Rational Drug Bulletin

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Editorial

With cough many patients present to a doctor. Cough itself is not a disease, but is a common symptom of many diseases. Cough occurs even in healthy individuals in certain conditions. Cough is a defence mechanism which protects the respiratory tract from harm. Most of the time it is irrational to suppress this protective mechanism.

The WHO list of essential drug does not contain any cough medicine. The Drug Control authority of our country has banned most of the cough preparations long back. But cough preparations continue to remain among top-selling brands in the Indian market.

In this issue of Rational Drug Bulletin, Community Development Medicinal Unit attempts to acquaint the doctors and health-workers of its member organizations with the rational management of cough.

Launch of 2nd edition of Standard Treatment Guidelines

On July 21, 2014 the 2nd edition of Standard Treatment Guidelines [STG] prepared by CDMU in collaboration with Social Initiatives for Growth and Networking was launched. The dignitaries who are present are as follows:

- Mr. Rajendra Prasad Singh, Minister of Finance, Commercial Taxes, Energy, Health & Parliamentary Affairs, Government of Jharkhand
- Telesphore P Cardinal Toppo, Archbishop of Ranchi
- Felix Toppo, Bishop of Jamshedpur
- Dr. Issac David, Prem Jyoti Community Hospital
- Mr. D P Poddar, Secretary, CDMU

The Minister appreciate the effort of CDMU and SIGN in bringing out this book. Fr. Christu Das also speak about the journey that CDMU and SIGN shouldered to publish the same. He also appreciated the role of CDMU in publishing t book. Mr. Poddar stressed on issue of sustainability and usage of STG at health centre.

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Managing Cough: the Rational Way

Cough is a powerful indispensable physiological defence mechanism that clears the central airways of foreign material and excess secretions. Although generally beneficial, cough is also a common symptom of diseases such as asthma, chronic obstructive pulmonary disease (COPD) and lung cancer. Cough is characterized by a violent expiration, which provides the high flow rates that are required to shear away mucus and remove foreign particles from the larynx, trachea, and large bronchi. Most sensory stimuli that cause coughing also increase airway secretion, which is beneficial as this provides a vehicle for explusion of particulate matter.

The most common causes of cough are the viral acute upper respiratory tract infections, when the cough is usually nonproductive and self-limiting. In some other patients cough is associated with increased mucus production or a chronic respiratory disease such as asthma. In some of patients, no such cause is obvious at presentation and cough may persist for many years. When cough is associated with sputum production, it is likely to be due to the excess secretion in the airway stimulating sensory nerves. In the absence of abnormal sputum production there is likely to be some other reason for the cough. The likely explanation would be an increased sensitivity of the cough reflex, which would lead to the abnormal response of the patient to "natural" inhaled stimuli.

Physiology of Cough

Cough usually results from the stimulation of sensory nerves in the airways. The nerves that initiate cough are predominantly in the upper airway, for it is here that the greatest protection against the ingress of foreign material is required. Cough caused by mechanical irritation results from stimulation of myelinated or non-myelinated sensory nerves in the larynx or the rapidly adapting stretch receptors in the lung, or both. Cough caused by direct chemical stimulation results from activation of receptors in the larynx (myelinated or non-myelinated) or activation of C fibre endings in the lung, or both.

The physiology of mucus and sputum production in the respiratory system

The main function of the respiratory system is to draw air into the lungs to allow the exchange of gases with blood circulating to the lungs. Tissues of the respiratory tract are thin and delicate, and become thinnest at the surfaces of the aveoli, where gaseous exchange occurs. The body has a number of mechanisms which protect these tissues and ensure that debris and bacteria do not reach them.

Tiny hairs called cilia trap large pieces of debris and waft them out of the airways; the reflexes of sneezing and coughing help to expel particles from the respiratory system and the production of mucus keeps the tissues moist and helps to trap small particles of foreign matter.

Mucus production in the airways is normal. Without it, airways become dry and malfunction. But sometimes the mucus is produced in excess and changes in nature. This results in the urge to cough and expectorate this mucus as sputum.

Sputum expectoration is not normal and there is almost always an underlying pathological cause. Mucus is secreted from two distinct areas within the lung tissue. In the surface epithelium, there are mucus-producing cells called goblet cells. The connective tissue layer beneath the mucosal epithelium contains seromucinous glands which also produce mucus. The mucous is composed of water, carbohydrates, proteins and lipids. The high water content helps to humidify the passing inspired air. Mucus contains glycoproteins (or mucins) as well as proteins derived from plasma, and products of cell death. Mucus is sticky and this helps to trap dust particles, bacteria and other inhaled debris. Mucus also contains natural antibiotics, which help to destroy bacteria - the epithelial cells secrete a substance called defensis. Mucus also contains lysozyme, which is an antibacterial enzyme.

Movement of mucus

Cilia in the nose move the mucus formed there towards the throat where it is swallowed and digested in the stomach. In cold weather, this process slows and the mucus sometimes gathers in the nose and drips or dribbles out—a runny nose.

Particles larger than 4mm in diameter usually become trapped in mucus in the nose and rarely get any further down the airways. The nasal mucosa has many sensory nerve endings and large particles irritate these nerves, stimulating a sneeze—a violent burst of air—which expels the particles along with mucus. Further down the airways, cilia in the trachea and bronchi also waft the mucus towards the pharynx to be swallowed. This movement, against the force of gravity, is sometimes called the mucus escalator. Normally, this upward movement is not noticeable, except when we clear our throats. However, if larger quantities of mucus build up, the cough receptors may be stimulated and air and mucus will be forcibly expelled from the trachea.

Moving down the airway, the mucosal epithelium gets thinner and changes in nature. There are only a few cilia and no mucus-producing cells in the bronchioles, so any airborne debris is removed by macrophages in the alveoli or coughed out.

Sputum production

Irritation of the respiratory system causes both inflammation of the air passages and a notable increase in mucus secretion. A person may become conscious of swallowing the mucus or the inflammation may trigger a coughing reflex so that they expectorate these secretions as sputum. It seems that the inflammation of the mucosa is responsible for sputum production rather than any of the other changes that occur in diseased lung tissue.

Expectorated sputum contains lower respiratory tract secretions, as well as secretions from the nose, mouth and pharynx, and cellular debris and micro-organisms.

Diagnosis of Persistent Cough

History taking

A careful clinical history can diagnose the cause of cough in about 80% of patients. History of respiratory infection, bronchial disease, rhinitis, postnasal drip, esophageal reflux, and treatment with angiotensin converting enzyme inhibitor should be taken. The patient should also be questioned about the factors that trigger attacks of coughing during daily life.

Investigations

- A chest x-ray is mandatory for patients with persistent cough and x-ray of the paranasal sinuses and upper tract should be performed if the history suggests a postnasal drip.
- Upper gastrointestinal endoscopy may help the diagnosis in esophageal reflux. Esophageal reflux is under-diagnosed in patients with cough and therapeutic trials of an H2 receptor antagonist may be helpful if Upper GI endoscopy is not available.
- Bronchoscopy should be performed if there is a specific indication.
- Spirometry before and after a bronchodilator and a histamine challenge should be performed to confirm/ exclude the diagnosis of asthma.
- Routine examination of blood sometimes points to the cause of cough, such as pulmonary eosinophilia.
- In countries like India, every patient having cough for 2-3 week should have their sputum tested for acid-fast bacilli.

Management of cough

Management depends on whether the cough is mainly productive or non-productive. The treatment of productive cough secondary to conditions such as chronic obstructive airways disease, cystic fibrosis, and bronchiectasis will depend on manipulation of mucus secretion (except during exacerbations), which so far does not appear to be possible in man. During exacerbations the increased cough and mucus production should respond to appropriate treatment of the infection and inflammation. The use of cough suppressants in these patients in theory could lead to retention of mucus and deterioration in the patient's underlying disease.

The non-productive cough should be treated in a different way. If an underlying cause for the cough is identified, the treatment of that condition may lead to relief of cough. For example, adequate and proper treatment of asthma usually greatly reduce cough associated with it. In other diseases, such as carcinoma and interstitial lung disease, cough may be less amenable to treatment. Patients who have cough associated with postnasal drip or esophageal reflux usually respond to treatment of the underlying cause. There are some patients with non-productive cough, including those with virus induced cough and chronic cough associated with an increased sensitivity of the cough reflex. In these patients the aim is either to avoid stimuli that cause coughing—that is, smoke, cold air, exercise, certain chemicals, etc. or to use cough-depressants. Cough associated with angiotensin converting enzyme inhibitor usually respond to stopping treatment with it.

The Pharmacology of Cough Suppression

In cough associated with the excessive production of mucus, suppression of the cough reflex is undesirable as mucus retention may occur. When cough is unproductive, disturbs rest and sleep, cough suppression may be desirable. However complete suppression of the cough reflex is dangerous as the respiratory tract is then deprived of an essential defence mechanism. An ideal drug would reduce the increased sensitivity of the reflex to normal. The only effective peripherally acting cough suppressant are demulcents and local anaesthetics. Drugs that affect cough can also do so indirectly. For example, bronchodilators can reduce the initiation of coughing without having any significant central effects. However, the most frequently used cough suppressants act in the midbrain and have many undesirable side effects.

Demulcents

Many proprietary cough preparations contain mainly sugar. They have been shown to reduce cough in normal individuals. The mechanism by which they do this is unknown. There are three possibilities:

- The sugar content of the cough mixture encourages saliva production and swallowing; the act of swallowing may interfere with the cough reflex.
- The sugar solution may coat sensory nerve endings in the epipharynx and cause their stimulation; this stimulation may suppress cough.
- The sugar solution may act as a protective barrier to sensory receptors that can either produce cough or heighten the cough reflex.

Opiates

The opiates are the oldest and the most studied of all cough suppressants, and are the standard by which all other cough suppressants are measured. The most commonly used are codeine, pholcodeine and dextromethorphan. There is little evidence in favour of using one drug in preference to another, all having a similar side effect profile at effective antitussive doses. The opiates exert their pharmacological action via p opioid receptors, though the site of the receptors concerned in the cough reflex is not clear. The likely possibilities are:

- They act on the sensory nerve endings responsible for initiating cough.
- They act within the central nervous system. This may be by a direct action on the cough centre in the medulla or by an action on the brainstem respiratory centres. When high doses of opiates are required to suppress cough, respiration is depressed and this may decrease peripheral sensory stimulation and therefore coughing.
- 3 p receptor stimulation may reduce mucus production or increase mucociliary clearance and so reduce the need for cough.

Local anaesthetics

Local anaesthetics prevent sensory nerve traffic in both myelinated and non-myelinated nerves and are the most consistently effective antitussive agents. As they can remove all the protective reflexes of the lung and may precipitate bronchoconstriction they must be used with extreme care. Interestingly, inhalation of lignocaine reduces cough at doses that do not affect reflex bronchoconstriction."

Expectorants

Some ingredients of the cough preparations are claimed to be expectorants. These have been studied in detail. Guaiphenesin, has been shown to be ineffective in patients with spontaneous cough and in suppressing citric acid induced cough, though patients reported a reduction in sputum thickness. Other drugs, such as ipecacuanha, may cause coughing by stimulating the chemotactic trigger zone in the midbrain. It may be possible to alter the rheological properties of mucus to aid clearance by altering the secretion rate or by physicochemical actions. It has not proved possible to show clinically important effects on cough from oral agents such as N-acetylcysteine. The use of these agents in the presence of an increased cough reflex would be expected to increase the frequency of coughing as more mucus would be present to stimulate the abnormally sensitive reflex.

Anti-asthma treatment

Inhaled bronchodilators such as beta2 agonists and antimuscarinic drugs may have a role as antitussive agents in patients with no airway obstruction.

How may bronchodilators alter the sensitivity of the cough reflex? Probably they reduce the input from stretch receptors by causing bronchodilatation even in normal airways and that this could lead to a reduction of the cough reflex. They may alter mucociliary clearance. Sodium cromoglycate and nedocromil sodium have also been shown to reduce cough in asthmatic subjects and to reduce cough in response to some but not all stimuli.

The use of any antiasthmatic drug for cough is not recommended in the absence of asthma.

Antihistamines

There is some evidence that antihistamines can be antitussive. They reduce postnasal drip, and this could lead to an indirect antitussive action. No direct antitussive effect of antihistamine has been shown. The problem with the antihistamines is that they dry up the secretions making management of cough difficult.

Our experience of managing cough in Shaheed Hospital in Chhattishgarh and in Shramik-Krishak Maitri Swasthya Kendra in Chengail, Howrah, West Bengal

In these two model rational therapy institutions, proprietary cough mixtures are not used.

Patients are advised to drink plenty of water and to inhale water vapor to make the sputum thin.

Postural drainage is advocated in patients of bronchiectasis, in old patients who can not expectorate.

Ordinary lozenges are used as demulcents, not the medicated lozenges.

Inhaled salbutamol and beclomethasone are used to control the cough associated with bronchial asthma.

In the latter institution, we had no occasion to use an anti-tussive since 2000.

We found codeine as the only cough medicine in the earlier editions of the WHO essential drug list. But the recent editions do not have a cough medicine.

The Business of Managing Cough

We, in Community Development Medicinal Unit, undertook a research project in 2010: 'Fixed-dose combination in India, inception, marketing– a study'.

During the study we found 167 irrational fixed dose combinations in 494 brands listed as cough and cold preparations in CIMS (Current Index of Medical Specialities), April—July 2010. Volume of business in July 2010 of Phensedyl Cough was Rs. 203.05 crore and of Corex was Rupees 118.92 crore.

We request CDMU member-organizations to manage cough in the rational way depriving the drug companies of their unethical profits.

Sources:

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3. Irrational FDCs: Cough and Cold Preparations, Thakur H, Chaturvedi A, Thawani V, Behl A, Chakraborty M, J Rational Pharmacother Res, Volume 1 No. 2, April-June 2013.
4. Report on research project: 'Fixed-dose combination in India, inception – marketing – a study'—CDMU and HAI, Asia-Pacific, 2010.

Cough Preparations, Banned in India

Fixed dose combination of Salbutamol or any other bronchodilator with centrally acting anti-tussive and/or antihistamine.	Substituted vide GSR NO. 290(E) Dated 16.04.2008
Fixed dose combination of centrally acting, antitussive with antihistamine, having high atropine like activity in expectorants.	GSR NO. 395(E) Dated 19.05.1999
Preparations claiming to combat cough associated with asthma containing centrally acting antitussive and/ or an antihistamine.	GSR NO. 395(E) Dated 19.05.1999

During Community Development Medicinal Unit—Health Action International Asia-Pacific conducted a research project: 'Fixed-dose combination in India, inception, marketing– a study' in 2010. We found the following brands with banned fixed dose combinations listed in CIMS, April—July 2010.

Sl no	Banned category	Composition	Brand	Manufacturer
1.	FDC of Salbutamol or any other bronchodilator with centrally acting anti-tussive and/or antihistaminics	Terbutaline + Ambroxol + Guaiphenesin + Chlorpheniramine Terbutaline +Chlorpheniramine Salbutamol + Cetirizine	ABROL PLUS CADICOFF VENTIREX	Glenmark Cadila Unimarck
2.	FDC of Phenobarbitone with any Anti-asthmatic drug	Phenobarbitone + Ephedrine + Aminophylline	CORTASTHMA	Zydus

CDMU news

Healthcare delivery needs of the common people cannot be accomplished totally by the government sector. In India, a number of NGOs appear to fill a large share of the gap in healthcare delivery. More often than not they cater to the needs of thousands of care seekers with too scarce resources which they manage to gather through assistance and donations of different kinds. While their motivation to run a regular health care activity is praiseworthy, most of such NGOs operating in the rural and remote areas are manned by health care workers who often lack formal training. The list of the program are as follows:

- Sensitization workshop for health workers on medical stores management & rational use of medicines in collaboration with Sarvik Vivekananda Gram Seva Sanastha on February 8, 2014
- Sensitization workshop for health workers on medical stores management in collaboration with Southern Health Improvement Samity on February 23, 2014
- Sensitization workshop for pharmacists of tea gardens on medical stores management & rational use of medicines in collaboration with Darjeeling Indian Tea Association on March 20, 2014
- Sensitization workshop for pharmacists of Tea Gardens on medical stores management & rational use of medicines in collaboration with Terai Branch Indian Tea Association on March 21, 2014

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