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**.

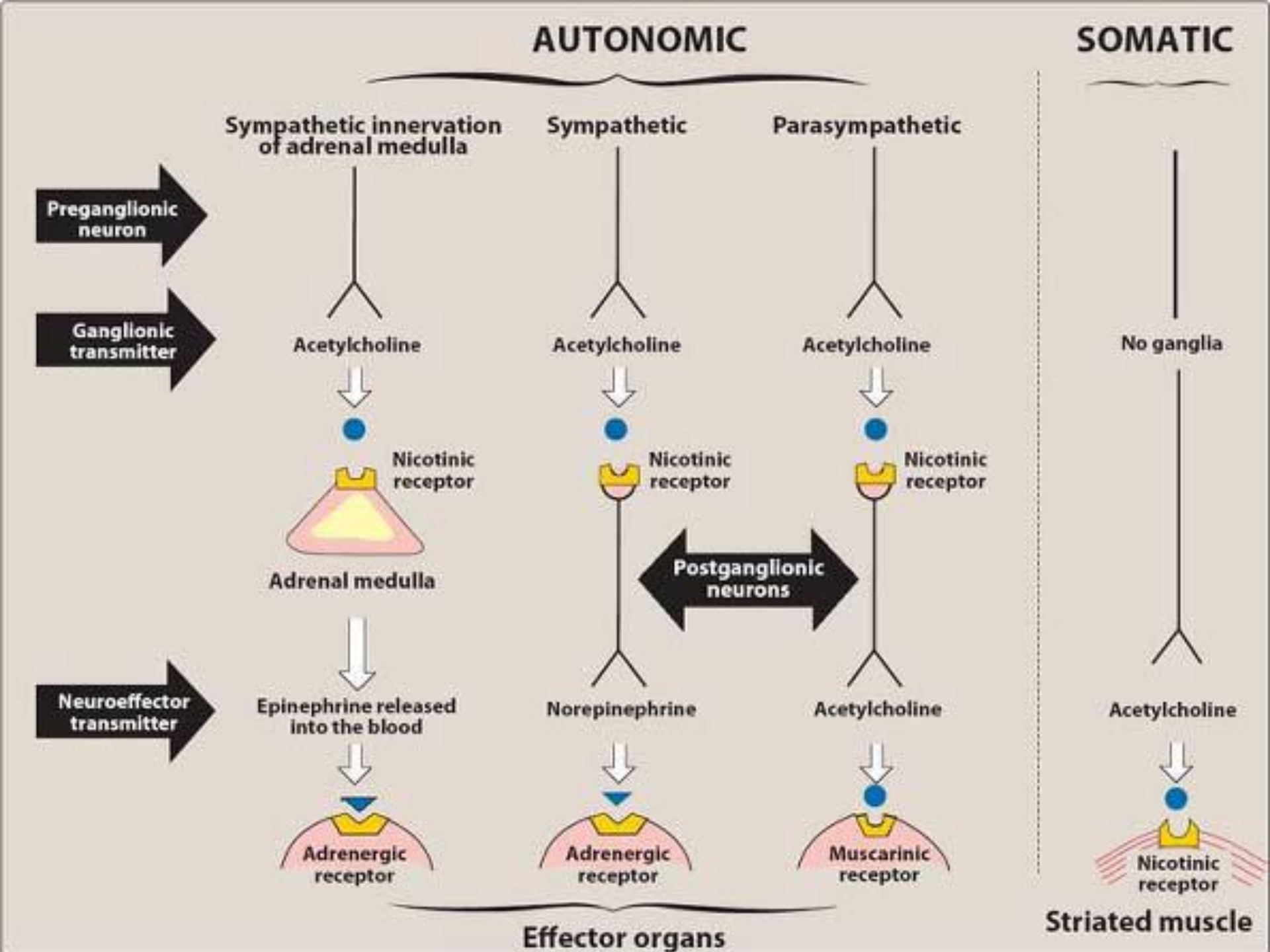
Autonomic neurons and their **receptors** govern sympathetic nervous system (**SNS**) and parasympathetic nervous system (**PNS**) activity throughout the body.

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**, while **anticholinergic** and some extrapyramidal symptoms (**EPS**) are common **ADRs**.

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 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.

Prolonged antipsychotic therapy **or** toxic **OD** can precipitate any or **most** of the **symptoms**.

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


The End