The New York Times

Health

MEDICINE'S DATA GAP -- Journals in a Quandary; A Medical Journal Quandary: How to Report on Drug Trials

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Published: June 21, 2004

The issue of The American Journal of Psychiatry that hit the desks of its 37,000 readers this month reported test results for the antidepressant drug Celexa, indicating it could help children and teenagers.

Before publication, the article received the kind of scrutiny common among medical journals. The study's authors had been asked to divulge their financial ties, if any, to the drug's marketer, Forest Laboratories Inc., which sponsored the clinical trial. And the report was sent to reviewers who examined the trial methodology and checked to make sure that the article reflected other relevant research about the use of antidepressants in youngsters.

But neither the article nor the 27 scholarly footnotes that accompanied it mentioned another major drug-industry-sponsored trial completed in 2002, which found that Celexa did not help depressed adolescents any more than a placebo. Nor would the article's reviewers have been likely to find any clues of that trial's existence. The results of that trial were first noted last year on a single line of a chart that appeared on Page 96 of a textbook -- one written in Danish.

Like most medical journals, The American Journal of Psychiatry does not require company sponsors of drug trials to divulge information about all relevant trials of a medication. But that may soon change, as some leading journal editors try to address what they see as shortcomings in the way clinical tests are designed and analyzed by the drug industry, and how test results are disclosed.

"There is so much sophistication, that if the journals are not careful they could end up being part of the drug industry's marketing arm," said Dr. Richard Smith, the editor of The British Medical Journal.

In written responses to inquiries from The New York Times, Forest stated that the negative Celexa test, sponsored by a related company, was not mentioned in the recent article because "there was no citable public reference for the authors to examine."

But drug makers often announce trials with positive results without waiting for the results to be published. Forest, for example, issued a news release three years ago that highlighted the outcome of the positive Celexa trial. That was shortly after the test's completion, when the findings were first presented at a medical conference, but before the study was even submitted to The American Journal of Psychiatry for consideration. Three of the authors of the Celexa drug article in this month's issue are Forest employees.

Dr. Smith and other editors say the challenges they face are not limited to the tendency by companies and academic researchers to showcase positive tests results while playing down trials with negative or inconclusive findings. Editors say they must also be vigilant against companies' cherry-picking favorable but limited data from a trial that had originally set out to test other aspects of a drug's performance.

Some companies, several editors said, have also apparently milked tests for maximum publicity by submitting different parts of them under different authors' names to different medical journals.

A group of 12 medical journals worldwide including The Journal of the American Medical Association, The New England Journal of Medicine, The Lancet and The Annals of Internal Medicine are weighing a proposal that would require a drug trial to be listed at its start in a public database or registry as a prerequisite to its results being considered for publication. The British Medical Journal is not part of that group, which is known as the International Committee of Medical Journal Editors, but Dr. Smith said he also supported the initiative.

Editors say that a database could offer several benefits. Assigning a test a unique number could allow it to be tracked from start to finish. The results, be they positive or negative, could then be put into context with other relevant trials of the same drug. Moreover, journal editors say that if a trial's objectives were listed at the outset, they would know how to better assess an article that presented its results.

"It would be useful for us from an editorial perspective if trials were registered, so we could see what was on the mind of investigators when they started," said Dr. Jeffrey M. Drazen, the editor of The New England Journal of Medicine.

Some critics, however, have argued that medical journals themselves have been a part of the problem. A growing number of studies in recent years have shown that journals publish more trials with positive results than those with negative or inconclusive ones. And critics say the journals have moved too slowly to address such issues.

Dr. Catherine D. DeAngelis, the editor of The Journal of the American Medical Association, said the idea of requiring trial registration had been kicking around among editors for about a decade. She said the issue came up again during a discussion at a meeting earlier this month of the International Committee of Medical Journal Editors, partly out of frustration.

"We have tried editorials," said Dr. DeAngelis. "We tried getting the pharmaceutical companies to do it. We tried talking to leaders in government. But it hasn't happened."

While Dr. Drazen and Dr. DeAngelis said their group was likely to decide over the coming months what course to follow, it is not clear how the drug industry will react. Last week, Merck said it would support the idea of a government-run test registry. And GlaxoSmithKline said it would soon begin posting on its company Web site the trial results of all its drugs on the market, including tests for potential new uses of them.

Some other companies and the drug industry's trade group, the Pharmaceutical Research and Manufacturers Association of America, said last week that they could not comment because they had not seen specific registry proposals. But one official of the trade group raised concerns that registries could release company trade secrets or present data in ways confusing to doctors and the public.

Whatever the case, the example of the little-known test of Celexa in adolescents shows how medical journals can now miss information about a major trial of a drug that is the subject of an article.

Dr. Nancy C. Andreasen, the editor of The American Journal of Psychiatry, which is the flagship publication of American Psychiatric Association, said it was the responsibility of a study's authors to provide a scholarly overview of the published articles discussed in their paper. She said that her publication did not specifically ask authors or companies that sponsor trials about unpublished studies.

"We didn't have a checklist that includes that question," Dr. Andreasen said. She added, though, that the publication regularly reviews its policies.

The Celexa trial in question was run in Europe from 1996 to 2002 and was sponsored by H. Lundbeck, the Danish company that developed the drug.

Forest Laboratories sells the drug, which is generically known as citalopram, in this country under a license with Lundbeck.

A spokesman for Lundbeck said the company reported the trial results to Forest, although he could not say when. Forest executives did not respond to written inquiries from The Times seeking that information.

But Forest executives apparently had an opportunity to know about the European test before the publication of the positive trial's results this month in The American Journal of Psychiatry. Forest executives said they presented safety data concerning potential suicide risk from both the positive study and the European trial last fall at a medical conference. It was around that time that regulators in Britain and this country expressed concerns that several antidepressants might cause some depressed teenagers to consider suicide; the issue is still under study.

The Lundbeck spokesman said that an abstract about the European trial had been presented in April at a Swedish medical meeting, and both companies said that an article about that trial was being prepared for publication. Both companies also said that they did not promote the drug's use in children because regulators had not approved it for pediatric use. (Doctors can legally prescribe a drug for any use, once it has been approved for at least one purpose.)

Dr. Andreasen and other journal editors interviewed said that a single failed trial of a drug did not mean that the treatment was ineffective, because the study's design might have been flawed. By the same token, of course, a single positive test of a drug does not necessarily mean that it works.

In a Lancet article in April, British researchers sought to compare the benefits and risks that widely used antidepressants pose for children and adolescents, based on published and unpublished data. They reported that their analysis of the pooled results from two unpublished Celexa trials -- the one since published in The American Journal of Psychiatry and the European study cited in the Danish textbook -- suggested that citalopram was unlikely to produce a "clinically important reduction in depressive symptoms."

"With no good evidence for efficacy and the potential for increasing the risk for suicide, the risk-benefit balance is unfavorable," the researchers reported.

Dr. Karen Dineen Wagner of the University of Texas Medical Branch in Galveston, who was the lead outside investigator on the study published in The American Journal of Psychiatry, did not respond to interview requests through a hospital spokeswoman. The two other outside researchers involved, however, both said that Celexa worked well in their test and that the young patients did not experience increased suicidal thoughts.

"I don't know what the raw data looks like from the European study," said one of them, Dr. Adelaide S. Robb of the Children's National Medical Center in Washington.

She said that she was informed by Forest executives in 1999 that the European study was under way but that she was never told that it had been completed.