The Therapeutic Applications of Cough Medicines in Respiratory Diseases

Nelisa Paidamwoyo Ganga[1*]

[1]*Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, Parktown Johannesburg 2193 Gauteng, South Africa.*

ABSTRACT

Cough medicines are mostly given to patients presenting with a cough due to acute respiratory tract infections. Although cough is mainly a symptom of acute respiratory tract infections, it is also a symptom of many other diseases which are not of the respiratory system. A cough can be classified as acute if it lasts for 3 weeks or less, prolonged acute if it lasts between 3-8 weeks and chronic if it lasts for longer than 8 weeks. There are many cough medicines available on the market currently such as centrally acting agents, however, some of these medicines lack scientific evidence to support their therapeutic benefits and safety. There is ongoing research to investigate the safety aspects and therapeutic benefits of cough medicines in the management of respiratory diseases. Consequently, a pharmacist must make an informed healthcare decision before dispensing a cough medicine to a patient, taking into consideration its safety and therapeutic aspects. This review article offers insight into the types of cough medicines and their therapeutic applications. This article aims to give pharmacists the knowledge that can assist them in making an informed healthcare decision when dispensing a cough medicine to a patient so that they can ensure optimal patient care.

Key Words: *Acute cough, Chronic cough, Dry cough, Wet cough, Cough medicine*

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INTRODUCTION

A cough is one of the common symptoms for which patients seek medical care, especially in primary healthcare settings worldwide [1]. Although cough is mainly a symptom of acute respiratory tract infections, it is also a symptom of many other diseases which are not of the respiratory system [1]. A cough can be classified as acute if it lasts for 3 weeks or less, prolonged acute if it lasts between 3-8 weeks and chronic if it lasts for longer than 8 weeks [1, 2]. A cough is an airway defense mechanism that helps to clear the airway upon irritation or obstruction through a protective reflex action so that breathing can occur normally [1-3]. An acute cough is mostly caused by a viral infection and rarely caused by a bacterial infection [2, 3].

It can be very difficult to manage an acute cough following a self-limiting viral respiratory tract infection and such a cough can impair the patient's quality of life [2, 3]. Coughs are also classified either as productive or non-productive [3]. A productive cough, also known as wet cough, allows the ejection of sputum or secretions from the lower respiratory tract so that breathing can continue normally [3]. On the other hand, a non-productive or dry cough does not bring up any secretions or mucus hence it has no useful purpose [3]. A cough can be treated symptomatically by both non-pharmacological and pharmacological approaches [2]. Many healthcare professionals, including pharmacists, usually recommend Over-The-Counter (OTC) cough medicines as the first-line treatment for a cough [3-5]. Even though many patients report to benefit from cough medicines, there continues to be a debate among researchers on the therapeutic benefits and safety aspects of these medicines [3]. Many researchers report that cough medicines have a placebo effect that helps to reduce the severity of symptoms [3].

Management

An acute cough caused by a viral infection is mostly self-limiting hence it is often unnecessary to give medication [3]. Nonetheless, many patients have reported that they have benefited from cough medicines while having an acute cough caused by a viral infection [3, 6]. Since a cough can be a symptom of a serious medical condition such as pneumonia, it is important to refer the patient to a

Corresponding author: Nelisa Paidamwoyo Ganga
Address: Department of Pharmacy and Pharmacology, Faculty of Health Sciences, University of the Witwatersrand, Parktown Johannesburg 2193 Gauteng, South Africa.
E-mail: ✉ nelisaganga@gmail.com
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doctor for further diagnosis [6]. **Figure 1** below gives the circumstances in which a referral is necessary for a patient presenting with a cough [2, 3, 6].

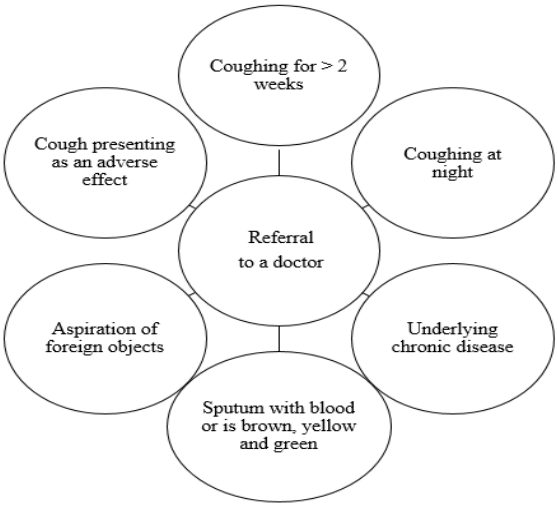

Figure 1. Circumstances in which a referral is needed for a coughing patient [2, 3, 6].

Cough medicines are made from a combination of different active ingredients which belong to various pharmacological classes [2, 3, 7]. There are many pharmacological classes, including but not limited to, centrally acting agents, antihistamines, demulcents, bronchodilators, mucolytics and expectorants [2, 3, 7].

Antihistamines

Many antihistamines are found in cough medicines, although there is insufficient evidence to support their therapeutic benefits and safety for a cough [2]. Antihistamines are known to act either as antitussives or cough suppressants when alleviating a cough [2, 3]. First-generation antihistamines can antagonize acetylcholine at neuronal and neuromuscular muscarinic receptors, while second-generation antihistamines cannot [8]. Since second-generation antihistamines lack anticholinergic effects, they cannot alleviate a cough [9]. As a result, first-generation antihistamines are found in cough medicines and second-generation antihistamines are not [9]. Antihistamines act by decreasing the cholinergic transmission of nerve impulses in the coughing reflex thus suppressing the cough [10]. The sedative effect of first-generation antihistamines is highly beneficial for a cough that disturbs sleep [10]. Antihistamines are beneficial for a patient presenting with a cough, associated with a cold because apart from alleviating the cough, they also dry up the mucus or phlegm [10]. However, this drying effect of antihistamines can lead to problems such as the thickening of mucus or phlegm [11].

Centrally acting agents

Centrally acting agents are more effective for a chronic cough than for acute cough [2]. Centrally acting agents are considered unsafe for children under the age of 6 hence they should not be given to such patients [2]. Centrally acting agents, also known as, cough suppressants or antitussives act by decreasing the release of nerve impulses that cause coughing at the coughing centre in the brain [3]. It is not recommended to give codeine for the alleviation of cough because it has a very high risk of causing adverse effects [3]. Codeine, which is a centrally acting agent did not show any benefit in alleviating a cough for two studies that were done [12].

Three clinical trials showed that dextromethorphan decreased the cough count by 19% to 36% in comparison to a placebo [12]. Although dextromethorphan is preferred to codeine for alleviating a cough, it can cause serious toxicity if an incorrect dose is used [13]. A summary of the common centrally acting agents used for alleviating cough and their properties is given in **Table 1** below [2, 3, 12, 13].

Table 1. Centrally acting agents [2, 3, 12, 13]

Example	Mechanism of Action	Adverse effects	Special Warnings
Codeine	Acts as a cough suppressant by suppressing the cough centre in the medulla	Constipation, Nausea and Sedation	Risk of drug addiction and abuse
Dextromethorphan	It is an N-Methyl D-aspartate (NMDA) receptor antagonist that acts directly by suppressing the medullary cough centre	Dizziness, Nausea, and Sedation	Risk of serious toxicity associated with excitation and confusion when an overdose is given

Pholcodine	Acts by directly suppressing the medullary centre	Constipation, Dizziness, Headache, Sedation, and Nausea	Risk of opioid dependence and abuse

Demulcents

Demulcents are also classified as cough suppressants or antitussives due to their voluntary suppression of cough [3, 6, 7]. Demulcents are usually recommended for infants under 2 years of age, children, and pregnant women because of their therapeutic benefits and safety profile [3, 6, 7]. Sucrose, honey, and alcohol are three examples of commonly used demulcents for alleviating a cough [11]. Demulcents act by coating the throat and soothing the irritated mucous membranes [11, 14]. They also increase saliva production and swallowing thus inhibiting the cough reflex [11]. However, cough medicines containing up to 40% alcohol are not recommended for use by patients [11]. Additionally, it is not recommended to use demulcents containing sugar for diabetic patients because this may increase their glucose levels [11].

Expectorants

Expectorants, also known as mucoactive agents, act by stimulating respiratory tract secretions thus increasing respiratory fluid volumes and decreasing the viscosity of the mucous [10]. Common adverse effects of expectorants include dizziness, rash, and a headache [10]. Expectorants must be used with caution in patients with gastrointestinal ulcers [10]. Ipecacuanha is an expectorant of choice which belongs to the complementary medicines class and it is very effective for alleviating a cough [10]. Other expectorants include creosote, menthol, and squill, however, these expectorants usually exhibit minimal therapeutic benefits when used at low doses [10]. The dose of guaifenesin required in an adult to effectively alleviate a cough is usually between 100-200mg hence it is important to ensure that the dose is within this range before dispensing the cough medicine to a patient [10].

Guaifenesin is the expectorant of choice which is usually recommended for patients [12]. Guaifenesin was found to reduce cough frequency and intensity by 75%, while placebo had a decrease of 31% in a particular clinical trial [12]. Guaifenesin can act by stimulating the cholinergic pathway thus increasing the release of mucous from glands in the airways [15]. Although ammonium chloride, sodium citrate, and glyceryl guaiacolate are commonly used as expectorants, they were found to produce less therapeutic benefits when compared with a placebo in several clinical trials [16].

Mucolytics

Mucolytics act mainly by decreasing the viscosity of the mucous and they are also referred to as mucoactive agents [13, 17]. Examples of commonly used mucolytics include carbocisteine, N-acetylcysteine and bromhexine [13]. Even though carbocisteine and bromhexine are routinely used as cough remedies, they still lack scientific evidence regarding their therapeutic benefits and safety profile to support their use [13, 18]. Carbocisteine also belongs to the pharmacological class of mucoregulators [18]. N-acetylcysteine was found to decrease cough frequency and intensity in children older than 2 years after six to seven days of therapy, in several clinical trials [18]. Carbocisteine acts by regulating the metabolism of mucous-producing cells thus decreasing the viscosity of mucous [18, 19]. The common adverse effects of carbocisteine include a headache and diarrhea [18]. Carbocisteine should be used in caution for patients with asthma and peptic ulcers [18]. Carbocisteine was found to reduce the adherence of pathogens such as bacteria and viruses to ciliated epithelial cells in vitro [18]. Carbocisteine also has anti-inflammatory properties and it can reduce inflammation caused by infections in the airway passages through the production of cytokines [18]. N-acetylcysteine can also protect against free radical damage [18, 20].

Mucokinetics

Mucokinetics are not recommended for acute coughing in non-asthmatic children [7]. Mucokinetics, also known as bronchodilators belong to the class of mucoactive agents [10]. Mucokinetics are subdivided into three categories which are β_2 agonists, muscarinic receptor antagonists, and xanthines [10]. Mucokinetics act by relaxing the smooth muscles in the airways, increasing the expiratory flow, and reducing the volume of mucous secreted thus alleviating the cough [10]. Orciprenaline and Terbutaline are the most used β_2 agonists [10]. The common adverse effects of β_2 agonists include tachycardia, tremors, and headaches [10]. As a result, β_2 agonists should be used with caution in patients having cardiac arrhythmias, ischaemic heart disease, and hyperthyroidism [10].

Theophylline is the most used xanthine for alleviating a cough [13, 21]. Theophylline has a very narrow therapeutic window meaning that serious toxicity or lack of efficacy can occur if doses fall outside of the therapeutic range [13, 21]. Monitoring of theophylline levels in the blood can be done as a way to prevent or identify toxic effects [13]. Theophylline should be used with caution especially in children and the elderly who have a greater risk of experiencing the toxic effects of theophylline [13, 21]. Since there is an increased risk of

toxicity, OTC medicines containing theophylline should not be taken at the same time as prescribed theophylline by an asthmatic patient [21].

Combination medicines

Many combination medicines are used for managing cough and they consist of various active ingredients belonging to different pharmacological classes [2, 3]. The goal of combination medicines is to allow synergistic mechanisms which will provide enhanced therapeutic benefits [2, 3]. Theophylline and orciprenaline are found in most combination medicines because when used in combination, their bronchodilatory effects are enhanced significantly [3, 6]. The combination of an antihistamine and an expectorant is not recommended for cough because these two classes have conflicting effects, while an antihistamine suppresses a cough, an expectorant promotes coughing [3, 7, 22]. The combination of an antihistamine and a centrally acting agent is usually recommended for a cough that is disturbing one's sleep because these two classes both act as cough suppressants, both cause sedation, and can be given at night [3, 7]. Combination medicines containing bronchodilators, expectorants, and nasal decongestants are recommended for use in patients experiencing a productive cough, nasal congestion, and wheezing simultaneously [7]. Nasal decongestants such as phenylephrine and pseudoephedrine are commonly used in combination medicines for alleviating a cough because they help in relieving nasal congestion [7].

A combination medicine containing a first-generation antihistamine and a nasal decongestant was found to relieve an acute cough and nasal congestion more effectively than a placebo, in one clinical trial [9]. One randomized clinical trial showed that naproxen, which is a Non-Steroidal Anti-inflammatory Drug (NSAID) was very effective in alleviating a cough hence this medicine can be investigated further before using it in practice [9]. Combination medicines for a cough containing antimuscarinic agents should be carefully considered before giving the patient because they are prone to suppress bronchial secretions and cause changes in the surface tension [23]. It is not recommended to use a combination medicine containing an expectorant and a centrally acting agent because a patient may fail to get any therapeutic benefit since these two pharmacological classes have contradictory effects [24].

Recommendations in practice

The choice of therapy is largely dependent upon the type of cough hence this should be taken into consideration before dispensing any medication [6, 7]. The pharmacist should ask the patient about the medication he or she is currently taking in order, to assess for any possible drug-to-drug interactions [7]. Cough suppressants containing dextromethorphan and pholcodine are usually recommended for a dry cough [7]. On the other hand, expectorants such as guaifenesin are mostly recommended for a wet cough [7]. Cough suppressants are also preferred when the cause of the cough is unknown and when the cough disturbs sleep [7]. However, cough suppressants are not recommended for a wet cough because they can cause the retention of mucus or phlegm in the lower respiratory tract thus increasing the risk of infection [7]. While cough suppressants reduce coughing, expectorants promote coughing hence it is not recommended to use these two medicines concomitantly [7]. It is highly recommended to use a full dose of one medicine when treating a cough that focuses on a specific part of the reflex [11]. The use of cough medicines particularly in infants and children needs to be carefully considered because such age groups are at a high risk of experiencing adverse effects of these medicines [25, 26]. Demulcents are recommended for children younger than 2 years and pregnant women because they have fewer adverse effects [25, 27]. Promethazine containing antihistamines are contraindicated for use in children under 2 years because of the risk of adverse effects [28].

CONCLUSION

The pharmacist must take into consideration the safety aspects, age, concurrent medication, and pre-existing conditions before dispensing a cough remedy to a patient because this will assist the pharmacist in making an informed healthcare decision. The pharmacist needs to give individualized therapy because each patient has his or her own specific healthcare needs. Further studies need to be done on the therapeutic and safety aspects of cough medicines which lack scientific evidence to support their use. Since drug abuse and addiction such as opioid abuse is on the rise worldwide, the pharmacist needs to assess patients requesting cough remedies for any signs of drug abuse and addiction. Every pharmacist must practice the responsible provision of cough medicines to achieve definite therapeutic outcomes that improve the patient's quality of life.

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