

Dr. Drug Rep

By DANIEL CARLAT, November 25, 2007

On a blustery fall New England day in 2001, a friendly representative from Wyeth Pharmaceuticals came into my office in Newburyport, Mass., and made me an offer I found hard to refuse. He asked me if I'd like to give talks to other doctors about using Effexor XR for treating [depression](#). He told me that I would go around to doctors' offices during lunchtime and talk about some of the features of Effexor. It would be pretty easy. Wyeth would provide a set of slides and even pay for me to attend a speaker's training session, and he quickly floated some numbers. I would be paid \$500 for one-hour "Lunch and Learn" talks at local doctors' offices, or \$750 if I had to drive an hour. I would be flown to New York for a "faculty-development program," where I would be pampered in a Midtown hotel for two nights and would be paid an additional "honorarium."

I thought about his proposition. I had a busy private practice in [psychiatry](#), specializing in psychopharmacology. I was quite familiar with Effexor, since I had read recent studies showing that it might be slightly more effective than S.S.R.I.'s, the most commonly prescribed [antidepressants](#): the Prozac's, Paxils and Zolofts of the world. S.S.R.I. stands for selective serotonin reuptake inhibitor, referring to the fact that these drugs increase levels of the neurotransmitter serotonin, a chemical in the brain involved in regulating moods. Effexor, on the other hand, was being marketed as a dual reuptake inhibitor, meaning that it increases both serotonin and [norepinephrine](#), another neurotransmitter. The theory promoted by Wyeth was that two neurotransmitters are better than one, and that Effexor was more powerful and effective than S.S.R.I.'s.

I had already prescribed Effexor to several patients, and it seemed to work as well as the S.S.R.I.'s. If I gave talks to primary-care doctors about Effexor, I reasoned, I would be doing nothing unethical. It was a perfectly effective treatment option, with some data to suggest advantages over its competitors. The Wyeth rep was simply suggesting that I discuss some of the data with other doctors. Sure, Wyeth would benefit, but so would other doctors, who would become more educated about a good medication.

A few weeks later, my wife and I walked through the luxurious lobby of the Millennium Hotel in Midtown Manhattan. At the reception desk, when I gave my name, the attendant keyed it into the computer and said, with a dazzling smile: "Hello, Dr. Carlat, I see that you are with the Wyeth conference. Here are your materials."

She handed me a folder containing the schedule of talks, an invitation to various dinners and receptions and two tickets to a Broadway musical. "Enjoy your stay, doctor." I had no doubt that I would, though I felt a gnawing at the edge of my conscience. This seemed like a lot of money to lavish on me just so that I could provide some education to primary-care doctors in a small town north of Boston.

The next morning, the conference began. There were a hundred or so other [psychiatrists](#) from different parts of the U.S. I recognized a couple of the attendees, including an acquaintance I hadn't seen in a while. I'd heard that he moved to another state and was making a bundle of money, but nobody seemed to know exactly how.

I joined him at his table and asked him what he had been up to. He said he had a busy private practice and had given a lot of talks for Warner-Lambert, a company that had since been acquired by [Pfizer](#). His talks were on [Neurontin](#), a drug that was approved for [epilepsy](#) but that my friend had found helpful for [bipolar disorder](#) in his practice. (In 2004, Warner-Lambert pleaded guilty to illegally marketing Neurontin for unapproved uses. It is illegal for companies to pay doctors to promote so-called off-label uses.)

I knew about Neurontin and had prescribed it occasionally for bipolar disorder in my practice, though I had never found it very helpful. A recent study found that it worked no better than a placebo for this condition. I

asked him if he really thought Neurontin worked for bipolar, and he said that he felt it was “great for some patients” and that he used it “all the time.” Given my clinical experiences with the drug, I wondered whether his positive opinion had been influenced by the money he was paid to give talks.

But I put those questions aside as we gulped down our coffees and took seats in a large lecture room. On the agenda were talks from some of the most esteemed academics in the field, authors of hundreds of articles in the major psychiatric journals. They included Michael Thase, of the [University of Pittsburgh](#) and the researcher who single-handedly put Effexor on the map with a meta-analysis, and Norman Sussman, a professor of psychiatry at [New York University](#), who was master of ceremonies.

Thase strode to the lectern first in order to describe his groundbreaking work synthesizing data from more than 2,000 patients who had been enrolled in studies comparing Effexor with S.S.R.I.'s. At this time, with his Effexor study a topic of conversation in the mental-health world, Thase was one of the most well known and well respected psychiatrists in the United States. He cut a captivating figure onstage: tall and slim, dynamic, incredibly articulate and a master of the research craft.

He began by reviewing the results of the meta-analysis that had the psychiatric world abuzz. After carefully pooling and processing data from eight separate clinical trials, Thase published a truly significant finding: Effexor caused a 45 percent remission rate in patients in contrast to the S.S.R.I. rate of 35 percent and the placebo rate of 25 percent. It was the first time one antidepressant was shown to be more effective than any other. Previously, psychiatrists chose antidepressants based on a combination of guesswork, gut feeling and tailoring a drug's side effects to a patient's symptom profile. If Effexor was truly more effective than S.S.R.I.'s, it would amount to a revolution in psychiatric practice and a potential windfall for Wyeth.

One impressive aspect of Thase's presentation was that he was not content to rest on his laurels; rather he raised a series of potential criticisms of his results and then rebutted them convincingly. For example, skeptics had pointed out that Thase was a paid consultant to Wyeth and that both of his co-authors were employees of the company. Thase responded that he had requested and had received all of the company's data and had not cherry-picked from those studies most favorable for Effexor. This was a significant point, because companies sometimes withhold negative data from publication in medical journals. For example, in 2004, [GlaxoSmithKline](#) was sued by [Eliot Spitzer](#), who was then the New York attorney general, for suppressing data hinting that [Paxil](#) causes [suicidal](#) thoughts in children. The company settled the case and agreed to make clinical-trial results public.

Another objection was that while the study was billed as comparing Effexor with S.S.R.I.'s in general, in fact most of the data compared Effexor with one specific S.S.R.I.: [Prozac](#). Perhaps Effexor was, indeed, more effective than Prozac; this did not necessarily mean that it was more effective than the other S.S.R.I.'s in common use. But Thase announced that since the original study, he had analyzed data on Paxil and other meds and also found differences in remission rates.

For his study, Thase chose what was at that time an unusual measure of antidepressant improvement: “remission,” rather than the more standard measure, “response.” In clinical antidepressant trials, a “response” is defined as a 50 percent improvement in depressive symptoms, as measured by the Hamilton depression scale. Thus, if a patient enters a study scoring a 24 on the Hamilton (which would be a moderate degree of depression), he or she would have “responded” if the final score, after treatment, was 12 or less.

Remission, on the other hand, is defined as “complete” recovery. While you might think that a patient would have to score a 0 on the Hamilton to be in remission, in fact very few people score that low, no matter how deliriously happy they are. Instead, researchers come up with various cutoff scores for remission. Thase chose a cutoff score of 7 or below.

In his study, he emphasized the remission rates and not the response rates. As I listened to his presentation, I wondered why. Was it because he felt that remission was the only really meaningful outcome by which to compare drugs? Or was it because using remission made Effexor look more impressive than response did? Thase indirectly addressed this issue in his paper by pointing out that even when remission was defined in different ways, with different cutoff points, Effexor beat the S.S.R.I.'s every time. That struck me as a pretty convincing endorsement of Wyeth's antidepressant.

The next speaker, Norm Sussman, took the baton from Thase and explored the concept of remission in more detail. Sussman's job was to systematically go through the officially sanctioned "slide deck" — slides provided to us by Wyeth, which we were expected to use during our own presentations.

If Thase was the riveting academic, Sussman was the engaging populist, translating some of the drier research concepts into terms that our primary-care-physician audiences would understand. Sussman exhorted us not to be satisfied with response and encouraged us to set the bar higher. "Is the patient doing everything they were doing before they got depressed?" he asked. "Are they doing it even better? That's remission." To further persuade us, he highlighted a slide showing that patients who made it all the way to remission are less likely to relapse to another depressive episode than patients who merely responded. And for all its methodological limitations, it was a slide that I would become well acquainted with, as I would use it over and over again in my own talks.

When it came to side effects, Effexor's greatest liability was that it could cause [hypertension](#), a side effect not shared by S.S.R.I.'s. Sussman showed us some data from the clinical trials, indicating that at lower doses, about 3 percent of patients taking Effexor had hypertension as compared with about 2 percent of patients assigned to a placebo. There was only a 1 percent difference between Effexor and placebo, he commented, and pointed out that treating high blood pressure might be a small price to pay for relief from depression.

It was an accurate reading of the data, and I remember finding it a convincing defense of Effexor's safety. As I look back at my notes now, however, I notice that another way of describing the same numbers would have been to say that Effexor leads to a 50 percent greater rate of hypertension than a placebo. Framed this way, Effexor looks more hazardous.

And so it went for the rest of the afternoon.

Was I swallowing the message whole? Certainly not. I knew that this was hardly impartial medical education, and that we were being fed a marketing line. But when you are treated like the anointed, wined and dined in Manhattan and placed among the leaders of the field, you inevitably put some of your critical faculties on hold. I was truly impressed with Effexor's remission numbers, and like any physician, I was hopeful that something new and different had been introduced to my quiver of therapeutic options.

At the end of the last lecture, we were all handed envelopes as we left the conference room. Inside were checks for \$750. It was time to enjoy ourselves in the city.

II. The Art and Science of Detailing

Pharmaceutical "detailing" is the term used to describe those sales visits in which drug reps go to doctors' offices to describe the benefits of a specific drug. Once I returned to my Newburyport office from New York, a couple of voice-mail messages from local Wyeth reps were already waiting for me, inviting me to give some presentations at local doctors' offices. I was about to begin my speaking — and detailing — career in earnest.

How many doctors speak for drug companies? We don't know for sure, but one recent study indicates that at least 25 percent of all doctors in the United States receive drug money for lecturing to physicians or for helping to market drugs in other ways. This meant that I was about to join some 200,000 American physicians who are being paid by companies to promote their drugs. I felt quite flattered to have been recruited, and I assumed that the rep had picked me because of some special personal or professional quality.

The first talk I gave brought me back to earth rather quickly. I distinctly remember the awkwardness of walking into my first waiting room. The receptionist slid the glass partition open and asked if I had an appointment.

"Actually, I'm here to meet with the doctor."

"Oh, O.K. And is that a scheduled appointment?"

"I'm here to give a talk."

A light went on. "Oh, are you part of the drug lunch?"

Regardless of how I preferred to think of myself (an educator, a psychiatrist, a consultant), I was now classified as one facet of a lunch helping to pitch a drug, a convincing sidekick to help the sales rep. Eventually, with an internal wince, I began to introduce myself as “Dr. Carlat, here for the Wyeth lunch.”

The drug rep who arranged the lunch was always there, usually an attractive, vivacious woman with platters of gourmet sandwiches in tow. Hungry doctors and their staff of nurses and receptionists would filter into the lunch room, grateful for free food.

Once there was a critical mass (and crucially, once the [M.D.](#)'s arrived), I was given the go-ahead by the Wyeth reps to start. I dove into my talk, going through a handout that I created, based on the official slide deck. I discussed the importance of remission, the basics of the Thase study showing the advantage of Effexor, how to dose the drug, the side effects, and I added a quick review of the other common antidepressants.

While I still had some doubts, I continued to be impressed by the 10 percent advantage in remission rates that Effexor held over S.S.R.I.'s; that advantage seemed significant enough to overcome Effexor's more prominent side effects. Yes, I was highlighting Effexor's selling points and playing down its disadvantages, and I knew it. But was my salesmanship going to bring harm to anybody? It seemed unlikely. The worst case was that Effexor was no more effective than anything else; it certainly was no less effective.

During my first few talks, I worried a lot about my performance. Was I too boring? Did the doctors see me as sleazy? Did the Wyeth reps find me sufficiently persuasive? But the day after my talks, I would get a call or an e-mail message from the rep saying that I did a great job, that the doctor was impressed and that they wanted to use me more. Indeed, I started receiving more and more invitations from other reps, and I soon had talks scheduled every week. I learned later that Wyeth and other companies have speaker-evaluation systems. After my talks, the reps would fill out a questionnaire rating my performance, which quickly became available to other Wyeth reps throughout the area.

As the reps became comfortable with me, they began to see me more as a sales colleague. I received faxes before talks preparing me for particular doctors. One note informed me that the physician we'd be visiting that day was a “decile 6 doctor and is not prescribing any Effexor XR, so please tailor accordingly. There is also one more doc in the practice that we are not familiar with.” The term “decile 6” is drug-rep jargon for a doctor who prescribes a lot of medications. The higher the “decile” (in a range from 1 to 10), the higher the prescription volume, and the more potentially lucrative that doctor could be for the company.

A note from another rep reminded me of a scene from “Mission: Impossible.” “Dr. Carlat: Our main target, Dr. , is an internist. He spreads his usage among three antidepressants, [Celexa](#), [Zoloft](#) and Paxil, at about 25-30 percent each. He is currently using about 6 percent Effexor XR. Our access is very challenging with lunches six months out.” This doctor's schedule of lunches was filled with reps from other companies; it would be vital to make our sales visit count.+

Naïve as I was, I found myself astonished at the level of detail that drug companies were able to acquire about doctors' prescribing habits. I asked my reps about it; they told me that they received printouts tracking local doctors' [prescriptions](#) every week. The process is called “prescription data-mining,” in which specialized pharmacy-information companies (like IMS Health and Verispan) buy prescription data from local pharmacies, repackage it, then sell it to pharmaceutical companies. This information is then passed on to the drug reps, who use it to tailor their drug-detailing strategies. This may include deciding which physicians to aim for, as my Wyeth reps did, but it can help sales in other ways. For example, Shahram Ahari, a former drug rep for [Eli Lilly](#) (the maker of Prozac) who is now a researcher at the University of California at San Francisco's School of Pharmacy, said in an article in The Washington Post that as a drug rep he would use this data to find out which doctors were prescribing Prozac's competitors, like Effexor. Then he would play up specific features of Prozac that contrasted favorably with the other drug, like the ease with which patients can get off Prozac, as compared with the hard time they can have withdrawing from Effexor.

The [American Medical Association](#) is also a key player in prescription data-mining. Pharmacies typically will not release doctors' names to the data-mining companies, but they will release their Drug Enforcement Agency numbers. The A.M.A. licenses its file of U.S. physicians, allowing the data-mining companies to match up [D.E.A.](#) numbers to specific physicians. The A.M.A. makes millions in information-leasing money.

Once drug companies have identified the doctors, they must woo them. In the April 2007 issue of the journal PLoS Medicine, Dr. Adriane Fugh-Berman of Georgetown teamed up with Ahari (the former drug rep) to describe the myriad techniques drug reps use to establish relationships with physicians, including inviting them to a speaker's meeting. These can serve to cement a positive relationship between the rep and the doctor. This relationship is crucial, they say, since "drug reps increase drug sales by influencing physicians, and they do so with finely titrated doses of friendship."

III. Uncomfortable Moments

I gave many talks over the ensuing several months, and I gradually became more comfortable with the process. Each setting was somewhat different. Sometimes I spoke to a crowded conference room with several physicians, nurses and other clinical staff. Other times, I sat at a small lunch table with only one other physician (plus the rep), having what amounted to a conversation about treating depression. My basic Effexor spiel was similar in the various settings, with the focus on remission and the Thase data.

Meanwhile, I was keeping up with new developments in the research literature related to Effexor, and not all of the news was positive. For example, as more data came out comparing Effexor with S.S.R.I.'s other than Prozac, the Effexor remission advantage became slimmer — more like 5 percent instead of the originally reported 10 percent. Statistically, this 5 percent advantage meant that only one out of 20 patients would potentially do better on Effexor than S.S.R.I.'s — much less compelling than the earlier proportion of one out of 10.

I also became aware of other critiques of the original Thase meta-analysis. For example, some patients enrolled in the original Effexor studies took S.S.R.I.'s in the past and presumably had not responded well. This meant that the study population may have been enriched with patients who were treatment-resistant to S.S.R.I.'s, giving Effexor an inherent advantage.

I didn't mention any of this in my talks, partly because none of it had been included in official company slides, and partly because I was concerned that the reps wouldn't invite me to give talks if I divulged any negative information. But I was beginning to struggle with the ethics of my silence.

One of my most uncomfortable moments came when I gave a presentation to a large group of psychiatrists. I was in the midst of wrapping up my talk with some information about Effexor and [blood pressure](#). Referring to a large study paid for by Wyeth, I reported that patients are liable to develop hypertension only if they are taking Effexor at doses higher than 300 milligrams per day.

"Really?" one psychiatrist in the room said. "I've seen hypertension at lower doses in my patients."

"I suppose it can happen, but it's rare at doses that are commonly used for depression."

He looked at me, frowned and shook his head. "That hasn't been my experience."

I reached into my folder where I kept some of the key Effexor studies in case such questions arose.

According to this study of 3,744 patients, the rate of high blood pressure was 2.2 percent in the placebo group, and 2.9 percent in the group of patients who had taken daily doses of Effexor no larger than 300 milligrams. Patients taking more than 300 milligrams had a 9 percent risk of hypertension. As I went through the numbers with the doctor, however, I felt unsettled. I started talking faster, a sure sign of nervousness for me.

Driving home, I went back over the talk in my mind. I knew I had not lied — I had reported the data exactly as they were reported in the paper. But still, I had spun the results of the study in the most positive way possible, and I had not talked about the limitations of the data. I had not, for example, mentioned that if you focused specifically on patients taking between 200 and 300 milligrams per day, a commonly prescribed dosage range, you found a 3.7 percent incidence of hypertension. While this was not a statistically significant higher rate than the placebo, it still hinted that such moderate doses could, indeed, cause hypertension. Nor had I mentioned the fact that since the data were derived from placebo-controlled clinical trials, the patients were probably not representative of the patients seen in most real practices. Patients who are very old or who

have significant medical problems are excluded from such studies. But real-world patients may well be at higher risk to develop hypertension on Effexor. +

I realized that in my canned talks, I was blithely minimizing the hypertension risks, conveniently overlooking the fact that hypertension is a dangerous condition and not one to be trifled with. Why, I began to wonder, would anyone prescribe an antidepressant that could cause hypertension when there were many other alternatives? And why wasn't I asking this obvious question out loud during my talks?

I felt rattled. That psychiatrist's frown stayed with me — a mixture of skepticism and contempt. I wondered if he saw me for what I feared I had become — a drug rep with an M.D. I began to think that the money was affecting my critical judgement. I was willing to dance around the truth in order to make the drug reps happy. Receiving \$750 checks for chatting with some doctors during a lunch break was such easy money that it left me giddy. Like an addiction, it was very hard to give up.

There was another problem: one of Effexor's side effects. Patients who stopped the medication were calling their doctors and reporting symptoms like severe [dizziness](#) and lightheadedness, bizarre electric-shock sensations in their heads, [insomnia](#), sadness and tearfulness. Some patients thought they were having strokes or nervous breakdowns and were showing up in emergency rooms. Gradually, however, it became clear that these were "withdrawal" symptoms. These were particularly common problems with Effexor because it has a short half-life, a measure of the time it takes the body to metabolize half of the total amount of a drug in the bloodstream. Paxil, another short half-life antidepressant, caused similar problems.

At the Wyeth meeting in New York, these withdrawal effects were mentioned in passing, though we were assured that Effexor withdrawal symptoms were uncommon and could usually be avoided by tapering down the dose very slowly. But in my practice, that strategy often did not work, and patients were having a very hard time coming off Effexor in order to start a trial of a different antidepressant.

I wrestled with how to handle this issue in my Effexor talks, since I believed it was a significant disadvantage of the drug. Psychiatrists frequently have to switch medications because of side effects or lack of effectiveness, and anticipating this potential need to change medications plays into our initial choice of a drug. Knowing that Effexor was hard to give up made me think twice about prescribing it in the first place.

During my talks, I found myself playing both sides of the issue, making sure to mention that withdrawal symptoms could be severe but assuring doctors that they could "usually" be avoided. Was I lying? Not really, since there were no solid published data, and indeed some patients had little problem coming off Effexor. But was I tweaking and pruning the truth in order to stay positive about the product? Definitely. And how did I rationalize this? I convinced myself that I had told "most" of the truth and that the potential negative consequences of this small truth "gap" were too trivial to worry about.

As the months went on, I developed more and more reservations about recommending that Effexor be used as a "first line" drug before trying the S.S.R.I.'s. Not only were the newer comparative data less impressive, but the studies were short-term, lasting only 6 to 12 weeks. It seemed entirely possible that if the clinical trials had been longer — say, six months — S.S.R.I.'s would have caught up with Effexor. Effexor was turning out to be an antidepressant that might have a very slight effectiveness advantage over S.S.R.I.'s but that caused high blood pressure and had prolonged withdrawal symptoms.

At my next Lunch and Learn, I mentioned toward the end of my presentation that data in support of Effexor were mainly short-term, and that there was a possibility that S.S.R.I.'s were just as effective. I felt reckless, but I left the office with a restored sense of integrity.

Several days later, I was visited by the same district manager who first offered me the speaking job. Pleasant as always, he said: "My reps told me that you weren't as enthusiastic about our product at your last talk. I told them that even Dr. Carlat can't hit a home run every time. Have you been sick?"

At that moment, I decided my career as an industry-sponsored speaker was over. The manager's message couldn't be clearer: I was being paid to enthusiastically endorse their drug. Once I stopped doing that, I was of little value to them, no matter how much "medical education" I provided.

IV. Life After Drug Money

A year after starting my educational talks for drug companies (I had also given two talks for Forest Pharmaceuticals, pushing the antidepressant Lexapro), I quit. I had made about \$30,000 in supplemental income from these talks, a significant addition to the \$140,000 or so I made from my private practice. Now I publish a medical-education newsletter for psychiatrists that is not financed by the pharmaceutical industry and that tries to critically assess drug research and marketing claims. I still see patients, and I still prescribe Effexor. I don't prescribe it as frequently as I used to, but I have seen many patients turn their lives around because they responded to this drug and to nothing else. +

In 2002, the drug industry's trade group adopted voluntary guidelines limiting some of the more lavish benefits to doctors. While the guidelines still allow all-expenses-paid trips for physicians to attend meetings at fancy hotels, they no longer pay for spouses to attend the dinners or hand out tickets to musicals. In an e-mail message, a Wyeth spokesman wrote that Wyeth employees must follow that code and "our own Wyeth policies, which, in some cases, exceed" the trade group's code.

Looking back on the year I spent speaking for Wyeth, I've asked myself if my work as a company speaker led me to do bad things. Did I contribute to faulty medical decision making? Did my advice lead doctors to make inappropriate drug choices, and did their patients suffer needlessly?

Maybe. I'm sure I persuaded many physicians to prescribe Effexor, potentially contributing to blood-pressure problems and withdrawal symptoms. On the other hand, it's possible that some of those patients might have gained more relief from their depression and [anxiety](#) than they would have if they had been started on an S.S.R.I. Not likely, but possible.

I still allow drug reps to visit my office and give me their pitches. While these visits are short on useful medical information, they do allow me to keep up with trends in drug marketing. Recently, a rep from [Bristol-Myers Squibb](#) came into my office and invited me to a dinner program on the antipsychotic Abilify.

"I think it will be a great program, Dr. Carlat," he said. "Would you like to come?" I glanced at the invitation. I recognized the name of the speaker, a prominent and widely published psychiatrist flown in from another state. The restaurant was one of the finest in town.

I was tempted. The wine, the great food, the proximity to a famous researcher — why not rejoin that inner circle of the select for an evening? But then I flashed to a [memory](#) of myself five years earlier, standing at a lectern and clearing my throat at the beginning of a drug-company presentation. I vividly remembered my sensations — the careful monitoring of what I would say, the calculations of how frank I should be.

"No," I said, as I handed the rep back the invitation. "I don't think I can make it. But thanks anyway."

Daniel Carlat is an assistant clinical professor of psychiatry at Tufts University School of Medicine and the publisher of The Carlat Psychiatry Report.