Antipsychotic Polypharmacy
Rational Decision Making and Evidence Based Approach

Jonathan G Leung, PharmD, BCPS, BCPP
October 6-8, 2016
Intercontinental Chicago Magnificent Mile
Chicago, IL
Disclosure

Relevant Financial Relationships
  None

Off-Label/Investigational Uses
  None
Learning Objectives

• Describe factors leading to antipsychotic polypharmacy
• Discuss rational antipsychotic combinations
• Recall primary literature supporting the use of antipsychotic polypharmacy
After Partial Response or Failure?
Antipsychotic Polypharmacy

“I would most likely consider antipsychotic polypharmacy…”

A. To delay the need for clozapine therapy
B. When partial response to a non-clozapine antipsychotic is achieved
C. as augmentation following a clozapine partial response
D. When clozapine fails
Failed Trial?
• Length of trial?
• Maximized dose?
• Adherence?
• Side effects?
• Other causes of disrupted therapy?
Treatment Resistance: Kane Criteria

• The criteria for being classified as refractory to treatment included the following:

  1. At least 3 periods of treatment in the preceding 5 years with antipsychotic each without significant symptomatic relief
     • Trials are from at least 2 different chemical classes
     • Dosages are greater than 1000 mg chlorpromazine equivalents for given for a minimum of 6 weeks

  2. Absence of any period of good functioning within the preceding 5 years
Clozapine

- Two SGAs?
- Mortality FIN11
- ≥ 2 Failed Trials
- Superior Efficacy
- Tx Adherence
- ↓S/I InterSePT
- Concern of ADRs

Low EPS

X

X
Psychiatrists’ Attitudes Towards Clozapine

• 2010 Denmark survey
  • 66% stated patients were not satisfied with treatment and felt weight gain and labs were most problematic
  • 64.7% would rather combine 2 antipsychotics
  • 9% were able to identify 4 symptoms of myocarditis

• 2015 UK survey
  • “Reasons for delayed clozapine” included concerns about side effects (80%), blood draws refused (74%) and lack of experience (71%)
  • 33% were felt the risk of neutropenia was the same over time
  • 36% felt it was not easy to identify suitable patients
Clozapine Failures

• Antipsychotic of choice for treatment resistant schizophrenia
  • >40% of patient will be deemed to have a treatment failure or inadequate response to clozapine

• Do not give up too quickly
  • Better with time: Increased response rate from 37% after 3 months to 61% after 6 months
  • Serum levels >350 ng/mL are more likely to result in positive outcomes
  • Assess smoking status
When Clozapine Cannot Be Utilized

![Graphs showing discontinuation rates for different medications due to various reasons: Any Cause, Lack of Efficacy, Intolerability, and Patient Decision.](image-url)
When Clozapine Cannot Be Utilized…

• Olanzapine
  • Double-blind, randomized, controlled trial reported that up to 45 mg demonstrated similar efficacy to clozapine in treatment-resistant patients
  • A 5-year open-label trial reported that treatment could be maintained in patients who have failed multiple previous trials (mean 4.6 trials)

• Risperidone
  • Double-blind, randomized, controlled trial found risperidone tolerated and as effective as medium doses of clozapine
    • Biased due to inclusion of both clozapine failures and intolerant cases
  • Double-blind, multicenter, parallel-group study found clozapine to have superior efficacy over risperidone
After Partial Response or Failure?

Polypharmacy  ?  Monotherapy
How prevalent is polypharmacy

• New Hampshire Medicaid claims noted antipsychotic polypharmacy increased from 5.7% in 1995 to 24.3% in 1999

• European studies also noted a high prevalence of antipsychotic polypharmacy: 27-42%

• A study involving 9 Asian countries reported a rate of 43.4%

• In 2004 a study from Singapore reported the highest percentage of polypharmacy of 71.7%
How prevalent is polypharmacy

• The Joint Commission in 2011 requiring inpatient hospitals to document a rationale and monitor polypharmacy
  1. A history of 2 or more failed antipsychotic
  2. Cross-titrating antipsychotics to monotherapy
  3. Clozapine augmentation

• Recent studies around the globe report antipsychotic polypharmacy still as problematic
What's so *wrong* with polypharmacy?

- **Antipsychotic efficacy**
  - Response rate with a first trial is reported to be as high as 75%.
  - Response rate to a second trial is significantly lower (<20%).

- **Other illnesses use in-class polypharmacy:**
  - Major depressive disorder
  - Bipolar disorder

- **Many other disease states utilize a combination of medications to enhance efficacy or improve outcomes**
  - Diabetes mellitus, human immunodeficiency virus, hypertension
What *is* wrong with polypharmacy

- Not considered standard of care or endorsed
  - American Psychiatric Association (APA)
  - Texas Medication Algorithm (TIMA) guidelines
- Lack of evidence
- Additive acute side effects
- Additive long-term side effects
- Exorbitant costs
- Decline in patient medication adherence
Why does polypharmacy happen?

**Intentional**
- Enhance D2 antagonism
- To achieve antagonism of specific receptors
- To achieve agonism at certain receptors
- To reduce adverse effects
- To manage challenging symptoms

**Unintentional**
- “The cross-taper trap”
  - In 1 study 39% of patients on receiving two antipsychotics were intended to have a cross-taper
  - Only 50% were back on monotherapy after 6-12 months
- “Don’t rock the boat…”
What is being done?

• The Joint Commission in 2011
  • Began requiring inpatient hospitals to monitor antipsychotic polypharmacy
  • If there is polypharmacy providers much documentation of validated appropriate justifications:
    • A history of 3 or more failed antipsychotic
    • Cross-titrating antipsychotic medications to work toward monotherapy
    • Clozapine augmentation

Rational Decisions

• Due to the lack of primary literature consider different factors when deciding to utilize more than one antipsychotic
  • Evidence
  • Medicinal chemistry
  • Primary route of metabolism
  • Side effect profiles
  • Receptor affinity profiles, occupancy, dissociation
  • Cost
Rational Decisions

• Medicinal Chemistry
  • Phenothiazines
    • Chlorpromazine
    • Thioridazine
    • Perphenazine
    • Fluphenazine
    • Trifluoperazine
Rational Decisions

- Medicinal Chemistry
  - Benzamide derivatives
    - Clozapine
    - Olanzapine
    - Loxapine
    - Quetiapine
Rational Decisions

• Side effect profiles
  • Consider the consequence of additive effects:
    • Anticholinergic side effects: clozapine + olanzapine
    • Metabolic complications: clozapine + olanzapine
    • Orthostatic hypotension: clozapine + quetiapine
    • Risk of EPS: FGA + risperidone
SGA Receptor Affinities

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Clozapine (K&lt;sub&gt;i&lt;/sub&gt;, nM)</th>
<th>Risperidone (K&lt;sub&gt;i&lt;/sub&gt;, nM)</th>
<th>Olanzapine (K&lt;sub&gt;i&lt;/sub&gt;, nM)</th>
<th>Quetiapine (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</th>
<th>Ziprasidone (K&lt;sub&gt;i&lt;/sub&gt;, nM)</th>
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<td>&gt;1000&lt;sup&gt;c&lt;/sup&gt;</td>
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Rational Decisions

• Receptor Occupancy
  • Clozapine and quetiapine at therapeutic doses
    • ~70% D$_2$ receptor occupancy
  • Risperidone and high potency FGAs
    • High D2 affinity and occupancy
    • D2 predominant effects

• Combination of agents with similar properties may provide limited benefit with increased risk
Rational Combinations

• Receptor Dissociation
  • “The hit and run”

<table>
<thead>
<tr>
<th>SGA</th>
<th>Time to 50% Dissociation</th>
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<tr>
<td>Haloperidol</td>
<td>38 minutes</td>
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<td>Olanzapine</td>
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<tr>
<td>Aripiprazole</td>
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<tr>
<td>Quetiapine</td>
<td>16 seconds</td>
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<td>Clozapine</td>
<td>15 seconds</td>
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Antipsychotic Polypharmacy
A Brief Overview on SGA Combinations and Review of the Literature
General Problems

• Paucity of literature
  • Few well conducted trial
  • Case series
  • Case reports

• Small sample sizes

• Length of trials

• Outcome measures

• Publication bias
Clozapine Combinations

• Clozapine + risperidone: Randomized controlled trials
• Clozapine + aripiprazole: Randomized controlled trials
• Clozapine + haloperidol: Randomized controlled trial
• Clozapine + ziprasidone: Open-label data, case reports
• Clozapine + olanzapine: Case reports
• Clozapine + quetiapine: Case series, case reports
Non-antipsychotic Clozapine Combinations

- Clozapine + lamotrigine: Randomized controlled trials
- Clozapine + other in randomized controlled trials
  - Donepezil (1 negative)
  - Memantine (mixed based on outcome)
  - Topiramate (1 negative, 1 positive)
  - Mirtazapine (mixed based on outcome)
  - Duloxetine (1 positive)
  - Minocycline (mixed data based on outcome)
- Clozapine + lithium or valproate
- Clozapine + ECT
Risperidone Combinations

• Risperidone + olanzapine
  • Case series
  • Case reports

• Risperidone + quetiapine
  • Case reports
  • One case of reduction of TD s(x)

• Risperidone + aripiprazole
  • Case reports of worsening psychosis
Olanzapine Combinations

• Olanzapine + quetiapine
  • Case reports

• Olanzapine + aripiprazole
  • Case reports
  • Two case reports of worsening psychosis
Other Combinations

- Quetiapine + ziprasidone
  - 1 case and subsequent cardiac arrhythmia

- Quetiapine + aripiprazole
  - 1 case report of worsening psychosis

- Ziprasidone + aripiprazole
  - Only one case of worsening psychosis

- Any antipsychotic + long-acting injectable agent
  - Not well studied
  - May provide a “safety net” if oral medication is abruptly stopped
Newer Agents: Snapshot

• **Brexpiprazole**
  - **Mechanism**
    - D2 and 5HT1A partial agonist
    - 5HT2A antagonist
    - Low H1 and M1 affinity
    - Similar to aripiprazole
  - **Side effects**
    - Akathisia

• **Cariprazine**
  - **Mechanism**
    - D2 and 5HT1A partial agonist
    - 5HT2A antagonist
    - Low H1, M1, alpha1 affinity
    - Preference for D3 > D2
      - Results clinically unknown
      - D3 may regulate motivation and reward-related behavior
  - **Side effects**
    - Akathisia, parkinsonian symptoms
Conclusions

- Antipsychotic polypharmacy is still very prevalent
- The APA discourages early use of polypharmacy and The Joint Commission has aimed to evaluate these practices
- There is a lack of data to be able to make evidence based recommendations
- Clinicians should examine primary literature and other properties of antipsychotics to make rational decisions about polypharmacy
- Further research is needed in this area of question
Learning Objectives

• Describe factors leading to antipsychotic polypharmacy
• Discuss rational antipsychotic combinations
• Recall primary literature supporting the use of antipsychotic polypharmacy
Questions & Discussion