Study Identifies Bias in Favor of Publishing Positive Antidepressant Trials

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January 17, 2008 — A study of Food and Drug Administration (FDA)–registered clinical trials of 12 antidepressants found a bias toward publication of positive results. Almost all studies viewed by the FDA as positive were published. The clinical trials that the FDA deemed negative or questionable were largely not published or, in some cases, were published as positive outcomes.

For each of the 12 drugs, at least 1 study was not published or was reported in the literature as positive despite a conflicting judgment by the FDA.

The overall effect size of the antidepressants (vs placebo) that was reported in the published literature was nearly one-third larger than the effect size for these agents that was derived from FDA data.

"Selective reporting of clinical-trial results may have adverse consequences for researchers, study participants, healthcare professionals, and patients," they conclude.

These findings are published in the January 17 issue of the *New England Journal of Medicine*.

Evidence-Based or Biased Evidence?

"You might get the impression from the published literature that [these drugs] are consistently effective; however, the outcome of this study is that they are effective, but inconsistently so," lead study author, Eric H. Turner, MD, from Oregon Health and Science University, in Portland, Oregon, told *Medscape Psychiatry*.

"Evidence-based medicine is valuable to the extent that the evidence is complete and unbiased," he noted, adding that selective publication of clinical trials can alter the apparent risk/benefit ratio of drugs, which can affect prescribing decisions.

The current study sought to examine how accurately the published literature conveys data on drug efficacy to the medical community.

The team identified the phase 2 and 3 clinical-trial programs for 12 antidepressants approved by the FDA between 1987 and 2004, which involved 12,564 adult patients. They also determined whether the FDA judged the studies to be positive or negative with respect to primary end points.

To identify matching study publications, the researchers conducted a systematic literature search and contacted the sponsors of the drug studies.

Among the 74 FDA-registered antidepressant studies, the team found that 23 trials (31%) had not been published.

Among the 38 of 74 studies (51%) that the FDA deemed to be positive, 37 were published.

The remaining 36 studies (49%) were deemed to be either negative (24 studies) or questionable (12). Of these 36 studies, 22 were not published, 11 were published as positive, and 3 were published as negative.

Publication Status of FDA-Registered Antidepressant Studies

Publication Status	Number of Studies, n (%)
Published results agree with FDA decision	40 (54)
Published results conflict with FDA decision (published as positive)	11 (15)
Results not published	23 (31)
Total	74 (100)

For each drug, the effect-size value based on published literature was higher than the effect-size value based on FDA data. The increase in size ranged from 11% to 69% for individual drugs and was 32% overall.

"We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, decisions by journal editors and reviewers not to publish submitted manuscripts, or both," the group writes.

"Each drug, when submitted to a meta-analysis, was superior to placebo. On the other hand, the true magnitude of each drug's superiority to placebo was less than a diligent review of the literature would indicate," they note.

More Negative Studies Need to Be Published

"This is one of the first efforts to actually quantify the impact [of publication bias] in terms of reported efficacy, by medication," David Fassler, MD, from the University of Vermont College of Medicine, in Burlington, and a trustee-at-large of the American Psychiatric Association (APA), told *Medscape Psychiatry*. When published literature may overstate the efficacy or understate the risks of specific medications or interventions, this is clearly a significant problem for physicians, researchers, and the general public, he added.

Organized psychiatry has been in the forefront of trying to address this issue, he noted. In July 2004, the APA and the American Academy of Child and Adolescent Psychiatry (AACAP) brought a resolution about this topic to the American Medical Association, which prompted that organization to join in the call for a national registry, he added.

As a result of these and other efforts, today most major journals follow a policy set by the International Committee of Medical Journal Editors (ICMJE) and will consider only papers based on trials entered into 1 of 5 accepted, centralized, publicly accessible clinical-trial registries prior to study enrollment, he observed.

Additional steps are needed. "Journal editors need to ensure that well-designed studies with negative results are accepted for publication at the same rate as comparable studies with positive findings," Dr. Fassler said.

"Researchers involved in clinical trials should have the ability to publish or present data from their efforts.

Physicians, the media, and the general public . . . need to read and interpret new studies with appropriate caution."

APA and AACAP Renew Call for Mandatory Registry

In light of the report by Turner and colleagues, the APA and AACAP issued a statement renewing their call for a mandatory, public registry for clinical trials and reiterating their support for federal legislation to provide open access to clinical-trials data.

"Our patients deserve the best healthcare available, and having full disclosure of research findings — both positive and negative — will help clinicians develop the most effective treatment plans," APA president Carolyn Robinowitz, MD, said in the statement. Issues involving publication bias are not unique to psychiatry, she noted. "Publication bias has been well documented with cardiovascular and anti-inflammatory medications. A clinical-trials registry set up and overseen by the federal government would be good for all of medicine."

"Greater transparency in the clinical-trials process, particularly including open access to important data, is of significant benefit to the research community, to practitioners in the field, and to our patients," said AACAP president Robert L. Hendren, MD. "A national registry will allow patients to have access to data on a complete range of treatment options, including medication, to discuss with their physician."