

ANTICHOLINERGIC EFFECTS

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Introduction to Anticholinergic Effects

The term **anticholinergic effects** refers broadly to the physiological and psychological outcomes--encompassing both intended therapeutic benefits and unintended adverse reactions--that result from the inhibition of **acetylcholine (ACh)** signaling within the nervous system. Specifically, these effects arise when a medication or substance acts as an antagonist, blocking the action of ACh at its receptor sites, predominantly the muscarinic receptors. While commonly discussed in the context of undesirable **side effects** associated with various medications, the definition also recognizes that blocking cholinergic transmission is the core mechanism of action for many crucial therapeutic agents used across specialties including psychiatry, gastroenterology, urology, and anesthesia. These effects are also frequently designated as **antimuscarinic effects**, highlighting the specific subclass of cholinergic receptors primarily targeted by these agents, distinguishing them from nicotinic receptor blockade.

The spectrum of anticholinergic effects is highly variable, depending heavily on the specific receptor subtype affinity of the drug, its dose, and its ability to cross the **blood-brain barrier (BBB)**. Peripheral effects are the most commonly recognized and include the classic signs often summarized by the mnemonic "dry as a bone, red as a beet, hot as a pistol, blind as a bat, mad as a hatter, and full as a flask." This classic description captures symptoms such as decreased glandular secretions leading to **dry mouth** (xerostomia) and dry eyes, impaired thermoregulation, visual disturbances like **blurry vision** (due to cycloplegia and mydriasis), and difficulties with elimination, specifically **constipation** and **urinary problems** (retention). Understanding the scope of these effects is crucial for clinical practice, as they represent a significant cause of medication non-adherence, morbidity, and emergency room visits, particularly among vulnerable populations.

It is essential to recognize that anticholinergic effects are not exclusive to drugs classified strictly as anticholinergics. They are frequently observed as off-target actions of various other pharmacological classes, including many older generation psychiatric medications such as **tricyclic antidepressants (TCAs)**, first-generation antipsychotics, and certain antihistamines. The severity of these effects generally correlates with the drug's binding strength to muscarinic receptors. Furthermore, the cumulative impact of multiple medications, each possessing mild anticholinergic activity, can result in a significant **anticholinergic burden**, leading to severe adverse events, including the potentially life-threatening condition known as **anticholinergic syndrome**. Therefore, clinicians must assess the total anticholinergic load when prescribing new treatments, focusing on minimizing these unintended consequences while achieving therapeutic goals.

Neurochemical Basis and Mechanism of Action

The foundation of anticholinergic effects lies in the modulation of the cholinergic system, which

utilizes the neurotransmitter **acetylcholine (ACh)**. ACh is vital for signal transmission in the central nervous system (CNS) and the peripheral nervous system (PNS), playing critical roles in the autonomic nervous system (ANS) and in brain regions associated with memory and cognition. Anticholinergic agents exert their influence by acting as **competitive antagonists** at cholinergic receptors. This means they bind to the receptor sites normally reserved for ACh without activating them. By occupying these sites, the drugs effectively prevent endogenous acetylcholine from binding and initiating the normal biological response, thereby dampening or completely blocking cholinergic transmission throughout the affected organ system.

Cholinergic receptors are categorized into two main superfamilies: nicotinic and muscarinic receptors. Anticholinergic effects, as conventionally discussed in the context of adverse drug reactions, primarily target the **muscarinic receptors (mAChRs)**. There are five subtypes of muscarinic receptors, labeled M1 through M5, which are distributed heterogeneously throughout the body and mediate distinct physiological functions. M1 receptors are prevalent in the CNS and autonomic ganglia; M2 receptors are critical in the heart, mediating inhibitory effects; M3 receptors are found on smooth muscle (regulating contraction) and glandular tissue (controlling secretion); M4 and M5 receptors are predominantly located in the CNS. The varying affinity of an anticholinergic drug for these specific subtypes dictates its side effect profile, often resulting in a predictable constellation of symptoms based on the blockade location.

The mechanism involves a dose-dependent relationship regarding the severity of blockade. At therapeutic or low doses, medications may selectively block only the most sensitive muscarinic receptors, resulting in mild, isolated side effects. As the dose increases, or as the total anticholinergic burden rises due to **polypharmacy**, the blockade becomes more widespread across multiple receptor subtypes and organ systems. This widespread blockade explains the transition from mild annoyance (e.g., slightly dry mouth) to serious clinical toxicity (e.g., paralytic ileus or acute delirium). Furthermore, many therapeutic agents exhibiting anticholinergic effects are designed to target other neurotransmitter systems (such as histamine or serotonin receptors); their anticholinergic activity is considered an undesirable off-target effect resulting from a lack of high pharmacological selectivity. The degree to which these agents penetrate the BBB determines the ratio of peripheral to central anticholinergic symptoms experienced by the patient.

Peripheral Manifestations and Clinical Triad

The peripheral manifestations of anticholinergic blockade are the most immediate and recognizable set of adverse effects, stemming from the inhibition of parasympathetic input to various organ systems. These symptoms are often grouped into the classic triad affecting the eyes, secretory glands, and smooth muscle systems. **Ocular effects** include **mydriasis** (pupil dilation) due to M3 receptor blockade in the sphincter pupillae muscle, and **cycloplegia** (paralysis of the ciliary muscle). Cycloplegia impairs accommodation, resulting in difficulty focusing on near objects,

commonly described by patients as **blurry vision**. Mydriasis also carries the risk of precipitating acute angle-closure glaucoma in susceptible individuals due to the narrowing of the drainage angle necessary for aqueous humor outflow.

Effects on glandular secretions are pervasive and result from M3 receptor blockade. Inhibition of salivary gland function leads to **xerostomia** (dry mouth), which can impair swallowing, speech, and taste, and significantly increase the risk of dental caries and periodontal disease due to the loss of protective saliva. Similarly, reduced lacrimation causes **dry eyes**, leading to irritation and corneal damage. Inhibition of sweating (anhidrosis) is a critical peripheral effect, particularly at high doses or in toxic states. Since sweating is essential for evaporative cooling, the inability to dissipate heat can rapidly lead to **hyperthermia**. This is often accompanied by cutaneous vasodilatation, resulting in flushed, hot, and dry skin--justifying the descriptive phrases "hot as a pistol" and "red as a beet." This impairment of thermoregulation is extremely dangerous, especially in hot environments or during strenuous activity.

The **gastrointestinal (GI)** and **genitourinary (GU)** systems are heavily reliant on cholinergic stimulation for normal function. In the GI tract, anticholinergic action decreases smooth muscle tone and motility, resulting in delayed gastric emptying and severe **constipation**. In cases of significant toxicity, this reduction in peristalsis can progress to **paralytic ileus**, a potentially life-threatening condition requiring urgent medical intervention. In the GU system, M3 receptor blockade relaxes the detrusor muscle of the bladder and increases the tone of the internal sphincter. This combination leads to impaired bladder emptying and **urinary retention**, causing discomfort, increasing the risk of urinary tract infections (UTIs), and potentially leading to permanent damage from chronic bladder distension. Cardiovascular effects, mediated primarily through M2 receptor blockade in the heart, typically involve **tachycardia** (increased heart rate), as the vagal inhibition normally provided by acetylcholine is removed.

Central Nervous System (CNS) Impact and Toxicity

The severity of central nervous system (CNS) effects is directly dependent on the ability of the anticholinergic agent to penetrate the **blood-brain barrier**. Drugs that are highly lipophilic and non-ionized (e.g., scopolamine, high doses of TCAs, or diphenhydramine) readily enter the brain and interfere with cholinergic neurotransmission in areas critical for cognitive function, memory, and consciousness, particularly the hippocampus and cortex. Even at therapeutic doses, this can manifest as mild **cognitive impairment**, characterized by difficulty concentrating, reduced processing speed, and subtle short-term memory deficits. These effects are often subtle and frequently misattributed to age-related decline or early dementia, posing a significant diagnostic challenge, especially in geriatric care.

As the central anticholinergic burden increases, the risk of acute neurocognitive deterioration rises

sharply, leading to **delirium**. Anticholinergic-induced delirium is a state of acute brain failure characterized by fluctuating levels of consciousness, profound disorientation, disorganized thinking, hallucinations (often vivid and visual), and significant agitation, fulfilling the notorious description "mad as a hatter." This is a medical emergency that necessitates immediate recognition and cessation of the offending agent(s). The severity of the delirium is directly correlated with the degree of central muscarinic receptor blockade. Furthermore, chronic exposure to anticholinergic medications has been strongly linked in numerous epidemiological studies to an increased long-term risk of developing irreversible cognitive disorders, including **Alzheimer's disease**, suggesting that chronic cholinergic deficit may contribute to neurodegeneration.

Other significant CNS effects include **sedation** and somnolence, which contribute substantially to the risk of falls, particularly in older patients. Paradoxically, high doses can sometimes lead to excitation, restlessness, seizures, and hyperreflexia. The distinction between peripheral toxicity and central toxicity is crucial for diagnosis and treatment. For example, while peripheral signs include dry, hot skin, severe central toxicity presents with marked behavioral changes and profound confusion. The combination of central and peripheral effects constitutes the **anticholinergic syndrome**, a toxidrome characterized by a dangerous constellation of symptoms including dilated pupils, flushed skin, tachycardia, hyperthermia, urinary retention, and altered mental status ranging from confusion to coma, requiring urgent pharmacological intervention.

Pharmacological Agents Implicated

A wide array of drug classes possesses anticholinergic activity, often unintentionally, due to structural similarities that allow them to bind non-selectively to muscarinic receptors as an off-target effect. One of the most historically significant groups are the **Tricyclic Antidepressants (TCAs)**, such as amitriptyline, imipramine, and doxepin. Although effective for depression and chronic pain, their potent anticholinergic profile contributes heavily to common side effects like dry mouth, constipation, blurred vision, and sedation, necessitating careful titration and monitoring. Similarly, older generation **Antipsychotics**, particularly low-potency agents like chlorpromazine and thioridazine, exhibit strong anticholinergic properties which contribute to their adverse effect profiles, including movement disorders and potentially dangerous cardiac conduction delays.

Another major contributor to the cumulative anticholinergic burden is the class of **Antihistamines**, especially the first-generation H1 receptor antagonists such as diphenhydramine and hydroxyzine. These agents are highly lipophilic, allowing them to readily cross the blood-brain barrier. They are frequently used for sleep, allergies, or anxiety, leading to significant central anticholinergic effects like daytime sedation and cognitive impairment, particularly in sensitive populations. In contrast, newer, second-generation antihistamines are designed to be less lipophilic, minimizing CNS penetration and subsequently reducing anticholinergic side effects. Furthermore, many agents used for gastrointestinal motility or spasm, such as dicyclomine, or those used in pulmonology like

ipratropium and tiotropium (though primarily acting locally), exert direct anticholinergic effects that contribute locally or systemically.

The list of agents contributing to the overall anticholinergic burden is extensive and diverse, including certain anti-Parkinsonian drugs (e.g., benztropine, trihexyphenidyl), muscle relaxants (e.g., cyclobenzaprine), and various antispasmodics. Assessing the cumulative risk is essential because patients are frequently prescribed multiple medications from different classes, all contributing additive anticholinergic activity. Tools such as the **Anticholinergic Cognitive Burden (ACB) Scale** or the **Anticholinergic Risk Scale (ARS)** have been developed to quantify this total burden by assigning numerical scores based on a drug's known potential to cause cognitive impairment. These scales are invaluable for helping clinicians identify high-risk regimens and implement strategies to switch to safer alternatives with minimal or no anticholinergic activity, thereby reducing the likelihood of adverse drug events and improving patient safety outcomes.

Therapeutic Applications of Anticholinergic Blockade

While the negative effects of anticholinergic activity are a primary clinical concern, the targeted blockade of muscarinic receptors forms the basis for several important and life-changing therapeutic interventions. By understanding the specific receptor subtypes and their anatomical locations, highly selective anticholinergic agents can be designed to achieve desired positive outcomes with minimized systemic side effects. For instance, in **urology**, antimuscarinic drugs like oxybutynin, tolterodine, darifenacin, and solifenacin are critical treatments for **overactive bladder (OAB)** and urinary incontinence. These agents primarily block M2 and M3 receptors in the detrusor muscle of the bladder, reducing involuntary contractions and increasing bladder capacity, thus effectively mitigating symptoms of urgency and frequency.

In **respiratory medicine**, anticholinergics are routinely used as bronchodilators. Agents such as ipratropium (short-acting) and tiotropium (long-acting) are inhaled to treat chronic obstructive pulmonary disease (COPD) and asthma. By blocking muscarinic receptors in the smooth muscle of the bronchi, they inhibit parasympathetic-mediated bronchoconstriction, leading to airway widening and improved airflow. Because these drugs are administered via inhalation, their systemic absorption is typically low, minimizing peripheral side effects compared to oral formulations, although dry mouth remains a common local complaint. Furthermore, anticholinergic drugs like scopolamine are highly effective in treating **motion sickness** and preventing nausea and vomiting, owing to their action in the vestibular system and associated CNS pathways that regulate balance and emesis.

Anticholinergics also hold significant roles in treating specific neurological and cardiovascular conditions. In **Parkinson's disease**, agents such as trihexyphenidyl or benztropine are used, particularly in younger patients, to help restore the balance between dopamine and acetylcholine

by blocking the excitatory cholinergic input in the basal ganglia. This helps reduce symptoms such as tremor and rigidity, which are often caused by relative cholinergic excess in the context of dopamine deficiency. In **cardiology**, atropine is a life-saving drug used in emergency settings to treat symptomatic bradycardia (slow heart rate) by blocking the inhibitory M2 receptors in the sinoatrial (SA) node, thereby increasing heart rate and improving cardiac output. These diverse, targeted applications underscore that anticholinergic action is a powerful pharmacological tool when utilized selectively and judiciously.

Management and Treatment of Anticholinergic Syndrome

Management of adverse anticholinergic effects ranges from simple dose adjustments for mild side effects to aggressive life support for severe **anticholinergic syndrome (AS)**. For therapeutic effects that are merely bothersome, such as dry mouth or mild constipation, conservative, non-pharmacological interventions are often successful. These include increasing fluid and fiber intake, using artificial tears for dry eyes, and employing sugar-free chewing gum or artificial saliva products for xerostomia. If the side effects persist or worsen, the first and most critical step in management is to identify and immediately discontinue or reduce the dose of the causative agent(s). Switching to alternative medications with low or negligible anticholinergic activity is the preferred clinical strategy whenever feasible to reduce the overall burden.

In cases of acute, severe toxicity leading to the full **anticholinergic syndrome**--characterized by marked hyperthermia, severe confusion or delirium, and peripheral signs (mydriasis, flushed skin, tachycardia)--treatment requires intensive supportive care within a supervised medical setting. Key supportive measures include external cooling methods (e.g., cooling blankets, misting) to manage hyperthermia, sedation (typically with benzodiazepines, carefully avoiding agents like phenothiazines which possess intrinsic anticholinergic properties) to control agitation and prevent injury, and continuous cardiac and respiratory monitoring due to the risk of arrhythmias and respiratory compromise. Monitoring for and managing complications such as seizures, rhabdomyolysis (due to prolonged hyperthermia), and acute urinary retention (often requiring catheterization) are essential components of supportive therapy.

For rapidly reversing severe central anticholinergic toxicity, particularly when marked delirium, hallucinations, or coma is present, the specific antidote is **physostigmine**. Physostigmine is a centrally acting acetylcholinesterase inhibitor that temporarily increases the concentration of endogenous acetylcholine at the synaptic clefts, thereby competitively overcoming the blockade imposed by the anticholinergic drug. Because physostigmine can cross the blood-brain barrier, it is highly effective at reversing both central and peripheral manifestations of AS. However, its use is reserved for severe cases due to the risk of significant side effects, including bradycardia, seizures, and cholinergic crisis if administered inappropriately. Before administering physostigmine, absolute contraindications--such as known history of tricyclic antidepressant overdose with QRS widening

(due to potential for worsening cardiotoxicity)--must be carefully excluded. The effectiveness of physostigmine, leading to a prompt reversal of delirium, can also serve as a definitive diagnostic tool for confirming anticholinergic syndrome.

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