Update on the Treatment of Psychosis

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Objectives

- Evaluate existing data in regards to the appropriate treatment of schizophrenia
- Review risks and benefits of antipsychotic therapy in the management of acute psychosis
- Discuss the monitoring of psychotic symptoms as well as the monitoring and management of short and long-term adverse effects associated with antipsychotic therapy

Symptoms of Schizophrenia

- Patients must have experienced > 2 of the following symptoms:
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Disorganized or catatonic behavior
  - Negative symptoms

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

Symptoms of Schizophrenia

- At least 1 of the symptoms must be the presence of delusions, hallucinations, or disorganized speech
- Continuous signs of the disturbance must persist for at least 6 months, during which the patient must experience > 1 month of active symptoms, with social or occupational deterioration problems occurring over a significant amount of time. These problems must not be attributable to another condition

Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

Symptoms of Schizophrenia

Positive Symptoms

- Hallucinations
- Delusions
- Disorganized speech
- Grossly disorganized behavior or catatonia

Negative Symptoms

- Apathy
- Lack of emotion
- Social withdrawal
- Poor social functioning

Cognitive Symptoms

- Difficulty maintaining/shifting attention
- Problems with memory
- Impaired executive function
- Deficits in skill acquisition

Diagnostic Evaluation

- Comprehensive history
- Involve family/caregivers if necessary
- Physical exam
- CMP/BMP
- Electrocardiogram
- Chest X-Ray
- CBC
- LFT's
- Urinalysis
- Urine drug screen
- TSH
- Pregnancy Test
Clinical Course
- Lifetime Prevalence < 1%
- Many have prodromal phase
  - Primarily negative and cognitive symptoms
- Typical onset late teens-early 30's
  - Women slightly later onset
- Chronic disease
  - Most have moderate to severe disability but can have periods of recovery
  - Adherence to treatment will improve patient functioning and outcomes

Schizophrenia Pathophysiology
- Pathophysiology Theories
  - Excessive dopamine (D2) in the mesolimbic pathway
  - Low dopamine in mesocortical area
  - Low levels of serotonin (5-HT)
  - Low Glutamate
- Risk factors
  - Perinatal factors: hypoxia, fetal distress
  - Biological
  - Cannabis use

Treatment Considerations
- Some treatment guidelines recommend starting second-generation antipsychotic (SGA) as first-line therapy
- Others guidelines recommend to start a SGA or first generation (FGA) antipsychotic
- Symptoms typically respond within 2 weeks but may take up to 4-6 weeks
  - Some data suggest switching AP if poor response in first 2 weeks
- Continually assess for reduction in positive symptoms, improvement in negative and cognitive symptoms, and medication adherence
- Continually assess for adverse effects and treat as needed (or change to an alternate AP)

Treatment Considerations
- Continue antipsychotic for at least 1 year for first-episode of schizophrenia
- Continue for at least 2-5 years if 2 or more episodes
- If > 2 episodes/5 years, patients may need to be on lifelong treatment*
- Consider changing patients to a long-acting antipsychotic (LAI) to improve medication adherence
  - Ensure patient can tolerate PO formulation

http://psychiatryonline.org/guidelines accessed 9/17*

First-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA-approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>Thorazine</td>
<td>1957</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>Trilafon</td>
<td>1957</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>Stelazine</td>
<td>1959</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Haldol</td>
<td>1967</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>Navane</td>
<td>1967</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>Mellaril</td>
<td>1962</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>Prolixin</td>
<td>1972</td>
</tr>
<tr>
<td>Loxapine</td>
<td>Loxitane</td>
<td>1975</td>
</tr>
</tbody>
</table>

First-Generation Antipsychotics (FGA's)
First-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Forms</th>
<th>Starting Dose</th>
<th>Average Dose</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>PO/IM/IV</td>
<td>30-75mg/day div. in 2-4 doses</td>
<td>200-600mg/day Max &lt; 1000mg/day</td>
<td>Reduce dose in liver disease</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>PO</td>
<td>4-8mg/day div. in 3 doses</td>
<td>8-64mg/day Max 64mg/day</td>
<td>Reduce dose in liver disease</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>PO</td>
<td>2.5mg/day div. in 2-4 doses</td>
<td>20-40mg/day Max 40mg/day</td>
<td>Contrasted, In liver disease</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>PO/IM/IV oral soln.</td>
<td>1-10mg/day div. in 2-3 doses</td>
<td>10-50mg/day Max 100mg/day</td>
<td></td>
</tr>
<tr>
<td>Thorazine</td>
<td>PO</td>
<td>6-10mg/day div. in 3 doses</td>
<td>20-50mg/day Max 50mg/day</td>
<td>Reduce dose in liver disease</td>
</tr>
<tr>
<td>Thiothixene</td>
<td>PO</td>
<td>50-100mg/day div. in 5 doses</td>
<td>50-400mg/day Max 800mg/day</td>
<td>Reduce dose in liver disease</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>PO</td>
<td>50-100mg/day div. in 5 doses</td>
<td>50-800mg/day</td>
<td></td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>PO/IM/oral soln.</td>
<td>2.5-10mg/day div. in 1-2 doses</td>
<td>20-40mg/day Max 40mg/day</td>
<td>Contrain. In liver disease</td>
</tr>
<tr>
<td>Loxapine</td>
<td>PO/INH</td>
<td>20-50mg/day div. in 2-4 doses</td>
<td>20-100mg/day Max 250mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>FDA-approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Clozaril</td>
<td>1989</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Risperdal</td>
<td>1993</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Zyprexa</td>
<td>1996</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Seroquel</td>
<td>1997</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Geodon</td>
<td>2002</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Abilify</td>
<td>2006</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>2009</td>
</tr>
<tr>
<td>Asenapine</td>
<td>Saphris</td>
<td>2009</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>2010</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Rexulti</td>
<td>2015</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>Vraylar</td>
<td>2015</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Invega</td>
<td>2006</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>Fanapt</td>
<td>2009</td>
</tr>
<tr>
<td>Asenapine</td>
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<tr>
<td>Lurasidone</td>
<td>Latuda</td>
<td>2010</td>
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</tbody>
</table>

Newest Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage Forms</th>
<th>Starting Dose</th>
<th>Dosage Range</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone</td>
<td>PO</td>
<td>6 mg/day</td>
<td>6-12mg/day</td>
<td>Adjust dose in renal impairment</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>PO</td>
<td>40mg/day</td>
<td>40-120mg/day</td>
<td>Take with food (&gt; 350 cal); Contraindicated with strong 3A4 inhibitors/inhibitors</td>
</tr>
</tbody>
</table>
Brexpiprazole (Rexulti®)

- Approved as monotherapy for adults with schizophrenia and as adjunctive treatment for adults with major depressive disorder
- Dose: Days 1-4 → 1mg/day; Days 5-7 → 2mg/day; Days 8+ → 2-4mg/day
- Starter sample packs available
- Half- dose of patients taking strong 2D6/3A4 inhibitors OR poor 2D6 metabolizers
- Mechanism of action:
  - Partial agonist at 5HT1A and D2 receptors and 5HT2A antagonist
  - Antagonist of alpha-receptors

CYP450 Interactions

<table>
<thead>
<tr>
<th>Strong 3A4 inhibitors</th>
<th>Strong 2D6 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nelfinavir</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Triacazolene</td>
</tr>
<tr>
<td>Pidilizamide</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Nevirapine</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Saquinavir</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Suboxone</td>
</tr>
<tr>
<td>Pidilizamide</td>
<td>Telithromycin</td>
</tr>
</tbody>
</table>

http://medicine.iupui.edu/clinpharm/ddis/main-table

Precautions/contraindications

- Impairment in judgement, thinking, and motor skills
- Caution driving or operating heavy machinery

Adverse effects

- Akathisia, increased weight, diarrhea, dyspepsia, tremor, increased CPK, sedation

Cost: Approximately $1000/month

Cariprazine (Vraylar®)

- Approved for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder and the treatment of Schizophrenia in adults
- Dosing:
  - Starting dose 1.5mg/day
  - Dosage range: 1.5-6mg/day
  - Not recommended for severe liver or renal disease
  - Dose should be reduced by half when using with strong 3A4 inhibitors
- Mechanism of action:
  - Partial agonist at 5HT1A and D2 receptors and a 5HT2A antagonist

Cost: $770-1200/month
CYP450 Interactions

<table>
<thead>
<tr>
<th>3A4 Inducers</th>
<th>Strong 3A4 inhibitors</th>
</tr>
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<tbody>
<tr>
<td>Carbamazepine</td>
<td>Indinavir</td>
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<td>Efavirenz</td>
<td>Nelfinavir</td>
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<tr>
<td>Nevirapine</td>
<td>Ritonavir</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Telithromycin</td>
</tr>
</tbody>
</table>

Pimavanserin (Nuplazid)

- **SGA approved for the treatment of psychosis and hallucination in patients with Parkinson’s Disease**
- **Dosing:** 34 mg PO daily
- **Mechanism of action**
  - Selective serotonin inverse agonist (SSIA) designed to target 5-HT2A and 5-HT2C receptors (not dopamine)

Long-Acting Injectable Antipsychotics (LAI)

- **Efficacy/tolerability**
  - Decreased psychotic symptoms seen in 2-6 weeks
  - No change in motor control and ADR’s vs. placebo
- **Precautions/Contraindications:** Caution use with drugs known to elevate QT interval, severe renal/liver impairment
- **Adverse Effects:** Peripheral edema, confusion, nausea
- **Cost:** > $2000/month

LAI Dosing Considerations

- Ensure patient can tolerate oral version of preferred LAI prior to initiation
- Ideally wait until at least a partial positive response in addition to assessing tolerability prior to starting a LAI
- All LAI are available as an “IM” injection
  - Deltoid administration - All
  - Gluteal administration - Olanzapine only
- Review manufacturer product information if patient has missed dose(s)

Long-Acting Antipsychotics

<table>
<thead>
<tr>
<th>Name/Year Approved</th>
<th>Monthly Cost*</th>
<th>Dosing Range</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>$220</td>
<td>6.25-100mg q2-3 wks (usual 6.25-25mg)</td>
<td>Loading dose is approx. 1.25 x PO dose; Continue PO for at least 1 week; SS in 4-6 wks</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>$15</td>
<td>20-400mg q3-4 wks</td>
<td>Cannot inject &gt; 3mL; IM; 15-24 mos.</td>
</tr>
<tr>
<td>Risperidone</td>
<td>$440-1800</td>
<td>25-50 mg q2wks</td>
<td>Continue PO for 3 wks</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>$1200-1800</td>
<td>300mg (given q4wks or split q2wks)-300mg q2wks</td>
<td>Glucocorticoid injection only; No PO overlap needed; REMS program; rare risk of post-delinium syndrome</td>
</tr>
</tbody>
</table>

*www.drugs.com Accessed 9/17
**LAI Additional Information**

- **Haloperidol decanoate**
  - Loading dose strategy – 10-20 x PO dose
  - Reduce PO dose if use loading dose
  - If initial dose > 100mg, give initial 100mg dose, followed by remainder in 3-7 days
- **Risperdone LAI**
  - Approximate equivalent doses:
    - < 3mg/day → 25mg q2wks
    - > 5mg/day → 50mg q2wks

**Long-Acting Antipsychotics**

<table>
<thead>
<tr>
<th>Brand/Trademark</th>
<th>Approval Date</th>
<th>Loading Dose</th>
<th>Dosing Range</th>
<th>Max Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paliperidone palmitate (Invega Sustenna) 2009</td>
<td>3420-2500</td>
<td>Day 2-20mg followed by 156mg q 7 days; Then 256mg q month; DOSAGE RANGE 30-236mg q month</td>
<td>Discontinue PO with 1st dose</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole Abilify Maintena 2011</td>
<td>11500-2000</td>
<td>400mg q month</td>
<td>Continue PO for 14 days, Adjust dose if poor CYP2D6 metabolizers</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole lauroxil Aristada LAI 2015</td>
<td>11200-2800</td>
<td>441-882mg q month or 1064 mg q6wks</td>
<td>Continue PO for 23 days; Adjust dose if poor CYP2D6 metabolizers</td>
<td></td>
</tr>
<tr>
<td>Paliperidone palmitate (Invega Sustenna) 2015</td>
<td>8830-2500</td>
<td>273-839mg q3mo.</td>
<td>Switch after stabilized on Invega Sustenna for 4 yrs.</td>
<td></td>
</tr>
</tbody>
</table>

*www.drugs.com-Accessed 5/7*

**CYP450 Interactions**

<table>
<thead>
<tr>
<th>3A4 Inducers</th>
<th>Strong 3A4 Inhibitors</th>
<th>Strong 2D6 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Indinavir</td>
<td>Bupropion</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Nevirapine</td>
<td>Floxetine</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Ritonavir</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Clarithromycin</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Phenytion</td>
<td>Itraconazole</td>
<td></td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Ketoconazole</td>
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<td>Rifampin</td>
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<td>St. John’s Wort</td>
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<td>Rifabutin</td>
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<tr>
<td>Pioglitazone</td>
<td>Telithromycin</td>
<td></td>
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<tr>
<td>Troglitazone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

http://medicine.iupui.edu/clinpharm/ddis/main

**LAI Additional Information**

- **Olanzapine pamoate**
  - Can stop PO dose up to a week before 1st dose
  - Equivalent doses
    - 10mg/day PO → 300mg q month
    - 20mg/day PO → 400mg q month
  - Rare risk of post-injection delirium syndrome
  - Caused by rapid increases of olanzapine serum concentrations
  - Dizziness, confusion, disorientation, slurred speech, elevated BP, mild-severe sedation, up to 3 hrs following injection
  - Drug only available by a ZYPREXA RELPREVV Patient Care Program
  - Prescriber, patient, healthcare facility, and pharmacy must be registered

**LAI Additional Information**

- **Aripiprazole monohydrate**
  - Approximate equivalent doses
    - 10mg/day PO → 300mg q month
    - 20mg/day PO → 400mg q month
  - Reduce dose to 300mg q month if poor CYP2D6 metabolizer, and/or strong 2D6 or 3A4 inhibitors
  - Avoid medications that induce CYP3A4 for > 14 days
- **Aripiprazole lauroxil**
  - Approximate equivalent doses
    - 10mg/day PO → 441mg q month
    - ≥ 20mg/day PO → 882 mg q month
  - Can give 882 mg dose q6wks
  - Dose adjustments recommended for CYP450 interactions

**LAI Additional Information**

- **Paliperidone Palmitate (Invega Sustenna)**
  - Decrease dose in renal impairment (CrCl < 50mL/min)
  - Approximate equivalent doses:
    - 3mg/day PO → 39-78mg q month
    - 12mg/day PO → 234 mg q month
  - First injection should be given in deltoid; subsequent injections can be given in gluteal or deltoid muscle
LAI Additional Information

- **Paliperidone palmitate (Invega Trinza)**
  - Equivalent doses of Invega Sustenna → Invega Trinza
    - 78 mg/mos. → 273 mg q3mos.
    - 117 mg/mos. → 410 mg q3mos.
    - 156 mg/mos. → 546 mg q3mos.
  - Can be given up to 2 weeks early or 1 month late

FGA and SGA

Adverse Effects

First-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>ACH</th>
<th>Sedation</th>
<th>QTc Prolongation</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>++</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>Very low</td>
<td>Very low</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Thiopropizine</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>++</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>++</td>
<td>++</td>
<td>***</td>
<td>+</td>
</tr>
<tr>
<td>Loxapine</td>
<td>+</td>
<td>++</td>
<td>No</td>
<td>++</td>
</tr>
</tbody>
</table>

ACH= Anticholinergic side effects
EPS= Extrapyramidal side effects

Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Metabolic ADR</th>
<th>Sedation</th>
<th>QTc Prolongation</th>
<th>EPS</th>
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</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>Very low</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
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<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>Very low</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>very low</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Mortality Risk in Elderly Patients

- Black-box warning on all antipsychotic drugs increase the all-cause risk of death in elderly patients with dementia-related psychosis
  - Primarily SGA studied vs. placebo
  - Risk of death 1.6- to 1.7-times AP vs. placebo-treated patients
  - Death primarily attributed to cardiovascular and infectious disease causes
Antipsychotics Adverse Effects

- Serotonin syndrome
- Risk with SGA’s
- Neuroleptic malignant syndrome (NMS)
  - Hyperpyrexia, muscle rigidity, altered mental status, autonomic instability, elevated CPK, ARF, myoglobinuria
  - Immediately d/c medication and treat symptoms
- Increased risk of death in patients with dementia
- Black box warnings with atypical antipsychotics but thought to occur with typical antipsychotics
- Increased suicidal thoughts/behaviors in patients aged 24 years old and younger
- Black box warning for SGA approved for the adjunctive treatment of depression

Extrapyramidal Side Effects (EPS)

Most EPS due to blockade of the dopamine receptors in the basal ganglia
- FGA > SGA
- High-potency > Low-potency FGA
- Dose-dependent risk

Examples
- Dystonic Reactions
- Akathesia
- Pseudoparkinsonism
- Tardive dyskinesia

Extrapyramidal Side Effects (EPS)

Dystonic Reactions
- Involuntary sustained muscular contractions occurring within first few days of treatment
  - Retrocollis, torticollis, oculogyric crisis, etc.
- Higher risk in young males; FGA > SGA; dose-dependent

Treatment options
- Diphenhydramine 25-50mg PO/IM q4-6 hrs
- Benztropine 1-2 mg PO/IM q6hrs
- Discontinue antipsychotic or decrease dose

EPS-Akathesia

Most cases occur within 1-3 months of antipsychotic initiation
- Sensation of inner restlessness; patients cannot sit still
- May be misdiagnosed as agitation/anxiety
- Highest risk with aripiprazole and cariprazine

Treatment options:
- Decrease dose or change antipsychotic
- Propranolol 10-20mg PO 2-4 times daily
- Most evidence for efficacy
- Benzodiazepines
- Anticholinergics

EPS-Pseudoparkinsonism

Typically occurs within days/weeks of starting antipsychotic
- Includes slowed movements, masked facies, cogwheel rigidity, resting tremor, etc.

Treatment options:
- Decrease dose or change antipsychotic
- Anticholinergics
  - Benztropine 1-6mg PO daily, diphenhydramine 25-300mg/day (divided)
  - Amantadine 100-400mg/day (divided)
- Propranolol
- Treatment resistant cases

Tardive Dyskinesia

Irreversible drug-induced disorder that is characterized by involuntary choreoathetoid movements of the tongue, mouth, face, extremities, and/or trunk
- Risk increases with patient age, cumulative dose of AP, and duration of therapy
- Higher incidence with FGA vs. SGA
- Highest risk with agents which have more potent dopamine blockade
Tardive Dyskinesia

- Chronic anticholinergic treatment have been associated with higher risk of developing tardive dyskinesia
- Treatment options include
  - Discontinue antipsychotic
  - Vitamin E supplementation
  - Conflicting data
  - Pyridoxine (vitamin B6) 400-1200mg/day
  - Deep Brain Stimulation
  - Treatment resistant cases

Valbenazine (Ingrezza™)

- Approved for the treatment of tardive dyskinesia
- Dosing:
  - Starting dose 40 mg/day x 1 week, then increase to 80mg/day if needed
  - Dose should be reduced by half when using with strong 3A4 inhibitors
- Mechanism of action:
  - Selectively inhibits VMAT2 in presynaptic neurons which reversibly reduces dopamine in synaptic cleft and reduces the amount of dopamine available to postsynaptic D2 receptors

Metabolic Adverse Effects

- Includes drug-induced weight gain, diabetes risk, and dyslipidemia
- Thought to be caused by ....
  - Seen more with SGA vs. FGA
- Weight gain
  - Highest with olanzapine and clozapine
  - Monitor weight at baseline and periodically thereafter

Other Adverse Effects

- Hyperprolactinemia
  - Associated with sexual dysfunction, gynecomastia, irregular menstrual periods
  - More common with risperidone and paliperidone
- Orthostasis/syncope
  - Quetiapine
  - Seen when initiating or increasing dose
- Seizures
  - All seizures decrease seizure threshold
- Anticholinergic adverse effects
  - Constipation, blurry vision, dry mouth, urinary retention
**QTc Prolongation**
- All antipsychotics can increase QTc interval
  - Highest risk with thioridazine and ziprasidone
  - Avoid/caution use with other medications that can increase QT prolongation (assess risk vs. benefit)
  - Avoid if history of cardiac arrhythmias, symptomatic bradycardia, hypomagnesemia, hypokalemia, underlying elevated QT interval
  - Use low-risk AP's
  - Monitor EKG regularly

**Other Adverse Effects**
- Increased impulse-control disorders
  - Warning added to aripiprazole labelling in 2016
  - ? Possible with brexiprazole and cariprazine?
- Dizziness
  - Titrate dose of iloperidone

**Clozapine Adverse Effects**
- Drug-induced neutropenia
  - Rare but life-threatening
  - < 3 cases/1000 patient years
  - Typically seen within first 6 months of therapy
  - Severe neutropenia
  - Agranulocytosis
    - Absolute Neutrophil Count (ANC) of < 500/mm^3
    - ANC= Total WBC count X Neutrophil % (Segs % + Bands %)

**Conclusion**
- Patients diagnosed with schizophrenia should be started on a SGA or FGA
- Consider clozapine after trials of 2 antipsychotics from different classes
- Consider long-acting antipsychotic provided patient tolerates PO form to improve adherence
- Assess for improvement in positive, negative, and cognitive symptoms
- Assess and treat adverse effects or consider changing AP as needed
1. Which of the following are symptoms seen in schizophrenia?
   a) Grossly disorganized speech and/or behavior
   b) Delusional thoughts
   c) Lack of emotion
   d) Impaired executive functioning
   e) All of the above

2. Dosage adjustments are necessary with brexipiprazole (Rexulti®) in patients also prescribed strong cytochrome p450 3A4 and 2D6 inhibitors.
   a) True
   b) False

3. Cariprazine (Vraylar®) is considered safe to use in the treatment of psychosis in elderly patients with dementia.
   a) True
   b) False

4. Which of the following statements are true for valbenazine (Ingrezza™)?
   a) FDA approved for the acute treatment of manic or mixed episodes associated with Bipolar I Disorder and the treatment of Schizophrenia in adults following knee/hip replacement
   b) The dose should be doubled when used with strong cytochrome p450 3A4 inhibitors
   c) It works by selectively inhibiting VMAT2 in presynaptic neurons which reversibly reduces dopamine in synaptic cleft and reduces the amount of dopamine available to postsynaptic D2 receptors
   d) The monthly cost is less than $1000/month

5. The most effective treatment for antipsychotic-induced tardive dyskinesia is oral anticholinergics prescribed daily (vs. PRN).
   a) True
   b) False