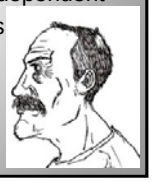
The Good, the Bad, and the *Ugly* of Anticholinergic Drugs in Hospice and Palliative Care

Thomas R. Palmer M.D.7th Palliative Care Collaborative, October 11, 2013

- No conflicts of interest related to this presentation.
- Some of the indications for medications discussed are not FDA approved.

Frank

- 60 year old man admitted to the Hospice Residence from home due to sudden onset of agitation.
- He was very restless, paranoid, and loud
  - Previously cognitively normal and independent
  - No history of mental health problems
- What do you do ???



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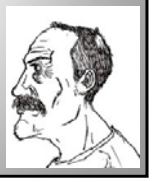
Frank

- Diagnosis: Metastatic lung cancer
- Recently he developed chest congestion
- He had been started on Transderm Scop



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Outline

The Good, the Bad, and the *Ugly* of Anticholinergic Drugs in Hospice and Palliative Care

- Pharmacology
- History
- Adverse effects (the Bad and the *Ugly*)
- Evidence for use in symptom control (the Good)
- Approach to their usage in Hospice and Palliative Care patients

Receptors

- The components of a cell or organism that interact with endogenous regulatory molecules or drugs
- They are protein macromolecules
  - Their biochemical or biophysical activities are altered by the interaction

Types of Receptor Interactions

- Agonists
  - Bind to the receptor and cause it to generate a chemical signal as a result
- Antagonists
  - Bind to the receptor without generating a signal
  - Block agonists from activating the receptor

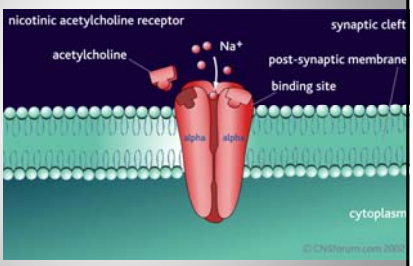
Types of Acetylcholine Receptors

- Nicotinic
  - Bound by nicotine from tobacco

- Muscarinic
  - Bound by muscarine, a toxin from the mushroom *Amanita muscaria*
  - Five subtypes M_1 - M_5

Nicotinic Receptors

- Fast signal transmission
- Ligand gated ion channels
- Nerves or muscles

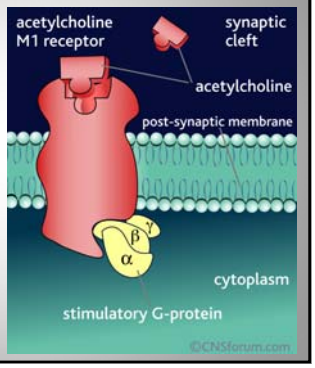


Nicotinic Receptors

- Autonomic nervous system
  - Acetylcholine from preganglionic fibers modulates the postganglionic fibers at nicotinic receptors
    - Sympathetic: Release of norepinephrine
    - Parasympathetic: Release of acetylcholine
- Neuromuscular transmission
  - Myasthenia gravis
    - An autoimmune condition caused by damage to neuromuscular nicotinic receptors by autoantibodies

Muscarinic Receptors

- Binding causes a shape change which releases intracellular G protein
- G protein acts as an enzyme to catalyze intracellular events



"Anticholinergic" drugs means "Antimuscarinic" drugs

Black Henbane

Cleopatra

*Contains hyoscyamine (l-atropine) & scopalamine

*Visual hallucinations, sensation of flight, dilated pupils, restlessness, flushed skin, rapid heart beat

Mandrakes

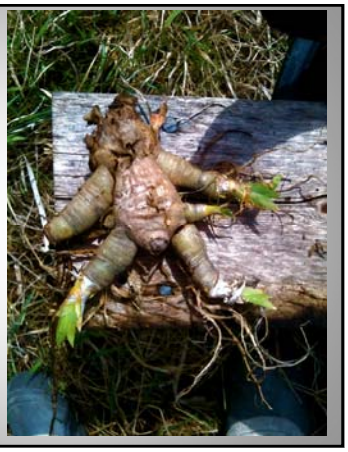
- Contains atropine, scopalamine, and hyoscyamine.
- Thought to promote fertility
- Roots long used in magic rituals

Erowid.org

Mandrakes

- According to legend when the root is dug up, it screams and kills all who hear it.

http://www.hangovernurse.com/2011/04/mandrake-incident.html



Mandrakes

http://library.uthscsa.edu/

P.I. Nixon Medical Historical Library

The Anticholinergic Risk Scale and Anticholinergic Adverse Effects in Older Persons

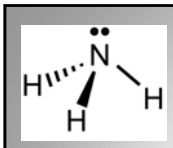
- Medications are ranked from
  - Zero “no or low risk” to
  - Three “high anticholinergic potential”.
- The risk score is the sum of points for each medication the patient is taking.
- “Higher ARS scores are associated with statistically significantly increased risk of anticholinergic adverse effects in older patients.”

Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. Arch Intern Med. 2008;168(5):508-513.

Factors Affecting Anticholinergic “Burden”

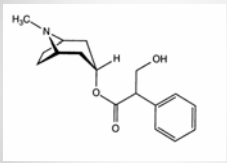
- Strength of binding to the receptor
- Dose of the medication
- Number of receptors available
- Tertiary amine or quaternary ammonium compound

www.globalgear.com.au

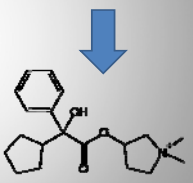


Ammonia

Unlikely to cause delirium



Atropine (Tertiary amine)
Crosses blood-brain barrier



Glycopyrolate (Quaternary ammonium)
Does not cross blood-brain barrier

Anticholinergic Risk Scale
3 points (Strongly Anticholinergic)

- Amitriptyline (*Elavil*)
- Atropine
- Benztropine (*Cogentin*)
- Carisoprodol (Soma)
- Chlorpheniramine
- Chlorpromazine (*Thorazine*)
- Cyproheptadine (*Periactin*)
- Dicyclomine (*Bentyl*)
- Diphenhydramine (*Benadryl, Tylenol PM*)
- Fluphenazine (*Prolixin*)
- Hydroxyzine (*Atarax, Vistaril*)
- Hyoscyamine = L-atropine (*Levsin*)
- Imipramine (*Tofranil*)
- Meclizine (*Dramamine, Antivert*)
- Oxybutynin (*Ditropan*)
- Promethazine (*Phenergan*)
- Scopolamine *
- Tizanidine (*Zanaflex*)

* Carnahan RM, et al 2006

Anticholinergic Risk Scale
2 points (Moderately anticholinergic)

- Amantadine (*Symmetrel*)
- Baclofen (*Lioresal*)
- Cetirizine (*Zyrtec*)
- Cimetidine (*Tagamet*)
- Cyclobenzaprine (*Flexeril*)
- Desipramine (*Norpramin*)
- Loperamide (*Imodium*)
- Loratadine (*Claritin*)
- Nortriptyline (*Pamelor*)
- Olanzapine (*Zyprexa*)
- Prochlorperazine (*Compazine*)
- Tolterodine (*Detrol*)

Anticholinergic Risk Scale
1 point (Mildly anticholinergic)

- Carbidopa-Levodopa (*Sinemet*)
- Entacapone (*Comtan*)
- Haloperidol (*Haldol*)
- Methocarbamol (*Robaxin*)
- Metoclopramide (*Reglan*)
- Mirtazapine (*Remeron*)
- Paroxetine (*Paxil*)
- Pramipexole (*Mirapex*)
- Quetiapine (*Seroquel*)
- Ranitadine (*Zantac*)
- Risperidone (*Risperdal*)
- Selegiline (*Eldepryl*)
- Trazodone (*Desyrel*)

Diphenoxylate 2.5 mg/ Atropine 0.025 mg (Lomotil)

- Antidiarrheal
- Diphenoxylate is μ opioid receptor agonist
  - Crosses the blood – brain barrier
- Atropine added to discourage abuse
  - May cause “weakness and nausea”
  - 1/40 of standard oral theraputic dose

The bad

Adverse Effects of Anticholinergic's

Hot as a hare,
Blind as a bat,
Dry as a bone,
Red as a beet,
Mad as a hatter,
And full as a flask

Adverse Effects of Anticholinergic's

Hot as a hare

Decreased sweating

Katedaviesdesigns.com

Adverse Effects of Anticholinergic's

Blind as a bat

Pupillary dilitation, cycloplegia, decreased lacrimation

Animals.nationalgeographic.com

Adverse Effects of Anticholinergic's

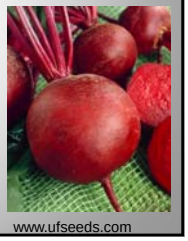
Dry as a bone

Xerostomia (dry mouth)

Adverse Effects of Anticholinergic's

Red as a beet

Decreased sweating



www.ufseeds.com

Adverse Effects of Anticholinergic's

Mad as a hatter

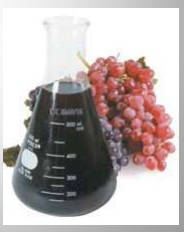
Hypo or hyperactive delirium

Walt Disney

Adverse Effects of Anticholinergic's

And full as a flask

Urinary retention



http://news.ucdavis.edu/search/news_detail.lasso?id=7676

Acute Urinary Retention

- Anticholinergic medications
  - Reduce detrusor contractility
  - Reduce bladder sensation
  - Relative risk of 8.3 (compared to nonusers) with anti-muscarinic use of 30 days or less.

Martin-Merino E, et al. Do oral antimuscarinic drugs carry an increased risk of acute urinary retention? *J Urol.* 2009,182, 1442-1448.

Adverse Effects of Anticholinergics

- Inhibit GI motility
  - Increased GI transit time
  - Increased risk of ileus
- Relax lower esophageal sphincter
  - Increased GI reflux

Drugs as Risk Factor for Ileus

- Anticholinergic drugs inhibit GI motility
- Opioids inhibit GI motility
  - Activate mu-opioid receptors in GI tract
- Increased risk when used concurrently

Radiopaedia.org

The *ugly*

The Scream: Edvard Munch

Confusion Assessment Method for **Delirium** (CAM)

- Feature 1. Acute onset and fluctuating course and
- Feature 2. Inattention with either
- Feature 3. Disorganized thinking or
- Feature 4. Altered level of consciousness

Delirium = Features 1 and 2 and either 3 or 4.

Inouye SK, et al; Ann Int Med; 113:941, 1990

Delirium, Risk Factors

- **Dementia**
- **Medications**
- **Serious illness**
- Depression
- Immobilization
- Sensory impairment
- Pain
- Physical restraints
- Bladder catheter use
- Older age
- Male sex
- ICU admission
- Dehydration
- Metabolic abnormalities
- Hypoxia
- Functional dependence
- Alcoholism
- Hip fracture

Non Anticholinergic Drugs causing Delirium

- Benzodiazepines
- Narcotics
- Anti-Parkinsons drugs
- NSAIDS (indomethacin)
- Digoxin
- Corticosteroids
- Sudden stopping of psychoactive drugs

Treatment of Delirium

- Identify and treat reversible causes
  - Stop contributing medications
- Provide support and orientation
- Provide a stable, quiet environment
- Identify and treat sensory impairments
- For agitated delirium: haloperidol

Terminal Congestion "Death Rattle"

- The sound caused by an inability to clear lung secretions by coughing.
- Occurs in 23 to 92 % of dying patients
- A concern to family and friends
- Secretions produced by
  - Salivary glands
  - Bronchial mucosa

Types of "Death Rattle"

- Type 1
  - Salivary secretions that accumulate near death when unable to swallow
  - Usually in last few hours of life
- Type 2
  - Bronchial secretions that accumulate as ability to cough declines
  - May accumulate over days
  - Patient may be awake

Bennett, MI 1996

How do we treat terminal Congestion?

Terminal congestion

- Salivary secretions
  - Greatly reduced by anticholinergics
- Bronchial glands secretions are
  - Vagally induced
  - Also stimulated by
    - Adrenergic nerves
    - Inflammation
    - Cough receptor stimulation
  - Anticholinergics reduce basal secretory rate by mean of 39 %

Do Anticholinergics Help Terminal Congestion?

- 31 patients randomized to scopolamine 0.5 mg in 1 ml saline vs. 1 ml saline IV push or subcutaneous.
- Injections at 0, 4, and 8 hours
- Death rattle, pain, and restlessness assessed every 2 hours
- No significant difference between groups in death rattle
- No significant difference between groups in restlessness
- Expressions of pain were significantly greater in the scopolamine group compared to placebo

Likar R, Molnar M, et al. Klinische Utersuchung über die Wirkung von Scopolamin-Hydrobromicum Beim terminalen Rasseln. *Palliativmedizin* 2002; 3(1):15-19

Do Anticholinergics Help Terminal Congestion?

- 137 patients randomized to 2 atropine 1% opth drops (1 mg) sublingual vs. placebo
- RNs quantified noise at 2 and 4 hours
  - 0: None
  - 1: Audible only close to patient
  - 2: Clearly audible at the end of the bed
  - 3: Clearly audible at 20 feet (room door)
- Trial stopped prematurely at 2nd interim analysis (2/3 of participants) due to futility.
- Noise reduction at 2 hours: 37.7% atropine & 41.3% placebo (P=0.73)
- Noise reduction at 4 hours: 39.7% atropine & 51.7% placebo (P=0.21)

Heisler, M, et al. Randomized Double-Blind Trial of Sublingual Atropine vs. Placebo for the Management of Death Rattle. *J Pain Symp Manag* 2013;45(1)14-21.

Anticholinergic Load and Terminal Congestion

- Retrospective study of 199 deaths in a PC unit
  - Demographics, diagnoses, & use of parenteral fluids determined
    - 83 % malignancy diagnosis
  - Anticholinergic load of all medications was calculated at the beginning of the deteriorating phase for each patient
  - 120 received antisecretory medication in the last 72 hours of life (terminal phase)
  - Logistic regressions showed that a high anticholinergic load from medications was not protective and instead predicted the need for treatment for noisy respiratory secretions at the end of life.
    - Odds ratio 2.9 for those with the highest anticholinergic load

Sheehan C, Clark K, et al. A retrospective analysis of primary diagnosis, comorbidities, anticholinergic load, and other factors on treatment for noisy respiratory secretions at end of life. *J of Pall Med* 2011;14(11) 1211-1218.

Do Anticholinergics Help Terminal Congestion?

- Case report
- 1 patient with metastatic pancreas cancer to the lung with cough, upper airway secretions, and dyspnea was given 3 atropine 1% ophthalmic drops sublingual 3 times daily and rescue dose at any time.
- "Satisfactorily suppressed the audible upper airway secretions and persistent cough by clearing the airway, with no adverse effects such as tachycardia or somnolence."
- Continued 2 weeks until he died.

Shinjo S, Okada M Atropine eyedrops for Death Rattle in a Terminal Cancer Patient *Journal of Palliative Med* 2013:16(2) 212-213

Terminal Congestion

WHAT DO YOU DO ?

The good !

Malignant Bowel Obstruction

- Frequency
  - 5 to 42 % in advanced ovarian cancer
  - 4 to 24 % in advanced colorectal cancer
  - Melanoma and breast cancer are the most common non GI primary causes
- Proximal distention of GI tract and pain
  - Bowel wall edema
  - Vicious cycle of distention-secretion-motor activity

Malignant Bowel Obstruction

Symptoms

- Anorexia
- Nausea and vomiting
- Abdominal distention
- High pitched or diminished bowel sounds
- Pain

Dr. Aribam Devadutta Sharma, e-pao.net

Malignant Bowel Obstruction, Treatment

- Surgery to correct obstruction
- Venting gastrostomy or stent
- Nasogastric tube
- Medications
  - Opioids for pain
  - Antinausea agent
  - Octreotide (*Sandostatin*)
  - Corticosteroids
  - And…

Dr. Aribam Devadutta Sharma, e-pao.net

Malignant Bowel Obstruction: Anticholinergic Medications

- Decrease tone and peristalsis in smooth muscle
  - Direct action on smooth muscle cholinergic receptors
  - Impairment of ganglionic neural transmission in the bowel wall
- Decrease secretions of intestinal mucosal cells
- Improved control of colic and of vomiting

Metoclopramide

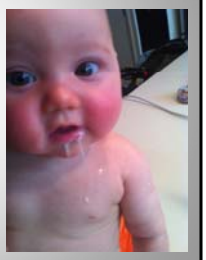
- Metoclopramide (*Reglan*)
  - Prokinetic
  - Final mode of action is through stimulating cholinergic receptors in the bowel
  - **Anticholinergics block its prokinetic effect**

Paraneoplastic Pyrexia and Sweating

1) Antipyretic (Acetaminophen or NSAID)
2) Anticholinergic
   a) Amitriptyline 25-50 mg q HS
   b) Transdermal scopalamine patch q 3 days
   c) Glycopyrolate 2 mg po TID
3) Other options
   a) Propranolol (*Inderal*) 10-20 mg BID-TID
   b) Cimetidine (*Tagamet*) 400-800 mg BID-TID
   c) Olanzapine (*Zyprexa*) 5 mg BID
   d) Thalidomide 100 mg q HS

Sialorrhea

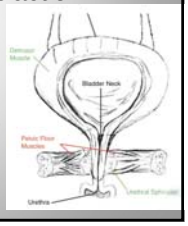
- Average 1.5 liters / day of saliva
- Poor oral / facial muscle control
- ALS, Parkinson's, stroke
- Medications
  - Glycopyrolate
    - 0.5 – 2 mg po up to TID
  - Transdermal scopolamine



Paula Szuchman, www.Itsthe dishes.com

Bladder

- M1 & M2 (80%), and M3 (20%) receptor subtypes
- M3 receptors responsible for parasympathetic detrusor contraction
  - Found in smooth muscles and glands
  - Release of acetylcholine from parasympathetic nerves causes simultaneous contraction of smooth muscle and micturation



Anticholinergics in OAB

- Overactive bladder (spastic bladder, urge incontinence)
  - Sudden urge to urinate, sometimes with painful spasms, may be incontinence
  - Oxybutynin (*Ditropan*), tolterodine (*Detrol*) commonly used to treat
    - Most cost effective
    - Solifenacin, trospium, darifenacin, fesoterodine, oxybutynin transdermal, propantheline also available

Leaking Foley Catheter

- Often caused by bladder spasms
  - Sudden contraction of bladder
  - Volume to excrete more than the catheter allows
  - May also occur with a blocked catheter
  - Larger balloon (> 5 – 10 ml) may cause by irritating the trigone
- Anticholinergics may help

Pruritis

- Oral or IV antihistamines (H1 receptor antagonists) often used to treat
  - Diphenhydramine (*Benadryl*)
  - Hydroxyzine (*Atarax, Vistaril*)
  - Loratadine (*Claritin*)
  - Cetirizine (*Zyrtec*)
  - Fexofenadine (*Allegra*)
- But…

Pruritis

- Histamine is the mediator for itch in
  - Most forms of urticaria
  - Insect bites
  - Cutaneous mastocytosis
  - Drug allergy rashes
- Is not the mediator in
  - Atopic dermatitis
  - Cholestasis
  - Uremia

Suggested Approach to Using Anticholinergics in End of Life Care

1) Unless there is a good reason for using it, don't !
2) Is there evidence that anticholinergic medication will help the symptoms?
3) What are the families expectations?
   a. The importance of educating them
4) What risk factors does the patient have for adverse reactions?

Suggested Approach to Using Anticholinergics in End of Life Care

5) What other medications are they taking?
   a) Risk of drug-drug interactions?
6) Use the lowest effective dose.
7) Consider glycopyrolate.
8) What is the cost?
9) **Unless there is a good reason for using it, don't !**

Any questions?