The use of indirect comparisons to compliment RCT evidence

A practical example

Mudge et al (2005) A comparison of olanzapine versus risperidone for the treatment of schizophrenia: a meta-analysis of randomised clinical trials. International Journal of Psychiatry in Clinical Practice 9 (1): 3-15.

SSAI
Statistical Society of Australia Inc.

APBG
Australian Pharmaceutical Biostatistics Group

Aim of analysis

- To compare the efficacy, safety and tolerability of olanzapine vs risperidone
  - Efficacy: PANSS, BPRS, CGI-S, QLS
  - Safety: Anticholinergic use
  - Tolerability: withdrawals

Background

- 2x28 week HTH trials of olanzapine vs risperidone used to demonstrate cost-effectiveness for PBS listing in 1997
- CEA supported by
  - Greater number of 'responders'
  - Lower incidence of side effects [extrapyramidal symptoms]
  - Supplemented by an indirect comparator analysis using data from trials of both agents vs haloperidol

Background

- Issues with
  - Dose of comparators
    - Goldilocks effect – too low, just right and too high
    - Recommended dose of comparators changed over time
  - Short vs longer term trials
    - Clinical effect developed over time
  - Different definitions of a ‘responder’
    - Symptomatic improvement
    - Drop out rates (all-cause discontinuation)

Methods

- Meta-analysis
  - Analyses grouped into short-term (< 12 weeks) and longer-term (> 12 weeks)
  - Head-to-head comparison using olanzapine vs risperidone studies
  - Indirect comparison using olanzapine vs haloperidol and risperidone vs haloperidol studies
    - Analysis of all doses (1)
    - Limiting to 'clinically relevant' doses (2)

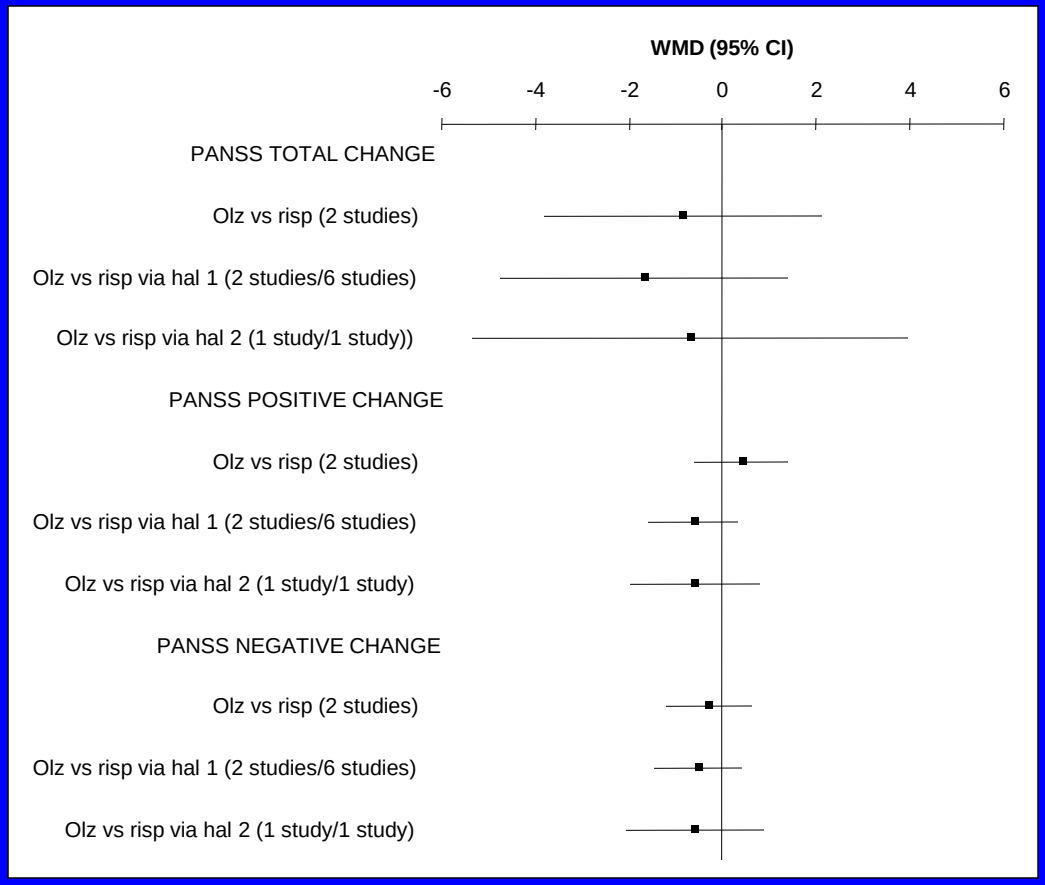
Methods

- Head-to-head analysis
  - Standard meta-analysis; performed using RevMan/Meta-View; FEM for non-heterogeneous comparisons; REM for heterogeneous comparisons
- Indirect analysis
  - Standard meta-analysis to compare olanzapine and risperidone with haloperidol; followed by meta-regression

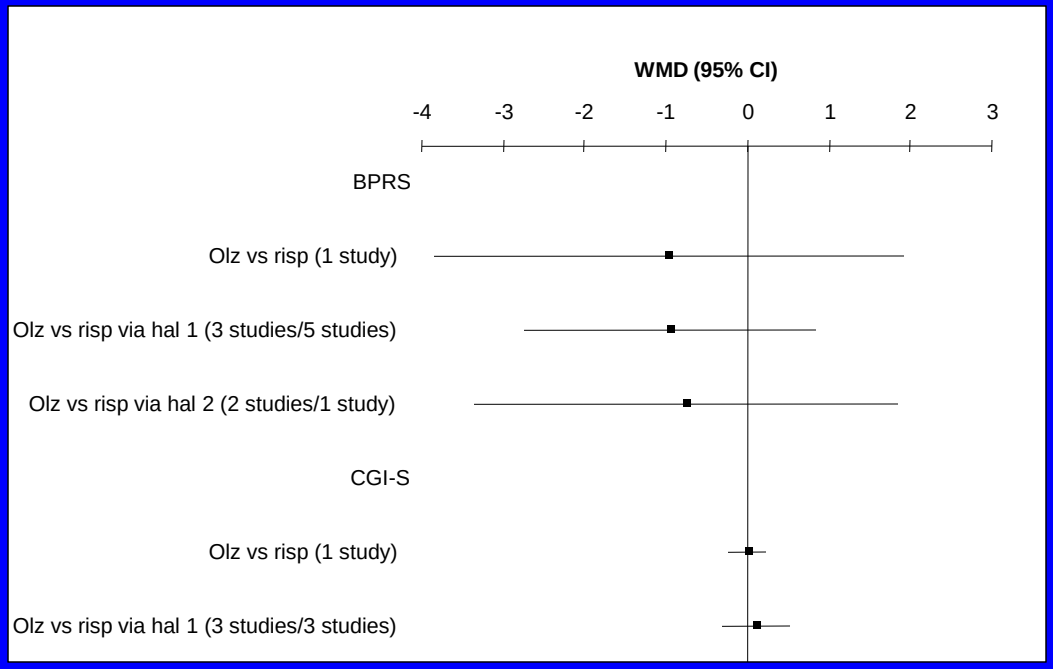
Results

- Short-term analysis only
  - Contains both head-to-head and indirect comparisons
- Efficacy outcomes only
  - Weighted mean difference presented for both head-to-head and indirect comparisons
  - Safety/tolerability outcomes used OR for head-to-head comparison and difference (log OR) for indirect comparison, so difficult to show similarities graphically

Results


WMD (95% CI)
-6
-4
-2
0
2
4
6
PANSS TOTAL CHANGE
Olz vs risp (2 studies)
Olz vs risp via hal 1 (2 studies/6 studies)
Olz vs risp via hal 2 (1 study/1 study))
PANSS POSITIVE CHANGE
Olz vs risp (2 studies)
Olz vs risp via hal 1 (2 studies/6 studies)
Olz vs risp via hal 2 (1 study/1 study)
PANSS NEGATIVE CHANGE
Olz vs risp (2 studies)
Olz vs risp via hal 1 (2 studies/6 studies)
Olz vs risp via hal 2 (1 study/1 study)

Results

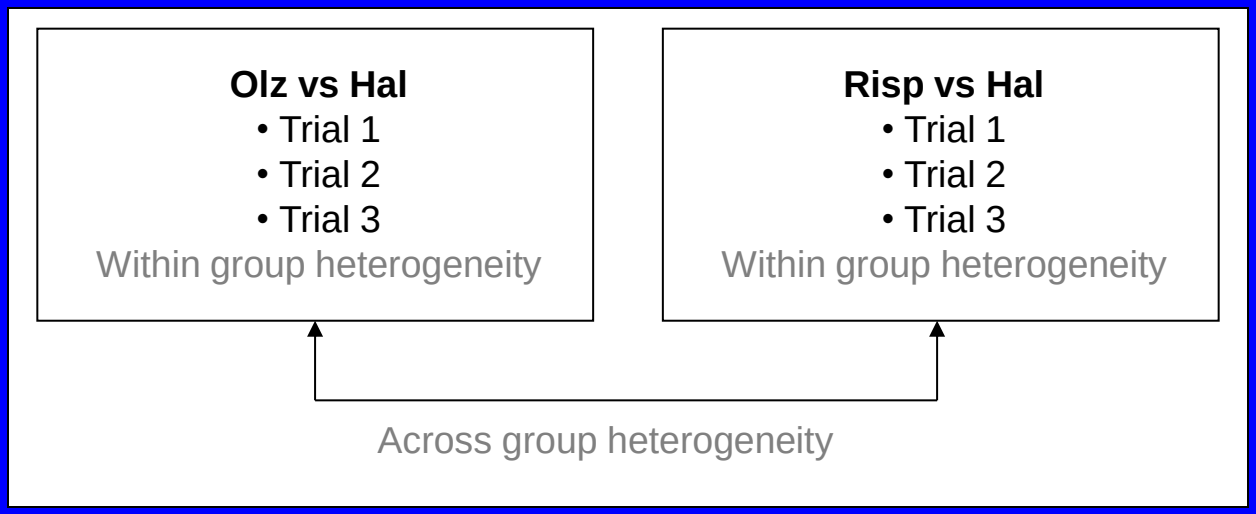

WMD (95% CI)
-4
-3
-2
-1
0
1
2
3
BPRS
Olz vs risp (1 study)
Olz vs risp via hal 1 (3 studies/5 studies)
Olz vs risp via hal 2 (2 studies/1 study)
CGI-S
Olz vs risp (1 study)
Olz vs risp via hal 1 (3 studies/3 studies)

Summary

- Indirect comparisons are a useful method to compliment head-to-head evidence, particularly when there are few head-to-head trials
- Indirect analysis results were consistent with head-to-head analysis results

Conclusion

- **Heterogeneity potentially a greater problem with indirect comparisons compared with head-to-head comparisons**
  - **Differences between trials both within groups and across groups**



Conclusion

- Heterogeneity in indirect comparisons can be addressed by:
  1. Including only trials with similar characteristics as was carried out in this analysis (eg, study duration and dosing)
  2. Using techniques such as Bayesian analysis to adjust for potential confounders