Antipsychotics

Something Old, Something New, Something Used to Treat the Blues
Objectives

• To provide an overview of the key differences between first and second generation agents
• To an overview the newer second generation antipsychotics
  • Indications
  • Dosage regimens and dosage form
  • Adverse effect profiles
  • Drug Interactions
First Generation Antipsychotics

- Haloperidol, chlorpromazine, fluphenazine, thioridazine, thiothixene, and pimozide
- High affinity dopamine $D_2$ receptor antagonism
- Effective in treating positive symptoms of psychosis
- Negative symptoms, mood symptoms, and cognitive deficits minimally responsive
- Unfavorable adverse effect profile
  - High rates of EPS, tardive dyskinesia
  - Adverse effects due to action at other receptor sites
    - Sedation, dry mouth
    - Weight gain
Second Generation Antipsychotics

• Key distinction from FGA is decreased risk of extrapyramidal side effects.
• This is possibly due to their lower affinity for the dopamine 2, or D2 receptor.
• Work mainly on
  • Dopamine and serotonin receptors in the central nervous system
  • Cholinergic, adrenergic, and histaminergic receptors.
• The degree and selectivity of receptor inhibition varies which results in the differing side effect profiles that are observed.
• SGAs differ from the FGA, as the serotonin 5-HT2 receptor binding can exceed their affinity for dopamine D2 receptors.
Second Generation Antipsychotics

- “Older” SGAs
  - Clozapine
  - Olanzapine
  - Quetiapine
  - Risperidone
- “Newer” SGAs
  - Asenapine (Saphris)
  - Aripiprazole (Abilify)
  - Lurasidone (Latuda)
  - Paliperidone (Invega)
  - Ziprasidone (Zeldox)
Second Generation Antipsychotics

- Clozapine, olanzapine, quetiapine, risperidone
  - Improved efficacy for mood symptoms or stabilization
  - Minimal EPS, but metabolic effects
- Asenapine, Aripiprazole, Lurasidone, Paliperidone, Ziprasidone
  - Partial agonists at D2 or 5-HT receptors
    - Bind to receptor, initiating a partial response without full inhibition
    - Potential for similar efficacy as older second generation antipsychotics with less pronounced metabolic effects and sedation
FGAs versus SGAs

- All FGAs and SGAs have similar efficacy in treating the positive (psychotic) symptoms of schizophrenia and related disorders.
  - Clozapine may be more efficacious
  - Clozapine is has proven efficacy in treatment resistance schizophrenia
- For first-episode psychosis, SGAs may be more effective
  - Negative symptoms, mood, cognition
  - Studies have had mixed results, inconsistent
- Major differences between the FGAs and SGAs (and among individual SGAs)
  - Side effect profiles, safety and tolerability
# Approved Indications

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia</th>
<th>Bipolar Disorder</th>
<th>Major Depressive Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>X</td>
<td>X</td>
<td>X (Adjunctive)</td>
</tr>
<tr>
<td>Asenapine</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Aripiprazole (Abilify)

- Dosage and Indications (adults)
  - Schizophrenia
    - 10 mg to 30 mg daily
  - Bipolar disorder
    - Monotherapy: 15 mg to 30 mg daily
    - Co-therapy: 10 mg to 30 mg daily
  - Adjunctive therapy in MDD
    - 2 mg to 5 mg daily
- Dosage forms: 2, 5, 10, 15, 20 and 30 mg tablets
- Usually given in the morning because it can be activating and cause insomnia
- Changes in dosage should be made no more frequently than every 14 days
  - Uniquely long half-life
Aripiprazole Injection (Abilify - Maintena)

- Once monthly IM injection
- Recommended starting and maintenance dose of 400 mg.
- Dose titration not required.
- Tolerability of aripiprazole should be assessed with oral formulation prior to use.
- After first injection, treatment should be continued with 10 mg to 20 mg oral for 14 consecutive days
- Switching from oral antipsychotics
  - Continue current oral antipsychotic for 14 days following the first dose
- 300mg and 400mg vials that must be reconstituted prior to administration
Aripiprazole – Drug Interactions

- Metabolized via CYP2D6 and CYP3A4 transformations
- Has active metabolite
- 50% dose reduction recommended if concurrently taking potent inhibitor of
  - CYP2D6 (eg, fluoxetine, paroxetine, bupropion)
  - CYP3A4 (eg, clarithromycin)
- Dose increase recommended if concurrently taking potent inducer of CYP (eg, carbamazepine).
- Half-life prolonged in CYP2D6 slow metabolizers.
- Unpredictable effect in combination with other antipsychotics.
Asenapine (Saphris)

- **Dosage and Indications**
  - **Schizophrenia**
    - 5mg to 10mg bid
    - No clear benefit of 10mg dose over 5mg
  - **Bipolar disorder**
    - Monotherapy: 5mg to 10mg bid
    - Co-therapy: 5mg to 10mg bid

- **Dosage forms**
  - 5 and 10 mg sublingual tablet
  - Cannot eat or drink within 10 mins of administration
Asenapine – Drug Interactions

- Hepatically metabolized by CYP1A2 and glucuronidation (UGT1A4)
- Fluvoxamine (CYP1A2 inhibitor) should be coadministered with caution or avoided when possible
- Asenapine weakly inhibits CYP2D6
  - Caution recommended if coadminister with drugs that are both metabolized by CYP2D6 and can inhibit this enzyme
    - E.g. paroxetine, dextromethorphan
- Pharmacodynamic considerations
  - Additive QTc prolongation
  - Alpha-1 antagonism
    - Potentiation of alpha blockers – hypotension, dizziness
Lurasidone (Latuda)

- Dosage and Indications
  - Schizophrenia
    - 40 mg to 80 mg daily
  - Bipolar disorder (depressive episodes)
    - Usual dose of 20 mg-60 mg/day as monotherapy or adjunctive therapy with lithium or valproate

- Dosage forms:
  - 40, 80 and 120 mg tablets

- Should be administered with food
  - At least 350 calories independent of fat content

- Dosage adjustment required for renal impairment
Latuda – Drug Interactions

• Hepatic metabolism includes CYP3A4 transformation and active metabolites
• Coadministration with strong CYP3A4 inhibitors (eg, oral ketoconazole) or inducers (eg, rifampin) is contraindicated
• Maximum recommended dose with moderate CYP3A4 inhibitors (eg, diltiazem) is 80 mg per day.
• Grapefruit interactions
Paliperidone (Invega)

- Schizophrenia
  - Extended-release tablet: 3 to 12 mg once daily
  - Must be swallowed whole and must not be chewed, divided, or crushed.
- Dosage forms
  - 3, 6, and 9mg extended release tablets
  - Food increases absorption; however, clinical trial dosing was carried out without regards to meals
    - Taken in the morning, without regard to food
    - Change in absorption with food not considered clinically meaningful
Paliperidone (Invega Sustena)

- Schizophrenia
  - Prolonged-release injection: 150 mg on day 1, 100 mg on day 8, then 25–150 mg once monthly
    - usual maintenance dose is 75 mg monthly
- Dosage forms
  - 50 mg, 75 mg, 100 mg, and 150 mg prolonged release injection (Invega Sustenna)
Paliperidone – Drug interactions

- Minimal hepatic metabolism
- Paliperidone is excreted primarily unchanged in urine necessitating dose reduction in renal insufficiency.

Pharmacodynamic considerations
  - Additive QTc prolongation
  - Alpha-1 antagonism
    - Potentiation of alpha blockers
Ziprasidone (Zeldox)

- Schizophrenia
  - 20 mg twice daily to 100 mg
- Bipolar disorder
  - 40 mg twice daily to 80 mg
- Dosage forms
  - 20, 40, 60, and 80 mg capsules
- Should be administered with a meal
  - Absorption increased up to 2-fold
Ziprasidone – Drug Interactions

• Hepatic metabolism includes CYP3A4 and other transformations
  • Dosage adjustments may be required in presence of inducers and inhibitors of CYP3A4, but clinical significance of such drug interactions remains unknown.

• Pharmacodynamic considerations
  • Additive QTc prolongation
  • Alpha-1 antagonism
    • Potentiation of alpha blockers
Comparative Adverse Effects
Receptor Binding and Adverse Effects

<table>
<thead>
<tr>
<th>NEUROTRANSMITTER AND RECEPTORS</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine—D1, D2, D3, D4</td>
<td>Dyskinesia, extrapyramidal symptoms, hyperprolactinemia</td>
</tr>
<tr>
<td>Serotonin—5HT1A, 5HT2A, 5HT2C</td>
<td>Sedation, weight gain, sexual dysfunction</td>
</tr>
<tr>
<td>Histamine—H1</td>
<td>Somnolence, sedation, weight gain</td>
</tr>
<tr>
<td>Alpha—alpha1, alpha2</td>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Dry mouth, tachycardia, urinary retention</td>
</tr>
</tbody>
</table>
## Selected Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Weight gain/DM</th>
<th>↑ Chol</th>
<th>EPS/TD</th>
<th>Prolactin elevation</th>
<th>Sedation</th>
<th>Anti-chol SE</th>
<th>Ortho-static hypotension</th>
<th>QTc prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>−</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>−</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>−</td>
<td>−</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>
Metabolic Monitoring for Patients Taking Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Base</th>
<th>At 4 weeks</th>
<th>At 8 weeks</th>
<th>At 12 weeks</th>
<th>Every 3 months</th>
<th>Annual</th>
<th>Every 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical history⁵</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (BMI)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Waist circumference</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

⁵From ADA–APA (32)

⁶Personal and family history of obesity, diabetes, hypertension, and cardiovascular disease
Summary

• A number of newer atypical antipsychotics have entered the market over the past few years
• Provide alternatives to those patients not adequately managed on second generation atypicals or who are intolerant
• Within the newer agents there are differences in
  • Dosage form
  • Approved indications
  • QTc interval prolongation
  • Use in renal impairment
• Selection amongst agents may be influenced by a number of factors