Newsweek

PRINT THIS

HEALTH

Pfizer's Headache

Lawsuit charges drugmaker was deceptive about Neurontin.

By Mary Carmichael | NEWSWEEK
Published Oct 8, 2008

After it paid $430 million to settle a 2004 lawsuit over illegal promotion of its anti-seizure drug Neurontin, Pfizer, the world's largest pharmaceutical company, may have thought its legal troubles with that medication were over. Not so fast: A new lawsuit, brought by the same attorney, alleges that the company's misdeeds went much further than originally charged. According to newly unsealed court documents, not only did the company and its subsidiaries push Neurontin for unapproved uses—the practice at the center of the first suit, which Pfizer admitted to as part of its settlement—they did so knowing that the drug was ineffective for several of those conditions (the settlement involved allegations of both criminal and civil violations). Pfizer, according to the documents, engaged in "outright deception of the biomedical community, and suppression of scientific truth"—stalling or stopping the publication of negative study results; manipulating both trial designs and data to make the drug look more effective than it was; and using questionable tactics to enhance the drug's image and increase its sales.

These practices were "highly unethical, harmful to science, wasteful of public resources, and potentially dangerous to the public's health," writes Kay Dickersin, the author of the longest of the documents and the director of the Center for Clinical Trials at Johns Hopkins University.

On Tuesday, Pfizer released a statement saying that it was "committed to the communication of medically or scientifically significant results of all studies, regardless of outcome. Company policy requires that, in all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner with a discussion of the strengths and limitations of the study, and are reported regardless of the outcome of the study."

The lawsuit is in early stages; Boston attorney Thomas Greene (who represented David Franklin, the whistleblower in the first Neurontin case) is seeking permission to bring it as a class-action case. Judge Patti Saris rejected a request to that effect in

August, but at the time, says Greene, she had not seen 12 expert reports that now comprise the bulk of the argument against the company. The reports, written by a wide variety of respected academics and submitted to the judge as part of the complaint, cite provocative emails sent by employees of Pfizer and its subsidiaries. They also analyze studies, both published and unpublished, that the company commissioned to test Neurontin's effectiveness at treating four conditions for which it is not approved: nociceptive pain ("think, 'I just hit my finger with a hammer,'" says Greene), bipolar disorder, migraines and headaches, and neuropathic pain, a chronic condition resulting from an injury to the nervous system. A final report concludes that Pfizer encouraged doctors to prescribe Neurontin at higher doses than those approved by the FDA.

In the case of nociceptive pain, the documents suggest a simple pattern of misbehavior: commissioning tests but declining to publish results that showed the drug did not work. The documents list several randomized controlled trials of Neurontin for this acute form of pain. All were commissioned by Pfizer, all turned out negative, and none were ever published in journals.

With bipolar disorder, the documents are not as straightforward. Dickersin's report analyzed all the relevant studies of Neurontin and says they were "marked by extensive spin and misrepresentation of data." Some of the negative ones were published, but only after long delays. Others were published but not cited in marketing literature. According to one of the most comprehensive of the 12 lawsuit reports, by John Abramson, a clinical instructor at Harvard Medical School, Pfizer emphasized studies of low quality that were "not blinded, not randomized, and not controlled." Meanwhile, it says, three double-blind randomized controlled trials—studies performed to the highest possible standard—had shown that Neurontin was in fact no better at treating the condition than a placebo was.

Neurontin is often used off-label as a treatment for migraine headaches, and this, too, is controversial. Among the 12 reports is one by Dr. Douglas McCrory, a clinical trials analyst at Duke University, concerning Pfizer's trials of Neurontin for migraines. "The most notable studies are two negative trials" performed internally, says the report; both of those "have remained unpublished." Meanwhile, "a single positive study is small, with a questionable analysis." That study initially seems to have yielded negative results—but when it was published in 2001 in the journal Headache, it was written up with positive ones. How did this happen? The trial initially looked at patients who had taken anywhere from 1800 to 2400 milligrams of Neurontin per day. But the published results considered only those who had received 2400 milligrams. Limiting the results to the smaller, higher-dose group appears to have yielded a more striking and statistically significant positive result, according to McCrory. "I conclude that this was an unplanned or post hoc subgroup analysis... reported as the primary analysis in order to give the false impression that this was a positive study," the McCrory report says. "There is an enormous misrepresentation of the study."

Dr. Ninan Mathew, the author of the study and the director of the Houston Headache Clinic, defended his approach on Tuesday. "Higher doses are more effective generally in clinical practice, and there was not a hidden analysis or anything. It was spelled out in the publication," he said. "There can be criticism about

that type of analysis, and there are people who may not like it, but it is done sometimes." Abramson, the Harvard trials analyst, responded in an interview on Tuesday that regardless of whether or not the endpoint identified by the manufacturer in its original study plan was optimal, the results published in Headache were not based on that pre-identified endpoint. "It's clear they were cherry-picking the way to look at the data that would give them the best results," he said.

Perhaps the most subtle example of allegedly manipulated research described in the documents is a trial published in 1998 in the Journal of the American Medical Association. (The trial is colloquially known as "Backonja," after lead author Miroslav Backonja, a neurologist at the University of Wisconsin-Madison.) The trial focused on neuropathic pain—a major focus of Pfizer's marketing strategy in the early 2000s, judging by internal company documents. "Backonja's" design may have resulted in "unblinding," allowing patients to figure out whether they were on the drug or the placebo it was being tested against. "By the time they got to the 3600 milligram daily dose of Neurontin—and they were required to take doses that high as part of the trial—about half the patients had side effects such as somnolence or dizziness," Abramson explained in an interview. "Those side effects tipped people off that they were on the drug, and what that essentially does is give the study a lesser weight of evidence." In studies of pain, a patient's knowledge that he is on a drug can ruin any objective attempts to measure how much pain he is actually feeling. (If he thinks he's on the drug, he may actually start to feel better.) Nicholas Jewell, a biostatistician at the University of California, Berkeley, re-analyzed the Backonja data to see if there was an unblinding effect. His conclusion, in yet another of the lawsuit's 12 reports: "Almost the entire apparent treatment effect reported in Backonja et al disappears when data after the occurrence of treatment-related central nervous system side effects is eliminated. I conclude that the trial provides no basis of any clinical efficacy for gabapentin over placebo in reducing pain in this population."

Even assuming that "Backonja" was a perfectly legitimate trial—and it was clearly deemed solid enough to run in JAMA, one of the world's top medical journals—it was not the only one of its kind. There were three other high-level studies of Neurontin and neuropathic pain commissioned by Pfizer, all of which turned out negative. "Pfizer knew about [the other trials], the FDA knew about them, and Pfizer's own consultants looked at them and said 'this drug doesn't work for neuropathic pain.' But the company cynically went forward and carried on this enormous program to communicate to physicians that it did," Abramson said in an interview. Documents in his report back him up. He cites, for instance, an email in which one company employee asks another how to make a particular negative trial for neuropathic pain "sound better than it looks on the graphs." Another study was rewritten by a company employee, who changed the outside author's conclusion that Neurontin caused a "modest improvement;" the rewrite called the same data a "substantial reduction" in pain. A third trial, which found "no statistically significant difference" between Neurontin and the placebo "at any time throughout the trial," set off a flurry of emails within the company. Examples: "We should take care not to publish anything that damages Neurontin's marketing success." "I think we can limit the potential downsides of the 224 study by delaying the publication for as long as possible and also from where it is published." "This is the negative study that we were talking about.... As you can imagine, I am not in a hurry to publish it."

Pfizer no longer markets Neurontin; the drug is now off-patent and available in generic form. But the drug company is sure to fight all these charges mightily. On Tuesday, Pfizer responded to some of them, noting that in one case it did publish a negative study of Neurontin and bipolar disorder; that in another it submitted a negative study on neuropathic pain to two small journals (the study was rejected by both of them); and that in a third it presented an abstract at a conference showing that Neurontin "did not reduce pain in a statistically significant way in the primary endpoint analysis." (The same abstract, however, noted that the drug had some positive secondary effects.) Tuesday's statement also said that Pfizer "will respond to plaintiffs' specific allegations at the appropriate time." When that moment arrives will now depend on Judge Saris's decision about whether the case should proceed.

In the meantime, Abramson—who wrote about many similar cases in the 2004 book "Overdosed America"—said in an interview that the new charges are just one more example of corruption in the pharmaceutical industry. "There was just a wanton manipulation of what physicians believed to be true," he said. "Physicians have to be able trust certain sources. They can't analyze all the data on all the drugs they prescribe themselves; if they did, the medical system would grind to a halt. So the question is, how do doctors typically receive knowledge? Pfizer knew how that happens—through articles, through continuing medical education, through reviews. And they knew how to jam those airwaves."