The Role of High-Dose Second Generation Antipsychotics in Treatment-Resistant Schizophrenia

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Learning Objectives:
1. Briefly describe the pathophysiology of schizophrenia.
2. Compare and contrast varying definitions of treatment-resistant schizophrenia.
3. Discuss options for pharmacologic management of treatment-resistant schizophrenia.
4. Review evidence supporting the role high-dose atypical antipsychotics in the management of treatment-resistant schizophrenia.
I. Schizophrenia
A. Background and Epidemiology
1. Definition
   a. “...a disorder that lasts for at least 6 months and includes at least 1 month of active-phase symptoms (i.e., two or more) of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms)”
   b. Syndrome characterized by long duration, delusions, negative symptoms, and affective symptoms
2. Subtypes of schizophrenia
   a. Paranoid type
   b. Disorganized type
   c. Catatonic type
   d. Residual type
   e. Undifferentiated type
3. Prevalence
   a. Observed worldwide
   b. 0.5-1.5% of adults
   c. Difference among populations (e.g., higher prevalence among lower versus higher socio-economic classes)
   d. Geographic differences (e.g., higher prevalence in more developed versus less developed countries)
B. Etiology
1. Genetic factors
   a. First degree relative: 10 times greater risk of developing schizophrenia than general population
   b. Twin studies
      i. Risk for monozygotic twin: 40-50%4
      ii. Risk for dizygotic twin: 10-15%4
   c. Specific genes associated with schizophrenia: DTNBP1, DAOA, DISC1, NRG1, DRD1-4, GRM3
2. Environmental factors
   a. During pregnancy
      i. Maternal infections (e.g., influenza, rubella, toxoplasmosis, etc.)
      ii. Nutritional deficiency during first and early second trimesters of pregnancy
      iii. Fetal hypoxia
   b. Paternal age greater than 40 years
   c. Birth during late winter or early spring
   d. Childhood risk factors
      i. Trauma, head injury
      ii. Parental separation or death
      iii. Adverse child rearing
      iv. Infection
      v. Urbanicity
      vi. Migration
   e. Cannabis use
   f. Social adversity and stressful life events
C. Pathophysiology
1. Neurodegeneration: decrease in grey matter, enlargement of ventricles
   alteration of white matter tracts
2. Dopamine pathways
Table 1. Dopaminergic Tracts and Effects of Dopamine Blockade^5,6

<table>
<thead>
<tr>
<th>Dopamine Tract</th>
<th>Origin</th>
<th>Innervation</th>
<th>Function</th>
<th>Dopamine Blockade Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Midbrain ventral tegmentum</td>
<td>Nucleus accumbens</td>
<td>Pleasure sensations, motivation; positive symptoms of psychosis</td>
<td>Relief of psychosis</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Midbrain ventral tegmentum</td>
<td>Prefrontal cortex</td>
<td>Cognition, communication; possible role in affective symptoms</td>
<td>Worsening of cognition and affective symptoms</td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>Substantia nigra</td>
<td>Basal ganglia, striatum</td>
<td>Motor function and movement</td>
<td>Movement disorder</td>
</tr>
<tr>
<td>Tuberoin–fundibular</td>
<td>Hypothalamus</td>
<td>Pituitary gland</td>
<td>Controls prolactin secretion</td>
<td>Increased prolactin concentrations</td>
</tr>
</tbody>
</table>

a. Dysregulation of dopamine, rather than a presence of “too little” or “too much” dopamine, is thought to be largely responsible for the symptoms of schizophrenia

3. Glutamate pathways: decreased functioning of NMDA receptors within the glutamate pathways may be responsible for not only the symptoms of schizophrenia but also dysregulation of dopamine due to decreased gabaminergic tone^3,5

4. GABA^3
   a. Patients exhibit insufficiencies in transcripts that encode GABA neurons and regulators involved in GABA neurotransmission
   b. Abnormalities are thought to cause impairments in cognitive function

D. Clinical Course^1,7
1. Onset
   a. Early to mid twenties for men
   b. Late twenties for women
   c. Prodromal phase often occurs (schizophreniform disorder)
   d. Early onset schizophrenia (EOS)^7

2. Varying clinical course^1
   a. Negative symptoms more common early on (prodromal phase) and also persist into later stages of disease
   b. Positive symptoms occur later, but respond better to treatment

3. Symptoms of schizophrenia^5

Figure 1: Symptoms of Schizophrenia
II. Treatment Resistant Schizophrenia

A. The evolving definition\(^{8-12}\)
   1. In the 1970s, hospitalization \(\geq 2\) years was used as a criterion for treatment resistance
   2. Persistent positive symptoms were also thought to be predominant in treatment resistance, but this underestimates the importance of other symptoms
   3. A more specific definition was introduced in the trial by Kane, et al., which established clozapine as the gold standard for treatment-resistant schizophrenia
      a. Persistent positive psychotic symptoms: score \(\geq 4\) on \(\geq 4\) positive symptom items on the BPRS
      b. Current presence of at least moderately severe illness
         i. Total BPRS score \(\geq 45\) on 18-item scale
         ii. \(\geq 4\) on Clinical Global Impressions Scale
      c. At least 3 periods of treatment in the preceding 5 years
      d. Treatment must be with antipsychotics from \(\geq 2\) different chemical classes
      e. Utilized dosages must be \(\geq 1,000\) mg/day of chlorpromazine equivalents
      f. Length of treatment must have been for a period \(\geq 6\) weeks
      g. Significant relief of symptoms did not occur with any of the treatments
      h. Patients have had no period of good functioning in the preceding 5 years
   4. What constitutes treatment-resistance is unclear\(^{9-11,13}\)
      a. Dosages equivalent to or greater than 400-600mg/day of chlorpromazine now accepted as adequate dosing
      b. Four to six weeks now recognized as an adequate trial of treatment\(^{10,11}\)
      c. Practice guidelines define it as little or no symptomatic response to at least two antipsychotic trials of at least 6 weeks at an adequate dose\(^{13}\)
   5. Current guidelines for use of clozapine\(^{11,13}\)
      a. Patients should fail to respond to 2 separate trials of antipsychotics (at least one second-generation agent) before being treated with clozapine
      b. Consider for a patient with persistent suicidal ideation or behavior that has not responded to other treatment\(^{13,14}\)

B. Prevalence\(^{8,9,11,13}\)
   1. One-fifth to one-third of patients with schizophrenia are resistant to drug treatment\(^{13}\)
   2. Thirty percent of patients are only partially responsive\(^{9,13}\)
   3. Among patients who are initially responsive to antipsychotic drugs, 20-30% may relapse during the first years of maintenance treatment\(^{8}\)

C. Characteristics of patients with treatment-resistant schizophrenia\(^{10,11}\)
   1. Highly symptomatic; may require extensive periods of hospital care
   2. Patients with treatment-resistant schizophrenia appear to have increased cortical atrophy on MRI\(^{10}\)
   3. Increased rates of violence towards others and themselves\(^{10}\)

D. Confounders of treatment resistance
   1. Non-compliance\(^{10,11,15}\)
      a. In controlled trials, approximately 1 in 3 patients become noncompliant within 1 year
      b. Due to embarrassment and stigma, lack of insight, lack of information, adverse effects, and lack efficacy
      c. Effects of non-compliance can mimic treatment resistance
   2. Relapse rates with intermittent treatment are twice as high as with continuous treatment\(^{13,15}\)
   3. Duration of maintenance treatment\(^{13}\)
a. Indefinite maintenance treatment is recommended for patients with multiple previous episodes or 2 relapses in the past 5 years
b. Without maintenance treatment, 60-70% of patients relapse within 1 year; 90% relapse within 2 years
c. Can consider discontinuation of treatment after 1 year of continuous remission or optimal response has been achieved

4. Chronic hospitalization vs treatment resistance\textsuperscript{10,11}
   a. Chronicity cannot solely predict response to therapy
   b. Chronic hospitalization can occur even with low levels of symptoms
   c. Risks for chronic hospitalization can include inadequate psychosocial treatment, history of violence

5. Extrapyramidal side effects can mimic true treatment resistance\textsuperscript{10,11,15}

6. Substance abuse can cause exacerbation of symptoms, rehospitalization, persistent psychotic symptoms\textsuperscript{12}

7. Patients who are rapid metabolizers may appear to be treatment-resistant to certain medications

III. Management of Treatment-Resistant Schizophrenia

A. Defining response\textsuperscript{11,16}
   1. Twenty percent or greater decrease in total BPRS
   2. Either a final score of 35 on the BPRS or a decrease of 1-2 points on the Clinical Global Impression Scale
   3. Dose response is demonstrated when there is an increase in efficacy as dose increases\textsuperscript{16,17}

B. Options for improving response to antipsychotic treatment\textsuperscript{16,18}
   1. Wait for potentially delayed response
   2. Switch to long-acting, depot formulation
   3. Augment with another medication
      a. Polypharmacy with antipsychotics not generally recommended\textsuperscript{19}
      b. Reserved until failure of clozapine\textsuperscript{19}
   4. Switch to another medication (i.e., clozapine)
   5. Increase dose beyond upper dose range recommended by the FDA

C. Clozapine\textsuperscript{8,10,14,20}
   1. First appeared on market in Europe in 1972\textsuperscript{20}
   2. Belongs to chemical class of dibenzodiazepines; chemically related to loxapine
   3. Serotonergic (S\textsubscript{2}), adrenergic (\(\alpha_1\)), and histaminic (H\textsubscript{1}) blocking activity; potent muscarinic acetylcholine receptor antagonist
   4. Weak binding of D\textsubscript{1} and D\textsubscript{2} receptors; higher affinity for D\textsubscript{4}
   5. 1975: granulocytopenia developed in 17 patients in Finland with agranulocytosis developing in 13; Clozapine is subsequently withdrawn from US market
   6. Kane, et al., conduct their landmark trial and demonstrate superiority of clozapine over typical antipsychotics in treatment-resistant schizophrenia
   7. More effective in reducing violent behavior and hostility\textsuperscript{10}
   8. Only atypical antipsychotic shown to significantly reduce suicidality\textsuperscript{14}
   9. Patient must comply with monitoring parameters, as well as be tolerant of numerous side effects, for treatment to be successful

IV. High-Dose Atypical Antipsychotics

A. Rates of use in the USA and Europe vary from 15.4-41.9\%\textsuperscript{21}

B. Higher doses are associated with particular patient characteristics\textsuperscript{21-23}
   1. Younger age
   2. Positive symptoms (i.e., delusions, hallucinations)
   3. Aggressive behavior
   4. Multiple admissions
5. Longer hospitalizations
6. Treatment with both first- and second-generation antipsychotics
7. African-Americans
8. Smokers

C. Product labeling versus current practice
1. Studies that determine recommended dosing usually exclude patients with significant comorbidities and those resistant to treatment
2. Recommended dosing may not adequately reflect needs of chronically ill and treatment-resistant patients
3. In efficacy studies, the goal of showing superiority over placebo must be weighed against proving safety and tolerability.

D. Risk of use of higher doses is primarily increased risk of occurrence of adverse effects

Table 2: Recommended Dosing, Maximum Dosing, and Chlorpromazine Equivalence for Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Recommended Target Dosing Range (mg/d)</th>
<th>Maximum Recommended Dose (mg/d)</th>
<th>1000 mg Chlorpromazine Equivalent (mg/d)</th>
<th>400-600 mg Chlorpromazine Equivalent (mg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>300-450</td>
<td>900</td>
<td>500</td>
<td>200-300</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10-15</td>
<td>20</td>
<td>50</td>
<td>20-30</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300-500</td>
<td>800</td>
<td>750</td>
<td>300-450</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4-8</td>
<td>16</td>
<td>20</td>
<td>8-12</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40-160</td>
<td>200</td>
<td>600</td>
<td>240-360</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-15</td>
<td>30</td>
<td>75</td>
<td>30-45</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6</td>
<td>12</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10</td>
<td>20*</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>12-24</td>
<td>24</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

* Doses > 10mg/d have not shown added benefit; doses > 20mg/d have not been evaluated in clinical studies

E. Risperidone
1. No studies available that evaluate use of risperidone in treatment-resistant patients in doses greater than maximum recommended
2. However, due to the increased risk of EPS at higher quantities, doses > 8mg/d are rarely used in clinical settings

   a. Prospective, double-blind, multicenter, parallel-group study comparing efficacy and safety of clozapine and risperidone in patients with chronic schizophrenia and poor response to previous treatment
   b. Methods
      i. Study conducted at 41 centers in France and Canada
      ii. Patient population
         • Patients aged 18-65 years
         • Baseline score ≥ 4 on CGI, and BPRS ≥ 45.
         • No previous treatment with clozapine or risperidone
         • Current episode of schizophrenia treated at least 6 mo without significant improvement
         • One unsuccessful trial of antipsychotic = 20mg/day of haloperidol for at least 6 weeks
         • No period of good functioning in the past 24 mo despite period of use of 2 antipsychotics from at least 2 chemical
Phase 1: Single-blind placebo run-in at least 3 days long: all psychotropics withdrawn

Phase 2 (4 weeks): Starting daily doses of 12.5mg clozapine or 1mg risperidone increased to 300mg/d or 4mg/d over 9 days

Patients who could not tolerate 300mg/d and 4mg/d on the 10th day were withdrawn from study

Patients could be titrated to 600mg/d and 6mg/d, and were maintained in the study unless doses reached < 300mg/d or < 4mg/d

Phase 3 (8 weeks): Flexible-dose period in which doses could be adjusted at 2 week intervals within range of 200-900mg/d clozapine or 2-15 mg/d risperidone

Figure 2: Titration Schedule for Clozapine and Risperidone

iv. Primary efficacy measure: magnitude of improvement in BPRS and CGI
v. Secondary measures: total, positive, negative, and general psychopathology scores of the PANSS, Psychotic Anxiety Scale, Psychotic Depression Scale, and Calgary Depression Scale

c. Results
i. 273 patients randomized (N=138 for clozapine and N=135 for risperidone)
ii. 201 patients completed study
   • Clozapine, N=100
   • Risperidone, N=102
   • Calculations indicated 150 patients needed per group to give 90% power in detecting difference
iii. Median doses acheived

Table 3: Median Achieved Doses

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>ITT Population</th>
<th>Per Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>600mg/d</td>
<td>600mg/d</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6mg/d</td>
<td>9 mg/d</td>
</tr>
</tbody>
</table>
iv. Efficacy measures

Table 4: Changes from Baseline

<table>
<thead>
<tr>
<th>Efficacy Measure and Population</th>
<th>Baseline Value</th>
<th>Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Clozapine Mean (SD)</td>
<td>Risperidone Mean (SD)</td>
</tr>
<tr>
<td>BPRS Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>63.7 (10.3)</td>
<td>61.2 (9.9)</td>
</tr>
<tr>
<td>Per-Protocol</td>
<td>64.0 (9.9)</td>
<td>60.8 (9.7)</td>
</tr>
<tr>
<td>CGI Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT</td>
<td>5.6 (0.8)</td>
<td>5.5 (0.9)</td>
</tr>
<tr>
<td>Per-Protocol</td>
<td>5.7 (0.8)</td>
<td>5.6 (0.9)</td>
</tr>
</tbody>
</table>

Table 5: Analysis of Primary Efficacy Measures

<table>
<thead>
<tr>
<th>Efficacy Measure and Population</th>
<th>Analysis of Change from Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ANCOVA F</td>
</tr>
<tr>
<td>BPRS</td>
<td>13.01</td>
</tr>
<tr>
<td>ITT</td>
<td>12.31</td>
</tr>
<tr>
<td>Per-Protocol</td>
<td>2.68</td>
</tr>
<tr>
<td>CGI - total</td>
<td>3.30</td>
</tr>
</tbody>
</table>

- Patients experiencing mean BPRS score reduction of ≥ 20% and ≥ 30% significantly higher in clozapine group for ITT and per-protocol populations
- At end of study, 48.4% of clozapine ITT group and 43.1% of risperidone ITT group were classified as responders (x² = 0.78, df=1, p<0.38)
- Significantly more patients in the risperidone group withdrew due to treatment failure (p<0.01, Fisher’s exact test)

v. Tolerability (Please refer to Appendix B.)
- No significant difference in either withdrawal due to adverse events or occurrence of adverse events

d. Comments
i. Criteria for treatment-resistance followed clozapine labeling in France
ii. Short washout period may result in residual EPS and treatment effects
iii. Flexible dosing may have prevented all patients from reaching adequate serum levels
iv. Superiority of clozapine demonstrated despite not meeting power criteria

4. Other literature (Please refer to Appendix B.)

F. Olanzapine
1. CATIE: olanzapine was the only antipsychotic showing superiority in the outcomes of all-cause discontinuation, time to all-cause discontinuation, discontinuation for lack of efficacy, duration of "effective" treatment, and hospitalization for illness exacerbation; it was also only antipsychotic for which doses exceeding the maximum recommended amount were allowed (7.5-30mg/day; mean 20.1mg/day)
2. **A Randomized, Double-Blind Comparison of Clozapine and High-Dose Olanzapine in Treatment-Resistant Patients with Schizophrenia**, Meltzer, et al. 2008.38 (Refer to Appendix B.)
   a. A randomized, double-blind, parallel-group study comparing the efficacy and tolerability of olanzapine and clozapine in patients with treatment-resistant schizophrenia or schizoaffective disorder
   b. Methods
      i. Patient population
         • Men and women, age 18-58 y/o
         • PANSS score ≥ 4 on ≥ 2 of 4 positive symptoms
         • Failure of ≥ 2 trials of typical or atypical antipsychotics of 2 different classes at adequate doses for ≥ 6 weeks
         • Patients excluded for nonresponsiveness to clozapine or olanzapine
      ii. Interventions
         • Previous medication tapered to 10mg/d haloperidol equivalent over 7-14 days, then discontinued
         • Study medication titration

   ![Figure 3: Titration of Olanzapine and Clozapine](image)

   - Each patient continually had 9 capsules of 5mg olanzapine, 100mg clozapine, or placebo
   - Treatment could be raised or lowered by one or more capsule containing active drug at a time
   - Use of lorazepam, benzotropine, and fluoxetine permitted on prn basis during maintenance phase

   iii. Primary endpoint: change in total PANSS
   iv. Other outcome measures: change in SANS, SAPS, GAF, CGI, CGI-S
   v. Safety assessed with BARS, modified SAS, AIMS
   vi. Cognitive performance also measured with tests for verbal memory, working memory, sustained attention, verbal fluency, and executive functioning/reasoning

c. Results
   i. N=40
      • Clozapine, N=21
      • Olanzapine, N=19
      • 80% power to show superiority of clozapine in producing reduction in BPRS score (17 patients per treatment group required)
   ii. Mean dosage
iii. Efficacy measures

Table 6: Dosage of Clozapine and Olanzapine at 6 Weeks and 6 Months

<table>
<thead>
<tr>
<th>Medication (Time Period)</th>
<th>Mean ± SD, mg/d</th>
<th>Percent of Subjects at ≥ 500mg/d Clozapine or ≥ 35mg/d Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine (6 wk)</td>
<td>400 ± 158</td>
<td>23</td>
</tr>
<tr>
<td>Clozapine (6 mo)</td>
<td>564 ± 243</td>
<td>56</td>
</tr>
<tr>
<td>Olanzapine (6 wk)</td>
<td>32.7 ± 5.94</td>
<td>47</td>
</tr>
<tr>
<td>Olanzapine (6 mo)</td>
<td>33.6 ± 11.2</td>
<td>71</td>
</tr>
</tbody>
</table>

iii. Efficacy measures

Table 7: Efficacy Measures, Least-Squares

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Timepoint</th>
<th>Clozapine, Mean (SE)</th>
<th>Olanzapine, Mean (SE)</th>
<th>Difference, Mean (SE)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANSS Total</td>
<td>Baseline</td>
<td>91.9 (2.3)</td>
<td>92.2 (2.4)</td>
<td>-0.35 (3.3)</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>84.0 (2.8)</td>
<td>85.9 (2.5)</td>
<td>-1.90 (3.8)</td>
<td>.61</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>72.1 (3.4)</td>
<td>71.7 (2.8)</td>
<td>0.41 (4.3)</td>
<td>.92</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>72.1 (3.4)</td>
<td>71.7 (2.8)</td>
<td>0.41 (4.3)</td>
<td>.92</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>Baseline</td>
<td>23.1 (0.8)</td>
<td>23 (0.8)</td>
<td>0.07 (1.1)</td>
<td>.95</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>19.3 (0.9)</td>
<td>21.2 (0.9)</td>
<td>-1.89 (1.3)</td>
<td>.14</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>15.1 (1.1)</td>
<td>17.8 (0.9)</td>
<td>-2.67 (1.4)</td>
<td>.07</td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>Baseline</td>
<td>22.1 (0.8)</td>
<td>23.0 (0.9)</td>
<td>-0.97 (1.2)</td>
<td>.43</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>22.1 (1.0)</td>
<td>22.1 (0.9)</td>
<td>-0.03 (1.4)</td>
<td>.98</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>20.9 (1.2)</td>
<td>19.1 (1.0)</td>
<td>1.72 (1.6)</td>
<td>.28</td>
</tr>
<tr>
<td>GAF</td>
<td>Baseline</td>
<td>45.2 (1.5)</td>
<td>45.1 (1.6)</td>
<td>0.02 (2.2)</td>
<td>.99</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>50 (1.9)</td>
<td>50.7 (1.7)</td>
<td>-0.70 (2.5)</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>62.4 (2.1)</td>
<td>54.8 (1.8)</td>
<td>7.61 (2.8)</td>
<td>.01</td>
</tr>
<tr>
<td>CGI</td>
<td>Baseline</td>
<td>1.6 (0.5)</td>
<td>2.4 (0.05)</td>
<td>-0.79 (0.7)</td>
<td>.29</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>3.4 (0.5)</td>
<td>3.7 (0.06)</td>
<td>-0.26 (0.8)</td>
<td>.75</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>2.6 (0.8)</td>
<td>2.3 (0.6)</td>
<td>0.32 (1.0)</td>
<td>.76</td>
</tr>
<tr>
<td>CGI-S</td>
<td>Baseline</td>
<td>4.7 (0.2)</td>
<td>4.7 (0.2)</td>
<td>-0.05 (0.2)</td>
<td>.83</td>
</tr>
<tr>
<td></td>
<td>6 weeks</td>
<td>4.2 (0.2)</td>
<td>4.1 (0.2)</td>
<td>0.15 (0.3)</td>
<td>.55</td>
</tr>
<tr>
<td></td>
<td>6 months</td>
<td>3.6 (0.2)</td>
<td>3.6 (0.2)</td>
<td>-0.08 (0.3)</td>
<td>.78</td>
</tr>
</tbody>
</table>

- At 6 weeks, 18% of olanzapine patients and 7% of clozapine patients reached ≥ 20% decrease in baseline PANSS
- At 6 months, 50% of olanzapine patients and 60% of clozapine patients achieved response criteria

iv. Tolerability (Please refer to Appendix B.)
- At 6 months, mean weight gain was 3.5 lb for clozapine and 15.9 lb for olanzapine (p=0.01)
- Mean increase in BMI was 0.3 for clozapine and 2.2 for olanzapine (p=0.006)

d. Comments
i. High drop-out rates for clozapine (28.6%) vs olanzapine (10.5%) possibly due to slower titration rate of clozapine; study attempted slower titration with olanzapine to minimized difference
ii. Small sample size may have made it difficult to detect changes in EPS
iii. Carried out for 6 months (longest trial of its kind to date)
iv. Large percentage of patients required higher doses, supporting belief that treatment-resistant patients are underdosed with package insert recommendations
v. Lack of placebo group
vi. Flexible dosing may have not produced optimal plasma levels for a response

3. Other literature (Please refer to Appendix B.)

G. Quetiapine

1. Examinations of dosing trends have revealed a growing percentage of patients who receive more than 750mg/d

2. **A Canadian, Multicentre, Double-Blind, Randomized, Parallel-Group Study of the Safety, Tolerability, and Efficacy of Treatment with Higher Doses of Quetiapine Fumarate (Seroquel®) Greater Than 800mg/d in Schizophrenic or Schizoaffective Subjects**, MacEwan, et al. 2005.51 (Refer to Appendix B.)
   a. Study designed to compare safety, efficacy and tolerability of quetiapine 800mg/d with doses > 800mg/d over an 8 week period in patients non- or partially responsive to 800mg/d of quetiapine
   b. Methods
      i. Patient population
         • Men and women, age 18-65 years
         • Persistent positive or negative symptoms
         • 70 ≤ PANSS Total Score < 110
         • Clinical Global Improvement- Severity of Illness (CGI-S) score ≥ 4 (moderately ill)
         • Treated as in- or outpatients
      ii. Interventions
         • Previous antipsychotic medication tapered off over 7 days
         • 4-week open-label phase identified responders to 800mg/d
         • Non- or partial responders then randomized to doses > 800mg/d or 800mg/d in 2:1 fashion
      iii. Primary endpoint was increase in total Simpson-Angus Scale using LOCF approach
      iv. Secondary endpoints used ITT approach
         • Occurrence of other adverse effects
         • Change in weight, BMI, ECG, metabolic laboratory values
         • Reduction in PANSS Total
   c. Results
      i. After 4-week open-label phase, 43 patients were randomized to 800mg quetiapine; 88 patients were randomized to doses > 800mg
      ii. 120 patients required for statistical power of 80% for non-inferiority trial in extrapyramidal events
      iii. Safety measures

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Figure 4: Mean Total SAS scores by treatment

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Efficacy and pharmacokinetic results

There was no statistical difference observed between treatment groups, based on the mean change in Total PANSS scores from baseline to end of treatment (Figure 1).

Figure 1: Mean Total PANSS Score by treatment, Seroquel 800mg and Seroquel >800mg (Observed cases, Full Analysis set)

* Increase of 3.1% (95% CI: -7.8% to +14%, p=0.7553) in percent of patients experiencing increase in EPS in both groups (no significant increase observed in > 800mg group)

iv. Efficacy measures

![Figure 5: Mean Total PANSS score by treatment](image)

- No significant difference observed between treatment groups

b. Comments
   i. Study sponsored by AstraZeneca®
   ii. Primary objective to prove safety of higher doses
   iii. Listed secondary objective to obtain indication for treatment with doses > 800mg/d
   iv. Not a treatment-resistant population
   v. No indication of target dose for group treated with > 800mg/d

3. Other literature (Please refer to Appendix B.)
   a. Case reports demonstrate use up to 2400mg/d
   b. Treatment with higher doses is successful in most case reports
   c. Significant weight gain resulted with most patients

H. Ziprasidone

   (Refer to Appendix B.)
   a. Letter to the editor describing a retrospective electronic record review to determine safety, efficacy, and tolerability of ziprasidone administered in higher doses in a treatment-resistant population
   b. Methods
      i. Patient population
         - Review of 14,000 patient records from July 1998 – November 2004 → 106 evaluable records of patients with schizophrenia and affective spectrum disorders
         - Inpatient, partial hospital, and outpatient settings
         - Had partial response to 160mg/d of ziprasidone
         - Free from side effects at 160mg/d of ziprasidone
         - Enough time had elapsed for a complete response to be seen
      ii. Efficacy measures
         - Symptom severity assessed with 5-point Likert scale (1=no symptoms; 5=extreme symptoms)
         - Comparison of Global Assessment of Functioning
         - Effect size: change in Likert scale/SD for each symptom
c. Results
   i. One month > time of treatment > 2 years (mean = 138.3 d)
   ii. Dosages ranged from 180-640mg/d (mean= 283.8 mg/d)
       • Most common: 240mg (n=45) and 320mg/d (n=41)
   iii. Efficacy measures

Table 8: Symptom Improvement With Doses >160mg/d\textsuperscript{55}

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Effect Size*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorganized thought</td>
<td>1.87</td>
</tr>
<tr>
<td>Delusions</td>
<td>1.40</td>
</tr>
<tr>
<td>Internal preoccupation</td>
<td>1.11</td>
</tr>
<tr>
<td>Bizarre elements</td>
<td>1.05</td>
</tr>
<tr>
<td>Suicide risk</td>
<td>1.65</td>
</tr>
<tr>
<td>Anger</td>
<td>1.36</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0.95</td>
</tr>
<tr>
<td>Irritability</td>
<td>0.86</td>
</tr>
<tr>
<td>Rapid Mood Changes</td>
<td>0.84</td>
</tr>
</tbody>
</table>

*Large improvement ≥1
Moderate improvement 0.7-0.99

iv. Safety measures
   • 77.4% of patients treated reported no adverse events (please see Appendix D for specific events reported)
   • 2 of the 24 patients who reported events required ziprasidone discontinuation (1 for restless legs and 1 for akathisia)
   • No evidence of a correlation between ziprasidone dose and QTc interval was found
   • Odds of reporting adverse event increased 1.11-fold (11%) for each increase of 80mg/d (95% confidence interval, 0.74-1.68; p=0.673)

v. Comments
   • Retrospective electronic record review
   • Treatment resistance criteria = partial response to 160mg/d

2. Other literature (Please refer to Appendix B.)
   a. One report of debilitating dystonia requiring hospitalization at dose of 240mg/d\textsuperscript{56}
   b. Case series demonstrates no significant increase in QTc at doses of 240-320mg/d\textsuperscript{57}

I. Aripiprazole
   1. Only case reports available for review\textsuperscript{58-61} (Please refer to Appendix B.)
      a. Five reports of treatments up to 60mg/d\textsuperscript{58-60}
         i. Two successful treatments\textsuperscript{59,60}
         ii. Other patients had to be switched to other therapies\textsuperscript{58,60}
      b. One report of 45mg/d treatment was unsuccessful, and patient was restarted on haloperidol \textsuperscript{60}
      c. One report of patient titrated to 75mg/d over 13 weeks\textsuperscript{61}
         i. Dose maintained for 14 weeks
         ii. Tapered to discontinuation over 10 moths with no relapse of symptoms reported
      d. Reported side effects are minimal, with significant weight loss occurring in 4 patients
J. Paliperidone
   1. Recommended dosing = 6-12 mg/day\textsuperscript{24}
   2. Phase III clinical trial evaluated fixed doses of paliperidone 3, 9, and 15mg/day and found no significant difference in response (measured by change in PANSS) between 9mg and 15mg groups\textsuperscript{62}
   3. Possible role in treatment-resistance and effectiveness of higher dosing remains unknown

V. Conclusions
   A. Package insert dosing is determined with studies that often exclude treatment-resistant patients to establish efficacy in the general treatment population
   B. Clozapine is still the drug of choice (and the only antipsychotic indicated) for treatment resistance
   C. For patients who are unable or unwilling to comply with monitoring parameters for clozapine treatment, higher dose atypical antipsychotics may offer an alternative
   D. For treatment-resistant schizophrenia, olanzapine currently has the best evidence supporting use of doses higher than that recommended by the FDA
References: