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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.[1] 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.[2] 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.[3] 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.[3]

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 studies among the studies included in the recent comprehensive systematic review of antipsychotics in schizophrenia by Leucht *et al*.[4] Second, we rechecked the studies included in the systematic review by Baethge *et al*.[3] Relapse-prevention studies were excluded.

We calculated the proportion of studies that evaluated blinding success among the included studies and quantified the blinding successfulness in two ways: (1) the proportion of correctly guessing the allocation and (2) kappa statistics between the guesses and true allocations from each study. The kappa statistic ranges between 0 and 1, with values closer to 0 meaning that blinding is adhered to.

Findings

We found 188 double-blinded or more-blinded placebo-controlled antipsychotic trials for schizophrenia in the database. The earliest study was conducted in 1955, and the most recent in 2021.

From this database, we identified three studies with blinding assessments.[5–7] All three were old studies conducted in the 1950s and the 1960s. These studies used first-generation antipsychotics, such as chlorpromazine,[5 7] haloperidol[6] and promazine.[5] Thus, the proportion of RCTs with blinding assessment was only 1.6% (3/188) in this comprehensive database of double-blinded or more-blinded antipsychotic trials for schizophrenia.

The systematic review by Baethge *et al*[3] identified five RCTs in schizophrenia which had checked blinding success. Only one of these was an antipsychotic trial.[8] This study was a drug development trial, and the products were administered via subcutaneous injection.

All in all, we found four studies with blinding assessments. Table 1 presents details of these studies. Blinding was broken in all the 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

Study	Intervention and comparison (n)	Types of RCT	Who guessed?	Proportion of correctly guessed	Kappa statistics
Hall and Dunlap[7]	Chlorpromazine (87): 750 mg maximum Placebo (88)	Parallel	Psychiatrists and psychologists	Psychiatrists: 70.3% Psychologists: 74.3% (only 'unchanged' cases)	Psychiatrists: 0.37 Psychologists: 0.47 (only 'unchanged' cases)
Simpson *et al*[6]	Haloperidol 6 mg (8) Haloperidol 30 mg (8) Placebo (8)	Parallel	Doctors and nurses	Doctors: 91% Nurses: 89.5%	Not calculable
Engelhardt *et al*[5]	Chlorpromazine (103): mean 180 mg (range 50–800 mg) Promazine (109): mean 180 mg (range 50–800 mg) Placebo (99)	Parallel	Doctors	76.8% (combined active drugs)	0.45 (combined active drugs)
George *et al*[8]	Dihydrexidine (20): 20 mg Placebo (20)	Crossover	Participants and raters	Participants: 86% Raters: 80%	Not calculable

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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