Pharmacological Strategies in Delirium and Agitation

Doris Flynn
Geriatric Emergency Management Nurse, Kingston General Hospital

Pam Hamilton
Psychogeriatric Resource Consultant, KFLA, Geriatric Psychiatry Program, Providence Care

Anya Kelly
Clinical Pharmacist, Day Hospital Program Specialized Geriatric Services, Providence Care
Overview

- Introduction
- Drugs commonly precipitating delirium
- Overview of resources – where to turn?
- Review of a framework to confidently engage in discussion with patient / family, and other health care members concerning drugs relating to delirium / agitation
- Review of pharmacological considerations in delirium / agitation
Introduction
Delirium

- Rarely needs medication to “treat”
- Often has medication as a “cause”
Medications that notoriously can cause Delirium - ‘Deliriumogenic’

Anticholinergics!!!!

- Antihistamines (e.g., Diphenhydramine, Hydroxyzine)
- CVS drugs (e.g., Captopril, Digoxin, Furosemide, Hydrochlorothiazine, Warfarin)
- CNS drugs (e.g., Amitriptyline, Codeine, Diazepam, Phenobarbital)
- Corticosteroids (Prednisolone, Dexamethasone)
- GI drugs (e.g., Ranitidine)
- Immunosuppressants (e.g., Cyclosporin)
- Anti-infectives (e.g., Ampicillin, Clindamycin, Vancomycin)
- Muscle relaxants (e.g., Pancuronium)
- Respiratory drugs (e.g., Theophylline)

Consider the cumulative effect.
Lack of Medications that can cause Delirium

- Withdrawal (more on that later)
- Poorly managed pain!!!
- Poorly managed heart failure
- Poorly managed diabetes
- etc.
Resources to Help You

1. Hartford Institute for Geriatric Nursing
   http://www.hartfordign.org/trythis
   A rich compendium of free downloadable resources on medications/delirium/ etc.

2. Articles in your binder

3. Geriatrics interprofessional interorganizational collaboration. Free registration to various resources at
   http://giic.rgps.on.ca/, e.g.
   http://www.rgpc.ca/best/GiiC%20Resources/GiiC/polypharmacy.html
Challenging Delirium / Agitation Situation ....

- Now what?
Psychototropic Framework
(Within the Context of the P.I.E.C.E.S. 3-Q Template)

1. **Detect:** When should a psychotropic be used or considered?
2. **Select:** How do I contribute to the selection of the right medication?
3. **Effect:** How do I monitor the response and side effects?
Three Reasons to Use a Psychotropic

1. For a specific mental health disorder (e.g., depression, schizophrenia etc.)
2. For a specific behaviour associated with a mental health disorder (e.g., behaviour associated with dementia)
3. As an adjunct (supportive) therapy (e.g., delirium)
Detect: When should a Psychotropic be used?

- **Not** effective for:
  - Aimless wandering
  - “Inappropriate” urination / defecation
  - “Inappropriate” dressing / undressing
  - “Annoying” perseverative activities
  - Verbally disruptive
Detect: When should a Psychotropic be used? – Cont’d

- **Not** effective for:
  - Eating inedibles
  - Tugging / removal restraints
  - Pushing wheelchair-bound co-patient
  - Hiding / hoarding
Detect: When should a Psychotropic be used? – Cont’d

- **May be** effective for:
  - Verbal / physical aggression
  - Anxiety & restlessness
  - Depressive symptoms e.g., crying, anorexia, insomnia
  - Withdrawal / apathy
Detect: When should a Psychotropic be used? – Cont’d

- May be effective for:
  - Manic-like symptoms
  - Persistent delusions / hallucinations
  - Sexually “inappropriate” behaviour with agitation
Treatment of Delirium

Anya Kelly, Clinical Pharmacist, Day Hospital Program Specialized Geriatric Services, Providence Care
Medications that cause Delirium

- Corticosteroids
- Furosemide
- Skeletal muscle relaxants
- Amantadine
- Antispasmodics (e.g., Tolterodine, Oxybutynin)

- H2-blockers (Cimetidine, Ranitidine)
- Herbs: Mandrake, Henbane, Jimson weed, Atropine / Belladonna extract
Medications that cause Delirium – *Cont’d*

- Sedatives, e.g., Benzo’s
- Narcotics, e.g., Demerol, Codeine, Fentanyl, Morphine
- Antibiotics: Fluoroquinolones (e.g., Cipro)
- Antihistamines: Hydroxyzine, Benadryl
- Antiparkinsonian: Sinemet, Dopamine, Agonists, Benztropine, Anticholinergics

- Antidepressants, e.g., Tricyclics, Paxil)
- Lithium
- Antipsychotics (Chlorpromazine)
- Antiemetics (Prochlorperazine, Dimenhydinate, Scopolamine)
- Cardiovascular agents (Betablockers, Methyldopa, Digoxin, Dopamine, Lidocaine)
- Anticonvulsants (Phenytoin, Phenobarbital)
Anticholinergic Side Effects

- **Peripheral:**
  - Blurred vision
  - Dry mouth
  - Constipation
  - Urinary retention
  - Orthostatic hypotension

- **Central**
  - Delirium
  - Confusion
  - Impaired memory
Antipsychotics - History

► **Chlorpromazine** (Largactil, Thorazine, etc.)
  - 1950 - 1954, France
  - Antipsychotic effect - chance discovery
  - Antiemetic, ++ other effects

► **Haloperidol** (Haldol, etc.)
  - 1957, Belgium
  - U.S. approval delayed until late 1960s (re. Thalidomide)

► **Clozapine** (Clozaril)
  - First “Atypical”
  - First developed in 1961
  - Became available in U.S. 1990 (Risperidone approved in the U.S. in 1994)

Dr. S. Gill
Antipsychotics

- **Typicals:**
  - High potency (e.g., Haldol)
  - Medium potency (e.g., Perphenazine)
  - Low potency (e.g., Chlorpromazine)

- **Atypicals:**
  - Clozapine (Clozaril)
  - Risperidone (Risperdal)
  - Olanzapine (Zydis)
  - Quetiapine (Seroquel)
Adverse Effects of Antipsychotics

- Extrapyramidal symptoms
- Anticholinergic effects
- Orthostatic hypotension
- Sedation
- Falls
- Akathesia (restlessness)

- Increased risk of stroke
- Weight gain
- Diabetes
- Dyslipidemia
- Cardiac: QT interval prolongation
  …arrhythmia
QT Prolongation (Some Risk Factors)

- Cardiomyopathy
- (MI, HF, LVH)
- Anorexia
- Hypokalemia
- Hypomagnesemia
- Age
- Female sex
- Drugs

- Congenital long QT interval
QT Prolonging Drugs (Some)

- Amiodarone
- Disopyramide
- Flecanide
- Procainamide
- Quinidine
- Sotalol
- Tricyclic antidepressants
- Macrolides (E’mycin, etc.)
- Quinolones (Cipro, etc.)
- Azole antifungals (Fluconazole, etc.)
- Calcium channel blockers (Dil, Verap)
- HIV: protease inhibitors
- etc.
Delirium Types

- Hyperactive: agitated, hallucinations
- Hypoactive: withdrawn, lethargic, sluggish, somnolent
- Mixed: combination of both
Target Symptoms

- Hallucinations
- Delusions
- Hostility
- Aggression
- Agitation
- Violent behaviours
Treating Symptoms of Delirium

- Treatment of delirium is indicated for **acute** agitation, when the safety of the patient or others is in question or when it would result in the interruption of essential therapy, e.g. mechanical ventilation or central venous catheters.
- Use anti-psychotics for **shortest time** possible and in the **lowest dose** possible.
- Reassess need for it every few days and taper / discontinue antipsychotic as soon as possible.
- When possible, obtain an ECG prior to starting the medication.
- Avoid use of PRN antipsychotics.
Treating Symptoms of Delirium – Cont’d

There is little evidence to guide dosage.

- Some suggestions:
  - **Haloperidol**: 0.5 mg - 1 mg po twice daily, with additional doses q4h prn; peak effect, 4 - 6 hours (Max. 2 mg/day); 0.5mg - 1 mg IM; observe after 30 - 60 min., and repeat if needed (peak effect 20 - 40 min.) (max. 2 mg/day)
  - **Risperidone**: 0.25 mg po od-bid (max. 2 mg/day)
  - **Olanzapine**: 1.25 mg to 2.5 mg po once daily (max. 7.5 mg/day)
  - **Quetiapine**: 12.5 to 50 mg po once daily
# Antipsychotics Available

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (Haldol)</td>
<td>Tablets; oral solution, regular injection &amp; depot injection</td>
</tr>
<tr>
<td>Risperidone (Risperdal)</td>
<td>Oral-disintegrating tablets (Risperdal M-tab), oral solution, long-acting injection (Risperdal Consta)</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>Regular tablets, oral dissolving tabs (Zyprexa Zydis) &amp; injection</td>
</tr>
<tr>
<td>Quetiapine (Seroquel)</td>
<td>Regular tablets</td>
</tr>
</tbody>
</table>
# Antipsychotic Properties

<table>
<thead>
<tr>
<th>Med.</th>
<th>Sedation</th>
<th>EPS</th>
<th>AC</th>
<th>Orthostasis</th>
<th>QT incr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haldol</td>
<td>+</td>
<td>++++</td>
<td>+</td>
<td>+</td>
<td>4.7 msec</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>6.4 msec</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>14.5 msec</td>
</tr>
<tr>
<td>Risperidone</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>10 msec</td>
</tr>
</tbody>
</table>
Drug Interactions - Some

- Careful with medications that prolong the QT interval (cf list) .. Antibiotics (Macrolides, Quinolones), Azole Antifungals (Fluconazole, etc.)
- SSRIs (Paxil, Zoloft, Prozac) ...*increase* AP levels
- Haldol plus Lithium …*avoid*
- With Oxybutynin, Scopolamine, Tolterodine, etc. (A/C side effects)
- Antiarrhythmics (Amiodarone, Quinidine) >> Cyp 2D6 inhibition.
# Antipsychotic Drug Interactions

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmic (quinidine,</td>
<td>Increased levels (inhib. 2D6); additive cardiac depression <strong>DO NOT COMBINE</strong></td>
</tr>
<tr>
<td>amiodarone, procainamide,)</td>
<td></td>
</tr>
<tr>
<td>Antibiotics (Clarithromycin;</td>
<td><strong>Do not combine</strong> ... cardiac conduction effects ... due to inhibition of CYP 3A4</td>
</tr>
<tr>
<td>Erythromycin,)</td>
<td></td>
</tr>
<tr>
<td>Antifungals (the ‘conazoles’)</td>
<td>CYP 3A4 inhibition ... increase levels of all APs ... cardiac conduction effects; QT prolongation</td>
</tr>
<tr>
<td>Calcium Channel Blocker (Vera,</td>
<td>&gt; Quetiapine levels from CYP 3A4 inhibition</td>
</tr>
<tr>
<td>Diltiazem)</td>
<td></td>
</tr>
<tr>
<td>Antitubercular (Isoniazid, Rifampin)</td>
<td>Isoniazid …&gt; Haldol (inhib. metabolism) Rifampin ... &lt; Haldol (induction of metabolism)</td>
</tr>
<tr>
<td>Lithium</td>
<td>Haldol; EPS; increased neurotoxicity</td>
</tr>
</tbody>
</table>
## Antipsychotic Drug Interactions – *Cont’d*

<table>
<thead>
<tr>
<th>Codeine</th>
<th>Inhibits Conversion of C to M with Haldol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protease Inhibitor (Ritonavir, Indinavir)</td>
<td>Avoid re. cardiac conduction effects; &gt; Haldol &amp; Risperidone levels &lt; Olanzapine CYP 1A2 enz. induction</td>
</tr>
<tr>
<td>Evening Primrose Oil</td>
<td>May lower seizure threshold</td>
</tr>
<tr>
<td>Aricept (Donepezil)</td>
<td>Exacerbation of EPS</td>
</tr>
<tr>
<td>Benzos (Alprazolam, Clonazepam, Lorazepam)</td>
<td>&lt; Haldol levels; more sedation.</td>
</tr>
<tr>
<td>Grapefruit Juice</td>
<td>Increased anti-psychotic levels (CYP 3A4 inhibition)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Decrease INR</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Reduced Antipsychotic levels</td>
</tr>
<tr>
<td>Absorbents, e.g., Antacids, Questran</td>
<td>&lt; Antipsychotic absorbed (significant)</td>
</tr>
</tbody>
</table>
Antipsychotic Drug Interactions – *Cont’d*

<table>
<thead>
<tr>
<th>Metoclopramide</th>
<th>Increased risk of EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Antidepressants</td>
<td>- Case reports of dose-related mania and serotonin syndrome when combined; increase Risperidone &amp; Haldol;</td>
</tr>
<tr>
<td>- Paxil, Zoloft, Prozac</td>
<td>- Increase Risperidone and Haldol</td>
</tr>
<tr>
<td>- Fluvoxamine</td>
<td>- Increases Haldol x 2; also increases Olanzapine and Quetiapine</td>
</tr>
<tr>
<td>- Paxil</td>
<td>- Increases Haldol x 4</td>
</tr>
<tr>
<td>- Antidepressants: RIMA (Moclobamide)</td>
<td>- Additive Hypotension</td>
</tr>
<tr>
<td>- Serotonin Syndrome:</td>
<td>Nausea, diarrhea, chills, sweating, dizziness, increased temperature and BP, palpitations, tremor, myoclonic jerks, hyperreflexia, restless, agitation, confusion, delirium; may progress to rhabdomyolysis, coma &amp; death</td>
</tr>
<tr>
<td>Occurs within 24 hours of new medication being added (i.e., other serotonergic agents)</td>
<td></td>
</tr>
</tbody>
</table>
Neuroleptic Malignant Syndrome

- Muscular rigidity, tachycardia, hyperthermia, altered consciousness, autonomic dysfunction, increase in CPK.
- It is rare.
- Occurs with any class of antipsychotic, with any dose and at anytime (increased risk in hot weather).
- Risk factors: polypharmacy, mood disorders, organic brain disorders, dehydration, low serum sodium, agitation, exhaustion.
Withdrawal Symptoms

- Benzodiazepine
- Opioid
- Alcohol
- Nicotine
- Antidepressants
- Recreational drugs
Benzodiazepine Withdrawal Symptoms

- Psychiatric symptoms:
  - Acute anxiety states
  - Phobias
  - Perceptual disorders
  - Irritability
  - Aggression

- Somatic symptoms:
  - Tremors
  - Muscle pains
  - Blurred vision
  - Seizures
  - Ataxia
Treat Benzo Withdrawal

- Start a Benzo (e.g., Lorazepam) and titrate to the minimum effective dose. Taper the dose over days to weeks
Opioid Withdrawal Symptoms

- Sweating
- Rhinorhea
- Lacrimation
- Yawning
- Tremor
- Weakness
- Insomnia
- Feeling hot and cold
- Flushing
- Restlessness
- Irritability
- Nausea
- Vomiting
- Diarrhea
- Mydriasis
- Tachycardia
- Piloerection
Treat Opioid Withdrawal

- Start an Opioid and titrate to the minimum effective dose. NB: Opioids are commonly used in elderly for chronic pain …safe meds when prescribed / used properly.
- Taper the dose over days to weeks.
Antidepressant Withdrawal Symptoms

- Tricyclics:
  - Nausea, vomiting, diarrhea
  - “Flu-like” symptoms
  - Fatigue
  - Anxiety
  - Agitation
  - Nightmares
  - Sleep disturbance
  - Abdominal pain

- SSRI’s & SNRI’s:
  - Dizziness
  - Nausea; Anxiety
  - “Electric shock-like” sensations
  - Lethargy
  - Headache, Tremor
  - Balance problems
  - Insomnia
  - Nightmares
Treat Antidepressant Withdrawal

- Restart usual medication as soon as possible and taper off.
- Treat symptomatically.
Alcohol Withdrawal Symptoms

- Most effects seen within 5 days after stopping
- Symptoms range from tremor, tachycardia, diaphoresis, labile BP, nausea, vomiting, anxiety, to perceptual disturbances (auditory and visual), to seizures
- Delirium Tremens occur after 72 hours
Treat Alcohol Withdrawal

- Use an a Benzo first line, titrating to the minimum effective dose. Taper the dose over several days.
- Collaborative best practice pre-printed order at KGH suggests Lorazepam vs. Diazepam for older adults.
Nicotine Withdrawal Symptoms

- Bradycardia
- Irritability
- Anxiety
- Dysphoria
- Depressed mood
- Slowed cognition
- Sleep disruption

- Anger
- Difficulty concentrating
- Increased appetite
- Impatience
- Craving
- Constipation
- Increased sensitivity to pain
Treating Nicotine Withdrawal

- Some evidence to suggest the use of nicotine replacement therapy given as a patch where the patient has a history of heavy tobacco use.
- Clonidine and nicotine patch may be used together if the withdrawal reaction is especially intense.
- KGH collaborative best practice pre-printed orders for smoking cessation.
Take Home Messages

- Antipsychotics are the mainstay of treatment of delirium (unless Alcohol / Benzo withdrawal).
- Although the research in elderly is limited, Haldol is the 1st line agent for delirium treatment (unless LBD or PD).
- AP is given for a specific agreed target of effect (guides monitoring).
- Smallest dose possible, monitored frequently and discontinued as soon as possible.