Antipsychotic Adverse Effects: Monitoring and Management
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2014 Fall Distance Learning Experience

Objectives
1. Recommend strategies for managing the extrapyramidal symptoms associated with antipsychotics based on a patient’s presenting symptoms.
2. Evaluate a patient’s risk for QTc prolongation based on the antipsychotic they are taking, cardiac history, age, and concurrent medications.
3. Develop a monitoring plan for metabolic effects associated with second-generation antipsychotics according to the ADA/APA consensus document on antipsychotic drugs and obesity and diabetes.
4. Create evidence-based treatment regimens to clinically manage the adverse effects associated with clozapine therapy (e.g. seizures, constipation, sialorrhea, etc.) when presented with a patient case.
5. Describe the significant differences in adverse effects among the second-generation antipsychotics.

First-Generation Antipsychotics (FGAs)

- Chlorpromazine (Thorazine®)
- Fluphenazine (Prolixin®)
- Haloperidol (Haldol®)
- Loxapine (Loxitane®)
- Perphenazine (Trilafon®)
- Thoridazine (Mellari®)
- Thiothixene (Navane®)
- Trifluoperazine (Stelazine®)
First-Generation Antipsychotics (FGAs)

<table>
<thead>
<tr>
<th>Potency</th>
<th>Antipsychotics</th>
</tr>
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<tbody>
<tr>
<td>Low</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td></td>
<td>Thioridazine</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Perphenazine</td>
</tr>
<tr>
<td></td>
<td>Loxapine</td>
</tr>
<tr>
<td>High</td>
<td>Trifluoperazine</td>
</tr>
<tr>
<td></td>
<td>Thiothixene</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
</tr>
<tr>
<td></td>
<td>Fluphenazine</td>
</tr>
</tbody>
</table>

Second-Generation Antipsychotics (SGAs)

- Clozapine (Clozaril®)
- Risperidone (Risperdal®)
- Olanzapine (Zyprexa®)
- Quetiapine (Seroquel®)
- Ziprasidone (Geodon®)
- Aripiprazole (Abilify®)
- Paliperidone (Invega®)
- Asenapine (Saphris®)
- Iloperidone (Fanapt®)
- Lurasidone (Latuda®)

Bold indicates drug product is available in brand name only.

Adverse Effects

- Agranulocytosis
- Anticholinergic
- Cardiac
- Enuresis
- Extrapyramidal symptoms
- Gastrointestinal (GI)
- Hepatic
- Hyperprolactinemia
- Metabolic
- Neuroleptic malignant syndrome (NMS)
- Ocular and skin deposits
- Orthostatic hypotension
- Osteoporosis
- Photo sensitivity
- Sedation
- Seizures
- Sexual dysfunction
- Venous thromboembolism
Extrapyramidal Symptoms

Extrapyramidal Symptoms (EPS)

- Akathisia
- Dystonia
- Pseudoparkinsonism
- Tardive dyskinesia

Akathisia

- Symptoms
  - Inability to sit or stand still
  - Restlessness
  - Pacing
  - Shifting
  - Tapping feet
  - Marching in spot

- Monitoring
  - Barnes Akathisia Scale (BAS, BARS)

Akathisia

- **Treatment**
  - Discontinue antipsychotic or reduce dose
  - Switch to SGA
  - Beta-blockers
    - Propranolol
    - Benzodiazepines

Dystonia

- **Symptoms**
  - Torticollis
  - Laryngospasm
  - Oculogyric crisis
  - Retrocollis
  - Trismus
  - Glossospasm
  - Blepharospasm
  - Opisthotonus

- **Monitoring**
  - Modified Simpson Angus Scale (MSAS)

Dystonia

- **Treatment**
  - Discontinue antipsychotic or reduce dose
  - Switch to SGA
  - Anticholinergics
    - Benztropine (po/IM/IV)
    - Trihexyphenidyl (po)
    - Diphenhydramine (po/IM/IV)
  - Benzodiazepines
Pseudoparkinsonism

• Symptoms
  – Akinesia - Masked face
  – Bradykinesia - Shuffling gate
  – Resting tremor - Stooped posture
  – Cogwheel rigidity - Micrographia

• Monitoring
  – Modified Simpson Angus Scale (MSAS)

Pseudoparkinsonism

• Treatment
  – Discontinue antipsychotic or reduce dose
  – Switch to SGA
  – Anticholinergics
  – Dopamine agonists
    • Amantadine

Tardive Dyskinesia (TD)

• Incidence
  – Approximately 5% per year
  – Approximately 20-25% with long-term treatment

• Risk factors
  – Long-term antipsychotic use - FGA
  – High dose antipsychotic - Increasing age
  – Occurrence of acute EPS - Female gender
  – Organic mental disorder


Tardive Dyskinesia (TD)

• Prevention
  – Confirm indication for antipsychotic
  – Use SGA
  – Use minimum effective dose
  – Discontinue anticholinergics
  – Assess for signs using rating scales


Tardive Dyskinesia (TD)

• Monitoring
  – Abnormal Involuntary Movement Scale (AIMS)
  – Dyskinesia Identification System - Condensed User Scale (DISCUS)
    • Administer at least every 3 to 6 months


Tardive Dyskinesia (TD)

- Symptoms
  - Orofacial movements
    - Tongue thrusting
    - Tongue rolling
    - Chewing or lateral jaw movements
    - Frequent blinking
    - Brow arching
    - Lip smacking
  - Extremity movements
    - Choreiform
    - Athetoid
    - Ballistic
    - Axial hyperkinesia


- Treatment
  - May be irreversible
  - No FDA-approved medications
    - Taper or discontinue antipsychotic if appropriate
      - Withdrawal dyskinesia
    - Switch antipsychotics
      - More or less potent agent
      - Clozapine
    - Discontinue anticholinergic medications
    - Trial of antidysonkinetic medication


Tardive Dyskinesia (TD)

- Antidyskinetic medications

<table>
<thead>
<tr>
<th>Should be considered</th>
<th>Might be Considered</th>
<th>Should Not be Considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>Amantadine</td>
<td>Otiliazem</td>
</tr>
<tr>
<td>Ginkgo biloba</td>
<td>Tetrabenazine</td>
<td>Galantamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Eicosapentaenoic acid</td>
</tr>
</tbody>
</table>

Insufficient Evidence to Support or Refute Use

- Acetazolamide
- Bromocriptine
- Thiamine
- Baclofen
- Vitamin E
- Vitamin B6
- Selegiline
- Melatonin
- Nifedipine
- Levetiracetam
- Buspirone
- Yi-gan san
- Betulunum tosin
- Reserpine
- Methylpoda
- Vitamin E
- ECT
- Deep brain stimulation

Neuroleptic Malignant Syndrome

- Incidence: ~0.01-0.02%
- Onset: Usually within 30 days
- Risk factors
  - High potency FGAs - Agitation
  - Parenteral administration - Restraint
  - Higher doses - Dehydration
  - Faster titration rates - Antipsychotic
  - Prior episode of NMS - naïve
Neuroleptic Malignant Syndrome

• Signs/Symptoms
  – Hyperthermia – Mental status changes
  – Muscle rigidity – Autonomic instability
  – Elevated creatine kinase

• Non-Pharmacologic Treatment
  – Discontinue all dopamine antagonists
  – Supportive care
    • Hydration
    • Correct electrolyte abnormalities
    • Cooling measures

Neuroleptic Malignant Syndrome

• Pharmacologic Treatment
  – Benzodiazepines – lorazepam 1 to 2mg IV every 4 to 6 hours
  – Amantadine 200 to 400mg/day po or NG in divided doses
  – Bromocriptine 2.5mg po or NG BID or TID (may increase to 45mg/day)
  – Dantrolene 1 to 2.5mg/kg IV followed by 1mg/kg every 6 hours

• Electroconvulsive therapy 6 to 10 treatments
Relationship between QTc and Torsades de Pointes (TdP)

- QTc prolongation >500 msec or a change in baseline >30-60 msec are of particular concern

<table>
<thead>
<tr>
<th>QTc Increase (msec)</th>
<th>Risk</th>
</tr>
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<tbody>
<tr>
<td>≤ 5</td>
<td>Does not appear to cause TdP</td>
</tr>
<tr>
<td>&gt;5 and &lt;20</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>&gt;20</td>
<td>Increased risk for TdP</td>
</tr>
</tbody>
</table>

Risk Factors for QTc Prolongation

- Female
- Advanced age
- Congenital long QT syndrome (LQTS)
- Electrolyte abnormalities
- Anorexia nervosa
- Malnutrition
- Diuretics
- Bradycardia
- Heart disease
- Renal and hepatic dysfunction
- Hypothyroidism
- CNS injury
- Diabetes
- Medications
- Drug-drug interactions

Risk of QTc Prolongation with Antipsychotics

<table>
<thead>
<tr>
<th>Medication (n)</th>
<th>Dose (mg/day)</th>
<th>Mean Duration of Treatment (days)</th>
<th>Mean Change in Baseline QT (msec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol (27)</td>
<td>15</td>
<td>18</td>
<td>7.1</td>
</tr>
<tr>
<td>Ziprasidone (31)</td>
<td>160</td>
<td>15</td>
<td>15.9</td>
</tr>
<tr>
<td>Quetiapine (27)</td>
<td>750</td>
<td>17</td>
<td>5.3</td>
</tr>
<tr>
<td>Olanzapine (24)</td>
<td>20</td>
<td>20</td>
<td>1.7</td>
</tr>
<tr>
<td>Risperidone (25)</td>
<td>6-8</td>
<td>25</td>
<td>3.9</td>
</tr>
<tr>
<td>Thioridazine (30)</td>
<td>300</td>
<td>16</td>
<td>30.1</td>
</tr>
</tbody>
</table>

No patient had a QTc interval ≥500 msec during the study.

References:


Risk of QTc Prolongation with Ziprasidone

- Modest effect on QTc interval
  - Does not appear to be dose-related
- Incidence of QTc prolongation ≥500 msec is ~0.06%
  - No episodes of TdP among 4571 patients treated
  - Rates of rapid and unexpected deaths comparable with other antipsychotics
  - No reports of significant cardiac events with overdose

Prevention of QTc Prolongation

- Confirm indication for antipsychotic
- Only use high doses when there is a clear therapeutic advantage
- Avoid administration with other QT prolonging medications
- Avoid QT prolonging drugs in patients with:
  - Pre-existing heart disease
  - Ventricular arrhythmias
  - Electrolyte abnormalities
- Monitor ECG in hospital setting if:
  - Initiation of drug known to cause TdP
  - Overdose on proarrhythmic agent
  - New-onset bradycardia
  - Severe hypokalemia or hypomagnesemia
Monitoring for QTc Prolongation

- No consistent data exist on how and when to monitor QT interval with antipsychotics
- Measure QT interval during peak plasma concentration of antipsychotic
- Assess QTc at baseline and intermittently post-initiation for patients with risk factors
- Monitor ECG at baseline and then at least daily with IV haloperidol

Monitoring for QTc Prolongation – LQTS Experts

- One third to one half of LQTS experts would check an ECG before and after starting an antipsychotic
- Check ECG before and after starting a drug if it has very probable, probable, or possible potential for causing QT prolongation

<table>
<thead>
<tr>
<th>Very Probable</th>
<th>Probable</th>
<th>Possible</th>
</tr>
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<tbody>
<tr>
<td>Thoridazine</td>
<td>Ziprasidone</td>
<td>Chlorpromazine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Olanzapine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Risperidone</td>
</tr>
</tbody>
</table>

Orthostasis and Syncope
Orthostasis and Syncope

- Risk factors
  - Treatment with clozapine, iloperidone, chlorpromazine and thioridazine
  - Rapid dose titration
  - Initial treatment period
  - Elderly
  - Dehydration
  - Alcoholic neuropathy
  - Concomitant medications that affect hemodynamic tone
  - Disorders of the autonomic nervous system

- Non-pharmacologic management
  - Rise slowly to standing position
  - Compression stockings
  - Salt-containing diet
  - Drink plenty of fluid

- Pharmacologic treatment
  - Switch antipsychotics
  - Titrate dose slowly
  - Specific dose titration schedule for iloperidone
  - Use initial iloperidone titration schedule if >3 days missed
  - Lower the dose
  - Fludrocortisone 0.2 to 2 mg daily (divided in 2-3 doses)

Hyperprolactinemia
Hyperprolactinemia

- Risk factors
  - Treatment with FGAs, risperidone, or paliperidone
  - Children/adolescents
  - Premenopausal women
- Symptoms
  - Gynecomastia - Infertility
  - Galactorrhea - Sexual dysfunction
  - Amenorrhea - Osteoporosis

Hyperprolactinemia

- Monitoring
  - Obtain prolactin level at baseline, 3 months, or if any clinical feature appears
- Treatment
  - Reduce antipsychotic dose
  - Switch to a different antipsychotic
  - Adjunct dopamine agonist
    - Bromocriptine
    - Cabergoline
    - Amantadine
  - Adjunct aripiprazole

Metabolic Effects
**Metabolic Effects**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metabolic Syndrome</th>
<th>Weight Gain</th>
<th>Risk for Diabetes</th>
<th>Worsening Lipid Profile</th>
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<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>+</td>
<td>+++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
<td>++</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* = increased effect, - = no effect; D = discrepant results

** = Newer drugs with limited long-term data

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**Relative Risk for Metabolic Syndrome**

- Low
  - Aripiprazole
  - Ziprasidone
  - Lurasidone

- Moderate
  - Asenapine
  - Paliperidone

- High
  - Risperidone
  - Olanzapine
  - Clozapine
Monitoring Protocol for Metabolic Effects

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>Every 5 years</th>
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<tbody>
<tr>
<td>Personal/Family history</td>
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<td>X</td>
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<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting plasma glucose</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipid profile</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*More frequent assessments may be warranted based on clinical status

Treatment of Metabolic Effects

- Consider intervention if patient gains ≥ 5% of initial body weight
  - Diet and exercise
  - Switch to SGA with low metabolic liability
  - Medically treat metabolic side effects
  - Appetite suppressants or weight loss drugs
  - Metformin
  - Topiramate?

Mortality in Elderly Patients with Dementia-Related Psychosis
Mortality in Elderly Patients with Dementia-Related Psychosis

- Black box warning for all antipsychotics
  - Increased mortality in elderly patients with dementia-related psychosis
  - Most deaths are cardiovascular or infectious in nature
- Prevention
  1. Determine underlying factors for behavior
  2. Eliminate precipitating factors
  3. Implement non-pharmacologic treatment
  4. Initiate pharmacotherapy if necessary
  5. Maintain lowest effective dose and reassess need for antipsychotic


Clozapine

Clozapine – Highlighted Adverse Effects

- Agranulocytosis
- Seizures
- Myocarditis
- Cardiomyopathy
- Fever
- Gastrointestinal hypomotility
- Sialorrhea
- Enuresis
- Hepatic impairment
Clozapine - Agranulocytosis

- Incidence: ~1%
- Onset: Usually within the first 8 weeks
- Risk factors
  - Elderly
  - Female gender
  - Cachectic
  - Between months 1 and 6 of therapy
- Symptoms
  - Sore throat
  - Fever
  - Erythema

**Prevention – Slowly titrate dose**

<table>
<thead>
<tr>
<th>Day</th>
<th>Dose</th>
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<tbody>
<tr>
<td>1</td>
<td>12.5 mg po in the AM and HS</td>
</tr>
<tr>
<td>2</td>
<td>25 mg po in the AM</td>
</tr>
<tr>
<td>3</td>
<td>25 mg po in the AM and HS</td>
</tr>
<tr>
<td>4</td>
<td>25 mg PO in the AM and 50 mg PO at HS</td>
</tr>
<tr>
<td>5</td>
<td>50 mg PO in the AM and at HS</td>
</tr>
<tr>
<td>6</td>
<td>50 mg PO in the AM and 75 mg PO at HS</td>
</tr>
<tr>
<td>7</td>
<td>50 mg PO in the AM and 100 mg PO at HS</td>
</tr>
<tr>
<td>8</td>
<td>75 mg PO in the AM and 100 mg PO at HS</td>
</tr>
<tr>
<td>9</td>
<td>100 mg PO in the AM and 100 mg PO at HS</td>
</tr>
<tr>
<td>10</td>
<td>100 mg PO in the AM and 125 mg PO at HS</td>
</tr>
<tr>
<td>11</td>
<td>100 mg PO in the AM and 150 mg PO at HS</td>
</tr>
<tr>
<td>12</td>
<td>100 mg PO in the AM and 175 mg PO at HS</td>
</tr>
<tr>
<td>13 &amp; 14</td>
<td>100 mg PO in the AM and 200 mg PO at HS</td>
</tr>
</tbody>
</table>

**Prevention – WBC/ANC monitoring and registry**

<table>
<thead>
<tr>
<th>Hematologic Values for Monitoring</th>
<th>Frequency of WBC and ANC Monitoring</th>
</tr>
</thead>
</table>
| WBC ≤ 1500/mm³ and ANC ≤ 2000/mm³ | Do not initiate if WBC < 1500/mm³ or ANC < 2000/mm³  
Monitor weekly for the first 6 months  
Monitor every 2 weeks from 6 months to 12 months of therapy  
Monitor every 4 weeks after 12 months of therapy |
| WBC > 1500-3000/mm³ and/or ANC > 1500-2000/mm³ | May continue clozapine  
Monitor twice weekly until WBC > 1500/mm³ and ANC > 2000/mm³ |
| WBC > 2000-3000/mm³ and/or ANC > 1500-1500/mm³ | Hold clozapine  
Monitor daily until WBC > 3000/mm³ and ANC > 1500/mm³  
Monitor twice weekly WBC > 3000/mm³ and ANC > 1500/mm³  
May rechallenge when WBC > 3000/mm³ and ANC > 2000/mm³ |
| WBC < 2000/mm³ and/or ANC < 1500/mm³ | Discontinue clozapine and do not rechallenge  
Monitor until normal and for at least four weeks from day of discontinuation as follows:  
Daily until WBC > 1500/mm³ and ANC > 1500/mm³  
Twice weekly until WBC > 1500/mm³ and ANC > 2000/mm³  
Weekly after WBC > 1500/mm³ |
### Clozapine - Agranulocytosis

- **Treatment**
  - Discontinue clozapine
  - Supportive care
  - Antibiotics when indicated
  - Pharmacologic treatment
    - Granulocyte colony-stimulating factor (G-CSF)
    - Lithium

### Clozapine - Seizures

- **Dose related seizure activity**
  - <300mg/day: 1%
  - 300-600mg/day: 2.7%
  - >600mg/day: 4.4%

- **Management**
  - Reduce dose by 50%
  - Consider anticonvulsant if recurrent seizures

### Clozapine – Myocarditis and Cardiomyopathy

- **Incidence:** 0.015% to 0.188%
- **Onset**
  - Myocarditis – within 2 months
  - Cardiomyopathy – after 2 months
- **Symptoms**
  - Tachycardia
  - Dyspnea
  - Chest pain
  - Palpitations
  - Fever
  - Flu-like symptoms
  - Diarrhea/vomiting
  - Dysuria
**Clozapine – Myocarditis and Cardiomyopathy**

- Proposed monitoring
  - Vital signs, C-reactive protein (CRP), troponin
- Proposed management

<table>
<thead>
<tr>
<th>Symptom/Sign</th>
<th>Management Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of unidentified illness OR HR ≥ 120 bpm or increased by &gt; 30 bpm OR CRP ≥ 100 mg/L OR Troponin ≥ 2 ULN</td>
<td>Continue clozapine</td>
</tr>
<tr>
<td>CRP &gt; 100 mg/L OR Troponin &gt; 2 ULN</td>
<td>Discontinue clozapine</td>
</tr>
</tbody>
</table>

**Clozapine - Fever**

- Characteristics
  - Spiking with temperatures below 104°F
  - Lasts ~2.5 days
  - Not dose related
  - Associated with respiratory and GI symptoms
  - Occurs within the first month of therapy
- Management
  - Rule out NMS, agranulocytosis, and myocarditis
  - WBC with differential, troponin, CRP, urinalysis, blood cultures, creatine kinase
  - Acetaminophen

**Clozapine – GI Hypomotility**

- May result in:
  - Constipation
  - Bowel necrosis
  - Fecal impaction
  - Death
  - Feculent vomiting
- Risk factors
  - High clozapine dose
  - Concomitant anticholinergic medications
  - Concomitant medical illness
**Clozapine – GI Hypomotility**

- Symptoms
  - Abdominal pain
  - Nausea
  - Abdominal distention
  - Vomiting
  - Constipation

- Prevention/Treatment
  - No established guidelines
  - No clear consensus on best laxative
  - Try lifestyle modifications first
    - Exercise, dietary fiber, hydration

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**Step Management Strategies**

<table>
<thead>
<tr>
<th>Step</th>
<th>Management Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fiber 2 scoops po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 100mg po BID</td>
</tr>
<tr>
<td>2</td>
<td>Lactulose 15ml po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 100mg po BID</td>
</tr>
<tr>
<td>3</td>
<td>Lactulose 30ml po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 200mg po BID</td>
</tr>
<tr>
<td>4</td>
<td>Lactulose 45ml po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 200mg po BID</td>
</tr>
<tr>
<td>5</td>
<td>Lactulose 45ml po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 200mg po BID</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl 10mg po BID</td>
</tr>
<tr>
<td>6</td>
<td>Lactulose 45ml po BID</td>
</tr>
<tr>
<td></td>
<td>Docusate 200mg po BID</td>
</tr>
<tr>
<td></td>
<td>Bisacodyl 20mg po BID</td>
</tr>
<tr>
<td></td>
<td>Milk of magnesia 30ml pm for steps 1-5</td>
</tr>
<tr>
<td>7</td>
<td>Magnesium citrate 300ml po x 1</td>
</tr>
<tr>
<td></td>
<td>Fleets enema BID x 3 days</td>
</tr>
<tr>
<td></td>
<td>Polyethylene glycol 4-6 liters per day until clean</td>
</tr>
<tr>
<td></td>
<td>Consult GI</td>
</tr>
</tbody>
</table>

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**Clozapine – Sialorrhea**

- Mechanism
  - Agonist activity at muscarinic M4 receptors
  - Antagonist activity at alpha2-adrenergic receptors

- Non-pharmacologic management
  - Chew sugarless gum
  - Cover pillow with a towel
**Clozapine - Sialorrhea**

- **Pharmacologic treatment**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscarinic receptor antagonist (anticholinergic)</td>
<td>- Benztropine 0.5 to 6mg po daily</td>
</tr>
<tr>
<td></td>
<td>- Trihexyphenidyl 2 to 15mg po daily</td>
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<tr>
<td></td>
<td>- Amitriptyline 15 to 100 mg po daily</td>
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<tr>
<td></td>
<td>- Scopolamine 1.5mg patch topically every 72 hrs</td>
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<tr>
<td></td>
<td>- Atropine 1% eye drops – 1 to 6 drops sublingually daily</td>
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<tr>
<td></td>
<td>- Ipratropium bromide nasal spray 0.03-0.06% - 2 to 6 sprays sublingually daily</td>
</tr>
<tr>
<td>Alpha2-adrenergic receptor agonist</td>
<td>- Clonidine 0.05 to 0.1mg po daily or 0.1 to 0.2mg patch topically weekly</td>
</tr>
<tr>
<td></td>
<td>- Guanfacine 1mg po daily</td>
</tr>
</tbody>
</table>

- **Inhibit acetylcholine release in salivary glands**
  - Botulinum toxin 150 units injected into parotid glands

**Clozapine - Enuresis**

- **Non-pharmacologic management**
  - Monitor fluid intake
  - Use toilet regularly
  - Avoid caffeine
  - Enuresis alarm

- **Pharmacologic treatment**
  - Desmopressin 0.2mg po QHS
  - Oxybutynin 5mg po daily
  - Imipramine 25mg po QHS

**Clozapine – Hepatic Impairment**

- **Ranges from LFT elevations to liver failure**
- **Occurs during first months of treatment**
- **Monitoring**
  - Routine LFT measurement may lead to unnecessary discontinuation
  - Measure LFTs with clinical symptoms: jaundice, malaise, rash
  - Monitor more closely if LFTs are elevated
- **Discontinue if LFTs >3 times the ULN**

LFT = liver function test
ULN = upper limit of normal
Summary

- Antipsychotics are associated with multiple adverse effects that make adherence difficult for patients and monitoring/management difficult for providers.
- SGAs are often better tolerated than FGAs but are associated with more metabolic side effects.
- Clozapine demonstrates superior efficacy but has multiple adverse effects that limit its use.
- Pharmacists can play a large role in helping monitor and manage side effects associated with antipsychotics.