Are Two Antipsychotics Better Than One?

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National Council for Behavioral Health
Montefiore Medical Center
Northwell Health
New York State Office of Mental Health
Netsmart Technologies
Objectives

• Reviewing the data on adding a second antipsychotic to preexisting treatment with a single antipsychotic for:
  • Inadequate symptom response to the single antipsychotic
  • Management of hyperprolactinemia from the single antipsychotic

• Highlighting recommendations for medication treatment strategies based on these data
Common reasons antipsychotics do not work for a particular patient

• The medications are not taken
• If taken, they are not effective
We tend to underestimate the role of non-adherence
Non-adherence in the treatment of chronic disorders

• In developed countries, about 50% of patients with chronic diseases adhere to long-term therapy\(^1\)

• 33–69% of all medication-related hospital admissions in the US are due to poor medication adherence\(^2\)

• One-third of all prescriptions are never filled\(^3\)

• >50% of filled prescriptions are associated with incorrect administration (not taken as prescribed)\(^3\)

U.S. Patients Do Not Take Medications as Prescribed

- 100% Rx prescribed
- 88% Rx filled
- 76% Rx taken
- 47% Rx continued

* 22% of U.S. patients take less of the medication than is prescribed

Stopping medication is the most powerful predictor of relapse

• Survival analysis: risk of a first or second relapse when not taking medication is approximately 5 times greater than when taking it

Percentage of non-adherent patients identified by different methods

Nonadherence defined on the basis of electronic monitoring. Nonadherent patients took <80% of prescribed medication over a 12-week period.

<table>
<thead>
<tr>
<th>Method</th>
<th>Nonadherent Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self Report</td>
<td>16</td>
</tr>
<tr>
<td>Physician Report</td>
<td>42</td>
</tr>
<tr>
<td>In-Home Pill Count</td>
<td>56</td>
</tr>
</tbody>
</table>

Poor antipsychotic adherence over time in schizophrenia

Analysis of 34,128 VA patients with schizophrenia receiving regular outpatient mental healthcare. Poor antipsychotic adherence defined as annual MPR < .80. 18% had poor antipsychotic adherence in all 4 years.

- MPR = medication possession ratio; VA = Veterans Affairs.
If you have eliminated non-adherence as the cause of poor response, what should you do?

Is there a scientific basis for choosing one antipsychotic over another for refractory psychosis?
Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis

Stefan Leucht, Andrea Cipriani, Loukia Spineli, Dimitris Mavridis, Deniz Örey, Franziska Richter, Myrto Samara, Corrado Barbui, Rolf R Engel, John R Geddes, Werner Kissling, Marko Paul Stapf, Bettina Lässig, Georgia Salanti, John M Davis

212 trials with 43049 participants
Clozapine was the most effective for treatment of psychosis

“Clozapine was significantly more effective than all other drugs. After clozapine, amisulpride, olanzapine and risperidone were significantly more effective than the other drugs apart from paliperidone and zotepone. These effect sizes were small (range-0.11 to -0.33)”
Clozapine was the most effective for treatment of psychosis.

**Figure 3: Forest plot for efficacy of antipsychotics drugs compared with placebo.**
Treatments are ranked according to their surface under the cumulative ranking (SUCRA) values (appendix p98). SMD = standardised mean difference. Crl = credible interval.
What about two antipsychotics instead of one for persistent symptoms?
PORT guidelines from 2009

The 2009 Schizophrenia PORT Psychopharmacological Treatment Recommendations and Summary Statements

Robert W. Buchanan¹,², Julie Kreyenbuhl³,⁴, Deanna L. Kelly², Jason M. Noel⁵, Douglas L. Boggs², Bernard A. Fischer², Seth Himelhoch³, Beverly Fang⁶, Eunice Peterson⁶, Patrick R. Aquino⁶, and William Keller⁶

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There continue to be major gaps in our knowledge, including limited information on (1) the use of adjunctive pharmacological agents for the treatment of persistent positive symptoms or other symptom domains of psychopathology, including anxiety, cognitive impairments, depressive symptoms, and persistent negative symptoms and (2) the treatment of co-occurring substance or medical disorders that occur frequently in individuals with schizophrenia.

Key words: acute treatment/antipsychotic medications/clozapine/first-episode schizophrenia/maintenance treatment/side effects
Antipsychotic polypharmacy

Summary Statement. Many individuals with schizophrenia have an incomplete symptom response to antipsychotic monotherapy. The use of combinations of antipsychotic medications (antipsychotic polypharmacy) has become an increasingly common treatment approach for people who have failed to adequately respond to previous antipsychotic treatment. The majority of studies of combinations of antipsychotic medications have examined the efficacy and safety of a single combination: clozapine and risperidone. These studies have failed to document sufficient efficacy and safety of this combination to support a recommendation in people with treatment-resistant schizophrenia.
Anticonvulsants and lithium

Anticonvulsants and Lithium for Treatment-Resistant Positive Symptoms

Summary Statement. A substantial proportion of people with schizophrenia treated with antipsychotic medications continue to exhibit residual positive symptoms. Lithium and anticonvulsants are used extensively to augment antipsychotic treatment of these symptoms. However, few studies have been conducted to formally evaluate the efficacy of these approaches. Of the anticonvulsants, carbamazepine, valproate/valproic acid, lamotrigine, and topirimate have been the most extensively studied, but none of these agents have demonstrated sufficient efficacy to support a recommendation in people with residual positive symptoms. There is little evidence to support the efficacy of lithium for these symptoms.
A recent meta-analysis

Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis

Britta Gallng1,2, Alexandra Roldán4, Katsuhiko Hagi2,5, Liz Rietschel6, Frozan Walyzada2, Wei Zheng7, Xiao-Lan Cao8, Yu-Tao Xiang9, Mathias Zink10, John M. Kane2,3,11,12, Jimmi Nielsen13,14, Stefan Leucht15, Christoph U. Correll2,3,11,12

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(0World Psychiatry 2017; 16:77–89)
Targeted studies

• Studies comparing adding a second antipsychotic to continuing antipsychotic monotherapy in schizophrenia
• Studies comparing starting two antipsychotics simultaneously were excluded

- Potentially relevant articles (N=17,653)
  - Articles excluded at abstract level (N=17,427)
  - Full text articles retrieved for evaluation of eligibility (N=226)
    - Articles excluded (N=195)
      - No augmentation (N=84)
      - Not randomized (N=27)
      - Medication different from required or no comparison with monotherapy (N=28)
      - Outcome different from required (N=26)
      - Review, letter to the Editor (N=9)
      - < 20 patients (N=2)
      - Duplicate data publication (N=12)
      - Diagnosis different from required (N=3)
      - Age different from required (N=2)
      - Cross-over study (N=1)
      - No full text (N=1)

- Randomized controlled trials included in the meta-analysis (N=31)
Total symptom reduction

• Adding an antipsychotic was superior to monotherapy in open-label and poor quality studies but not in double-blind and high quality studies

• Similar pattern for studies augmenting clozapine with FGAs or SGAs
Treatment response

• Defined as 20-25% reduction in PANSS/BPRS scores depending upon the study

• Overall, response did not differ between antipsychotic augmentation and monotherapy

• Response was superior in open-label/poor quality studies but not in double-blind/high quality studies
All cause discontinuation

• Did not differ between antipsychotic augmentation and monotherapy
Depressive symptoms

• Did not differ between antipsychotic augmentation and monotherapy
Negative symptoms

• Improved with antipsychotic augmentation
• Only significant in studies augmenting D2 antagonists with a partial D2 agonist (aripiprazole)
• Replicated in high quality studies
<table>
<thead>
<tr>
<th>Study-defined response</th>
<th>Overall symptom reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMD</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>Anil Yagcioglu et al.</td>
<td>0.860</td>
</tr>
<tr>
<td>Chang et al.</td>
<td>-0.108</td>
</tr>
<tr>
<td>Freudenreich et al.</td>
<td>-1.706</td>
</tr>
<tr>
<td>Friedman et al.</td>
<td>0.243</td>
</tr>
<tr>
<td>Gunduz-Bruce et al.</td>
<td>0.447</td>
</tr>
<tr>
<td>Honer et al.</td>
<td>3.500</td>
</tr>
<tr>
<td>Joslassin et al.</td>
<td>1.000</td>
</tr>
<tr>
<td>Kane et al.</td>
<td>6.000</td>
</tr>
<tr>
<td>Muscatello et al.</td>
<td>1.186</td>
</tr>
<tr>
<td>Nielsen et al.</td>
<td>1.155</td>
</tr>
<tr>
<td>Shiikoh et al.</td>
<td>-1.243</td>
</tr>
<tr>
<td>Weiner et al.</td>
<td>-0.367</td>
</tr>
<tr>
<td>High quality overall</td>
<td>-0.299</td>
</tr>
<tr>
<td>Low quality studies</td>
<td>-1.119</td>
</tr>
<tr>
<td>Overall</td>
<td>-0.530</td>
</tr>
</tbody>
</table>
Should you add aripiprazole to another antipsychotic for negative symptoms?

• The negative symptom effect may be a direct effect of aripiprazole and not the effect of a combination of aripiprazole and another antipsychotic

• Switching to aripiprazole may have the same beneficial effect on negative symptoms while avoiding the potential side effect burden with multiple antipsychotics
A Randomized Comparison of Aripiprazole and Risperidone for the Acute Treatment of First-Episode Schizophrenia and Related Disorders: 3-Month Outcomes

Delbert G. Robinson*1,4, Juan A. Gallego1,3, Majnu John1,2,5, Georgios Petrides1,4, Youssef Hassoun2,3, Jian-Ping Zhang1,3, Leonardo Lopez2,3, Raphael J. Braga2,3, Serge M. Sevy6, Jean Addington7, Charles H. Kellner8, Mauricio Tohen9, Melissa Naraine2, Natasha Bennett2, Jessica Greenberg2, Todd Lencz1,4, Christoph U. Correll1,4,10, John M. Kane1,4,10,11, and Anil K. Malhotra1,4,11
One hundred ninety-eight participants aged 15-40 years with schizophrenia, schizophreniform disorder, schizoaffective disorder or psychotic disorder Not Otherwise Specified, and who had been treated in their lifetime with antipsychotics for 2 weeks or less were randomly assigned to double masked aripiprazole (5-30 mg/d) or risperidone (1-6 mg/d) and followed for 12 weeks.

Positive symptom response rates did not differ (62.8% vs. 56.8%) nor did time to response.
Aripiprazole-treated patients had better outcomes on the SANS avolition-apathy domain.

Fig. 2. SANS Avolition-Apathy Global Score. Medication-by-time interaction, $F = 2.18$, $df = 8,1162$, $P = .03$. SANS, Scale for the Assessment of Negative Symptoms.
What if clozapine doesn’t work for persistent symptoms, should another antipsychotic be added?
Don’t forget the PORT guidelines from earlier....

Antipsychotic Polypharmacy

Summary Statement. Many individuals with schizophrenia have an incomplete symptom response to antipsychotic monotherapy. The use of combinations of antipsychotic medications (antipsychotic polypharmacy) has become an increasingly common treatment approach for people who have failed to adequately respond to previous antipsychotic treatment. The majority of studies of combinations of antipsychotic medications have examined the efficacy and safety of a single combination: clozapine and risperidone. These studies have failed to document sufficient efficacy and safety of this combination to support a recommendation in people with treatment-resistant schizophrenia.
If there is no evidence that augmenting clozapine with another antipsychotic or a mood stabilizer works...

What else can help clozapine-refractory psychosis?
Make sure clozapine level is sufficient, and recognize some patients may take longer to respond

- 30% of patients will respond by 6 weeks
- 20% of patients will respond by 3 months
- 10-20% of patients will respond by 6 months
- Some patients will take more than 6 months to respond
- A trial of clozapine monotherapy of 6-12 months is reasonable
- Consider augmentation with ECT after suboptimal response at adequate plasma level (450ng/mL) for adequate duration
Electroconvulsive Therapy Augmentation in Clozapine-Resistant Schizophrenia: A Prospective, Randomized Study

Georgios Petrides, M.D., Chitra Malur, M.D., Raphael J. Braga, M.D., Samuel H. Bailine, M.D., Nina R. Schooler, Ph.D., Anil K. Malhotra, M.D., John M. Kane, M.D., Sohag Sanghani, M.D., Terry E. Goldberg, Ph.D., Majnu John, Ph.D., Alan Mendelowitz, M.D.

Objective: Up to 70% of patients with treatment-resistant schizophrenia do not respond to clozapine. Pharmacological augmentation to clozapine has been studied with unimpressive results. The authors examined the use of ECT as an augmentation to clozapine for treatment-refractory schizophrenia.

Method: In a randomized single-blind 8-week study, patients with clozapine-resistant schizophrenia were assigned to treatment as usual (clozapine group) or a course of bilateral ECT plus clozapine (ECT plus clozapine group). Nonresponders from the clozapine group received an 8-week open trial of ECT (crossover phase). ECT was performed three times per week for the first 4 weeks and twice weekly for the last 4 weeks. Clozapine dosages remained constant. Response was defined as ≥40% re-

Results: The intent-to-treat sample included 39 participants (ECT plus clozapine group, N=20; clozapine group, N=19). All 19 patients from the clozapine group received ECT in the crossover phase. Fifty percent of the ECT plus clozapine patients met the response criterion. None of the patients in the clozapine group met the criterion. In the crossover phase, response was 47%. There were no discernible differences between groups on global cognition. Two patients required the postponement of an ECT session because of mild confusion.

Conclusions: The augmentation of clozapine with ECT is a safe and effective treatment option. Further research is required to determine the persistence of the improvement and
A possible role for two antipsychotics in management of hyperprolactinemia
Acute symptomatic hyperprolactinemia in men and women

Byerly et al 2007
The first line treatment for patients with symptomatic hyperprolactinemia is switching to an antipsychotic that does not cause prolactin elevation.
A study showing that adding a dopamine partial agonist (aripiprazole) can reverse prolactin elevations from other antipsychotics

• Chen and colleagues (Psychoneuroendocrinology 2015) randomly assigned patients with schizophrenia and risperidone-induced hyperprolactinemia to...

• 8 weeks of placebo (n=30) or oral aripiprazole 5mg/day (n=30), 10mg/day (n=29), or 20mg/day (n=30) added on to fixed dose risperidone treatment

• Serum prolactin levels were measured at baseline and after 2, 4 and 8 weeks
A study showing that adding a dopamine partial agonist (aripiprazole) can reverse prolactin elevations from other antipsychotics

• 89.9% of patients completed the study
• All three aripiprazole doses resulted in...
  • Significantly lower prolactin levels (beginning at week 2)
  • Higher response rates (≥30% prolactin reduction)
  • Higher prolactin normalization rates than placebo
• Effects were significantly greater in the 10 and 20mg/day groups than the 5mg/day group
Situations when switching isn’t possible

• The patient has a history of lack of response or intolerance to a variety of antipsychotics and is doing well with their current antipsychotic except for symptomatic hyperprolactinemia

• The patient has insurance limitations that would make a switch difficult
  • For example, a patient who needs/wants LAI treatment but their insurance only covers a limited range of LAIs (insurance does not cover the LAI formulations: aripiprazole monohydrate or aripiprazole lauroxil)
Summary

• Always consider non-adherence as a cause of lack of response to antipsychotics

• The evidence is poor that adding a second antipsychotic to improve symptom response helps patients who are already taking one antipsychotic

• Adding dopamine partial agonists may help treat negative symptoms but this might be achieved by a simple switch to a dopamine partial agonist

• Adding dopamine partial agonists may help antipsychotic-induced hyper prolactinemia

• Print and review companion materials
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