The American Cough Conference is supported by

Reckitt Benckiser

Logistics Management provided by SRxA – Strategic Pharmaceutical Advisors.
Dear Colleagues,

Welcome to Washington Dulles and the American Cough Conference!

On behalf of the 5th American Cough Conference, I am delighted that you have joined us for the premier 2015 educational event in cough at the Westin Washington Dulles hotel, which will serve as the meeting headquarters.

Over the next two days you will hear from our world class faculty and meet many of the thought leaders in the field of cough as we explore the past, present and future of cough research, evaluation, and management.

The scientific agenda includes a Pro/Con debate, promising lively discussion on multi-component versus single component therapy in the treatment of acute cough as well as an oral abstract symposium showcasing previously unpublished research in both basic science and clinical aspects of cough. Other highlights include an overview of cough in COPD, GERD and sarcoidosis.

Throughout the meeting, I encourage you to “cough it up” and actively participate in the debates, discussions and Q&A. During the breaks, please take the time to meet with the faculty, your peers and our industry supporters and educational grant providers.

Our goal is to provide you with an outstanding program and networking opportunities. I hope you enjoy your time at the American Cough Conference, and look forward to meeting you.

Sincerely,

Peter V. Dicpinigaitis

Peter V. Dicpinigaitis, MD
American Cough Conference Chairman
Friday June 5, 2015

7:30 am   Registration Desk Opens
7:30 am   Exhibit Hall Opens
7:30 am   Breakfast

8:15 am   Chairman’s Introduction – Peter Dicpinigaitis

Viruses, Colds, and Cough
Chair: Peter Dicpinigaitis
8:45 am   Cough and common cold. Mechanisms and Treatments – Ronald Eccles
9:10 am   Effect of respiratory viral infection on cough receptors – Brad Undem

Issues in Clinical Cough
Chairs: Ron Turner & Surinder Birring
9:35 am   Update on pediatric cough – Ahmad Kantar
10:00 am  Cough in COPD – Jacky Smith
10:25 am  Cough in Sarcoidosis – Surinder Birring
10:50 am  Use of Expectorants/Muco-active drugs in Managing Chest Congestion and Cough – A US Perspective – Helmut Albrecht

11:15 am  Networking coffee break & Exhibits

Critical Review of Currently Available Antitussives
Chairs: Brendan Canning & Jacky Smith
11:30 am  Levodropropizine – Clive Page
11:55 am  Benzonatate – Lorcan McGarvey
12:20 pm  Dextromethorphan – Alyn Morice
12:45 pm  Amitriptyline & Gabapentin – Kian Fan Chung

1:10 pm   Lunch
Friday June 5, 2015

2:10 pm  **Oral Abstract Presentations - Session 1**  
**Moderators: Peter Dicpinigaitis & Lorcan McGarvey**

Effect of Flurbiprofen 8.75mg on Coughing in Patients with Upper Respiratory Tract Infection – **Berndard Schachtel**

Obstructive Sleep Apnea in patients at a Voice Disorders Clinic and its Relationship to Cough Intensity in Patients with Irritable Larynx Syndrome – **Krishna Sundar**

Red Alert! Rescuing the Larynx from the Inevitable Effects of Cough. A Voice Pathologist’s Perspective – **Catherine L. Ballif**

ATP Cough Challenge in Healthy Volunteers – **Helen Fowles**

The Effect of Female Hormonal Profile on Selected Cough Parameters – **N. Kavalcikova-Bogdanova**

Association of Esophageal Dysfunction with Therapeutic Efficacy of Baclofen in Patients with Refractory Gastroesophageal Reflux-Induced Chronic Cough – **Xianghuai Xu**

3:30 pm  **Networking coffee break & Exhibits**

3:45 pm  **Oral Abstract Presentations Session 2**  
**Moderators: Donald Bolser and Bradley Undem**

Effect of Esophageal Acid Infusion on Cough Reactivity in the Guinea Pigs with Chronic Capsaicin Inhalation – **Qiang Chen**

Ozone induces a hypertussive response to inhaled citric acid in rabbits – **Clive Page**


Patterns of Inappropriate Antibiotic Use in Cough – **Alike van der Velden**

A Randomized Clinical Trial of Levodropropizine Effect on Respiratory Center Output in Patients with Intractable Chronic Cough – **Giovanni A. Fontana**

Mothers’ and School Nurses’ Assessment of Cough and Cold Impact on Children’s Quality of Life – **Laurence E. Flint (Presented by Marilyn Morrisey)**

5:00 pm  **John Widdicombe Award Presentation**
Saturday June 6, 2015

8:00 am  Registration Desk Opens
8:00 am  Exhibit Hall Opens
8:00 am  Breakfast

**Pro/Con Debate: Treatment of acute cough due to the common cold: multicomponent, multi-symptom therapy is preferable to single-component, single-symptom therapy**

*Chair: Peter Dicpinigaitis*

9:00 am  Pro: Ronald Eccles
9:30 am  Con: Ronald Turner
10:00 am Discussion

**Future Directions in Antitussive Drug Development**

*Chairs: Clive Page & Maria Belvisi*

10:20 am  Does it all end with dextromethorphan? NMDA receptor antagonists as potential antitussives – **Brendan Canning**
10:45 am  P2X3 antagonism using AF-219: clinical potential in pathological cough and other conditions – **Anthony Ford**
11:10 am  Update 2015: TRPA1/TRPV1 antagonists as potential antitussives – **Maria Belvisi**

11:35 am  Networking Lunch Break & Exhibits

**New Concepts in Cough Evaluation and Therapy**

*Chairs: Alyn Morice & Lorcan McGarvey*

12:30 pm  Use of surface-evoked laryngeal sensory action potential (SELSAP) testing in the evaluation of chronic cough – **Jonathon Bock**
12:55 pm  Regulation of repetitive coughing: Lessons from CO₂ – **Donald Bolser**

**Cough and GERD**

*Chairs: Alyn Morice & Lorcan McGarvey*

1:20 pm  Evaluation of GERD-associated cough: when to stop empiric trials and initiate diagnostic studies – **Kenneth DeVault**
1:45 pm  Diagnosis of reflux-related cough and the importance of non-pharmacological management – **Jamie Koufman**
2:10 pm  Concluding Remarks – **Peter Dicpinigaitis**
Chairman

Peter Dicpinigaitis, MD
Professor of Clinical Medicine
Albert Einstein College of Medicine
Director, Medical-Surgical Intensive Care Unit
Montefiore Medical Center
Director, Montefiore Cough Center
Bronx, New York
USA

Dr. Peter Dicpinigaitis is Professor of Clinical Medicine at the Albert Einstein College of Medicine, in New York. He is triple board-certified in Internal Medicine, Pulmonary Diseases and Critical Care Medicine. He serves as the Director of the Medical-Surgical Intensive Care Unit of the Einstein Division of Montefiore Medical Center, and is the founder and director of the Montefiore Cough Center, one of the few specialty centers in the world exclusively committed to the evaluation and management of patients with chronic cough.

In addition to experience in all aspects of clinical medicine within the spectrum of pulmonary and critical care, Dr. Dicpinigaitis has been very active in cough-related research. He has authored numerous peer-reviewed journal articles and book chapters on cough, and is considered an international authority on the performance of cough challenge studies in clinical research. He served as a co-author on cough management guidelines published by the American College of Chest Physicians as well as the European Respiratory Society, and is the founder and chairman of the biannual American Cough Conference.
Since 2008, Dr. Albrecht is running H2A Associates, LLC, a consulting firm for innovation & product development strategy, technology & opportunity assessments and claims support for Rx and OTC pharmaceutical products. Prior to starting this company, Helmut filled the roles of Sr. VP for R&D at Adams Respiratory Therapeutics and VP in US & global leadership roles in R&D at Novartis Consumer Health. Earlier in his career he held key positions in the areas of clinical development and pharmaceutical medicine with focus on prescription drugs, the Rx & OTC drug development space and the support of OTC medicines and dietary supplement products at SmithKline Beecham, Procter & Gamble, and Altana Pharma in Germany and the North America.

Helmut has an MD degree from the Universities of Heidelberg and Hamburg, a Master of Science in Management & Policy, and other qualifications in HC and Pharmaceutical Medicine. He is a fellow and former board member of the Faculty of Pharmaceutical Medicine (RCP) in the UK.

Dr. Albrecht has a faculty appointment at Florida International University (FIU), as Associate Professor, Dept. of Cellular Biology & Pharmacology, Herbert Wertheim College of Medicine and he is the current Industry Liaison member of FDA’s Gastrointestinal Drugs Advisory Committee (GIDAC).
Professor Maria Belvisi is head of the Respiratory Pharmacology group at the National Heart and Lung Institute, Imperial College, London.

She was awarded a BSc in pharmacology in 1986 by Chelsea College, now King’s College London, and a PhD by the National Heart & Lung Institute in 1990. Professor Belvisi is an internationally recognized expert in the respiratory field with both academic and industrial experience. Her research is focused on the cellular and molecular mechanisms of asthma, COPD and chronic cough, and developing therapies for these diseases. Her research is translational and takes data generated in vitro through to in vivo models and clinical studies with collaborators. Together with Peter Barnes at NHLI she was involved in generating key data sets during the development of tiotropium bromide (Spiriva) a long acting muscarinic receptor antagonist used as a bronchodilator for the treatment of chronic obstructive pulmonary disease.

Professor Belvisi also worked for a period at Rhone-Poulenc Rorer/Aventis Pharma, leading a team in the company’s Respiratory Research Therapeutic area. During this time she was involved in the development of Ciclesonide (Alvesco) an inhaled corticosteroid for asthma with an improved therapeutic ratio.

Professor Belvisi has an extensive publication record in peer review journals and serves on the editorial board of several publications. She has also received several prizes and awards, including the Women in Inflammation Science (2009), awarded by the World Inflammation Society, and the AstraZeneca Women in Pharmacology Prize (2011). She was elected fellow of the British Pharmacological Society in 2005.

In 2010 she formed, together with Dr Mark Birrell, IR Pharma a preclinical respiratory drug discovery organization which is part of the Imperial Innovations portfolio of companies http://www.irpharma.co.uk/
Dr Surinder Birring is a Consultant Respiratory Physician at King’s College Hospital and Guy’s Hospital, London and Honorary Senior Lecturer at King’s College London. Dr Birring leads a specialist clinic for Cough. His research interests are the assessment, pathogenesis and treatment of cough and the development of patient reported outcome measures for chronic lung disorders. Dr Birring and colleagues have developed the Leicester Cough Questionnaire (LCQ), Leicester Cough Monitor, King’s Brief ILD (KBILD) and Kings’ Sarcoidosis Questionnaires (KSQ).

Dr Birring was awarded a British Lung Foundation Fellowship in 2001 to investigate the pathogenesis of Idiopathic Chronic Cough. In 2006, he undertook a visiting Senior Fellowship to the Department of Respiratory Medicine, Concord Hospital, Sydney, Australia. He has contributed to BTS, ERS and ACCP cough guidelines. He is currently chief investigator of several multi-center clinical trials of antitussive therapies.
Jonathan M. Bock, MD, FACS
Assistant Professor, Dept. of Otolaryngology & Communication Sciences
Medical College of Wisconsin
Consultant Otolaryngologist, Children’s Hospital of Wisconsin and Clement J. Zablocki Veterans Administration Hospital
Milwaukee, Wisconsin
USA

Jonathan M. Bock, MD, FACS is an Assistant Professor in the Division of Laryngology and Professional Voice in the Department of Otolaryngology & Communication Sciences at the Medical College of Wisconsin, Milwaukee, Wisconsin. He also serves as a consultant otolaryngologist for the Childrens Hospital of Wisconsin and the Clement J. Zablocki Veterans Administration Hospital in Milwaukee, Wisconsin.

Dr. Bock attended college at Yale University in New Haven, CT where he obtained a degree in Molecular Biochemistry and Biophysics and also performed with the Yale Whiffenpoofs acapella ensemble. He attended medical school at the Medical College of Wisconsin in Milwaukee, WI, and subsequently completed an internship in General Surgery, NIH T32-funded research fellowship in Molecular Oncology, and 4 years of training in Otolaryngology – Head and Neck Surgery at the University of Iowa, Iowa City, IA. He completed his clinical training with a final year of subspeciality fellowship training by studying Laryngology & Care of the Professional Voice with Dr. Robert Ossoff and Dr. Gaelyn Garrett at the Vanderbilt Voice Center, Department of Otolaryngology – Head and Neck Surgery, Vanderbilt University, Nashville, TN.

His clinical practice at the Medical College of Wisconsin focuses on the management of voice and swallowing disorders. Dr. Bock has published more than 30 original peer-reviewed papers and a book chapter on otolaryngology and dysphagia topics, including studies of NSAID drugs on head and neck cancer growth and proliferation, immunologic testing for pertussis, chronic cough management, practice patterns in management of Zenker’s Diverticulum, and experimental approaches to EMG study in patients with voice and swallowing disorders. He is an active singer and performer with his band Bockenplautz. He currently lives in Milwaukee, Wisconsin with his wife and four children.
Dr. Bolser received his BS in Biology from the Florida Institute of Technology in Melbourne, Florida in 1980. He then went on to perform graduate training at the University of South Florida in Tampa and receive his PhD in Respiratory Physiology in 1985. Dr. Bolser conducted postdoctoral research first at the University of Calgary and then at the University of Oklahoma. He then went on to work at the Schering Plough Research Institute. He has served on NIH study sections, including a special emphasis panel on computational modeling and systems biology in tuberculosis. He was a member of the first (2006) and second (2012) American College of Chest Physicians Panel on Evidence Based Guidelines for the Diagnosis and Management of Cough. He has served as an external referee for the National Science Foundation, the Burroughs Welcome Trust, and the Veterans Administration Merit Review Board. Dr. Bolser’s research has focused on the neurogenesis of reflexes that protect the airway from aspiration, in particular cough and swallow. He has discovered the existence of a novel control system for airway protection in the brainstem that coordinates the expression of airway defensive behaviors and breathing. This coordinating mechanism accommodates very different motor patterns for breathing, cough, swallow and other airway protective behaviors. He is investigating this control system with advanced computational neural network modeling and simulation with in vivo investigation of the brainstem neural circuitry for cough and swallow. His aim is to employ neural network simulations to predict the regulation and coordination of cough and swallow motor patterns. These predictions will ultimately lead to better diagnostic and therapeutic tools for clinicians. His research has been funded by over $8 million dollars in grants and contracts from private and public sources including the National Institutes of Health.

Dr. Brendan J. Canning is an Associate Professor of Medicine at the Johns Hopkins Medical Institutions. His research has focused on airway neural control with an emphasis on the physiological and pharmacological properties of the cough reflex. Dr. Canning is an Associate Editor of the Journal of Pharmacology and Experimental Therapeutics, Associate Editor of Frontiers in Respiration Physiology and a Review Editor for Pulmonary Pharmacology and Therapeutics. Dr. Canning’s research focuses on airway neural control and is funded by the National Institutes of Health and through collaborations with industry.
Professor Chung is Professor of Respiratory Medicine and Head of Experimental Studies Medicine at National Heart & Lung Institute, Imperial College London, and is Consultant Physician at the Royal Brompton Hospital, London.

His current interests are focused on the role of airway smooth muscle and effects of oxidant stress on muscle function, on the mechanisms underlying corticosteroid resistance and ways of reversing it in asthma and COPD, and on the impact of environmental pollution and nanoparticles on lung disease. He also has an interest in neuropathic cough and in developing new antitussives. He has co-led the severe asthma UBIOPRED project.


Ken DeVault, MD is Professor and Chair of the Department of Medicine at Mayo Clinic Florida. He received his undergraduate degree from the University of Tennessee and his medical degree from the Bowman Gray School of Medicine at Wake Forest University. He completed his internship and residency in internal medicine at Vanderbilt University and completed a combined clinical and research fellowship at Jefferson Medical College.

Dr. DeVault was Chair of the Division of Gastroenterology and Hepatology at the Mayo Clinic Florida from 2005-2010. He is a Fellow and Trustee of the American College of Gastroenterology and will be President in 2015-2016.

Dr. DeVault conducts research on disorders affecting all aspects of the esophagus and has written over 250 book chapters, abstracts, editorials and original articles on subjects ranging from treatment of GERD, dysphagia, esophagitis, and Barrett’s esophagus to laparoscopic antireflux surgery and managed care issues in the treatment of GERD. He also has interest in gastrointestinal health in the third world and in improving professionalism in both trainees and practicing physicians.
Professor Ron Eccles is Director of the Common Cold Centre based in the School of Biological Sciences at Cardiff University, Wales UK. Professor Eccles is an expert on the symptoms of common cold and flu and medicines used to treat colds and flu. He graduated from Liverpool University with a BSc and PhD in Pharmacology and later obtained a Doctor of Science degree for his research work. He has spent his career at Cardiff University since his appointment in 1973, and he established the Common Cold Centre in Cardiff in 1988. The centre is a self-funded Clinical Research Organisation that conducts scientific and clinical research on treatments for cough, colds and flu. His main research interests are in the symptoms of common cough, cold and flu and how these can be controlled by popular medicines and other treatments. His recent research has studied the effects of chilling on the onset of common cold symptoms and the effects of placebo treatments. He has special interests in studying nasal congestion and cough, and has published many scientific papers on these topics. He is the author of some 250 publications and has contributed to many medical textbooks.

Dr. Ford is a pharmacologist with many years’ experience in drug design, discovery and development. He was a former vice president of research at Roche Pharmaceutical in Palo Alto where he initiated and drove several innovative medicinal design programs in peripheral and sensory neurobiology, which included advancing the first in class P2X3 antagonist into clinical studies. Following almost 20 years of R&D at Syntex and then Roche, Dr. Ford co-founded the start-up company Afferent Pharma with VC investors in 2009, in order to progress P2X3 antagonists, licensed from Roche, into studies in patients with chronic sensory disorders such as pain, urological dysfunction and respiratory symptoms (cough). He was trained in pharmacology at Bradford University (1984), holds a Ph.D. in neuropharmacology from Nottingham University (1988), and has published his research findings extensively with a strong focus on therapeutics for visceral disorders and pain.
Ahmad Kantar, MD, PhD, MSc.
Director of Pediatric Cough and Asthma Center
Head of Pediatric Unit
Istituti Ospedalieri Bergamaschi
Hospital and University Research
Ponte San Pietro, Bergamo
Italy

Ahmad Kantar, MD, PhD, MSc. is the Director of the Pediatric Asthma and Cough Center and head of the pediatric unit, at the Institute Hospital Bergamo in Ponte San Pietro, Italy. He is a member of the Italian Pediatric respiratory Society, the Italian Society of pediatric Allergy & Immunology, American Thoracic Society and the European Respiratory Society. He has published extensively on topics relating to cough and cough hypersensitivity syndrome.

Jamie Koufman, MD
Founder and Director of the Voice Institute of New York
Clinical Professor of Otolaryngology
New York Eye and Ear Infirmary
Mt. Sinai Health System
New York, NY
USA

Dr. Jamie Koufman is one of America’s leading laryngologists and has lectured widely, both nationally and internationally. With three decades of clinical and bench research focused on the diagnosis, treatment, cell biology, and epidemiology of reflux, Dr. Koufman is one of the world’s authorities on reflux disease. She coined the terms laryngopharyngeal reflux, silent reflux, and airway reflux. She is a New York Times best selling author of Dropping Acid: The Reflux Diet Cookbook &Cure, a book that offers refluxers good understanding of silent reflux and a natural cure. She is also author of The Chronic Cough Enigma.

Dr. Koufman is the Founder and Director of the Voice Institute of New York, a comprehensive voice treatment center. She was a pioneer of laryngeal framework surgery, minimally-invasive laryngeal laser surgery, and transnasal esophagoscopy. Dr. Koufman is Professor of Otolaryngology at the New York Eye and Ear Infirmary of the Mt. Sinai Medical System.

Dr. Koufman has received the Honor Award and the Distinguished Service Awards of the American Academy of Otolaryngology - Head and Neck Surgery, the Broyles-Maloney Award of the American Broncho-Esophagological Association, and the Casselberry and Newcomb Awards of the American Laryngological Association. The latter is a Lifetime Achievement Award for research and publications in Laryngology. She is a past-president of the American Broncho-Esophagological Association and is currently the president of New York Laryngology Society. Dr. Koufman has been listed among the Top Doctors in America every year since 1994.
Dr Lorcan McGarvey is Consultant Physician at the Royal Victoria Hospital and Senior Lecturer in Respiratory Medicine at Queen’s University of Belfast, N Ireland. He graduated with Honours in Medicine from Queen’s University Belfast in 1990 and trained in respiratory medicine in Belfast and Sydney, Australia. He is Lead Clinician for the Northern Ireland Respiratory Clinical Research Network.

His main programme of research has focused on the clinical and scientific aspects of acute and chronic cough. He has been a core contributor to the British Thoracic Society and European Respiratory Society Cough guidelines and serves on the American College of Chest Physicians Cough Guidelines Expert Committee. He is currently investigating the expression and functional characteristics of novel ion channels in the airways of asthmatic and cough patients. He has lectured regularly at national and international meetings and published extensively on airways disease. His work has been funded by MRC, Asthma UK, NC3R, British Heart Foundation, Northern Ireland Chest Heart & Stroke, NI RDO and HEA North-South Programme.

Professor Morice qualified at Cambridge University and after House jobs in London undertook research (MD) into the pharmacology of asthma at St Mary’s Hospital. As Clinical Lecturer at Addenbrooke’s Hospital, Professor Morice developed his interest in cough, demonstrating cough hypersensitivity caused by ACE inhibitors. In 1989 Professor Morice was appointed as Senior Lecturer in Sheffield developing a Pulmonary Vascular service and the first UK Cough Clinic. In 1998 Professor Morice was appointed to the Foundation Chair in Respiratory Medicine in Hull University, now part of the Hull York Medical School. The Cough Clinic has become the largest centre within Europe with an international pattern of referral. Unique investigational strategies provide diagnosis and treatment advances which are incorporated into national and international guideline documents. Professor Morice has led the European Respiratory Society and British Thoracic Society Taskforces on Cough.
Clive P. Page, BSc, PhD
Professor of Pharmacology and Director of the Sackler Institute of Pulmonary Pharmacology
King’s College Hospital
London
UK

Clive Page is a Professor of Pharmacology, King’s College London and Director of the Sackler Institute of Pulmonary Pharmacology, King’s College London. Clive’s main research interests are in the pharmacology of inflammation and respiratory disease and he has published over 250 scientific papers.

Clive is also the co-founder of Chairman of the Board of Verona Pharma plc, an AIM listed company developing new drugs for the treatment of Respiratory Diseases. He is a Non Executive Director of Babraham Biotechnology Ltd, as well as being a Trustee of the Babraham Institute in Cambridge. Clive started his early career in the Pharmaceutical Industry at Sandoz Ltd, Basel, Switzerland and regularly consults to both the Pharmaceutical and Biotech Industry.

Clive is a recent former Chairman of the Animal Science Group of the Society of Biology and has contributed widely to the public debate about the use of animals in research.

He was awarded the Society of Biology President’s Medal at its 2012 Annual General Meeting. The Medal is awarded annually to individuals who have made an outstanding contribution to the life sciences over the previous year.

Jacky Smith, MD, PhD
Professor of Respiratory Medicine
University of Manchester
Honorary Consultant
University Hospital of South Manchester NHS Foundation Trust
Wythenshawe, Manchester
UK

Jacky Smith is a Professor of Respiratory Medicine at the University of Manchester and an Honorary Consultant at the University Hospital of South Manchester NHS Foundation Trust. She runs a multi-disciplinary research team whose focus is on understanding mechanisms underlying pathological cough and a regional clinical service seeing patients with refractory chronic cough.

She has considerable experience in the assessment of cough in clinical trials of novel antitussive therapies. In collaboration with Vitalograph Ltd she and her team have developed an ambulatory cough monitoring system for quantifying the effect of therapies. She also has a strong interest in the translation of findings in animal models through to human disease.
Ronald Turner, MD, is Professor of Pediatrics at the University of Virginia School of Medicine. Dr. Turner earned his MD degree from Southern Illinois University and did his training in Pediatrics and Pediatric Infectious Diseases at Columbus Children’s Hospital (Ohio State University) and the University of Virginia. He subsequently served in faculty positions at the University of Utah and the Medical University of South Carolina. Dr. Turner has clinical care and teaching responsibilities in Pediatric Infectious Diseases. His research interests are directed at the pathogenesis and treatment of viral respiratory infections.

Bradley J. Undem, PhD
Professor of Medicine
Johns Hopkins University School of Medicine
Baltimore, Maryland
USA

Dr. Undem received his Ph.D. in Pharmacology from University of Wisconsin in 1985. In 1997 he was appointed to his present position of Full Professor in the Department of Medicine of Johns Hopkins University. He has joint appointments in The Center for Sensory Biology in the Department of Molecular Medicine, and in the department of Respiratory Physiology at the Bloomberg School of Public Health. Dr. Undem has published extensively on the role of airway sensory and autonomic nerves in health and disease. He has also enjoyed consulting with over 20 pharmaceutical companies regarding drug discovery for controlling the causes and symptoms of inflammatory airway diseases.
Friday June 5, 2015

7:30 am   Registration Desk Opens
7:30 am   Exhibit Hall Opens
7:30 am   Breakfast

8:15 am   Chairman’s Introduction – Peter Dicpinigaitis

Viruses, Colds, and Cough
Chair: Peter Dicpinigaitis
8:45 am   Cough and common cold. Mechanisms and Treatments – Ronald Eccles
9:10 am   Effect of respiratory viral infection on cough receptors – Brad Undem

Issues in Clinical Cough
Chairs: Ron Turner & Surinder Birring
9:35 am   Update on pediatric cough – Ahmad Kantar
10:00 am  Cough in COPD – Jacky Smith
10:25 am  Cough in Sarcoidosis – Surinder Birring
10:50 am  Use of expectorants in the treatment of cough and chest congestion – Helmut Albrecht

11:15 am  Networking Coffee Break & Exhibits

Critical Review of Currently Available Antitussives
Chairs: Brendan Canning & Jacky Smith
11:30 am  Levodropropizine – Clive Page
11:55 am  Benzonatate – Lorcan McGarvey
12:20 pm  Dextromethorphan – Alyn Morice
12:45 pm  Amitriptyline & Gabapentin – Kian Fan Chung

1:10 pm   Lunch

2:10 pm   Oral Abstract Presentations - Session 1
Moderators: Peter Dicpinigaitis & Lorcan McGarvey

3:30 pm   Networking Coffee Break & Exhibits

3:45 pm   Oral Abstract Presentations - Session 2
Moderators: Peter Dicpinigaitis & Lorcan McGarvey

5:00 pm   John Widdicombe Award Presentation
Cough and common cold. 
Mechanisms and Treatments

Ronald Eccles, BSc, PhD, DSc, Cardiff University, Wales, UK

The problem of developing new treatments for cough associated with common cold is confounded by the fact that current treatments already work too well.

Despite the fact that the media regularly attacks over-the-counter cough medicines as being useless, not worth the money and no better than a placebo treatment, my view is that the problem is really that our current OTC medicines work too well and it will be a difficult task to beat them in any placebo controlled or comparator clinical trial.

I start by explaining what is the mechanism of cough associated with common cold or acute upper respiratory tract viral infection (URTI), and compare URTI cough with reflex cough caused by aspiration of food or fluid.

I then go on to explain why current OTC cough treatments are so effective by discussing three mechanisms; sweetness, stimulation of salivation and swallowing, and the presence of flavours such as menthol. In particular I look at cough syrups, cough drops and vapo-rubs.

The talk focuses on the importance of the sensation of irritation that leads to voluntary cough associated with URTI and how OTC treatments may influence this sensation.

In conclusion; Sweet tasting menthol cough drops are an effective treatment for cough due to URTI but the effects are relatively short lived. This may not be an issue as multiple lozenges can be taken during the day. Sucking lozenges at night during sleep is not possible but a mentholated vapo-rub could provide nighttime relief from cough. However, the most important advance would be to reduce the sensation of irritation, which leads to coughing associated with URTI. Influencing the effects of inflammatory mediators on airway sensory nerves would be a means to influence the sensation of irritation but this may be difficult because of the involvement of multiple mediators and multiple receptors on airway nerves.
Effect of respiratory viral infection on cough receptors

Brad Undem, PhD, Johns Hopkins University School of Medicine, Baltimore, MD

The persistent itchy urge-to-cough that often accompanies respiratory viral infections is an obvious reminder that the function of the airway sensory nerves have been corrupted. The primary afferent nerves that initiate the coughing comprise vagal C-fibers and a unique type of vagal Aδ fiber. These sensory nerves can be modulated in basically three ways. First, they can be acutely affected in such a manner that action potentials are discharged. Secondarily, they can be rendered electrically hyperexcitable such that the threshold for an activating stimulus is decreased and the stimulus-induced action potential discharge frequency is enhanced. These effects are likely associated with various inflammatory responses and terminate once the inflammation subsides. Thirdly, the nerves can be modulated in a more persistent fashion by changing the expression of relevant genes, i.e. neuroplasticity. In this case, the modulation can outlive the virus infection, just as some important negative consequences of viral infections such as asthma exacerbations and development of a chronic unproductive cough can outlive the actual acute viral inflammation. This viral mediated plasticity likely involves the production of particular neurotrophic factors that interact with high affinity neurotrophic factor receptors on the nerve terminals. Activation of these receptors results in changes in gene expression in the cell soma situated in the distant sensory ganglia. We have found that infection with the respiratory virus parainfluenza 3 can lead to the de novo production of tachykinins and TRP channels in Aδ cough receptors. This plasticity is associated with a hypertussive state, and is mimicked by exogenous application of BDNF, a neurotrophic factor that is produced by the airway epithelium upon viral infection.
Issues in Clinical Cough: Update on Pediatric Cough

Ahmad Kantar, MD, PhD, MSc, Pediatric Asthma and Cough Centre, University and Research Hospitals, Ponte San Pietro - Bergamo, Italy

Despite the high prevalence of cough in children, the subject is relatively poorly researched. Although to pediatricians, children are clearly different to adults, this seems less recognizable to many health professionals. During childhood, the respiratory tract and nervous system undergo a series of anatomical and physiological maturation processes that influence the cough reflex. In addition, immunological response undergoes developmental and memorial processes that make infection and congenital abnormalities the overwhelming causes of cough in children.

Coughing in childhood is common, and of these a significant proportion will develop chronic cough. Most cases of chronic cough in children are caused by post-infectious cough, protracted bacterial bronchitis, airway malacia (primary or secondary), bronchiectasis or some combination of these. Other causes of chronic cough, such as asthma, gastroesophageal reflux and upper respiratory syndrome appear to be less frequent.

Regardless of setting and age, children with chronic cough should be evaluated carefully using children-specific protocols. Knowledge of the pathophysiology of the different conditions that cause chronic cough is vital for making a correct diagnosis and prescribing efficacious treatment. The prevalence of each etiology depends on the population under consideration, epidemiology of infectious diseases, age, and the local health system. Literature review demonstrates differences in the definition of chronic cough in children, in the characteristics of diagnostic procedures, the settings in which the studies were conducted and in the prevalence of the main causes. Few studies regarding epidemiology and quality are reported. Moreover, many therapeutic approaches suggested as being useful in adults with chronic cough seem to be less effective in children.

As cough can intensely interfere with the quality of life, it is not surprising that parents are often anxious about their children’s cough and regularly seek medical advice and remedy. Chronic cough in children is associated with a high burden of illness, including doctor visits and parental stress. Moreover, it is generally associated with relevant economic and social costs. Misdiagnosis or non-treatment of chronic cough may drive the development of structural alterations affecting the airways in children. The benefits to the child of making an accurate diagnosis and prescribing adequate treatment therefore extend well beyond merely eliminating cough.
Issues in Clinical Cough: Cough in COPD

Jacky Smith, PhD, University of Manchester, UK

Many respiratory diseases are associated with excessive coughing, but little is known about the extent to which this may be a consequence of increased activation of vagal afferents by airway pathology (i.e. by mucus hyper-secretion, inflammatory mediators etc.) or as result of heightened nerve function. Cough is one of the principle symptoms of COPD and using objective cough monitoring, inhalational cough challenges and an animal model of COPD, we have provided insights into the drivers of cough in this common condition.

We have studied objective cough frequency over a 24hr period in 68 subjects with COPD (mean age 65.6yrs±6.7), 67.6% male, 23 smokers, 45 ex-smokers) and 24 healthy volunteers (mean age 57.5yrs±8.9), 37.5% male, 12 smokers, 12 non-smokers). The highest cough frequencies were observed in COPD patients who were current smokers [median 9.0c/h (IQR 4.3-15.6), almost double that of COPD ex-smokers [4.9c/h (2.3-8.7) (p=0.018)] and healthy smokers [5.3c/h (1.2-8.3) (p=0.03)], whereas healthy volunteers coughed the least [0.7c/h (0.2-1.4)]. Reported sputum production, current cigarette consumption and previous smoking history (pack years smoked) strongly predicted cough frequency, explaining a total of 45.1% variance in a general linear model (p<0.001). In 39/68 COPD patients in whom acceptable sputum samples were induced, a similar model suggested 33.0% of the variance (p=0.002) in day cough frequency (as sputum was collected during the day) was explained by the percentage of neutrophils (p=0.006), and current cigarettes per day (p=0.003).

In a further study, we have modelled the changes observed in cough reflex sensitivity in COPD, to investigate the underlying mechanisms and determine how these changes translate to those in COPD patients. In a cigarette smoke (CS) driven guinea pig model, changes in airway sensory nerve function and cough responses were compared with cough responses to inhaled irritants in patients with COPD, asthma, refractory chronic cough, smokers and healthy volunteers. Capsaicin caused a greater number of coughs in CS-exposed guinea pigs; heightened capsaicin responses were also observed in ex vivo vagus nerve tissue and jugular ganglion neuron cell bodies whereas nodose ganglion neurons displayed evidence of phenotypic switching, newly responding to capsaicin. In contrast, both cough responses, vagus tissue and neuronal responses to PGE2 were decreased by CS-exposure. Consistent with these findings, patients with COPD had heightened cough responses to capsaicin and reduced responses to PGE2 compared with healthy volunteers. Furthermore, the different patient groups all exhibited different patterns of modulation of cough responses.

In conclusion, we have provided evidence for some of the determinants of cough in stable patients with COPD; exposure to cigarette smoke, both past and present, mucus hyper-secretion and neutrophilic inflammation appear important. Cigarette smoke exposure is capable of inducing the changes in airway afferent nerve function seen in patients with COPD. Furthermore, the different profile of cough response across patient groups supports the concept of ‘disease-specific’ phenotypic change in airway nerve function. These findings have important implications for how cough might be best treated in stable COPD.
Sarcoidosis is a multisystem disorder of granulomatous inflammation that most commonly affects the lungs. Approximately 50% of subjects with pulmonary sarcoidosis have a cough. Recent studies have reported a raised cough frequency and impaired quality of life. (Sinha A et al, submitted) Cough reflex sensitivity to capsaicin is heightened, similar to patients with idiopathic chronic cough and cough hypersensitivity syndrome (CHS). Patients report multiple triggers of cough, laryngeal paraesthesia such as a tickle sensation in the throat and urge to cough. This is associated with the degree of cough reflex hypersensitivity, suggesting it the latter is a potential mechanism of cough. Other mechanisms include parenchymal infiltration and distortion due to fibrosis, mechanical effects of significant hilar and mediastinal lymphadenopathy and disease of the upper respiratory tract affecting the nose, larynx and vocal cords. There are no randomised controlled trials available in sarcoidosis cough to guide management. A RCT of inhaled corticosteroids in sarcoidosis reported a reduction in cough symptoms. 1 Corticosteroids are recommended by the ACCP guidelines for sarcoidosis cough. 2 Future studies should investigate the mechanism of cough and evaluate antitussive therapy in well-conducted trials.

Use of Expectorants/Muco-active drugs in Managing Chest Congestion and Cough – A US Perspective

Helmut Albrecht, MD, MS, FFPM, President H2A-Associates, LLC, Miami, Florida

Background: Human airways are lined with a protective mucus layer. Its critical function is to: 1) protect the respiratory tract from fluid loss, 2) entrap and clear inhaled particles, irritants, and pathogens, and 3) inhibit pathogen growth and biofilm formation. Respiratory diseases associated with hyper-secretion and decreased clearance of mucus (e.g., acute viral upper respiratory tract infections [URTIs] or chronic bronchitis) can produce symptoms of chest congestion and cough that may be relieved with muco-active drugs. While several different types of muco-active medicines are available in markets around the world, health care professionals (HCPs) and consumers in the US have very limited choices.

Methods: Relevant clinical methods, studies and specific surveys are being reviewed to examine available muco-active treatment choices in the US, as well as attitudes of consumers and HCPs about the usefulness of, and the risk concerns related to, these options.

Observations and Conclusions: The limited choice of FDA-approved muco-active drugs (mostly expectorants), as well as the paucity of recent clinical studies on their use in treating mucus-related chronic bronchitis or URTI symptoms, may have curbed the awareness and popularity of these products with HCPs in the US. Recently published survey results have shown that consumers rely on these products for symptom relief, and 75% of respondents did not seek HCP advice to manage cough, chest congestion or other mucus-related URTI symptoms. The tolerability of the expectorants available in the US is well documented, and neither HCPs nor consumers seem to have significant concerns about their safety.

The lack of validated clinical models and recent clinical trials for chest congestion may have created a disconnect between HCPs’ perception, and the actual everyday consumer experience of satisfactory relief from mucus-related symptoms with these products. This field is in desperate need of innovative scientific methods and instruments. Several options are being explored to find better ways to align clinical evidence with consumer-reported experience. The combination of scientific and clinical data with consumer surveys in a standardized “Big Data” approach for novel analyses and could be a promising technique worthy of exploration in hopes of getting to the needed breakthrough in assessing the efficacy of muco-active drugs in the treatment of URTI symptoms.
Levodropropizine (Levo) is a peripherally acting non opioid drug that has been used as an anti-tussive drug since the 1980s in many countries. Whilst there are many clinical studies in the literature describing the clinical benefit of Levo, much less is known about the mechanism of action underlying the anti-tussive effect of this drug. Indeed, one of the few studies that have investigated the mechanism of action of Levo was the work of Shames et al, 1996 who demonstrated that Levo could inhibit phenylbiguanide induced stimulation of pulmonary C-fibres. Furthermore we have recently reported that Levo inhibits ozone-induced hypertussive responses to inhaled citric acid in experimental animals (Clay et al, abstract presented to this meeting). A recent meta analysis covering 7 controlled clinical studies of Levo including 2633 patients and a further 4 clinical studies involving 780 children concluded that the drug is well tolerated and effective anti-tussive drug, particularly demonstrating a highly statistically significant anti-tussive effect in paediatric patients (De Blasio et al, 2014).


Critical Review of Currently Available Antitussives: Benzonatate

Lorcan McGarvey, MD, FRCP, Queen’s University Belfast, N. Ireland

Benzonatate was first synthesized in 1956 and is a long chain polyglycol derivative chemically related to procaine. Evidence of its anti-tussive effect in humans was reported shortly after in 1957\(^1\). In this open label study benzonatate was reported to be more effective than codeine in inhibiting citric acid induced cough. As benzonatate is known to be a potent sodium channel blocker the presumed mechanism for its anti-tussive effect is the peripheral anaesthesia and inhibition of afferent vagal airway nerves\(^2\). Further evidence of its efficacy was reported in a number of studies and despite limitations in the trial design, benzonatate was marketed as Tussalon Perles and approved as an anti-tussive by the U.S. Food and Drug Administration (FDA) in 1958. It is quite remarkable that since then very few studies on this drug have been undertaken. Its side effect profile is relatively benign although recent concerns have been raised as to its safety with case reports of seizures\(^3\) and cardiac arrest\(^4\). However Benzonatate remains a prescription drug for the relief of cough in patients over the age of 10 years, but the FDA has recently issued a drug safety communication\(^5\). In this brief lecture the historical clinical trial literature and more recent experimental studies using this interesting compound will be discussed with some insight into why this compound was developed and remains a widely used therapy.

---

Dextromethorphan was first reported to be an antitussive agent in the year of my birth. Like me it has no thoughts of retirement. Indeed it is one of the most widely used OTC medicines for the treatment of acute cough. It is the dextro isomer of levorphanol methylether and is supported to suppress the cough reflex in the postulated medullary cough centre. Its molecular mode of action is still unknown but has been postulated to be through an action on the NMDA, Sigma 1, or serotonergic mechanisms. Dextromethorphan has a prolonged activity probably through retention within the central nervous system and metabolism is a polymorphic through CYP2D6.

Clinically, dextromethorphan has been studied in seven studies using either citric acid or the capsaicin cough challenge. There is clear evidence of the efficacy in these models which suggest that maximum efficacy is achieved at a 60 mg a day dose in the adult as opposed to the currently licensed 30 mg a day. This latter dose has been studied in three clinical trials using subjective end points. Unfortunately these trials are also relatively poor quality without placebo control. In contrast, Parvesi performed the first study to demonstrate drug efficacy of any sort in acute cough by way of acoustic recording. This was reported as a meta-analysis of six double blind, placebo-controlled studies and showed a significant reduction in objective cough. Lee, using a different cough counting methodology called cough sound pressure level also demonstrated a significant reduction in objective cough counting compared with placebo, however other measures were not significantly different.

In children, dextromethorphan has been studied in fewer patients, usually using subjective measures. Here, there is little evidence of significant effect over placebo syrup or honey. However given the small number of subjects studied, the possibility of data type II error is high given the relatively small degree of cough suppression shown in the adult studies of approximately 15%. In children and young adults there is also the risk of the drug being used as a substance of abuse at high doses. For this reason regulatory restrictions have been placed on sale in the certain jurisdictions.
Opiates such as morphine and codeine have been used as antitussives but their utility in treating chronic cough is finely balanced in terms of their effectiveness/side-effect ratio. Non-narcotic antitussives such as amitriptyline and gabapentin have been introduced, with their utility derived from their established use in the treatment of neuropathic pain. Amitriptyline was first reported to cause substantial reduction of chronic cough in 11 of 12 such patients. In a prospective, randomised, controlled, open-label trial to compare the effectiveness of amitriptyline with codeine plus guaifenesin for chronic cough with suspected post-viral vagal neuropathy, most patients in the amitriptyline group achieved a complete response, whereas none of the patients in the codeine plus guaifenesin group had a complete response. Gabapentin effectively reduced cough in patients with chronic cough in a randomised, double-blind trial. Measures that were improved included 24 hour cough counts, Leicester cough questionnaire scores and subjective VAS scores. However, gabapentin has also been reported to be beneficial in patients with chronic cough who had laryngeal sensory neuropathy.

A major issue with gabapentin and amitriptyline is that of side effects, particularly CNS effects including drowsiness and interference with mental activity. A gradual titration of the dose of gabapentin over a period of time is likely the best approach. Clinically, the response to these two antitussives can still be considered as modest, but they represent an important advance in the treatment of chronic cough.

Both amitriptyline and gabapentin have central antinociceptive actions. For example, gabapentin reduces pain via modulation of GABAergic neurotransmission or voltage-gated ion channels in the spinal cord, midbrain, thalamus, and sensory and insula cortices in the brain. Gabapentin had no effect on capsaicin sensitivity, which argues against a suppressive effect on cough reflex pathways. Since cortical responses to airway irritation share remarkable similarity with those associated with painful stimuli, amitriptyline and gabapentin might reduce cough and pain via similar mechanisms at brainstem and supramedullary sites.

Potentially new antitussives includes TRPV1 and TRPA1 antagonists, although a small study of a TRPV1 antagonist failed to show any effect on chronic cough, partly due to its modest effect in blocking capsaicin cough response. P2X3 antagonist appears more promising.
Oral Abstract Presentations
Moderators: Peter Dicpinigaitis & Lorcan McGarvey

Session 1
Effect of Flurbiprofen 8.75mg on Coughing in Patients with Upper Respiratory Tract Infection – Berndard Schachtel
Obstructive Sleep Apnea in patients at a Voice Disorders Clinic and its Relationship to Cough Intensity in Patients with Irritable Larynx Syndrome – Krishna Sundar
Red Alert! Rescuing the Larynx from the Inevitable Effects of Cough. A Voice Pathologist’s Perspective – Catherine L. Ballif
ATP Cough Challenge in Healthy Volunteers – Helen Fowles
The Effect of Female Hormonal Profile on Selected Cough Parameters – N. Kavalcikova-Bogdanova
Association of Esophageal Dysfunction with Therapeutic Efficacy of Baclofen in Patients with Refractory Gastroesophageal Reflux-Induced Chronic Cough – Xianghuai Xu

Session 2
Effect of Esophageal Acid Infusion on Cough Reactivity in the Guinea Pigs with Chronic Capsaicin Inhalation – Qiang Chen
Ozone induces a hypertussive response to inhaled citric acid in rabbits – Clive Page
Extended-Release Guaifenesin/Pseudoephedrine Together with a “Wait and See” Approach to antibiotic prescribing for Upper Respiratory Tract Infections – Hipolito G. Mariano (Presented by Tim Shea)
Patterns of Inappropriate Antibiotic Use in Cough – Alike van der Velden
A Randomized Clinical Trial of Levodropropizine Effect on Respiratory Center Output in Patients with Intractable Chronic Cough – Giovanni A. Fontana
Mothers’ and School Nurses’ Assessment of Cough and Cold Impact on Children’s Quality of Life – Laurence E. Flint (Presented by Marilyn Morrisey)
Saturday June 6, 2015

8:00 am  Registration Desk Opens
8:00 am  Exhibit Hall Opens
8:00 am  Breakfast

**Pro/Con Debate: Treatment of acute cough due to the common cold: multicomponent, multi-symptom therapy is preferable to single-component, single-symptom therapy**
*Chair: Peter Dicpinigaitis*

9:00 am  Pro: Ronald Eccles
9:30 am  Con: Ronald Turner
10:00 am Discussion

**Future Directions in Antitussive Drug Development**
*Chairs: Clive Page & Maria Belvisi*

10:20 am Does it all end with dextromethorphan? NMDA receptor antagonists as potential antitussives – **Brendan Canning**

10:45 am P2X3 antagonism using AF-219: clinical potential in pathological cough and other conditions – **Anthony Ford**

11:10 am Update 2015: TRPA1/TRPV1 antagonists as potential antitussives – **Maria Belvisi**

11:35 am **Networking Lunch Break & Exhibits**

**New Concepts in Cough Evaluation and Therapy**
*Chairs: Alyn Morice & Lorcan McGarvey*

12:30 pm Use of surface-evoked laryngeal sensory action potential (SELSAP) testing in the evaluation of chronic cough – **Jonathon Bock**

12:55 pm Regulation of repetitive coughing: Lessons from CO$_2$ – **Donald Bolser**

**Cough and GERD**
*Chairs: Alyn Morice & Lorcan McGarvey*

1:20 pm Evaluation of GERD-associated cough: when to stop empiric trials and initiate diagnostic studies – **Kenneth DeVault**

1:45 pm Diagnosis of reflux-related cough and the importance of non-pharmacological management – **Jamie Koufman**

2:10 pm Concluding Remarks – **Peter Dicpinigaitis**
Treatment of acute cough due to the common cold: multicomponent, multi-symptom therapy is preferable to single-component, single-symptom therapy: Pro

Ronald Eccles, BSc, PhD, DSc, Cardiff University, Wales, UK

The type of cough we are considering is cough due to common cold. A common cold is an acute disease lasting on average for a week. Cough persisting after all other common cold symptoms are resolved, is in my view not under discussion in this debate as the title of our debate refers to acute cough due to common cold, and we are not considering cough as a single symptom that may persist for weeks after a common cold. It is self evident that multi-symptom therapy is for multiple symptoms and not for cough as a single symptom.

Common cold is by definition a multi-symptom syndrome. A combination of several symptoms usually persists for the duration of the illness over a week or more. Patients regularly use multiple therapies to treat a range of simultaneous symptoms such as sore throat, headache, muscle aches, nasal congestion, runny nose and cough. The benefits of multi-symptom-therapy compared to single symptom therapy in multi-symptom common cold are;

COMPLIANCE
In any medical treatment it is self-evident that the simpler the dosing regimen the more likely it is that the medicines will be taken in the correct dose at the correct time. If a patient needs to take three different medicines, it greatly simplifies the treatment regimen, if all the medicines can be taken in a single dose.

EFFICACY
The efficacy of any medicine depends on taking the correct dose at the correct times. Under-dosing by missing a dose, or taking doses of medicine at extended dose intervals will affect the efficacy of any medicine. The combination of several active ingredients into a single dose ensures that the needed medicines are all taken together.

SAFETY
It is self evident that taking several medicines in combination in one dose is safer for the patient than taking each medicine individually, as doses may be taken at the wrong times and the patient may accidentally overdose. No evidence has been found that multi-symptom relief medicines are inherently less safe than single-active ingredient medicines.

COST AND CONVENIENCE
Multi-symptom therapies are much cheaper than purchase of two, three or four separate therapies and the convenience of a single dose from a single product is self evident.
Treatment of acute cough due to the common cold: multicomponent, multi-symptom therapy is preferable to single-component, single-symptom therapy: Con

Ronald Turner, MD, University of Virginia, Charlottesville, Virginia

Combination products are most useful when the drugs in the combination are directed at different symptoms that consistently occur together in the course of an illness or when the different drugs provide additive or synergistic effects on a specific target symptom. When these conditions are met, and the pharmacologic properties of the drugs are compatible, combination products may be less costly and more convenient for the patient.

There are no antiviral treatments available for routine use in the common cold. Thus, treatment of these illnesses is confined to symptomatic treatments directed at the individual symptoms. The prominent symptoms of the common cold are sore throat, rhinorrhea, nasal obstruction and cough. There is considerable variability in both the presence and severity of these symptoms over the course of the illness and among different individuals with a common cold illness.

The symptomatic treatments that are available are only modestly effective and can be associated with annoying side effects. The antihistamines are useful for rhinorrhea and cough but cause drowsiness in many patients. The topical adrenergic agents are quite effective for congestion while the oral adrenergic agents provide only modest relief and are associated with insomnia in some patients. Analgesics are useful for pain related symptoms such as sore throat and headache. The beneficial effect of these treatments is limited to the target symptoms. Thus, there does not appear to be any beneficial effect of the oral adrenergic agents on rhinorrhea or cough nor of the antihistamines on nasal congestion. Combining these drugs into a combination product delivers useless treatment to patients who do not have the target symptom while exposing the patient to the potential for unnecessary side effects. Provision of these treatments as single agents allows the patient to select treatment based on which symptoms are most bothersome and which side effects are most tolerable.
Does it all end with dextromethorphan?
NMDA receptor antagonists as potential antitussives

Brendan J. Canning, PhD, Johns Hopkins Asthma and Allergy Center, Baltimore, Maryland

Dextromethorphan (DXM) is perhaps the most frequently used medicine for cough suppression. Multiple mechanisms of action have been ascribed to DXM, including Sigma receptor activation, Calcium channel blockade and nicotinic receptor antagonism. Although each of these neuronal targets may account in part for the therapeutic benefits (and risks for abuse and safety liabilities) of DXM, the best validated mechanism for cough suppression ascribed to DXM is N-Methyl-D-Aspartate (NMDA) receptor antagonism. Indeed, with studies performed in humans and multiple other mammalian species (dogs, cats, rabbits, guinea pigs, rats, mice) and with multiple NMDA receptor/channel blockers evaluated (DXM, ketamine, memantine, MK801, AP-5, NBQX, SDZ-220581), NMDA receptors may be the best validated therapeutic target in cough (Canning, 2009).

NMDA receptors are neuronal receptors for the excitatory amino acid glutamate, the primary excitatory neurotransmitter in the central nervous system. NMDA receptors are ionotropic receptors comprised of 2 subunits, designated NR1 and NR2, respectively. There are 4 subtypes of NR2 subunits, each with unique pharmacological properties and distribution patterns in brain. NMDA receptors are unique in several ways, most notably their requirement of 2 excitatory ligands, with glutamate interacting with NR2 subunits, and the endogenous co-agonists glycine or D-serine binding to the NR2 subunits. With both binding sites engaged, the NMDA receptor/ion channel gates influx of sodium and calcium, promoting excitation and intracellular signaling, including formation of nitric oxide by nitric oxide synthase.

There are multiple therapeutic strategies for targeting NMDA receptor signaling. Drugs may interact with either the glycine/D-serine binding site or the glutamate binding site. NR2/glutamate binding site selective antagonists have been described and evaluated clinically in several diseases. The NMDA receptor channel may also be targeted, a mechanism shared by MK-801, ketamine, memantine and DXM. Alternatively there are allosteric binding sites on the NR2 subunit that may be a target for endogenous neurotransmitters (e.g. dynorphin), neuromodulators (e.g. polyamines, Zinc, protons) and exogenously administered therapeutics. As NMDA receptors are widely distributed in brain and involved with both homeostatic and pathophysiologic functions, the challenge targeting NMDA receptors in cough and in other diseases is balancing therapeutic benefits while limiting side effects and abuse potential, as NMDA receptors are also a target for drugs of abuse, including PCP, ketamine and DXM.

Based on the rationale provided above and because of its unique pharmacological properties as a use dependent blocker of NMDA receptor/channels, memantine has been evaluated as a novel antitussive drug in both preclinical and clinical settings (Smith et al., 2012; Dicpinigaitis et al., 2015). Memantine markedly reduced evoked cough responses in guinea pigs, and comparable results were obtained in cough challenge study performed in healthy human subjects. We will review the preclinical and clinical rationale for NMDA receptor antagonism in cough.
P2X3 Antagonism using AF-219: clinical potential in pathological cough and other conditions

Anthony Ford, PhD, Chief Scientific Officer, Afferent Pharmaceuticals, San Mateo CA, USA

ATP plays a prominent role in sensory function and is recognized as being able to activate & sensitize signal transmission at multiple sites along the sensory axis. The most established sensory action of ATP is to excite primary afferent neuron (PAN) peripheral terminals, linking receptive fields across tissues and organs to the CNS. The action of ATP on unmyelinated PANs (C-fibers) is mediated via two populations of P2X3-containing trimeric cation channels, P2X3 (P2X3.3.3) and P2X2/3 (P2X3.2.3): the former mostly operating to sensitize nociceptive C-fibers, driving common pathological signs and symptoms, and the latter restricted to certain non-nociceptive viscerosensory C-fibers.

In recent years, drug-like P2X3 antagonists have emerged, that show broad activity in inflammatory, neuropathic & visceral models of hyperalgesia and irritation. Significantly, these compounds have no overt CNS action & are inactive versus acute defensive reflexes to noxious stimuli. The only such P2X3 antagonist to have advanced into clinical studies is AF-219, an orally active small molecule with peripherally restricted distribution. AF-219 shows high specificity for P2X3 channels, with preferential antagonist potency (IC50 of 20-30nM) for homotrimeric P2X3 channels over heterotrimeric P2X2/3. AF-219 has now advanced through completion of nine clinical studies to date: four undertaken in patients with distressing and poorly managed musculoskeletal, urological or respiratory signs and symptoms. Several more clinical studies will be completed in 2015.

The most pronounced efficacy responses seen using AF-219 have been in patients with severe chronic symptoms associated with two major “hollow organ” systems – the airways (chronic cough) and the lower urinary tract (bladder pain syndrome), likely reflecting the major role ATP release plays in such tubes and sacs as a chemical distress signal of underlying pathology. The unprecedented efficacy demonstrated by AF-219 in a 14 day placebo controlled cross-over trial in patients with refractory chronic cough, in which objectively assessed daytime cough frequency was attenuated >75%, with concordant effect on subjective symptoms and QOL measures, has triggered extensive clinical effort studying AF-219 in additional dose-finding pathological cough studies and in additional cough populations. These efforts are directed to understand the optimal use of this P2X3 antagonist for troublesome cough, elucidating optimal dosing strategies to achieve best control for patients. Recently, new preclinical data have been generated using Afferent’s P2X3 antagonists that may open avenues for management of additional chronic signs and symptoms in patients with chronic airways disease, as further evidence of the role of ATP activation of P2X3 receptors in conditions of chronic pathology.
Airway sensory nerves are known to express a variety of receptors and ion channels that are activated by a variety of exogenous and endogenous mediators to cause cough. A greater understanding of the mechanisms of how these receptors and ion channels are involved in cough may lead to the development of new and effective therapies. Particular focus has been on TRPV1, TRPA1, TRPV4 and TRPM8, in the activation of airway sensory nerves and in the control of tussive responses and various drug discovery initiatives are progressing.

Several TRPV1 antagonists have been developed and profiled in clinical trials; however most of those that have entered clinical trials cause hyperthermia as a side effect. In both animal and human studies, the use of TRPV1 antagonists is known to cause hyperthermia and impaired perception of noxious heat which is clearly an issue for potential development compounds. Antagonizing TRPV1 with certain compounds has been shown to raise the core body temperature of the patient to an unacceptable level and also impairs noxious heat sensation raising the probability of scalding injuries. Nevertheless, several small molecule TRPV1 antagonists have been developed that have overcome these problems.

Selective TRPA1 inhibitors are also potential therapeutic agents for chronic cough as TRPA1 plays an important role in respiratory symptoms induced by endogenous and exogenous irritants, and is also a sensor of oxidative stress. In addition, TRPA1 antagonists have not yet been shown to have the same temperature regulation safety concerns as TRPV1, which would suggest that perhaps this channel is a more suitable target. Several TRPA1 channel antagonists in the clinic to combat chronic cough, although several are in pre-clinical development outlined below for potential use in cough and also asthma.

As not much is in the public domain about the role of TRPV4 in initiating cough, there are currently no antagonists in the clinic for the treatment of cough or respiratory disorders. However, it has been suggested that TRPV4 does cause cough via a different mechanism to that seen with TRPA1 and TRPV1. In addition, activation of TRPV4 has been shown to cause contraction of both human and animal airway smooth muscle. Therefore TRPV4 antagonists could prove to be an attractive target for lung disease to combat both bronchoconstriction and cough, and could be used alongside a TRPA1 or TRPV1 antagonist to target a different population of airway afferent fibres.

Contrary to activation of TRPA1, TRPV1 and TRPV4, activation of TRPM8 by menthol has instead been shown to have an antitussive effect. Menthol has been used for years in a number of OTC therapies, for its antitussive properties. In addition, menthol has been added to cigarettes for a number of years to reduce airway irritancy. Although preliminary data from our laboratory suggests that the anti-tussive activity of menthol is mediated via a TRPM8-independent mechanism.
Laryngeal sensation is difficult to directly measure, and most previously described techniques involve mechanoreceptor testing only. We have recently reported a new surface technique for studying sensory conduction in the superior laryngeal nerve (SLN). Using this technique, we are able to perform surface stimulation of the vagus nerve 7-10 cm proximal to a surface electrode placed over the cricothyroid muscle was performed in controls and in subjects with needle electromyographic (EMG)-confirmed laryngeal neuropathy. Cathodal stimulation was applied below the mastoid process behind the sternocleidomastoid muscle. Nerve conduction parameters have been determined in patients with EMG-confirmed laryngeal neuropathy and in normal healthy controls. Non-invasive SLN evoked potential studies were performed on healthy volunteers (n=28) as well as neuropathic subjects (n=27). Compared to controls, the neuropathic subjects had statistically significant differences in baseline-to-peak amplitude, conduction velocity, and intra-subject side-to-side amplitude ratio (p < 0.01) of their surface evoked laryngeal sensory action potential (SELSAP). Based on these studies, we determined that Laryngeal sensory nerve conduction can be determined non-invasively by evaluating SELSAP waveform. This study provides a reproducible method for electrophysiological evaluation of a sensory branch of the superior laryngeal nerve.

Additional work has evaluated the role that SELSAP testing can help inform care for patients with suspected neurogenic chronic cough (NCC), which is a poorly understood cause of cough and challenging to treat. Laryngeal EMG data including SELSAP waveform testing from chronic cough patients was directly compared to a control population without significant laryngeal symptoms and statistical analysis of unilateral and bilateral neuropathy injury subgroups was performed. Thirty patients with a chief complaint of chronic cough underwent laryngeal EMG testing with needle EMG and surface nerve conduction studies. SELSAP waveform analysis in unilateral and bilateral laryngeal neuropathy demonstrated significantly lowered median SELSAP peak amplitude compared to controls (P < 0.01). We were able to demonstrate that patients with suspected NCC demonstrate statistically significant alterations in SELSAP waveform that can support a diagnosis of laryngeal sensory neuropathy. This suggests that SELSAP waveform morphology changes may be able to predict superior laryngeal nerve neuropathy and possibility of response to neuroleptic medications. Ongoing work is being performed to assess the ability of this technique to predict response to treatment.
Paroxysmal coughing represents relatively uncontrollable repetitive cough that is associated with significant morbidity, including dizziness and breathlessness. In animal models, repetitive cough episodes induce significant hyperventilation (PCO$_2$ values of < 20 mmHg, and arterial pH of > 7.5). Current hypotheses propose that the cough motor pattern is controlled by a brainstem circuit that also controls breathing. However, the brainstem respiratory rhythm generator is a CO$_2$ dependent system. Cough-induced hyperventilation in animal models typically brings systemic CO$_2$ well below apneic threshold, yet vigorous respiratory muscle contractions continue. This cough-induced derangement of blood gases presents a challenge for the respiratory control system especially during the cough-to-eupnea transition. We have investigated cough-induced hyperventilation in an anesthetized cat model. We hypothesized that following cough-induced hyperventilation: a) there would be limited apnea, and b) the eupneic breathing cycles would be relatively unaffected by the previous level of hyperventilation. Repetitive cough was elicited by mechanical stimulation of the intra-thoracic trachea in anesthetized, spontaneously breathing cats. During repetitive coughing, end-tidal CO$_2$ levels dropped from a mean of 33 ± 2 mm Hg to 12 ± 4 mm Hg. The cough-to-eupnea transition was marked by hypopnea durations of 18 ± 8 s but very short (approximately 3s) apneas. In comparison, mechanical ventilation is a separate group of animals to similar levels of end-tidal CO$_2$ resulted in apneas in excess of 45 s. These results support a significant reduction in apneic threshold during the cough-to-eupnea transition. A widely variant apneic threshold suggests that the respiratory control system alters how it is regulated based on the function of the behavior that it produces at any one time. While breathing is a homeostatic behavior controlling gas exchange, cough is solely a defensive behavior that accelerates alveolar gas to generate airway shear forces. The lowered apneic threshold during/following cough a) allows cough to be produced when CO$_2$ is low, and b) functions to buffer cough-induced hyperventilation. This buffering following coughing minimizes the probability of further oscillations in blood gases and pH as the respiratory system returns to homeostasis.
Evaluation of GERD-associated cough: when to stop empiric trials and initiate diagnostic studies

Kenneth DeVault, MD, Mayo Clinic of Florida, Jacksonville, FL

The association between chronic cough and reflux has been reported for over 20 years and treatment of reflux is a common part of most health care provider’s approach to cough. That having been said, the response to those trials is often unsatisfactory. I would advocate for early confirmatory testing in these patients for the following reasons:

1. Even typical symptoms (heartburn and regurgitation) are not completely predictive of GERD and certainly do not reliably predict the severity of disease.
2. Adding a therapeutic trial of reflux therapy in typical symptoms is confirmatory, but not so much in cough
   a. 2 RCT’s of esomeprazole BID compared to placebo did not show a benefit for PPI in cough (Respirology 2011;16:1150, Aliment Pharmacol Ther 2011;33:225)
   b. Similarly an RCT of esomeprazole BID in patients with throat symptoms and a suggestive laryngoscopy did not show a benefit for PPI (Laryngoscope 2006;116:254).
   c. Even response to reflux surgery is lower in patients with cough and well-established reflux.
3. Reflux surgery should NEVER be considered in a patient without objective evidence of reflux

Ambulatory reflux monitoring should thus be considered in most patients with cough and possible reflux. Important points include (Dis Esophagus. 2013;26:755):

1. Excess acid exposure (>5%) is the best marker of pathologic acid reflux
2. Almost all ambulatory reflux testing should be done off acid suppressing medication.
3. Capsule based (BRAVO) testing allows comfortable multiple day testing, but only monitors one location in the esophagus and does not allow impedance monitoring for non- and weakly acidic reflux.
4. Adding proximal monitoring provides helpful information in tube-based tests
5. Impedance monitoring allows identification of non- and weakly acidic events. This significance of these events in a patient off PPI therapy is not clear.
6. Symptom indices (SI and SAP) add to the information from a reflux study, but declaring a study “positive” with normal acid exposure but a positive SI and/or SAP.
7. New technologies (acoustic cough monitoring, Restec, etc) may pay a role in these difficult to diagnose and manage patients.

In summary, the cough/reflux interactions are possible, but likely over-diagnosed. Symptoms, laryngoscopic signs and even response to therapy are neither sensitive nor specific. Off therapy, ambulatory reflux monitoring is as close to a gold standard as exists and should be liberally applied to these patients.
Diagnosis of reflux-related cough and the importance of non-pharmacological management

Jamie Koufman, MD, FACS, Mt. Sinai Health System, New York, NY

Background: Chronic cough is one of the most common symptoms for which a patient seeks medical attention; however, most patients with non-pulmonary chronic cough often fail to obtain an accurate diagnosis and effective treatment.

Materials and Methods: Retrospective review of 50 consecutive chronic cough patients. None of the subjects had primary (inflammatory or neoplastic) pulmonary disease; although 54% (26/50) had been previously diagnosed with asthma. All subjects underwent laryngeal examination, 92% reflux testing, 72% esophagoscopy, and 60% laryngeal electromyography.

Results: The clinical diagnosis for chronic cough was respiratory reflux alone in 40% (20/50), neurogenic (cough) alone in 14% (7/50), and both (reflux-related and neurogenic cough) in 46% (23/50). Eighty-six percent (43/50) had pH-documented reflux; 56% had neuropathic findings on laryngeal EMG; and 46% met criteria for both reflux and vocal fold paresis. The mean number of pH-documented pharyngeal reflux events pH <5 was 146. Of the 43 abnormal pH studies, 93% (43/46) had pharyngeal reflux, but only 37% (16/43) had abnormal esophageal pH data (pH <4). Thus, had those subjects undergone traditional esophageal or impedance reflux testing, 63% (27/43) would have been falsely considered negative. In addition, 36 subjects underwent esophagoscopy and 64% (23/36) had significant pathology. Eighty-eight percent (44/50) responded favorably to dietary, lifestyle, and drug treatment; however, acid-suppression alone with PPIs was never a sufficient intervention.

Conclusions: Although other causes must be excluded, non-pulmonary chronic cough is usually related to respiratory airway reflux and/or a neurogenic cause. Respiratory reflux testing for chronic cough requires specific pharyngeal pH-monitoring technology that is not yet widely available; however, accurate diagnosis is essential to provide effective, patient-specific treatment. In addition, the alarmingly high rate of esophageal pathology in this series of chronic cough patients underscores the need for esophageal screening in patients with respiratory reflux.
RB (Reckitt Benckiser), the maker of Mucinex®, Children’s Mucinex® and Delsym®

is proud to support the membership at its

5th American Cough Conference

Come visit us at our booth
SILVER SPONSORS

McNeil Consumer Healthcare

Don’t wait until allergies are written all over his face.

Recommend ZYRTEC® right from the start of symptoms:

ZYRTEC® Allergy relieves sneezing, runny nose, itchy, watery eyes, and itchy throat or nose.

Register at ZyrtecProfessional.com for FREE ZYRTEC® samples and education materials.

Use only as directed.

©McNEIL-PPC, Inc. 2015
Don’t wait until allergies are written all over his face. Recommend ZYRTEC® right from the start of symptoms.

* Register at ZyrtecProfessional.com for FREE ZYRTEC® samples and education materials.

Use only as directed.

© McNEIL-PPC, Inc. 2015

ZYRTEC® Allergy relieves sneezing, runny nose, itchy, watery eyes, and itchy throat or nose.
Real chocolate taste makes kids smile.

Nighttime cough + cold relief makes moms smile.

They don’t call me wise for nothing.

DR. COCOA®

NIGHTTIME COUGH+COLD MEDICINE FOR CHILDREN.

The trusted, effective ingredients calm coughs and relieve stuffy, runny noses at night, and the 10% real cocoa gives it a rich, soothing, chocolate taste. Also available in Daytime Cough+Cold relief and 8-Hour Cough relief formulations.

RELIEF WITH A SMILE ™

For more information, or to request professional samples, visit us at DrCocoa.com.

Use as directed. ©Copyright infirst Healthcare Inc. 2015

BRONZE SPONSORS

Our Commitment to Respiratory

Dompé

www.dompé.com
Real chocolate taste makes kids smile.
Nighttime cough + cold relief makes moms smile.
They don’t call me wise for nothing.

DR. COCOA® NIGHTTIME COUGH+COLD MEDICINE FOR CHILDREN. The trusted, effective ingredients calm coughs and relieve stuffy, runny noses at night, and the 10% real cocoa gives it a rich, soothing, chocolate taste. Also available in Daytime Cough+Cold relief and 8-Hour Cough relief formulations.

For more information, or to request professional samples, visit us at DrCocoa.com.

Use as directed. ©Copyright infirst Healthcare Inc. 2015
P&G serves nearly five billion people around the world with its brands. The Company has one of the strongest portfolios of trusted, quality, leadership brands, including Always®, Ambi Pur®, Ariel®, Bounty®, Charmin®, Crest®, Dawn®, Downy®, Duracell®, Fairy®, Febreze®, Gain®, Gillette®, Head & Shoulders®, Lenor®, Olay®, Oral-B®, Pampers®, Pantene®, SK-II®, Tide®, Vicks®, Wella® and Whisper®. The P&G community includes operations in approximately 70 countries worldwide. Please visit http://www.pg.com for the latest news and in-depth information about P&G and its brands.

Vernalis is a revenue generating, commercial stage pharmaceutical company with significant expertise in drug development. The Group has two approved products; Tuzistra™ XR targeting the US prescription cough cold market and, frovatriptan for the acute treatment of migraine. It has an exclusive licensing agreement to develop and commercialise multiple novel products focussed on the US prescription cough cold market as well as eight programmes in its NCE development pipeline. Vernalis has also significant expertise in fragment and structure based drug discovery which it leverages to enter into collaborations with larger pharmaceutical companies. The Company’s technologies, capabilities and products have been endorsed over the last five years by collaborations with leading pharmaceutical companies, including AKP, Biogen Idec, Endo, GSK, Genentech, Lundbeck, Menarini, Novartis, Servier Taisho and Tris.
We are pleased to recognize the following exhibitors for their support of the American Cough Conference:

- rb
- Reckitt Benckiser
- infirst
- Pfizer Consumer Healthcare
- Vernalis Therapeutics
- Vitalograph