

# Cough: neurophysiology, methods of research, pharmacological therapy and phonoaudiology

Tosse: neurofisiologia, métodos de pesquisa, terapia farmacológica e fonoaudiológica

*Aracy Pereira Silveira Balbani*<sup>1</sup>

1) PhD in Medicine. Otorhinolaryngologist.

Institution: Author's Own practice.  
Tatuí – SP – Brazil.

Mailing address: Aracy P. S. Balbani - Capitão Lisboa Street, 715 - Tatuí / SP – Brazil - Zip-code: 18270-070 - Telephone: (+55 15)3259-1152 - E-mail: a\_balbani@hotmail.com  
Article received in March 13, 2011. Article approved in June 25, 2011.

## SUMMARY

**Introduction:** The cough is the more common respiratory symptom in children and adults.

**Objective:** To present a revision on the neurophysiology and the methods for study of the consequence of the cough, as well as the pharmacotherapy and phonoaudiology therapy of the cough, based on the works published between 2005 and 2010 and indexed in the bases Medline, Lilacs and Library Cochrane under them to keywords “cough” or “anti-cough”.

**Synthesis of the data:** The consequence of the cough involves activation of receiving multiples becomes vacant in the aerial ways and of neural projections of the nucleus of the solitary treatment for other structures of the central nervous system. Experimental techniques allow studying the consequence of the cough to the cellular and molecular level to develop new anti-cough agents. It does not have evidences of that anti-cough exempt of medical lapsing they have superior effectiveness to the one of placebo for the relief of the cough. The phonoaudiology therapy can benefit patients with refractory chronic cough to the pharmacological treatment, over all when paradoxical movement of the vocal folds coexists.

**Final Comments:** The boarding to multidiscipline has basic paper in the etiological diagnosis and treatment of the cough. The otolaryngologist must inform the patients on the risks of the anti-cough of free sales in order to prevent adverse poisonings and effect, especially in children.

**Keyword:** anti-cough, codeine, dextromethorpha, expectorants, cough.

## RESUMO

**Introdução:** A tosse é o sintoma respiratório mais comum em crianças e adultos.

**Objetivo:** Apresentar uma revisão sobre a neurofisiologia e os métodos para estudo do reflexo da tosse, bem como a farmacoterapia e terapia fonoaudiológica da tosse, baseada nos trabalhos publicados entre 2005 e 2010 e indexados nas bases Medline, Lilacs e Biblioteca Cochrane sob os unitermos “tosse” ou “antitussígenos”.

**Síntese dos dados:** O reflexo da tosse envolve ativação de múltiplos receptores vagais nas vias aéreas e de projeções neurais do núcleo do trato solitário para outras estruturas do sistema nervoso central. Técnicas experimentais permitem estudar o reflexo da tosse ao nível celular e molecular para desenvolver novos agentes antitussígenos. Não há evidências de que antitussígenos isentos de prescrição médica tenham eficácia superior à do placebo para o alívio da tosse. A terapia fonoaudiológica pode beneficiar pacientes com tosse crônica refratária ao tratamento farmacológico, sobretudo quando coexiste movimento paradoxal das pregas vocais.

**Comentários Finais:** A abordagem multidisciplinar tem papel fundamental no diagnóstico etiológico e tratamento da tosse. O otorrinolaringologista deve informar os pacientes sobre os riscos dos antitussígenos de venda livre a fim de prevenir intoxicações e efeitos adversos, especialmente em crianças.

**Palavras-chave:** antitussígenos, codeína, dextrometorfano, expectorantes, tosse.

## INTRODUCTION

The cough is a mechanism of protection of the aerial ways and also the more common respiratory symptom in children and adults. It can elapse of innumerable infectious causes (Table 1) and not infectious (Table 2), to be characterized as it dries or productive, and classified, in accordance with the duration, in acute (less than 3 weeks), sub-acute (3-8 weeks) or chronicle (more than 8 weeks) (1,2).

The cough paroxysms can harm the quality of life of the patient for intervening with sleep, to provoke dysphonia, vomits, chronic headache or urinary incontinence.

Anti-cough and mucolytics - many of which are exempt of medical lapsing, are between consumed medicines more in the world. They offer to risk of

adverse effect and poisoning, over all in infancy. Survey made in 63 Casualties North Americans disclosed that 5.7% of the poisonings in minors of 12 years had been provoked by anti-cough and anti-flu, with predominance of the cases (64%) in children of two the five years of age (3).

The toxicity of the exempt anti-cough of lapsing and the inconclusive data of its clinical effectiveness (4) had taken the authorities of health of Canada to contraindicate them in the minors of six years and to adopt measured of security you add: warning in papal brief on the cares in the use for children of 6 the 12 years and standardization of packings (bottle to the test of opening for the child, followed of batcher cup) (5). In Brazil, the warning consists in papal brief of that anti-cough they do not have to be used in lesser children of two years of age, and the pharmaceutical industries are not obliged to use packings to the manuscript test for children.

**Table 1. Infectious causes of cough.**

		Examples of etiological agents
Virus	Cooled common	adenovirus, coronavirus, enterovirus, parainfluenza
	Influenza (flu)	virus influenza A e B
	Bronchiolitis	respiratory syncytial virus (VSR)
	Tranqueobronquitis acute	virus influenza, VSR
	Hantavirus	virus Jucuitiba, Araraquara, Castelo dos Sonhos, Laguna Negra, Anajatuba
Bacteria	Whooping Cough	<i>Bordetella pertussis</i>
	Tranqueobronquitis acute	<i>Mycoplasma pneumoniae</i>
	Rinosinusites (syndrome of the cough of the by airmail superior one)	<i>Streptococcus pneumoniae</i> <i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i>
	Bacterial Pneumonia	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Chlamydia pneumoniae</i> <i>Haemophilus influenzae</i>
	Mycobacteriosis typical and atypical	<i>Mycobacterium tuberculosis</i>
Parasites	Eosinophilia pulmonary parasitic (Syndrome of Loeffler)	<i>Ascaris lumbricoides</i> <i>Ancylostoma duodenale</i> <i>Strongyloides stercoralis</i>
	Chronic Schistosomiasis Pulmonary	<i>Schistosoma mansoni</i>
	Larva migrans visceral	<i>Toxocara canis</i> , <i>Toxocara cati</i>
Singamus	<i>Singamus laryngeus</i>	
Protozoan	Visceral Leishmaniasis	<i>Leishmania chagasi</i>
Fungus	Aspergillosis	<i>Aspergillus spp</i>
	Blastomycosis	<i>Blastomyces dermatitidis</i>
	Cryptococcosis	<i>Cryptococcus neoformans</i>
	Histoplasmosis	<i>Histoplasma capsulatum</i>
	Paracoccidioidomycosis	<i>Paracoccidioides brasiliensis</i>
	Pneumocystosis	<i>Pneumocystis jiroveci</i>

**Table 2. Not infectious causes of cough.**

Medicines	Inhibitors of the converting enzyme of the angiotensin Beta blockers Interferon peguilado (bronchial mod) Methotrexate (pneumonitis)
Cardiovascular Diseases	Pulmonary Edema Pulmonary Embolism
Gastroesophageal Reflux	
Foreign Body Aspiration	
Neoplasias	
Asthma	Variant of the asthma with cough <sup>(a)</sup>
Pulmonary illness obstructive chronicle	
Inhalation of irritating	Gas mustard, formaldehyde
Pneumoconiosis	Silicosis
Others	After-infectious cough Atopic Cough <sup>(b)</sup> Psychogenic Cough

Note:

(a) Variant with cough of the asthma: responsive chronic cough to the bronchodilator use or inhalator/systemic corticosteroids.

(b) Atopic cough: chronic cough without reversible blockage of the aerial flow nor bronchial hyperresponsiveness, in which there is sanguineous eosinophilia or in sputum, or rise of the specific serum IgE, or coetaneous test of positive immediate hypersensitivity. Refractory to the therapy with responsive bronchodilator and to the use of corticosteroids inhalation or antihistaminic H1.

In 2007, a manufacturer removed of the world-wide market, preventively, anti-cough contends hydrochloride of clobutinol, for the risk to draw out interval QT and to induce cardiac arrhythmia (*torsades of pointes*) (6). However, this active principle still is commercialized by other companies (7).

The otolaryngologist use to take care of cases of followed cough of pharyngeal irritation or unchained by contact with perfumes and other inhalants, variations of temperature and acts of speaking, laughing or to sing. Frequent the physician and pediatrician direct patients to the specialist investigates the syndrome of the cough of the by airmail superior one, before called dripping after-nasal.

For everything this, is necessary that the otolaryngologist knows the scientific neurophysiologies of the cough, methods for its study and the pharmacologic and phonoaudiologic treatment for relief of the symptom, boarded subjects in this revision.

## LITERATURE REVIEW

The original works had been searched for this not systematic revision, of revision, meta-analysis and published between 2005 and 2010 and indexed stories of case in the bases Medline, Lilacs and Library Cochrane under them to keywords "cough" or "anti-cough".

## Neurofisiology of the Cough

### Peripheral Components

The reflected arc of the cough is initiated in the respiratory epithelium, diaphragm, pericardium, pleura, peritoneum or esophagus through the stimulation of mecanoreceivers, nociceptors (chemoreceptors) or Aä staple fibers (1). In the 2,3%-4,2% of the population consequence it can also be evoked by the palpation of the external auditory meatus - more commonly of its wall postero-inferior, in one or both the ears -, for stimulation of the auricular branch of vacant nerve (nerve of Arnold) (8,9).

In experimentation animals, the bilateral section of the superior laryngeal nerve does not modify the consequence of the cough. The bilateral section of the recurrent laryngeal nerve abolishes the cough provoked for mechanical or electric stimulation of the mucous of the larynx and superior portion of the trachea, but does not intervene with the consequence provoked for the acid vapor inhalation.

The mechanoreceptors of low threshold answer the mechanical stimulations. The pulmonary receivers of sprain (slowly adapting stretch receptors - SARs and rapidly adapting stretch receptors - RARs) are activated physiological by the variation of the pulmonary volume during the

breath, while the mechanossensors of esophageal tension are stimulated by the deglutition. In pathological conditions, edema of the mucosa or the bronchoconstriction can activate them. Such receivers have the small sensitivity the chemical stimulations (acid).

The nociceptors or chemoreceptors answer the chemical stimulations (capsaicin, bradixinin, prostaglandins, acid), heat (temperature above of 42°C) and some extreme mechanical stimulations.

The myelinated staple fibers of fast adaptation A $\alpha$ , called receiving of cough, have important paper in the defense of the aerial ways; therefore they are very sensible to the contact of liquids or main particles with the mucous of the larynx, trachea and principal bronchis. They possess distinct physiological characteristics of the ones of the RARs and SARs, not activated by the capsaicin or bradixinin (10) and it believes that its main function is the regulation of the consequence of the cough evoked in the extra pulmonary aerial ways.

The myelinated staple fibers of type C are not the nociceptors become vacant more numerous in the bronchis and lungs the (11) and responsible for the bother of the impulse to cough. They express some ionic canals of membrane, between which *transient receiving potential vanilloid* (TRPV) 1 the 4 - numerous also in larynx mucous (12) -, and *transient receiving potential ankyrin-1* (TRPA-1), activated directly for irritating chemistries (10) as the allicina of the onion and the garlic, the isothiocyanate of the mustard and formaldehyde (13).

The ideal anti-cough of peripheral action would have to inhibit staple fibers C selectively, to abolish the pathological paroxysms of cough without harming the physiological mechanism of defense of the A $\alpha$  staple fibers against aspiration. This could occur for the use of: 1) an antagonist of ionic canals TRPV or TRPA-1, or 2) of a similar medicine to the local anesthetics, capable to block specifically a sodium canal regulated for voltage and, thus, to inhibit the potential of action in staple fibers C (10). The current lines of research of new anti-cough test molecules with these actions.

### Core components

The afferent ways of the cough converge to the nucleus of the solitary treatment in the brainstem, main point of the regulation of the consequence. Of their break multiple there neural projections to: the reticular formation, ambiguous nucleus, periaqueductal cinereous substance and dorsal nucleus of rafe (14).

In the experimental models, the cough provoked

for the stimulation mechanics of the trachea is intensified by the instillation of capsaicin in the nasal mucous or esophageal, indicating that in the brainstem there are integration between the sensitive afferents of the triplet nerve in the nasal mucous and the wander afferents trachea-bronchial and esophageal (15,16). This would be one of the predisposing mechanisms to the cough in the patients with sinonasal conditions (syndrome of the cough of the by airmail superior one) or gastroesophageal reflux.

The glutamate seems to be the main excitatory neurotransmitter of the ways central offices of the cough, while the neurocinines (substance P, neurocinines and the B) would be neuromodulatory. It has been searched the anti-cough central action of antagonists of the receiver of neurocinines (17).

The consequence suffers voluntary control from the cerebral cortex. The selective stimulation of staple fibers C with capsaicin in animals under general anesthesia does not evoke cough (16,17). In human beings, the impulse to cough generally precedes the motor act of the cough and can be suppressed voluntarily (18). On the other hand, the psychogenic cough, that answers for 3 to 10% of the cases of chronic cough in infancy, can be provoked by the patient and if to reveal with or without ticks (motor or vocal), ceasing during sleep (19).

The efferent ways of the cough pass through the nerves vacant and phrenic and of the spinal motoneuron until the expiratory musculature, resulting in the characteristic sequence of respiratory movements already exhaustingly described in literature (1,2,7).

### Reflection Modulation

The consequence of protection of the aerial ways is a dynamic mechanism that follows the coming-of-age of the central nervous system (SNC) and suffers influence from hormone and neuro-humoral factors.

In the just-born mammals, especially the premature, the presence of secretion, gastric content or other liquids in the superior aerial ways (VAIN) result in movements of deglutition and closing of glottis, apnea, bradycardia and redistribution of the sanguineous flow for vital agencies. The action of the interleukins in the SNC sensitizes the consequence and draws out apneas (20), what would explain the biggest risk of sudden death in the neonates with infections of the superior aerial ways (IVAS).

In pig younglings are observed biochemists changes and bioelectric in the motoneuron respiratory in the first month of life. Gradual it diminishes the occurrence of deglutition and apnea, and the cough starts to be the main

of the protective consequence of the aerial ways, characteristic component that it is remained in adult life (20,21).

In human beings the sensitivity of the consequence of the cough is bigger in the women and patients with IVAS or variant with cough of asthma (tussigenic asthma) (22).

It has given controversial on the effect of the smoking in the threshold of the consequence of the cough. Some studies show increase of the threshold in smokers, perhaps for central or peripheral action of the nicotine, or for the increase of the thickness of the layer of respiratory mucus, that it would difficult the activation of the receivers you become vacant tracheobronchial. This phenomenon is reversible in few weeks, reasons for which many people complain of cough more after to stop to smoke. However, other smoking suffer of chronic cough - possibly for the inflammatory process in the aerial ways -, alleviated for the abstinence of cigarette (23).

The converting enzyme of the angiotensin (ECA) degrades not only the angiotensin, but also the bradycinin, substance P and neurokinines, which sensitize staple fibers C. For this reason, about 20% of the patients who use inhibiting antihypertensives of the ECA have cough as collateral effect (1,24). The symptom tends to disappear after about four weeks the interruption of the use of antihypertensive (25).

### **Methods of study of cough**

Although it has numerous afferent sensitive in the aerial ways, rats and mice do not present the typical motor act of the cough, making it difficult its evaluation. Thus, the guinea pig is the specie of small postage more used in experiments (13,16).

In the experimental works the cough can be provoked by the direct electric micro stimulation of the nucleus of the solitary tract after decerebration (26), or by stimulation electric/mechanics of the mucous of the aerial ways in conscientious animals or under general anesthesia.

As much in the experimental works how much in the physicians some chemical stimulations can be used or cough agent: capsaicin, acid (citric, ascorbic, tartaric) and ultrasonic nebulized of distilled water ("fog").

The capsaicin is the causes of cough more used, managed in dose only or project dose-reply. It provokes cough immediately, reason for which recommends evaluate the effect in the 15 seconds after the nebulizer. Generally the parameter analyzed in the studies dose-reply is the

concentration of capsaicin capable to provoke five or more motor acts of cough. The method is considered reproducible and safe in human beings, but some individuals complain of transitory pharynx irritation after exposition to the capsaicin.

The acid citric has greater probability to cause sensation of breathlessness and ardor in pharynx. The ultrasonic nebulizer of distilled water is insufficient to activate the consequence of cough in up to 20% of the people, but it can induce bronchospasm symptomatic in others, what it reduces the reproducibility and security of the method.

Studies of the effectiveness of anti-cough can suffer the bias from the demulcent effect (stimulation to the saliva secretion and mucus in the VAS for the sugars) of placebo formulated in boiled (22) or of the voluntary inhibition of the cough.

In the clinical research, the use of questionnaires (*Burden of Cough Questionnaire, Cough Specific Quality of Life Questionnaire, Leicester Cough Questionnaire*) is useful to evaluate the impact of the cough in the quality of life of patient (27).

## **Pharmacologic therapy of cough**

### **Anti-cough of peripheral action**

The dropropizine and its levodropropizine enantiomers reduce the sensitivity of staple fibers C become vacant (28). In Brazil, several of its presentations in boiled must contain sugar and a presentation of the dropropizine in tablets has tartrazine yellow colouring, what it contraindicates them, respectively, for diabetic and people with intolerance to the acetylsalicylic acid.

### **Anti-cough of central action**

The dextromethorphan, clobutinol and the Cloperastine fendizoate have not narcotic action in the brainstem.

The dextromethorphan is agonist of the receptor not opioid sigma-1 and antagonist of receiving N-metil-D-aspartate (NMDA) of the glutamate. Its action is similar to the one of acid LSD (LSD), ketamine and psilocybin. The dextromethorphan is metabolized by cytochrome P450 (enzyme CYP2D6), and individuals that metabolizes it slowly are more susceptible to the psychoactive effect, exactly in the therapeutically doses. The medicine interacts with inhibitors of monoamine oxidase (MAO) and inhibiting antidepressants of the reuptake of serotonin (29). It has

register of fatal poisoning for dextromethorphan in child (30).

Clobutinol delays the ventricular repolarization and is arrhythmogenic (31). Already it had relate of anaphylaxis for medicine (32).

The Cloperastine fendizoate is sedative of the cough and also it has peripheral action, desensitize the afferents you become vacant tracheobronchial. It interacts with inhibitors of the HAND.

*Anti-cough narcotic* (morphine and codeine) primarily acts in the opioid receptors in the nucleus of the solitary treatment in the guinea pig. However, naloxone, antagonist of these receptors, does not hinder the anti-cough action of codeine in cat (14). It is possible, then, that the narcotics also act in not-opioid receptors - perhaps of glutamate, serotonin or nociceptin - in SNC (17,26).

The codeine is one of the anti-cough most efficient, however commonly it provokes collateral effect (nauseas, intestinal constipation) and can cause dependence (26).

The anti-cough of central action can boosting the effect depressor of the SNC of the alcohol, hypnotic and sedatives.

### Inhibitors of the protonic bomb

In many cases of chronic cough it has symptoms or signals of gastroesophageal reflux (RGE), and the inhibitors of the protonic bomb (IBPs), associates or not to the prokinetic ones (bromoprid, domperidone), commonly are prescribed as therapeutically test. However, the meta-analysis of 18 randomized and controlled studies, being five in children and 13 in adults, indicates that it does not have benefit of the indiscriminate use of the IBPs in chronic cough (33).

HUNT *et al.* (2006) (34) had evaluated 22 adult patients with chronic cough and 22 healthy volunteers how much to the occurrence of cough and the measures of pH of the condensed vapor of the air exhaled in the half following hour to the lemonade ingestion. It had decline of pH after about 15 minutes, significantly more accentuated in the individuals with chronic cough of what in the volunteers.

The eight patients who cough in the period where pH of exhaled air remained below of 7,4 had been the ones that had answered to the therapy made with IBP during one month - the pharmaceutical, doses and dosage had not been specified. The researchers suggest to apply this method in the selection of the cases of chronic cough to

detect, of not invasive form, the acidification of VAS for gastroesophageal reflux, and thus to prevent the unnecessary use of IBPs.

### Expectorants, mucolytics and others

The guaifenesin expectorant is glyceril ether of guaiacol, resin of the plant *Guajacum officinale* L., the guaiacol. This species does not have to be confused with the guaco (*Mikania glomerata Spreng.*), whose leaves popularly are used in Brazil in the preparation of infusion or decoction for the combat to the cough.

The guaifenesin has anti-cough effect in patients with IVAS, but it does not inhibit the consequence of cough in submitted healthy volunteers to the capsaicin inhalation. Its accurate mechanism of action completely is not clarified and the more frequent adverse effect are: chronic headache, nausea and vomits.

The vasicine is an originally isolated alkali of leaves of *Adhatoda vasica*, indicated for Ayurveda as expectorant (35). Also the leaves of *Sida cordifolia* L. (Malvaceae), popularly known in Brazil as mauve-white, they contain vasicine.

The hydrochloride of bromhexine is a synthetic derivative of the vasicine. The hydrochloride mucolytics of ambroxol is an active metabolite of the bromhexine and has antirust, anti-inflammatory properties, surfactant and of local anesthetic, the last one for blockade of sodium canals. Their adverse effects are: nausea, vomits, abdominal pain and coetaneous eruption. The super dosage can provoke dyspnea, ataxia and convulsions (36). Ambroxol is not approved by the Food and Drug Administration for use in U.S.A. (37).

The potassium iodide still is found in the formularization of some expectorants and its drawn out use can induce hypothyroidism.

Clinical studies show that the monotherapy with n-acetyl-cysteine or erdosteine does not have anti-cough effect, but the mucolytics are good coadjutants in the treatment of respiratory above, presumably for its antirust effect (25).

Some commercial marks of exempt anti-cough of medical lapsing associate the dropropizine, the levodropropizine or the dextromethorphan with classic H1 antihistamines (diphenhydramine, doxylamine) in the formularization. These antihistamines help to alleviate the cough thanks to its peripheral action and to the control of the atopy, but its effect in the SNC cause sleepiness (25).

In the consulted systematic revisions did not prove that the effectiveness of guaifenesin (4), of methylxanthines (theophylline, aminophylline and caffeine) (38), of antihistamines (39) and the antagonist of the receiver of montelukast leukotriene (40,41) either superior to the one of placebo for relief of the cough in children.

Since immemorial times the common sense recommends the honey of bee for relief of the dry cough. The honey is demulcent and contains phenols with antirust and antimicrobial. It is cheap and safe for use in bigger children of one year and, pasteurized, rare provokes allergic reaction (42).

A randomized study compared the effect of the administration, 30 minutes before sleeping, 5 ml of honey or dextromethorphan on the nocturnal cough and the quality of the sleep of 105 children and adolescents with IVAS. One third group of patients did not receive treatment. The dextromethorphan was formulated in order to have similar aspect and flavor to the ones of the honey, so that the participants of the study could not distinguish them. The patients who had used honey had significant reduction of the nocturnal cough in comparison with that they had not received treatment, benefit not gotten with dextrometorfane (43).

Another randomized work analyzed the effect of a nocturnal dose of 2,5 ml of honey, or 7,5 mg of dextromethorphan, or 6,25 mg of diphenhydramine, or nasal hygiene with physiological serum on the nocturnal cough of 139 children of two the five years with IVAS. The frequency and the intensity of the nocturnal cough, according to story of the parents, had been significantly lesser in the group of children that used honey (44).

Although these favorable results, there is not scientific consensus on the indication of the honey in the therapy of the acute cough in children (45).

### **Phonoaudiologic therapy on cough**

It is esteem that half of the patients with chronic cough present some degree of motor dysfunction of the vocal folds (PPVV), the larynx dyskinesia, in which there is involuntary paradoxical supply of the PPVV during the inspiration or expiration (46). The larynx dyskinesia can be unchained by: inhalation of irritating (smoke or vapors), low temperature or extreme humidity of air, motor acts that involve the respiratory musculature (physical exercise, speaks, laugh, deep inspiration or deglutition) or stresses (47). In these patients the pulmonary test of function and the oxymetry of pulse generally are normal, and the cough is refractory to the pharmacologic treatment with anti-

cough, antihistamines and inhibitors of protonic bomb (46,48). The diagnosis is confirmed through the nasofibrolaryngoscopy.

Researchers had followed during two months 87 adults with chronic cough to medicines, having been 73% of the feminine sex, divided in a group have randomly controlled and other submitted the individual sessions of phonoaudiologic therapy (orientations of vocal hygiene, exercises for abdominal breath and voluntary relaxation of the larynx musculature). They had evaluated the cough and the vocal quality of the participants (analysis acoustics and for electroglottography) and had only evidenced significant improvement of both in the group submitted to phonoaudiologic therapy (48).

MURRY researchers and cols. (2010) (47) had evaluated the sensitivity of the mucous larynx in 16 adults with chronic cough, larynx dyskinesia and refractory symptoms of laryngopharynx reflux to the treatment with IBP. The nasofibrolaryngoscopy was made before and after three months of treatment with IBP managed two times to the day (drugs and doses not informed) combined with respiratory retrain (exercises for acquisition of respiratory rhythm and stimulation to the abdominal breath, made during 10 to 15 minutes, two times to the day). The threshold of the consequence of adduce of the PPVV was gotten when applying air pulses compressed with changeable pressure in the mucous of the aryepiglottic fold, innervated for the superior laryngeal nerve, with visualization of the movement of adduce of the PPVV to the nasofibrolaryngoscopy. The sensitivity of the mucous was significantly bigger to the ending of the treatment, and the 12 patients who had completed the study had presented cure of the larynx dyskinesia and the cough. The authors consider that edema derive from the larynx mucosa of acid reflux would reduce the sensitivity of the mechanoreceptors becomes vacant, and the cough and the adduce of the PPVV would be adaptive answers for defense of the aerial ways against aspiration in this circumstance.

---

## DISCUSSION

---

The neurophysiology of the cough is complex, involving activation of receiving multiples in the aerial ways and of neural projections of the nucleus of the solitary treatment for other structures of the central nervous system.

To unmask the physiopathology relation between the cough, the acidification of the aerial ways and the larynx dyskinesia is a field of instigate research in Laryngology. Recent studies point that many patients with chronic cough have sensitive neuropathic of the recurrent

laryngeal nerve, extending the understanding of the problem and opening the perspective of therapeutically with neuromodulatory as the gabapentin and the pregabalin (49-51).

The importance of the etiological diagnosis of the cough is unquestionable. However, many sick people appeal to the self-medication with anti-cough and mucolytics - or they request that the doctor prescribes them - to attenuate the discomfort until identifies the cause of the symptom and if she initiates the specific treatment.

The dextromethorphan and clobutinol had started to be commercialized in the decade of 1950. Since then, it remains questionable the advantage of these anti-cough in relation to placebo and have succeeded the stories of serious collateral effect. Therefore, it is desirable that the Brazilian associations of medical specialties and the National Agency of Sanitary Monitoring, based in scientific literature, guide the professionals of health and the lay public and act next to the manufacturers of anti-cough to hinder the indiscriminate use of these products and to prevent poisonings. In this direction, it is convenient to standardize in the Country the packings of anti-cough for pediatric use, becoming obligator the bottle the test of opening for the child and the batchers small glass.

Although the innumerable experiments of neuropharmacological of the cough to the cellular and molecular level made in recent years, the clinical research of new more efficient and safe anti-cough has been disappointing. The good results gotten in the control of the cough in the experimental models nor always are reproduced in human beings, and the incorporated innovation most recent to the practical clinic continues being the levodropropizine, launched in the decade of 1980.

More clinical studies are necessary double-blind people randomized on the benefit of the honey of bee and other demulcents in the treatment of the dry cough. In the same way, research that shows the positive impact of the phonoaudiologic therapy in cases of refractory chronic cough to the pharmacologic treatment encourages to the accomplishment of protocols of laryngeal evaluation for the otolaryngologist and phonoaudiologic. This confirms the necessity of attendance to multidiscipline and multiprofessional to the cases of chronic cough to better assure quality of life to the patients.

---

## FINAL COMMENTS

---

There is no evidences of that anti-cough exempt of medical lapsing have superior effectiveness to the one of

placebo for the relief of the cough. Also is not proven the effectiveness of the guaifenesin, the methylxanthines, montelukast and antihistamines for the treatment of the cough in children.

The phonoaudiologic therapy can benefit patients with refractory chronic cough to the pharmacologic treatment.

---

## ACKNOWLEDGEMENTS

---

The author is thankful the Mrs. Márcia Arruda and Marinalva Aragão for the valuable assistance with the bibliography.

---

## BIBLIOGRAPHIC REFERENCES

---

1. Fiess E. II Diretrizes brasileiras no manejo da tosse crônica. *J Bras Pneumol*. 2006, 32 (supl. 6):S403-46.
2. Bouajaoude ZC, Pratter MC. Clinical approach to acute cough. *Lung* 2010, 188 (suppl. 1):S41-6.
3. Schaefer MK, Shehab N, Cohen AL, Budnitz DS. Adverse events from cough and cough medications in children. *Pediatrics*. 2008, 121:783-7.
4. Smith SM, Schroeder K, Fahey T. Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database Syst Rev*. 2008; (1):CD001831.
5. Shefrin AE, Goldman RD. Use of over-the-counter cough and cold medications in children. *Can Family Phys* 2009; 55: 1081-3.
6. Boehringer Ingelheim. Retirada do mercado do Cloridrato de Clobutinol (Silomat® e Silomat® Plus). [2007] Encontrado em URL: [http://portal.anvisa.gov.br/wps/wcm/connect/96a21d804237610cbd70fd01cce3dc94Carta+da+empresa+Boehringer+Ingelheim+sobre+a+retirada+do+mercado+dos+medicamentos+Silomat%C2%AE+e+Silomat%C2%AE+Plus\\_.pdf?MOD=AJPERES](http://portal.anvisa.gov.br/wps/wcm/connect/96a21d804237610cbd70fd01cce3dc94Carta+da+empresa+Boehringer+Ingelheim+sobre+a+retirada+do+mercado+dos+medicamentos+Silomat%C2%AE+e+Silomat%C2%AE+Plus_.pdf?MOD=AJPERES).
7. Reis AMM, Figueras A. Analysis of the evidence of efficacy and safety of over-the-counter cough medications registered in Brazil. *Braz J Pharm Sci*. 2010, 46:135-45.
8. Gupta D, Verma S, Vishwakarma SK. Anatomic basis of Arnold's ear-cough reflex. *Surg Radiol Anat*. 1986, 8: 217-20.
9. Tekdemir I, Aslan A, Elhan A. A clinico-anatomic study of

- the auricular branch of the vagus nerve and Arnold's ear-cough reflex. *Surg Radiol Anat.* 1998, 20:253-7.
10. Udem BJ, Carr MJ. Targeting primary afferent nerves for novel antitussive therapy. *Chest.* 2010, 137:177-84.
11. Kollarik M, Ru F, Udem BJ. Acid-sensitive vagal sensory pathways and cough. *Pulm Pharmacol Ther.* 2007, 20:402-11.
12. Hamamoto T, Takumida M, Hirakawa K, Takeno S, Tatsukawa T. Localization of transient receptor channel vanilloid subfamilies in the mouse larynx. *Acta Otolaryngol.* 2008, 128:685-93.
13. Geppetti P, Pattachine R, Nassini R, Materazzi S. Cough: the emerging role of the TRPA-1 channel. *Lung.* 2010, 188(suppl.1):S63-8.
14. Takahama K, Shirasaki T. Central and peripheral mechanisms of narcotic antitussives: codeine-sensitive and -resistant coughs. *Cough.* 2007, 3:8.
15. Plevkova J, Antosiewicz J, Varechova S, Poljacek I, Jakus J, Tatar M et al. Convergence of nasal and tracheal neural pathways in modulating the cough response in Guinea pigs. *J Physiol Pharmacol.* 2009, 60:89-93.
16. Mazzone SB, Mori N, Canning BJ. Synergistic interactions between airway afferent nerve subtypes regulating the cough reflex in guinea pigs. *J Physiol.* 2005, 569:559-73.
17. Canning BJ. Central regulation of the cough reflex: therapeutic implications. *Pulm Pharmacol Ther.* 2009, 22:75-81.
18. Canning BJ. Encoding the cough reflex. *Pulm Pharmacol Ther.* 2007, 20:396-401.
19. Veras TN, Pinto LA. Tosse psicogênica em criança: relato de caso. *Sci Med.* 2008, 18:54-7.
20. Thach BT. Maturation of cough and other reflexes that protect the fetal and neonatal airway. *Pulm Pharmacol Ther.* 2007, 20:365-70.
21. Dragomir A, Akay Y, Curran AK, Akay M. Investigating the complexity of respiratory patterns during the laryngeal chemoreflex. *J Neuroeng Rehab.* 2008, 5:17.
22. Dicipinigaitis PV. Experimentally induced cough. *Pulm Pharmacol Ther.* 2007, 20:319-24.
23. Sitkauskienė B, Dicipinigaitis PV. Effect of smoking on cough reflex sensitivity in humans. *Lung.* 2010, 188(suppl.1):S29-32.
24. Morice AH. The cough hypersensitivity syndrome: a novel paradigm for understanding cough. *Lung.* 2010, 188(suppl.1):S87-90.
25. Bolser DC. Pharmacologic management of cough. *Otolaryngol Clin North Am.* 2010, 43:147-55.
26. Minamizawa K, Goto H, Ohi Y, Shimada Y, Terasawa K, Haji A. Effect of d-pseudoephedrine on cough reflex and its mode of action in Guinea pigs. *J Pharmacol Sci.* 2006, 102:136-42.
27. Leconte S, Ferrant D, Dory V, Degryse J. Validated Methods of Cough Assessment: A Systematic Review of the Literature. *Respiration.* 2010, DOI: 10.1159/000321231.
28. Schönfeldt PG, Céspedes JG, Sepúlveda R, Salamanca ME. Aumento del umbral tusígeno en sujetos sanos con el uso de levodropropizina. *Rev Chil Enf Respir.* 2005, 21:165-70.
29. Mutschler J, Koopmann A, Grosshans M, Hermann D, Mann K, Kiefer F. Dextromethorphan withdrawal and dependence syndrome. *Dtsch Arztebl Int.* 2010, 107:537-40.
20. Rimsza ME, Newberry S. Unexpected Infant Deaths Associated With Use of Cough and Cold Medications. *Pediatrics.* 2008, 122:e318.
31. Takahara A, Sasaki R, Nakamura M, Senda A, Sakurai Y, Namekata I et al. Clobutinol delays ventricular repolarization in the guinea pig heart: comparison with cardiac effects of HERG K<sup>+</sup> channel inhibitor E-4031. *J Cardiovasc Pharmacol.* 2009, 54:552-9.
32. Seitz CS, Bröcker EB, Trautmann A. Allergy evaluation after emergency treatment: anaphylaxis to the over-the-counter medication clobutinol. *Emerg Med J.* 2007, 24:e19.
33. Chang AB, Lasserson TJ, Gaffney J, Connor FL, Garske LA. Gastro-oesophageal reflux treatment for prolonged non-specific cough in children and adults. *Cochrane Database Syst Rev.* 2005, (2):CD004823.
34. Hunt J, Yu Y, Burns J, Gaston B, Ngamtrakulpanit L, Bunyan D et al. Identification of acid reflux cough using serial assays of exhaled breath condensate pH. *Cough.* 2006, 2:3.
35. Soni S, Anandjiwala S, Patel G, Rajani M. Validation of Different Methods of Preparation of *Adhatoda vasica* Leaf

Juice by Quantification of Total Alkaloids and Vasicine. *Indian J Pharm Sci.* 2008, 70(1):36-42.

36. Gupta PR. Ambroxol - Resurgence of an old molecule as an anti-inflammatory agent in chronic obstructive airway diseases. *Lung India.* 2010, 27:46-8.

37. Chang CYC, Sachs HC, Lee CE. Unexpected Infant Deaths Associated With Use of Cough and Cold Medications [carta]. *Pediatrics.* 2009, 123:2:e359.

38. Chang AB, Halstead RA, Petsky HL. Methylxanthines for prolonged non-specific cough in children. *Cochrane Database Syst Rev.* 2005, (3):CD005310.

39. Chang AB, Peake J, McElrea MS. Anti-histamines for prolonged non-specific cough in children. *Cochrane Database Syst Rev.* 2008, 2:CD005604.

40. Chang AB, Winter D, Acworth JP. Leukotriene receptor antagonist for prolonged non-specific cough in children. *Cochrane Database Syst Rev.* 2006, 2:CD005602.

41. Chang CC, Cheng AC, Chang AB. Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. *Cochrane Database Syst Rev.* 2007, (4):CD006088.

42. Warren MD, Pont SJ, Barkin SL, Callahan ST, Caples TL, Carroll KN et al. The effect of honey on nocturnal cough and sleep quality for children and their parents. *Arch Pediatr Adolesc Med.* 2007, 161:1149-53.

43. Paul IM, Beiler J, McMonagle A, Shaffer ML, Duda L, Berlin Jr. CM. *Arch Pediatr Adolesc Med.* 2007, 161:1140-6.

44. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A comparison of the effect of honey, dextromethorphan, and diphenhydramine on night cough and sleep quality in children and their parents. *J Altern Compl Med.* 2010, 787-93.

45. Oduwole O, Meremikwu MM, Oyo-Ita A, Udoh EE. Honey for acute cough in children. *Cochrane Database Syst Rev.* 2010, 1:CD007094.

46. Vertigan AE, Theodoros DG, Gibson PG, Winkworth AL. Efficacy of speech pathology management for chronic cough: a randomised placebo controlled trial of treatment efficacy. *Thorax.* 2006, 61:1055-69.

47. Murry T, Branski CK, Yu K, Cukier-Blaj S, Dufflo S, Aviv JE. Laryngeal sensory deficits in patients with chronic cough and paradoxical vocal fold movement disorder. *Laryngoscope.* 2010, 120:1576-81.

48. Gibson PG, Vertigan AE. Speech pathology for chronic cough: a new approach. *Pulm Pharmacol Ther.* 2009, 22:159-62.

49. Lee JK, Mintz S. Chronic cough as a sign of laryngeal sensory neuropathy: diagnosis and treatment. *Ann Otol Rhinol Laryngol.* 2006, 115:871.

50. Halum SL, Sycamore DL, McRae BR. A new treatment option for laryngeal sensory neuropathy. *Laryngoscope.* 2009, 119:1844-7.

51. Norris BK, Schweinfurth JM. Management of recurrent laryngeal sensory neuropathic symptoms. *Ann Otol Rhinol Laryngol.* 2010, 119:188-91.