Blinding successfulness in antipsychotic trials of acute treatment for schizophrenia: a systematic review

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BACKGROUND
Blinding of randomised controlled trials (RCTs) is very important for the accurate assessment of drug efficacy. Without proper blinding, the effect of the intervention may be overestimated. Fergusson et al investigated the top journals in psychiatry from 1998 to 2001 and reported that blinding assessments were conducted in only 8 of 94 studies across psychiatric disorders. However, no studies on antipsychotic drugs were included among these eight. Hróbjartsson et al investigated RCTs published in 2001, and blinding assessments were conducted in 12 psychiatric studies. There were only two studies on antipsychotics but these did not focus on schizophrenia. Baethge et al searched for studies on schizophrenia and affective disorders from 2000 to 2010 to assess whether blinding was appropriately performed. Only 5 of the 672 schizophrenia studies, including those on pharmacotherapies and physical therapies, reported blinding assessment, and studies on schizophrenia tended to assess blindness less frequently than studies on affective disorders.

Thus, of the many double-blind RCTs of antipsychotic drugs conducted to date in the field of schizophrenia, it is unclear how many studies in total have assessed the successfulness of their blinding and if they were successful. Therefore, the objectives of this study were to clarify: (1) the proportion of RCTs of antipsychotics for schizophrenia in which blinding was assessed and (2) the degree of their blinding successfulness.

STUDY SELECTION AND ANALYSIS
We searched for antipsychotic drug trials in two sources. First, we looked up double-blinded or more-blinded placebo-controlled antipsychotic RCTs conducted from the 1950s to the present. We were able to find three new studies, and with the addition of one already discovered, we now have a total of four studies. The three newly found studies were old studies conducted in the 1950s and the 1960s, and one that had already been found was a drug development trial conducted in 2007. In addition to these, we found four studies with blinding assessment among all four studies that we had identified. The proportion of correctly guessed allocation ranged between 70% and 91%, with kappa statistics between 0.37 and 0.47.

CONCLUSIONS AND CLINICAL IMPLICATIONS
This is the first study to investigate studies with blinding assessment among all placebo-controlled double-blinded or more-blinded antipsychotic RCTs conducted from the 1950s to the present. We were able to find three new studies, and with the addition of one already discovered, we now have a total of four studies. The three newly found studies were old studies conducted in the 1950s and the 1960s, and one that had already been found was a drug development trial conducted in 2007. In all of these studies, blindness was clearly broken. However, it remains unclear whether these results apply to second-generation antipsychotics.

The Consolidated Standards of Reporting Trials (CONSORT) statement, revised in 2010, no longer recommend statements on assessment on blinding success due to lack of empirical evidence to support such reporting. This change in the CONSORT statement may have led to an even further decrease in the number of studies reporting blinding assessments. Furthermore, there is currently no consensus on how successfulness of blinding can be assessed and quantified.
Table 1  Summary of the four RCTs with blinding assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention and comparison (n)</th>
<th>Types of RCT</th>
<th>Who guessed?</th>
<th>Proportion of correctly guessed</th>
<th>Kappa statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall and Dunlap⁷</td>
<td>Chlorpromazine (87): 750 mg maximum Placebo (88)</td>
<td>Parallel</td>
<td>Psychiatrists and psychologists</td>
<td>Psychiatrists: 70.3%</td>
<td>Psychiatrists: 0.37</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Psychiatrists: 74.3% (only ‘unchanged’ cases)</td>
<td>Doctors: 91%</td>
<td></td>
</tr>
<tr>
<td>Simpson et al⁷</td>
<td>Haloperidol 6 mg (8) Haloperidol 30 mg (8) Placebo (8)</td>
<td>Parallel</td>
<td>Doctors and nurses</td>
<td>Doctors: 91%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Nurses: 89.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engelhardt et al⁷</td>
<td>Chlorpromazine (103): mean 180 mg (range 50–800 mg) Promazine (109): mean 180 mg (range 50–800 mg) Placebo (99)</td>
<td>Parallel</td>
<td>Doctors</td>
<td>Doctors: 76.8% (combined active drugs)</td>
<td>0.45 (combined active drugs)</td>
</tr>
<tr>
<td>George et al⁷</td>
<td>Dihydrexidine (20): 20 mg Placebo (20)</td>
<td>Crossover</td>
<td>Participants and raters</td>
<td>Participants: 86%</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Rates: 89%</td>
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</table>

RCT, randomised controlled trial.

There remains suspicion that treatment effects of antipsychotics for schizophrenia may be overestimated unless the trials are properly blinded. Researchers should therefore be encouraged to conduct blinding assessment and report the results in each RCT. We then need to integrate the results of more studies to examine the exact rate at which blinding is broken and how they may or may not affect the effect size estimates.

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Contributors At, TAF and SL conceived the study. AT, TAF, JS-T and SL designed the study, AT, KS, SK, RT, YF, MI, KY, YH and TT did the literature search and extracted the data. AT did the analyses. AT and TAF wrote the first draft of the manuscript. All authors contributed to the interpretation of the findings and subsequent edits of the manuscript. JS-T and SL provided overall supervision to the project. AT is the guarantor and accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

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