Lung (2014) 192:1–7
DOI 10.1007/s00408-013-9552-7

Abstracts from the Fourth American Cough Conference

The Fourth American Cough Conference was held in New York City on June 7th and 8th, 2013. Distinguished faculty from around the world participated in this premier educational conference focused on the field of cough. This edition of LUNG features selected abstracts and state-of-the-art reviews that were presented at the meeting. The six reviews cover a spectrum of topics of interest to the basic scientist and clinician and include two pro- con-debates. The 15 abstracts touch on a variety of topics, including new therapies, antireflux treatment, exercise and the cough reflex, methods to assess cough frequency, H4 receptor antagonists, aromatic volatile substances, transient receptor potential channels, paradoxical vocal fold movement, definitions and treatment pathways for chronic cough, and postinfectious cough.

A Meta-Analysis on the Efficacy of Levodropropizina in Adults and Children with Cough

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Introduction: Cough in adults and children is amid the most common symptoms managed by healthcare professionals. Usual causes in adults are common airways infection, GERD, and postnasal drip, whereas in children acute cough is commonly due to URTI. Empiric treatment often is needed. Levodropropizine is a very well tolerated peripheral drug, whereas central cough suppressants (opioids and nonopioids) may be associated with side effects, especially in children.

Methods: After comprehensive systematic literature search, we performed a standardized meta-analysis of seven controlled, clinical studies of levodropropizine (5 vs. central antitussives and 2 vs. placebo) assessing efficacy cough outcomes, including a total of 2,633 patients, both adults and children. Main efficacy parameters were cough frequency, severity, and night awakenings. The purpose of this meta-analysis was to evaluate the overall efficacy of levodropropizine vs. control. In order to make the efficacy outcomes comparable, we standardized the variables of different studies, in particular: cough severity, frequency of cough, and nocturnal sleeping quality. The overall reduction of the severity of all efficacy parameters was higher in the levodropropizine group, and the difference vs. controls was highly statistically significant ($P < 0.01$). The meta-analytic chart is reported in Fig. 1.

Conclusions: Our meta-analysis indicates that levodropropizine is an effective antitussive drug both in adults and children, with statistically significant better overall efficacy outcomes vs. central antitussives (codeine, cloperastine, dihydrocodeine, dextromethorphan), in terms of reducing cough intensity, frequency, and nocturnal awakenings. These results further reinforce the favorable benefit/risk profile of levodropropizine in the management of cough.

Efficacy of Sequential Stepwise Anti-Reflux Therapy on Refractory Chronic Cough Due to Gastroesophageal Reflux

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Background: Pharmacotherapy is a preferable strategy for the treatment of refractory gastroesophageal reflux induced cough (GERC). However, it is still unclear which therapeutic strategy is appropriate for simply and efficiently selecting drugs. The purpose of this study was to evaluate the efficacy of sequential stepwise antireflux therapy on refractory GERC.

Methods: Thirty-six consecutive patients with suspected GERC refractory to the standard pharmacological antireflux therapy were recruited and treated with the high dose of proton pump inhibitor (omeprazole 40 mg, twice daily) plus prokinetic agent (domperidone 10 mg, three times daily), adding histamine H2 receptor antagonist (ranitidine 20 mg, twice daily) to the current treatment and the combination of proton pump inhibitor (omeprazole 20 mg, twice daily) with transient lower esophageal sphincter relaxation inhibitor (baclofen 20 mg three times daily) in a sequential and step-up way. The primary endpoint was the overall rate of cough control, and the

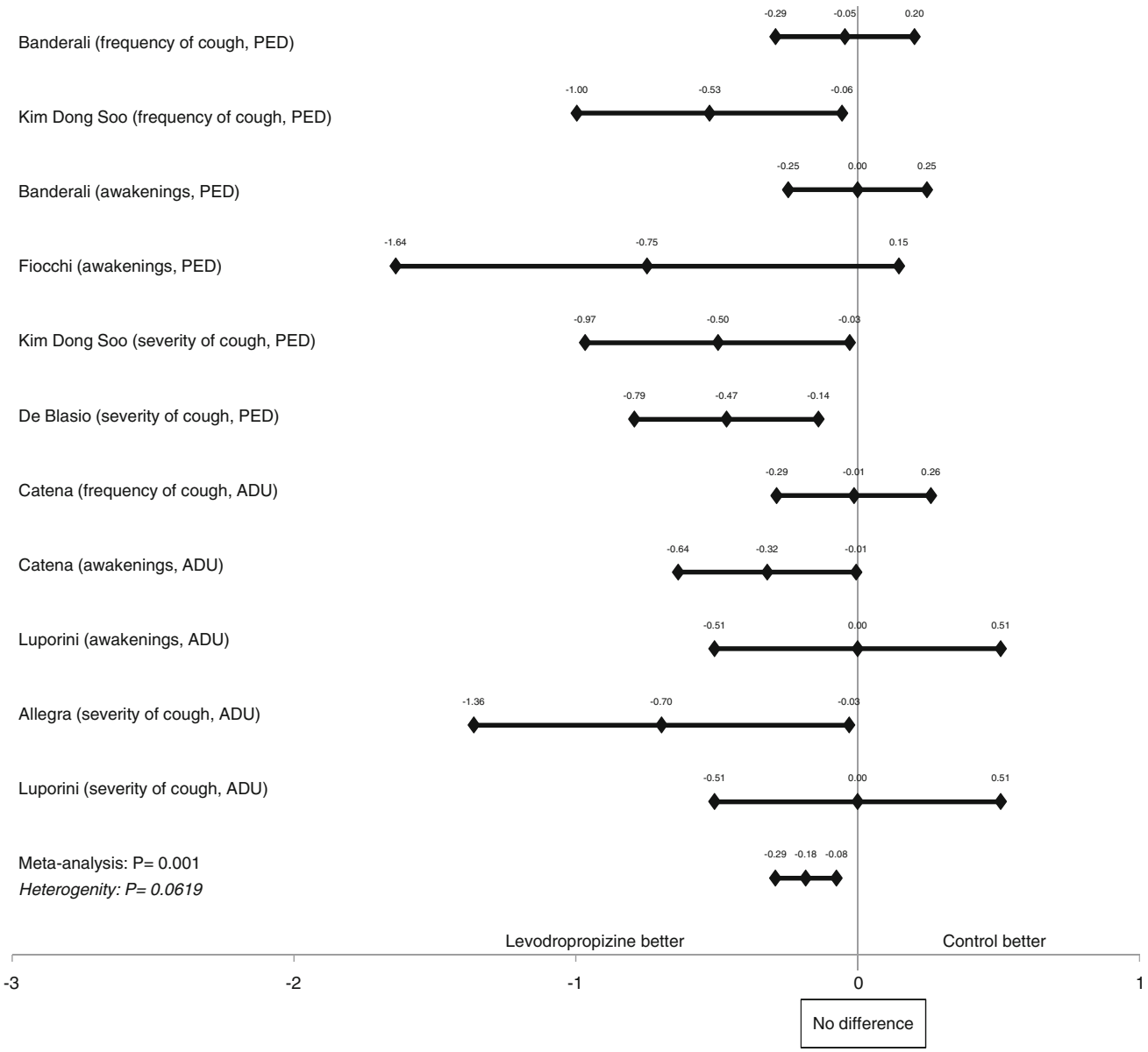

Fig. 1 Meta-analysis of levodropropizine versus control in children and adult

second endpoints included the rate of cough control at each step, the treatment duration required, and changes in cough symptom score, gastroesophageal reflux diagnostic questionnaire (GerdQ) score, and capsaicin cough sensitivity.

Results: The cough resolved in 38.9 % ($n = 14$) of the patients with the high dose of proton pump inhibitor plus prokinetic agent, including 12 cases of acid GERC and 2 cases of non-acid GERC; in a further 13.9 % ($n = 5$) with the addition of histamine H2 receptor antagonist, comprising 3 cases of acid GERC and 2 cases of nonacid GERC, and in another 30.5 % ($n = 11$), consisting of 7 cases of acid GERC and 4 cases of nonacid GERC. In total, the sequential stepwise therapy was successful in 83.3 % ($n = 30$) of the patients, with the mean treatment duration of 11.52 ± 1.98 weeks, 10.08 ± 1.7 weeks and 10.96 ± 1.72 weeks at each step respectively. Cough symptom score decreased from 3(1) to 1(0) for daytime ($P = 0.000$) and from 1(1) to 0(1) for nighttime ($P = 0.000$), with a parallel reduction of GerdQ score from 8.6 ± 1.7 to 6.8 ± 0.7 ($P = 0.000$). Conversely, capsaicin cough threshold increased from 0.49 (0.73) to 1.95 (2.92) μmol/L for C2 ($P = 0.000$) and from 1.95 (2.92) to 7.8 (5.85) μmol/L for C5 ($P = 0.000$).

Conclusions: Sequential stepwise antireflux therapy is a useful therapeutic strategy for the patients with refractory GERC.

Downregulation of Cough Reflex During Exercise in Healthy Children

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Background: Exercise-induced symptoms, such as cough and wheeze, are frequently reported in asthma questionnaires. It is known that the airways contract after a short exercise bout in asthmatics, but dilate during the exercising period in both asthmatics and controls. On the other hand, the exact time sequence of cough and exercise is not precisely known. The issue is important in the context of identifying those mechanisms that eventually regulate the cough reflex. The purpose of the study was to test whether cough is downregulated during exercise in children.
Methods: Twenty healthy, nonasthmatic, nonatopic children aged 7–11 years (11 boys; 9 girls) were studied using the single-breath capsaicin cough challenge with inspiratory flow limitation (Eur Respir J 2007;29:1256–1276). A capsaicin dose–response curve was established up to the concentration (0.61–1,250 μmol/l) causing five or more cough efforts occurring within 30 s of the inhalation (C5). Saline aerosols were randomly distributed among the 12 capsaicin administrations. The random C5-saline challenge was then repeated at baseline as well as during a 6 min treadmill exercice at 80 % predicted maximum heart rate, respectively 1 and 2 h after the C5 titration.
Results: C5 geometric mean was 28.5 μmol/l (CI: 13.1–62.2 μmol/l) and independent of gender. During exercise, the number of coughs at C5 was reduced in 16 of 20 children, unchanged in 2, augmented in another 2. The median (IQR) number of coughs at C5 was significantly diminished from 5.0 (4.0–6.5) at baseline to 2.5 (2.0–4.0) during exercice ($p = 0.0005$).
Conclusions: The study indicates depression of cough during exercice in healthy children. Because the inspiratory flow was controlled, the observation is unlikely to express redistribution of capsaicin deposition within the airways during the hyperventilation of exercise. The data strongly suggest downregulation of the cough reflex by exercice-related neural mechanisms.
The study was supported by Contrat de Programme Recherche Clinique (CPRC) of the University Hospital Center (CHU) of Nancy, France, ARAIRLOR association (Aide Insuffisants Respiratoire Lorraine) and DevAH 3450 from the "Ministère de l'éducation et de la Recherche," France.

Antibiotic or Symptomatic Therapy in Pediatric Acute Cough

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Introduction: Acute cough is a widespread symptom in children, the disproportionate use of antibiotic prescription increases parental satisfaction, although URTI are generally self-limiting.
Objective: We analyzed treatment effect of antibiotics and symptomatic drugs (antitussives and mucolytics) in two trials on pediatric URTI-related cough.
Methods: The first study involved 59 children with acute moist cough, treated with antibiotics or inhaled mucoactive drugs. Cough was measured, by means of a verbal category descriptive (VCD) score. The second study included 305 children with acute cough. Severity, frequency, and type of cough were assessed after 6 days of treatment using a standardized questionnaire administered to parents.
Results: In the retrospective series, patients treated with inhaled mucoactive drugs (sobrerol or *N*-acetylcysteine) showed a significant improvement after 7 days compared with the group receiving antimicrobial therapy ($p < 0.01$). In the prospective study, children treated with antibiotics alone showed lower percentage of cough resolution after 6 days than patient treated with antitussive only, no difference was detected between children treated with antitussive alone versus patients receiving antibiotics and antitussives. The use of levodropropizine demonstrated a statistically significant effect in terms of cough resolution compared with centrally acting antitussive drugs (codeine or cloperastine) (47 vs. 28 %, $p = 0.0012$).
Conclusions: Our analysis showed that the effect of antibiotics on acute cough caused by URTI is inferior to symptomatic therapy. Antibiotics are not generally useful for treating cough, both alone and in association with antitussives. Use of antibiotics is of little benefit that is outweighed by adverse effects.

The Assessment of Cough Frequency: The Leicester Cough Monitor Experience

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Background: Recent advances in recording technology have made objective assessment of cough detection more feasible and use of cough frequency as a primary endpoint possible. The Leicester cough monitor (LCM) is an ambulatory and automated cough detection monitor that can record up to 48 h. It consists of an MP3 recording device and microphone, and proprietary software that analyses cough and bout frequencies. The validation, performance qualification, and evaluation of the LCM system to date are described herein. The accuracy of a revised version of LCM v2.0 (improved user interface and regulatory compliance; no change to cough detection algorithm) was also evaluated.
Methods: Literature, identified through a PubMed search, was reviewed by two investigators. The sensitivity of automated cough detection, comparison with subjective endpoints and evaluation of cough frequency in therapeutic studies were evaluated. As a bridging study, data from nine patients with chronic cough (previously recruited in study *ERJ*, 2008; 31:1013) underwent cough analysis with the LCM v2.0 and data compared with previous findings utilizing v1.0. The cough counts on the recordings were manually evaluated three times (Observer 1 once and Observer 2 twice) and compared with automated cough counts obtained with LCM v1.0 (original) and v2.0.
Results: The sensitivity for cough detection LCM v1.0 ranged from 84 to 91 %, with specificity of 99 %. There was a weak to moderate association of cough frequency with health status [Leicester cough questionnaire (LCQ) and visual analogue scale (VAS)]; consistent with that reported with other cough monitors. The LCM has been utilized in a range of therapeutic studies that included randomized clinical trials of Erythromycin, Gabapentin, and FP01 (currently being evaluated in a Phase 2 chronic cough clinical trial). The sensitivity and specificity of LCM v2.0 compared with manual counts were 88 and 99 %, respectively. The Intra-Class Coefficient between cough frequency detected with LCM v1.0 and v2.0 was 0.94 ($p < 0.0001$).
Conclusions: There is growing evidence that cough frequency assessment is practical in the clinic and in clinical trials. The validity of the LCM software for cough detection is supported by manually counted data and expected association with subjective endpoints. The

LCM system is a valid tool for assessing cough frequency as a primary outcome in clinical trials.

Efficacy of H4 Receptor Antagonists in the Animal Model of Upper Airway Cough Syndrom

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Background: Chronic cough associated with upper airway diseases (upper airway cough syndrome UACS) could be intractable problem, decreasing considerably the patient's quality of life together with the rhinitis and/or rhinosinusitis symptoms. Older generation antihistamines are empirically used in subjects with UACS; however, the data about their efficacy share conflicting evidence. The effect on cough is believed to be mediated via antihistamine, anticholinergic, and central sedative effects. Nowadays, attention is given to the new categories of histamine receptor antagonists (H4), which are abundantly expressed on the immune cells, nasal nerves, and glands, decreasing severity of nasal inflammation and magnitude of nasal symptoms. The purpose of our study was to assess the efficacy of H4 receptor antagonist JNJ 7777120 on nasal symptoms magnitude and cough in ovalbumin (OVA)-induced allergic rhinitis in guinea pigs.
Methods: Experimental animals ($n = 15$) were sensitized by intraperitoneal administration of OVA and successful sensitization was confirmed 21 days later by skin prick tests. Animals were repeatedly challenged with nasal OVA to induce allergic rhinitis and upregulate cough reflex. When the reliability of the model was confirmed, animals were pretreated with JNJ 7777120 (0.25 mg/kg and 0.5 mg/kg intraperitoneally 30 min before OVA administration). Cough was induced by inhalation of citric acid 0.4 M, in plethysmograph for 10 min. Final count of coughs was confirmed using traces of sudden interruption of the basal breathing by cough pattern (pneumotachograph), and software SinicVisualiser to distinguish coughs, sneezes, and artifacts.
Results: Allergic rhinitis up regulated the cough response from 11 ± 2 to 19 ± 3 cough per provocation, med $\pm$ IQR ($p < 0.05$). Pretreatment with 0.25 mg/kg showed a tendency to decrease cough responsiveness and suppress nasal symptoms; however, the data did not reach significance. Dose 0.5 mg/kg significantly suppressed the nasal symptoms, and number of cough obtained during provocation from 19 ± 3 to 10 ± 1, med $\pm$ IQR ($p < 0.05$). Animals showed considerable excitation and "caffeine-like" effect after intraperitoneal JNJ 7777120; therefore, we used telemetric system, and already surgically pre-prepared guinea pigs with implanted sensors for the heart rate and muscle activity to assess the excitation. The data from objective telemetric recording did not confirm significant change of selected physiological functions.
Conclusions: JNJ7777120 in a dose 0.5 mg/kg significantly suppressed the rhinitis symptoms and cough induced by citric acid. It does not influence heart rate and spontaneous motoric activity of the guinea pigs assessed by telemetric system.

Relevance of Aromatic Volatile Substance in the Management of Cough

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Background: Although acute cough, which is usually associated with viral airway infection, is not a problem to manage, growing attention has been given to the field of chronic cough. Chronic cough is usually the dominant, or only, patient complaint, leading to frequent consultations but without any relevant treatment. Its presence and unsatisfactory management may lead to complications and decreases quality of life. A specific group of chronic coughers are subjects with upper airway diseases, lately categorized as having postnasal drip syndrome. There is an increasing pool of evidence that cough is not only upregulated by the pathological process in the nose and/or sinuses, but stimulation of distinct population of trigeminal sensory and olfactory afferents could downregulate cough too.
Methods: Conscious and anaesthetized animals were used to study the effects of nasal menthol, thymol, and eucalyptol administration on cough induced in experimental conditions (naive animals and animals with the model of upper airway cough syndrome). Cough was induced by citric acid, and cough latency, cumulative count of coughs, and total cough response was analyzed by two independent trained scientists based on the airflow traces (ACQ Knowledge) and cough sound analysis (Sonic Visualiser). Experimental protocols were further translated to human subjects, where we studied cough induced by inhalation of capsaicin (validated standardized capsaicin cough challenge) after nasal challenges of vehicle, menthol, thymol, and eucalyptol challenges respectively.
Results: In a series of the studies in animal models and human healthy volunteers, we showed that nasal application of aromatic substance, such as menthol, thymol, and eucalyptol (10^{-3} M in humans), reduces total count of coughs, cough threshold, and urge to cough. The effect is probably mediated by the combination of trigeminal and olfactory signalling.
Conclusions: These data are objective evidences for the relevance of the aromatherapy, and it also documents the importance of cortical mechanisms in modulation of cough reflex.

A Novel Human In Vitro Model for the Study of Nociceptive Responses in Sensory Nerves

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Background: The orofacial region and upper airways are densely innervated by the peripheral sensory neurons of the trigeminal nerve. These neurons are activated by a variety of specialised ion channels, including the transient receptor potential (TRP) channels. When activated by thermal, mechanical, or chemical stimuli, TRP channels stimulate an electrical signal, which induces noxious pain and contributes to neurogenic inflammation. Due to their importance in nociception, TRP channels merit investigation as possible druggable targets and hold promise for the treatment of cough. Study of TRP channel expression and regulation in human trigeminal nerve fibres is limited by the fact that peripheral neurons lack cell bodies (which are housed in the trigeminal ganglion). To overcome this limitation, we have differentiated stem cells from redundant human dental pulp toward a neuronal phenotype, termed peripheral neuronal equivalents (PNEs). These PNEs are a novel source of human neurons containing cell bodies for use with in vitro studies.
Methods: PNEs were grown on substrate-coated coverslips and used to investigate the expression of neuronal markers and TRP channels using immunofluorescence. TRP channel functionality on PNEs was investigated using whole cell patch clamping and calcium microfluorometry.

Results: We have demonstrated that dental pulp stem cells undergo phenotypic switching during the differentiation process and that PNEs express specific neuronal markers (PGP9.5, synaptophysin) but not fibroblast markers (FSP). We also have shown the expression of TRP channels (TRPV1, TRPV4, TRPA1, TRPM8) on PNEs. Data acquired using microfluorometry showed increased $[Ca^{2+}]_i$ in PNEs stimulated with the TRPA1 agonist cinnamaldehyde suggesting TRPA1 functionality. TRPA1 activation in response to cinnamaldehyde was confirmed by patch clamping.
Conclusions: These findings indicate that dental pulp stem cells can be differentiated into functional PNEs that are a suitable for in vitro studies of human trigeminal neuronal function.
This work was funded by NC3Rs.

Opinions on the Definition of Chronic Cough and Current Treatment Pathways: An International Qualitative Study

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This study was partly funded by GSK. We acknowledge the help provided by Double Helix Market Research, London, UK.
Background: The pathogenesis of chronic cough is not well understood and treatment options are limited. In this study, we sought to explore the current understanding and management of chronic cough across an international group of specialists.
Methods: This was an international study of cross sectional qualitative design. In depth interviews were performed with "Respiratory Specialists" experienced in treating COPD, idiopathic pulmonary fibrosis (IPF), idiopathic chronic cough (ICC), and/or lung cancer patients and with "Disease Experts" (DEs) in the field of chronic cough. Participants in the study were recruited from four countries for specialists (United States, United Kingdom, Germany, and Japan) and DEs (United States, United Kingdom, Australia, and Ireland). Interviews with specialists were held at research facilities and were audio recorded, videotaped, and observed. These were preceded by the specialists completing case records of cough patients they had recently seen. Interviews with DEs were conducted over the telephone. All interviews were conducted by trained moderators using a semistructured interview guide script. This was designed to elicit the definition of chronic cough, explore the unmet needs for each disease state, define therapy goals, identify patient phenotypes, and give an overview of the treatment pathway.
Results: Seventy-six specialists (32 each from the United States and United Kingdom and 12 from Japan) and 10 DEs took part in the study. More than two thirds (70 %) of respondents defined chronic cough as "cough lasting more than 8/12 weeks" (range 2 weeks to 2 years). Physicians emphasised three interdependent aspects of clinical diagnosis: impact on quality of life, type of cough (productive versus nonproductive), and pathology. Respiratory specialists emphasised treating the underlying cause rather than the cough, this being most prominent in Japan. DEs as a group focussed on chronic cough as an independent condition. Evaluation of the respiratory system, GI tract, and upper airway (ENT) for establishing an underlying cause was recommended. The type of cough (productive vs. nonproductive) and impact on quality of life influenced treatment initiation. Thirty-three percent of patients with ICC were prescribed antitussives. With associated diagnoses of COPD, IPF, or lung cancer, the emphasis was on treating the underlying condition. Alternatives to pharmacological treatments were frequently considered.
Conclusions: There is significant international variation in our understanding and management of chronic cough. Further work is required by all interested parties to bring forth clear guidance and effective medicines for these patients.

Baseline Cough Frequency in a Randomized, Placebo-Controlled, Phase 2 Clinical Trial in Subjects With Upper Respiratory Tract Infection

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Background: Cough is the most common presenting symptom in patients seeking primary medical care. Cough also remains a condition for which symptomatic treatments are ineffective. The mainstays of symptomatic antitussive therapy, dextromethorphan, and codeine were introduced 50 years ago, are no better than placebo in the majority of clinical efficacy studies, and have high abuse potential. Studies in the guinea pig citric acid model of cough have demonstrated that the sensitivity of the cough reflex is under a variety of medullary control mechanisms, including NMDA and neurokinin neurotransmission. The blockade of these systems, and other neuromodulatory approaches provide potential opportunities to establish antitussive effects without abuse concerns.
Methods: A Phase II trial (Clin01-002-A) was conducted with a novel product, FP01, to treat cough via a combination of peripheral and CNS effects. This randomized, placebo-controlled, double blind study in subjects with cough associated with upper respiratory tract infection (URTI) enrolled 208 subjects in a multinational, multicenter study. Subjects were admitted to a clinical unit and equally randomized to placebo, low-dose, or high-dose FP01. Cough frequency was measured using the Leicester Cough Monitor (Dr. S. Birring). On day 1, all subjects received 3 doses of placebo in blinded form TID during awake hours to obtain a 24-h baseline cough recording.
Results: Cough counts decreased precipitously on day 1 after initiation of cough monitoring, suggestive of a 2- to 4-h acclimatization period as subjects with acute illness were admitted to a study unit and stabilized. On day 2, during the second and final 24-h treatment period, subjects received study drug (3 administrations of placebo, low, or high-dose) and a 24-h cough recording was obtained. Average cough frequency decreased by 10 coughs per hour on day 2 compared with day 1 in placebo-treated subjects. Cough frequency was correlated with a Visual Analog Scale ($r = 0.39$, $p < 0.0001$) and the Leicester cough questionnaire—acute ($r = -0.27$, $p = 0.0002$).
Conclusions: These preliminary results demonstrate the feasibility of performing trials for treatment of cough associated with URTI and the feasibility and validity of automated cough counting as a measure of effect.

Montelukast for Adults with Post-Infectious Cough (MAC): A Double-Blind, Randomized, Placebo-Controlled Trial

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Background: Postinfectious cough is commonly encountered in primary care but has no proven effective treatments. In vitro evidence suggests that leukotrienes are involved in postinfectious cough, particularly if caused by pertussis (whooping cough). Because pertussis presents as postinfectious cough, we determined the effectiveness of montelukast, a cysteinyl leukotriene receptor antagonist, for the treatment of postinfectious cough.
Methods: Adults with postinfectious cough ($n = 276$) were randomized to montelukast ($n = 137$) or placebo ($n = 139$) for 2 weeks and were given the option of continuing study medication for another 2 weeks. All subjects were tested for pertussis (oral fluid antipertussis toxin IgG). Effectiveness was assessed using the Leicester Cough Questionnaire to measure changes in cough-specific quality of life between baseline and two follow-up stages (2 weeks and 4 weeks).
Results: Improvements in cough-specific quality of life were observed in both groups after 2 weeks [montelukast: mean 2.7 (95 % confidence interval 2.2–3.3); placebo: 3.6 (2.9–4.3)], but the difference between groups was not clinically significant [mean difference −0.9 (− 1.7 to −0.04), $p = 0.04$]. Eighty-seven patients discontinued study medication at the 2-week stage (montelukast, $n = 39$; placebo, $n = 48$). There was no significant difference in change in cough-specific quality of life between baseline and 4 weeks (mean difference −0.5, 95 % CI −1.5 to 0.6, $p = 0.38$). Seventy patients had laboratory-confirmed pertussis (25 %).
Conclusions: Montelukast is not an effective treatment for postinfectious cough. This study demonstrates that pertussis is prevalent among adults with postinfectious cough and primary care is an ideal setting for conducting future trials of antitussive treatments.

Laryngeal Hypersensitivity in Chronic Refractory Cough and Paradoxical Vocal Fold Movement

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Background: Patients with chronic refractory cough (CRC) frequently complain of laryngeal discomfort. The purpose of this paper was to explore laryngeal sensation in patients with CRC and the related condition of Paradoxical Vocal Fold Movement (PVFM). A secondary goal was to develop a tool to assess the patient experience of abnormal laryngeal sensation that could be used in conjunction with objective tests, such as cough reflex sensitivity testing and fibreoptic endoscopic examination of swallowing with sensory testing.
Methods: Laryngeal function and sensation were compared between three groups of patients: CRC ($n = 33$), PVFM ($n = 28$), and healthy controls ($n = 13$). Specific tests included Symptom Frequency and Severity Rating, Voice Handicap Index, Laryngeal Paraesthesia Questionnaire, Capsaicin Cough Reflex Sensitivity Testing, 24-h ambulatory cough monitoring, Hypertonic Saline Challenge, Timed Swallow Test, Acoustic Voice Assessment, Auditory Perceptual Voice Assessment, and Voice Stress Test. The Laryngeal Paraesthesia Questionnaire was developed as a 14-item tool to assess self-reported laryngeal irritation. This tool distinguished patients from controls, showed good retest reliability, and demonstrated improvement following speech pathology intervention.
Results: Capsaicin cough reflex sensitivity and hypertonic saline challenge test results were worse in the CRC and PVFM groups than the control group. Cough frequency monitoring showed that mean coughs per hour were highest in the PVFM group followed by the CRC group then the healthy controls. Symptom Frequency and Severity ratings were significantly worse in the CRC and PVFM groups than controls. As expected, breathing scores were worse in the PVFM than the CRC group; however, surprisingly cough scores were slightly worse in the PVFM than the CRC group. Results of the Voice Handicap Index, auditory perceptual voice analysis, and acoustic voice testing were significantly worse in the CRC and PVRM groups than healthy controls. Patient reports of laryngeal sensation showed a consistent description of laryngeal irritation that subsequently triggered cough, of cough being triggered by nontussive stimuli, such as cold air and talking, and by subthreshold exposure to tussive stimuli. Cross-stimulus responses showed that voice quality deteriorated following the capsaicin cough test for patients in the CRC and PVFM groups. Furthermore, the voice stress test resulted in increased urge to cough, significant fall in FIF50, and increased cough frequency in the patient groups.
Conclusions: Abnormal laryngeal sensation is common in patients with CRC and PVFM and cough is a significant factor for many patients with PVFM. In fact for some patients, the laryngeal discomfort can be almost as distressing as the cough. The data support a central mechanism and is consistent with previous descriptions of the Cough Hypersensitivity Syndrome. The concepts used in chronic pain, namely hypersensory, paresthesia, and allodynia could be applied in CRC.

Comparison of pH Monitoring, Reflux Finding Score and Reflux Symptom Index Results with Multichannel Intraluminal Impedance in Diagnosis of Gastroesophageal Reflux Related Cough

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Background: Gastroesophageal reflux (GER) is one of the most frequent causes of chronic cough. It appears when GER either irritates vagal nerve endings in esophagus or causes aspiration and irritation of receptors in larynx or airways. There are different diagnostic devices that may directly or indirectly assess the presence of GER. Although multichannel intraluminal impedance (MII) is the most precise, its availability is limited. The goal was to assess whether pH-monitoring used alone or in combination with Reflux Finding Score (RFS) and Reflux Symptom Index (RSI) may be helpful in GER-related cough diagnostics compared with MII results.
Methods: Adult patients admitted to the hospital due to diagnosis of cough longer than 8 weeks were included in the study if they had normal chest radiogram, did not smoke for at least 1 year, and were not treated with inhibitors of angiotensin-converting enzyme nor proton pomp inhibitors. Among the tests done for the most frequent causes of chronic cough, pH-monitoring and MII were performed. For assessment of proximal GER, RFS based on video laryngological evaluation was assessed and RSI was calculated (assessed abnormal if >7 and 13 points, respectively). The patients were divided into three groups according to test results: (1) no GER; (2) GER coexisting with cough; and 3) GER-related cough based on symptom association

probability (SAP). Results of all tests were compared with MII and statistically analyzed.
Results: Fifty-two patients were included in the study: mean age 49 years; 34 women; mean cough duration 302 weeks. Based on pH-monitoring and MII results, GER-related cough was diagnosed in 16 and 22 patients, respectively, and GER coexisting with cough in 13 and in 26 subjects, respectively. Comparison of both studies results showed only 29 % match of diagnoses, with EpHM sensitivity of 27 %, specificity of 63.6 % and diagnostic accuracy of 47.4 %. A new calculation formula using two parameters from pH-monitoring was proposed that improved the match of pH-monitoring and MII results up to 68 %. Based on RFS and RSI, GER was diagnosed in 49 and in 38 patients, respectively. No correlation with MII results was observed, although $p < 0.05$ was observed when comparing RFS with some MII parameters.
Conclusions: pH-monitoring used alone or in combination with RSF and RSI is still not precise compared with MII. Using proposed formula based on pH-monitoring parameters, we are able to improve the results. Further studies are mandatory for better assessment of correlation between MII and RFS.

Urge to Cough and Airway Protection in Parkinson's Disease

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Background: Pneumonia and lung infection are leading causes of death in persons with idiopathic Parkinson's disease (PD). The pathogenesis of these infections is largely attributed to the presence of silent aspiration (or aspiration without cough response). There are no studies investigating reflex cough thresholds in PD utilizing capsaicin as the tussigenic agent. Additionally, no studies have investigated urge to cough (UTC) ratings in PD. The goal of this study was to test reflex cough thresholds and associated UTC ratings in participants with PD. Secondarily, we tested whether cough thresholds and UTC ratings differed in participants who had dysphagia versus nondysphagic participants.
Methods: Twenty participants with mild to moderate PD were recruited for this study. Participants completed a capsaicin challenge. Three randomized blocks of 0, 50, 100, and 200 μM of capsaicin were presented. Following each presentation, participants rated their UTC by modified Borg scale. The concentration of capsaicin that elicited the 2-cough response (Cr2) was recorded and served as our measure of cough reflex sensitivity. Participants also completed a videofluoroscopic evaluation of swallowing. Swallowing dysfunction and airway compromise was evaluated using the penetration-aspiration scale.
Results: Most participants did not have a reliable C2 cough response to 200 μM of capsaicin (12/20 participants). When a cough was elicited at 200 μM of capsaicin, median UTC scores were five. In cases where a cough was not elicited at 200 μM of capsaicin, the median UTC score was 2. Additionally, all nondysphagic participants had cough thresholds of at least 200 μM of capsaicin. UTC ratings for dysphagic participants at 200 μM of capsaicin were significantly lower than those for nondysphagic participants.
Conclusions: UTC ratings may be important in understanding the mechanism underlying morbidity related to aspiration pneumonia in people with PD and dysphagia. Further understanding decreased UTC in people with PD and dysphagia will be essential for the development of strategies and treatments to address deficits of airway protection in this population.

Sequential Cough in Parkinson's Disease

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Background: Parkinson's disease causes deficits in airway protection typically defined in terms of dysfunctional swallowing, or dysphagia. Previous research from our group and others indicate deficits in cough effectiveness characterized primarily by reduced peak expiratory airflows as measured from single voluntary coughs. However, the typical reflex cough response consists of at least 2 cough reaccelerations (CRs). The goal of this study was to evaluate sequential cough peak expiratory flow (PEF), cough volume acceleration (CVA), and total volume of air expired (CEV) in persons with Parkinson's disease (PD) with and without co-occurring airway protection deficits, specifically dysphagia.
Methods: Twenty-one patients with moderate stage PD participated. Ability to protect the airway during swallowing was assessed videofluoroscopically. Participants were grouped as "dysphagic" or "nondysphagic" according to penetration-aspiration score, a validated measure of functional swallowing ability. To measure cough, participants were outfitted with a facemask and pneumotachograph and were instructed to cough "as if food or liquid had entered the airway." Cough airflow was recorded across two sequential cough trials.
Results: Participants produced multiple CRs, ranging from 2 to 9. As expected, both dysphagic and nondysphagic groups exhibited decreases in PEF and CEV according total CRs, and the position of a CR in the sequence (for example, first versus fourth cough). However, the *pattern* of change was significantly different between the two groups, showing differences in the organization of sequential coughing in PD where dysphagia is present. For example, the % CEV was greater for the second cough in the series for PD participants with dysphagia versus those without.
Conclusions: Not only single coughs, but also sequential coughs with multiple CRs, should be considered when assessing cough in the context of airway protection. In PD, the relationship between CRs within a series is different between participants who exhibit other deficits in airway protection, specifically during swallowing. Our results indicate a breakdown in multiple aspects of airway protection in PD, and the combination of these deficits likely contributes to the nearly inevitable development of aspiration pneumonia in this population.