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Antipsychotic Trials Biased Towards Sponsor's Drug, Study Suggests

Clinical trial protocols for head-to-head comparisons of antipsychotic drugs should be reviewed by regulatory authorities like FDA to eliminate potential sources of bias, according to a recent analysis published in the *American Journal of Psychiatry*.

In a February 2006 article reviewing head-to-head studies of second-generation antipsychotics that were funded by pharmaceutical companies, 90.0% of studies found favorable results for the sponsor's drug ($p<0.001$). "Different trials comparing the same two drugs have had contradictory conclusions," the study notes. "This effect may not be totally unrelated to the funding sources of the trials."

Various sources of bias - including elements of clinical trial design - were identified in the analysis. Review of trial protocols by FDA or other regulators was suggested as one way to control for potential bias.

"Responsible agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMEA) might be given the chance to look at the protocol before the study is begun in order to allow the correction of obvious flaws," Stephan Heres (Technical University of Munich) *et al.* recommend.

The study examined 33 head-to-head studies sponsored by a pharmaceutical company that were identified through a MEDLINE search from 1966 to September 2003. Additional studies were selected from conference proceedings for the period from 1999 to February 2004.

The study looked at head-to-head studies involving several commonly prescribed second-generation antipsychotics, including Johnson & Johnson subsidiary Janssen's ***Risperdal*** (risperidone), Lilly's ***Zyprexa*** (olanzapine), Novartis' ***Clozaril*** (clozapine), Pfizer's ***Geodon*** (ziprasidone) and Sanofi-Aventis' ***Solian*** (amisulpride).

Of the 42 reports identified, 32 were fully or partially funded by pharmaceutical companies. The blinded review included 30 abstracts and found that the overall outcome was positive for the sponsor's drug in 27 cases. Looking at peer-reviewed studies only did not significantly alter the results: only three of 21 cases did not favor the sponsor's drug.

In addition to the overall pattern of positive findings, the analysis also found that studies by different sponsors had contradictory results (*see chart: "*[1]Home Court Advantage?*"*).

"Pair-wise comparisons revealed contrasting outcomes, depending on the sponsor of the study, although the outcomes were derived from trials involving the same drugs," Heres *et al.* noted.

"On the basis of these contrasting findings in head-to-head trials, it appears that whichever company sponsors the trial produces the better antipsychotic drug."

Dosing was identified as a possible source of bias, although the authors also found problems with entry criteria and study population, statistics and methods, and reporting and wording of results.

"Dose ranges and dose escalation are crucial factors that potentially influence trial outcome," the study states. "In numerous trials, dose ranges are scheduled according to the manufacturer's package insert, which is problematic with antipsychotic drugs."

For example, in Risperdal trials sponsored by J&J, a dose range of 2 mg to 6 mg per day was used, and even lower doses were used in elderly patients. Competitors, however, used higher doses that are associated with greater side effects but not greater efficacy.

In trials involving Zyprexa, the upper dose range limit is often set at 15 mg/day, thus excluding the most effective 20 mg/day dose, the study says. "Use of this limited dose range possibly reduces olanzapine's efficacy and may result in a misleading conclusion of the competitor's therapeutic superiority or equality."

"Finding the optimum dose escalation schedules for both compounds in a study is difficult and may be another source of bias. In some cases, the bias may derive from the fact that titration is mandatory for some drugs (risperidone, clozapine, sertindole), while the comparator (for example, olanzapine) does not require a stepwise dose escalation," the article states.

"This difference plays a major role in studies evaluating efficacy over a brief period of time."

Heres *et al.* acknowledge that there may be other sources of bias their analysis did not articulate. "Other readers may have different opinions, especially about the more subtle potential sources of bias."

The authors included several disclaimers about their research. Heres cautioned that the study is not a review or meta-analysis examining efficacy or tolerability, but rather " an exploratory approach to clarifying partly contradictory study results in the field of schizophrenia treatment."

The authors also added a statement that they were not implying that the bias was intentional on the part of sponsors: "Most of the identified factors were indeed rather subtle and did not reflect an attempt by the drug trial sponsors to intentionally misinterpret their findings or to willfully mislead readers."

"Although at least some of the biases we identified seemed very obvious, our analysis remains speculative, and there is no proof that the factors we identified really influenced the results."

Despite concerns regarding industry-sponsored trials, the authors acknowledge they are vital for clinical research and often surpassed non-industry sponsored trials in the quality of research methods. "Industry-independent studies are not necessarily free of bias and are often too underpowered to find clinically significant differences to allow any generalization," the study notes.

The article outlines "relatively simple measures" to overcome potential bias in industry-sponsored studies.

For problems with dosing, the study suggests study initiators solicit suggested dose ranges and titration schedules from the manufacturers, "as the manufacturer of a drug knows its properties best."

Defining a valid study population is critical in patients with treatment-resistant conditions that focus on antipsychotic effectiveness, the study adds. Previous treatment discontinuation elements, such as medication intolerance, shouldn't be used as alternative inclusion criteria. "Otherwise, it is unclear which aspect is related to the superiority of a compound," the authors said.

Peer reviewers also have a responsibility, Heres *et al.* suggest, since the wording and phrasing of study results are "surely the most debatable sources of bias."

"A complete disclosure of all results of the head-to-head comparison would appear to be mandatory but is not always provided," the study states. "Furthermore, reporting of adverse events seems to be selective."

"It is again the responsibility of *peer reviewers* for scientific journals to demand balanced reporting of the results," Heres *et al.* concluded.

A study appearing in the Feb. 2, 2006 issue of the *New England Journal of Medicine* appears to confirm Heres' analysis of bias in head-to-head studies of antipsychotics. The study, supported by the Stanley Medical Research Institute and authored by William Honer (University of British Columbia) *et al.*, found no beneficial effects of risperidone augmentation in schizophrenic patients not responding to clozapine.

"In contrast, two previous trials, which were industry-funded, showed a clear benefit for risperidone augmentation," John Davis (University of Illinois at Chicago) pointed out in an accompanying editorial.

The discrepancies may be due to a lower average dose than what investigators in the two industry-sponsored studies utilized, Davis suggested. In addition, the trial "may have focused on patients who were too sick for augmentation to make a difference. Nonetheless, the Honer trial was carefully conducted, and its negative findings introduce palpable doubt about the efficacy of augmentation therapy in refractory schizophrenia."

Davis added that previous studies evaluating the primary antipsychotics used to treat schizophrenia also had inconsistent results. He included among his citations the NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) ([2" The Pink Sheet" Sept. 26, 2005, p. 4](#)).

[Editor's note: Coverage of a related AJP study appeared in the "The Pink Sheet" DAILY Feb. 1. To read the article and sign up for a free trial, visit our website, www.ThePinkSheetDAILY.com.]