Q2: In individuals with psychotic disorders (including schizophrenia), is the use of two or more antipsychotic medications concurrently more effective and safer than the use of one antipsychotic only?

Background

Combination treatment with more than one antipsychotic agent is an increasingly common practice in schizophrenia (>30% of patients). However, clinical guidelines promote antipsychotic monotherapy and some of them include clear recommendations against polypharmacy. The current strength of evidence in support of combinations is weak and its clinical significance is a matter of debate, even in patients who do not respond to a single antipsychotic. Moreover, there has been increased concern over the safety of antipsychotic combination, and studies addressing safety issues are inadequate. A clear recommendation on antipsychotic combinations appears critical in clinical practice, especially in non-specialized settings of low and middle income countries (LAMIC).

Population/Intervention(s)/Comparator/Outcome(s) (PICO)

Population: patients with psychotic disorders, including schizophrenia (partial or non-response)

Interventions: antipsychotic combination therapy (two antipsychotics concurrently)

Comparisons: antipsychotic monotherapy

Outcomes: symptoms severity
prevention of relapses
disability and functioning
adverse effects of treatment
quality of life
all-cause mortality, including by suicide
Combination of two or more antipsychotic medications for psychotic disorders

treatment adherence or concordance

users’ and families’ satisfaction with care (including users and families involvement)

**List of the systematic reviews identified by the search process**

*INCLUDED IN GRADE TABLES OR FOOTNOTES*


*EXCLUDED FROM THE GRADE TABLES OR FOOTNOTES*

The following reference was not used while it states that there is little evidence to support the use of combinations of antipsychotics even if monotherapy proves to be ineffective, without using any RCT.


The following reviews were not included because they focus on non-responder patients with schizophrenia:


Combination of two or more antipsychotic medications for psychotic disorders


**PICO Table**

<table>
<thead>
<tr>
<th>Serial no.</th>
<th>Intervention/Comparison</th>
<th>Outcomes</th>
<th>Systematic reviews used for GRADE</th>
<th>Explanation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Antipsychotic combination/ Antipsychotic monotherapy</td>
<td>Symptoms severity</td>
<td>Correll et al, 2009</td>
<td>The review by Correll et al, 2009 is the most recent and the only one including RCT in patients without treatment resistance or partial response to monotherapy.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prevention of relapses</td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disability and functioning</td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adverse effects of treatment</td>
<td>Correll et al, 2009</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Quality of life</td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality</td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treatment adherence</td>
<td>No evidence available</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Users' and families' satisfaction with care</td>
<td>No evidence available</td>
<td></td>
</tr>
</tbody>
</table>
Combination of two or more antipsychotic medications for psychotic disorders

Narrative description of the studies that went into the analysis

Correll et al, 2009 included in their review 19 studies with 1216 participants. Sample sizes ranged from 17 to 233 (median 57). In 10 studies, 1 antipsychotic combination treatment was compared with 1 monotherapy group. In 9 studies, 1 antipsychotic combination treatment was compared with 2 antipsychotic monotherapy groups (n = 658, 54.1%). Fifteen studies were double blind, the others were single blind, open or not specified. The mean duration was 12 (SD = 11.3) (range 4–52, median 8) weeks. In 13 studies, the combination treatment was initiated at the start of the trial, while in 6 studies, the second antipsychotic was added after nonresponse to an adequate antipsychotic monotherapy. In 14 studies, the monotherapy and polytherapy arms had comparable mean doses and dose ranges, while in 5 studies, one or both of the antipsychotics in the combination arm were dosed considerably lower than in the monotherapy arm. Participants were 33 (SD = 5) years old, 62% were male; and 88% were inpatients. Most participants were in the chronic illness phase; only 4 studies were conducted in acute patients. The mean illness duration was 10 (SD = 7) (median 7) years, with 4 psychiatric hospitalizations. All but 4 studies used some form of standardized diagnostic criteria, but criteria varied across time and country of origin.

The 28 monotherapy group included 14 FGA arms and 14 SGA. The 19 combination arms consisted of cotreatment with 2 FGAs (N = 6), an FGA + SGA (N = 7), and 2 SGAs. Antipsychotics: clozapine (N = 11), chlorpromazine (N = 6); risperidone (N = 6); sulpiride (N = 5), others.

GRADE Tables

Table 1

Author(s): Corrado Barbui and Lorenzo Tarsitani
Date: 2009-06-03
Question: Should Antipsychotic combination therapy vs Antipsychotic monotherapy be used for Schizophrenia (chronic or treatment resistant)?
Settings: Largely in Hospital
Combination of two or more antipsychotic medications for psychotic disorders

<table>
<thead>
<tr>
<th>Lack of Efficacy (symptoms severity) (follow-up mean 12 weeks; BPRS or PANSS or CGI or other 50% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19 trials</td>
</tr>
<tr>
<td>Treatment acceptability (total dropout) (follow-up mean 12 weeks)</td>
</tr>
<tr>
<td>19 trials</td>
</tr>
<tr>
<td>All cause mortality</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Disability and functioning</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>User’s and families’ satisfaction</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

1 From 19 studies that contributed to 22 comparisons (fig. 2 of Correll et al 2009).
2 3 of 19 studies are not blinded, plus 1 trial has more than 30% of dropouts, 1 trial has dropouts that are not similarly distributed.
3 Heterogeneity exceeds 75% (I-squared = 78.9%).
4 88% are inpatients with mean number of 4 past hospitalizations.
5 Funnel Plot suggests some asymmetry. Fig 4 Correll et al 2009.
6 In term of percentages, dropout rates from the 19 included studies are very similar between treatment groups. However, the meta-analysis that included only 9 studies, suggested a beneficial effect of combination vs monotherapy.

Additional information that was not GRADEd

Tranulis C et al (2008): The potential hazards of combining antipsychotics include additional adverse effects (e.g. sedation, hypotension, anticholinergic toxicity, worsening metabolic profile), loss of advantages of second-generation antipsychotics (e.g. increased risk of tardive dyskinesia when adding a first-generation
Combination of two or more antipsychotic medications for psychotic disorders

agent and presence of metabolic adverse effects), pharmacokinetic interactions and higher costs. Moreover, complex prescriptions decrease compliance; thus, exacerbating a clinical problem often encountered in patients with schizophrenia or other psychotic disorders.

Correll CU et al (2007): Compared with patients receiving antipsychotic monotherapy, patients on antipsychotic polytherapy have higher rates of metabolic syndrome and lipid markers of insulin resistance.

Additionally, there is observational evidence suggesting that increasing the number of antipsychotic drugs, decreases the survival probability.

- A prospective cohort study of 88 patients showed that prescription of more than one antipsychotic was associated with a 2.46 relative risk (95% CI 1.10-5.47; P = 0.03) of reduced survival at 10 years. [Waddington et al (1998)]

- In a 17 years follow up study of 99 patients with schizophrenia, the number of neuroleptics used at the time of the baseline survey showed a graded relation to mortality. Adjusted for age, gender, somatic diseases and other potential risk factors for premature death, the relative risk was 2.50 (95% CI 1.46-4.30) per increment of one neuroleptic. [Waddington et al (1998)]

General information

Guidelines do not recommend antipsychotic combinations as a first or second line treatment.

Gaebel W et al (2005): About one third of the guidelines worldwide include a recommendation against antipsychotic polypharmacy in schizophrenia.

Combinations most frequently described in the literature include a Second Generation Antipsychotic. This might reduce feasibility and cost-effectiveness of combined antipsychotic therapy, especially in LAMIC.

In usual clinical practice, combination strategies are based on complicated pharmacodynamic considerations, which are not feasible for non-specialist health personnel.
Combination of two or more antipsychotic medications for psychotic disorders

Reference List


**Combination of two or more antipsychotic medications for psychotic disorders**


**From evidence to recommendations**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Explanation</th>
</tr>
</thead>
</table>
| **Narrative summary of the evidence base** | Evidence base consist of 19 RCT with 1216 participants. Most participants were in the chronic illness phase (the mean illness duration was 10 years, with a mean of 4 psychiatric hospitalizations); 88% were inpatients.  

The Relative Risk for lack of efficacy (symptom severity) showed a significant advantage [RR = 0.76 (CI 0.63 to 0.90)] for antipsychotic combination therapy. A similar advantage for combination therapy was observed for treatment acceptability (total dropout) [RR = 0.65 (CI 0.54 to 0.78)].  

There is no evidence available on adverse events and on other important outcomes. |
| **Summary of the quality of evidence** | There is VERY LOW quality of evidence supporting antipsychotic combination therapy compared to antipsychotic monotherapy in reduction of symptom severity and LOW quality of evidence on reducing total dropouts. |
| **Balance of benefits versus harms** | Although antipsychotic combination seems to provide better symptom reduction and less dropouts than monotherapy in the short term for chronic and non-responder individuals, observational evidence suggest higher risk of adverse effects and less safety. |
| **Values and preferences including any** | Important issues are poor response to treatment and its consequences, and |
Combination of two or more antipsychotic medications for psychotic disorders

<table>
<thead>
<tr>
<th>variability and human rights issues</th>
<th>concerns about safety and tolerability associated with antipsychotic combination therapy. A further important issue is a decreased adherence to complex treatment regimes.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costs and resource use and any other relevant feasibility issues</td>
<td>There are additional resource use and cost associated with antipsychotic combination therapy in terms of acquisition costs, laboratory and clinical monitoring. Health care providers require additional training and pharmacological skills to prescribe antipsychotic combinations.</td>
</tr>
</tbody>
</table>

Recommendation(s)

Routinely, one antipsychotic should be prescribed at a time in individuals with psychotic disorders (including schizophrenia). Strength of recommendation: STRONG

For individuals with psychoses (including schizophrenia) who do not respond to adequate dose and duration of more than one antipsychotic medicine (using one medicine at a time), antipsychotic combination treatment may be considered by primary health care professionals preferably under the supervision of mental health professionals with close clinical monitoring. Strength of recommendation: STANDARD

Any additional remarks

Long term safety and tolerability trials and comparisons of specific combinations are required.

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. No new systematic reviews were found to be relevant.