Network Meta-Analyses of Antipsychotics for Schizophrenia: Clinical Implications

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BEHIND THE VEIL OF NETWORK META-ANALYSIS

- How to be sure your trials are well regarded in Network Meta-Analysis.
- Why do Network Meta-Analysis?
- Try to provide an intuitive understanding for those who are not mathematically inclined.
- Meta-Analysis is: 1) a scientific tool, 2) used to inform clinicians of drug properties and to support public policy.
SUMMARIZE
NETWORK META-ANALYSIS OF
ANTI-PSYCHOTIC DRUGS

- Use data to test the assumption(s) of Network Meta-Analysis.
- Difference between *Paired Meta-Analysis* and *Network Meta-Analysis*.
- While great effort is made to avoid bias in meta-analysis, Meta-Analysts have their own biases.
**Why Do We Need Systematic Reviews?**

- In 10,000 medical journals 2 million articles are published every year.
- A general practitioner would have to read 19 articles everyday, 365 days per year to cover relevant reports.
Why is Meta-Analysis Done?
The dogma of equal efficacy of all antipsychotics goes back to an early influential review.
Principle of Meta-Analysis

Example:
Olanzapine vs. Quetiapine for Schizophrenia

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atmaca 2003</td>
<td>74.86</td>
<td>6.41</td>
<td>13</td>
<td>77.24</td>
<td>6.08</td>
<td>14</td>
<td>1.8%</td>
<td>-0.37 [-1.13, 0.39]</td>
</tr>
<tr>
<td>Kinon 2006b</td>
<td>-11.3</td>
<td>18.3</td>
<td>166</td>
<td>-7.2</td>
<td>21.2</td>
<td>169</td>
<td>23.2%</td>
<td>-0.21 [-0.42, 0.01]</td>
</tr>
<tr>
<td>Lieberman 2005</td>
<td>-11.27</td>
<td>22.31</td>
<td>330</td>
<td>-6.08</td>
<td>22.31</td>
<td>329</td>
<td>45.6%</td>
<td>-0.23 [-0.39, -0.08]</td>
</tr>
<tr>
<td>McEvoy 2006</td>
<td>-7.7</td>
<td>9.8</td>
<td>10</td>
<td>-1.3</td>
<td>19.23</td>
<td>8</td>
<td>1.2%</td>
<td>-0.41 [-1.36, 0.53]</td>
</tr>
<tr>
<td>McEvoy 2007</td>
<td>-18.4</td>
<td>9.73</td>
<td>37</td>
<td>-15.6</td>
<td>10.68</td>
<td>44</td>
<td>5.5%</td>
<td>-0.27 [-0.71, 0.17]</td>
</tr>
<tr>
<td>Mori 2004</td>
<td>69.4</td>
<td>10.8</td>
<td>20</td>
<td>72.9</td>
<td>15.1</td>
<td>20</td>
<td>2.8%</td>
<td>-0.26 [-0.88, 0.36]</td>
</tr>
<tr>
<td>Riedel 2007</td>
<td>-17.88</td>
<td>20.71</td>
<td>17</td>
<td>-21.5</td>
<td>23.39</td>
<td>16</td>
<td>2.3%</td>
<td>0.16 [-0.52, 0.84]</td>
</tr>
<tr>
<td>Stroup 2006</td>
<td>-8.2</td>
<td>22.31</td>
<td>66</td>
<td>2</td>
<td>22.31</td>
<td>63</td>
<td>8.7%</td>
<td>-0.45 [-0.80, -0.10]</td>
</tr>
<tr>
<td>Svestka 2003b</td>
<td>-45.65</td>
<td>11.96</td>
<td>20</td>
<td>-43.91</td>
<td>20.94</td>
<td>22</td>
<td>2.9%</td>
<td>-0.10 [-0.70, 0.51]</td>
</tr>
<tr>
<td>Voruganti 2007</td>
<td>48.5</td>
<td>9.9</td>
<td>42</td>
<td>49.4</td>
<td>12</td>
<td>43</td>
<td>5.9%</td>
<td>-0.08 [-0.51, 0.34]</td>
</tr>
</tbody>
</table>

Total (95% CI) 721 728 100.0% -0.23 [-0.34, -0.13]

Heterogeneity: $I^2 = 0.00$; $I^2 = 3.85$, $df = 9$ ($P = 0.92$); $I^2 = 0$
Test for overall effect: $Z = 4.39$ ($P < 0.0001$)

Komossa et al. Cochrane review 2010
Meta-Analysis

Clinical Trials: Meta Analysis

- FORMULATION OF STUDY QUESTION
- LITERATURE SEARCH
- STUDY SELECTION
- DATA EXTRACTION/QUALITY ASSESSMENT
- STATISTICAL ANALYSIS

Here's your "multiple studies of related intervention"...!!!
I. BEFORE: Writing a Protocol

- Which patients
- Which interventions
- Which outcomes
- Literature search (databases, search strings)
- Statistical method

The protocol is reviewed by two editors of the Cochrane Schizophrenia Group and it is published in the Cochrane Library
II. Literature Search

- Not only MEDLINE
- Not only English
- Electronic databases, conference abstracts, books, book chapters, contact pharmaceutical companies, contact study authors, FDA webpage
Bias Assessment

Appendix 6b: Risk of bias graph: review authors' judgements (Low, Unclear and High) about each risk of bias item presented as percentages across all included studies.
Network Meta-Analysis of 15 Antipsychotic Drugs in Schizophrenia (212 studies, 43,049 participants)

Leucht et al. Lancet. 2013 Sep 14;382(9896):951-62
### Tolerability

<table>
<thead>
<tr>
<th>Weight gain (SMD)</th>
<th>EPS (OR)</th>
<th>Prolactin (SMD)</th>
<th>QTc (SMD)</th>
<th>Sedation (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAL</td>
<td>CLO</td>
<td>ARI</td>
<td>LUR</td>
<td>AMI</td>
</tr>
<tr>
<td>ZIP</td>
<td>SER</td>
<td>QUE</td>
<td>ARI</td>
<td>PAL</td>
</tr>
<tr>
<td>LUR</td>
<td>OLA</td>
<td>ASE</td>
<td>QUE</td>
<td>PAL</td>
</tr>
<tr>
<td>ARI</td>
<td>QUE</td>
<td>OLA</td>
<td>OLA</td>
<td>HAL</td>
</tr>
<tr>
<td>AMI</td>
<td>ILO</td>
<td>CHL</td>
<td>ILO</td>
<td>ZIP</td>
</tr>
<tr>
<td>ASE</td>
<td>HAL</td>
<td>ILO</td>
<td>LUR</td>
<td>ILO</td>
</tr>
<tr>
<td>PAL</td>
<td>SER</td>
<td>RIS</td>
<td>RIS</td>
<td>ARI</td>
</tr>
<tr>
<td>RIS</td>
<td>ZIP</td>
<td>ARI</td>
<td>ZIP</td>
<td>SER</td>
</tr>
<tr>
<td>QUE</td>
<td>ASE</td>
<td>SER</td>
<td>LUR</td>
<td>AMI</td>
</tr>
<tr>
<td>SER</td>
<td>PAL</td>
<td>HAL</td>
<td>PAL</td>
<td>ZIP</td>
</tr>
<tr>
<td>CHL</td>
<td>RIS</td>
<td>RIS</td>
<td>RIS</td>
<td>ASE</td>
</tr>
<tr>
<td>ILO</td>
<td>CLO</td>
<td>AMI</td>
<td>AMI</td>
<td>ILO</td>
</tr>
<tr>
<td>CLO</td>
<td>CHL</td>
<td>ZOT</td>
<td>QUE</td>
<td>ASE</td>
</tr>
<tr>
<td>ZOT</td>
<td>OLA</td>
<td>PAL</td>
<td>LUR</td>
<td>ZOT</td>
</tr>
</tbody>
</table>

SMD=standardised mean differences; OR=odds ratio

Drug-Placebo Differences Have Decreased Over Time (n=153)

Mean effect size 0.49

B=-0.07 (-0.12,-0.03)
[10-year increase]
Example for Meta-Regression

Increasing Placebo Response in Antipsychotic Drug Trials Over Time

Leucht et al. in preparation
Placebo-Response Has Increased Over Time

B = 2.70 (1.41, 3.99) [10-year increase]
Drug Response Has Remained Constant Over Time

\[ B = 0.54 \ ( -0.85, 1.93) \]
[10-year increase]

Antipsychotic more effective

Drug Response Has Remained Constant Over Time
Assumption: In flexible dose, double-blind studies, clinicians titrate the drugs to the mean optimum dose. These doses are identified for each drug and then used to calculate dose equivalence.

Limitation: the mean doses obtained in flexible dose studies depend among others on the allowed dose ranges.

n = 73
Dose Response Meta-Analysis

Leucht et al. manuscript in preparation
Cohort Effect?

- Could be suggested by the fact that the four most effective second-generation antipsychotics were the first to be developed.

- However, two meta-regression analyses did not change the efficacy hierarchy:
  - One with publication year as continuous moderator.
  - One comparing studies in the past 15 years with older ones.

- Example of paliperidone:
  - Ranks next to risperidone in most domains.
  - More effective than several drugs developed previously.
Differences in Haloperidol Doses?

- In the past, pair-wise meta-analyses suggested that some, but not all second-generation antipsychotics were more effective than haloperidol, but these studies were criticized for differences in haloperidol doses.

- However, exclusion of all haloperidol comparisons in this analysis did not affect the efficacy hierarchy.
# Overall Efficacy of Antipsychotic Drugs vs Placebo

Overall change in symptoms, SMD (95% credible interval)

<table>
<thead>
<tr>
<th>Drug</th>
<th>SMD (95% CI)</th>
<th>Favours active drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>-0.88 (-1.03 to -0.73)</td>
<td></td>
</tr>
<tr>
<td>Amisulpride</td>
<td>-0.66 (-0.78 to -0.53)</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>-0.59 (-0.65 to -0.53)</td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>-0.56 (-0.63 to -0.50)</td>
<td></td>
</tr>
<tr>
<td>Paliperidone</td>
<td>-0.50 (-0.60 to -0.39)</td>
<td></td>
</tr>
<tr>
<td>Zotepine</td>
<td>-0.49 (-0.66 to -0.31)</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>-0.45 (-0.51 to -0.39)</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>-0.44 (-0.52 to -0.35)</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>-0.43 (-0.52 to -0.34)</td>
<td></td>
</tr>
<tr>
<td>Sertindole</td>
<td>-0.39 (-0.52 to -0.26)</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>-0.39 (-0.49 to -0.30)</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>-0.38 (-0.54 to -0.23)</td>
<td></td>
</tr>
<tr>
<td>Asenapine</td>
<td>-0.38 (-0.51 to -0.25)</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>-0.33 (-0.45 to -0.21)</td>
<td></td>
</tr>
<tr>
<td>Iloperidone</td>
<td>-0.33 (-0.43 to -0.22)</td>
<td></td>
</tr>
</tbody>
</table>

SMD = standardised mean differences

Efficacy of Second-Generation vs First-Generation Antipsychotic Drugs: Meta-Analysis of 215 Studies

An increasing placebo response could possibly account for decreased efficacy values for newer antipsychotics.

However, the exclusion of all placebo comparisons did not change the effects much in the analysis (apart from asenapine turning out more effect than in the primary analysis).
The Results of Meta-Analyses Are Consistent

The effect size of haloperidol versus placebo derived from 11 double-blind trials with 1540 participants, which is used as a benchmark. The effect sizes of the SGAs compared to FGAs have been added to haloperidol versus placebo for illustration.

HAL, haloperidol; AMI, amisulpride; ARI, aripiprazole; CLO, clozapine; OLA, olanzapine; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone; ZOT, zotepine; SGA, second-generation antipsychotics; FGA, first-generation antipsychotics

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Differences in Efficacy

- Differences in efficacy were small (median 0.24).

- However, differences compared to placebo were only medium (median 0.44).

- So, differences in efficacy are possibly substantial enough to be clinically relevant.
Limitations of Meta-Analyses

- The „apples and oranges problem“ - heterogeneity, different study quality etc.

- In meta-analysis there are many judgement calls

- The original studies are frequently so poorly reported that meta-analytic procedures are not possible

- *Publication bias*

- Although meta-analyses are methodologically objective, the results can be interpreted differently
Effect Sizes of General Medicine and Psychiatric Drugs

- Review of:
  - 94 meta-analyses of 48 general medicine drugs
  - 33 meta-analyses of 16 psychiatric drugs
  - Main result: psychiatric drugs not generally less effective than other general medicine drugs

Antipsychotics for relapse prevention

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“My studies in this area lead me to a very uncomfortable conclusion: Our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good.”

- Peter Gøtzsche, MD; Co-founder of the Cochrane Collaboration

Sources for Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Health

In ORGANIZED CRIME . . . they make you an offer you cannot refuse . . . 

In NETWORK META-ANALYSIS . . . we make you an offer you cannot understand
Limitation: The effective dose medication arms were taken from head-to-head trials, not only from placebo-controlled trials.
“Network meta-analyses and mixed treatment comparisons represent the uppermost level in the evidence hierarchy for decision-making, in medicine as well as in other scholarly fields.”

From:

Network Meta-Analysis: Evidence Synthesis with Mixed Treatment Comparison

Editors:

Guiseppe Biondi-Zoccai, Assistant Professor in Cardiology Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Italy
Publication Bias

• Is probably the greatest problem of ‘evidence based medicine’ – EVIDENCE BIASED MEDICINE (Melander et al. 2004)
• Studies without significant results are considered less interesting by journals and thereby have a reduced likelihood of getting published
• Pharmaceutical companies are not interested in publishing studies with results that were unfavourable for their product.
“My studies in this area lead me to a very uncomfortable conclusion: our citizens would be far better off if we removed all the psychotropic drugs from the market, as doctors are unable to handle them. It is inescapable that their availability creates more harm than good.”

Peter Gotzsche, MD
Co-founder of the Cochrane Collaboration

Sources for Deadly Medicines and Organised Crime: How Big Pharma Has Corrupted Health
Statistics

- Sensitivity analyses: comparing different doses of the same drug with another drug
  - e.g. Haloperidol <7.5 and >7.5 mg/day and <12 and >12 mg/day and CPZ <600 and >600 mg/day
  - e.g. CPZ <600mg/day and >600mg/day
  - Using Olanzapine equivalents

- Meta-Regression used for:
  - Sponsorship trials
  - Mean age of participants
  - Duration of illness
„Funnel-plot“ without publication bias

„Funnel-plot“ showing possible publication bias
Statistics

• Multiple-treatments meta-analysis: Hierarchical models
  – Common heterogeneity model- Fixed effects model
  – SUCRA (surface under cumulative ranking)
    • Comparison to an “Imaginary drug” and effectiveness compared to that
  – Assumption of Transitivity in Pairwise comparisons
    • Networks do not differ
Are all antipsychotics similar?

- Klein and Davis (1969) found that all first-generation antipsychotics were equally efficacious with marginal differences in side effects.
- Introduction of meta-analysis to Psychiatry, before the term meta-analysis was coined. In same paper, I used a poor man’s survival analysis.
META-ANALYSIS IS SCIENCE

EXAMPLE OF HOW META-ANALYSIS LEADS TO A NEW DISCOVERY

[SLIDE TEXT STILL IN PREPARATION]