Cholinergic Drugs

Affecting the **Somatic** and **Parasympathetic** Nervous Systems

Drugs related to Acetylcholine

*In this fact sheet, we will be looking drugs used for their effects on the Somatic AND the Parasympathetic (PNS) nervous system. This means we will see drugs acting at a variety of receptors including: ion channels (nicotinic), GPCRs (muscarinic) and the enzyme acetylcholinesterase.*

Diseases related to ACh include Myasthenia gravis and Overactive bladder. *Really?*

You know the poison arrow frogs of the Amazon? The frogs secrete a toxin called Curare, from which all our “curariform” drugs are derived (like [Pancuronium](https://en.wikipedia.org/wiki/Pancuronium)) – though the frogs probably get the toxin from plants. These are neuromuscular junction blocking agents used to cause skeletal muscle paralysis.

But an autoimmune condition, called myasthenia gravis, can cause paralysis too.

How can these different conditions be related to ACh?

ACh is very important in the periphery. It is the only neurotransmitter in the Somatic and Parasympathetic nervous systems. In the Somatic nervous system, ACh activates a type of nicotinic receptor only found on skeletal muscle.

But because the various types of ACh receptors are everywhere... we will see that drugs with cholinergic, or anticholinergic, effects fall into many categories.

Parasympathetic outflow from the cranium flows through cranial nerves III, VII, IX and X. There are also sacral parasympathetic nerves enervating the bladder, rectum and genitalia.
The nicotinic ACh Receptor has neuronal & muscle sub types

The nicotinic receptor is a ligand-gated ion channel found in the nervous system and on skeletal muscles. Slight differences in the sub types of the nicotinic receptor mean that drugs that affect the skeletal muscle type (like Pancuronium and Succinylcholine), have little to no effect on the neuronal form of the receptor (where Varenicline has its primary effect). An early NMJB, tubocurarine, did affect both neuronal and muscular nicotinic receptors, and because of that, it had a lot of side effects. Those side effects limited its usefulness so, Pancuronium and others have almost completely replaced tubocurarine.

Typically, the chemistry of a drug will determine if it is active in the just the periphery, or also in the CNS. Drugs that aren’t CNS active are usually charged or are substrates of the blood brain barrier pump, P-glycoprotein. If they can’t get into the CNS, they can’t cause an effect on the neuronal nicotinic receptors.

Of the two anticholinesterase agents, Donepezil and Neostigmine, only Donepezil crosses the blood brain barrier.

Myasthenic Syndromes

Myastenia gravis is an autoimmune condition, and like all autoimmune diseases, the severity of the condition fluctuates, which can make treatment a challenge. The drugs used to treat the condition become toxic during periods of improvement.

Many drugs are associated with causing, unmasking, or worsening Myasthenic syndromes. You have a handout that lists drugs commonly associated with inducing skeletal muscle weakness. Important examples: magnesium, many antibiotics, general anesthetics, neuromuscular blocking agents, beta-blockers, lithium & AEDs.
Drug affecting the nicotinic receptors

Note: drugs that stimulate the nicotinic receptor also cause block. Take a look at the YouTube video linked on page 2. The block occurs following continued stimulation of the receptor. There are two types of block: (1) voltage-gated sodium channels are inactivated leading to decreased electrical excitability and (2) the nicotinic receptor becomes insensitive and requires increased levels of stimulation to be activated.

NICOTINIC AGONISTS

Direct acting Nicotinic agonists are not currently used. The partial agonist, Varenicline (Chantix), is used to help people quit smoking (another trade name of varenicline is featured in the YouTube video linked on page 2).

Indirect cholinergic agonists include the anticholinesterase agents, Donepezil and Neostigmine. They act as agonists by preventing the breakdown of ACh.

NICOTINIC ANTAGONISTS - NEUROMUSCULAR JUNCTION BLOCKERS (NMJB)

These drugs are used as paralytic agents to allow for mechanical ventilation of patients. There are two basic types, (1) non-depolarizing NMJB (Pancuronium) and (2) depolarizing NMJB (Succinylcholine).

The main difference is that Pancuronium (Pavulon) binds to and does not activate the receptor, so you get an immediate, flaccid paralysis. When Succinylcholine (Anectine) binds, it activates the receptor causing an initial increase in muscle activity, which can lead to overheating (malignant hyperthermia).

NOTE: The NMJB are NOT analgesic, anxiolytic or anesthetic. The patient will feel pain and anxiety, but will be unable to move or tell you.
DRUGS AFFECTING MUSCARINIC RECEPTORS

MUSCARINIC AGONISTS

We are covering two muscarinic agonists. These drugs are not used all that commonly and are not on the Top 200 lists. They provide us with examples of muscarinic agonists and what they can be used to treat.

First, is Bethanechol (Urecholine), a drug used to give the bladder or GIT a kick-start when another condition interrupts parasympathetic motor functions. It is used for non-obstructive urinary retention, otherwise known as neurogenic bladder.

Another agonist is Pilocarpine (Isopto Carpine, Salagen), a drug used as eye drops to treat a form of glaucoma, or as pills to treat dry mouth caused by conditions like Sjøgren’s or radiation therapy.

The mnemonics for overdose on a muscarinic agonist are SLUDGE and DUMBELS.

- SLUDGE is salivation, lacrimation, urination, defecation (diarrhea), GI upset and emesis.
- DUMBELS or DDUMBBELS is Defecation/Diaphoresis (sweating), urination, miosis (pin point pupils), bronchospasm/ bronchorrhea, emesis, lacrimation and salivation.

We also cover two indirect cholinergic agonists. They are both inhibitors of the enzyme that breaks ACh down, leading to increased levels of ACh. One, Donepezil (Aricept) is active in the CNS so is used to treat early onset Alzheimer’s. The other Neostigmine (Prostigmin) can not cross the blood brain barrier, so is only active peripherally. It is used to treat myasthenia gravis, so should be considered an indirect nicotinic agonist. Neostigmine may also be used to reverse the effects of Pancuronium (NOT Succinylcholine!).

http://www.atsdr.cdc.gov/csem/cholinesterase/images/muscarinic_receptor.png
(continued)

MUSCARINIC ANTAGONISTS

Much more commonly used are muscarinic antagonists. Many classes of drugs have antimuscarinic side effects.

The classic antimuscarinic, or “anticholinergic,” is atropine, a drug originally isolated from the deadly nightshade plant. It is a belladonna alkaloid. Many plants produce toxic alkaloids, and in fact, one explanation for the number and variety of Cytochrome P450 enzymes is that they are the mammalian answer to toxic plant defenses! As plants produce toxins to protect themselves from grazers, the consumers must come up with detoxification strategies... like CYP450’s!

Back to atropine, it is used for a number of purposes, most commonly to dry secretions and to dilate pupils (for an ophthalmic exam).

Scopolamine is another antimuscarinic drug. It is available as a transdermal patch (Transderm Scop) to treat motion sickness, which along with drying secretions, are the two most common uses of scopolamine.

Urinary antispasmodics including Solifenacin (VesiCare) are antimuscarinic, too. They are only used to treat overactive bladder syndrome.

It is important to remember the mnemonic, “dry as a bone, hot as a poker, red as a beet, blind as a bat, fast as a hart, mad as a hatter.” The antimuscarinic drugs share a number of potential adverse effects. They may cause:

- **Dry as a bone** signs and symptoms (S&S)
  - Urinary retention
  - Constipation, nausea, GI pain, ileus
  - Dry mouth, eyes, skin (no secretions)

- **Blind as a bat** S&S
  - Worsening of narrow-angle glaucoma, blurred vision, photophobia, mydriasis

- **Mad as a hatter** S&S
  - CNS effects including confusion, dizziness, headache, hypnosis and hallucinations

- **Hot as a poker, Red as a beet** S&S
  - Overheating (lack of sweat)
  - Vasodilation

- **Fast as a hart** S&S
  - Tachycardia

- **They also may cause severe allergic reactions**

Other drugs with significant anticholinergic effects:

- 1st generation antihistamines
- Tricyclic antidepressants
- Antipsychotics

Populations Sensitive to Anticholinergic Risks….

- Patients with allergies or asthma are at risk of angioedema (with airway obstruction) and anaphylactic reactions
- Alzheimer’s or dementia patients are at risk due to confusion, hallucinations, delirium and somnolence
- Patients with arrhythmias or epilepsy
- Liver disease due to changes in liver enzymes
- Renal impairment due to reduced excretion (increased risk of toxicity)
- Glaucoma
- GERD, ileus, colitis, any obstructive disease of the GIT or bladder
- Patients with myasthenia gravis
- Because of a reduced ability to sweat heat prostration is a real hazard.
- Use with caution in the elderly, kids, Down’s...
- Use with caution in gastric ulcer patients due to delayed gastric emptying time
- FALL HAZARD!!!

Most images from the National Library of Medicine Image collection, unless otherwise noted, except for the image of the author and her dog, Val.

Homework and Exercises

1. Read the “START HERE” announcement in Laulima for updates and instructions.
2. Read Chapters 17 & 18, Cholinergic Agonists and Antagonists in Adams & Urban, PHARMACOLOGY Connections to Nursing Practice. Review Chapter 16, Neurotransmitters and the Autonomic Nervous System.
3. Review the Power Points and listen to the audio from the face-to-face lecture. You may opt to watch the appropriate videos for this lecture. Review any handouts available for this lecture in the Course Index.
4. Complete the SLO Practice Set in Tasks, Tests and Surveys.
5. Use “Chat,” “Discussions and Private Messages” or the lecture “Forum” to ask questions and find answers or assistance.
6. Complete the online quiz in Laulima Tasks, Tests and Surveys.

If you have any questions, email me at abeale@hawaii.edu