Sickening

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How Big Pharma Broke American Health Care and How We Can Repair It

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2

NEURONTIN: FRAUD AND RACKETEERING

Some will rob you with a six-gun,
And some with a fountain pen.

— WOODY GUTHRIE, "Pretty Boy Floyd"

In 2003, a tall, fit, conscientious medical student whom I'll call Steve presented a case to the primary care tutorial group I was teaching. The patient he discussed was being treated with Neurontin, a drug from Pfizer that had been approved by the FDA in 1994 as a secondary treatment for epilepsy and then in 2002 for persistent nerve pain after herpes zoster (shingles). Steve shared how taken aback he was when the neurologist he was working with said of Neurontin: "There is no other drug being used to treat so many different conditions with so little benefit."

To understand the neurologist's concern, we need to be aware that the use of Neurontin to treat these "many different conditions"—except for the two approved by the FDA—was off-label. Prescribing a drug off-label means using an FDA-approved drug to treat a condition that the drug has not been specifically approved to treat. In 2001, 21 percent of all prescriptions in the United States

were off-label. And, as the neurologist suspected, the drug most frequently prescribed off-label that year was Neurontin.

Although off-label *prescribing* is not illegal, the *marketing* of drugs by manufacturers to treat off-label conditions *is*,* and with good reason. It turns out that almost three-quarters of off-label prescriptions written by U.S. physicians have "little or no scientific support." In other words, although journal articles (often sponsored by the manufacturer) may report that a given drug is efficacious for an unapproved use, until it has been formally reviewed and approved by the FDA for that use, the drug generally cannot be relied upon to provide effective and safe treatment for that condition. As this chapter will show, Pfizer got caught red-handed in an off-label-marketing scheme that accounted for the vast majority of its Neurontin sales. But the financial penalties for this scam, even when scientific and marketing malfeasance is proven in a court of law, are rarely higher than the profits made. And thus, this rapacious and sometimes deadly game of cat and mouse goes on.

KAISER FOUNDATION HEALTH PLAN V. PFIZER

Fast-forward seven years to 2010 and the U.S. District Court in Boston, where Pfizer, then the world's largest pharmaceutical company, was being sued by Kaiser Foundation Health Plan, the nation's largest HMO, for Pfizer's alleged off-label marketing of Neurontin. Serving as an expert witness for the plaintiffs, I stood next to the jury box and drew a graph to explain the statistical shenanigans Pfizer had used to persuade doctors to prescribe Neurontin off-label for nerve pain.

As mentioned, the drug had two FDA-approved indications, ep-

* With one exception: If a doctor requests information about a specific off-label use, drug companies may provide relevant articles.

ilepsy and nerve pain following shingles (post-herpetic neuralgia). Kaiser alleged that Pfizer had pushed doctors to use Neurontin to treat bipolar disorder and to prescribe dosages up to twice the FDA-approved maximum for *all* types of nerve pain, despite the fact that the company's own science had failed to provide convincing evidence of benefit for these off-label uses.*

Kaiser's burden in proving the alleged wrongdoing was substantial: To win the case, lawyers had to prove not just that the doctors *didn't* know the truth about Neurontin but that they *couldn't* have known the truth about Neurontin due to Pfizer's manipulation of the scientific evidence that the company alone controlled. Pfizer had convinced doctors to prescribe Neurontin off-label for bipolar disorder by delaying publication and ignoring the results of its own study, which had shown the drug was *significantly worse* than placebo. For non-shingles-related nerve pain, Pfizer used other techniques, which included misrepresenting the results of one nerve-pain study, rigging another, and suppressing the results of two more. That they knew better was evident from an internal e-mail from Pfizer's own medical director, which disparaged Neurontin as "the 'snake oil' of the twentieth century."

Kaiser also claimed that Pfizer's deceptions had been perpetrated through a racketeering enterprise and violated the federal RICO law (enacted in 1970 to curtail the activities of organized crime). If the jury found Pfizer guilty of fraudulently influencing physicians through participation in racketeering activity, the financial damages would be tripled.

In 2003, the year my student presented his case, annual sales of Neurontin had reached $2.1 billion in the United States alone. And Steve didn't know the half of it; as I noted in the report I submitted to the court in advance of my testimony, in that year, nine out of ten prescriptions for Neurontin written in the United States were for non-

* Neurontin was originally marketed by Parke-Davis, a subsidiary of Warner-Lambert, which was acquired by Pfizer in 2000. For simplicity, I attribute all research and marketing activities regarding Neurontin to Pfizer.

FDA-approved uses, a testament to the success of Pfizer's off-label marketing strategy. Further, owing to the unique effectiveness of aggressive marketing of new drugs in the United States, 86 percent of worldwide Neurontin sales in 2001 had been in this country.

For most of the year preceding the trial, I worked with a team of lawyers, combing through literally millions of pages of Pfizer corporate documents. These documents allowed me to compare the data from Pfizer's clinical trials—the real data—to what doctors were reading in medical journals. I also compared Pfizer's data to its internal marketing documents to determine whether Pfizer's "educational" meetings and conferences had presented doctors with a reasonably balanced version of the truth about Neurontin.

About a week before the trial began, I asked Tom Sobol, the Kaiser attorney who would question me in court, when we were going to prepare. I had worked with Tom on other drug cases, but I had never testified in an open trial with a live jury, and I expected to spend at least one intense day preparing with him. I was stunned when Tom, a fastidious lawyer, responded that we were not going to meet beforehand; we were just going to have a "conversation in the courtroom."

Although I was not scheduled to testify until the second day of the trial, I went to the federal courthouse the first day to hear the lawyers' opening statements. After passing through security, I noticed an inscription carved into stone on the atrium wall: THE RIGHT TO SUE AND DEFEND IN THE COURTS IS THE ALTERNATIVE OF FORCE. IN AN ORGANIZED SOCIETY, IT IS THE RIGHT CONSERVATIVE OF ALL OTHER RIGHTS, AND LIES AT THE FOUNDATION OF ORDERLY GOVERNMENT. This statement, made in 1907 by the U.S. Supreme Court justice William H. Moody, was a sobering reminder that the trial would be about far more than the fraudulent marketing of a single drug. Ultimately, it was about whether drug companies had the right to withhold and misrepresent crucial information about their products and thereby mislead doctors and the public.

Before the jury entered the courtroom, federal district judge Patti B. Saris laid down some ground rules. The testimony in this

trial would remain focused on Neurontin, she said, not on the pharmaceutical industry in general. Therefore, no drug-company bashing would be allowed. Then she asked (in a stern voice), "Is Dr. Abramson in the courtroom?" I raised my hand from the gallery. She looked directly at me: "That means you."

I initially felt intimidated but then realized why she had singled me out. Two years earlier, I had made an unsolicited call to the U.S. Attorney's Office in Boston to see if they might be interested in the findings in my expert report on Bextra (another Pfizer product). I'd explained I was bound by a confidentiality agreement and could not share my report unless I was subpoenaed by the Department of Justice. I was duly subpoenaed, and, as mentioned in the introduction, I presented my testimony under oath to the DOJ and the FBI. Six months later, I learned that Pfizer had pleaded guilty to a felony and been assessed a record-breaking $1.195 billion fine. Now in Judge Saris's courtroom, I certainly got the message: I was not to discuss any of that — or make general statements about the pharmaceutical industry's behavior — in this trial.

My testimony began the next day. After being sworn in, I sat down in the witness stand and noticed that the jury box, which was on the other side of the expansive courtroom, was so far away that I could barely see the jurors' faces. As I answered questions about my background and credentials, I wondered how effectively I was going to be able to communicate with them. When I lecture, I typically feel a few butterflies before starting, especially with big audiences, but I generally get comfortable as soon as I begin my talk and can see how the audience is reacting. Here, that audience was so distant, I knew that would be difficult.

Marketing Neurontin to Treat Bipolar Disorder

The first issue I testified about was Pfizer's promotion of Neurontin for treating bipolar disorder. Pfizer's Pande study (named after the lead researcher) tested the effectiveness of the drug for severe bi-

polar disease in a double-blind randomized controlled trial (RCT). The study enrolled 117 manic patients already receiving but not responding adequately to drug therapy.

Dr. David Kessler, FDA commissioner from 1990 through 1997 and former cochair of President Biden's coronavirus task force, testified before I did. He explained to the jury that in a *randomized controlled trial* patients were randomly assigned to one of two study groups, one of which would receive the active treatment, in this case Neurontin, and the other a placebo. This ensured that the two groups were similar at the beginning of the study, so differences in outcomes between the groups would most likely be due to their different treatments. Furthermore, in the Pande study, bipolar patients were assigned to the two groups in a "double-blind" fashion, meaning that neither the subjects nor the researchers knew which patients were receiving the active drug and which were getting the placebo. The results were straightforward: At the end of the study, manic symptoms were *significantly worse* in the patients treated with Neurontin than in those treated with placebo. The clinical trial was completed in 1997, but, it should be noted, the results were not published as an independent study until 2000.

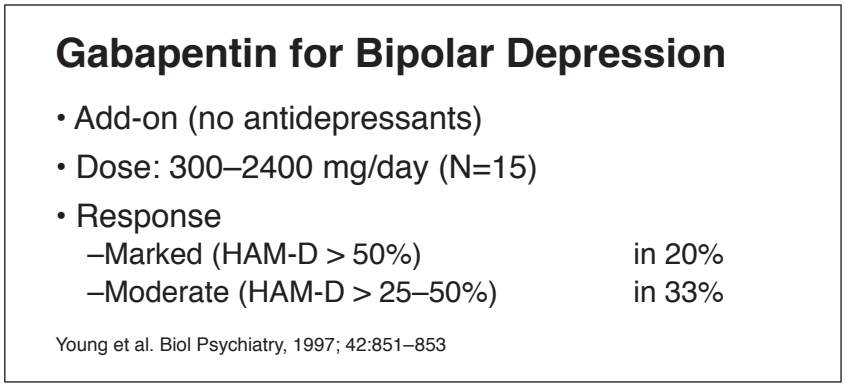
Three more RCTs found Neurontin to be no better than placebo for bipolar disorder. Nevertheless, between February 1996 and November 1999, the use of Neurontin for bipolar disorder increased fiftyfold, going from 8,000 to 402,000 prescriptions filled annually. What had caused this stunning increase when the study results had not only failed to provide evidence that the drug was helpful but, in one case, actually demonstrated that it was harmful?

My written report showed how this had happened: Pfizer had "educated" doctors about the unsubstantiated off-label use of Neurontin to treat bipolar disorder. In the spring of 1998 Pfizer sponsored fifty CME "Psychiatry Dinners" in expensive restaurants. (*CME* stands for "continuing medical education"; most states require physicians to take fifty hours of CME a year to maintain their medical licenses. CME programs are often sponsored by drug and device manufacturers.) All the lecturers at these dinners had pres-

tigious academic positions. During the same period, Pfizer held sixteen ninety-minute psychiatry teleconferences and hired a company to provide thirty medical-education seminars, which were attended by more than eleven thousand doctors.

The information presented at these meetings included a recommendation to treat bipolar disorder with Neurontin. A physician with the title "Distinguished Senior Scientist" included the slide shown below at a Pfizer-sponsored program at the 1998 U.S. Psychiatric and Mental Health Congress; it was also shown to the jury as I testified about these CME seminars.

This slide reports the results of the Young study, which was completed in 1997. It shows that more than half the patients treated with Neurontin responded with marked or moderate improvement (20 percent and 33 percent, respectively). In truth, since the number of patients in this study was only fifteen, this translated to positive responses from three and five patients, respectively. Further, all the patients in this small study were treated with Neurontin (there was no control group — no placebo, no comparison drug, nothing), and both the subjects and the medical staff knew this. As I told the



Results of small open-label study of Neurontin (generic name gabapentin) for bipolar depression shown at educational meetings sponsored by Pfizer *This slide is discussed in my testimony in Kaiser v. Pfizer, February 23, 2010; data published in Robb Young et al., "Acute Treatment of Bipolar Depression with Gabapentin," Biological Psychiatry 42, no. 9 (November 1997).*

jury, the most damning thing about Pfizer presenting this slide at its "educational" meetings in 1998 was that the much larger randomized controlled double-blind Pande study had been completed a year earlier, but its results were not published for two more years. Therefore, until 2000, even the most conscientious doctors would not have been able to find the results of Pfizer's gold-standard study, which showed that Neurontin was worse than nothing.

I explained to the jury that when doctors attend lectures presented by experts, we assume the information is accurate: "Our job is not to go back to the medical library and look up the Young article and see what the study really was. So it's critically important [that] doctors get presented a fair and accurate and balanced representation of scientific evidence."

This was particularly true for Pfizer's off-label claims, which, by definition, addressed drug use that the FDA had not reviewed and approved. I reminded the jury, "The doctors are on their own when they're prescribing off-label."

On their own, that is, except for what they were told by Pfizer. During her turn in the witness chair, plaintiffs' expert and economist Meredith Rosenthal, professor at the Harvard School of Public Health, showed that Pfizer's promotional marketing of Neurontin for the treatment of bipolar disorder was strongly linked to an increase in Neurontin prescriptions for that use. As she explained to the jury, her analysis showed that 99.4 percent of these prescriptions were the result of Pfizer's "fraudulent marketing."

Marketing Neurontin to Treat Neuropathic Pain

Next came Pfizer's marketing of Neurontin for the treatment of nerve pain. To unravel Pfizer's commercial deception, I needed to compare the company's documents showing each study's design and data analysis plan with its presentation of the results.

Pfizer's analysis of an early RCT — the Gorson study, completed in 1997 — claimed Neurontin had the potential to reduce diabetic

nerve pain. The Gorson results were presented at a large conference and published in the journal *Neurology* with this conclusion: "[Neurontin] may be effective in the treatment of painful diabetic neuropathy." This must have looked like a slam dunk to health-care professionals — nerve pain in patients with diabetes was difficult to treat, but Neurontin might provide relief. Why wouldn't a doctor want to treat patients suffering from chronic pain with a potentially effective non-narcotic drug?

But that wasn't what the study results actually showed. The report Dr. Gorson faxed to Pfizer in 1997 presented a far less enthusiastic conclusion: "[Neurontin] is probably no more effective than placebo in the treatment of painful diabetic neuropathy." My task was to explain how this discouraging but scientifically accurate statement from the lead researcher had morphed into the Pfizer-friendly "Neurontin may be effective." Again, it wasn't complicated.

This time, I needed to carefully explain the meaning of *controlled* in the term *randomized controlled trial*. The purpose of an RCT is not to see whether people treated with the study drug (Neurontin, in this case) are better at the end of the study than at the beginning; that would be an *uncontrolled* study (like the Young study described above). The purpose of an RCT is to see if those treated with the study drug experience *significantly more* improvement than those in the group treated with placebo. For the Gorson study, comparison of the change in pain level between the two groups was important because the placebo effect came into play: A subjective end point, like pain, is far more susceptible to distortion than an objective end point, like blood-sugar levels or changes on an electrocardiogram. Also, people tend to volunteer for trials when their symptoms are at their worst, so with just the passage of time, pain is likely to return to its average symptom level without any treatment (called "regression to the mean").

For these reasons, the Gorson study had been appropriately designed to compare the *difference* in improvement between the Neurontin- and placebo-treated groups. But Pfizer's conclusion relied only on the change in the level of pain of patients *within* the Neu-

rontin group, not on the difference *between* the Neurontin and placebo groups, and by doing this, the company was violating its own study design.

This was the crucial point I needed to get across. But without being able to see how the jury was reacting to my explanation, I couldn't tell if they were understanding me. I started to explain Pfizer's infraction against good science again, thinking I could make it clearer, but out of the corner of my eye, I saw Tom Sobol hold up a blue marker. "May I interrupt you, Dr. Abramson? Would it be helpful to draw a brief diagram to show this or no?" And at that point, I noticed an easel had been set up right next to the jury box.

"Yes," I said, trying not to respond too enthusiastically.

I decamped from the witness stand and walked across the courtroom, past the judge, past the Pfizer and Kaiser lawyers, to the position I described near the start of this chapter, just a few feet from the jury. From my new vantage point, the jurors' faces were no longer distant, undifferentiated blurs. There was a young gentleman in a camel-colored sport coat taking notes; a man in the back with his name sewn on his shirt; a young woman in a Red Sox jacket; and an elderly man who was sitting rapt. The Pfizer attorneys and the rest of the courtroom were behind me, out of sight and mostly out of mind.

Once I took that blue marker, I was no longer an expert witness for the plaintiffs—I was a teacher explaining to twelve motivated students with obviously different backgrounds how Pfizer had violated the rules of good science and how that scientific sleight of hand had led doctors to believe that Neurontin effectively treated the pain of diabetic neuropathy when the company's study had not shown that.

Standing at the easel, I could observe each juror to make sure he or she understood me as I explained how Pfizer used statistics in a deceptive way. First I sketched a graph of the results of the Gorson study, with a line descending from left to right to show how pain had steadily decreased over each of the six weeks of the study in the patients treated with Neurontin—just as Pfizer had claimed. Then

I drew a second line for the placebo group, also descending from left to right—almost mirroring the first line. The two lines, representing the average pain level in the two groups each week, were similar. Both groups had improved. For Pfizer to say that the Neurontin group saw a decrease in pain was correct, but it wasn't the comparison the study had been designed to make. What the study actually showed was that there was not a significant difference between the improvement in the Neurontin and placebo groups, and therefore using Neurontin to treat patients with painful diabetic neuropathy was unlikely to be helpful.

The study had been designed to investigate Neurontin's effectiveness in treating pain (that was the "primary outcome measure"), and the results showed exactly what Dr. Gorson had written in his original report: that Neurontin was "probably no more effective" than a sugar pill to treat pain. But in Pfizer's account of the study, there was no mention that a placebo group had shown similar results, so doctors could be tricked into believing the pain reduction in the people treated with Neurontin was due to the drug when it might just as well have been the placebo effect combined with the tincture of time.

At that point, the judge told Tom Sobol that it was time to finish up testimony for the day. I looked over at the jury and could see they understood how Pfizer had misrepresented the results of the Gorson study. More important, they now understood that scientific malfeasance was not out of bounds in the hardball world of pharmaceutical marketing.

Tom asked me one more question: If, rather than comparing changes in pain levels between the Neurontin group and the placebo group, one compared—as the manufacturer had—only Neurontin from the beginning to the end of the study, "have you essentially gotten rid of your control [group]?" Tom wanted to make absolutely sure the jury grasped this idea.

I responded, "You have . . . so you don't have a randomized controlled trial."

At which point the judge said, "Thank you, see you tomorrow."

Tom had set me up to finish the day by stating unambiguously that Pfizer had not followed its own study design.

The next morning my testimony picked up with another Pfizer-sponsored study of Neurontin for diabetic nerve pain. This was the Backonja study (again named for the lead researcher), by far Pfizer's most influential study of nerve pain, though neither the biggest nor the most rigorously designed. This study randomized 165 people with diabetic nerve pain to receive either Neurontin or placebo for eight weeks in what was ostensibly a double-blind RCT. The results, according to the 1998 article published in the *Journal of the American Medical Association*, showed that, compared to placebo, Neurontin significantly reduced daily pain scores. Pfizer hired a public relations firm to "educate both consumers and medical professionals" about the benefit of Neurontin, delivering its commercially advantageous message to Americans eighty-five million times through TV and radio, newspapers and magazines, even video clips shown to captive audiences of airline passengers.

But the devil was in the details of the study's design. It was a "forced titration" study, meaning the dose of Neurontin was increased over four weeks from 900 milligrams up to 3,600 milligrams per day—twice the FDA-approved maximum of 1,800 milligrams per day—and the dose was increased even if people experienced pain relief at a lower dose. Not surprisingly, by the end of the study, more than half of the Neurontin group had experienced side effects compared to only 15 percent in the placebo group.

The problem was more than simply the number of people who had experienced side effects. As I explained to the jury, developing symptoms like dizziness or sleepiness could have tipped off study participants that they were receiving Neurontin rather than a placebo. And this unblinding could have introduced bias because people experiencing side effects would have surmised they were probably receiving Neurontin and so would have expected to get relief from their pain. With this in mind, the authors of the *JAMA* article conducted further analyses, ostensibly to make sure side effects had not biased the study results. First, they removed the records

of subjects who had reported dizziness (and so presumably knew they were receiving Neurontin, not a placebo) from the analysis of pain scores; they found the results still showed Neurontin superior to placebo. Then they repeated the exercise, removing the records of subjects who had experienced sleepiness; again, the results were the same. Based on these two analyses, they concluded that the greater frequency of side effects in people treated with Neurontin and the possible unblinding which that created "did not account for the overall efficacy seen in the trial."

I had a brainstorming session with a younger doctor and a lawyer, trying to figure out why this study had found Neurontin helpful for diabetic nerve pain when Pfizer's other studies had not. We pored over the language and analyses in the *JAMA* article until the light bulb finally went on: The authors had pulled a fast one by removing the study participants who had experienced each of the two most common side effects *separately.* They showed that removing the 24 percent of people who had developed dizziness when treated with twice the FDA-approved maximum dose of Neurontin did not alter the study's results. Ditto for removing the 23 percent of people who developed sleepiness. But they never checked to see if comparing those Neurontin-treated patients who developed *neither dizziness nor sleepiness* (and so presumably did not know if they were receiving the study drug) with the placebo-treated patients still showed that Neurontin provided significant pain relief.

Because we were in litigation, the lawyers could request the individual patient-level trial data from Pfizer. Nick Jewell, professor of biostatistics and statistics at the University of California, Berkeley, and also a plaintiffs' expert in this trial, reanalyzed the results using the pain levels of participants recorded at the last visit *before* they experienced side effects. Using the pre-side-effect pain scores provided a statistical way to remove the bias created by forcing the dose of Neurontin up to twice the FDA-approved maximum and causing side effects that could have tipped off half the people treated with Neurontin that they had been assigned to the ac-

tive-treatment group. Indeed, Professor Jewell's reanalysis showed that 90 percent of the improvement in pain attributed to Neurontin had occurred *after* the onset of side effects. Analyzing only pre-side-effect pain scores showed that the pain reduction associated with Neurontin was no better than placebo.

More than ten years after that highly publicized but misleading *JAMA* article was published, Professor Jewell and his colleagues published their findings in two biostatistics journals. Sadly, few if any doctors would be influenced by these highly technical statistical articles appearing many years after they had already accepted the results published in their trusted *JAMA*.

An important contrast is provided by another Pfizer study of Neurontin for diabetic nerve pain, the Reckless study (again named for the lead researcher), which had no trickery in its design. In this study, completed in 1999, three times more people were treated with Neurontin than in the Backonja study, and, instead of forced titration, this design was much hardier: Three groups treated with fixed doses of Neurontin — 600, 1,200, and 2,400 milligrams per day — were compared to patients treated with placebo. Pfizer's research report stated unequivocally that "there was no statistically significant difference between any of the gabapentin groups and the placebo group for end point mean pain score or at any time throughout the trial."

Published in a timely and forthright fashion, these results would have had a definite impact on doctors' beliefs about the efficacy of Neurontin for diabetic neuropathy. But in stark contrast to the Pfizer-sponsored PR blitz that followed publication of the Backonja study, the results of this far more important study made an impression on few consumers or medical professionals. This is because the results were never published as an independent article, robbing doctors of the opportunity to integrate these negative findings into their treatment plans. Pfizer did, however, issue an internal communication about the Reckless study, which I read to the jury. It stated: "Although I would love to publish

SOMETHING about [the study], Donna McVey [a Pfizer medical director] made it very clear that we should take care not to publish anything that damages neurontin's [*sic*] marketing success." Pfizer's Neurontin Publication Subcommittee agreed that the results of the Reckless study "should not be pushed for publication." Clearly, Pfizer's commitment was not to patients' welfare but to selling Neurontin, even if it meant withholding from doctors the most important clinical trial data about Neurontin's benefits (or lack thereof). Pfizer never did publish the results of the fixed-dose study as an independent article.

Despite the negative results of this well-designed study, Pfizer continued to pursue the holy grail of pain-medicine sales: FDA approval of Neurontin for the treatment of all types of nerve pain. But when they met with the FDA in May 2001 to discuss their application to make treatment of nerve pain an approved indication, the FDA—knowing what Pfizer's data showed—wouldn't even allow Pfizer to file the application.

Pfizer then did the right thing. In September 2001 its executives convened a meeting of independent pain consultants and requested honest advice about how to win FDA approval. After reviewing Pfizer's clinical trial data, both published and unpublished, the consultants were as disparaging as the FDA. One said there was "substantial evidence against a broad neuropathic pain claim." Another concluded concisely, "You're done." Ultimately, Neurontin never received FDA approval for the treatment of any type of pain other than persistent post-shingles pain.

THE MISUSE OF KEY MESSAGES

Meanwhile, Pfizer was pursuing another strategy, one that ignored the FDA and the company's own pain consultants and actively misled doctors about the effectiveness of Neurontin for neuropathic pain. This involved not just withholding negative clinical trial re-

sults but making affirmative claims about the drug that its own clinical trials had shown to be untrue. My access to the documents in this litigation provided a rare opportunity to see how blatantly this had been done.

In mid-July 2001, Pfizer started working with the consulting firm Medical Action Communications on developing key messages to be incorporated into a review article recommending that doctors prescribe Neurontin to treat neuropathic pain. First on the list of "Neurontin Publication Plan Key Messages" presented in an e-mail dated July 30, 2001, was "proven efficacy for neuropathic pain," which, as we've just seen, Pfizer was well aware had not been proven. The following day, another key message recommended increasing the dose of Neurontin to 1,800 milligrams per day—the FDA-approved maximum dose—by the second week of therapy *even if the patient was experiencing relief at a lower dose*. A third key message went even further: "Gabapentin doses up to 3600 mg/d have been proven well tolerated and effective in clinical studies." Just to be clear, this was two months after the FDA said that, based on the available evidence, it would not even consider an application for approval of Neurontin to treat neuropathic pain, two months before Pfizer's own pain consultants opined that the evidence did not support approval of Neurontin for the treatment of neuropathic pain, and in spite of 1,800 milligrams being the maximum daily dose approved by the FDA.

In January 2003 the review article was published in the journal *Clinical Therapeutics,* and its conclusion precisely reflected the key messages developed back in July 2001: "At doses of 1800 to 3600 mg/d, gabapentin was effective and well tolerated in the treatment of adults with neuropathic pain." A Pfizer e-mail told its drug reps: "Because this is a key publication for Neurontin," the information in that review article should be included in all marketing activities related to the treatment of neuropathic pain.

After I read this to the jury, a juror raised her hand, was recog-

nized by the judge, and asked, "Is it legal to promote off-label applications? Is any of this legal?"

I responded:

> It is not legal to promote—to market off-label. . . . If a drug rep came in and said, "Hey, Neurontin is a good drug for adjunctive therapy for seizures," and the doctor asked, "Well, it's an anti-seizure medicine, might it work for neuropathic pain?" then the drug rep is allowed, having received an unsolicited request, to show information that would make that case. But unless the drug rep is specifically asked that question, it's not legal.

The juror responded, "So this was arming [the drug reps] with the information should they be asked?"

I answered, "No, I don't think that's true." The juror acknowledged my comment, and I added, "I think this was proactive," by which I meant the purpose of training the reps to tout the merits of treating neuropathic pain with Neurontin was not simply so they would be prepared to respond to an unsolicited question but to offer the "education" even *before* having received a specific inquiry.

The juror said, "Understood."

At the end of my testimony about neuropathic pain, Tom Sobol circled back to ask me why it was so important that doctors understand the bias that might have been introduced into the 1998 Backonja study of Neurontin for diabetic neuropathy by unblinding. Why, he asked, wasn't this "just sort of a geeky statistical" point?

Doing my best not to sound geeky, I explained,

> Well, that is really important because doctors work very hard, and they want to get the bottom line of the research: Does this study show that the drug works for patients with diabetic neuropathy or not? And these fine details . . . really change the meaning of the study. So it's essential for doctors to understand the fine print here, and yet . . . there are a few clues, but there's no way you can expect a practicing physician to unravel the incomplete correc-

tion for the unblinding that happened [because of] the forced titration design of the study.

I don't think I succeeded in not sounding geeky, but the jury seemed to understand what I was saying.

THE VERDICT AND BEYOND

The trial lasted six weeks. After deliberating for two days, the jury found that Pfizer had fraudulently promoted Neurontin to doctors for off-label use, and it awarded Kaiser $47 million. The jury also found — for the first time in a drug company case — that Pfizer had violated the RICO Act (that is, it had committed racketeering violations), which automatically tripled the penalty to $142 million. Pfizer appealed the decision and lost.

Pfizer hadn't acted like the gangsters of the past — no machine guns, no bank heists, no hit men. Rather, as Judge Saris pronounced in her "Findings of Fact and Conclusions of Law," Pfizer had engaged in a "nationwide effort to unlawfully market this drug for off-label uses for which there was little or no scientific evidence of efficacy."

The outcome of this litigation might look like a resounding defeat for Pfizer and a victory for the integrity of the data that doctors rely on to make their clinical decisions. But time has shown just the opposite. The financial penalties Pfizer paid in this and all the other Neurontin litigation amounted to a relative pittance, less than half the revenues from one year of Neurontin sales. No one went to jail, and the press coverage of this trial was minimal, so Pfizer suffered little reputational damage.

I had hoped that once the truth was presented in court, doctors would understand how their patient care was being undermined by Pfizer's illegal marketing of Neurontin. That didn't happen; among the health-care professionals I speak to, only a small percentage are aware this trial ever took place. A 2019 update of clinical tri-

als of gabapentin shows the clinical evidence hasn't changed significantly in the intervening years and concludes that "clinicians who prescribe [gabapentin] off-label for pain should be aware of the limited evidence and should acknowledge to patients that potential benefits are uncertain for most off-label uses." Nonetheless, once doctors get in the habit of prescribing a certain drug to their patients, their belief in its purported benefit takes on an indelible quality—even when the source of that belief is the manufacturer's illegal marketing of the drug. The result: Even today, generic Neurontin (gabapentin) is the sixth most frequently prescribed drug in the United States, and most of those prescriptions are for off-label use.*

The *Kaiser v. Pfizer* trial provided two key lessons about drug company marketing: First, because drug companies fund most of the research about their own drugs and control the resulting data, they can (and do) mislead physicians in order to increase sales. And second, under our current system, it is more profitable for large pharmaceutical companies to commit crimes and pay the fines than to obey the law. Why dedicated doctors can be so predictably misled will be addressed in part II.

* Some of the overreliance on gabapentin to treat pain is a reaction to the recent overprescribing of opioids.

3

THE TRUTH ABOUT STATINS

> The statins saga forces us to confront the deep flaws in our current system for evaluating medicines and guiding clinical decisions. In particular, how can it be right to recommend mass treatment of healthy people without independent review of the patient level data?
>
> — EMMA PARISH, THEODORA BLOOM, AND FIONA GODLEE, *British Medical Journal*

The first two chapters showed how sales of individual drugs were jacked up by their manufacturers' manipulation of the scientific information made available to (or withheld from) doctors. This chapter presents a similar phenomenon but for an entire class of drugs: cholesterol-lowering statins, which are by far the most frequently prescribed class of drugs in the United States. As with most widely used classes of drugs, doctors prescribe statins based on clinical practice guidelines issued by their professional societies and relevant nonprofit organizations.

To understand the importance of those guidelines, meet Jane, a bright, hardworking, and socially committed baby boomer. Jane married in 1970, soon after graduating from college, and spent the next four decades doing it all; she was a wife, the mother of three, and a dedicated full-time fifth-grade teacher for twenty years, first in a rural town in the Pacific Northwest and then in a suburb of Boston. Every weekday, teaching and family responsibilities filled her