First-episode Schizophrenia: Setting the Stage for Successful Outcomes
Learning Objectives

• Initiate low-dose antipsychotic medication that minimizes physical health hazards
• Preemptively assess for and mitigate new side effects during treatment
• Incorporate psychosocial interventions to help patients set and achieve life goals
For an acutely psychotic patient at risk of imminent danger to self or others, but who is naïve to antipsychotic medication, the best choice would be:

1. IM benzodiazepine such as lorazepam
2. IM olanzapine with lorazepam
3. IM haloperidol with lorazepam
4. IM olanzapine without lorazepam
5. Seclusion and restraints without medication
Case Presentation:
First-Onset Psychosis

• A 22-year-old man is brought to the ER by his parents. They report that the man has been yelling at the television when the news comes on, muttering to himself frequently, and insisting on closing all of the blinds in the house during the day and night.

• In the waiting room, the man paces back and forth, clenching and unclenching his fists and mumbling to himself. He appears unkempt and has a slight odor. He now begins pacing faster and shouting a few words from time to time.
TREATING FIRST-EPISTODE PSYCHOSIS
Rapid Emergency Treatments for Acutely Psychotic Patients

- Reduce stressful environmental factors
- De-escalation techniques for cooperative patients
- Short-acting parenteral antipsychotic
  - With or without parenteral benzodiazepine
    - Greater risk of respiratory depression
  - With or without parenteral anticholinergic
    - Can cause oversedation; limit to use in setting of EPS
- Rapidly dissolving oral formulations or oral concentrates
- Ideally, choose antipsychotics or benzodiazepines with short half-lives and use at the lowest effective doses
- Reserve seclusion and mechanical restraints as last resorts

# Parenteral Options for Acutely Psychotic Patients

<table>
<thead>
<tr>
<th>Onset</th>
<th>Initial Dose</th>
<th>Considerations</th>
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<tbody>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
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<tr>
<td>Aripiprazole</td>
<td>60 m</td>
<td>9.75 mg IM</td>
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<tr>
<td>Haloperidol</td>
<td>1–2 m IV</td>
<td>5 mg IM/IV</td>
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<tr>
<td></td>
<td>30–60 m IM</td>
<td>IV haloperidol carries increased risk of QTc prolongation; slow IV drip may be used with appropriate cardiac monitoring</td>
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<tr>
<td>Olanzapine</td>
<td>15–45 m</td>
<td>10 mg IM</td>
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<tr>
<td></td>
<td>1–2 mg IM/IV</td>
<td>Use with a BZ increases risk of cardiopulmonary depression</td>
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<tr>
<td>Ziprasidone</td>
<td>30–45 m</td>
<td>20 mg IM</td>
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<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diazepam</td>
<td>30 m</td>
<td>5–10 IV</td>
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<tr>
<td></td>
<td></td>
<td>Avoid IM because of unpredictable absorption</td>
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<tr>
<td>Lorazepam</td>
<td>2–5 m IV</td>
<td>1–2 mg IM/IV</td>
</tr>
<tr>
<td></td>
<td>15–30 m IM</td>
<td>Most frequently used; also available as intranasal</td>
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<tr>
<td>Midazolam</td>
<td>120 IV</td>
<td>2.5–5 mg IM/IV</td>
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<tr>
<td></td>
<td>4–6 h IM</td>
<td>Higher risk of respiratory depression compared to diazepam or lorazepam</td>
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</tbody>
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After Acute Stabilization: Therapeutic Alliance and Low-Dose Antipsychotic

- Educate patient
- Establish relationship with family
- Careful documentation of symptoms (may change over time)
- Low-dose antipsychotic
  - No evidence favoring any antipsychotic—or antipsychotic class—over another
- May need to use adjunct benzodiazepine (short half-life) to relieve distress, insomnia, and behavioral disturbances while antipsychotic medication takes effect

Additional Considerations

- Affective psychopathology
- Adverse effects: first-episode patients have higher rates of:
  - EPS when treated at chronic antipsychotic doses
  - Possibly metabolic complications
- Monitor weight, lipid profile, fasting blood sugar

REDUCING RELAPSE AND READMISSION
Factors Affecting Outcomes

- Duration of untreated psychosis >6 months
- No remission within 3 months
- Persistent substance/cannabis use
- Schizophrenia diagnosis vs. brief psychotic episode
- Poor/deteriorating premorbid social functioning
- Early age of onset
- Development of EPS
- Distressing emotional environment

## Duration of Untreated Psychosis


<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Correlation (95% CI)</th>
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<tbody>
<tr>
<td>General symptomatic outcome (n = 15)</td>
<td>−0.15 (−0.22 to −0.09)</td>
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<tr>
<td>Positive symptoms (n = 8)</td>
<td>−0.14 (−0.22 to −0.07)</td>
</tr>
<tr>
<td>Negative symptoms (n = 18)</td>
<td>−0.13 (−0.21 to −0.05)</td>
</tr>
<tr>
<td>Hospital treatments (n = 11)</td>
<td>−0.09 (−0.22 to 0.04)</td>
</tr>
<tr>
<td>Social functioning (n = 14)</td>
<td>−0.18 (−0.27 to −0.09)</td>
</tr>
<tr>
<td>Employment (n = 7)</td>
<td>−0.05 (−0.16 to 0.06)</td>
</tr>
<tr>
<td>Global outcome (n = 19)</td>
<td>−0.17 (−0.26 to −0.07)</td>
</tr>
<tr>
<td>Quality of life (n = 7)</td>
<td>−0.10 (−0.22 to 0.01)</td>
</tr>
<tr>
<td>Remission (n = 10)</td>
<td>−0.14 (−0.23 to −0.06)</td>
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No Remission Within 3 Months: Consider Clozapine?

- Applied treatment algorithm: 2 sequential SGA trials followed by clozapine
- Findings reinforce high proportion of response initially in FEP
- But <20% response to second SGA in those with a poor response to the first
- Olanzapine was superior to risperidone
- Response rate increased for those who agreed to a trial of clozapine

Continued vs. Discontinued Cannabis Use in Patients With Psychosis

Greater risk of psychosis relapse in nonuser
Greater risk of psychosis relapse in continued cannabis user

Rates of Relapse With Continued vs. Discontinued Treatment

178 asymptomatic patients treated for ≥1 year with AP. Randomized to quetiapine 400 mg/day (n=89) or placebo (n=89).

Quet: 41% (95% CI 29–53). PBO: 79% (95% CI 68–90) (p<0.001).

Chen EYH et al. BMJ 2010;310:c4024.
Most First-Episode Patients Will Accept an LAI

- 46 first-episode patients with $\leq 16$ weeks of lifetime antipsychotic exposure randomly assigned to continuation of oral vs. LAI (1:2 ratio)
- Those randomized to LAI were given option of opting out to continue oral
- Primary outcome: adherence at week 12
- Results
  - 73% of those randomized to LAI (19/26) chose to stay on LAI
  - Patients accepting LAI were significantly more likely to be adherent at the week 12 endpoint ($p=0.035$)

Treatment Beyond the Positive Symptoms: Psychosocial Strategies

- Patients want jobs and independent living
- Combined supported employment/education program
- Assertive community treatment (ACT)
- Social skills training
- Cognitive behavior therapy (CBT)
- Weight management
- Cognitive remediation
- Peer support and peer-delivered services
- Combined psychosocial interventions
- Family intervention

Coordinated Specialty Care (CSC)

• Team-based
• Assertive case management
• Individual or group psychotherapy
• Supported employment and education services
• Family education and support
• Low-dose antipsychotic
RAISE Early Treatment Program: NAVIGATE vs. Community Care

- NAVIGATE participants:
  - Were more likely to endorse receipt of key services
  - Remained in treatment longer

Primary Outcome: QLS Total

Effect size: 0.31

Summary

- Early identification and treatment can limit functional loss in schizophrenia
- Antipsychotic treatment should be dosed low
- First-episode patients are more sensitive to side effects
- Onset of psychosis completely upends the lives of individuals who are transitioning into adulthood; psychosocial strategies and support are ESSENTIAL