Use of Antipsychotics in Treating Schizophrenia and other Psychotic Disorders

Nurse Practitioners of Idaho
Neurodegenerative process
Multiple theories of causation
Current treatment is palliative
Significant social and occupational disruption
Life expectancy is 20% shorter
Suicide will claim 10%
Medical diseases under-recognized & undertreated
Over-represented in homeless, jail and prison populations
and other Psychotic Disorders
(proposed DSM-V and other classification)

- Schizophrenia (DSM-IV)
  - Delusions
  - Hallucinations
  - Disorganized speech
  - Disorganized or catatonic behavior
  - Negative symptoms
- Marked dysfunction
- Duration 6 or more months
- Excludes Schizoaffective and Mood Disorder
- Not due to SA
Schizophrenia Subtypes

- Paranoid
- Disorganized
- Catatonic
- Undifferentiated
- Residual
First Rank Symptoms

- Delusions of being controlled by an external force
- Belief that thoughts are being inserted or withdrawn from one’s conscious mind
- Belief that one’s thoughts are being broadcast to other people
- Hearing voices (AH) commenting on one’s thoughts or actions or hearing voices communicating with other voices
Positive Symptoms

- Hallucinations
  - AH most common
  - VH (often associated with substance abuse)
  - Tactile
  - Olfactory
  - Gustatory

- Delusions
  - Often bizarre, maybe paranoid, grandiose
  - Ego syntonic or dystonic
- Alogia: few words, little to say
- Blunted Affect: reduced perception, experience and expression
- Asociality: little or no social drive
- Anhedonia: loss of ability to experience pleasure
- Avolition: loss of desire, motivation, persistence
Impaired Cognition

- Working Memory
- Verbal Learning
- Visual Learning
- Processing Speed
- Attention/Vigilance
- Reasoning and Problem Solving ("Executive Functions")
- Social Cognition
Non pharmacological treatments

Are atypical antipsychotics really any better than typical antipsychotics?

What do we need to know about antipsychotics?

Off label use

Substance abuse Impact

How to get started?

When to ask for a consult or referral?
Non Pharmacological

- CBT
- Skills Training (social interactions, independent living, related psychosocial abilities)
- Family Interventions (NAMI, etc.)
- Supported Employment
- Assertive Community Treatment
- Wellness (SA, smoking, weight)
How do they work?

- **The Dopamine Theory: Dopamine Pathways:**
  - Mesolimbic hyperactivity (euphoria, hallucinations, delusions)
  - Mesocortical hypoactivity (cognitive, affective and negative symptoms)
  - Nigrostriatal (Extrapyramidal System)
  - Tuberofundibular (Prolactin secretion)
  - “Fifth Dopamine Pathway”
What makes them atypical?

- Rapid dissociation from binding sites
- Partial agonism of DA receptors (Abilify)
- Serotonin 5HT2A Receptor Antagonism
  (increase DA release to “tune” DA system)
- Full or partial agonism of 5HT1A receptors
- Many differences in receptor binding among the atypicals
Are they any better?

- CATIE, PORT, Cochrane Review:
  - No evidence that any antipsychotic has an advantage over any other for acute schizophrenia, except for Clozapine (PORT)
  - Young people with schizophrenia are particularly sensitive to metabolic SE (PORT)
  - Newer antipsychotics have similar efficacy and SE when compared with older agents (PORT)
Are they any better?

- No difference in mortality rates (PORT) between Typicals & Atypicalss
- No better at cognitive enhancement (CATIE)
- Moderate doses of mid-potency typical antipsychotics (Trilafon @ 20mg/day) are as effective with relatively few side effects

-- PORT, CATIE, Cochrane Review
What Do We Need to Know?

- Consider effectiveness in treating symptoms with drug safety/risk profile for each drug and individual patient.
- Effectiveness and tolerability are equally important to long term treatment.
- Long-term treatment adherence improves outcomes.
- Therapeutic Alliance is critical.
Hierarchy

- Symptom Management
- Physical Health
- Reduce Hospitalization
- Reduce Criminal Activity
- Reduce Substance Abuse
- Stable Housing
Hierarchy

- Employment
- Community Involvement
- Treatment Alliance
- Cognitive Ability
- Empowerment
- Recovery

Andrew J. Cutler, M.D.
NEI Conference 2012
## Typical (FGAs)

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>GENERIC NAME</th>
</tr>
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<tbody>
<tr>
<td>Haldol</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Loxitane</td>
<td>Loxapine</td>
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<tr>
<td>Orap</td>
<td>Pimozide</td>
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<tr>
<td>Thorazine</td>
<td>Chlorpromazine</td>
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<td>Prolixin</td>
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<td>Trilafon</td>
<td>Perphenazine</td>
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<tr>
<td>Stelazine</td>
<td>Trifluoperazine</td>
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<tr>
<td>Mellaril</td>
<td>Thioridazine</td>
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<tr>
<td>Navane</td>
<td>Thiothixene</td>
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Clinical Indications

- Schizophrenia - Acute and maintenance
- Acute Mania of Bipolar Disorder
- Acute Psychosis
- MDD with psychotic features
High Potency D2 blockers:
- Haldol, Navane, and Prolixin (oral)
- Haldol Lactate (Haldol, Ativan, Benadryl are all injectable, )
- Haldol Deconate and Prolixin Deconate (LAI); can improve absorption, tolerability, and adherence

“Low Potency” D2 blockers”
- Mellaril and Thorazine: Mellaril is less sedating with least EPS, but more ECG effects. Thorazine: more sedating, good for combative people, less EPS risk than Haldol but can cause hypotension and convulsions

“Mid Potency”: D2 blockers: Loxapine, Trilafon, and Stelazine: less sedating but more EPS risk
Typical Antipsychotics (FGAs):

- Anticholinergic
- Cardiovascular
- CNS (check ferritin levels)
  - Akathisia
  - Dystonia (prevent with ACA)
  - Parkinsonism
  - NMS
  - Rabbit Syndrome
- Tardive Dyskinesia
Typical Antipsychotics (FGAs):

- Endocrine effects
- EENT effects
- GI effects
- Hematologic effects
- Renal effects
- Sexual effects
- Skin, allergies, and temperature
- Drug and food allergies
<table>
<thead>
<tr>
<th>TRADE NAME</th>
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<tbody>
<tr>
<td>Clozapine</td>
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<td>Risperidone</td>
<td>Risperdal</td>
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<td>Olanzapine</td>
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<td>Ziprasidone</td>
<td>Geodon</td>
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<td>Aripiprazole</td>
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<td>Invega</td>
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<td>Fanapt</td>
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<tr>
<td>Asenapine</td>
<td>Saphris</td>
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<tr>
<td>Lurasidone</td>
<td>Latuda</td>
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</table>
FDA-Approved for SGAs

**Bipolar Disorder**
- Risperdal
- Zyprexa
- Seroquel
- Geodon
- Abilify
- Saphris

**Schizophrenia**
- Risperdal
- Clozaril
- Zyprexa
- Seroquel
- Geodon
- Abilify
- Invega
- Fanapt
- Saphris
- Lurasidone
More...

- Lower cost due to generic formulations:
  - Risperdal, Zyprexa, Seroquel (not XR)

- Abilify is the only DPA: exceptionally long half-life (75 and 94 hours); discontinuation kinesia delayed

- Zyprexa and Geodon: available in short-acting injectable

- Risperdal, Invega, Zyprexa and (coming-soon) Abilify: in LAI
More...

- **Clozaril**: 2\textsuperscript{nd} or 3\textsuperscript{rd} line in treating Schizophrenia; serious potential SE/requisite monitoring; may be most effective

- **Invega**: only atypical that does not require hepatic metabolism

- No evidence supporting concurrent use of 2 atypicals except in a cross-tapering situation

- Some support for concurrent use of an SGA and FGA in difficult to treat patients
Side Effects

- Hyperglycemia, glycosuria, DM Type II,
- Metabolic Syndrome
- Dyslipidemia
- Weight gain
- EPS including TD
- Sedation
- Prolactin elevation
Hematologic Effects:
- Agranulocytosis, eosinophilia, leukopenia
- Seizures
- Hypothyroidism
- Anticholinergic side effects
- Cardiovascular side effects
- EENT Effects
- GI Effects
- Renal effects
- Sexual side effects
- Skin, Allergies, and Temperature
- Drug and Food Interactions
Current (Worst)

- Polypharmacy
- Frequent switching
- Rare use of Clozapine
- Minimal individual and family support

Proposed (Best)

- Monotherapy SGAs and some FGAs with minimal adjuncts
- Use of Clozapine and LAIs
- Psychosocial, individual/family education, support Rx and CBT
Off Label Use

- AHRQ Review of Strength of Evidence for Efficacy for Off-Label Indications, July 2012
- Strength of Evidence Scale
  - **High Confidence** that evidence reflects true effect; further research unlikely to effect estimate of effect
  - **Moderate Confidence** that evidence reflects true effect; further research may effect estimate of effect
  - **Low Confidence** that evidence reflects true effect; further research likely to change confidence in estimate of effect
Conditions Reviewed

- Dementia
- MDD Augmentation
- MDD Monotherapy
- OCD Augmentation
- PTSD Adjunctive
- GAD
- Borderline Personality Disorder
- Anorexia Nervosa (body weight)
- Substance Abuse (reduction in use)
Agitation, Psychosis and Overall Condition

- Improves Symptoms:
  - Risperdal (High)
  - Abilify (Low to Moderate)
  - Seroquel & Zyprexa (Low)
Improves Symptoms:

- Risperdal (Moderate)
  - Remission NNT = 8
  - Response NNT = 7

Abilify, Zyprexa (with Fluoxetine), and Seroquel have approved indications
Improves Symptoms

- Zyprexa (Moderate)
- Seroquel (Moderate)
  - Remission NNT = 13
  - Response NNT = 6

**NO** trials for Abilify or Risperdal
Improves Symptoms

- Risperdal (Moderate): NNT=5
- Zyprexa (Low)
  (Head-to-head comparisons of Zyprexa and Risperdal are similar in effect)

**NO** trials for Abilify or Seroquel
Improves Symptoms of PTSD

- Risperdal for combat-related PTSD (Moderate)
  (Insufficient evidence for treatment of abused women; insufficient evidence for analysis for Zyprexa and Seroquel)

Improves Symptoms of GAD

- Seroquel (Moderate) NNT= 8
- Improves Symptoms in Borderline Personality Disorder
  - Abilify and Seroquel (Low)

- Does **NOT** Improve Symptoms for Anorexia Nervosa (body weight)
  - Zyprexa (Moderate)
  - Seroquel (Low)
Reduction in Use

Does **NOT** Improve Symptoms

- Alcohol
- Abilify (Moderate), Zyprexa (Low), Seroquel (Low)

- Methamphetamine
  - Abilify (Low)

- Cocaine
  - Zyprexa (Low), Risperdal (Low)

- Methadone
  - Risperdal (Low)
Adverse Effects

- In the Elderly:
  - Increased mortality: NNH 100 in 10-12 week trials; (NNH not available for Typicals used in trial)
  - Risperdal (NNH=34) associated with higher risk of CVA
  - Risperdal (NNH=53) and Zyprexa (NNH=48) associated with higher risk of cardiovascular events

Atypicals (AHRQ)
... in the Elderly

- EPS are common with Risperdal ($\text{NNH}=20$) and Zyprexa ($\text{NNH}=10$)

- Atypical antipsychotics associated with sedative effects ($\text{NNH}=8-16$) and fatigue ($\text{NNH}=18-21$)
... in the Elderly

- Atypical antipsychotics increase risk of urinary adverse effects (infections, incontinence);
- Degree of risk unable to be calculated
Adults 18-64 years

- Atypical antipsychotics are associated with weight gain (NNH=16-35); Zyprexa is associated with greater risk (NNH=3) than typicals or other atypicals

- Some atypicals carry a greater risk of endocrine and metabolic abnormalities (Zyprexa carries highest risk)
Adults 18-64

- Increased EPS risks for Atypicals:
  - Abilify (NNH=11 for EPS; NNH=7 for akathisia)
  - Seroquel (NNH=36)
  - Geodon (NNH-24)

- Increased risk of sedation and fatigue for Atypicals:
  - Abilify, Zyprexa, Seroquel, Risperdal, and Geodon NNH=3-11 for sedation, highest for Seroquel; and NNH=14-19 for fatigue
“Chicken or Egg”

- Marijuana, Methamphetamine, Cocaine, “Bath Salts”, “Spice” all can cause psychotic symptoms in general population, acute and chronic

- All can increase risk of developing a psychotic disorder, with continued use

- All are thought to worsen the course of established psychotic disorders, with continued use
For those with established psychotic disorder

- More relapses, hospitalizations
- Poorer psychosocial functioning
- Worsened course of illness
- More likely to get arrested
Why some patients with Schizophrenia use

- Self-medicating symptoms (positive and negative)
- Social milieu
- “rewards are immediate...adverse (effects) delayed”

Stahl’s Essential Psychopharmacology
Part 1: Psychosis and Related Cases
FGAs do not equal SGAs and...
Neither FGAs nor SGAs are homogeneous groups
Individualize treatment
Share decision making with patient and family
  - potential drugs, evidence for efficacy and side effect profile
  - consider existing health problems, required monitoring, lifestyle, substance use, any financial issues that could affect adherence
Trade-offs between benefits and risks:
  - What symptoms are most bothersome to your patient?
  - Time with medication adherence and no SA improve course of illness
Consultation or referral considerations:

- Before initiating antipsychotic therapy
- Treatment resistant psychosis
- When prescribing off-label
- Polypharmacy
Thank YOU!