PAIN AND COUGH

HIGHLIGHTS

Fondazione
Internazionale
Menarini

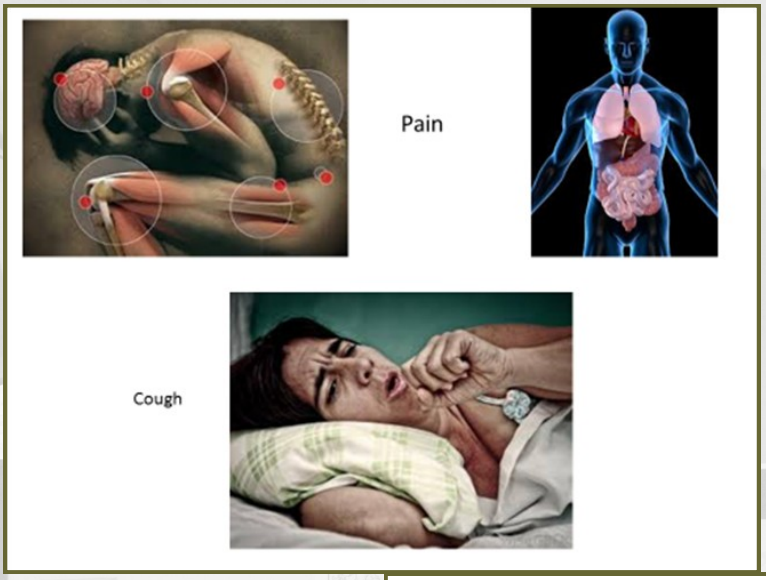
March 19-21, 2015
Florence

PAIN AND COUGH
March 19-21, 2015 Florence

Fondazione Internazionale Menarini

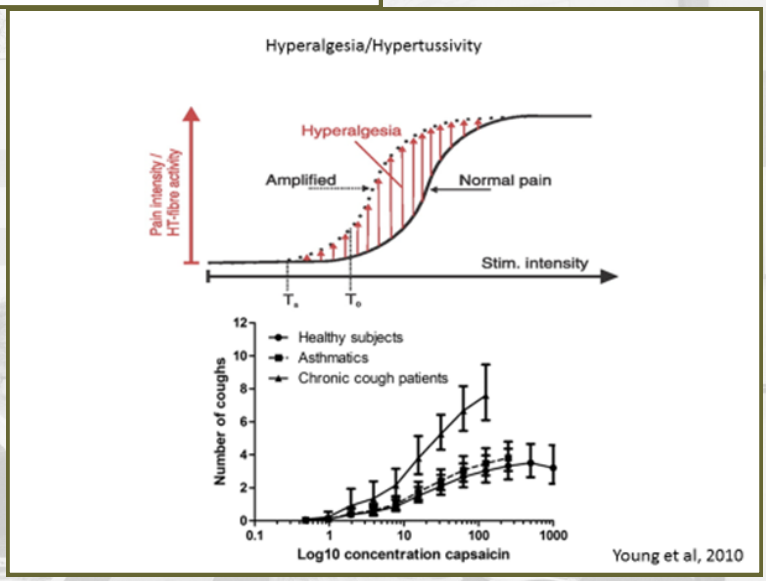
HIGHLIGHTS

From pain to cough: central and peripheral sensitisation mechanisms



Could there be similarities between the mechanisms that give rise to the genesis of painful stimuli and the genesis of cough? Prof. Bradley Undem of Baltimora, opened the symposium by addressing the physiological and physiopathological mechanisms underlying both stimuli, and explained how, despite being in different contexts, they have similarities and said similarities are the rule. In sensitised subjects there may be the onset of both hyperalgesia and hypertoxigenicity following apparently harmless stimuli such as skimming the skin surface in the former case, speaking, or laughing and even brushing teeth in the latter. Whereas in the first case we can speak about allodynia, in the second we speak about allotussicity. And in both cases, the degree of sensitisation increases to the level of the nociceptive terminations.

UNDEM BRADLEY
School of Medicine,
SOM DOM Bay
Clinical Immunology
The Johns Hopkins
University School of
Medicine
Baltimore (MD, USA)



What are the main mechanisms involved in these two phenomena? What are the main receptor channels? Are they located at a central or peripheral level?

To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

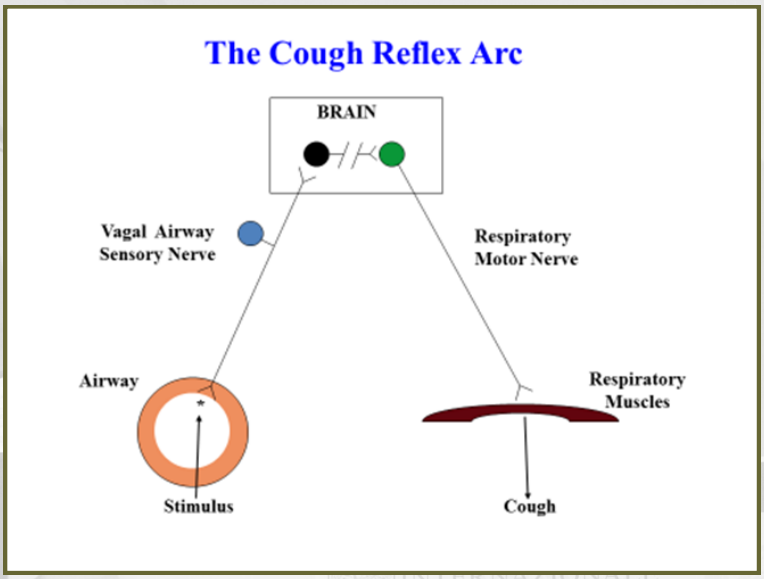
Fondazione Internazionale Menarini

HIGHLIGHTS

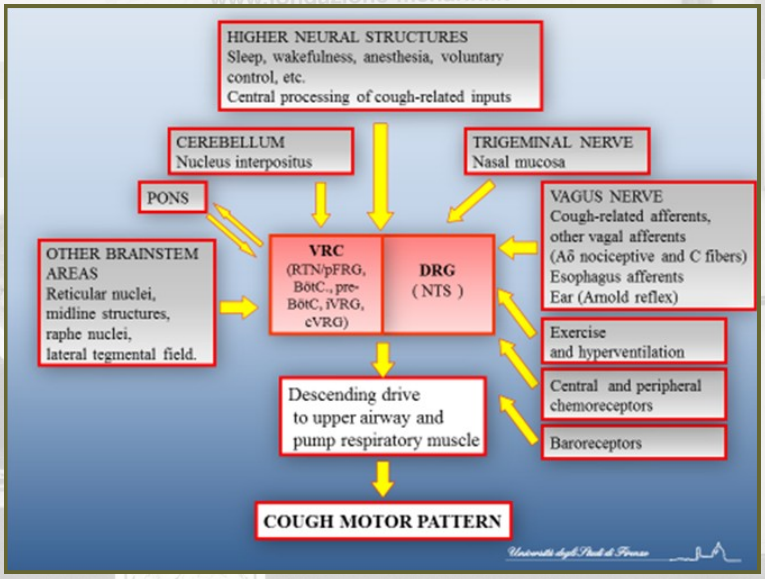
MUTOLO DONATELLA
Dipartimento di Medicina Sperimentale e Clinica
Florence (Italy)

CANNING BRENDAN J.
Asthma and Allergy Center
Johns Hopkins Asthma and Allergy Center
Hopkins Bayview Circle
Baltimore (MD, USA)

What are the main interactions between the central and peripheral mechanisms that control cough?



The interactions between the central and peripheral mechanisms that control a cough are extremely complex. Prof. Donatella Mutolo of Florence, and Prof. Brendan Canning of Baltimore, took turns in describing the main interaction mechanisms between the different nervous structures located at a central and peripheral level. In fact, the cough stimulus is modulated not only by the nerve centres of the cerebellum, pons, reticular nuclei or higher structures, but also by the trigeminal nerve and the vagus nerve; by baroreceptors and central and peripheral chemoreceptors, and by the tussigin stimuli to which people may be subjected at different levels, both central and peripheral. For example, asthma causes cough, likewise viral infections, and both involve the bradykinin pathway while the acidification of the respiratory tract or aspiration phenomena act through activation of the citric acid pathway. Other substances like ozone or atmospheric pollutants such as TDI (toluene diisocyanate) found in foam and soap-based compounds, act by triggering the TRPA1 receptors.



What are the links between these pathways, such as TRPA1, TRPV1, citric acid, bradykinin and Cough?

To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

Fondazione Internazionale Menarini

HIGHLIGHTS

How important is self-control of the cough stimulus?

Urge-to-Cough - The perception of a need to cough

Urge-to-Cough Category Scale

0	No need to cough
0.5	Very, very slight
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very, very severe (almost maximal)
10	Maximum Urge-to-Cough

Davenport, P.W., C.M. Sapienza and D.C. Bolser. Psychophysical assessment of the Urge-to-Cough. European Respiratory Review. 12(85): 249-253, 2002.

Prof. Paul Davenport of Gainesville addressed the issue of the urge to cough, in other words, that stimulus, or more correctly, that threshold beyond which we begin to cough. This topic is extremely important as coughing is a defence mechanism for the respiratory tract and it has to intervene every time an irritating stimulus comes in contact with it. There is a whole series of methods for assessing the threshold of the "urge to cough" in individual patients, as well as questionnaires and experimental tests such as the capsaicin test. In this way it is possible to identify patients at the risk of aspiration of toxic or irritating substances into the respiratory tract. Patients suffering from diseases that affect the muscular structures, such as Parkinson's, are among those with the highest risk of the onset of aspiration phenomena in the respiratory tract, especially in the presence of dysphagia. Even anxiety or the simple fear of coughing are other conditions that expose patients to the risk of aspiration in the respiratory tract. A condition which, in addition to being the gateway for inflammatory/infectious states, can also be the cause of suffocation in the more severe cases.

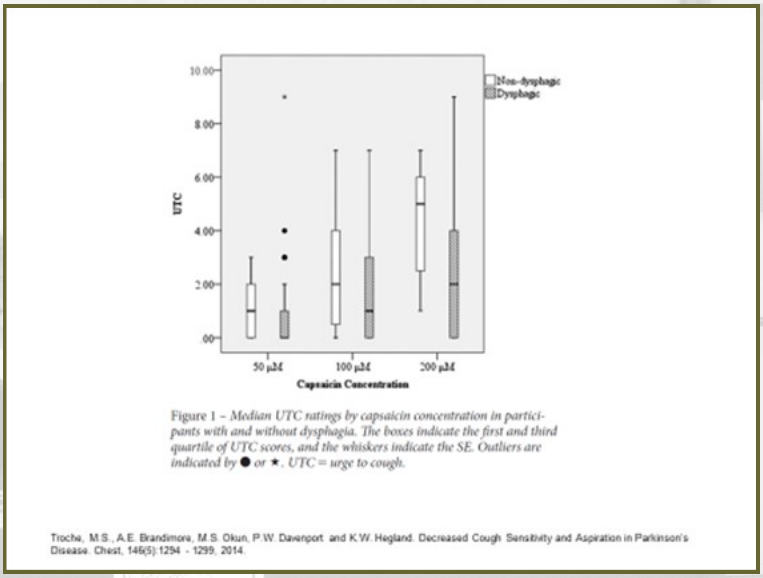


Figure 1 – *Median UTC ratings by capsaicin concentration in participants with and without dysphagia. The boxes indicate the first and third quartile of UTC scores, and the whiskers indicate the SE. Outliers are indicated by ● or ★. UTC = urge to cough.*

Trocha, M.S., A.E. Brandimore, M.S. Okun, P.W. Davenport and K.W. Hegland. Decreased Cough Sensitivity and Aspiration in Parkinson's Disease. Chest, 146(5):1294 - 1299. 2014.

DAVENTPORT PAUL W
Department of Physiological Sciences
Health Science Center
University of Florida
Gainesville (FL, USA)

What are the mechanisms responsible for this stimulus? And which areas of the brain are involved?

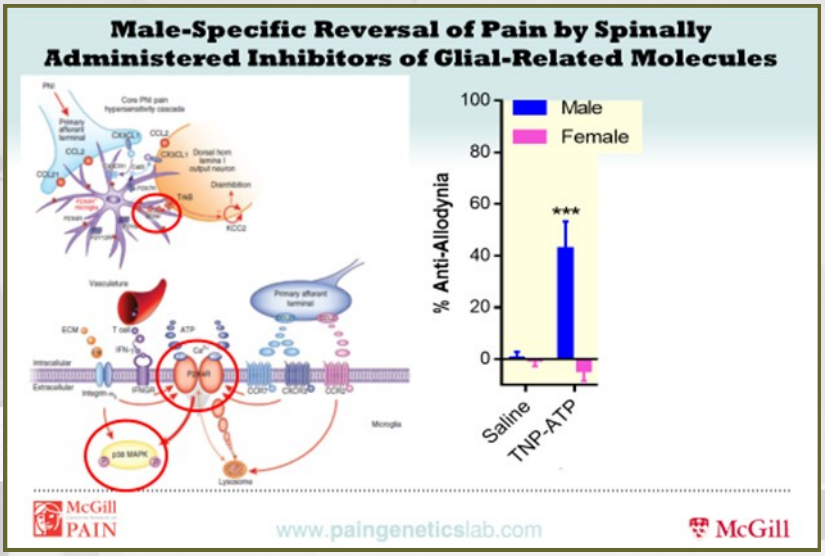
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

Fondazione Internazionale Menarini

HIGHLIGHTS

Who feel pain more: men or women?



Prof. Jeffrey Mogil of Montreal addressed this very interesting topic: is it men or instead women who are more sensitive to painful stimuli? First, it appears that the nociceptive pathways between the two genders are very different, indeed, the microglial cells are mainly involved in men, whereas in women the T-cells are the main mediators of the painful stimulus. There are also many quantitative and qualitative differences purely in pharmacological terms. From experiments in rats, the females showed greater sensitivity to pain, their nociceptive reaction was significantly faster compared to that of the males. If instead we compare the analgesic effect of morphine alone with the combination of morphine and dextromethorphan in males it becomes evident that the combination exerts a greater analgesic activity, while in females the two treatments have the same identical effect. Therefore, two different genders with radically different pathways and responses to pain.

MOGIL JEFFREY S.
Department of Psychology
McGill University
Montreal (QC, Canada)

We now need to answer the initial question: who are more sensitive to pain, men or women?

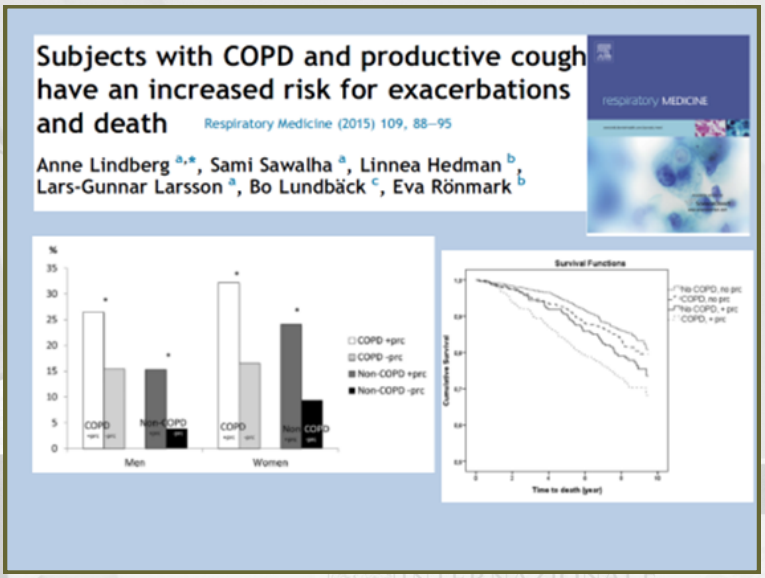
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/….. and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

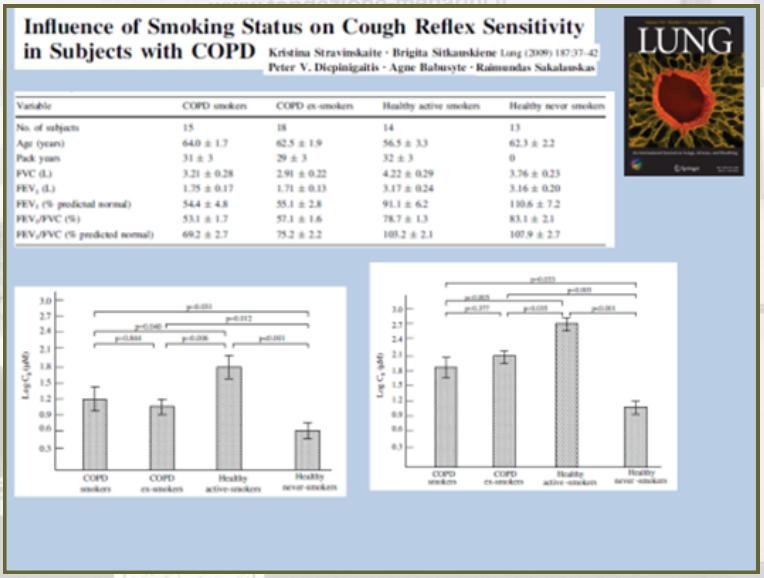
Fondazione Internazionale Menarini

HIGHLIGHTS

Cough: the most troublesome symptom in patients suffering from chronic obstructive bronchopneumopathy.



Cough is not mentioned in the most recent COPD classification, nevertheless it is anything but an innocent symptom, to the contrary, it is an extremely important factor, claims Prof. Giovanni Fontana of Florence. In fact, compared to patients without cough, those with COPD and cough have a higher risk of exacerbation of the disease and even death. But what are the mechanisms that cause cough in patients with COPD? Inflammatory states of the respiratory tract, excess mucous excretions, concomitant diseases, continuous inhalation of irritating substances such as cigarette smoke, and increased sensitisation of the cough reflex. Playing a role of primary importance among the concomitant diseases are bronchiectasis and the gastro-oesophageal reflux disease. Cigarette smoke acts by stimulating the inflammatory cells. Finally, the diagnosis and treatment of cough in patients with COPD. The diagnosis is based on data reported by patients in questionnaires and by counting the number of coughs in a specific unit of time..... and the treatment?



What are the main drugs used to treat cough in patients with COPD? Are they effective? What data are reported in literature?

To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

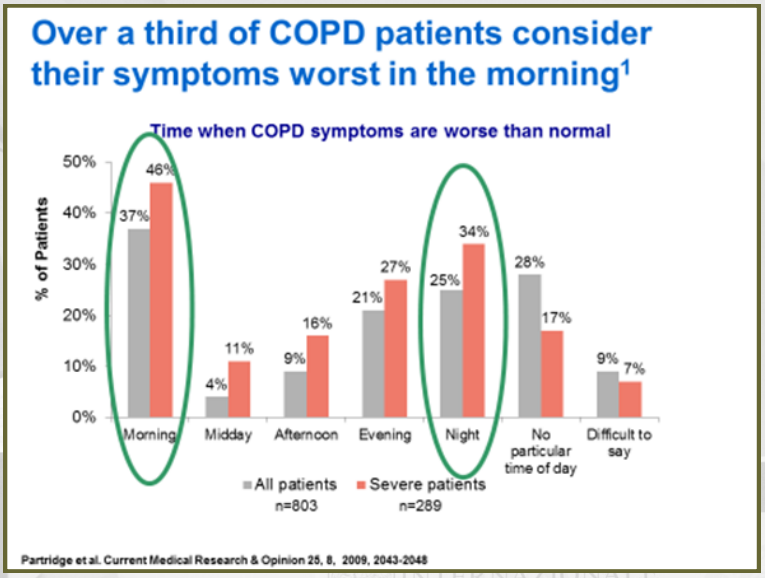
FONTANA GIOVANNI
Dipartimento di Medicina Sperimentale e Clinica
Università degli Studi di Firenze
Florence (Italy)

PAIN AND COUGH
March 19-21, 2015 Florence

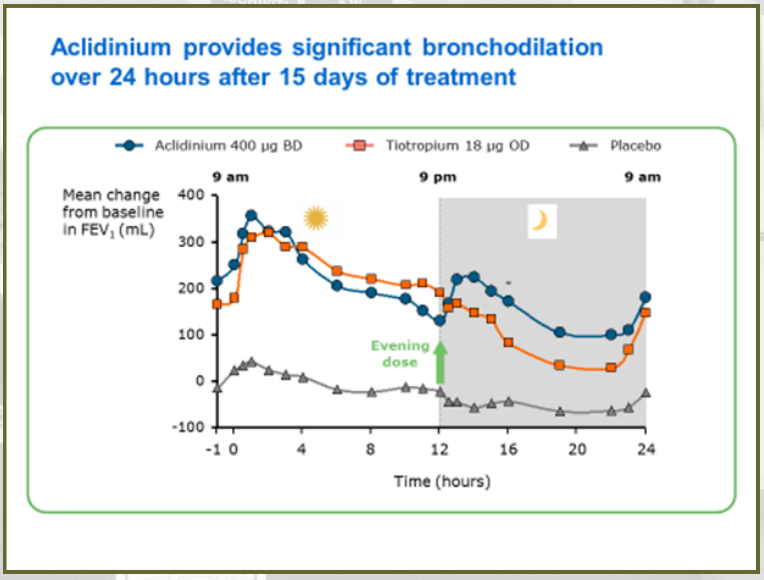
Fondazione Internazionale Menarini

HIGHLIGHTS

Improvement of symptoms in a 24-hour time span: are long-acting antimuscarinic agents all the same?



Prof. Paul Jones of London spoke about the symptoms related to COPD, in particular he explained the symptoms over a 24-hour time. Patients with COPD report more symptoms on waking up and during the night. Among these, they indicate the most predominant as cough, laboured breathing, a sense of oppression or chest congestion, and difficulty in expectorating. Due to these symptoms, patients wake numerous times during the night and are forced to resort to fast-acting treatment. Another fundamental aspect of COPD is linked to its frequently delayed diagnosis, based not so much on spirometric tests, as on the symptoms. In other words, the diagnosis is made when the disease is too often in the advanced stage. And what about the correlation between mortality and the presence of nocturnal dyspnoea? More specifically, the patients who report nocturnal dyspnoea tend to have a more negative outcome in terms of life expectancy compared to patients not suffering from this condition. Emerging within this context is the role of pharmacological treatment and more particularly, the use of long-acting antimuscarinic agents. Prof. Jones illustrated data demonstrating that some of these agents are more effective than others, especially when assessed over a 24-hour time.



JONES PAUL
Consultant Chest Physician
St George's Healthcare NHS Trust
University of London
London (UK)

Which is the most effective long-acting antimuscarinic agent? Do monotherapy and combination therapy have the same effects on the symptoms of COPD?

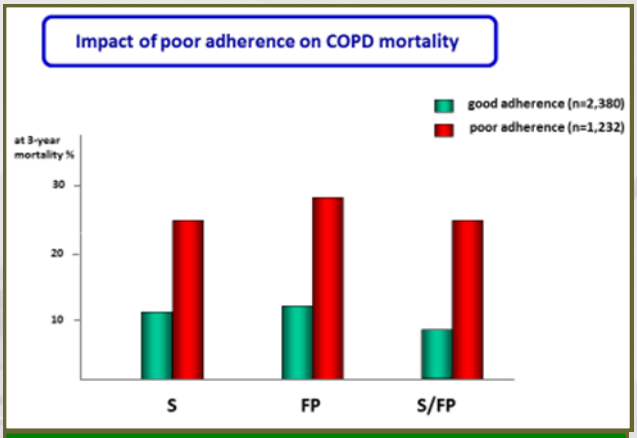
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

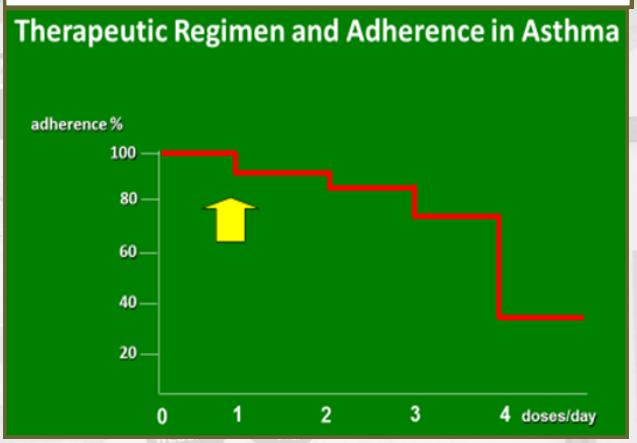
PAIN AND COUGH
March 19-21, 2015 Florence

Fondazione Internazionale Menarini

HIGHLIGHTS

Adherence with therapy: how much do the devices influence this parameter?

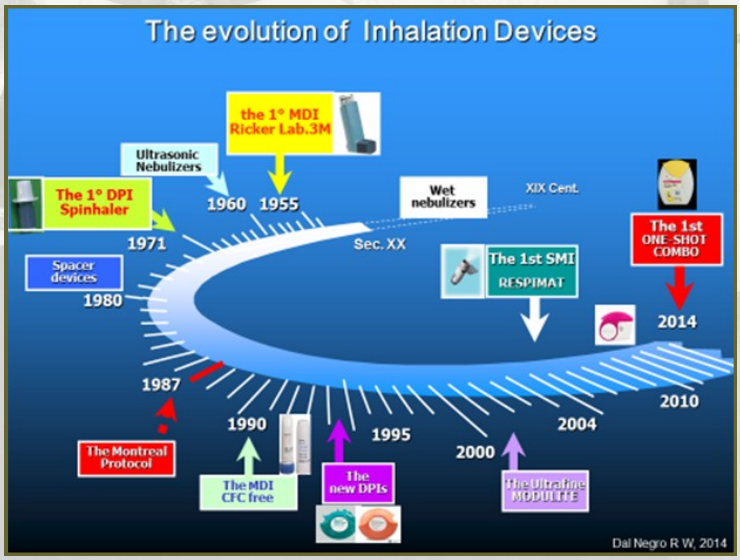




Prof. Dal Negro of the Hospital of Bussolengo addressed this vitally important issue: do patients manage to use the devices in the best possible manner in order to best exploit the effects of the drugs they contain? An initial disturbing fact involves the findings that patients with COPD have adherence to therapy which is at least a third lower than that of hypertensive patients, and patients with asthma have an adherence as much as two thirds lower than that of hypertensive patients. One might ask: but is this just the patients' fault? Another disturbing aspect is that poor adherence to therapy increases the risk of mortality at least twofold in these patients. What causes give rise to this poor adherence, especially in asthmatic patients? Lack of knowledge, underestimation of the disease, definitely insufficient information provided by the physician, all influencing factors but added to which are also other factors closely linked to the devices available on the market. What are the patients' preferences? Certainly the use of fewer pharmaceutical products, or administered only a few times a day, and the devices themselves also weigh heavily on these aspects.

DAL NEGRO ROBERTO
Divisione di Pneumologia
Azienda Sanitaria - U.L.S.S. N. 22
Regione Veneto
Ospedale "Orlandi"
BUSSOLENGO (VR - I)

What features should the ideal device possess? How many devices currently available on the market get close to this ideal? Which devices are more acceptable to patients?



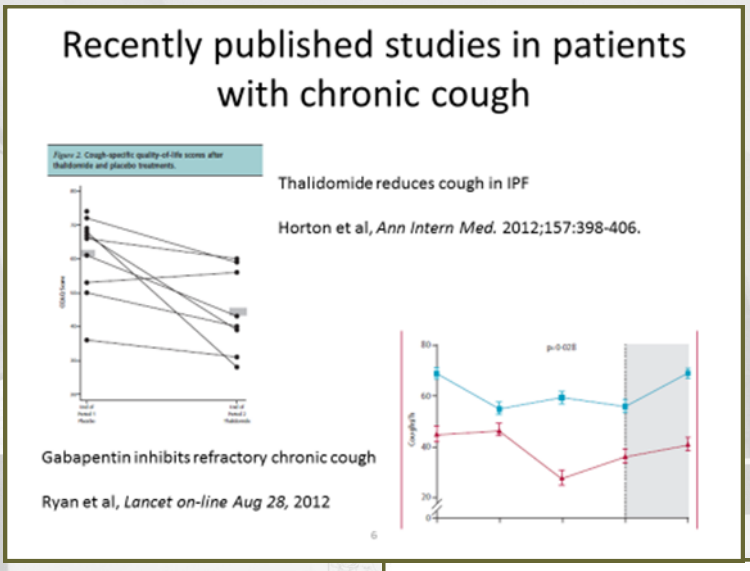
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

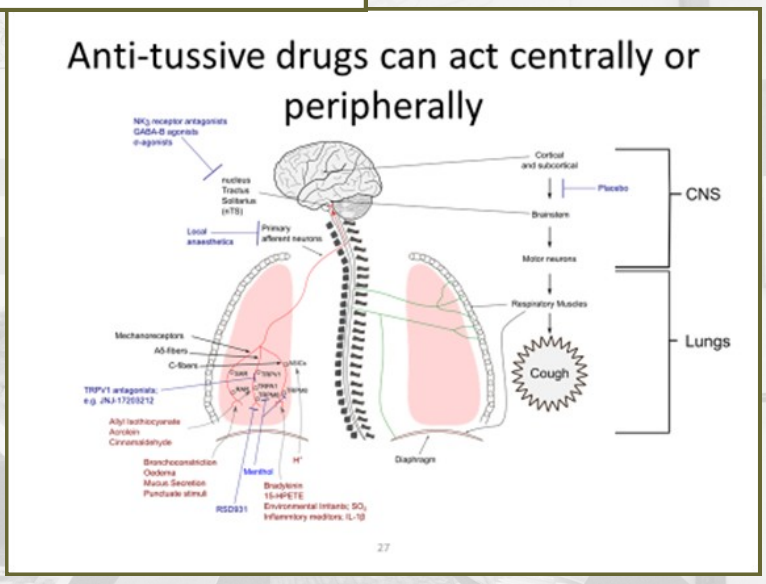
Fondazione Internazionale Menarini

HIGHLIGHTS

What new pharmaceutical products are being studied for treating cough?



Prof. Clive Page of London presented preliminary data on the new drugs currently being studied for treating cough. In some cases they are molecules at a very preliminary study stage, instead in others data on humans have already been published, even if in the early developmental phases. Classically, anti-cough drugs can act centrally or peripherally, but how many of these drugs are actually being studied? Prof. Page then illustrated the main drugs, with particular emphasis on the P2X3 receptor antagonists, TRPV1 and VPR 700. The latter have reached the clinical trial stages, however the results are contrasting, while positive in subjects suffering from untreatable cough, they are negative in patients with idiopathic pulmonary fibrosis.



PAGE CLIVE
Pharmacology and Head of Sackler Institute of Pulmonary Pharmacology
Institute of Pharmaceutical Science
King's College London
5th Floor, Franklin-Wilkins Building
London (UK)

What must still be done to identify new, more effective drugs for treating cough? How reliable in humans are the data produced on animal models?

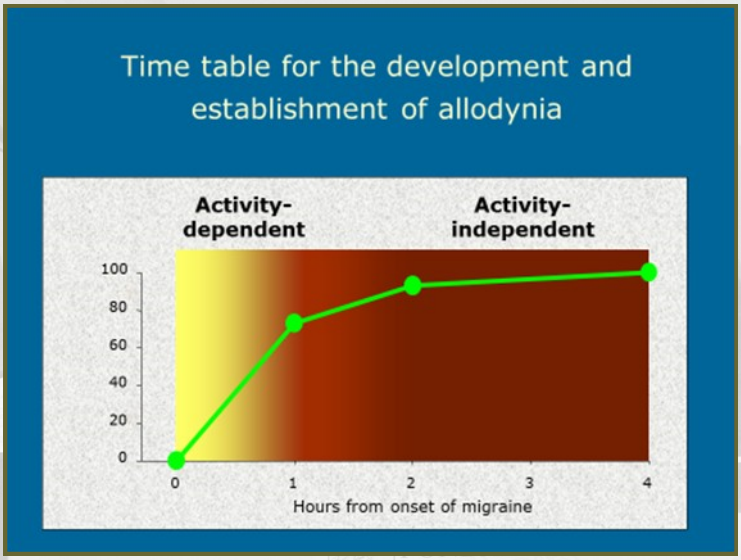
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

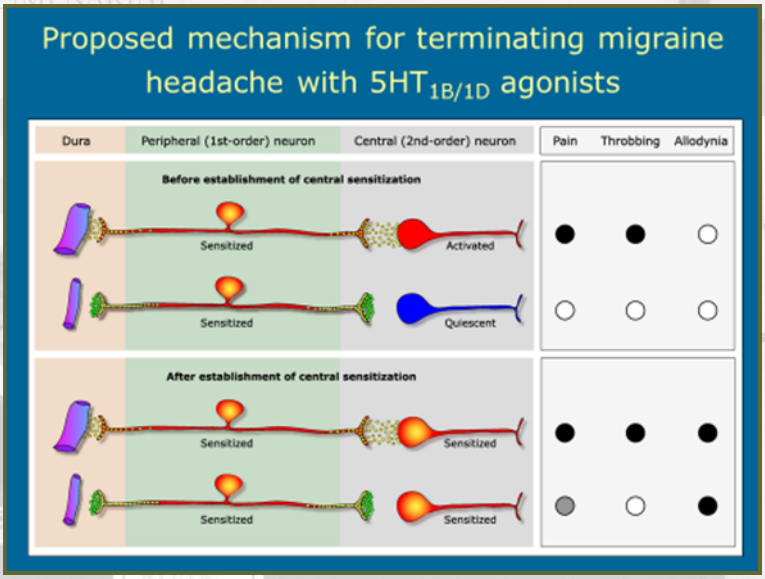
Fondazione Internazionale Menarini

HIGHLIGHTS

Migraine pain, which sensitisation phenomena prevail, central or peripheral?



Migraine is accompanied by one of the most severe painful symptoms ever experienced by patients, therefore it is vitally important to begin therapy in the early stages in order to inhibit the onset of this pain. Prof. Rami Burstein of Harvard illustrated the main sensitisation mechanisms at both a peripheral and central level that patients may face if the treatment is not started early enough. The peripheral sensitisation processes at the level of the trigeminovascular system are responsible in particular for the onset of pulsing pain in the area around the eyes, while the central sensitisation phenomena are responsible for the onset of cutaneous allodynia and also muscle tension. The triptan drugs, especially effective in treating the symptoms of migraine, must however be administered early in order to prevent the onset of sensitisation phenomena at the central level which are not reversible during a migraine attack and are the main cause of allodynia.



BURSTEIN RAMI
Comprehensive Headache Center
Anesthesia, Critical Care and Pain Medicine
Beth Israel Deaconess Medical Center
Brookline (MA, USA)

What are the main mechanisms that cause the onset of allodynia? Which regions are affected?

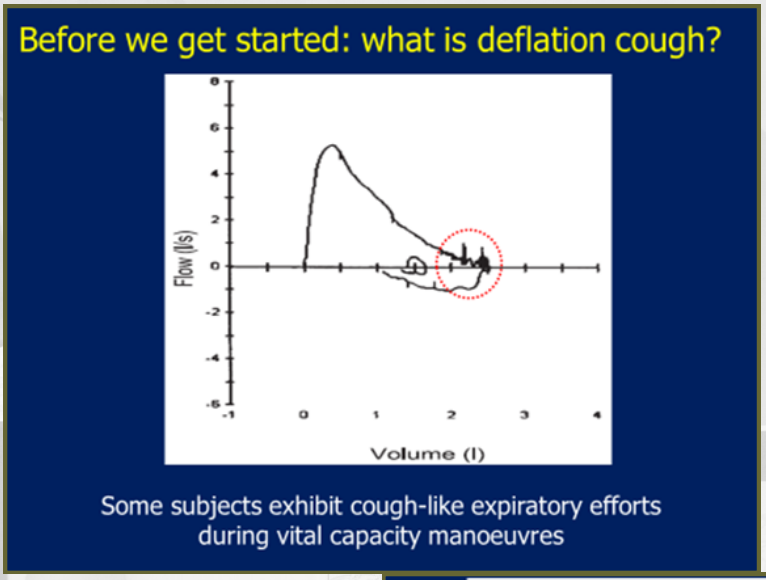
To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

PAIN AND COUGH
March 19-21, 2015 Florence

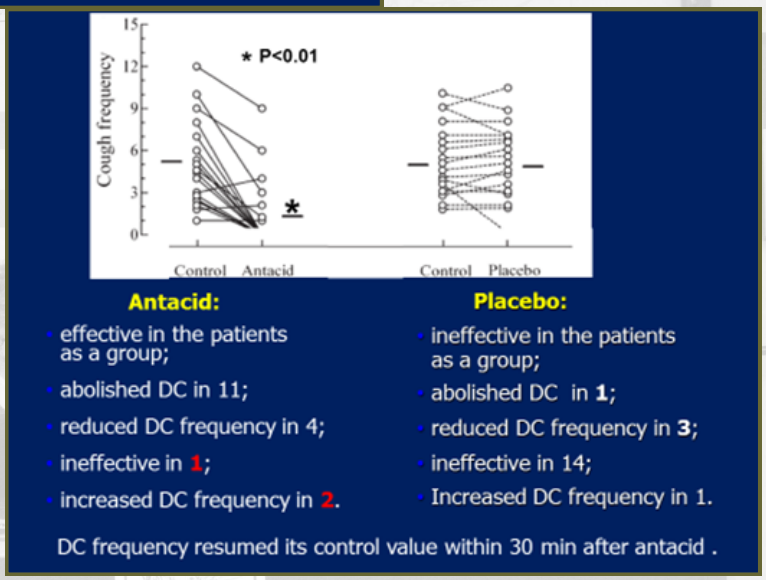
Fondazione Internazionale Menarini

HIGHLIGHTS

Cough in the exhaling stage: is it a paradoxical effect or an entity with a specific clinical significance?



Prof. Federico Lavorini of Florence, presented experimental data on a particular type of cough known as exhalation or deflation cough. These are fits of coughing that patients experience during the execution of slow or forced vital capacity manoeuvres. It is a phenomenon that occurs in a low percentage of patients, not more than 2.5% of the population who are subjected to lung functioning tests. In particular, 18 patients who had expiratory cough during the final phase of the vital capacity manoeuvre were studied according to a highly standardised method. In all patients there was expiratory cough in the presence of abdominal muscle contractions and a reduction of the pH at an oesophageal level. The administration of antacids gave rise to the reduction or disappearance of this phenomenon in 80% of the study population. This interesting response opens up the field with a specific question:



What can the clinical significance of expiratory or deflation cough be?

To find the answers to these questions and other questions and for more in-depth information click on the following link: www.fondazione-menarini.it/..... and after having logged in, access the multimedia material.

LAVORINI FEDERICO
Azienda Ospedaliera Careggi
Unità Funzionale di Medicina Respiratoria
Dipartimento di area critico medico chirurgica
Florence (Italy)

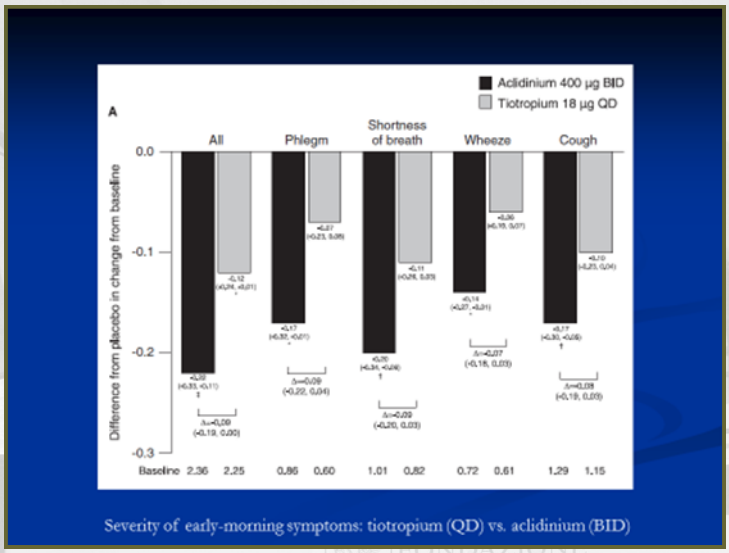
PAIN AND COUGH
March 19-21, 2015 Florence

Fondazione Internazionale Menarini

HIGHLIGHTS

DICPINIGAITIS PETER VYTAUTAS
Montefiore Medical Center
Department of Medicine (Critical Care)
Division of Pulmonary Medicine
Jack D. Weiler Hospital
Bronx (NY, USA)

Drugs with an anticholinergic and antimuscarinic action: new options for treating cough.



Severity of early-morning symptoms: tiotropium (QD) vs. aclidinium (BID)

Prof. Peter Dicpinigaitis presented data on the use of drugs with an anticholinergic and antimuscarinic action in patients with a cough, with special emphasis on two drugs belonging to both these classes: tiotropium and aclidinium. A comparison was made of their effects on morning symptoms in patients suffering from COPD, and aclidinium proved to be more effective in reducing cough. He also illustrated data on the use of diphenhydramine and amitriptyline. The data published on these products is certainly very encouraging and also particularly interesting in patients suffering from cough but not COPD.

What are the main action mechanisms via which these drugs reduce the frequency and number of coughs?

These are just a few of the topics discussed during the congress. For more in-depth information please enter the website of the Fondazione Internazionale Menarini which contains the full versions of the congress talks.

Go to the following link: www.fondazione-menarini.it/.....and after having logged in, access the multimedia material.

Fondazione Internazionale Menarini
Edificio L - Strada 6 Centro Direzionale Milanofiori 20089 Rozzano (MI)
Tel. +39 02 55308110 Fax +39 02 55305739 Email: milan@fondazione-menarini.it
www.fondazione-menarini.it - www.facebook.com/fondazionemenarini