ATYPICAL ANTIPSYCHOTICS FOR THE NON-PsYCHIATRIST

THE 47TH ANNUAL WINTER REFRESHER COURSE FOR FAMILY MEDICINE

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MILWAUKEE, WI

LEARNING OBJECTIVES

Upon completion of this session, participants will be able to:

- Identify key properties of the atypical antipsychotics - including safety and side effect profiles
- Review FDA-approved and off-label uses of atypical antipsychotics
- Illustrate the use of atypical antipsychotics for various mental health disorders

A CASE...

- A 54 year old male with a history of renal insufficiency, CAD, HTN, HLD, obesity and depression presents for a follow-up visit after a hospitalization for chest pain
- He verbalizes problems sleeping and a poor appetite
- It is only as he is ready to leave that his wife states that she is worried about him being depressed
- Upon further question he endorses symptoms of depression, anhedonia, hopelessness, and decreased energy along with poor concentration
- He is currently on a therapeutic dose of a SSRI for >3 months. Historically he had been on venlafaxine, bupropion, and mirtazapine with either intolerance or poor response
  - Now what???
  - The local psychiatrists are booking out >2 months

ANOTHER CASE...

- 82 year-old woman with a history of probable Alzheimer’s disease, CAD, and DM has been admitted from a nursing home for worsening confusion and behavioral problems.
  - This nursing personnel at the NH report that the symptoms have become progressively worse since she began having problems sleeping 3 days ago.
  - Attempts to examine the patient upon arrival to the floor are complicated by her attempts, as she eloquently states, to “Knock you on your ass!”
  - Review of the medical records from the ED report similar behavior and reports of “seeing things.”
  - She was given lorazepam prior to the CT of her head. She slept through the CT, which only showed atrophy and white matter disease, but is now quite awake, delirious, and potentially dangerous.
  - What are you going to do (other than call psychiatry consults)!

ANOTHER CASE...
ANTIPSYCHOTIC MEDICATIONS
A FAMILY HISTORY

Typical or First Generation Antipsychotics
- What makes an antipsychotic typical?
  - Dopamine antagonism
  - Risk of extrapyramidal symptoms (EPS)
- Different classifications
  - Low potency (chlorpromazine)
  - Medium potency (loxapine)
  - High potency (haloperidol)

Atypical or Second Generation Antipsychotics (SGAs)
- What makes an antipsychotic atypical?
  - Dopamine (D2) and serotonergic (5HT2) antagonism
  - Lower risk of EPS
  - Risk of metabolic side effects
  - There is no good data to support the theory that SGA are more effective in treating the negative or cognitive symptoms of schizophrenia

ANTIPSYCHOTIC MEDICATIONS
PHARMACOTHERAPY

All are dopamine antagonists
- Mesolimbic pathway
  - Responsible for antipsychotic effects
- Nigrostriatal pathway
  - Responsible for the EPS
- Tuberoinfundibular pathway
  - Responsible for hyperprolactinemia
- Other neurotransmitters sometimes involved
  - Serotonin
  - Histamine
  - Acetylcholine

ANTIPSYCHOTIC MEDICATIONS
PHARMACODYNAMIC CONCERNS

Dopamine antagonism
- Extrapyramidal side effects (EPS)
- Tardive dyskinesia
- Neuroleptic malignant syndrome

Histamine-1 antagonism
- Sedation
- Weight gain

α-1 antagonism
- Pruritus
- Urinary retention and constipation
- Cognitive impairment

Muscarinic antagonism
- Dry mouth
- Blurred vision
- Urinary retention and constipation

Inhibition of the HERG Potassium Channel
- QT prolongation
- Torsades de Pointe
- Inhibition of the HERG Potassium Channel
**Antipsychotic Medications**

**FDA Approval Timeline**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year of Original FDA Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>1989</td>
</tr>
<tr>
<td>Risperidone</td>
<td>1993</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>1996</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1997</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>2000</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>2001</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>2002</td>
</tr>
<tr>
<td>Risperidone (Fapril)</td>
<td>2003</td>
</tr>
<tr>
<td>Asenapine</td>
<td>2009</td>
</tr>
<tr>
<td>Paliperidone (Invega)</td>
<td>2009</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>2009</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>2010</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>2010</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>2015</td>
</tr>
</tbody>
</table>

**Derivation from FDA information at [http://www.accessdata.fda.gov](http://www.accessdata.fda.gov)**

**FDA-Approved Indications of the SGAs (Schizophrenia and Mania)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Treatment-resistant schizophrenia, reducing suicidal behavior in schizophrenia or schizoaffective disorder</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Schizophrenia and Bipolar I disorder</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Schizophrenia and Bipolar I disorder</td>
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<tr>
<td>Paliperidone</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Schizophrenia</td>
</tr>
</tbody>
</table>

**FDA-Approved Indications of the SGAs (Other Than for Schizophrenia and Mania)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Use</th>
<th>Date of Approved Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>Augmentation for MDD, Autism spectrum disorders</td>
<td></td>
</tr>
<tr>
<td>Olanzapine/Quetiapine</td>
<td>Bipolar depression</td>
<td></td>
</tr>
<tr>
<td>Quetiapine/Quetiapine ER</td>
<td>Bipolar depression</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Autism spectrum disorders</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>Bipolar depression</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Augmentation for MDD</td>
<td></td>
</tr>
</tbody>
</table>

**FDA-Approved Indications of the SGAs (For Children and/or Adolescents)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Approved Use</th>
<th>Ages (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Schizophrenia, Bipolar I disorder, Autism spectrum disorder</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Schizophrenia, Bipolar I disorder, Autism spectrum disorder</td>
<td></td>
</tr>
<tr>
<td>Quetiapine/Quetiapine</td>
<td>Bipolar I disorder</td>
<td></td>
</tr>
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<td>Lurasidone</td>
<td>Bipolar I disorder</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Augmentation for MDD</td>
<td></td>
</tr>
</tbody>
</table>

**A Few of the Reported Off-Label Uses of SGAs Atypical Antipsychotics**

<table>
<thead>
<tr>
<th>Reported Off-Label Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major depression disorder (non-treatment resistant, non-augmentation)</td>
</tr>
<tr>
<td>Obsessive-compulsive disorder</td>
</tr>
<tr>
<td>Insomnia</td>
</tr>
<tr>
<td>Seizure disorders</td>
</tr>
<tr>
<td>Generalized anxiety disorders</td>
</tr>
<tr>
<td>Personality disorders (borderline and schizotypal)</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
</tr>
<tr>
<td>Substance use disorders</td>
</tr>
<tr>
<td>Tourette's syndrome</td>
</tr>
</tbody>
</table>

**Schizophrenia**

- Atypical antipsychotics approved for the treatment of schizophrenia
  - All of ’em in adults
  - In children and adolescents
    - Risperidone, olanzapine, quetiapine, aripiprazole, and paliperidone
- How to choose?
  - Past response
  - Risk/Benefit ratio
  - Cost and/or access
  - Patient preference
**SCHIZOPHRENIA**

- Atypical antipsychotics approved for the treatment of schizophrenia
  - All of them in adults
  - Risperidone, olanzapine, quetiapine, aripiprazole, and paliperidone

How to choose?
- Choice is based on...
  - Past response
  - Risk:Benefit ratio
  - Cost and/or access
  - Patient preference

Clozapine is different!
- Treatment-resistant schizophrenia
- Reducing suicidal behavior in schizophrenia or schizoaffective

**BIPOLAR I DISORDER**

- Atypical antipsychotics approved for the treatment of bipolar I – manic or mixed phase
  - In adults → Risperidone, olanzapine, quetiapine, aripiprazole, and brexpiprazole
  - In children and adolescents → Risperidone, olanzapine, quetiapine, and aripiprazole

Potential benefits of atypical antipsychotics in the treatment of mania or mixed episodes of bipolar
- No need for monitoring medication blood levels
- Quicker titration and often faster efficacy
- Easier to use in patients with renal or hepatic dysfunction
- Safer in overdose
- May be used in combination with a more typical mood stabilizer

**MAJOR DEPRESSIVE DISORDER**

- Atypical antipsychotics approved for augmentation of antidepressant treatment and treatment-resistant depression
  - In adults → Aripiprazole, olanzapine/fluoxetine, quetiapine ER, and brexpiprazole

Potential benefits of atypical antipsychotics in the treatment of refractory depression
- A unique mechanism of action
- Potential disadvantages of atypical antipsychotics
  - Other methods carry less risk adverse events associated with atypical antipsychotics
  - Direct to consumer advertising

**OFF-LABEL USE**

- Behavioral symptoms of dementia
  - When studies are grouped (18 studies, >4000 patients) atypical antipsychotics improve behavioral symptoms of dementia (total, psychosis, agitation)
  - Effect sizes are small (global impression, psychosis, agitation)
  - When looked at individually, some atypical antipsychotics improve scores significantly compared to placebo
    - Risperidone improves scores on both agitation and psychosis subscales
    - Olanzapine improves scores on only agitation subscales
    - Aripiprazole improves scores on only agitation subscales
  - Strength of Evidence **High**

- Only one of the problems...
  - Antipsychotics (over a 10-12-week course of treatment) increase the risk of death in elderly patients with dementia.
  - The death of 1 in 100 patients can be attributed to the antipsychotic drug.
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OFF-LABEL USE INSOMNIA

- No meta-analyses or systematic reviews on the use of SGAs for insomnia treatment
- Quetiapine (1 study, 13 patients)
- Sleep outcomes were not statistically different from placebo
- The evidence for efficacy of atypical antipsychotics is insufficient to permit conclusions


ANTIPSYCHOTICS ADVERSE EFFECTS OF RECEPTOR ANTAGONISM

- Extrapyramidal Side Effects (EPS)
  - Dystonia
  - Involuntary muscle contraction
  - Akathisia
  - Sensation of motor restlessness
  - Parkinsonian symptoms
  - Rigidity, mental bradykinesia
- Tardive dyskinesia
  - Late-developing involuntary choreiform movement disorder
  - http://www.youtube.com/watch?v=NIKSBuWVA

ANTIPSYCHOTICS EXTRAPYRAMIDAL SIDE-EFFECTS


ANTIPSYCHOTICS SEDATION

- Forest Plots for Effect Sizes of Antipsychotic Drugs Compared with Placebo

ANTIPSYCHOTICS QTc PROLONGATION

- Forest Plots for Effect Sizes of Antipsychotic Drugs Compared with Placebo

### CARDIOVASCULAR DISEASE (CVD) RISK FACTORS

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Schizophrenia</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>45-55% (1.5-2)</td>
<td>21-49% (1-2)</td>
</tr>
<tr>
<td>Smoking</td>
<td>10-80% (2-3)</td>
<td>54-68% (2-3)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>10-15% (2)</td>
<td>8-17% (1.5-2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>19-38% (2-3)</td>
<td>15-41% (2-3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
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<td>33-38% (2-3)</td>
</tr>
<tr>
<td>Metabolic Syndrome</td>
<td>37-43% (2-3)</td>
<td>30-49% (1.5-2)</td>
</tr>
</tbody>
</table>

#### Framingham 10 year CHD Risk Score (CATIE)

Forest Plots for Effect Sizes of Antipsychotic Drugs Compared with Placebo


### QT PROLONGATION

**RISK FACTORS**
- Genetic factors
- LQTS
- Age >65
- Female gender
- Electrolyte abnormalities
- Bradycardia
- Pharmacologic
- Circadian rhythm
- CV disease

**Prolonged QT Interval**


http://www.accessdata.fda.gov/scripts/cder/drugsatfda

### WEIGHT GAIN

#### Forest Plots

**Weight Gain (SARI)**


**Forest Plots for Effect Sizes of Antipsychotic Drugs Compared with Placebo**

### CARDIOVASCULAR DISEASE RISK

#### Estimated prevalence and relative risk of modifiable CVD risk factors

- Obesity
- Smoking
- Diabetes
- Hypertension
- Dyslipidemia
- Metabolic Syndrome

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Schizophrenia</th>
<th>Bipolar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
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</table>

#### Framingham 10 year CHD Risk Score (CATIE)

**ANTIPSYCHOTIC ADVERSE EFFECTS**

**SUMMARY TABLE**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Weight Gain</th>
<th>EPS</th>
<th>QTc Prolongation</th>
<th>Prolactin Elevation</th>
<th>Sedation</th>
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</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+++</td>
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<td>+</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>++</td>
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</tr>
<tr>
<td>Ziprasidone</td>
<td>++</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>+++</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amsapine</td>
<td>+++</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>+</td>
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</tr>
</tbody>
</table>


Adapted from - *Treatment Guidelines from The Medical Letter* - June 1, 2013 (Issue 130)

**ANTIPSYCHOTICS**

**PHARMACOKINETIC CONCERNS**

**Substrate**

Medications which are metabolized by the isoenzyme

**Inhibitors**

- Inhibitors inhibit the metabolism of substrates
  - → level of substrate

**Inducers**

- Inducers induce the metabolism of substrates
  - → level of substrate

**2D6 Substrate**

- Risperidone
- Olanzapine
- Iloperidone
- Brexpiprazole

**2D6 Inhibitors**

- Fluoxetine
- Paroxetine
- Cimetidine

**2D6 Inducers**

- Carbamazepine

**3A4 Substrate**

- Clozapine
- Quetiapine
- Iloperidone
- Lurasidone
- Aripiprazole
- Brexpiprazole
- Cariprazine

**3A4 Inhibitors**

- Protease inhibitors
- Antibiotics (ciprofloxacin, erythromycin)
- Antifungals (fluconazole, ketoconazole)

**3A4 Inducers**

- St. John’s wort
- Modafinil

**1A2 Substrate**

- Clozapine
- Olanzapine
- Amsapine

**1A2 Inhibitors**

- Antibiotics (ciprofloxacin)
- Fluoxetine

**1A2 Inducers**

- Cigarette smoking
- Carbamazepine
- Phenytoin

**Renal Insufficiency**

- Paliperidone
- Lurasidone
- Brexpiprazole

**Hepatic Insufficiency**

- Iloperidone
- Amsapine
- Lurasidone
- Brexpiprazole

Require dose adjustment

**ANTIPSYCHOTICS**

**PHARMACOKINETIC CONCERNS**
CASE ONE

Vincent van Gogh 1890 painting At Eternity's Gate

Current visit
- PHQ-9 score = 21
- The SSRI is maintained at current dose
- Aripiprazole 2mg QAM is initiated

Follow-up phone call at 1 week
- He has been adherent with the medication
- No adverse events experienced

Follow-up appointment at 4 weeks
- PHQ-9 score has decreased to 18
- No adverse effects noted
- SSRI dose is maintained
- Aripiprazole dose increased to 5mg qAM

Follow-up appointment at 8 weeks
- PHQ-9 score has decreased to 10
- No adverse effects reported
- SSRI and aripiprazole dose maintained

SUMMARY

- Little data to suggest that SGA are more effective in treating the negative or cognitive symptoms of schizophrenia
- SGA are not built the same
  - Impact different neurotransmitters (pharmacodynamic characteristics)
  - Different pharmacokinetic properties
  - Different indications outside of schizophrenia
- Clozapine is different!

BIBLIOGRAPHY

- Treatment Guidelines from The Medical Letter • June 1, 2013 (Issue 130).
- The Medical Letter on Drugs and Therapeutics • February 21, 2011 (Issue 1358).
- http://www.accessdata.fda.gov