AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE
ISSN: 2996-5101 (online) | ResearchBib (IF) = 9.818 IMPACT FACTOR
Volume-3| Issue-6| 2025 Published: |30-06-2025|

COUGH AND ANTITUSSIVE DRUGS: MECHANISMS AND MANAGEMENT (LITERATURE REVIEW)

https://doi.org/10.5281/zenodo.15679056

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Abstract

The role of respiratory defense mechanisms, especially the cough reflex, is crucial in airway protection and disease modulation. Cough is a protective reflex that clears the airways of excessive secretions and foreign matter; however, it can become chronic or excessive, leading to significant patient discomfort and health burden. Cough is one of the most common symptoms prompting individuals to seek medical care. A wide array of antitussive drugs with varying mechanisms of action has been developed, but most exhibit central nervous system (CNS) side effects, limiting their tolerability and long-term use. The poor safety profile of traditional centrally acting antitussives underscores the need for new agents with better efficacy and safety. Among the newer treatments, levodropropizine**,** a peripherally acting antitussive, shows promise with fewer CNS side effects and comparable efficacy to traditional agents like dextromethorphan. This review summarizes the classification, mechanisms, and clinical considerations for antitussive drug therapy.

Key words

Respiratory tract; cough; polysaccharides; glaucine; libexin; levodropropizine.

Introduction

The **cough reflex** serves as a fundamental protective mechanism for the respiratory tract. It facilitates the clearance of mucus, pathogens, and foreign particles and may also be voluntarily initiated. Although beneficial, cough can

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sometimes become excessive or chronic, leading to discomfort, sleep disruption, and social or occupational limitations.

Acute cough (lasting <3–4 weeks) is most often associated with **upper respiratory tract infections (URTIs)**. In contrast, **chronic cough** (lasting >8 weeks) may signal more serious pulmonary disorders such as **asthma**, **chronic obstructive pulmonary disease (COPD)**, or **lung malignancies**, and can also result from extra-pulmonary causes like **gastroesophageal reflux disease (GERD)**. Chronic cough affects more than 12% of the general population and significantly reduces quality of life while incurring societal healthcare costs [1–4].

Despite its high prevalence, treatment options for chronic or non-productive cough remain limited. In many cases, the etiology remains idiopathic even after standard diagnostic workup [5]. Traditional antitussive therapies often act centrally on the **medulla oblongata** but are associated with adverse CNS effects, such as sedation, dependence, or cognitive impairment.

Antitussive Drug Classification

Antitussive agents are classified into two primary groups based on their mechanism of action:

1. Centrally Acting Antitussives

These suppress the cough center located in the medulla oblongata.

A. Opioid (narcotic) drugs

- **Codeine**
- **Ethylmorphine hydrochloride**

These are effective but have significant sedative and addictive properties.

B. Non-opioid (non-narcotic) drugs

- **Glaucine hydrochloride**
- **Oxeladine citrate**
- **Butamirate**

These offer cough suppression with relatively fewer CNS side effects compared to opioids, but tolerability still remains a concern.

2. Peripherally Acting Antitussives

- **Levodropropizine**
- **Libexin (prenoxdiazine)**

These act directly on the airways and cough receptors, avoiding CNS-related adverse effects. **Levodropropizine** in particular has shown comparable efficacy to centrally acting agents such as **dextromethorphan** and **dihydrocodeine**, with significantly fewer sedative effects [6].

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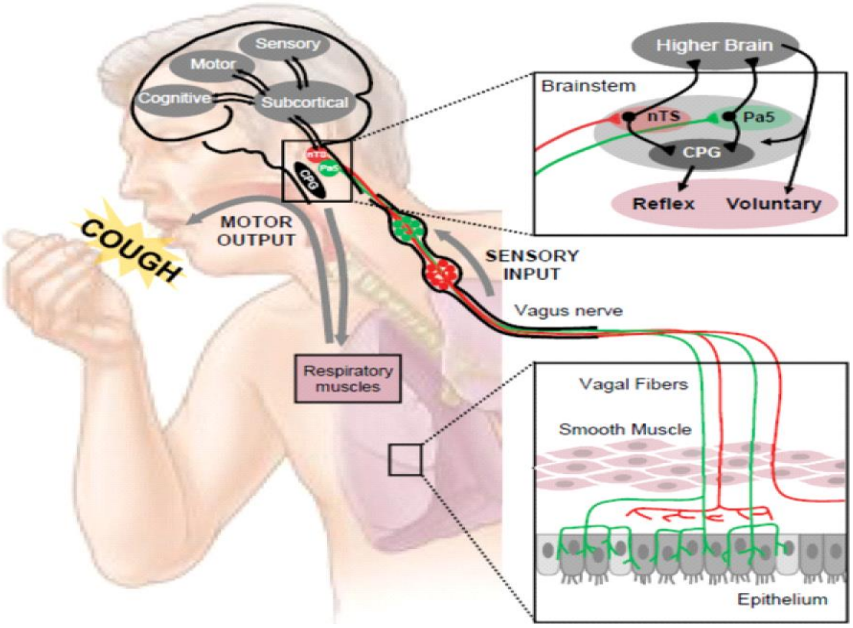
Mechanism of Action: Levodropropizine

Levodropropizine does not exert its effects through **bronchodilation** or **muscarinic receptor antagonism**. Rather, it acts **peripherally**, likely modulating the activity of **vagal C-fibers** involved in the cough reflex. It is approved in many countries for symptomatic cough treatment in adults and children over 2 years, available in syrup, drops, or tablet form.



Codeine (methylmorphine) is an alkaloid of the phenanthrene series included in opium (morphine group;). Opioid receptor agonist. It has strong cough suppressant properties. In addition, it has a weak analgesic effect. In therapeutic doses, codeine does not depress the respiratory center or this effect is manifested to a lesser extent. Regular from the drug may cause constipation when used. Also get used to and in some cases drug addiction may occur (mental and physical).

Mostly cough suppressants are used alone (codeine base) or codeine phosphate. In addition, codeine can be added to a number of other agents: Bekhterev's mixture: (adonis herb tincture, NaBr and codeine), "Codterpin" tablet (codeine expectorant

means - together with NaHCO3 and terpene hydrate).

This group of substances also includes ethylene hydrochloride (dionine), which is synthetically obtained from morphine. It is an opioid receptor agonist. Pharmacologically similar to codeine, but compared to it inhibits the excitability of the cough center more strongly, has a stronger anesthetic effect. Opioid analgesics (morphine hydrochloride, etc.) have a strong antitussive effect have However, they weaken the respiratory center. In addition, this drugs can cause dangerous drug addiction in the short term.

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Therefore, they can be used only temporarily when codeine and other antitussives are ineffective.

A number of drugs have been created that only selectively suppress the cough center, do not cause the development of learning addiction and habituation.

These drugs are called **nonopioid (nonnarcoti**c) antitussives. **Glaucine t**hem include hydrochloride (glauvent) and oxeladine citrate (tusuprex). Glaucine is an alkaloid obtained from plants, while tusuprex is obtained synthetically. Medicines are well absorbed by the body. Glaucin can cause dizziness, nausea.

Libexin is included in antitussives with peripheral effect. Its mechanism of action is related to the anesthetic effect on the mucous membrane of the upper respiratory tract, as well as certain broncholytic properties. Libexin central nervous system does not affect the system. Libexin does not develop drug dependence. Thus, libexin belongs to non-opioid (non-narcotic) antitussives.

If the humidity of the mucous membrane of the bronchi is reduced (dry), thick, sticky sputum is released from the bronchial glands, increasing the secretion of the glands in the mucous membrane of the bronchi, as well as reducing cough by liquefying sputum possible For this, expectorants, including inhalation of alkaline liquid aerosols, are prescribed.

Sinecod- active ingredient: butamirate (butamirate)

Clinical and pharmacological group: Antitussive drug

Pharmacotherapeutic group: Centrally acting antitussive

pharmachologic effect

Butamirate is a centrally acting antitussive. However, the exact mechanism of action of the drug is not known. Butamirate citrate has nonspecific anticholinergic and bronchospasmolytic effects.

Suppresses cough, having a direct effect on the cough center. Has a bronchodilator effect (expands the bronchi). Helps make breathing easier by improving spirometry (reduces airway resistance) and blood oxygenation (saturates the blood with oxygen).

In therapeutic doses, the drug is well tolerated. Butamirate in the form of an oral solution has a soothing effect on an irritated throat due to the moisturizing properties of glycerol.

Pharmacokinetics

Based on available data, it is assumed that butamirate ester is rapidly and completely absorbed and hydrolyzed in plasma, turning into 2-phenylbutyric acid and diethylaminoethoxyethanol. The effect of food on absorption has not been studied. The change in the concentration of 2-phenylbutyric acid and

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diethylaminoethoxyethanol occurs in proportion to the dose taken in the range of 22.5-90 mg.

Butamirate is rapidly and completely absorbed when taken orally, measured concentrations are detected in the blood 5-10 minutes after administration in doses of 22.5 mg, 45 mg, 67.5 mg and 90 mg. Cmax in blood plasma is achieved within 1 hour when taken in all 4 doses, the average is 16.1 ng/ml when taken orally at a dose of 90 mg.

After taking 150 mg of butamirate, Cmax in plasma of the main metabolite (2-phenylbutyric acid) is reached after approximately 1.5 hours and is 6.4 μg/ml. When the drug is re-administered, its concentration in the blood remains linear, no accumulation is observed

Average plasma concentrations of 2-phenylbutyric acid are achieved within 1.5 hours; Cmax was observed at a dose of 90 mg (3052 ng/ml); average plasma concentrations of diethylaminoethoxyethanol are reached within 0.67 hours; Cmax is observed after taking a dose of 90 mg (160 ng/ml).

Metabolism

Hydrolysis of butamirate, which results in the formation of 2-phenylbutyric acid and diethylaminoethoxyethanol, which have an antitussive effect, occurs very quickly, the concentrations of metabolites are detected after 5 minutes. 2-phenylbutyric acid undergoes further partial metabolism by hydroxylation at the para position.

Excretion of the three metabolites occurs primarily by the kidneys; After conjugation in the liver, the acidic metabolites are largely bound to glucuronic acid. Conjugates of 2-phenylbutyric acid are determined in urine in significantly higher concentrations than in blood plasma. Butamirate is detectable in urine within 48 hours, and butamirate excreted in urine during the 96-hour sampling period accounts for approximately 0.02, 0.02, 0.03, and 0.03% of the 22.5 mg, 45 mg, 67.5 mg, and 90 mg doses, respectively. . As a percentage, butamirate is excreted in the urine in greater quantities and in the form of diethylaminoethoxyethanol than unchanged butamirate or unconjugated 2-phenylbutyric acid. The measured T1/2 of 2-phenylbutyric acid, butamirate and diethylaminoethoxyethanol is 23.26-24.42, 1.48-1.93 and 2.72-2.90 h, respectively.

There is no data on changes in the pharmacokinetics of the drug in patients with impaired liver or kidney function.

Indications for the drug Sinekod

symptomatic treatment of dry cough of various etiologies.

Dosage regimen

The drug is taken orally.

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Do not exceed the recommended dose.

The maximum duration of use of the drug without consulting a doctor is 7 days.

The drug is taken before meals using a measuring cap (supplied). The measuring cap should be washed and dried after each use. If the drug is used by several patients, the measuring cap should be washed and dried between uses on different patients.

Adults - 15 ml (22.5 mg) 4 times a day.

The maximum daily dose is 60 ml (90 mg).

Children over 12 years old - 15 ml (22.5 mg) 3 times a day.

The maximum daily dose is 45 ml (67.5 mg).

Children aged 6 to 12 years - 10 ml (15 mg) 3 times a day.

The maximum daily dose is 30 ml (45 mg).

Children aged 3 to 6 years - 5 ml (7.5 mg) 3 times a day.

The maximum daily dose is 15 ml (22.5 mg).

If symptoms worsen or do not improve after 7 days of treatment, as well as if there is a fever, rash or persistent headache, you should consult a doctor for further examination.

Side effect

The adverse reactions presented below are listed according to the damage to organs and organ systems and the frequency of occurrence. The frequency of occurrence is defined as follows: very common (≥1/10), common (≥1/100 and <1/10), uncommon (≥1/1000 and <1/100), rare (≥1/10000 and <1 /1000), very rare (<1/10000, including isolated cases), frequency unknown (frequency cannot be estimated based on available data).

From the nervous system: rarely - drowsiness.

From the digestive system: rarely - nausea, diarrhea.

From the skin and subcutaneous tissues: rarely - urticaria; the development of allergic reactions is possible.

SYRUPUS TUSSIFENE

Active substances (XPN): aminophenazone and ephedrine hydrochloride

Drug form: syrup

Contents:100 ml of syrup contains:

active substances: aminophenazone - 0.6 g and ephedrine hydrochloride - 0.18 g;

excipients: sodium benzoate, sugar, saccharin, sodium bromide, liquid extract of sunflower, liquid extract of togjambil, ethyl alcohol, purified water.

Description: a syrupy liquid with a characteristic smell and a sweeter taste.

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Pharmacological properties

A mucolytic drug with a pronounced expectorant effect. The drug liquefies sputum by stimulating the serous cells of the mucous membrane of the bronchi. By normalizing the ratio of serous and mucous components of sputum, it stimulates the production of enzymes that break down the bonds between mucopolysaccharides of sputum, and the formation of surfactant. Due to the increase in the production of surfactant, the drug has an anti-inflammatory effect, has antioxidant properties and increases local immunity.

Pharmacokinetics

After oral administration, ambroxol is practically completely absorbed from the gastrointestinal tract. The maximum concentration (Smax) in the blood plasma is reached after about 0.3-0.5 hours. The bioavailability of the drug is 70-80%. Accumulation has not been determined.

Plasma protein binding is about 90%. It quickly enters the tissues and the highest concentration is determined in the lungs. It crosses the blood-brain barrier (GET) and the placental barrier and is excreted in breast milk.

It is metabolized in the liver by conjugation, forming pharmacologically inactive metabolites.

The plasma elimination half-life (T1/2) is 7-12 hours. Approximately 90% of the drug is excreted through the kidneys.

Application

It is used in the mucolytic treatment of acute and chronic respiratory tract diseases accompanied by sticky sputum (acute and chronic bronchitis, pneumonia, obstructive bronchitis, bronchial asthma with impaired secretion secretion, bronchiectatic disease, and to improve mucus thinning in nasopharyngeal inflammation).

Method of administration and doses

The drug should be taken after meals. During treatment, it is necessary to drink a lot of liquid (juice, tea, water), because it enhances the mucolytic effect of the drug.

In the absence of other indications, the following dosage is recommended:

The duration of treatment depends on the severity of the disease and is determined by the treating physician. It is impossible to take the drug for more than 4-5 days without a doctor's recommendation.

Side effects

The drug is usually well absorbed. In some cases, allergic reactions: skin rash, urticaria, angioneurotic edema, in rare cases, allergic contact dermatitis, in very rare cases, acute severe reactions of the anaphylactic type (anaphylactic shock),

increased salivation, dry mouth, difficulty urinating, when taking large doses for a long time - stomach pain, heartburn, gastralgia, nausea, vomiting, constipation can be observed.

Circumstances that cannot be used

Hypersensitivity to the drug or other components of the drug, pregnancy (first trimester) and lactation period, stomach and duodenal ulcer disease, and antitussive drugs cannot be taken at the same time.

Drug interactions

Taking the drug and antibacterial agents (amoxicillin, cefuroxime, doxycycline, erythromycin) at the same time contributes to the penetration of antibiotics into the lung tissue. Proportionate with birth control drugs.

When the drug is used in combination with antitussive drugs, due to suppression of the cough reflex, liquefied secretions can be dangerously humidified. Therefore, antitussives should be taken only according to the instructions of the attending physician.

Special instructions

Syrup can be taken only after consultation with the attending physician and under the supervision of a doctor in cases of impaired motility of the bronchi and in cases of increased mucus (for example, dangerous eyelash syndrome). In case of severe renal or hepatic dysfunction, it is necessary to use smaller concentrations or increase the interval between drug administrations.

Syrup can be taken during breastfeeding or especially during the II and III trimesters of pregnancy only on the recommendation of the attending physician.

Conclusion.

Cough remains one of the most frequently reported symptoms in clinical practice. While the reflex itself is protective, persistent or excessive cough significantly impacts patients' lives. Many currently available antitussive medications have limitations, particularly due to CNS-related side effects. Levodropropizine, a newer peripherally acting agent, represents a promising alternative with an improved safety profile. The development and clinical use of such agents are essential to improving cough management and reducing the burden of chronic cough on healthcare systems.Cough remains a serious unmet clinical problem, both as a symptom of a range of other conditions such as asthma, chronic obstructive pulmonary disease, gastroesophageal reflux, and as a problem in its own right in patients with chronic cough of unknown origin. This article reviews our current understanding of the pathogenesis of cough and the hypertussive state characterizing a number of diseases as well as reviewing the evidence for the different classes of antitussive drug currently in clinical use. For

completeness, the review also discusses a number of major drug classes often clinically used to treat cough but that are not generally classified as antitussive drugs. We also reviewed a number of drug classes in various stages of development as antitussive drugs. Perhaps surprising for drugs used to treat such a common symptom, there is a paucity of well-controlled clinical studies documenting evidence for the use of many of the drug classes in use today, particularly those available over the counter. Nonetheless, there has been a considerable increase in our understanding of the cough reflex over the last decade that has led to a number of promising new targets for antitussive drugs being identified and thus giving some hope of new drugs being available in the not too distant future for the treatment of this often debilitating symptom.

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