*. Chronic cough: eosinophilic bronchitis without asthma. *Lancet* 1989;**1**:1346–8.
107 **Hunter CJ**, Brightling CE, Woltmann G, *et al*. A comparison of the validity of different diagnostic tests in adults with asthma. *Chest* 2002;**121**:1051–7.
108 **Puolijoki H**, Lahdensuo A. Causes of prolonged cough in patients referred to a chest clinic. *Ann Med* 1989;**21**:425–7.
109 **Al-Mobeireek AF**, Al Sarhani A, Al Amri S, *et al*. Chronic cough at a non teaching hospital: are extrapulmonary causes overlooked? *Respirology* 2002;**7**:141–6.
110 **Kastelik JA**, Aziz I, Ojoo JC, *et al*. Investigation and management of chronic cough using a probability based algorithm. *Eur Respir J* 2005;**25**:235–43.
111 **Mise K**, Sviliicic A, Bradaric A. Foreign bodies in the bronchial system of adults (abstract). *Eur Respir J Suppl* 2004;**24**:48s.
112 **Poe RH**, Israel RH, Utell MJ, *et al*. Chronic cough: bronchoscopy or pulmonary function testing? *Am Rev Respir Dis* 1982;**126**:160–2.
113 **Packham S**. The role of bronchoscopy in the mangement of chronic cough (abstract). *Eur Respir J* 2001;**18**(Suppl 33):378s.
114 **Sen RP**, Walsh TE. Fiberoptic bronchoscopy for refractory cough. *Chest* 1991;**99**:33–5.
115 **El Hennawi DD**, Iskander NM, Ibrahim IH, *et al*. Persistent cough: prevalence of gastroesophageal reflux and study of relevant laryngeal signs. *Otolaryngol Head Neck Surg* 2004;**131**:767–72.
116 **Packham S**. The sensitivity of high resolution computed tomography and flexible bronchoscopy in the diagnosis of chronic cough (abstract). *Eur Respir J Suppl* 2002;**20**:450s.
117 **Ojoo JC**, Kastelik JA, Mulrennan SA. Selective use of thoracic computed tomographs in patients with chronic cough (abstract). *Eur Respir J Suppl* 2002;**20**:449s.
118 **Padley SP**, Hansell DM, Flower CD, *et al*. Comparative accuracy of high resolution computed tomography and chest radiography in the diagnosis of chronic diffuse infiltrative lung disease. *Clin Radiol* 1991;**44**:222–6.
119 **van der Bruggen-Bogaarts BA**, van der Bruggen HM, van Waes PF, *et al*. Screening for bronchiectasis. A comparative study between chest radiography and high resolution CT. *Chest* 1996;**109**:608–11.
120 **Volpe J**, Storto ML, Lee K, *et al*. High resolution CT of the lung: determination of the usefulness of CT scans obtained with the patient prone based on plain radiographic findings. *AJR Am J Roentgenol* 1997;**169**:369–74.
121 **Irwin RS**, Madison JM. The diagnosis and treatment of cough. *N Engl J Med* 2000;**343**:1715–21.
122 **Fitch PS**, Brown V, Schock BC, *et al*. Chronic cough in children: bronchoalveolar lavage findings. *Eur Respir J* 2000;**16**:1109–14.
123 **Higgins BG**, Britton JR, Chinn S, *et al*. Comparison of bronchial reactivity and peak expiratory flow variability measurements for epidemiologic studies. *Am Rev Respir Dis* 1992;**145**:588–93.
124 **Brightling CE**, Ward R, Goh KL, *et al*. Eosinophilic bronchitis is an important cause of chronic cough. *Am J Respir Crit Care Med* 1999;**160**:406–10.
125 **Brightling CE**, Bradding P, Symon FA, *et al*. Mast cell infiltration of airway smooth muscle in asthma. *N Engl J Med* 2002;**346**:1699–705.
126 **Pavord ID**, Brightling CE, Woltmann G, *et al*. Non eosinophilic corticosteroid unresponsive asthma (letter). *Lancet* 1999;**353**:2213–4.
127 **Green RH**, Brightling CE, Woltmann G, *et al*. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;**57**:875–9.
128 **Cheriyan S**, Greenberger PA, Patterson R. Outcome of cough variant asthma treated with inhaled steroids. *Ann Allergy* 1994;**73**:478–80.
129 **Dicpinigaitis PV**, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough variant asthma. *J Asthma* 2002;**39**:291–7.
130 **Rafferty P**, Jackson L, Smith R, *et al*. Terfenadine, a potent histamine H1 receptor antagonist in the treatment of grass pollen sensitive asthma. *Br J Clin Pharmacol* 1990;**30**:229–35.
131 **Brightling CE**, Ward R, Wardlaw AJ, *et al*. Airway inflammation, airway responsiveness and cough before and after inhaled budesonide in patients with eosinophilic bronchitis. *Eur Respir J* 2000;**15**:682–6.
132 **Braman SS**, Corrao WM. Chronic cough. Diagnosis and treatment. *Prim Care* 1985;**12**:217–25.
133 **Koh YY**, Jeong JH, Park Y, *et al*. Development of wheezing in patients with cough variant asthma during an increase in airway responsiveness. *Eur Respir J* 1999;**14**:302–8.
134 **Hancox RJ**, Leigh R, Kelly MM, *et al*. Eosinophilic bronchitis. *Lancet* 2001;**358**:1104.
135 **O'Connell F**, Thomas VE, Studham JM, *et al*. Capsaicin cough sensitivity increases during upper respiratory infection. *Respir Med* 1996;**90**:279–86.
136 **Ferrari M**, Olivieri M, Sembenini C, *et al*. Tussive effect of capsaicin in patients with gastroesophageal reflux without cough. *Am J Respir Crit Care Med* 1995;**151**:557–61.
137 **Benini L**, Ferrari M, Sembenini C, *et al*. Cough threshold in reflux oesophagitis: influence of acid and of laryngeal and oesophageal damage. *Gut* 2000;**46**:762–7.
138 **Chernow B**, Johnson LF, Janowitz WR, *et al*. Pulmonary aspiration as a consequence of gastroesophageal reflux: a diagnostic approach. *Dig Dis Sci* 1979;**24**:839–44.
139 **Corwin RW**, Irwin RS. The lipid laden alveolar macrophage as a marker of aspiration in parenchymal lung disease. *Am Rev Respir Dis* 1985;**132**:576–81.
140 **Crausaz FM**, Favez G. Aspiration of solid food particles into lungs of patients with gastroesophageal reflux and chronic bronchial disease. *Chest* 1988;**93**:376–8.
141 **Irwin RS**, French CL, Curley FJ, *et al*. Chronic cough due to gastroesophageal reflux. Clinical, diagnostic, and pathogenetic aspects. *Chest* 1993;**104**:1511–7.
142 **Giudicelli R**, Dupin B, Surpas P, *et al*. Gastroesophageal reflux and respiratory manifestations: diagnostic approach, therapeutic indications and results (in French). *Ann Chir* 1990;**44**:552–4.
143 **Ing AJ**, Ngu MC, Breslin AB. Pathogenesis of chronic persistent cough associated with gastroesophageal reflux. *Am J Respir Crit Care Med* 1994;**149**:160–7.
144 **Patti MG**, Debas HT, Pellegrini CA. Esophageal manometry and 24 hour pH monitoring in the diagnosis of pulmonary aspiration secondary to gastroesophageal reflux. *Am J Surg* 1992;**163**:401–6.
145 **DeMeester TR**, Bonavina L, Iascone C, *et al*. Chronic respiratory symptoms and occult gastroesophageal reflux. A prospective clinical study and results of surgical therapy. *Ann Surg* 1990;**211**:337–45.
146 **Fouad YM**, Katz PO, Hatlebakk JG, *et al*. Ineffective esophageal motility: the most common motility abnormality in patients with GERD associated respiratory symptoms. *Am J Gastroenterol* 1999;**94**:1464–7.
147 **Knight RE**, Wells JR, Parrish RS. Esophageal dysmotility as an important co factor in extraesophageal manifestations of gastroesophageal reflux. *Laryngoscope* 2000;**110**:1462–6.
148 **Kastelik JA**, Redington AE, Aziz I, *et al*. Abnormal oesophageal motility in patients with chronic cough. *Thorax* 2003;**58**:699–702.
149 **Ing AJ**, Ngu MC, Breslin AB. Chronic persistent cough and clearance of esophageal acid. *Chest* 1992;**102**:1668–71.
150 **Kastelik JA**, Jackson W, Davies TW, *et al*. Measurement of gastric emptying in gastroesophageal reflux related chronic cough. *Chest* 2002;**122**:2038–41.
151 **Ing AJ**, Ngu MC, Breslin AB. Chronic persistent cough and gastro oesophageal reflux. *Thorax* 1991;**46**:479–83.
152 **Ours TM**, Kavuru MS, Schilz RJ, *et al*. A prospective evaluation of esophageal testing and a double blind, randomized study of omeprazole in a diagnostic and therapeutic algorithm for chronic cough. *Am J Gastroenterol* 1999;**94**:3131–8.
153 **Kiljander TO**, Salomaa ER, Hietanen EK, *et al*. Chronic cough and gastro oesophageal reflux: a double blind placebo controlled study with omeprazole. *Eur Respir J* 2000;**16**:633–8.
154 **Ing AJ**, Ngu MC, Breslin AB. A randomised double blind placebo controlled crossover study of ranitidine in patients with chronic persistent cough associated with gastroesophageal reflux. *Am Rev Respir Dis* 1992;**145**:A11.
155 **Vaezi MF**, Richter JE. Twenty four hour ambulatory esophageal pH monitoring in the diagnosis of acid reflux related chronic cough. *South Med J* 1997;**90**:305–11.
156 **Kamel PL**, Hanson D, Kahrilas PJ. Omeprazole for the treatment of posterior laryngitis. *Am J Med* 1994;**96**:321–6.
157 **Kuo B**, Castell DO. Optimal dosing of omeprazole 40 mg daily: effects on gastric and esophageal pH and serum gastrin in healthy controls. *Am J Gastroenterol* 1996;**91**:1532–8.
158 **Xue S**, Katz PO, Banerjee P, *et al*. Bedtime H_2 blockers improve nocturnal gastric acid control in GERD patients on proton pump inhibitors. *Aliment Pharmacol Ther* 2001;**15**:1351–6.
159 **Nilsson M**, Johnsen R, Ye W, *et al*. Obesity and estrogen as risk factors for gastroesophageal reflux symptoms. *JAMA* 2003;**290**:66–72.
160 **Novitsky YW**, Zawacki JK, Irwin RS, *et al*. Chronic cough due to gastroesophageal reflux disease: efficacy of antireflux surgery. *Surg Endosc* 2002;**16**:567–71.
161 **Menon MS**, Mulrennan SA, Everett CF, *et al*. Experience with baclofen in cough secondary to gastro oesophageal reflux disease (abstract). *Proceedings of the American Thoracic Society* 2005;**2**:A323.
162 **Dicpinigaitis PV**. Effect of the GABA agonist baclofen on bronchial responsiveness in asthmatics. *Pulm Pharmacol Ther* 1999;**12**:257–60.
163 **Allen CJ**, Anvari M. Gastro oesophageal reflux related cough and its response to laparoscopic fundoplication. *Thorax* 1998;**53**:963–8.
164 **Allen CJ**, Anvari M. Preoperative symptom evaluation and esophageal acid infusion predict response to laparoscopic Nissen fundoplication in gastroesophageal reflux patients who present with cough. *Surg Endosc* 2002;**16**:1037–41.

165 **Irwin RS**, Zawacki JK, Wilson MM, *et al.* Chronic cough due to gastroesophageal reflux disease: failure to resolve despite total/near total elimination of esophageal acid. *Chest* 2002;**121**:1132 40.
166 **Morice AH**. Post nasal drip syndrome a symptom to be sniffed at? *Pulm Pharmacol Ther* 2004;**17**:343 5.
167 **Tanaka S**, Hirata K, Kurihara N, *et al.* Effect of loratadine, an H_1 antihistamine, on induced cough in non asthmatic patients with chronic cough. *Thorax* 1996;**51**:810 4.
168 **Dicpinigaitis PV**, Gayle YE. Effect of the second generation antihistamine fexofenadine on cough reflex sensitivity and pulmonary function. *Br J Clin Pharmacol* 2003;**56**:501 4.
169 **Gawchik S**, Goldstein S, Prenner B, *et al.* Relief of cough and nasal symptoms associated with allergic rhinitis by mometasone furoate nasal spray. *Ann Allergy Asthma Immunol* 2003;**90**:416 21.
170 **Puhakka T**, Makela MJ, Malmstrom K, *et al.* The common cold: effects of intranasal fluticasone propionate treatment. *J Allergy Clin Immunol* 1998;**101**:726 31.
171 **O'Connell F**, Thomas VE, Pride NB, *et al.* Capsaicin cough sensitivity decreases with successful treatment of chronic cough. *Am J Respir Crit Care Med* 1994;**150**:374 80.
172 **Birring SS**, Murphy AC, Scullion JE, *et al.* Idiopathic chronic cough and organ specific autoimmune diseases: a case control study. *Respir Med* 2004;**98**:242 6.
173 **Haque RA**, Usmani OS, Barnes PJ. Chronic idiopathic cough: a discrete clinical entity? *Chest* 2005;**127**:1710 3.
174 **Mund E**, Christensson B, Gronneberg R, *et al.* Noneosinophilic CD4 lymphocytic airway inflammation in menopausal women with chronic dry cough. *Chest* 2005;**127**:1714 21.
175 **Prudon B**, Birring SS, Vara DD, *et al.* Cough and glottic stop reflex sensitivity in health and disease. *Chest* 2005;**127**:550 7.
176 **Lee SY**, Cho JY, Shim JJ, *et al.* Airway inflammation as an assessment of chronic nonproductive cough. *Chest* 2001;**120**:1114 20.
177 **Boulet LP**, Milot J, Boutet M, *et al.* Airway inflammation in nonasthmatic subjects with chronic cough. *Am J Respir Crit Care Med* 1994;**149**:482 9.
178 **McGarvey LP**, Forsythe P, Heaney LG, *et al.* Bronchoalveolar lavage findings in patients with chronic nonproductive cough. *Eur Respir J* 1999;**13**:59 65.
179 **Niimi A**, Torrego A, Nicholson AG, *et al.* Nature of airway inflammation and remodeling in chronic cough. *J Allergy Clin Immunol* 2005;**116**:565 70.
180 **Birring SS**, Parker D, Brightling CE, *et al.* Induced sputum inflammatory mediator concentrations in chronic cough. *Am J Respir Crit Care Med* 2004;**169**:15 9.
181 **Mund E**, Christensson B, Larsson K, *et al.* Sex dependent differences in physiological ageing in the immune system of lower airways in healthy non smoking volunteers: study of lymphocyte subsets in bronchoalveolar lavage fluid and blood. *Thorax* 2001;**56**:450 5.
182 **Birring SS**, Pavord ID. Idiopathic chronic cough and organ specific autoimmune disease. *Chest* 2006;**129**:213 4.
183 **Birring SS**, Patel RB, Parker D, *et al.* Airway function and markers of airway inflammation in patients with treated hypothyroidism. *Thorax* 2005;**60**:249 53.
184 **Brightling CE**, Symon FA, Birring SS, *et al.* A case of cough, lymphocytic bronchoalveolitis and coeliac disease with improvement following a gluten free diet. *Thorax* 2002;**57**:91 2.
185 **Birring SS**, Morgan CN, Prudon B, *et al.* Respiratory symptoms in patients with treated hypothyroidism and inflammatory bowel disease. *Thorax* 2003;**58**:533 6.
186 **Raphael JH**, Stanley GD, Langton JA. Effects of topical benzocaine and lignocaine on upper airway reflex sensitivity. *Anaesthesia* 1996;**51**:114 8.
187 **Jackson J**, Wright CE, Menon M, *et al.* Opiate therapy in chronic intractable cough (abstract). *Proceedings of the American Thoracic Society* 2005;**2**:A321.
188 **National Collaborating Centre for Chronic Conditions**. Chronic obstructive pulmonary disease. National clinical guideline on management of chronic obstructive pulmonary disease in adults in primary and secondary care. *Thorax* 2004;**59**(Suppl I):1 232.
189 **Muers MF**, Round CE. Palliation of symptoms in non small cell lung cancer: a study by the Yorkshire Regional Cancer Organisation Thoracic Group. *Thorax* 1993;**48**:339 43.
190 **Crystal RG**, Fulmer JD, Roberts WC, *et al.* Idiopathic pulmonary fibrosis. Clinical, histologic, radiographic, physiologic, scintigraphic, cytologic, and biochemical aspects. *Ann Intern Med* 1976;**85**:769 88.
191 **Hope-Gill BD**, Hilldrup S, Davies C, *et al.* A study of the cough reflex in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;**168**:995 1002.
192 **Carney IK**, Gibson PG, Murree Allen K, *et al.* A systematic evaluation of mechanisms in chronic cough. *Am J Respir Crit Care Med* 1997;**156**:211 6.
193 **Lin L**, Poh KL, Lim TK. Empirical treatment of chronic cough: a cost effectiveness analysis. *Proc AMIA Symp* 2001:383 7.
194 **Chung KF**, Lalloo UG. Diagnosis and management of chronic persistent dry cough. *Postgrad Med J* 1996;**72**:594 8.
195 **Kim CK**, Kim JT, Kang H, *et al.* Sputum eosinophilia in cough variant asthma as a predictor of the subsequent development of classic asthma. *Clin Exp Allergy* 2003;**33**:1409 14.
196 **Gibson PG**, Hargreave FE, Girgis Gabardo A, *et al.* Chronic cough with eosinophilic bronchitis: examination for variable airflow obstruction and response to corticosteroid. *Clin Exp Allergy* 1995;**25**:127 32.
197 **Irwin RS**, Pratter MR, Holland PS, *et al.* Postnasal drip causes cough and is associated with reversible upper airway obstruction. *Chest* 1984;**85**:346 52.
198 **Bucca C**, Rolla G, Brussino L, *et al.* Are asthma like symptoms due to bronchial or extrathoracic airway dysfunction? *Lancet* 1995;**346**:791 5.
199 **Patterson RN**, Johnston BT, MacMahon J, *et al.* Oesophageal pH monitoring is of limited value in the diagnosis of ''reflux cough''. *Eur Respir J* 2004;**24**:724 7.
200 **Sifrim D**, Holloway R, Silny J, *et al.* Acid, nonacid, and gas reflux in patients with gastroesophageal reflux disease during ambulatory 24 hour pH impedance recording. *Gastroenterology* 2001;**120**:1588 98.
201 **Davidson TM**, Brahme FJ, Gallagher ME. Radiographic evaluation for nasal dysfunction: computed tomography versus plain films. *Head Neck* 1989;**11**:405 9.
202 **Belafsky PC**, Postma GN, Koufman JA. The validity and reliability of the reflux finding score (RFS). *Laryngoscope* 2001;**111**:1313 7.
203 **Dicpinigaitis PV**. Short and long term reproducibility of capsaicin cough challenge testing. *Pulm Pharmacol Ther* 2003;**16**:61 5.
204 **Morice AH**, Kastelik JA, Thompson R. Cough challenge in the assessment of cough reflex. *Br J Clin Pharmacol* 2001;**52**:365 75.
205 **Chang AB**, Newman RG, Carlin JB, *et al.* Subjective scoring of cough in children: parent completed vs child completed diary cards vs an objective method. *Eur Respir J* 1998;**11**:462 6.
206 **Coyle MA**, Keenan BD, Mayleben DW, *et al.* Objective assessment of cough over a 24 hr period in patients with COPD (abstract). *Am J Respir Crit Care Med* 2004:A606.
207 **Chang AB**, Newman RG, Phelan PD, *et al.* A new use for an old Holter monitor: an ambulatory cough meter. *Eur Respir J* 1997;**10**:1637 9.
208 **Corrigan DL**, Paton JY. Pilot study of objective cough monitoring in infants. *Pediatr Pulmonol* 2003;**35**:350 7.
209 **Munyard P**, Bush A. How much coughing is normal? *Arch Dis Child* 1996;**74**:531 4.
210 **Piirila P**, Sovijarvi AR. Differences in acoustic and dynamic characteristics of spontaneous cough in pulmonary diseases. *Chest* 1989;**96**:46 53.
211 **Hall LE**, Smith A, Earis JE, *et al.* Patterns of cough in cystic fibrosis and cryptogenic fibrosing alveolitis (abstract). *Thorax* 2001;**56**(Suppl III):iii71.
212 **McGarvey L**, Heaney L, MacMahon J, *et al.* Eosinophilic bronchitis is an important cause of chronic cough (letter). *Am J Respir Crit Care Med* 2000;**161**:1763 4.
213 **Chatkin JM**, Ansarin K, Silkoff PE, *et al.* Exhaled nitric oxide as a noninvasive assessment of chronic cough. *Am J Respir Crit Care Med* 1999;**159**:1810 3.
214 **Formanek W**, Inci D, Lauener RP, *et al.* Elevated nitrite in breath condensates of children with respiratory disease. *Eur Respir J* 2002;**19**:487 91.
215 **Adcock JJ**, Schneider C, Smith TW. Effects of codeine, morphine and a novel opioid pentapeptide BW443C, on cough, nociception and ventilation in the unanaesthetized guinea pig. *Br J Pharmacol* 1988;**93**:93 100.
216 **Mcleod RL**, Parra LE, Mutter JC, *et al.* Nociceptin inhibits cough in the guinea pig by activation of ORL(1) receptors. *Br J Pharmacol* 2001;**132**:1175 8.
217 **Bolser DC**, Mcleod RL, Tulshian DB, *et al.* Antitussive action of nociceptin in the cat. *Eur J Pharmacol* 2001;**430**:107 11.
218 **Advenier C**, Girard V, Naline E, *et al.* Antitussive effect of SR 48968, a nonpeptide tachykinin NK(2) receptor antagonist. *Eur J Pharmacol* 1993;**250**:169 71.
219 **Girard V**, Naline E, Vilain P, *et al.* Effect of the two tachykinin antagonists, SR 48968 and SR 140333, on cough induced by citric acid in the unanaesthetized guinea pig. *Eur Respir J* 1995;**8**:1110 4.
220 **Ichinose M**, Nakajima N, Takahashi T, *et al.* Protection against bradykinin induced bronchoconstriction in asthmatic patients by neurokinin receptor antagonist. *Lancet* 1992;**340**:1248 51.
221 **Fahy JV**, Wong HH, Geppetti P, *et al.* Effect of an NK1 receptor antagonist (CP 99,994) on hypertonic saline induced bronchoconstriction and cough in male asthmatic subjects. *Am J Respir Crit Care Med* 1995;**152**:879 84.
222 **Daoui S**, Cognon C, Naline E, *et al.* Involvement of tachykinin NK3 receptors in citric acid induced cough and bronchial responses in guinea pigs. *Am J Respir Crit Care Med* 1998;**158**:42 8.
223 **Hay DW**, Giardina GA, Griswold DE, *et al.* Nonpeptide tachykinin receptor antagonists. III. SB 235375, a low central nervous system penetrant, potent and selective neurokinin 3 receptor antagonist, inhibits citric acid induced cough and airways hyper reactivity in guinea pigs. *J Pharm Exp Ther* 2002;**300**:314 23.
224 **Bolser DC**, Aziz SM, DeGennaro FC, *et al.* Antitussive effects of GABAB agonists in the cat and guinea pig. *Br J Pharmacol* 1993;**110**:491 5.
225 **Bolser DC**, DeGennaro FC, O'Reilly S, *et al.* Peripheral and central sites of action of GABA B agonists to inhibit the cough reflex in the cat and guinea pig. *Br J Pharmacol* 1994;**113**:1344 8.
226 **Dicpinigaitis PV**, Dobkin JB, Rauf K, *et al.* Inhibition of capsaicin induced cough by the gamma aminobutyric acid agonist baclofen. *J Clin Pharmacol* 1998;**38**:364 7.
227 **Dicpinigaitis PV**, Dobkin JB. Antitussive effect of the GABA agonist baclofen. *Chest* 1997;**111**:996 9.
228 **Patel HJ**, Birrell MA, Crispino N, *et al.* Inhibition of guinea pig and human sensory nerve activity and the cough reflex in guinea pigs by cannabinoid (CB2) receptor activation. *Br J Pharmacol* 2003;**140**:261 8.
229 **Choudry NB**, Fuller RW, Anderson N, *et al.* Separation of cough and reflex bronchoconstriction by inhaled local anaesthetics. *Eur Respir J* 1990;**3**:579 83.
230 **McKemy DD**, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature* 2002;**416**:52 8.
231 **Caterina MJ**, Schumacher MA, Tominaga M, *et al.* The capsaicin receptor: a heat activated ion channel in the pain pathway. *Nature* 1997;**389**:816 24.

232 **Caterina MJ**, Leffler A, Malmberg AB, *et al*. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science* 2000;**288**:306 13.
233 **Lalloo UG**, Fox AJ, Belvisi MG, *et al*. Capsazepine inhibits cough induced by capsaicin and citric acid but not by hypertonic saline in guinea pigs. *J Appl Physiol* 1995;**79**:1082 7.
234 **Groneberg DA**, Niimi A, Dinh QT, *et al*. Increased expression of transient receptor potential vanilloid 1 in airway nerves of chronic cough. *Am J Respir Crit Care Med* 2004;**170**:1276 80.
235 **Fox AJ**, Barnes PJ, Venkatesan P, *et al*. Activation of large conductance potassium channels inhibits the afferent and efferent function of airway sensory nerves in the guinea pig. *J Clin Invest* 1997;**99**:513 9.

APPENDIX 1 PATIENT INFORMATION SHEET

Patient information sheet

You've got a  **cough**

Most short term coughs are due to a virus infection. Antibiotics won't help, even if you are bringing up phlegm, and you probaly don't need to see a doctor.

You'll probably feel tired, with a running or blocked nose, and perhaps have a mild fever and aching bones.

We recommend a home remedy, such as honey and lemon if you feel the need for treatment.

You can get treatment from a pharmacist (chemist). Cough remedies that contain dextromethorphan may be the most effective. Take some paracetamol. Menthol lozenges or vapour might help too.

Stop making it worse **STOP SMOKING**

Remember, coughs and sneezes do spread diseases, try not to infect others! Use a handkerchief and don't forget to wash your hands.

You should see your doctor if

- You cough up blood
- You are breathless
- You have prolonged fever and feeling unwell
- You have a medical condition such as chronic bronchitis (COPD), heart disease, diabetes, asthma
- You have recently been in hospital
- Your symptoms persist for more than three weeks

APPENDIX 2 PROTOCOL FOR THE EVALUATION OF CHRONIC COUGH IN AN ADULT

Appendix 2 Parts 1 and 2 is available online only at http://www.thoraxjnl.com/supplemental.

APPENDIX 3 COUGH ASSESSMENT QUESTIONNAIRE

Name
Age
Smoker: y / n / never packyears:
Occupation:
Duration of cough:
Preceding URTI: y / n

Describe cough (patients' words)

Dry / Productive
Sudden onset ? aspiration
Phlegm (if produced):
Nocturnal: y / n
Wakes from sleep: y / n
Difficulty getting to sleep: y / n

Typical precipitants

Exercise:	y / n	Talking/laughing/singing:	y / n
Cold air:	y / n	Eating:	y / n
Aerosols:	y / n	Positional:	y / n
Cough on rising:	y / n	Eating and postprandial:	y / n

Relieving medication (tick if tried y / n for response)

☐ Over the counter:	y / n	☐ Inhaled medication:	y / n (give details)
☐ Oral steroids course:	y / n	☐ Anti reflux:	y / n (give details)
☐ Antibiotics:	y / n	☐ Nasal sprays:	y / n (give details)
☐ Codeine/opiates:	y / n	☐ Homeopathic:	y / n (give details)

Associated respiratory symptoms

Wheeze:	y / n		
SOB:	y / n	Chest pain:	y / n

Associated symptoms

Heartburn/epigastric pain:	y / n
Postnasal drip:	y / n
Voice change:	y / n

PMHx (respiratory)

Childhood wheeze:	y / n	
Atopy:	y / n	cats / dogs / grasses / foods

PMHx (non respiratory)
DHx (particularly ACE I / β blocker/NSAID):
Family history of cough
Systematic questions
Examination
Investigations to date

APPENDIX 4 SETTING UP A SPECIALIST COUGH CLINIC SERVICE

Why set up a cough clinic service?

A specialist cough clinic service offers a number of distinct advantages

(1) Improved patient outcomes: treatment success is considerably higher for patients managed in a specialist cough clinic than in general respiratory clinics.
(2) Avoidance of inappropriate prescribing: diagnostic uncertainty often leads to inappropriate use of antibiotics and inhaled corticosteroids.
(3) Training: specialist cough clinics provide an environment for training and skill development for physicians (often specialist registrars in respiratory training programmes), pulmonary function technicians, and respiratory nurse specialists.
(4) Clinical research: an improved understanding of the pathophysiology of cough and need to develop and evaluate new cough treatments requires the collaboration of clinicians, scientists, and the pharmaceutical industry. Specialist cough clinics ensure the accurate characterisation of patients with cough and provide opportunities for trusts with an interest in clinical research and pharmaceutical trial participation.

Where to set up a cough clinic service?

A specialist cough clinic should provide a combination of diagnostic testing and treatment trials. Although specialist cough clinics have generally been set up in secondary care, they could be developed within a Primary Care Trust. There are no comparisons of treatment outcome or cost to recommend one or other.

Core requirements

(1) A named consultant or GP should have responsibility for the service.
(2) All staff should be provided with training appropriate to their role in providing care.
(3) To adequately supervise trials of treatment including assessment of cough severity (visual analogue scales and quality of life questionnaires).
(4) Pulmonary function testing with spirometry as a minimum requirement.
(5) Access to chest radiography and bronchial provocation challenge testing (methacholine inhalation challenge testing).
(6) Facility to refer for oesophageal testing in appropriate circumstances.
(7) Ear, nose and throat (ENT) assessment either on site (facility for direct laryngoscopy) or direct access to ENT clinic.
(8) Access to bronchoscopy and chest CT scanning in appropriate circumstances.
(9) The outcomes of the service should be subject to regular review.

Desirable requirements

(1) Facility to obtain and analyse induced sputum samples.
(2) Cough provocation testing.

Cost implications

Capital costs

- Essential items: spirometer (£200 2500)
- Non essential: flexible laryngoscope (approximately £7000); cough provocation testing, dosimeter and nebuliser (approximately £4000).

Recurring costs

- Staff costs should include physician, pulmonary function technician, nurse specialist, and clerical time.
- Consumables for example, methacholine challenge testing (approximately £50 per test).