

# ANTICHOLINERGIC DRUGS

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## ANTICHOLINERGIC DRUGS

**Primary Disciplinary Field(s):** Pharmacology, Neurobiology, Psychiatry, Internal Medicine

### 1. Core Definition

Anticholinergic drugs, often synonymously referred to as **antimuscarinic agents**, constitute a critical subclass of pharmacological compounds designed to interfere with or inhibit the activity of the neurotransmitter **acetylcholine (ACh)**. Acetylcholine is the principal neurotransmitter utilized by the parasympathetic division of the autonomic nervous system (PNS), and also plays crucial roles in the central nervous system (CNS), particularly in areas related to memory, arousal, and motor control. By blocking the effects of ACh, these drugs effectively depress the actions mediated by the parasympathetic system, which is commonly associated with the "rest and digest" bodily functions. The action site is primarily the **muscarinic receptors**--a type of G-protein coupled receptor--leading to the alternative nomenclature of antimuscarinic drugs. The clinical utility of these agents stems from their ability to modulate a wide variety of physiological processes, including glandular secretions, smooth muscle tone, heart rate, and gastrointestinal motility, thereby making them indispensable in the management of numerous conditions ranging from psychiatric disorders to ophthalmological examinations and acute poisonings. Their broad spectrum of effects, however, necessitates careful prescribing due to the potential for significant systemic side effects, especially in vulnerable populations such as the elderly.

The fundamental mechanism involves competitive antagonism at the postsynaptic receptor sites. When an anticholinergic drug molecule binds to the muscarinic receptor, it prevents endogenous acetylcholine from binding and initiating the standard physiological response. Since acetylcholine is responsible for activating nerve endings across the body, especially those governing visceral functions, the inhibition caused by anticholinergic drugs results in a generalized suppression of cholinergic transmission. While the primary action is on muscarinic receptors (M1 to M5 subtypes), larger doses or specific chemical structures may also exhibit effects on other neurotransmitter systems, most notably **serotonin** and **norepinephrine** pathways, contributing to the complex pharmacological profiles observed in drugs like tricyclic antidepressants. This non-specificity at high concentrations further complicates the clinical picture, often leading to a constellation of side effects that reflect the drug's widespread impact across different neurochemical systems beyond the primary cholinergic target.

### 2. Mechanism of Action: Muscarinic Receptor Antagonism

The efficacy and clinical profile of anticholinergic drugs are intrinsically linked to their interaction with the two primary classes of cholinergic receptors: muscarinic and nicotinic receptors. While some drugs, particularly neuromuscular blockers, target nicotinic receptors, the vast majority of

clinically defined anticholinergic agents exert their therapeutic action through **competitive antagonism** at the muscarinic receptors (mAChRs). There are five known subtypes of muscarinic receptors (M1-M5), which are distributed differentially throughout the body, dictating the specific effects of a given anticholinergic compound. For instance, M1 receptors are prevalent in the central nervous system and gastric glands; M2 receptors are primarily found in the heart, mediating cardiac slowing; and M3 receptors control smooth muscle contraction and glandular secretions, such as saliva and sweat. A drug that is highly selective for M3 receptors, such as those used for overactive bladder, will primarily affect smooth muscle function while theoretically minimizing central nervous system side effects associated with M1 blockade, although achieving absolute selectivity remains a major challenge in pharmacology.

The inhibition of these receptors disrupts the normal signaling cascade initiated by acetylcholine. In the heart, M2 blockade leads to an increase in heart rate (tachycardia) because the inhibitory effects of the vagus nerve (which uses ACh) are removed. In the respiratory system, M3 blockade results in **bronchodilation**, making these drugs useful for conditions like chronic obstructive pulmonary disease (COPD) and asthma. Similarly, in the gastrointestinal tract, M3 blockade decreases gut motility and spasms, providing relief for irritable bowel syndrome. Crucially, in the central nervous system, particularly the basal ganglia, a delicate balance exists between dopaminergic and cholinergic activity. Anticholinergic drugs serve to restore this balance when it is tipped toward excessive cholinergic tone, a phenomenon often observed in Parkinson's disease or as a side effect (extrapyramidal symptoms) of typical antipsychotic medications. This targeted intervention highlights the sophistication required in matching the specific receptor profile of a drug to the desired therapeutic outcome, minimizing off-target effects as much as possible.

Understanding the role of acetylcholine in cognitive functions is also paramount when considering the mechanism of action. Acetylcholine is deeply implicated in memory encoding and retrieval. Thus, central-acting anticholinergics (those that can cross the **blood-brain barrier**) can significantly impair cognition, leading to symptoms ranging from mild confusion and memory lapses to frank delirium, especially in susceptible individuals. This adverse cognitive effect is particularly problematic in older adults and represents a major drawback of many commonly used medications, including older antihistamines and certain psychiatric drugs. Conversely, agents that are designed to be peripherally restricted, such as glycopyrrolate, generally avoid these central side effects, making them safer for systemic use where cognitive function must be preserved.

### 3. Classification and Therapeutic Applications

Anticholinergic drugs are not a single class but rather a property shared by numerous compounds spanning several therapeutic categories, reflecting the ubiquity of cholinergic signaling in human physiology. They are broadly categorized based on their chemical structure or their primary clinical use. Significant clinical applications include the treatment of motion sickness, exemplified by

agents like scopolamine; the management of overactive bladder and urinary incontinence using drugs such as oxybutynin and tolterodine, which primarily target bladder smooth muscle; and the alleviation of symptoms in chronic respiratory diseases, where inhaled anticholinergics (e.g., ipratropium and tiotropium) provide effective bronchodilation by blocking M3 receptors in the airways.

In the field of psychiatry and neurology, anticholinergics play a vital supportive role. They are frequently co-administered with typical (first-generation) antipsychotic medications, such as haloperidol, to prevent or treat debilitating **extrapyramidal symptoms (EPS)**, including dystonia, akathisia, and drug-induced parkinsonism. Drugs like benztropine and trihexyphenidyl are classic examples used for this purpose. Furthermore, older classes of psychotropic drugs, notably the **tricyclic antidepressants (TCAs)** such as amitriptyline, possess potent inherent anticholinergic activity, which contributes significantly to both their therapeutic effects (e.g., pain relief) and their side effect profile (e.g., dry mouth). This dual nature means that patients taking TCAs receive an anticholinergic effect as an unavoidable byproduct of their primary antidepressant or analgesic therapy.

Beyond these specialized uses, many common, over-the-counter medications also possess significant anticholinergic activity. First-generation H1-antihistamines, such as diphenhydramine (Benadryl), are strong central-acting anticholinergics. This property is responsible for their sedating effects and is exploited in sleep aids, but it also carries a substantial risk of cognitive impairment. Similarly, certain antispasmodic agents used for gastrointestinal disorders (e.g., dicyclomine) rely on their anticholinergic effects to reduce smooth muscle contractions. The sheer diversity of drug classes exhibiting anticholinergic properties underscores the importance of the concept of **Anticholinergic Burden**, which requires clinicians to sum the cumulative anticholinergic effects of all medications a patient is taking, rather than focusing on a single agent, to accurately assess the overall risk of adverse events.

#### 4. Adverse Effects and Clinical Concerns (Toxicity)

The side effects associated with anticholinergic drugs are directly predictable from their mechanism of action--the widespread blockade of the parasympathetic nervous system. This predictable constellation of symptoms is often summarized by the mnemonic phrase: "Hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter." Each component corresponds to a specific physiological effect: "**Dry as a bone**" refers to reduced glandular secretions, leading to severe dry mouth (xerostomia), dry eyes, and inability to sweat (anhidrosis); "**Hot as a hare**" is a direct consequence of anhidrosis, as the inability to dissipate heat through sweating can lead to hyperthermia, particularly dangerous in warm environments or during physical exertion.

Peripheral blockade also causes significant ophthalmological and gastrointestinal issues. "**Blind as a bat**" refers to blurred vision and photophobia resulting from mydriasis (pupil dilation) and cycloplegia (paralysis of the ciliary muscle), which impairs the eye's ability to accommodate for near vision. The suppression of gut motility commonly leads to chronic **constipation**, which can progress in severe cases to paralytic ileus, a serious medical condition requiring immediate intervention. Urinary retention is another common and uncomfortable side effect, particularly in men with pre-existing benign prostatic hyperplasia (BPH), as smooth muscle relaxation prevents efficient bladder emptying. These peripheral effects alone represent a major cause of non-compliance and morbidity among patients utilizing these agents long-term.

Perhaps the most concerning toxicity involves the central nervous system, encapsulated by "**Mad as a hatter**." Central anticholinergic syndrome (CAS) occurs when centrally active drugs cross the blood-brain barrier in high concentrations, leading to a profound state of confusion, agitation, disorientation, hallucinations, and frank delirium. This syndrome is particularly prevalent in acute overdose situations but can also occur at therapeutic doses in the elderly, whose blood-brain barrier integrity and metabolic clearance mechanisms are often compromised. The elderly are disproportionately susceptible to cognitive decline and falls when exposed to anticholinergics, leading geriatric consensus guidelines (such as the Beers Criteria) to strongly recommend against the use of many such medications in this population due to the established risk of accelerated cognitive decline and dementia. Treatment for severe anticholinergic toxicity often involves the administration of **physostigmine**, a reversible acetylcholinesterase inhibitor that can cross the blood-brain barrier, thereby reversing both central and peripheral effects.

## 5. Anticholinergic Burden and Geriatric Risk

The concept of **Anticholinergic Burden (ACB)** is an increasingly critical consideration in polypharmacy, especially among older adults who often take multiple medications simultaneously. ACB refers to the cumulative, dose-dependent inhibitory effect on cholinergic transmission resulting from exposure to all drugs in a patient's regimen that possess anticholinergic activity, even if that activity is secondary to the drug's primary therapeutic goal. A patient might be taking a tricyclic antidepressant, an overactive bladder medication, and an antihistamine for allergies--each contributing independently to the total anticholinergic load. Studies have consistently demonstrated a direct relationship between a high Anticholinergic Burden score (calculated using validated tools like the Anticholinergic Cognitive Burden scale) and detrimental health outcomes.

The most severe risks associated with high ACB in the geriatric population include an increased incidence of falls and fractures due to confusion and impaired motor coordination, chronic cognitive impairment, and increased risk of developing **dementia**. Longitudinal studies suggest that continuous exposure to high anticholinergic loads may lead to irreversible neurocognitive deficits. This heightened vulnerability stems from several physiological changes associated with aging,

including a natural decline in cholinergic neurons in the brain, reduced kidney and liver function (leading to higher circulating drug concentrations), and increased sensitivity of the blood-brain barrier. Consequently, clinical guidelines strongly advocate for minimizing the use of drugs with anticholinergic properties in older patients, prioritizing alternative therapies that are less centrally active or lack cholinergic inhibitory effects entirely.

## 6. Key Characteristics

**Mechanism of Action:** Anticholinergic drugs primarily act as competitive antagonists at **muscarinic acetylcholine receptors** (M1-M5), thereby preventing acetylcholine from initiating parasympathetic responses.

**Nomenclature:** They are frequently referred to as **antimuscarinic drugs** due to their specific action site, and historically, they were sometimes called **parasympathetic drugs** due to their depressive effect on the parasympathetic nervous system.

**Widespread Effects:** Because cholinergic receptors are pervasive, these drugs exert broad physiological effects, including mydriasis, decreased glandular secretions (e.g., dry mouth), decreased gastrointestinal motility, and tachycardia.

**CNS Activity:** Agents capable of crossing the blood-brain barrier can cause central nervous system effects ranging from sedation to severe confusion, agitation, and delirium, especially in toxic doses or in geriatric patients.

**Therapeutic Diversity:** Anticholinergics are utilized across diverse medical fields, including treating respiratory diseases (bronchodilation), managing urinary incontinence, alleviating gastrointestinal spasms, and mitigating extrapyramidal side effects induced by antipsychotics.

**Toxicity Syndrome:** Acute overdose results in a characteristic clinical presentation known as Central Anticholinergic Syndrome (CAS), often described by the mnemonic "Hot as a hare, blind as a bat, dry as a bone, red as a beet, and mad as a hatter."

## 7. Further Reading

[Anticholinergic Drugs \(Wikipedia\)](#)

[Cholinergic Toxidrome \(StatPearls - NCBI Bookshelf\)](#)

[Anticholinergic drug effects and anticholinergic burden in older adults \(UpToDate\)](#)