

Combination cold and flu medicines: an overview of autonomic nervous system receptors

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Abstract

In the pharmacy, colds and flu are commonly treated illnesses, and medicines that contain decongestants, antihistamines, analgesics, cough suppressants and expectorants are used alone, or in combination, to relieve typical symptoms. Combination cold and flu medicines can have certain adverse effects on the autonomic nervous system. This article provides an overview of the functioning of the autonomic nervous system (ANS), the pharmacological effects of the common ingredients in cold and flu medicines on the ANS, as well as the contraindications to consider when offering these medicines.

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Introduction

The autonomic nervous system regulates the body's key internal organs and functions, such as the heart muscle and those of the intestinal tract, as well as sexual response. Therefore, it is important to consider any adverse effects and contraindications of medicines on this nervous system. Combination cold and flu products contain ingredients that can have adverse effects on the autonomic nervous system, and may aggravate blood pressure and heart problems, breathing and swallowing difficulties, and erectile dysfunction in men.¹ The risk of developing anticholinergic syndrome also exists, which may be caused by intentional overdose, inadvertent ingestion, medical non-compliance, and geriatric polypharmacy.²

The autonomic nervous system

Function

The nervous system comprises two main parts: the central nervous system (CNS), which includes the cortex and brain stem, and the peripheral nervous system (PNS). The PNS, which effectively connects the CNS with the rest of the body, is, in turn, made up of voluntary and autonomic nervous systems, the latter of which is divided into sympathetic and parasympathetic divisions.³

The functioning of the two divisions of the autonomic nervous system can be summarised as sympathetic division, whose main function is to prepare the body for stressful or emergency situations, i.e. for fight or flight; and a parasympathetic division, whose main function is to prepare the body for ordinary situations.⁴ (See Table I).

Table I: The neurotransmitters and nerve fibres involved, and their effect on the autonomic nervous system⁵

Neurotransmitter	Nerve fibre	Effects
Noradrenaline	Adrenergic	Sympathetic (stimulating)
Acetylcholine	Cholinergic	Parasympathetic (inhibiting)

Acetylcholine has some sympathetic effects. For example, it sometimes stimulates sweating, or makes the hair stand on end.⁵ The autonomic nervous system (ANS) connects the brain stem and spinal cord with internal organs, including the blood vessels, stomach, intestine, liver, kidneys, bladder, genitals, lungs, pupils and muscles of the eye, heart, and sweat, salivary, and digestive glands.⁵ It regulates internal body processes that require no conscious effort,⁴ for example, the control of blood pressure, heart and breathing rates, body temperature, digestion, metabolism, the balance of water and electrolytes (such as sodium and calcium), the production of body fluids (saliva, sweat, and tears), urination, defecation, sexual response, and other processes.⁵

The autonomic nervous system is activated mainly by centres in the spinal cord, brain stem, and hypothalamus of the brain. Two neurons are interposed between the CNS and the viscera (intestines). The neuron that arises from the CNS is called a preganglionic fibre, and the second neuron, or postganglionic fibre, goes directly to the structure to be innervated. Sympathetic ganglia are located close to the spinal cord, while parasympathetic ganglia are located near the effector organs. Parasympathetic preganglionic fibres pass all the way to the organ. The postganglionic neurons are located in the wall of the organ.³

Effects

Sympathetic stimulation causes excitatory effects in some organs, but inhibitory effects in others; and likewise for parasympathetic stimulation. In some organs, such as the heart, the two systems act reciprocally. However, most organs are dominantly controlled by one or the other. Since both systems are continuously active, the interplay between the parts can increase or decrease the activity of each organ.³ For example, the sympathetic division increases pulse, blood pressure and breathing rates, and the parasympathetic system decreases each of them.⁴ Stimulant effects occur when a drug mimics the neurotransmitter and stimulates the receptor on its own as an agonist, and inhibitory effects occur when the receptor site is blocked by an inhibitor or antagonist, so that the normal neurotransmitter cannot interact to send an impulse.⁶ (See Table II)

Since the same neurotransmitter is used in many organ systems, it can be predicted that medication used for control at one organ may produce side-effects in the others. For example, an anticholinergic medication may be given to control gastric spasm by blocking stimulation of the parasympathetic system. Generally, the main side-effect of the drug is to lower all activities in the parasympathetic system, with consequent dominance of the sympathetic system. Examination of Table II will reveal that the side-effects may include pupil dilation, dryness of the nose and mouth, constipation and an increased pulse.⁶

In men, difficulty initiating and maintaining an erection (erectile dysfunction) can be an early symptom of an autonomic disorder. Autonomic disorders commonly cause

dizziness or light-headedness due to an excessive decrease in blood pressure when a person stands (orthostatic hypotension). People may sweat less, or not at all, and become intolerant of heat. The eyes and mouth may be dry. After eating, a person with an autonomic disorder may feel full prematurely, or even vomit because the stomach empties very slowly (gastroparesis).⁵

Some people pass urine involuntarily (urinary incontinence), often because the bladder is overactive. Constipation may occur, or control of bowel movements may be lost. The pupils may not dilate and constrict as light changes.⁵

Pharmacological effects of cold and flu medicines on the ANS

The ANS is concerned primarily with visceral functions, such as cardiac output, blood flow to various organs and digestion.⁸ Therefore, when providing cold and flu medicine to a patient, medicines to be concerned about are those that may increase blood glucose or blood pressure, or constrict blood vessels.⁹ (see Table III)

Analgesics or antipyretics

Analgesics are included in cold and flu preparations to treat symptoms such as a headache, shivering, fever, and aches and pains. Paracetamol is the most commonly used analgesic in these preparations, with aspirin and ibuprofen making up the analgesic content of the other preparations. Many of these preparations also contain caffeine which improves the analgesic effect of the painkiller, and helps to combat lethargy in flu as it is a mild stimulant.¹⁰

Table II: Functions of the body controlled by the autonomic nervous system^{6,7}

Affected organ	Sympathetic adrenergic effects	Parasympathetic cholinergic effects
Eye (pupil)	Dilates the pupil	Constricts the pupil
Nose	Vasoconstriction Reduced mucus secretion	Vasodilatation Copious mucus secretion
Mouth or salivary flow	Weak stimulation of salivary flow (decreased saliva) Dryness in the mouth	Copious saliva secretion (strong stimulation of salivary flow)
Tear glands	No effect on the tear glands	Stimulates the tear glands
Heart, arterioles	Accelerates the heart Constricts the arterioles Contraction force is increased	Inhibits the heart (cardiac rate slowed) Dilates the arterioles Arterial contraction force is decreased
Lungs (bronchi)	Dilates the bronchi	Constricts the bronchi
Gastrointestinal tract	Constipation, relaxation of the intestines, decreased peristalsis and tone	Nausea, vomiting, abdominal cramps, diarrhoea, increased peristalsis and tone, relaxation of the sphincters
Pancreas	Inhibits the pancreas	Stimulates the pancreas
Bladder	Relaxes the bladder	Contracts the bladder
Sexual function	Stimulates ejaculation	Stimulates erection

Table III: Summary of the adverse effects of common ingredients in cold and flu medicines, including effects on the autonomic nervous system^{9,12-14}

Class	Therapeutic use	Ingredient	Adverse effect
Analgesics or antipyretics	Fever, headache, muscle aches, pain	Aspirin Ibuprofen Paracetamol	Gastric irritation, abdominal pain and nausea
Antihistamines	Runny nose, sneezing, watery eyes, itchiness of nose, throat and eyes	Chlorpheniramine Diphenhydramine Mepyramine Pheniramine Triprolidine	Central nervous system depression, i.e. sedation, dizziness, poor coordination and headache. Anticholinergic effects, i.e. constipation, dry mouth, dry eyes, blurred vision, thickened respiratory tract secretions, and urinary retention Gastrointestinal effects, i.e. nausea, vomiting, diarrhoea and anorexia.
Decongestants	Systemic decongestion of nose, sinuses and eustachian tubes	Phenylephrine Pseudoephedrine	Central nervous system stimulation, i.e. anxiety, nervousness, insomnia. Also headache, tremors, tachycardia, palpitations and cardiac arrhythmias.
Antitussives (cough suppressants)	Cough	Codeine Dextrometorphan	Dizziness, excitation or drowsiness, gastrointestinal effects, i.e. constipation, nausea, vomiting, and respiratory depression

Paracetamol is the analgesic of choice, since, when taken at the recommended dose, it is safer than any other analgesic. It is the only recommended analgesic for use by children under the age of 12 years, since aspirin can cause Reye's syndrome. Care must be taken to avoid other forms of paracetamol while taking cold and flu preparations. Cold and flu preparations containing aspirin or ibuprofen should be taken with, or after food, to avoid an upset stomach: the main side-effect of these drugs.¹⁰ However, these medicines do not affect the autonomic nervous system.

Antihistamines

Antihistamines compete with histamine at H¹-receptor sites on effector cells. Histamine is not a major mediator of the common cold, and the benefits of antihistamine in relieving congestion appear to be secondary to its anticholinergic properties. Atropine, the prototype of anticholinergics, and other substances with anticholinergic properties, competitively inhibit the muscarinic effect of acetylcholine by blocking its action in the autonomic ganglia, and at the neuromuscular junctions of the voluntary muscle system. They affect the peripheral and central ANSs.¹¹

Antihistamines are effective in treating rhinorrhoea, sneezing and watering eyes associated with colds and flu. Their anticholinergic side-effects include a dry mouth, dry eyes, blurred vision, thickened respiratory tract secretions, constipation and urinary retention.¹²

Toxicity is caused by anticholinergic properties, and is demonstrated by CNS depression or agitation, hyperactivity or psychosis, blurred vision, or abdominal discomfort. The less-sedating antihistamines have minimal anticholinergic effects, and may be preferred in patients with urinary or visual disorders, or problems with constipation.¹¹ However, these antihistamines may not be beneficial in relieving nasal

congestion associated with the common cold.

Side-effects may be enhanced with co-administration of other medicines that also have anticholinergic effects, such as some antidepressants, medicines used in psychiatric conditions, and medicines used for Parkinson's disease.¹¹

Due to their anticholinergic effects, antihistamines are contraindicated in patients with asthma, emphysema, closed-angle glaucoma, urinary retention and epilepsy.¹³

Decongestants

A decongestant, e.g. pseudoephedrine or phenylephrine, is a sympathomimetic agent which stimulates alpha-adrenoceptors mainly, and to a lesser degree, beta-adrenoceptors.¹³ Decongestants work by constricting the blood vessels in the nose, and thereby limiting the secretions and swelling of the membranes of the nasal passage. They may affect blood pressure and circulation⁹ as a result of the constriction of other blood vessels in the body, and should not be used in patients with uncontrolled hypertension and heart disease.¹⁴ Other contraindications include hyperthyroidism, diabetes mellitus, coronary artery disease, raised intraocular pressure or prostatic hypertrophy.¹³

Antitussives (cough suppressants)

Cough syrups may contain several different ingredients, including decongestants. Therefore, they may alter circulation or blood pressure. However, most health care providers would agree that if a patient's blood pressure is stable and reasonably well-controlled, the short-term use of over-the-counter (OTC) cough and cold products should be of little risk.⁹

Dextrometorphan is often present in combination with pseudoephedrine, antihistamines or anticholinergics, and paracetamol,¹¹ with contraindications including hepatic

disorders, decreased respiratory reserve and severe asthma. Codeine is contraindicated in patients with respiratory depression, head injuries, acute alcoholism, acute asthma, and heart failure secondary to chronic lung disease.¹³

Anticholinergic syndrome

Anticholinergic syndrome may follow the ingestion of a wide variety of prescription and OTC medications.² The mnemonic, “dry as a bone, red as a beet, hot as a hare, mad as a hatter and blind as a bat,” summaries the classic combination of central and peripheral anticholinergic effects. Other manifestations of toxicity, such as seizures, cardiac arrhythmias and hypotension, are not uncommon, and may be explained by mechanisms other than anticholinergic effects.¹⁵

Anticholinergic syndrome can be characterised by peripheral manifestations, which include dry mucus membranes and hot, dry, flushed skin, resulting from inhibition of secretions from the salivary glands, bronchioles, and sweat glands. Vasodilation occurs in the peripheral blood vessels, especially of the face and skin surfaces. Patients appear flushed and warm without sweating, despite agitation. The body temperature rises due to an inability to sweat, and because of altered CNS thermoregulation. Pupils are markedly dilated and vision is blurred, with loss of accommodation. Lack of cholinergic stimuli alters peristalsis, and may cause an intestinal ileus. Symptoms of the central anticholinergic syndrome may include disorientation, agitation, impairment of short-term memory, nonsensical or incoherent speech, and meaningless motor activity that includes repetitive picking or grabbing. Visual hallucinations may be prominent.¹⁵

Conclusion

To achieve the maximum efficacy of a medication, drug-drug interactions, drug-disease interactions, and timing of administration with respect to food, should be examined thoroughly before co-administration of multiple medications. The best advice is to monitor blood pressure routinely when starting or stopping any OTC agents, and to adjust medications if necessary.⁹

Clinicians should be certain that caregivers understand the importance of administering cough and cold medications

only as directed, and the risk of overdose if they administer additional medications that might contain the same ingredient.¹⁶

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