Clinical Considerations for the Use of Atypical Antipsychotics in the Treatment of Depression

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Clinical Considerations for the Use of Atypical Antipsychotics for Treatment of Depression: Differentiating between Depression and Schizophrenia

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Learning Objectives

- Describe and discuss the background and presentation of schizophrenia and depression
- Compare and contrast the clinical presentation of schizophrenia with depression
- Evaluate patient case scenarios and analyze symptomatology
Active Learning
“Pop Quiz”

SCHIZOPHRENIA
- What are some risk factors?
- What/which neurotransmitter(s) is/are associated with pathophysiology?
- List hallmark symptoms

DEPRESSION
- What are some risk factors?
- What/which neurotransmitter(s) is/are associated with pathophysiology?
- List hallmark symptoms
Agenda

Schizophrenia Review
- Epidemiology
- Pathophysiology
- Clinical Presentation
- Patient Case

Depression Review
- Epidemiology
- Pathophysiology
- Clinical Presentation
- Patient Case

Summary
- Schizophrenia/Depression
- Patient Case
Schizophrenia Review: Epidemiology

- U.S. lifetime prevalence of schizophrenia ranges from 0.6% to 1.9% (average of 1%)
- Onset in late adolescence or early adulthood
- Prevalence equal in both genders, but onset earlier in males (earlier 20s) versus females (20-30s)
Disease accounts for large cause of disability in U.S.
  - 10% of permanently disabled population in U.S.

Estimated direct and indirect costs accounted for $62.7 billion annually (2002)
  - 2.5% of total health care costs in U.S. (annual)

70% schizophrenic patients receive Rx through Medicaid

Genetic factors

- Strong genetic predisposition
  - 10-fold increase in risk if parent schizophrenic
  - 9-fold increase in risk if sibling schizophrenic
  - Risk also increased if first degree relative with bipolar disorder
- 1000+ studies have yet to yield a consistent genetic pattern or association
- Accepted that no single genetic determinant of schizophrenia risk exists, but that multiple genetic factors contribute

Lichtenstein P. Lancet. 2009 Jan 17;373(9659):234-9
Schizophrenia Review: Pathophysiology

- Environmental factors
  - A variety of factors have been identified with plausible connections to neurodevelopment
    - Advanced paternal age
    - 1st and 2nd trimester alterations in fetal development
      - Viral infection
      - Starvation
      - Toxin exposure
    - Perinatal anoxia, trauma or toxin exposure
    - Adolescent exposure to psychoactive drugs
Schizophrenia Review: Pathophysiology

- Neurotransmitters
  - Dopamine hypothesis
    - Hyperactivity of dopamine receptors in midbrain and anterior cortex causes psychotic symptoms
    - Decreased prefrontal activity suspected as etiology of negative and cognitive symptoms
    - Hypothesis supported by clinical efficacy of antipsychotic medications with strong affinity for D₂ dopamine receptor
Schizophrenia Review: Pathophysiology

Source: http://commons.wikimedia.org/wiki/File:Dopamine_Pathways.png
Schizophrenia Review: Pathophysiology

- **Neurotransmitters**
  - **Glutamate**
    - Major excitatory neurotransmitter
    - N-methyl-D-aspartate (NMDA) receptor inhibition exacerbates cognitive impairment and psychosis in schizophrenic patients
  - **Serotonin**
    - $5\text{-HT}_{2A}$-receptor stimulation creates hallucinatory effects (e.g., lysergic acid diethylamide [LSD])
    - $5\text{-HT}_{2C}$-receptor stimulation modulates release of dopamine in cortex and limbic region
Schizophrenia Review: Clinical Presentation

- Characteristic symptoms:
  - Two or more of the following, each persisting for a significant portion of at least a 1-month period:
    - Delusions
    - Hallucinations
    - Disorganized speech
    - Grossly disorganized or catatonic behavior
    - Negative symptoms

- Social/occupational dysfunction:
  - For a significant portion of the time since onset of the disorder, one or more major areas of functioning such as work, interpersonal relations, or self-care are significantly below baseline

- Duration:
  - Continuous signs of the disorder for at least 6 months.
  - This 6 months may include prodromal or residual symptoms.
  - Schizoaffective or mood disorder has been excluded

American Psychiatric Association. DSM-IV-TR.
Schizophrenia Review: Clinical Presentation

- Positive symptoms
  - Perceptual and thought disturbances associated with psychosis:
    - Suspiciousness
    - Paranoia
    - Delusions (65%)
    - Hallucinations (50%)
    - Disorganized thought processes

- Negative symptoms
  - Deficit in psychosocial functioning, emotional expression and interpersonal interactions
    - Blunted affect
    - Decreased interest/involvement in social and occupational activities
    - Decreased grooming and hygiene.
Schizophrenia Review: Clinical Presentation

- **Cognitive symptoms**
  - All cognitive domains are affected by schizophrenia
    - Attention
    - Language
    - Memory
    - Executive function
  - Deficits may be present from birth, followed by additional decline after the onset of illness

- **Affective symptoms**
  - Problems with mood and affect are common
    - Dysphoria
    - Demoralization
    - Depression
Patient Case #1

**CC:** “The CIA has implanted a device in my skull and they keep talking to me, giving me orders non-stop...please help me cut it out of me!”

**HPI:**
- DF is a 28 year Caucasian male presenting to the ED alert and oriented but stating that he is being recruited to carry out top secret missions for the CIA.
- DF appears unkempt and unwashed, and is rambling as he describes the orders from the CIA agents, jumping from one subject to another.
- His roommate states that DF is a PhD student but has not been showing up at the University and has been acting “wacko” for the past half of a year (since he moved in).

**PMH:**
- The patient denies any prior hospitalization for mental problems and denies any illicit substance use.
Patient Case #1: Clinical Presentation

- **Characteristic symptoms:**
  - Two or more of the following, each persisting for a significant portion of at least a 1-month period:
    - Delusions
    - Hallucinations
    - Disorganized speech

- **Social/occupational dysfunction:**
  - For a significant portion of the time since onset of the disorder, one or more major areas of functioning such as work or self-care are significantly below baseline

- **Duration:**
  - Continuous signs of the disorder for at least 6 months.

American Psychiatric Association. DSM-IV-TR.
Depression Review: Epidemiology

- Public health problem associated with increased disability and mortality
- Annual economic consequences of depression estimated at 83 billion dollars in the United States (2000)
- 16.2% of the population has had history of major depressive disorder in lifetime
  - More than 6.6% had an episode within the past 12 months

Kessler RC. JAMA 2003;289:3095–3105
Depression Review: Epidemiology

- Women are at increased risk of depression from early adolescence with a lifetime rate that is 1.7 to 2.7 times greater than for men.
- Adults 18 to 29 years of age experience the highest rates of major depression during any given year.
- The estimated lifetime prevalence of major depression in individuals aged 65 to 80 years recently was reported to be 20.4% in women and 9.6% in men.
Depression Review: Pathophysiology

RISK FACTORS

- **Internalizing factors**
  - Genetics
  - Neuroticism
  - Low self-esteem
  - Early-onset anxiety disorder
  - Past history of major depression

- **Externalizing factors**
  - Genetics
  - Substance misuse
  - Conduct disorder

- **Adversity**
  - Childhood or adult trauma
  - Parental loss
  - Marital problems
  - Lack of social support
Depression Review: Pathophysiology

Neurotransmitters

Biogenic Amine Hypothesis

- Depression caused by diminished activity of several key monoamines (either single or multiple):
  - Norepinephrine (NE)
  - Serotonin (5-HT)
  - Dopamine (DA)
  - Hypothesis that there is a subtype that is dopamine-sensitive and resistant serotonin and norepinephrine targeted treatment
- Changes in receptor sensitivity explain delayed therapeutic onset (i.e., downregulation, desensitization)
Depression Review: Pathophysiology

- **Neurotransmitters**
  - **Gamma-aminobutyric acid (GABA)**
    - Decreased levels in depression patients
  - **Glutamate**
    - Increased levels in depression patients
  - **Endocannabinoids (CB1)**
    - Decreased circulating endocannabinoid ligands

- **Cortisol**
  - Overproduction of corticotropin releasing hormone causes excess activity of the hypothalamic-pituitary-adrenal axis
Depression Review: Pathophysiology

- **Cortisol**
  - Overproduction of corticotropin releasing hormone causes excess activity of the hypothalamic-pituitary-adrenal axis

- **Thyroid**
  - Diminished thyroid-stimulating hormone response to thyrotropin-releasing hormone.
Depression Review: Pathophysiology

Source: http://commons.wikimedia.org/wiki/File:Dopamine_and_serotonin_pathways.gif
Depression Review: Clinical Presentation

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either **depressed mood or loss of interest or pleasure**:  
  - Depressed mood most of the day nearly every day  
  - Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day  
  - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day  
  - Insomnia or hypersomnia nearly every day  
  - Psychomotor agitation or retardation nearly every day  
  - Fatigue or loss of energy nearly every day  
  - Feelings of worthlessness or excessive or inappropriate guilt nearly every day  
  - Diminished ability to think or concentrate, or indecisiveness, nearly every day  
  - Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

American Psychiatric Association. DSM-IV-TR.
Depression Review: Clinical Presentation

- Emotional symptoms
  - Persistent, diminished ability to experience pleasure
  - Pessimism
  - Worthlessness
  - Inappropriate guilt
  - Anxiety

- Cognitive symptoms
  - Decreased ability to concentrate
  - Slowed thinking
  - Poor memory for recent events.
  - Can appear confused and indecisive
Depression Review: Clinical Presentation

- **Physical symptoms**
  - Chronic fatigue
  - Generalized pain
  - Headache
  - Sleep dysfunction
  - Appetite disturbances
  - Decreased libido
  - Gastrointestinal
  - Cardiovascular (palpitations)

- **Psychomotor**
  - Slowed physical movements, thought processes and speech
  - Psychomotor agitation
Patient Case #2

CC: “I am tired, have no appetite and keep getting headaches”

HPI:

- MP is a 65 year female presenting to the Internal Medicine clinic alert with fatigue and headache.
- She appears confused and reports a decreased appetite and insomnia.
- Upon questioning MP admits that she doesn’t enjoy gardening any more and rarely wants to leave her home.

PMH:

- The patient reports previous mood issues (unknown)
- Hypertension
Patient Case #2: Clinical Presentation

- Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either depressed mood or loss of interest or pleasure:
  - Markedly diminished interest or pleasure in all, or almost all, activities most of the day nearly every day
  - Significant weight loss when not dieting or weight gain or decrease or increase in appetite nearly every day
  - Insomnia or hypersomnia nearly every day
  - Fatigue or loss of energy nearly every day
  - Diminished ability to think or concentrate, or indecisiveness, nearly every day
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

American Psychiatric Association. DSM-IV-TR.
Agenda

Schizophrenia Review
- Epidemiology
- Etiology
- Clinical Presentation
- Patient Case

Depression Review
- Epidemiology
- Etiology
- Clinical Presentation
- Patient Case

Summary
- Schizophrenia/Depression
Summary: Epidemiology

**SCHIZOPHRENIA**
- Prevalence ranges from 0.6% to 1.9%
- Equal in both genders, but onset earlier in males
- Onset in late adolescence/early adult
- 2.5% of total health care costs in U.S
- 70% patients Medicaid prescription coverage

**DEPRESSION**
- Associated with increased disability and mortality
- 16.2% of population has had depressive disorder in life
- Adults 18 to 29 years of age experience the highest rates of major depression
- Women are at increased risk with rate that is 1.7 to 2.7 times greater than for men
- Annual cost estimated at 83 billion dollars
Summary: Pathophysiology

**SCHIZOPHRENIA**
- Strong genetic predisposition
- Environmental factors also implicated
- Dopamine neurotransmitter dysfunction
- Other targets: glutamate and serotonin?

**DEPRESSION**
- Internalizing factors
  - Genetics, neurosis, self-esteem
- Externalizing factors
  - Genetics, substance misuse
  - Serotonin, norepinephrine, dopamine neurotransmitter dysfunction
- Other targets: glutamate, GABA?
Summary: Clinical Presentation

SCHIZOPHRENIA

- Positive symptoms
  - Psychosis
    - delusions, hallucinations, disorganized thoughts
- Negative symptoms
  - Deficit in psychosocial functioning
    - Affect, involvement, hygiene
- Cognitive symptoms
  - All domains are affected
- Affective symptoms
  - Mood and affect problems common

DEPRESSION

- Emotional symptoms
  - Persistent, diminished ability to experience pleasure
- Cognitive symptoms
  - Ability to concentrate
- Physical symptoms
  - Fatigue, pain, libido
- Psychomotor symptoms
  - Slowed physical movements and thought processes
  - Agitation
Active Learning
“Final Exam”

SCHIZOPHRENIA
- What are some risk factors?
- What/which neurotransmitter(s) is/are associated with pathophysiology?
- List hallmark symptoms

DEPRESSION
- What are some risk factors?
- What/which neurotransmitter(s) is/are associated with pathophysiology?
- List hallmark symptoms
Questions?

- Describe and discuss the background and presentation of schizophrenia and depression
- Compare and contrast the clinical presentation of schizophrenia with depression
- Evaluate patient case scenarios and analyze symptomatology

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References

- Baldessarini RJ, Tarazi FI. Pharmacotherapy of Psychosis and Mania" (Chapter 18).In: Brunton LL, Lazo JS, Parker KL, Eds: Goodman & Gilman's The Pharmacological Basis of Therapeutics, (11e).
Recommendations on Treating Patients Already Using Antidepressants

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Introduction

- Patients who fail ADT
  - Frequency
  - Long-term sequelae
- Management strategies
- Rationale for AAP use

Review of evidence

- Limitations with trial data
- Comparison of AAPs
  - Populations studied
  - Outcomes
  - Adverse effects
- Guideline recommendations

Summary

Abbreviations
ADT = Antidepressant therapy
AAP = Atypical antipsychotics
TRD = Treatment-resistant depression
Treatment-Resistant Depression (TRD)

- Efficacy of antidepressants\(^1\)
  - 50% demonstrate response to monotherapy
  - 30% achieve remission
    - Lower rates for patients with multiple treatment failures

- Does treatment-resistant depression = treatment-refractory depression = difficult-to-treat depression?

\(^1\)J Psychiatr Pract. 2008 Jan;14(1):34-44.
Adverse Outcomes of TRD

- Presence of residual depressive symptoms\(^2\)
  - ↑ risk of relapse and recurrence
  - More chronic depressive episodes
  - ↑ in overall mortality rate

Management of Partial or Non – responders to ADT

- 4 common strategies\(^2\)
  - ↑ dose of ADT
  - Switch to different ADT
  - Combine initial ADT with 2\(^{nd}\) ADT
  - Augment treatment regimen with non-ADT
    - Lithium
    - T3
    - Dopaminergic agents
    - Buspirone
    - Atypical antipsychotics (AAP)

Rationale for AAP Use in TRD

- Enhanced monoamine neurotransmission\(^3\)
  - 5-HT\(_2\) antagonist activity
  - 5-HT\(_{1A}\) agonist activity
  - ↑ dopamine activity

- Similarities between major depressive disorder and schizophrenia

\(^3\)CNS Drugs. 2009;23(5):369-77.
General AAP Trial Limitations

- Short study duration
- Small sample size
- Various TRD inclusion criteria
- Various ADT use
- Use of multiple depression scales
  - Statistical vs. clinical significance
  - Limited disclosure of change in scale item(s)
- Limited sub-group analysis
AAP Meta-analysis

- Nelson et al., 2009\(^4\)
  - 16 trials with 3480 patients
  - Adjunctive AAPs were significantly more effective than placebo
    - Response: OR 1.69
      - 95%CI 1.46-1.95, p<0.00001
    - Remission: OR 2
      - 95% CI 1.69-2.37, p<0.00001

\(^4\)Am J Psychiatry. 2009 Sep;166(9):980-91.
Which of the following statements about the evidence for AAP use in treatment-resistant depression are **TRUE**?

A. Numerous head-to-head trials comparing AAPs to other augmenting strategies have consistently demonstrated superior remission rates with AAPs.

B. In trials with AAP augmentation, response typically occurred quickly (i.e. within the first 1-2 weeks of treatment).

C. Head-to-head trials comparing different AAPs have demonstrated superiority of specific agents within the class.

D. When used for augmentation in TRD, effective AAP doses are lower than those used to treat schizophrenia.
AAPs Studied

- Aripiprazole
- Quetiapine
- Olanzapine
- Risperidone
- Ziprasidone
  - No blinded, placebo-controlled trials currently available
Aripiprazole

- Berman et al., 2007
  - 8-week, prospective treatment phase (n=781)
    - Patients prescribed escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine XR
    - Continuation to double-blind treatment phase if experienced <50% reduction in HAMD17, HAMD17 total score ≥ 14, CGI-I ≥ 3
  - 6-week, double-blind treatment phase (n=362)
    - Adjunctive placebo or aripiprazole 2-20 mg daily
    - Primary endpoint: mean change in MADRS total score

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Aripiprazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of current episode, months (SD)</td>
<td>43.6 (53.8)</td>
<td>38.6 (59)</td>
</tr>
<tr>
<td>No. of prior adequate ADT trials in current episode, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 trial</td>
<td>117 (66.5)</td>
<td>121 (66.5)</td>
</tr>
<tr>
<td>2 trials</td>
<td>45 (25.6)</td>
<td>45 (24.7)</td>
</tr>
<tr>
<td>3 trials</td>
<td>14 (8)</td>
<td>16 (8.8)</td>
</tr>
<tr>
<td>Depressive episode, N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>53 (30.1)</td>
<td>39 (21.4)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>123 (69.9)</td>
<td>143 (78.6)</td>
</tr>
<tr>
<td>MADRS total score, mean (SD)</td>
<td>25.9 (6.5)</td>
<td>26 (6.1)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>86.2 (20.7)</td>
<td>84.5 (19.5)</td>
</tr>
</tbody>
</table>
Aripiprazole (continued)

- **Findings**
  - Variable ADT use
    - 29.6% escitalopram (most)
    - 8.9% paroxetine (least)
  - Mean adjunctive aripiprazole dose
    - 11.8 mg/day

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=176)</th>
<th>Aripiprazole (n=182)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong>*</td>
<td>23.8%</td>
<td>33.7%</td>
</tr>
<tr>
<td><strong>Remission</strong>*</td>
<td>15.7%</td>
<td>26%</td>
</tr>
<tr>
<td><strong>MADRS</strong>**</td>
<td>-5.8</td>
<td>-8.8</td>
</tr>
<tr>
<td>≥ 1 Adverse Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>62.5%</td>
<td>81.9%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4.5%</td>
<td>23.1%</td>
</tr>
<tr>
<td>EPS-related events</td>
<td>3.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td>Weight gain**</td>
<td>9.7%</td>
<td>27.5%</td>
</tr>
<tr>
<td></td>
<td>+2.01 kg</td>
<td>+0.34 kg</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.001
Aripiprazole: Post-hoc Analysis

- Suicidality\(^6\)
  - No suicides reported in the 2 studies
  - Aripiprazole decreased mean MADRS item 10 score by 0.3 points over placebo (p<0.001)

- Metabolic assessment\(^7\)
  - Effects of aripiprazole on mean body weight change were not dose or baseline BMI dependent
  - No statistically significant differences between aripiprazole and placebo in TC, HDL, LDL, FPG, or HbA1c levels

Quetiapine

- Bauer et al, 2009  
  - 6-week, randomized, double-blind study (n=493)  
  - Included patients with HAMD17 score ≥20, HAMD item 1 score ≥2, hx of inadequate response to ADT for ≥ 6 weeks  
  - Patients maintained on entry antidepressant dose, randomly assigned to receive quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo  
  - Primary endpoint: change in MADRS total score

### Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Quetiapine XR 150 mg</th>
<th>Quetiapine XR 300 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depressive episode, N (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>31 (19.4)</td>
<td>32 (19.3)</td>
<td>29 (18)</td>
</tr>
<tr>
<td>Recurrent</td>
<td>129 (80.6)</td>
<td>134 (80.7)</td>
<td>132 (82)</td>
</tr>
<tr>
<td><strong>No. of depressive episodes in past year, mean (SD)</strong></td>
<td>0.9 (1.9)</td>
<td>1 (1.5)</td>
<td>1.2 (4.6)</td>
</tr>
<tr>
<td><strong>MADRS total score, mean (SD)</strong></td>
<td>28.2 (5.6)</td>
<td>28.6 (5.4)</td>
<td>28.4 (5.5)</td>
</tr>
</tbody>
</table>
Findings

- Variable ADT use
  - ~70% SSRI
  - ~25% SNRI
  - ~5% other

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=160)</th>
<th>Quetiapine XR 150 mg (n=166)</th>
<th>Quetiapine XR 300 mg (n=161)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>46.3%</td>
<td>55.4%</td>
<td>57.8%*</td>
</tr>
<tr>
<td>Remission</td>
<td>23.8%</td>
<td>36.1%*</td>
<td>31.1%</td>
</tr>
<tr>
<td>MADRS (estimates)</td>
<td>-12</td>
<td>-15**</td>
<td>-15**</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>3.7%</td>
<td>6.6%</td>
<td>11.7%</td>
</tr>
<tr>
<td>EPS</td>
<td>3.1%</td>
<td>16.8%</td>
<td>23.3%</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>4.2%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

*p<0.05
**p<0.01
Quetiapine vs. lithium

- Doree et al, 2007\(^9\)
  - 8-week, open label comparative study (n=20)
  - Included pts with HAMD $\geq$ 20 and CGI $\geq$ 4 despite ADT treatment $\geq$ 4 weeks
  - Patients maintained on entry antidepressant dose, randomly assigned to receive:
    - Lithium 600 mg/day (adjusted to attain level = 0.8-1.2 mmol/L)
    - Quetiapine 400-800 mg/day

- Primary endpoint(s): change in MADRS total score, change in HAMD total score

Quetiapine vs. lithium

Findings

- Variable ADT use
  - 12/20 taking non-SSRIs
  - 11/20 taking 2 ADTs
- Mean doses / level
  - Lithium 0.78 mmol/L
  - Quetiapine 430 mg/day

<table>
<thead>
<tr>
<th></th>
<th>Lithium (n=10)</th>
<th>Quetiapine (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Remission</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Adverse Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>0%</td>
<td>25%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>HAMD</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>0</td>
<td>7</td>
<td>14</td>
<td>28</td>
<td>42</td>
<td>56</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25.8</td>
<td>19</td>
<td>10</td>
<td>6.9</td>
<td>3.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Lithium</td>
<td>28.4</td>
<td>17</td>
<td>18</td>
<td>16</td>
<td>16.5</td>
<td>15.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MADRS</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Quetiapine</td>
<td>35.7</td>
<td>26.5</td>
<td>15.9</td>
<td>8.7</td>
<td>6.1</td>
<td>6.7</td>
</tr>
<tr>
<td>Lithium</td>
<td>40.2</td>
<td>23.7</td>
<td>25.2</td>
<td>22.8</td>
<td>24.9</td>
<td>22.1</td>
</tr>
</tbody>
</table>
Olanzapine

- Corya et al., 2003
  - 76-week, multicenter, open label study (n=560)
  - Included pts with MDD (per DSM-IV) and CGI-S score ≥3
    - TRD defined as ≥2 ADT failures (4 week therapy suggested minimum)
  - Prescribed olanzapine 6 mg / fluoxetine 25 mg starting; dose adjusted per clinical judgment
  - Primary endpoint: change in MARDS total score

## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Patients with TRD</th>
<th>Patients without TRD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median days in current episode</td>
<td>256</td>
<td>336</td>
<td>235</td>
</tr>
<tr>
<td>&gt;3 MDD episodes lifetime, %</td>
<td>39.1</td>
<td>45.5</td>
<td>36.9</td>
</tr>
<tr>
<td>&gt;2 MDD episodes in last 2 yrs, %</td>
<td>12.5</td>
<td>13.8</td>
<td>12</td>
</tr>
<tr>
<td>Pts with psychotic features, %</td>
<td>5.5</td>
<td>2.8</td>
<td>6.5</td>
</tr>
<tr>
<td>MADRS total score, mean (SD)</td>
<td>32.3 (6.7)</td>
<td>32.8 (6.9)</td>
<td>32.1 (6.6)</td>
</tr>
<tr>
<td>CGI-S total score, mean (SD)</td>
<td>4.5 (0.7)</td>
<td>4.8 (0.7)</td>
<td>4.4 (0.7)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>28.3 (7.1)</td>
<td>29.9 (6.9)</td>
<td>28.8 (7.1)</td>
</tr>
</tbody>
</table>
Olanzapine (continued)

- Findings
  - Mean modal dose (entire sample)
    - 7.5 mg olanzapine / 46.1 mg fluoxetine
  - Mean modal dose (TRD)
    - 7.7 mg olanzapine / 49.5 mg fluoxetine
  - Mean modal dose (non-TRD)
    - 7.4 mg olanzapine / 44.9 mg fluoxetine

- Trial completion
  - 8 weeks (77.7%); 16 weeks (62.1%); 32 weeks (45.4%); 52 weeks (31.6%); 76 weeks (25.5%)
Findings

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=552)</th>
<th>Patients with TRD (n=145)</th>
<th>Patients without TRD (n=407)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td>61.6%</td>
<td>53.1%</td>
<td>64.6%</td>
</tr>
<tr>
<td><strong>Remission</strong></td>
<td>56.3%</td>
<td>44.1%</td>
<td>60.7%</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>14.8%</td>
<td>25%</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MADRS (mean decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Week</strong></td>
<td>½ 1 8 72</td>
</tr>
<tr>
<td><strong>All patients</strong></td>
<td>-6.5 -10.5 -18.1 -21.8</td>
</tr>
<tr>
<td><strong>Patients with TRD</strong></td>
<td>-7.2 -10.8 -16.2 -19.2</td>
</tr>
<tr>
<td><strong>Patients without TRD</strong></td>
<td>-6 -10.3 -18.6 -22.3</td>
</tr>
</tbody>
</table>
Olanzapine (continued)

- Safety findings
  - EPS
    - 19% of patients reported tremor
    - 11.3% of patients reported akathisia
  - Weight
    - Mean weight gain: 5.6 + 6.6 kg
    - 31% gained ≥10% from baseline
  - Labs / Metabolic changes
    - 4 new cases (0.7%) of treatment-emergent diabetes mellitus
    - 1.5% developed hypercholesterolemia at endpoint
Risperidone

- Rapaport et al, 2006\textsuperscript{11}
  - 4-6 week prospective treatment phase
    - Monotherapy with citalopram 60 mg/day (target dose)
    - Continuation to open-label phase if pt experienced <50% reduction in HAMD17
  - 4-6 week open label phase
    - Augmentation with risperidone 0.5-1 mg/day (target dose)
    - Progression to double-blind continuation phase if achieved HAMD17 score ≤7 or CGI score of 1-2
  - 24-week double-blind continuation phase
    - Randomized to continue on risperidone + citalopram or receive placebo + citalopram
    - Primary endpoint: time to relapse
      - HAMD17 total score ≥16, CGI-C of 6-7, discontinuation due to lack of effect, or self-injury/suicidal intent

\textsuperscript{11}Neuropsychopharmacology. 2006 Nov;31(11):2505-13
## Risperidone (continued)

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Open-label citalopram</th>
<th>Open-label risperidone</th>
<th>Risperidone augmentation</th>
<th>Placebo Augmentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration of current episode, years (SD)</td>
<td>2 (4.2)</td>
<td>2 (3.6)</td>
<td>2 (3.7)</td>
<td>2 (3.8)</td>
</tr>
<tr>
<td>No. of prior adequate ADT trials in current episode, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 trial</td>
<td>161 (32.9%)</td>
<td>119 (30.8%)</td>
<td>35 (28.7%)</td>
<td>36 (30.3%)</td>
</tr>
<tr>
<td>2 trials</td>
<td>320 (65.4%)</td>
<td>261 (67.6%)</td>
<td>85 (69.7%)</td>
<td>83 (69.8%)</td>
</tr>
<tr>
<td>Depressive episode in last 12 months, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>430 (87.9%)</td>
<td>338 (87.6%)</td>
<td>105 (86.1%)</td>
<td>103 (86.6%)</td>
</tr>
<tr>
<td>2</td>
<td>45 (9.2%)</td>
<td>38 (9.8%)</td>
<td>13 (10.7%)</td>
<td>13 (10.9%)</td>
</tr>
<tr>
<td>MADRS total score, mean (SD)</td>
<td>31.8 (5)</td>
<td>27.7 (7.2)</td>
<td>6.8 (4.7)</td>
<td>8.1 (4.6)</td>
</tr>
<tr>
<td>HAMD17 total score, mean (SD)</td>
<td>25.1 (3.5)</td>
<td>21.4 (5.2)</td>
<td>6 (3)</td>
<td>6.3 (2.9)</td>
</tr>
</tbody>
</table>
Risperidone (continued)

- **Findings**

<table>
<thead>
<tr>
<th></th>
<th>Risperidone (n=122)</th>
<th>Placebo (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MADRS total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>6.8±4.7</td>
<td>8.1±4.6</td>
</tr>
<tr>
<td>End-point change</td>
<td>11.2±12.6*</td>
<td>10.4±11.2*</td>
</tr>
<tr>
<td><strong>HAMD17 total</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>6±3</td>
<td>6.3±2.9</td>
</tr>
<tr>
<td>End-point change</td>
<td>7.6±8.8*</td>
<td>7.9±8.1*</td>
</tr>
</tbody>
</table>

*p<0.001 change score vs. baseline

- Relapse rates: 53.3% with risperidone augmentation vs. 54.6% with placebo augmentation
- Kaplan-Meier median time to relapse: 102 days with risperidone augmentation vs. 85 days with placebo augmentation (p=0.52)
Risperidone (continued)

- **Safety findings**
  - No clinically significant changes in mean SAS, BAS, or AIMS scores
  - Statistically significant increase in prolactin level at endpoint for patients taking risperidone; 2.5% reported galactorrhea
  - Mean weight change during double-blind phase
    - 1.3±3.8 kg with risperidone augmentation
    - -0.5±2.9 kg with placebo augmentation
  - % of patients who gained ≥7% of body weight
    - 8.3% in risperidone augmentation
    - 2.6% in placebo augmentation
# AAP Data Comparison: Select randomized controlled trials

<table>
<thead>
<tr>
<th></th>
<th>Quetiapine</th>
<th>Aripiprazole</th>
<th>Olanzapine</th>
<th>Risperidone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of randomized pts with ≥1 post-treatment rating</strong></td>
<td>432</td>
<td>343</td>
<td>286</td>
<td>268</td>
</tr>
<tr>
<td><strong>Study duration (with AAP)</strong></td>
<td>6 wk</td>
<td>6 wk</td>
<td>12 wk</td>
<td>6 wk</td>
</tr>
<tr>
<td><strong>% pts with recurrent depression</strong></td>
<td>92</td>
<td>74</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>% Response AAP augmentation vs. placebo</strong></td>
<td>59 vs. 46</td>
<td>34 vs. 24</td>
<td>43 vs. 34 (no placebo)</td>
<td>46 vs. 30</td>
</tr>
<tr>
<td><strong>% Remission AAP augmentation vs. placebo</strong></td>
<td>43 vs. 25</td>
<td>15.7 vs. 26</td>
<td>30 vs. 18 (no placebo)</td>
<td>25 vs. 11</td>
</tr>
<tr>
<td><strong>Baseline MADRS</strong></td>
<td><img src="https://i.imgur.com/4c.png" alt="" /></td>
<td>26</td>
<td>30</td>
<td>24 (used HAMD17)</td>
</tr>
<tr>
<td><strong>MADRS over placebo</strong></td>
<td>-3</td>
<td>-3</td>
<td>-2.4</td>
<td>-2.8</td>
</tr>
</tbody>
</table>

12 Int J Neuropsychopharmacol. 2010 Aug;13(7):917-32  
13 Depress Anxiety. 2006;23(6):364-72  
14 Ann Intern Med. 2007 Nov 6;147(9):593-602
US Guideline Recommendations

- American Psychiatric Association, 2000\textsuperscript{15}
  - “A combination of antipsychotic and antidepressant medications or ECT should be used for \textit{psychotic} depression. (Level I; recommended with substantial clinical confidence)

- Texas Medication Algorithm Project

Summary

What we’ve learned

- AAP augmentation doses for TRD are typically lower than those used in schizophrenia
- Changes in depression score
  - May occur quickly (1-2 weeks of augmentation)
  - Mean depression scores typically 2 to 3 points less than placebo

What we’d like to know

- Specifics regarding patient population
- Comparisons to other augmenting strategies
- Long-term effects of AAP augmentation
- Likelihood of long-term remission vs. relapse
  - (When) is it possible to discontinue AAP therapy?
Options for Treatment-Resistant Depression in Patients with Axis I Co-morbidities

David G. Fuentes, Pharm.D. BCPP, CGP
Assistant Professor
Pacific University Oregon
School of Pharmacy
dfuentes@pacificu.edu
Co-Morbid Axis I Disorders

- Depression + Other Axis I Mood Disorders $^{1,2}$
  - Bipolar I
  - Bipolar II
  - Fluctuating and mixed-states
Case Approach

- The process
  - What do you need to approach the case?
  - Did you get it all?
  - What is your pharmacotherapy plan?
  - What does the evidence say?
Case Vignette

- A patient (age 23) with diagnoses of Bipolar type II, major depression, and general anxiety

- Chief complaint: “I want to die…”

- Current treatment: valproic acid, trazodone, escitalopram, clonazepam.
Preparing for the Case

- Take some time to ask what you would like to know about this case
Potential Questions

- Age?
- Gender?
- Family history?
- Social history?
- Adherence?
- Health-belief model?
- Medication doses?
- Dosing intervals?
- Prior drug therapy?
- Intolerances / allergies?
Patient Information

- Please consult the Patient Information Form (PIF).
  - Contains the complete file of this patient
Questions you typically ask in practice...

- Practical / Consultations
- Regulations / Quality Assurance
- Patient Satisfaction
- Educational Purposes
- Medication Procurement
- Monitoring and Follow-up
Informing Decisions

- Does the information you gather affect your pharmacotherapy recommendations?
Reflection

- What are you missing?
- How will this process help enrich your practice?
- Please identify areas of interest about which you will learn more after this presentation pertaining to information-seeking
Augmentation therapy for TRD in patients with bipolar disorders

- Emerging measures of change
- Potential benefits in reduced bipolar switching
- Combination re-emergence?
- Implications on monitoring and safety
- Optimal outcomes in mixed-state misdiagnoses
- Comparisons with other agents
- Familiar dangers
Pros and Cons of Augmentation with Atypical Antipsychotics.

- **Limitations**
  - Alternative augmentation agents 8, 10, 11, 12, 13, 14, 15, 16, 17, 18
  - Side effects 9
  - Study design 9, 19
  - Novel dangers (drug-disease interactions)
  - More information is necessary 20, 14, 15

- **Benefits**
  - Clinically used in similar settings
  - Common side effects are well-documented 21, 14
Application Considerations

- Pharmacotherapy applications
  - Share your assessment and plan

- Monitoring and follow-up
- Implications for prescribing patterns \(^{22, 23, 24, 25}\)

- Adherence with multi-drug regimens
  - Share some challenges

- The future of depression pharmacotherapy
References

15. CNS Drugs. 2010 Mar 1;24(3):245-62.
Questions?