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CME Outfitters
Best Practices in Schizophrenia Management

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Disclosures

- **Research/Grants:** AstraZeneca Pharmaceuticals LP; National Institute of Mental Health (NIMH); Otsuka America Pharmaceutical, Inc.; Myriad Genetics Inc./Rules-Based Medicine, Inc.

- **Consultant:** Genentech, Inc.; Lilly USA, LLC
Learning Objective

Tailor treatments in young patients with schizophrenia for optimal outcome.
Arguments for and against the CT/MRI in the work-up of first-episode psychosis

Arguments against:
- Many incidental findings
- Abnormal finding does not establish causality
- Low yield

Arguments for:
- MRI can substitute for other screening (e.g. temporal lobe sclerosis of epilepsy; metabolic disorders affecting white matter)
- Medico-legal (missed brain tumor)
- Baseline for chronic disorder
- Negative CT/MRI provides reassurance and support of diagnosis of schizophrenia

† Not been empirically validated; CT = computed tomography; MRI = magnetic resonance imaging.
Results: Neuropsychology and Structural MRI

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

<table>
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<tr>
<th>Diagnosis</th>
<th>Schizophrenia</th>
<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted Schizophrenia</td>
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<td>13</td>
</tr>
<tr>
<td>Predicted Healthy Controls</td>
<td>11</td>
<td>34</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
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<th>Healthy Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted Schizophrenia</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Predicted Healthy Controls</td>
<td>3</td>
<td>44</td>
</tr>
</tbody>
</table>

LDA = Linear Discriminant Analysis
PCA = Primary Component Analysis
Figure 2. TMAP Antipsychotic Algorithm: 2006

Choice of antipsychotic should be guided by considering the clinical characteristics of the patient and the efficacy and side-effect profiles of the medication.

Forward stage(s) can be skipped depending on the clinical picture or history of antipsychotic failures, and returning to an earlier stage may be justified by history of past response.

Stage 1: First-Episode Schizophrenia
- Trial of a single SGA (aripiprazole, olanzapine, quetiapine, risperidone, or ziprasidone)
  - Partial or nonresponse

Stage 2
- Trial of a single SGA or FGA (not SGA tried in Stage 1)
  - Partial or nonresponse

Stage 3
- Clozapine
  - Partial or nonresponse

Stage 4
- Clozapine + (FGA, SGA, or ECT)
  - Inconsistent results in RCTs
  - Nonresponse

Stage 5
- Trial of a single agent FGA or SGA (not tried in Stages 1 or 2)

Stage 6
- Combination therapy eg, SGA + FGA, combination of SGAs, FGA or SGA + ECT, FGA or SGA + other agent (eg, mood stabilizer)

Consider earlier trial of clozapine in patients with a history of recurrent suicidality, violence, or comorbid substance abuse. Persistence of positive symptoms > 2 years warrants and > 5 years requires a clozapine trial, independent of number of preceding antipsychotic trials.

Value in clozapine failures not established

Case reports; no controlled studies of combinations in long-term treatment of schizophrenia.

Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of Early Psychosis: A Randomized, Double-Blind 52-Week Comparison

- Study assessed outcome by All-Cause Treatment Discontinuation of 52-week assignment to either olanzapine, quetiapine, or risperidone. Subjects also received PANSS rating scales as a secondary measure.
- Mean age ranged from 24.7 years for olanzapine, 25.0 years for quetiapine, to 23.9 years for risperidone, and a mean duration of illness of 12.9 months.
- While the All-Cause Treatment Discontinuation results were statistically similar for all three medications, there were significant differences on the secondary PANSS measures at certain points of the 52-week trial.
- All three medications were associated with drowsiness and weight gain. Menstrual irregularities were noted for those patients taking risperidone.

Cardiometabolic Risk of Second Generation Antipsychotic Medications During First-time Use In Children And Adolescents

- **Introduction:** Authors note concern of cardiometabolic effects of second-generation antipsychotics, but note little data in the literature

- **Methods:** In the SATIETY study, patients from age 4-19 were followed (N = 205); subjects had mood or schizophrenia spectrum diagnoses

- **Results**
  - Weight gain was significant for all four medications assessed, ranging from 4.4 kg-8.5 kg over 10 weeks
  - Weight gain in an untreated group was 0.2 kg
  - Metabolic measures increased for olanzapine and quetiapine, but only for triglycerides for risperidone
  - There was no difference between aripiprazole and untreated subjects

- **Conclusions:** Weight gain was seen for each second-generation group while there were differences across the group for metabolic measures

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 two-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.

Response Rates For Antipsychotic Trials 1 And 2 (Olanzapine Or Risperidone) Followed By Trial 3 (Clozapine)

Clinical Connections

- A medical work-up for first-episode psychosis combines broad screening, exclusion of specific diseases informed by treatability and epidemiology and medical baseline measures.
- Initiate treatment quickly in first episode patients and be aware that approximately 25% of these young people are not responding to first-line antipsychotics.
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