ANTICHOLINERGIC
&
NEUROLEPTIC DRUGS

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Anticholinergic Drugs

A variety of chemicals, drugs and herbal derivatives possess anticholinergic properties defined by their ability to block the neurotransmitter acetylcholine (ACh).

This effect is a result of a direct interference with either of two types of cholinergic receptors, peripheral muscarinic and nicotinic receptors.

Anticholinergic effects are also a consequence of adverse drug reactions (ADRs), as seen with the tricyclic antidepressants (TCAs) and phenothiazine antidepressants.

Many anticholinergic compounds exert their action by occupying central cholinergic receptors, thus producing alterations on the central nervous system.

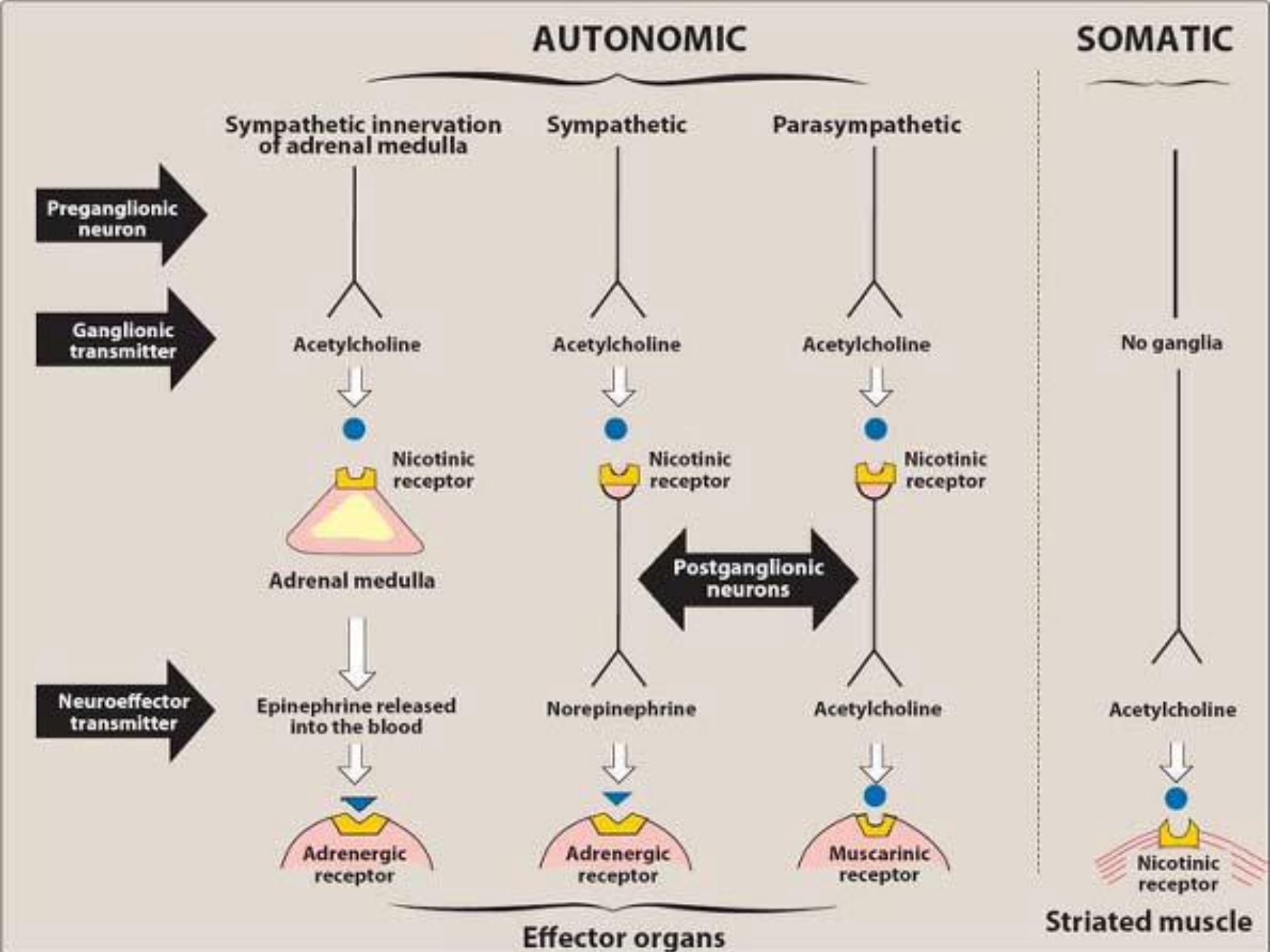
Autonomic neurons and their receptors govern sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity throughout the body.

Nicotinic receptors are present in the plasma membrane of dendrites and cell bodies of both SNS and PNS preganglionic neurons, and at the neuromuscular junction.

Activation of these receptors triggers postsynaptic neuronal excitation and skeletal muscle contraction.

Muscarinic receptors are present on cell membranes of smooth and cardiac muscle and in sweat glands.

Activation of these receptors by ACh delivers stimulation or inhibition depending on the effector organ.


AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle

ANTIHISTAMINES, GASTROINTESTINAL AND ANTI-PARKINSON DRUGS

Antihistamines (the H1-antagonists) are commonly found in over-the counter cough and cold preparations.

They frequently induce sedation and may adversely affect a child's learning ability.

Anti-Parkinson agents are indicated for the treatment of all forms of Parkinsonism, and are used to improve the extrapyramidal symptoms (EPS) associated with traditional neuroleptic drugs.

Like the anti-Parkinson agents, the anticholinergic properties of the GI agents are also therapeutically advantageous.

Category	Therapeutic classification	Compound	Proprietary name	Predominant anticholinergic effects
Antihistamines	H_1-antagonists	Brompheniramine Diphenhydramine Dimenhydrinate Chlorpheniramine Promethazine Meclizine Pyrilamine	Dimetane Benadryl Dramamine Chlortrimeton Phenergan Bonine, Antivert In combination with nasal decongestants	Dry mouth, mydriasis, drowsiness, dyspnea, facial flushing, sinus tachycardia
Anti-Parkinson agents	Anticholinergic[a]	Benztropine Trihexyphenydyl Procyclidine Biperiden	Cogentin Artane Kemadrin Akineton	Dry mouth, mydriasis, blurred vision, dyspnea, sinus tachycardia, toxic psychosis, coma, seizures, ataxia, EPS
Gastrointestinal anticholinergic agents	Antispasmodic	Atropine Homatropine Belladonna alkaloids Clidinium bromide L-Hyoscyamine Scopolamine Glycopyrrolate Dicyclomine Propantheline	Various Various Donnatal[b] Quarzan; Librax (with chlordiazepoxide) Levsin, Levsinex Scopace Robinul Bentyl Pro-Banthine	Dry mouth, mydriasis, drowsiness, dyspnea, excitement, agitation, constipation, blurred vision, sinus tachycardia

Signs and Symptoms of Acute Toxicity

Anticholinergic compounds exert their effects by blocking central and peripheral cholinergic receptors.

Dry mouth and mydriasis are the most common ADRs of all anticholinergic agents, as well as headache, dysuria and dyspnea.

Increased vascular permeability and capillary perfusion is mediated by an unregulated SNS stimulation from anticholinergic activity of these compounds and accounts for the facial and upper body flushing.

Sedation is an effect common mostly to antihistamines and is mediated primarily through blocking of central H1 receptors.

Sinus tachycardia is the most sensitive sign of toxicity and may exacerbate other conduction abnormalities.

Clinical Management of Acute OD

Acute anticholinergic toxicity necessitates careful supportive treatment.

Gastric lavage may be useful within one hour of ingestion.

Activated charcoal is useful to decrease drug absorption.

Agitation, seizures, hyperthermia and hypertension are treated conventionally in mild to moderate toxicity.

Benzodiazepines or barbiturates are effective in controlling seizures, while agitation is treated with benzodiazepines only.

Lidocaine is useful for controlling dysrhythmias.

Antiarrhythmic drugs of class IA, such as quinidine, procainamide, and disopyramide, should be avoided.

Cholinergic intervention is warranted when signs and symptoms result from moderate to severe anticholinergic toxicity.

Although controversial, IV physostigmine, a reversible cholinesterase inhibitor, is warranted only if conventional therapy fails to control seizures, agitation, and unstable dysrhythmia, coma with respiratory depression, malignant hypertension or hypotension.

Physostigmine administration is contraindicated in patients with cardiovascular or peripheral vascular disease, bronchospasm, heart block, intestinal or bladder obstruction.

Methods of Detection

Thin-layer chromatography (TLC) is suitable for qualitative toxicological screening of antihistamines.

- Different pH solvents are used to extract the chemical substance from the sample to facilitate isolation of the corresponding acidic, basic or neutral derivative.
- The extracted sample is applied as a spot on the plate (coated with either silica gel or alumina fixed phase).
- The relative migration of the sample components is influenced by the mobile phase; for antihistamines acetic acid:butanol:butyl ether (20:40:40), acetic acid:ethanol:water (30:50:20) or n-butanol:methanol (40:60) are the most common mobile phases.
- The separated components of interest on the TLC plate are visualized and characterized according to the formation of distinguishing colors.
- Ninhydrin is a typical spray reagent used for primary amines (violet, pink) and secondary amines (yellow).

TRICYCLIC ANTIDEPRESSANTS

The term “neuroleptic” has come to replace older terminology that described the clinical effects of this major class belonging to the psychotherapeutic agents.

These include the classes of compounds known as the major and minor tranquilizers, antipsychotic, antimanic, antipanic and antidepressant drugs.

Although TCAs and phenothiazine derivatives possess significant anticholinergic reactions, they may still be identified with the antidepressant and antipsychotic categories, respectively.

The phenothiazine derivatives, chlorpromazine and promethazine were the first neuroleptics synthesized in the 1950s, and are the pharmacological prototypes for all psychoactive compounds.

Because of their life-threatening toxicity and potential for inducing intentional suicide, especially in patients at increased risk for self-inflicted harm, treatment regimens are generally limited to one- or two- week supplies.

Pharmacology and Clinical Use

TCA neuroleptic agents have predominantly antiserotonergic and anticholinergic activity.

These central actions account for their utility as antipsychotics, particularly in producing sedation for agitation and in reducing hallucinations and delirium.

In addition, anticholinergic and antihistaminic effects confer desirable antiemetic/antinausea properties (prochlorperazine) and antihistaminic properties (promethazine) to some agents, respectively.

Toxicokinetics

TCA drugs are rapidly absorbed with quick onset.

They possess high protein binding and high volume of distribution (Vd) properties, providing a prolonged duration of action.

Their therapeutic effects however require five to seven days before benefits are observed, because of necessary depletion of neurotransmitter storage.

Mechanism of Toxicity

The toxic manifestations of this class of drugs are explained as toxicologic extensions of their pharmacology.

The effects are typically associated with the anticholinergic (antimuscarinic) blockade, their characteristic quinidine-like myocardial depressant action, and their ability to block the vagus nerve.

In addition to interference with cardiac function, neuroleptic-induced hypotension occurs as a result of peripheral α-receptor blockade associated with the TCAs.

Signs and Symptoms of Acute Toxicity

CNS depression, seizures and cardiac arrhythmias are generally observed with acute OD.

Decreased cardiac output and circulatory collapse are potentially life threatening and usually occur with ingestion of more than 10 mg/kg in adults.

Serious toxicity manifests within six hours of the OD.

Most common signs and symptoms appear as hypotension, respiratory depression, cardiac conduction delays, dysrhythmias, urinary retention, seizures and coma.

Death from neuroleptic OD is rare and is usually a consequence of multiple drug ingestion.

Neuroleptic-induced arrhythmias are a consequence of the quinidine-like myocardial depressant action of the compounds.

Patients with plasma concentrations approaching 100 mg/dL are at risk of developing decreased (AV) conduction, vagal blockade, widening of the QRS interval and prolongation of the QT interval.

CNS depression, agitation, delirium, confusion and disorientation are frequent consequences of neuroleptic administration.

Hypothermia or hyperthermia, and myoclonus (spastic skeletal muscle contraction) contribute to central dystonias.

Loss of short-term memory, seizures and respiratory depression are complications.

In general, tertiary amines have greater antimuscarinic potency than secondary amines, tetracyclics, or triazopyridines, of which amitriptyline is the most potent of the class.

Clinical Management of Acute OD

TCA OD requires that all patients receive activated charcoal (1 g/kg) orally or per nasogastric (NG) tube.

Cardiovascular and respiratory functions are monitored for 12 hours up to 6 days because of the prolonged reactions.

Treatment with IV fluids and vasopressors, such as norepinephrine or phenylephrine, is necessary for reversing neuroleptic-induced hypotension.

Quinidine-like effects, especially ventricular dysrhythmias, are managed with lidocaine, while the widening QRS complex requires sodium bicarbonate.

Class 1A antiarrhythmics, such as quinidine, procainamide, and disopyramide, should be avoided as these compounds may aggravate AV conduction.

Ventilatory support is required in patients experiencing significant respiratory depression.

Anticonvulsants, such as diazepam and Phenobarbital, are beneficial for seizure management.

Unlike in the treatment of anticholinergic OD, physostigmine is not recommended for TCA toxicity, due to potential induction of fatal asystoles.

Hemodialysis and hemoperfusion are also not useful because of the high Vd and high protein binding demonstrated with TCAs.

PHENOTHIAZINE, PHENYLBUTYLPIPERIDINE, AND THIOXANTHINE ANTIPSYCHOTICS

These drugs are indicated for the management of manifestations of psychotic disorders, antiemetics, cough suppressants and antivertigo agents.

They are also effective in the treatment of migraine headaches, and acute agitation in the elderly, although these are unlabeled indications.

As with the TCAs, OD is rarely fatal.

Pharmacology and Clinical Use

Antipsychotic agents exert their actions primarily by antagonizing dopamine receptors.

Varying degrees of selective dopamine blockade are seen in the cerebral limbic system and basal ganglia.

Physiologically, these central pathways are associated with skeletal movement (nigrostriatal tracts), hallucinations and delusions (mesolimbic), psychosis (mesocortical), and prolactin release (tuberoinfundibular).

Mechanism and Signs and Symptoms of Acute Toxicity

These drugs display moderate to significant CNS reactions, including sedation, muscle relaxation and lowering of the seizure threshold which sensitizes the individual to convulsions.

Antipsychotic drugs depress the reticular activating system (RAS) responsible for stimulating wakefulness (consciousness).

Antimuscarinic and antihistaminic effects, such as mydriasis, dry mouth, tachycardia and decreased GI activity, further complicate their toxic profiles.

Influence on hypothalamic nuclei is responsible for vasodilation, orthostatic hypotension and hypothermia or hyperthermia.

As with the TCAs, α-adrenergic blockade contributes to hypotension.

EPS (extrapyramidal symptoms) develop when an imbalance between antidopaminergic and anticholinergic activity is created.

The more overwhelming the antidopaminergic properties, the greater the severity of EPS reactions.

Higher potency phenothiazines are more likely to produce EPS than lower-potency TCA antidepressants or the newer neuroleptics.

Acute dystonic reactions appear in 95% of patients, predominantly young males, within four days of initiation of therapy or as dosage increases.

In contrast, *akathisia* affects mostly elderly patients in early treatment (first 60 days) and subsides with lower dosage.

Parkinsonism develops within 10 weeks of therapy and affects 90% of patients, although it is reversible at lower doses.

It is important to note that the risk of developing *tardive dyskinesia*, that will become irreversible, increases with the duration and with the total cumulative dose of the neuroleptic drug treatment.

Neuroleptic malignant syndrome is a potentially fatal idiosyncratic complication occurring in 2% of patients on antipsychotic therapy.

Clinical Management of Acute OD

As with TCA toxicity, cardiovascular and respiratory adverse effects with antipsychotics are monitored for 12 hours and up to 6 days.

Treatment for reversing neuroleptic-induced hypotension and quinidine-like effects, especially ventricular dysrhythmias are similarly managed with lidocaine and sodium bicarbonate.

Convulsions or hyperactivity are controlled with pentobarbital or diazepam.

Extrapyramidal adverse effects are not fatal and are best treated with anticholinergics or benzodiazepines.

Several days of treatment are necessary to reverse acute toxicity.

Prophylactic anticholinergic therapy is useful in prevention of EPS.

In severe situations, consideration should be given to discontinuation of the neuroleptic, since dystonic reactions usually subside within 24 to 48 hours after drug cessation.

Drug discontinuation and substitution with an atypical neuroleptic, such as clozapine, are usually considered (have a lower incidence of EPS).

Clozapine may also be effective in reversing phenothiazine-induced tardive dyskinesia.

Characterization of the EPS Associated with Neuroleptic Agents

Syndrome	Signs and symptoms	Clinical management
Acute dystonic reactions	Oculogyric crisis (upward-gaze paralysis); muscular spasms of neck (torticolis), back (opisthotonos), tortipelvis (abdominal wall)	Anticholinergics or benzodiazepines; antihistamine (diphenhydramine); dosage reduction or discontinuation
Akathisia	Motor restlessness and discomfort; inability to sit still	Anticholinergics or benzodiazepines; dosage reduction or discontinuation
Parkinsonism (akinesia)	Bradykinesia, shuffling gait, resting tremor (“pill rolling movements”), “masked face,” perioral tremors (“rabbit syndrome”)	Anticholinergics or benzodiazepines; antihistamine (diphenhydramine); dosage reduction or discontinuation
Tardive dyskinesia (older males) and tardive dystonia (younger males)	Choreoathetoid movements: involuntary, repeptitive, spasmodic movements of face, tongue, lips (chorea); slow, writhing, involuntary movements of fingers and hands (athetoid); may occur after years of neuroleptic therapy and are irreversible	Dosage reduction or discontinuation; clozapine as alternative and/or botulimuun toxin, tetrabenzaine, or reserpine
Neuroleptic malignant syndrome (NMS)	Catatonia, muscle (“lead pipe”) rigidity, stupor, hyperpyrexia, altered mental status, autonomic instability	For hyperprexia, benzodiazepines and rapid physical cooling; bromocryptine (DA agonist), dantrolene (for muscle rigidity); anticholinergics not recommended; withdraw neuroleptics for minimum of 14 days; clozapine as alternative