Clinical Implications of Research in Adolescent Schizophrenia

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Disclosure Information
S. Charles Schulz, M.D.

- I have the following financial relationships to disclose over the last five years:
  - Consultant for Eli Lilly, AstraZeneca,
  - Speaker’s Bureau for Eli Lilly, AstraZeneca
  - Grant/Research Support from Abbott, Eli Lilly, AstraZeneca, MIND Institute, NIMH
  - Stockholder in None
  - Honoraria from AstraZeneca, Eli Lilly
  - Employee of None

- I will discuss off label use and/or investigational use in my presentation

Can Children Recognize When They Have Problems?

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Objectives

- By utilizing a case example, provide scientific background for decisions in the approach to a young person with schizophrenia
- Review recently completed studies that address pharmacotherapy for young people with psychosis with a focus on efficacy, dosing, and side-effect profile
- Discuss recent work on steps to treat young people not fully responsive to initial treatment

Case Summary

Initial Presentation

- A 16 year old male is admitted to UMMC after voicing threats to kill his mother. Patient has 8 month history of paranoia, auditory hallucinations, poor self care. No symptoms of mania.
- Past history of depression, anxiety, and cannabis dependence. Symptoms were treated with SSRIs, but discontinued secondary to "activation."
- Physical exam WNL. Labs positive for cannabis.

Case Summary

Treatment Options – Step One

- Lithium carbonate
- Atypical antipsychotic
- SSRI
- Molindone and benztropine
- Watchful waiting / Substance Abuse Unit

Diagnosis and Epidemiology of Schizophrenia

When It Occurs in Adolescents

- Psychotic symptoms of people who develop schizophrenia frequently begin during teenage years – as many as 40% of cases in males (Loranger, 1984)
- The diagnosis of schizophrenia is generally stable in the first episode after 6 months from index interview (Carlson, 1994)
- Outcome may be poorer in earlier onset schizophrenia; however, large scale studies have not been performed (Röpcke, 2005)
Brain Imaging Studies Reveal Morphometric Differences Between Adolescent Schizophrenia Patients and Controls

- MRI studies reveal differences in ventricular and cortical areas (Frazier, 1996; Friedman, 1999; Kumra, 2000)
- Imaging studies suggest possibility of “progression” of imaging measures during adolescence (Rapoport, 1999), but not in all studies (James, 2002)
- Functional imaging studies also show differences between patients and controls (Jacobsen, 1997)

An MRI Study of Adolescent Patients with Either Schizophrenia or Bipolar Disorder as Compared to Healthy Control Subjects
Friedman L. et al., Biological Psychiatry, 1999

Frontal Cerebrospinal Fluid (CSF) Percent in Adolescent Schizophrenic Patients, Bipolar Patients, and Normal Controls

- Gender: $F = 0.71$, NS
- Contrast 1: Patients vs controls $t = -3.81$, $P = 0.003$
- Contrast 2: Schizophrenic vs bipolar $t = 0.00$, NS

Modified from Friedman L. et al., Biol Psychiatry 1999;46:78-88

Alterations in Patterns of Gyrification in Children and Adolescents with Schizophrenia
White et al. (2003) Biological Psychiatry
Progressive Cortical Change During Adolescence in Childhood-Onset Schizophrenia
Rapoport JL et al., Arch. Gen Psychiatry, 1999

Cognitive Impairment in Adolescents with Schizophrenia
Kenny et al., Am J Psychiatry, 1997

Objective: To assess adolescent subjects with schizophrenia using an objective neuropsychological battery
Methods: Adolescent patients (N=17) were compared to controls (N=17) utilizing an age-appropriate neuropsychological battery
Results: Patients were impaired on nearly all measures with their greatest difficulty seen in working memory and attention.
Conclusions: The subjects had a generalized cognitive dysfunction with greatest difficulties in attention and working memory
(The authors have utilized these findings to plan clinical treatments in day hospital and outpatient clinic)
MIND Clinical Imaging Consortium
Research Sites

- MIND Institute – Albuquerque, NM
- University of New Mexico – Albuquerque, NM
- University of Iowa – Iowa City, IA
- Harvard University – Boston, MA
- University of Minnesota – Minneapolis, MN

The sites participated in a multicenter assessment of schizophrenia patients (first episode, persistently ill, and controls) using MRI and neuropsychology testing. (Overview, Lauriello J et al., Schizophr Bull: 33,375-376) Over 300 subjects were included.

Subjects for First Episode Analysis

- Inclusion Criteria: Schizophrenia, schizophreniform disorder, or schizoaffective disorder
- Definition of First Episode: Four criteria used which balance length of illness and past antipsychotic treatment
- Assessment Method: CASH or SCID-I interview by trained assessors
- Neuropsychological assessment (Sponheim S et al., WinterWorkshop 2008) and MRI scanning (Morrow EM et al., Schizophr Bull 33:347-348, 2007) were performed

Results – Neuropsychology Tests Only

1. Stepwise LDA: Sensitivity = 78.5%, Specificity 85.1%
   - DX
   - Predicted SZ: 22
   - Predicted HC: 6

2. PCA-LDA: Sensitivity 78.5%, Specificity 91.5%
   - DX
   - Predicted SZ: 22
   - Predicted HC: 6

Results – sMRI Only

1. Stepwise LDA: Sensitivity = 53.6%, Specificity 74.5%
   - DX
   - Predicted SZ: 15
   - Predicted HC: 13

2. PCA-LDA: Sensitivity 67.9%, Specificity = 72.3%
   - DX
   - Predicted SZ: 19
   - Predicted HC: 9
Results – Neuropsychology and sMRI

1. Stepwise LDA: Sensitivity = 60.7%, Specificity = 72.3%

<table>
<thead>
<tr>
<th>DX</th>
<th>SZ</th>
<th>HC</th>
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</thead>
<tbody>
<tr>
<td>Predicted SZ</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Predicted HC</td>
<td>11</td>
<td>34</td>
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</table>

2. PCA – LDA: Sensitivity = 89.3%, Specificity = 93.6%

<table>
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<th>DX</th>
<th>SZ</th>
<th>HC</th>
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<tbody>
<tr>
<td>Predicted SZ</td>
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<td>3</td>
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<tr>
<td>Predicted HC</td>
<td>3</td>
<td>44</td>
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</table>

Relationship between Duration of Untreated Psychosis and Outcome in First-Episode Schizophrenia: A Critical Review and Meta-Analysis
Perkins DO et al., Am J Psychiatry 2005;162:1785-1804

Case Summary
Treatment Plan One

- Risperidone titrated to 4 mg po qhs which led to substantial symptom relief
- Mild EPS treated with benztpine
- Patient entered Mentally Ill/Chemically Dependent (MI/CD) partial hospital program

Studies of Atypical Antipsychotic Medications in Adolescents and Young Adults

- The side effect profile of the second generation antipsychotic (SGAs) medications – differences between adolescents and adults
- The efficacy of SGAs in adolescents and young adults – the initial controlled studies
Initial Anticholinergic Prophylaxis for Neuroleptic-Induced Extrapyramidal Syndromes

Incidence of extrapyramidal syndromes (EPS) for prophylaxis and no-prophylaxis groups by age decade. Individual syndromes are shown as insets. Asterisk indicates $p<0.001$; dagger, $p<0.05$.

Keepers GA et al., Arch Gen Psychiatry 40:1113-1117;1983

Note high risk for EPS in the 10-19 year old age group

Olanzapine Study Design
Findling et al., J Am Acad Child Adolesc Psychiatry 42:170-175;2003

- 8 week, open label trial of olanzapine
  - Patients seen bi-weekly throughout the trial.
- 16 subjects were enrolled
  - Subjects receive 2.5 – 20 mg/day of olanzapine
  - Medication to be increased every 3 days in 2.5 mg increments, as indicated/tolerated.

Movement Rating Scales
Mean Total Scores*

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<tr>
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<th>Baseline</th>
<th>Week 8</th>
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<tr>
<td>SAS</td>
<td>0.80</td>
<td>0.87</td>
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<tr>
<td>AIMS</td>
<td>0.73</td>
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</tr>
<tr>
<td>BAS</td>
<td>0.47</td>
<td>0.40</td>
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*No significant differences between average scores were found

Findling et al., J Am Acad Child Adolesc Psychiatry 42:170-175;2003

Weight Gain and Dosing Analysis

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>Week 8</th>
<th>Change</th>
<th>P-Value*</th>
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<tbody>
<tr>
<td>Average Weight (lbs)</td>
<td>145.83</td>
<td>159.5</td>
<td>13.67</td>
<td>&lt; .001</td>
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<table>
<thead>
<tr>
<th></th>
<th>Minimum</th>
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<th>Mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>End of Study Dose (mg)</td>
<td>3.75</td>
<td>20.00</td>
<td>12.42</td>
<td>5.31</td>
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</tbody>
</table>

*using paired t-test, and a LOCF intent-to-treat analysis

Findling et al., J Am Acad Child Adolesc Psychiatry 42:170-175;2003
Changes in Metabolic Parameters in Adolescents with Schizophrenia or Bipolar I Disorder During Treatment with Olanzapine: A Pooled Analysis of 4 Studies
Kryzanovskaya L et al. APA Annual Meeting, San Diego, CA, 2007 (NR 736)

- Metabolic effects of olanzapine have been observed in adults. The current study compared metabolic parameters measured in adolescents to an adult database.
- Adolescents had an increase in metabolic parameters and significantly more adolescents gained weight than in adults (65% vs 35%). Smaller changes were seen in adolescent patients in fasting glucose and triglycerides than in adults.
- The findings demonstrate differences in metabolic effects of olanzapine between teenagers and adults.

Medication Management: Controlled Trials of Atypical Antipsychotics in Young First-Episode Patients

- Lieberman et al. (2003): Benefit seen for olanzapine vs haloperidol (MMA) on PANSS score. Less EPS, but more weight gain. Significantly more subjects completed trial on olanzapine.
- Schooler et al. (2005): Both risperidone and haloperidol reduced symptoms, but risperidone forestalled relapse. More EPS seen on haloperidol and more prolactin with risperidone.
- McEvoy et al. (2007): Treatment discontinuation and symptom reduction similar for three medications tested – olanzapine, quetiapine, and risperidone.

A Pilot Study of Risperidone, Olanzapine and Haloperidol in Psychotic Youth: A Double-Blind, Randomized, 8-Week Trial
Sikich L et al., Neuropsychopharmacology 29:133-145;2004

- Introduction: A pilot study to assess the safety and efficacy of risperidone and olanzapine versus haloperidol in teenagers with at least one positive psychotic symptom.
- Methods: Subjects were between 8-19 years old and suffered from schizophrenia spectrum disorders or affective disorders. In all, 50 patients were studied over an 8-week period. Subjects were classified as responders/non-responders by CGI or BPRS.
- Results: The response rates were: 88% for olanzapine, 74% for risperidone, and 53% for haloperidol. There were no statistically significant differences between the groups. EPS was seen in many subjects with significantly more noted in the haloperidol group. Weight gain was seen in all three groups.
- Discussion: This represents the first double-blind study of psychotic adolescents using new antipsychotics. Results indicate that side-effects may be higher in youth.
A Comparative Pilot Study of Second-Generation Antipsychotics in Children and Adolescents with Schizophrenia-Spectrum Disorders


- There is limited data to guide clinicians in selecting a SGA in adolescents with psychotic disorders.
- In this study 30 subjects (10-18 years old) were randomly assigned to olanzapine, risperidone, or quetiapine. The study psychiatrist openly titrated medication dose.
- The results did not show differences between the medication on the primary outcome (PANSS scores) although variance was large. No significant AIMS scores were seen. Sixty-three percent of subjects had a greater than 7% increase in weight over 12 weeks.
- Although a small study, the results point so the importance of comparative studies to provide a basis for medication selection.

The Efficacy and Safety of Olanzapine in Adolescents with Schizophrenia: The Results from a Double-blind, Placebo-controlled Trial

The Efficacy and Safety of Risperidone in Adolescents with Schizophrenia

Haas M et al., J. Child Adolesc Psychopharmacol. 19:611-21;2009

- Introduction: Purpose of the study was to test two dose ranges of risperidone vs. placebo in adolescents with schizophrenia.
- Methods: An RTC of risperidone (1-3 mg/d) vs. risperidone (4-6 mg/d) vs. placebo over 6 weeks.
- Results: One hundred sixty seven patients participated in the study which showed greater improvement in both risperidone groups. AEs included somnolence, agitation, and headache in the low dose group and EPS in the higher dose group.
- Conclusions: Both sides were superior to placebo and well tolerated. The risk/benefit assessment favors 3 mg dosing.

Efficacy of Aripiprazole in the Treatment of Adolescents with Schizophrenia

Findling RL et al., Am J Psychiatry 165:1432-1441;2008

- Intro: Lack of options for schizophrenia in adolescents was noted.
- Methods: A six-week RTC was conducted comparing placebo to aripiprazole at 10 or 30 mg.
- Results: Three hundred two patients were studied and both doses of aripiprazole were statistically superior to placebo. Five percent of subjects discontinued aripiprazole secondary to adverse events.
- Conclusions: Both doses of aripiprazole were superior to placebo in this six-week study.
Efficacy of Aripiprazole in the Treatment of Adolescents with Schizophrenia
Robb AS et al., Presented at APA Annual Meeting, San Diego, CA 2007

Tolerability of Aripiprazole in the Treatment of Adolescents with Schizophrenia
Findling RL et al., APA Annual Meeting, May 19-24, 2007 (NR741)

• **Intro:** Authors note lack of evidence about efficacy and safety in schizophrenia.

• **Methods:** A six week RTC was conducted comparing placebo to aripiprazole at 10 or 30 mg.

• **Results:** Authors note 85% of the 302 subjects completed the study. The most common AEs for aripiprazole were EPS, somnolence, and headache. Greater than 7% weight gain was seen as follows: aripiprazole 10 mg (4.8%), aripiprazole 30 mg (6%), placebo (1%). Prolactin decreased in all three areas of the study.

• **Conclusions:** Aripiprazole was generally well tolerated.

Double-Blind Comparison of First- and Second-Generation Antipsychotics in Early-Onset Schizophrenia and Schizoaffective Disorder: Findings from the Treatment of Early Onset Schizophrenia Disorders (TEOSS) Study

• **Objective:** To assess the safety and efficacy of two atypical antipsychotic medications compared to a first-generation compound (plus an anticholinergic medication).

• **Method:** Pediatric patients were assigned to either olanzapine, risperidone or molindone plus benztropine in the 8-week trial. The primary measures were CGI and PANSS.

• **Results:** One hundred nineteen subjects were entered in the study and 70 completed the 8-week trial. The olanzapine arm was terminated early because of weight gain. Both atypicals showed significant weight gain and increased akathisia was associated with molindone.

• **Conclusions:** Risperidone and olanzapine did not show superiority. Adverse effects varied between the medications. The authors note that the findings bring into question the high use of second-generation antipsychotics.

Case Summary
Subsequent Course

• Patient refused suggestion of risperidone long-acting injectable and was re-started on oral risperidone and benztropine. Psychosis improved.

• Patient received care elsewhere for the next year including adequate trials of atypical antipsychotics.

• Returned to UMMC with significant psychotic symptoms.
Case Summary

Treatment Options

- Two atypical antipsychotics
- Atypical antipsychotics plus augmenting agent (e.g. lithium)
- ECT
- Clozapine

Psychobiologic Correlates of Treatment Response in Schizophrenia
Lieberman JA et al., Neuropsychopharmacology 14:135-215, 1996

- This paper reviews response rates and correlates of response of patients being treated for their first episode of psychosis. Mean age = 24.3 years old, N=70.
- Response to initial treatment was high with only 11/70 patients not remitting
- Assessment of response after subsequent relapse showed diminution of response rates.

Childhood-Onset Schizophrenia: A Double-blind Clozapine-Haloperidol Comparison
Kumra S et al., Arch Gen Psychiatry, 53:1090-1097, 1996

- Background: The safety and efficacy of clozapine was assessed in a treatment-refractory group on COS
- Methods: A six-week, double-blind comparison was performed with 21 subjects (mean age 14.0)
- Results: Clozapine was superior to haloperidol in treatment of psychosis. The authors note that the neutropenia and seizures were of concern
- Conclusions: Clozapine was superior to haloperidol in this difficult to treat population, but careful monitoring is needed.

Clozapine and “High-Dose” Olanzapine in Refractory Early-Onset Schizophrenia: A 12-Week Randomized and Double-Blind Comparison
Kumra S et al., Biol Psychiatry, 2008 epub

- Introduction: A study designed to evaluate clozapine versus “high dose” olanzapine in treatment refractory adolescents with schizophrenia.
- Methods: Young people (10-18 years old) who were treatment refractory received either clozapine or olanzapine for 12 weeks.
- Results: Clozapine response rates (66%) were significantly higher than olanzapine response rates (33%). Significant weight gain was seen in both groups.
- Conclusions: The results support the use of clozapine in early stage schizophrenia when refractory to first-line treatments.
Early Use of Clozapine for Poorly Responding first-Episode Psychosis

- The investigators note that a sub-group of first-episode patients have ongoing psychotic symptoms.
- Patients in the CAMH program followed a medication algorithm. Seventy-six percent of the 123 patients who agreed to try clozapine were compared to those who refused.
- The clozapine treated group had a 19 point reduction in BPRS scores (53-34) while the other patients had a 2 point increase.
- The authors note reluctance to use clozapine early in the illness and suggest that clozapine may have an important role in early stage patients.

Case Summary
Last Evaluation

- Patient started on oral disintegrating clozapine – titrated to 500 mg/day
- Psychosis improved significantly
- Patient currently full-time student in senior year at public high school

Clinical “Pearls”

- Even though there are many controversies, getting started early in treatment can lead to improved outcomes
- Emerging controlled trials are providing evidence about antipsychotic medication – remember that adolescents have significant sensitivities to these medications
- Evidence is emerging that poorly responsive young patients may benefit from advanced steps in treatment algorithms – including clozapine

Conclusions

- Schizophrenia occurring in adolescents is a serious development and is accompanied by neuropsychiatric measures similar to those in adults.
- Recently, controlled trials of atypical antipsychotic medications have emerged which are informative, but raise questions about unique safety and tolerability in teenagers.
- A recent controlled comparison study brings attention to the use of traditional antipsychotic medication plus benztropine.
- Although the majority of young people treated with antipsychotic medications respond to treatments, not all do and others do not achieve remission after relapse. Active treatment strategies are emerging for these patients.
Bibliography

5. Friedman L et al., Biological Psychiatry, 1999
10. Kumra S et al., Arch Gen Psychiatry, 53:1090-1097;1996
12. Loranger AW. Arch Gen Psychiatry, 41:157-161;1984
18. White et al. (2003) Biological Psychiatry

Juvenile-Onset Schizophrenia

Edited by Robert L. Findling, M.D., and S. Charles Schuls, M.D.
Assessment, Biogenesis and Treatment.