Treatment Resistance and Other Complicating Factors in the Management of Schizophrenia
Learning Objective

- Apply evidence-based treatment guidelines to the clinical care of patients with treatment-resistant schizophrenia
Pretest Question 1

A 37-year-old woman with schizophrenia has failed to respond to 2 sequential adequate trials of antipsychotic monotherapy (first olanzapine, then aripiprazole). Which of the following has the best evidence of efficacy for a patient in this situation?

1. High dose of her current monotherapy (aripiprazole)
2. Augmentation of her current monotherapy with another atypical antipsychotic
3. Switch to clozapine
4. 1 and 3
5. 1, 2, and 3
Meta-analysis of short-term clozapine augmentation with a second antipsychotic shows:

1. No significant improvement over clozapine monotherapy
2. Modest improvement over clozapine monotherapy; short-term tolerability concerns
3. Modest improvement over clozapine monotherapy; no short-term tolerability concerns
Treatment-Resistant Schizophrenia

- Prevalence ranges from 13% to 43%\(^1\)
- Non-response in first weeks predicts eventual non-response\(^2\)

Remission After Relapse:
WHO 15-Year Follow-up Study of Cohort of First-Contact Cases

Current Practice

Inadequate response

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

*Oral or long-acting injectable
Recommended Practice

Inadequate response

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- Switch to different antipsychotic monotherapy*
- Clozapine monotherapy

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Recommended Practice

Inadequate response

Obtain plasma drug level of antipsychotic

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

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Hypothetical Thresholds for Atypical Antipsychotic Drug Effects

Striatal D2 receptor blockade (%)

Dose; plasma concentration

EPS and hyperprolactinemia threshold

Antipsychotic effect threshold

Usual Doses to Achieve 60–80% D2 Receptor Occupancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose range (mg/d)</th>
<th>Rec plasma levels (ng/mL)¹</th>
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</thead>
<tbody>
<tr>
<td>CLOZ</td>
<td>300–450</td>
<td>350–600</td>
</tr>
<tr>
<td>RISP</td>
<td>2–8</td>
<td>20–60</td>
</tr>
<tr>
<td>PALI</td>
<td>3–6</td>
<td>20–60</td>
</tr>
<tr>
<td>OLANZ</td>
<td>10–20</td>
<td>20–80</td>
</tr>
<tr>
<td>QUET</td>
<td>400–800</td>
<td>100–500</td>
</tr>
<tr>
<td>ZIP</td>
<td>40–200</td>
<td>50–200</td>
</tr>
<tr>
<td>ARIP</td>
<td>15–30</td>
<td>150–500</td>
</tr>
<tr>
<td>ILOP</td>
<td>12–24</td>
<td>5–10</td>
</tr>
<tr>
<td>ASEN</td>
<td>10–20</td>
<td>2–5</td>
</tr>
<tr>
<td>LURAS</td>
<td>40–160</td>
<td>&gt;70²</td>
</tr>
</tbody>
</table>

Recommended Practice

Inadequate response

- Levels below therapeutic range
  - Adherent?
  - PK failure?
    - High-dose antipsychotic monotherapy

- Obtain plasma drug level of antipsychotic
  - Switch to different antipsychotic monotherapy*
  - Clozapine monotherapy

*Oral or long-acting injectable
PK Failure: Rapid Metabolizers May Appear Treatment Resistant

<table>
<thead>
<tr>
<th>Substrate for:</th>
<th>1A2</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Asenapine</td>
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</tr>
<tr>
<td>Clozapine</td>
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</tr>
<tr>
<td>Iloperidone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lurasidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td></td>
<td></td>
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<tr>
<td>Paliperidone</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
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<tr>
<td>Risperidone</td>
<td></td>
<td></td>
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<tr>
<td>Ziprasidone</td>
<td></td>
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Recommended Practice

Inadequate response

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<table>
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<tr>
<th>Drug</th>
<th>Usual dose range (mg/d)</th>
<th>Rec plasma levels (ng/mL)</th>
<th>High-dosing recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLOZ</td>
<td>300–450</td>
<td>350–600</td>
<td>Max generally 900 mg/d; &gt;550 mg/d may require adjunct anticonvulsant</td>
</tr>
<tr>
<td>RISP</td>
<td>2–8</td>
<td>20–60</td>
<td>Approved up to 16 mg/d, but high doses usually not tolerated</td>
</tr>
<tr>
<td>PALI</td>
<td>3–6</td>
<td>20–60</td>
<td>Max generally 12 mg/d</td>
</tr>
<tr>
<td>OLANZ</td>
<td>10–20</td>
<td>20–80</td>
<td>Up to 90 mg/d in forensic settings</td>
</tr>
<tr>
<td>QUET</td>
<td>400–800</td>
<td>100–500</td>
<td>Up to 1800 mg/d in forensic settings</td>
</tr>
<tr>
<td>ZIP</td>
<td>40–200</td>
<td>50–200</td>
<td>Must take with food; up to 360 mg/d in forensic settings</td>
</tr>
<tr>
<td>ARIP</td>
<td>15–30</td>
<td>150–500</td>
<td>Not usually more effective</td>
</tr>
<tr>
<td>ILOP</td>
<td>12–24</td>
<td>5–10</td>
<td>Not well studied; may be limited due to risk of orthostatic hypotension</td>
</tr>
<tr>
<td>ASEN</td>
<td>10–20</td>
<td>2–5</td>
<td>Not well studied</td>
</tr>
<tr>
<td>LURAS</td>
<td>40–160</td>
<td>&gt;70^2</td>
<td>Must take with food; not well studied</td>
</tr>
</tbody>
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Recommended Practice

Inadequate response

Obtain plasma drug level of antipsychotic
- Levels within therapeutic range
- Adverse effects

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

*Oral or long-acting injectable
Efficacy of Antipsychotic vs. Placebo
Multiple-Treatments Meta-analysis

Switching to Another Antipsychotic for Efficacy

- Is common: ~1/3 of patients\(^1,2\)

- Has limited evidence of clinically relevant improvement\(^2,3\)

- CATIE study\(^4\)
  - Allowed comparison of patients randomly assigned at baseline to the same antipsychotic with those assigned to a different antipsychotic
  - Switching yielded no significant advantage for symptoms, neurocognition, depression, quality of life, or neurological side effects

\(^3\)Weiden PJ. Postgrad Med 2006;(spec no):27-44.
CATIE Phase 2: For those with schizophrenia who prospectively failed to improve with an SGA, clozapine was more effective than switching to another SGA.
Switching at First Episode

- 244 FEP patients
- 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 subgroup with poor response to first SGA
- Olanzapine was superior to risperidone

Response: CGI of 1 or 2, and/or BPRS thought disorder subscale score ≤6

Switching to Another Antipsychotic: Clinical Considerations

• Confirm current medication is optimized before switching
• Risk of destabilization and new adverse effects
• Poorer outcome difficult to interpret
• Gradually cross-taper the 2 antipsychotics
• Little empirical evidence to support any AP over another
  – Exception: clozapine

Clozapine Is Underused

• Clozapine use in the US\(^1\)
  – 5.5% of TRS patients

• Mean theoretical delay from meeting NICE criteria for TRS to clozapine initiation: 4 years\(^2\)

• Before commencing clozapine:\(^2\)
  – Antipsychotic polypharmacy: 36%
  – High-dose treatment: 34%

Adequate Trial of Clozapine: Plasma Levels

• Plasma drug level
  – Pre-dose (trough) threshold: 350 ng/mL (adequate trial)
  – Clozapine bioavailability
    • Dose dependent (can the first pass be saturated?)
    • Basis of cautious dose titration
    • Clozapine accumulation in some patients
  – Smoking induces CYP1A2

• Clozapine:norclozapine ratio
  – Norclozapine: potentially active metabolite; longer plasma half-life
  – Clozapine:norclozapine ratio: mean 1.32 across dose range
    • >3 suggests not trough sample
    • <0.5 suggests poor compliance in preceding day(s)

Adequate Trial of Clozapine: Duration

- Period recommended varies from 4 to 12 months
- Adequate trial should be at least 8 weeks at therapeutic response dose
- Response may be delayed longer in a proportion of patients:
  - 6 weeks: 30% of patients will respond
  - 3 months: another 20%
  - 6 months: further 10–20%
- Reasonable to test clozapine monotherapy for 6 months

Recommended Practice

- Inadequate response
  - Obtain plasma drug level of antipsychotic
    - Levels within therapeutic range
      - No adverse effects
        - PD failure?
          - Clozapine monotherapy
          - High-dose antipsychotic monotherapy
          - Switch to different antipsychotic monotherapy*
            - Antipsychotic polypharmacy

*Oral or long-acting injectable
Treatment-Resistant Psychosis: Are Hypothetical Thresholds for Atypical Antipsychotic Drug Effects Altered? (Pharmacodynamic Failure?)

Striatal D2 receptor blockade (%)

treatment-resistant psychosis threshold?

Dose; plasma concentration

usual antipsychotic effect threshold

standard dose
aggression/violence dose?
Recommended Practice

Inadequate response

Obtain plasma drug level of antipsychotic

Levels within therapeutic range

No adverse effects

PD failure?

High-dose antipsychotic monotherapy

Switch to different antipsychotic monotherapy*

Clozapine monotherapy

Antipsychotic polypharmacy

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High-Dose Withdrawal

- Double-blind RCT: 23 high-dose haloperidol (plasma level ≥15 ng/mL) patients with schizophrenia (no recent violent behavior) assigned to dose maintenance or reduction (to target plasma level of 10 ng/mL)
- Both groups showed an average slight symptom reduction; no significant differences

High-Dose Antipsychotic Use in the Absence of PK Failure

Consensus Statement for Treatment-Resistant Schizophrenia

• High-dose antipsychotic (AP) used in a limited therapeutic trial

• Dose reduced back to conventional levels after a 3-month period unless clinical benefits evidently outweigh the risks

• Before resorting to high dose, evidence-based strategies for treatment resistance should be exhausted, including use of clozapine

Recommended Practice

Inadequate response

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  - PK failure?
  - High-dose antipsychotic monotherapy

Obtain plasma drug level of antipsychotic

Switch to different antipsychotic monotherapy*

Levels within therapeutic range
- No adverse effects
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Inadequate response
- Obtain plasma drug level
- Antipsychotic polypharmacy

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Hypothetical Thresholds for Atypical Antipsychotic Drug Effects

Striatal D2 receptor blockade (%)

- treatment-resistant psychosis threshold?

- standard dose of 1st antipsychotic
- standard dose of 2nd antipsychotic

Dose; plasma concentration

usual antipsychotic effect threshold
Combined Antipsychotics: Clinical Reasons

• Enhance/speed up therapeutic effect
• Avoid high doses of 1 AP and its associated side effects
• Manage particularly challenging symptoms
  – eg, persistent aggression
• Treat a side effect
  – eg, aripiprazole and hyperprolactinemia
• Target different symptom or symptom domain
  – eg, affective instability, anxiety, or insomnia
• Consequence of:
  – Poor communication between services
  – Patient/family choice
• Cross-titration, switching from one antipsychotic to another
• Prescription of PRN antipsychotic
• Clozapine augmentation with a second AP in TRS
Combined Antipsychotics: Risks and Concerns

- Contribute to high dose
- Drug-drug interactions
- Increased mortality
  - Duration of exposure rather than combination or dosage
- Greater side effect burden
  - EPS, metabolic, cognitive function
- Greater risk of nonadherence
- Cost
- Difficulty determining cause and effect; thus, implications for longer-term regimen

Combined Antipsychotics: Evidence of Efficacy

• Meager evidence of superior benefit when monotherapy has proved ineffective: schizophrenia generally and TRS in particular

• Review of 75 clinical trial reports, case reports, and reviews of AP involving SGAs (including clozapine) published between 1966 and 2006
  – "The available evidence does not allow for any endorsement of antipsychotic polypharmacy in routine practice
  – BUT, it cannot be confidently stated that such a strategy would never have a reasonable risk-benefit balance in an individual case”

Switching From Antipsychotic Polypharmacy to Monotherapy

- Higher proportion of all-cause discontinuation (of assigned treatment) in those switched, but two-thirds successfully switched to 1 AP
  - Bias in open study in favor of polypharmacy
- Groups did not differ on symptom control
- Switching resulted in weight loss; polypharmacy associated with weight gain

Clozapine Augmentation With a Second Antipsychotic

- Prevalence ranges from 18% to 44%; depends on clinical setting

- Proposed mechanism
  - Pharmacodynamic synergy
  - Add potent D2 blocker when only partial response to clozapine monotherapy
  - Alters interaction between 5HT and D2 to enhance efficacy

- Plasma levels do not increase

Clozapine Augmentation With a Second Antipsychotic: Meta-analysis of 14 Studies

Effect size by treatment duration; but meta-regression showed no relationship between duration of treatment and reduction in symptoms

Clozapine Augmentation Meta-analysis: Conclusions

- Modest benefit over placebo [effect size -0.239 (95% CI: -0.452, -0.026); \( P=0.028 \)]
- No short-term tolerability issues
- No evidence of publication bias

Clozapine Augmentation: Conclusions

- Modest improvements may occur within 6 weeks but might not be expected until at least 10 weeks of treatment.
- The RCT evidence relates to overall symptom severity rather than the key symptoms of individual patients.
- The antipsychotic drugs tested as augmenting agents in RCTS to date have not been systematically assessed for:
  - Compounding clozapine side effects (e.g., sedation, weight gain, metabolic side effects).
  - Problems such as akathisia or significant elevations in serum prolactin.
- Uncommon but severe side effects are unlikely to have been detected in these relatively small studies.

Recommended Practice

- High-dose antipsychotic monotherapy
- Switch to different antipsychotic monotherapy*
- Clozapine monotherapy

**Inadequate response**

- Obtain plasma drug levels of both drugs
- Antipsychotic polypharmacy

*Oral or long-acting injectable
Summary

• Treatment resistance emerges early with first-line drugs

• Compared to current practice, we should:
  – Consider clozapine earlier
  – Reserve polypharmacy as a last resort

• Clozapine-resistant schizophrenia may occur in >25%  
  – Augment with antipsychotic or another drug class

• All prescribing is an N=1 trial  
  – If clozapine and augmentation fail – try, trial, and try again

• Psychosocial interventions are always key