Trial Data on Anti-Seizure Drug Might Have Been Manipulated: Report

By Amanda Gardner
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WEDNESDAY, Nov. 11 (HealthDay News) -- An unusual look at internal documents from a pharmaceutical company suggests that clinical data was manipulated to make a popular anti-seizure drug, gabapentin (Neurontin), look more effective than it actually was, thereby increasing possibilities for its off-label usage, according to a new report.

"This means we're not seeing the full picture, and the picture we are seeing is suspect because perhaps there was selective reporting of outcomes so that only the positive outcomes were reported," said Kay Dickersin, senior author of a paper reporting the alleged deception in the Nov. 12 issue of the New England Journal of Medicine.

But this revelation may just be the tip of the iceberg, especially given that internal company research protocols are rarely available to outsiders, stated another expert.

"The reality is that a deliberate fraud is extremely difficult to unearth. If scientists and companies agree to report results in a way that wasn't initially intended, unless you have access to original documents, it is extremely difficult to actually figure out what happened and how it happened," said Dr. Steven Nissen, chairman of cardiovascular medicine at the Cleveland Clinic Foundation in Ohio. "How many other examples like this are there out there that we simply don't know about? That's what's frightening."

Dickersin, a professor of epidemiology at the Johns Hopkins Bloomberg School of Public Health in Baltimore, gained access to internal company documents when she was asked to testify for the plaintiff in a lawsuit alleging that Pfizer and Parke-Davis (now a division of Pfizer as a result of its Warner-Lambert acquisition) illegally tried to market the drug for off-label uses.

Neurontin is approved by the U.S. Food and Drug Administration to treat seizures and shingles, but is also widely used off-label to fight migraines, bipolar disorder and pain.

Dickersin compared internal company documents to 20 trials funded by Pfizer and Parke-Davis, 12 of which were published.

Typically, clinical trials are set up to track both primary and secondary outcomes. These initial decisions then dictate other aspects of the trial, such as how many participants will be included. And that feeds back into how valid the final results are for that specific trial design and that specific primary outcome.

But here, Dickersin and her colleagues discovered that the primary outcomes specified in the early company protocols were not always the same as those appearing in later reports.
"What appears to be happening is that outcomes are changing between what was planned and what was published," Dickersin said.

Sometimes researchers changed what the primary outcome was (if a different outcome cast the drug in a more positive light), neglected to report the primary outcome at all, turned a secondary outcome into the primary outcome or simply added new outcomes, the report said.

"This distorts the scientific evidence that's available on the benefits and risks of therapies," Nissen said.

On Tuesday, Pfizer issued a statement in response to the study, part of which read: "The suggestion that Pfizer attempted to mislead the medical community about the effectiveness of gabapentin [Neurontin] for certain off-label conditions is untrue. The review recently published in the New England Journal of Medicine, regarding the reporting of industry-sponsored trials for gabapentin for off-label use, was derived from a report created for litigation and coauthored by plaintiffs' expert witness, who was hired to produce opinions to support plaintiffs' arguments. We believe the review suffers from significant bias, insufficient data, poor methodology, and cannot pass the threshold of credible scientific research."

"The safety and efficacy of gabapentin has been widely published, both by Warner-Lambert/Pfizer as well as independent researchers, and Pfizer has supported the dissemination of the results of these studies, regardless of outcome. At Pfizer, science and medical integrity come first and foremost," the statement concluded.

Although regulations require that all clinical trials be registered at some point, the study authors feel that's not enough.

"We need to actually have the protocol itself available for people to look at so there aren't opportunities for people to fiddle around with what they submit," Dickersin said.

One possibility would be to register the protocol itself. "This doesn't necessarily fix it, but it does mean that it's transparent, that the public has access to what people say they're going to do before they do it," she added.

"The peer-reviewed scientific literature is how we write our guidelines and how we make decisions about what therapies to give patients," Nissen said. "If the material available to us is severely distorted by commercial influences, then the evidence we use to take care of patients is flawed. That is too high a price to pay."

More information

The U.S. National Institutes of Health has a registry of current clinical trials.

SOURCES; Kay Dickersin, Ph.D., professor, epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, director, Center for Clinical Trials, Johns Hopkins; Steven E. Nissen, chairman, department of cardiovascular medicine, Cleveland Clinic Foundation, Ohio; Nov. 10, 2009, statement, Pfizer Inc.; Nov. 12, 2009, New England Journal of Medicine

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