Cholinergic Agonists & Antagonists

- **Course:**
  Integrated Therapeutics I

- **Professor:**
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- **Email:**
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- **Material covered on:**
  Exam #1

- **Reading:**
  Katzung 12\textsuperscript{ed} Chapter 7, 8, 9, 10
Cholinergic Agonists Review
# Muscarinic Receptor subtypes

<table>
<thead>
<tr>
<th>M-receptors subtypes</th>
<th>M1</th>
<th>M2</th>
<th>M3</th>
<th>M4</th>
<th>M5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other name</td>
<td>neural</td>
<td>Cardiac muscarinic receptors</td>
<td>Glandular muscarinic receptors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Exocrine glands and autonomic ganglia</td>
<td>Atria and conducting tissue of the heart</td>
<td>Exocrine glands and smooth muscle</td>
<td>CNS</td>
<td>Substantia nigra (cns)</td>
</tr>
<tr>
<td>Function</td>
<td>Affects arousal attention, REM, emotional response, affective disorder</td>
<td>Cardiac inhibition</td>
<td>Lacrimal, salivary Mostly stimulatory effect</td>
<td>Direct regulatory action on K and Ca ion channels</td>
<td>May regulate dopamine release at terminals within the striatum</td>
</tr>
</tbody>
</table>
Muscarinic receptors:
(G protein-coupled)
M1-Type: 1, 3, 5
M2-Type: 2, 4

Neuronal nicotinic receptors:
(Ligand-gated ion channels)

Group II: α7
Group III-1: α2, α3, α4, α6
Group III-2: β2, β4
Group III-3: β3, α5
Muscarinic

M1, M3, M5

Orthosteric (ACh) binding site

Putative allosteric binding sites

M2, M4

Nicotinic

α7

α4β2

Ca^{2+}

Na^{+}

Ca^{2+}

Na^{+}

Ca^{2+}

Na^{+}

Key effectors (examples)

↑ PLCβ
↑ [Ca^{2+}]i
↑ MAPK

Key effectors (examples)

↑ AC
↑ MAPK
↑ GIRK ch.

Key effectors (examples)

↑ [Ca^{2+}]i
↑ VDCC
↑ PKC
1. HD has miosis, and needs to micturate much more frequently than usual and cannot stop salivating. HD took a pill this morning that he found in the medicine cabinet, thinking it was an aspirin. HD does not show twitching or muscle spasm upon exam. What type of medication do you suspect that HD took?

a. Sympathomimetic
b. Parasympathomimetic
c. An acetylcholinesterase inhibitor
d. Both A & C
e. Both B & C
f. None of the above
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   b. Muscarinic
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Why isn’t the answer C?
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   c. Both A & B
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Why isn’t the answer C? If the drug was working at nicotinic receptors, both the sympathetic & parasympathetic systems would be activated and cancel each other out.
EFFECTS OF ACTIVATION OF PARASYMPATHETIC NERVOUS SYSTEM

**EYES:** Constricts pupil: miosis

**SALIVARY GLANDS:** Increased salivation

**HEART:** Decreases heart rate; Slows conduction through AV node

**LUNGS:** Contraction of bronchial smooth muscle; Increased secretion

**GI TRACT:** Increased motility (contracts smooth muscle, relaxes sphincters); Increased secretions

**BLADDER:** Contraction (urination)

**VASCULAR SMOOTH MUSCLE:** NO EFFECT
PK was administered a choline ester. Which of the following drugs did PK possibly get?

a. Bethanacol
b. Methacholine
c. Pilocarpine
d. Physostigmine
e. Both A & B
f. Both B & D
g. None of the above
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a. Bethanacol  
b. Methacholine  
c. Pilocarpine  
d. Physostigmine  
e. Both A & B  
f. Both B & D  
g. None of the above
Parasympathomimetic drugs

Direct acting
- Choline ester
  - Acetylcholine
  - Methacholine
  - Carbachol
  - Bethanechol
  - Others
  - Aceclidine

Indirect acting
- Alkaloid
  - Pilocarpine
- Reversible ChE inhibitors
  - Physostigmine
  - Neostigmine
  - Edrophonium
- Irreversible ChE inhibitors
  - Ectothiophate
Which of the following choline esters has the most activity at nicotinic receptors?

a. Methacholine
b. Carbachol
c. Bethanacol
d. Both A & C
e. None of the above acts at nicotinic receptors
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b. Carbachol
c. Bethanacol
d. Both A & C
e. None of the above acts at nicotinic receptors
Cholinergic influences are prominent in many organ systems:

<table>
<thead>
<tr>
<th>Choline Ester</th>
<th>Sensitivity to ACHE</th>
<th>Cardiovascular</th>
<th>Gastrointestinal</th>
<th>Urinary Bladder</th>
<th>Eye (Topical)</th>
<th>Atropine Sensitive</th>
<th>Activity at Nicotinic Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
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<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Methacholine</td>
<td>☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
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<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Carbachol</td>
<td>No</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
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<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>No</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
<td>☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
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<td>☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐</td>
</tr>
</tbody>
</table>


Cholinergic Antagonists

Acetylcholine

Deadly nightshade (Atropa belladonna)

Scopolamine

Atropine
CHOLINERGIC ANTAGONIST DRUGS

Antimuscarinic drugs:
inhibit parasympathetic effects and sweating (sympathetic effect)

Antinicotinic drugs:
ganglion blockers and neuromuscular blockers
ANTICHOLINERGIC DRUGS:
COMMON SITES OF ACTION

Pre-Synaptic Neuron

Synapse

Post-Synaptic Site

ACh = acetylcholine

Acetylcholinesterase

Nicotinic Receptors

Muscarinic Receptors

Muscarinic Receptor Antagonists
DIRECT ACTING

Nicotinic receptor antagonists
DIRECT ACTING

ACh Release Inhibitors
INDIRECT ACTING
CHOLINERGIC ANTAGONISTS

• **Direct-acting antagonists**
  - Antimuscarinic drugs
    - Atropine
    - Scopolamine
    - Ipratropium
    - Oxybutynine
    - Tiotropium
    - Tolterodine
  - Antinicotinic drugs

• **Indirect-acting antagonists**
CHOLINERGIC ANTAGONISTS

Atropine

Scopolamine

Ipratropium
CHOLINERGIC ANTAGONISTS

Oxybutynine

Tiotropium

Tolterodine
CHOLINERGIC ANTAGONISTS

Curare
## ABSORPTION AND DISTRIBUTION

<table>
<thead>
<tr>
<th>Tertiary amines</th>
<th>Non-polar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>Well absorbed from gut, mucous</td>
</tr>
<tr>
<td></td>
<td>membranes, skin (scopolamine)</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>Widely distributed in the body</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Penetrate into CNS</td>
</tr>
<tr>
<td>Tolterodine</td>
<td></td>
</tr>
</tbody>
</table>

| Quaternary amines     | Highly polar                        |
|                       | Poorly absorbed                     |
| Glycopyrrolate        | Poorly distributed in body          |
| Ipratropium           | Do not penetrate into CNS           |
| Tiotropium            | More suitable for local/topical use |


ORGAN SYSTEM EFFECTS

- **Central nervous system**
  - Sedation and drowsiness at *lower concentrations*
  - Excitement, agitation, hallucinations and coma at *toxic concentrations*
  - Prevent *vestibular disturbances* and *motion sickness*

- **Eye**
  - Mydriasis (due to unopposed sympathetic activity)
  - Paralysis of ciliary muscle (*cycloplegia*)
    - Loss of lens accommodation
  - Increase in *intraocular pressure*
  - Reduction in *lacrimal secretion* (“sandy” eyes)
ORGAN SYSTEM EFFECTS

• Cardiovascular system
  – **Tachycardia**
    (inhibition of vagal effect on *sinoatrial node*)
  – **Reduction of PR interval**
    (inhibition of vagal effect on *AV node*)
  – **Ventricles** have a small number of **M receptors**
    • no significant effect on contractile function

• Respiratory system
  – Relaxation of bronchial smooth muscle – **bronchodilation**
  – **Inhibition of mucus secretion** by glands of airway
Vagus nerve
ORGAN SYSTEM EFFECTS

- **GI system**
  - Inhibition of *salivation*
  - Reduction of *gastric secretion* (HCL, pepsin, mucin)
  - Inhibition of *smooth muscle* tone and propulsive movements

- **Urogenital tract**
  - Relaxation of *smooth muscle* of ureter & bladder wall
  - Urine retention and *decreased speed of urination*

- **Sweat glands**
  - Suppression of *thermoregulatory sweating*
    - *sympathetic cholinergic fibers innervate*
    - *eccrine sweat glands*
  - Elevation of body temperature
TOXIC EFFECTS OF ANTI-MUSCARINIC DRUGS

- **Atropine poisoning** (from plant *Atrope belladonna*)
  - *Dry as a bone*: dry mouth, dry skin
  - *Blind as a bat*: mydriasis, visual difficulties
  - *Red as a beet*: hyperthermia (flushing)
  - *Mad as a hatter*: agitation, hallucinations
- Potentially **lethal hyperthermia** in children
- **Poisoning** with quaternary antimuscarinics
  - No CNS effects, but peripheral signs are present
CLINICAL USE OF ANTIMUSCARINICS

• Central nervous system disorders
  – Parkinson’s disease
    • Characterized
      – loss of dopaminergic neurons in (Substantia Nigra) brain
      – deficient dopaminergic transmission
      – reciprocal augmentation of muscarinic influence
    • Centrally acting antimuscarinic agents are used as adjunctive agents (NOT first choice drugs at present)
    • Benztropine mesylate, Biperiden, Procyclidine
  – Motion sickness
    • Responds to centrally acting antimuscarinics
    • Scopolamine
CLINICAL USE OF ANTIMUSCARINICS

• Benztropine
"Amnestic" MCI

- Memory impairment only
- Memory plus other domains impaired

- Alzheimer’s disease major subtype (Vascular dementia)

"Nonamnestic" MCI

- Single nonmemory domain
- Multiple nonmemory domains

- Frontotemporal dementias
  - Lewy body dementia
  - Primary progressive aphasia
  - Parkinson’s disease (Alzheimer’s disease) (Vascular dementia)
CLINICAL USE OF ANTIMUSCARINICs

• Ophthalmologic examination
  – Ciliary paralysis facilitate ophthalmologic examination (see retina better!)
  – Drugs applied topically as drops

<table>
<thead>
<tr>
<th>Antimuscarinics used in ophthalmology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>Atropine</td>
</tr>
<tr>
<td>Scopolamine</td>
</tr>
<tr>
<td>Homatropine</td>
</tr>
<tr>
<td>Cyclopentolate</td>
</tr>
<tr>
<td>Tropicamide</td>
</tr>
</tbody>
</table>
CLINICAL USE OF ANTIMUSCARINICS

• Respiratory disorders
  – Premedication in general anesthesia
    • Inhibit mucus secretion associated with irritant anesthetics
    • Prevent laryngospasm
    • Atropine, Scopolamine
  – Asthma
    • Cause bronchodilation
    • Inhibit mucus secretion
    • Used topically (as inhalational drugs)
      – Quaternary amines – poor distribution – no systemic side effects
      – Ipratropium, Tiotropium
CLINICAL USE OF ANTIMUSCARINICS

• Cardiovascular disorders
  – Depression of sinoatrial and AV nodes
    • leading to severe bradycardia and decreased cardiac output (from too much cholinergic input)
    • Atropine

• Gastrointestinal disorders
  – Diarrhea and other conditions of excessive motor function
    • Atropine in combination with opioids
CLINICAL USE OF ANTIMUSCARINICS

• Urinary disorders
  – Urinary incontinence (leaking bladder)
  – Urinary urgency associated with bladder inflammation
  – Relief of bladder spasm after urologic surgery
  – $M_3$ receptors are directly related to bladder smooth muscle contractions
  – $M_3$ selective antagonists are preferred – less adverse effects observed with their use
    • Tolterodine
    • Solifenacin
    • Darifenacin
CLINICAL USE OF ANTIMUSCARINICS

- Cholinergic agonists poisoning
  - Cholinesterase inhibitor - insecticides
  - Ingestion of wild mushrooms containing muscarinic agonists
  - Chemical warfare “nerve gases”
  - Symptoms: signs of cholinergic excess
- Treatments
  - Tertiary antimuscarinic agents (Atropine)
  - Cholinesterase regenerator compounds
    - (Pralidoxime)
Contraindications (withhold) to use atropine

- Glaucoma
  - Increases in ocular pressure
- Prostate Hyperplasia
  - Urinary retention
  - Increased pain
- Gastric ulcer
  - Slow gastric emptying
CLINICAL USE OF ANTIMUSCARINICS

Contraindications (withhold) to use atropine

- **Glaucoma**
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- **Prostate Hyperplasia**
  - Urinary retention
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- **Gastric ulcer**
  - Slow gastric emptying
CHOLINERGIC ANTAGONISTS

• Direct-acting antagonists
  Antimuscarinic drugs
  Antinicotinic drugs
    Ganglion blockers
      Mecamylamine
      Trimethaphan
    Neuromuscular blockers
      Succinylcholine
      Tubocurarine
      Rocuronium

• Indirect-acting antagonists
GANGLION BLOCKING AGENTS

- Competitive antagonists of ACh
  - at nicotinic receptors in autonomic ganglia
- Prevent depolarization
  - postsynaptic neuronal membrane
- Block effects of both sympathetic & parasympathetic innervation on organs and systems
GANGLION BLOCKING AGENTS

• **Effects on organs and systems** – depends on **pre-existing sympathetic & parasympathetic tone** (rate of firing, maintenance)
  
  – **Eye:**
    • Cycloplegia - loss of accommodation, effect on the pupil may vary
  
  – **Cardiovascular system:**
    • Decreased arterial pressure, orthostatic hypotension (dizzy spell), tachycardia, decreased cardiac contractility
  
  – **GI tract:**
    • Inhibition of motor function, constipation, reduced secretion
  
  – **Genitourinary system:**
    • Relaxation of bladder smooth muscle, urinary retention
    • Impairment of sexual function – inhibited erection and ejaculation
  
  – **Sweating:** thermoregulatory sweating is reduced
GANGLION BLOCKING AGENTS

- Clinical use
  - Not widely used presently
    - more selective autonomic drugs have become available
  - Trimethaphan
    - Used for treatment of hypertensive emergencies
    - Dissecting aortic aneurysm
    - To produce controlled hypotension during surgery
NEUROMUSCULAR BLOCKERS

- Ligand-gated membrane channel
- Five polypeptide subunits
- Binding of two ACh molecules
  - opens channel and increases permeability for Na⁺
- Na⁺ influx causes
  - membrane depolarization & muscle contraction
NEUROMUSCULAR BLOCKING DRUGS

- **Depolarizing blockers**
  - Succinylcholine

- **Nondepolarizing blockers**
  - Tubocurarine
  - Rapacuronium
  - Rocuronium
DEPOLARIZING AGENTS

Succinylcholine

• Agonist at nicotinic receptor
• Initial depolarization of end plate
• Produces **prolonged receptor stimulation** and depolarization
• After prolonged depolarization
  • membrane becomes **unresponsive** and **desensitized**
• An *acetylcholinesterase inhibitor*, e.g., Neostigmine
  • would **augment** effect
  • **should never** be used as an antidote
NONDEPOLARIZING DRUGS

Tubocurarine
Rapacuronium
Rocuronium

• Mechanism of Action

- Competitive antagonists –

  \textit{postsynaptic nicotinic receptor}

- Noncompetitive blockade at \textit{high doses}

  \textit{Blockade of presynaptic Na}^+ \textit{channel}

• Reversal of effect

  \textit{Effects reversed} by \textit{neostigmine}

\textit{acetylcholinesterase inhibitor}

used as an antidote
CLINICAL USE OF NEUROMUSCULAR BLOCKERS

• Adjuncts to general anesthesia
• Facilitate correction of dislocation & alignment of bone fractures
• Electroshock therapy to prevent injury
• Facilitate intubation with an endotracheal tube
• Treatment of convulsions
CHOLINERGIC ANTAGONISTS

- Direct-acting antagonists
  - Antimuscarinic drugs
  - Antinicotinic drugs
- Indirect-acting antagonists
  - Botox
**BOTOX**

- **Botulinum toxin A**
  - produced by bacteria *Clostridium botulinum*
- **Neurotoxin** responsible for *botulism*
- Binds to **nerve terminals** (pre-synaptic)
  - prevent vesicular *release of acetylcholine*
- **Result**
  - *inhibition of cholinergic function*
- Injected **locally**
  - to avoid systemic toxicity
- Onset of action – hours
- Duration of action – months
CLINICAL USES OF BOTOX

• **Somatic nerve terminals:** *skeletal muscle relaxation*
  – Eye movement disorders
    • lazy eye
  – Facial muscle spasms
    • prevent tics, drooling in neurological conditions
  – Cosmetic purposes
    • reduce wrinkles and frown lines

• **Autonomic post-ganglionic nerve terminals**
  – Injected near sweat glands
    • to reduce excessive underarm sweating
Religious Orders Study

The Religious Orders Study is a collaborative study with Rush and other U.S. medical centers. It involves more than 1,100 older religious clergy (nuns, priests and brothers) who have agreed to medical and psychological evaluation each year and brain donation after death. Researchers are using information from the study to discover what changes in the brain are responsible for memory and movement problems. The study also looks closely at the transition from normal functioning of the aging brain to the mild cognitive impairment that can be an early sign of Alzheimer’s disease.

Funding for the Religious Orders Study by the National Institute on Aging began in 1993, and current funding will continue through June 2016. By that time, the Religious Orders Study will have up to 22 years of clinical data on more than 1,100 people and brain tissue from over 350 people. This rich and diverse resource will allow the Study to continue supporting numerous investigators. It will also offer the Alzheimer’s disease research community new opportunities to use clinical pathologic studies in novel ways to understand the complex relation between cognitive decline and the neuropathology of Alzheimer’s disease.
### Drugs with ACB Score of 1

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alimemazine</td>
<td>Theraten™</td>
</tr>
<tr>
<td>Alverine</td>
<td>Spasmonal™</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Xanax™</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify™</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris™</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Tenormin™</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Wellbutrin™, Zyban™</td>
</tr>
<tr>
<td>Captopril</td>
<td>Capoten™</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Zyrtec™</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>Librium™</td>
</tr>
<tr>
<td>Clometidine</td>
<td>Tagomet™</td>
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<tr>
<td>Clonidinium</td>
<td>Librax™</td>
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<tr>
<td>Clorazepate</td>
<td>Tranxene™</td>
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<tr>
<td>Codeine</td>
<td>Contin™</td>
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<tr>
<td>Cдо humane</td>
<td>Colcrys™</td>
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<tr>
<td>Desloratadine</td>
<td>Clarinex™</td>
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<tr>
<td>Diazepam</td>
<td>Valium™</td>
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<tr>
<td>Digoxin</td>
<td>Lantox™</td>
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<td>Dipyridamole</td>
<td>Persantin™</td>
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<td>Disopyramide</td>
<td>Norpace™</td>
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<td>Fentanyl</td>
<td>Duragesic™, Actiq™</td>
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<td>Fluoxetine</td>
<td>Lexion™</td>
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<td>Fluvoxamine</td>
<td>Luvox™</td>
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<td>Haldol™</td>
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<td>Hydrochloride</td>
<td>Apresoline™</td>
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<td>Hydrocortisone</td>
<td>Cortisol™, Cortaid™</td>
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<tr>
<td>Iloperidone</td>
<td>Fanapt™</td>
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<td>Isosorbide</td>
<td>Isordil™, Ismo™</td>
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<td>Levocetirizine</td>
<td>Xyzal™</td>
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<td>Losartan</td>
<td>Immodium™, others</td>
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<tr>
<td>Loratadine</td>
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<td>Metoprolol</td>
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<td>Morphine</td>
<td>MS Contin™, Avinza™</td>
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<tr>
<td>Nifedipine</td>
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<td>Paliperidone</td>
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<td>Pindolol</td>
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<td>Theophylline</td>
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<tr>
<td>Trazodone</td>
<td>Desyrel™</td>
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<tr>
<td>Triamterene</td>
<td>Dyrenium™</td>
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<tr>
<td>Venlafaxine</td>
<td>Effexor™</td>
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<td>Warfarin</td>
<td>Coumadin™</td>
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### Drugs with ACB Score of 2

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<tr>
<th>Generic Name</th>
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<tr>
<td>Amantadine</td>
<td>Symmetrel™</td>
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<td>Belladonna</td>
<td>Multiple</td>
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<td>Carbamazepine</td>
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<tr>
<td>Cycozolazine</td>
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<td>Methotrexate</td>
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<td>Quinidine</td>
<td>Moban™</td>
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<tr>
<td>Nefopam</td>
<td>Nefosetin™</td>
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<tr>
<td>Oxcarbazepine</td>
<td>Trileptal™</td>
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<td>Pimozide</td>
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### Drugs with ACB Score of 3

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<td>Elavil™</td>
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<tr>
<td>Atropine</td>
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<td>Benztropine</td>
<td>Cogentin™</td>
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<tr>
<td>Brompheniramine</td>
<td>Dimetapp™</td>
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<tr>
<td>Carboxyzine</td>
<td>Histex™, Carbidopa™</td>
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<tr>
<td>Chlorpheniramine</td>
<td>Chlor-Trimeton™</td>
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<td>Chlorpropramide</td>
<td>Thorazine™</td>
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<td>Clemastine</td>
<td>Tavist™</td>
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<td>Clomipramine</td>
<td>Anafranil™</td>
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<tr>
<td>Clorgacine</td>
<td>Clozaril™</td>
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<tr>
<td>Darifenacine</td>
<td>Enbrel™</td>
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<tr>
<td>Desipramine</td>
<td>Norpramin™</td>
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<td>Dicyclomine</td>
<td>Bentyl™</td>
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<td>Dimenhydrinate</td>
<td>Dramamine™, others</td>
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<tr>
<td>Diphenhydramine</td>
<td>Benadryl™, others</td>
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<tr>
<td>Doxepin</td>
<td>Sinequan™</td>
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<td>Doxylamine</td>
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<td>Fesoterodine</td>
<td>Toviaz™</td>
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<tr>
<td>Flavoxate</td>
<td>Urispas™</td>
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<tr>
<td>Hydroxyzine</td>
<td>Atarax™, Vistaril™</td>
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<tr>
<td>Hyoscine</td>
<td>Anaspaz™, Levsin™</td>
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<td>Imipramine</td>
<td>Tofranil™</td>
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<tr>
<td>Medicane</td>
<td>Antivert™</td>
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<td>Methocarbamol</td>
<td>Robaxin™</td>
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<tr>
<td>Mirtazapine</td>
<td>Remeron™</td>
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<td>Nortriptyline</td>
<td>Pamelor™</td>
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<td>Orphenadrine</td>
<td>Norflex™</td>
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<td>Oxycarbamol</td>
<td>Ditropan™</td>
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<td>Paroxetine</td>
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<td>Propranolol</td>
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<td>Propiverine</td>
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<td>Quetiapine</td>
<td>Serquel™</td>
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<td>Scopolamine</td>
<td>Transderm Scop™</td>
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<td>Solifenacin</td>
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<td>Trihexyphenidyl</td>
<td>Artane™</td>
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<td>Trimipramine</td>
<td>Surmontil™</td>
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<tr>
<td>Tropium</td>
<td>Sanctura™</td>
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</table>

### Categorical Scoring:
- Possible anticholinergics include those listed with a score of 1; Definite anticholinergics include those listed with a score of 2 or 3

### Numerical Scoring:
- Add the score contributed to each selected medication in each scoring category
- Add the number of possible or definite Anticholinergic medications

### Notes:
- Each definite anticholinergic may increase the risk of cognitive impairment by 46% over 6 years. ³
- For each on point increase in the ACB total score, a decline in MMSE score of 0.33 points over 2 years has been suggested. ⁴
- Additionally, each one point increase in the ACB total score has been correlated with a 26% increase in the risk of death. ⁴

---

[www.agingbraincare.org](http://www.agingbraincare.org)
Medications Reviewed in 2012 Update

<table>
<thead>
<tr>
<th>Medications Added with Score of 1:</th>
<th>Medications Added with Score of 2:</th>
<th>Medications Added with Score of 3:</th>
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<tbody>
<tr>
<td>Aripiprazole (Abilify™)</td>
<td>Nefopam (Nefogesic™)</td>
<td>Doxylamine (Unisom™, others)</td>
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<td>Desloratadine (Clarinex™)</td>
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<td>Iloperidone (Fanapt™)</td>
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<td>Levocetirizine (Xyzal™)</td>
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<td>Duloxetine (Cymbalta™)</td>
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</table>

Criteria for Categorization:
Score of 1: Evidence from in vitro data that chemical entity has antagonist activity at muscarinic receptor.

Score of 2: Evidence from literature, prescriber’s information, or expert opinion of clinical anticholinergic effect.

Score of 3: Evidence from literature, expert opinion, or prescribers information that medication may cause delirium.

Complete References:


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Anticholinergic
Low potency antipsychotics
Oxybutinin
Ipratropium

Cholinergic
ACh receptor antagonists
AChEIs (i.e. Donepezil)

Opioid
Morphine
Heroin
Hydromorphone

Sympathomimetic
Epinephrine
Cocaine
Amphetamine & methylphenidate

Sedative-Hypnotic
Benzos & barbs
"Z-drugs" (i.e. zopiclone)
Antihistamines