

sons. Students constantly hear their mentors, as well as the media, discuss the monetary aspect of medicine; it permeates the training environment. Although money has always been part of medicine, it has never been so prominent, and it has not been the primary motivator of most doctors' practices. Today's medical students are being inducted into a culture in which their profession is seen increasingly in financial terms. Add in such pressures as the need to pay off enormous debts, and it is not surprising that students' choices are dictated by the desire to maximize income and minimize work time.

Some established primary care physicians are also making career choices in response to this new culture and fleeing to concierge practices, often citing their desire to escape the constant pricing of every aspect of their day. Since concierge practices collect yearly premiums from patients, such doctors may ironically be less "primed" by money at each encounter and may avoid feeling "nickel and dimed" by insurers. This arrangement creates an environment that can foster so-

cial interaction more than it does market exchange. But concierge medicine is unaffordable for most Americans, and it drives much-needed primary care providers away from the larger population.

How can we restore the balance between communal and market exchange in medicine in the current economic environment, given the imperative to cut costs? One answer may lie in an experimental new paradigm in primary care termed the "patient-centered medical home."⁵ The term itself suggests an emphasis on the social exchange that exists in a family rather than the market exchange of a business. The medical home is envisioned as a "compassionate partnership" of primary care providers and patients, with coordinated care for patients' ongoing problems and increased attention to preventive measures. The insurer would pay a set fee for each patient cared for in the medical home to cover what is now nonreimbursed time. Substantial cost savings are expected to result from coordination of care. As policymakers refine this model and extend it to include medical specialists, they should take into account the les-

sons of behavioral economics. Caregivers should be appropriately reimbursed but should not be constantly primed by money. Success in such a model will require collegiality, cooperation, and teamwork — precisely the behaviors that are predictably eroded by a marketplace environment.

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The Neurontin Legacy — Marketing through Misinformation and Manipulation

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Old drugs usually fade away. Sometimes, however, they leave surprising legacies. In 1997, for example, a study comparing the effects of brand-name and generic formulations of levothyroxine led to an uproar over the discovery that the manufacturer of the brand-name product sup-

pressed publication of the result that the two formulations were equivalent. Recently, lawsuits alleging damages from illegal marketing of another old drug, gabapentin (Neurontin), have yielded remarkable discoveries about the structure and function of pharmaceutical marketing.

Patented in 1977 and approved by the Food and Drug Administration (FDA) in 1993 in doses of up to 1800 mg per day as adjunctive therapy for partial complex seizures, Neurontin became a surprise blockbuster for Parke-Davis, a division of Warner-Lambert, which was purchased by Pfizer in

2000. U.S. sales rose from \$98 million in 1995 to nearly \$3 billion in 2004 before Neurontin faced generic competition and lost most U.S. sales.

The rise of Neurontin would have been unheralded except for a quirk of fate: a young biologist, David Franklin, went to work for Parke–Davis on April 1, 1996. Fresh out of postdoctoral training at Harvard, Franklin soon grew concerned that he was participating in illegal marketing. At a training seminar for “medical liaisons” on April 16, 1996, Franklin and his peers were told that FDA regulations required a fair and balanced presentation and prohibited promotion of a drug for off-label uses, selling by medical liaisons, and soliciting of inquiries from physicians. Six days later, a Parke–Davis executive reportedly told Franklin,

I want you out there every day selling Neurontin. . . . We all know Neurontin’s not growing for adjunctive therapy, besides that’s not where the money is. Pain management, now that’s money. Monotherapy [for epilepsy], that’s money. . . . We can’t wait for [physicians] to ask, we need [to] get out there and tell them up front. Dinner programs, CME programs, consultantships all work great but don’t forget the one-on-one. That’s where we need to be, holding their hand and whispering in their ear, Neurontin for pain, Neurontin for monotherapy, Neurontin for bipolar, Neurontin for everything. I don’t want to see a single patient coming off Neurontin before they’ve been up to at

least 4800 mg/day. I don’t want to hear that safety crap either, have you tried Neurontin, every one of you should take one just to see there is nothing, it’s a great drug.¹

Three months later, Franklin left Parke–Davis and filed a suit (ultimately, *United States of America ex rel. David Franklin vs. Pfizer, Inc., and Parke-Davis Division of Warner-Lambert Company*) alleging that off-label marketing of Neurontin constituted “false claims” designed to elicit payments from the federal government. On May 13, 2004, Warner–Lambert agreed to plead guilty and to pay more than \$430 million to resolve criminal charges and civil liabilities. A class-action suit was filed the next day in federal court on behalf of private parties who had paid for illegally marketed Neurontin; this case (now known as *In Re: Neurontin Marketing, Sales Practices, and Products Liability Litigation*) remains active.

The Franklin case placed more than 8000 pages of corporate documents in the public domain; these documents are now available in a searchable digital library at the University of California, San Francisco (www.dida.library.ucsf.edu). The class-action suit also generated detailed testimony and reports that are available through the Federal Judiciary’s Public Access to Court Electronic Records Service Center (e.g., <https://ecf.mad.uscourts.gov/doc1/09502786849>).

The Neurontin cases have revealed the mechanisms of action of a comprehensive marketing campaign — its goals and strategies, tactics and programs, and the participation of particular physicians and institutions.² The campaign involved the systematic use

of deception and misinformation to create a biased evidence base and manipulate physicians’ beliefs and prescribing behaviors. These marketing methods were not found to be illegal in themselves; they were illegal insofar as they promoted off-label prescription. Thus, the importance of the cases lies largely in the light they shed on marketing methods that may be widespread but remain unseen because companies are rarely prosecuted for illegal marketing.

The Neurontin marketing plan consisted of both general strategies — such as the promotion of Neurontin use among high-prescribing physicians and cultivation of thought leaders — and tactical programs.² Local physicians were recruited, trained, and paid to serve as speakers in “peer-to-peer selling” programs, which the company saw as “one of the most effective ways to communicate our message.” Academic leaders were solicited with educational grants, research grants, and speaking opportunities; some received up to \$158,250 over a 4-year period. Advisory boards and “consultants” were convened so that the firm could cultivate relationships with them and deliver “a hard-hitting message about Neurontin.”

Marketing “tactics” included education, publications, and research whose promotional intent was disguised, in addition to more transparent activities, such as advertising and sales visits.² “Educational programs” reflected the belief that “medical education drives this market!” Teleconferences involving practicing physicians were moderated by physicians who were paid as much as \$176,100 over 4 years. Parke–Davis formed speakers bureaus and

sought “strong Neurontin advocates and users to speak locally for Neurontin.” “Unrestricted educational grants” were made to for-profit medical-education companies that produced programs to discuss unapproved uses of Neurontin and to grant credit approved by the Accreditation Council for Continuing Medical Education.

A “publication strategy” was designed to increase the use of Neurontin for neuropathic pain and bipolar disorder, off-label indications with great revenue potential. Parke–Davis contracted with medical-education companies to produce articles on prespecified topics, target journals, titles, potential authors to be “chosen at the discretion of Parke–Davis,” and “a consistent message” in keeping with promotional goals; some articles were ghost-written.

“Research” was designed and commissioned specifically to promote Neurontin use. A large seeding trial was conducted to “teach physicians to titrate Neurontin to clinical effect” and “to give neurologists the opportunity to titrate to higher doses [up to twice the FDA-approved limit] when needed.” In a recently unsealed 318-page analysis of research sponsored by Parke–Davis, epidemiologist Kay Dickersin concluded that available documents demonstrate “a remarkable assemblage of evidence of reporting biases that amount to outright deception of the biomedical community, and suppression of scientific truth concerning the effectiveness of Neurontin for migraine, bipolar disorders, and pain.”³ For example, publication was delayed for a report on a multicenter, placebo-controlled study that found no effect of Neurontin on the primary outcome

measure for neuropathic pain because “we [Parke–Davis employees] should take care not to publish anything that damages neurontin’s marketing success.” Ultimately, ghost-written manuscripts downplayed the lack of effect on the primary outcome and emphasized other outcomes and subgroup analyses that favored Neurontin. Although guest authorship and commercial bias in research are a well-recognized threat to scientific integrity, the documentation of comprehensive manipulation of research and publication related to Neurontin is remarkable.

What is Neurontin’s legacy? First, we have learned that pharmaceutical marketing can be comprehensive, strategic, well financed, disguised as “education” and “research,” influential, and very effective. Promotion of Neurontin was neither discrete, compartmentalized, nor readily apparent; instead, it was intercalated in nearly every aspect of physicians’ professional lives, from the accoutrements of practice to lectures, professional meetings, and publications. Although some pharmaceutical marketing may be less opaque, deceptive, and manipulative, evidence indicates that drug promotion can corrupt the science, teaching, and practice of medicine.⁴

Second, such comprehensive marketing involved many people and institutions that apparently failed to recognize the serious ethical and legal problems with their actions. Employees of Parke–Davis, the medical-education companies it hired, and many physicians (consultants, advisors, educators, and researchers) all participated knowingly. Universities, hospitals, professional organizations, and foundations also

participated, and oversight agencies such as the FDA and the Department of Justice did not intervene quickly. Apparently, there was a shared acceptance that Parke–Davis’s marketing was simply business as usual.

Finally, these cases substantiate the emerging conviction that “drastic action is essential” to preserve the integrity of medical science and practice and to justify public trust.⁴ We believe that such action should include the routine placement of legally discovered documents in the public domain, the study of such documents to inform strategies for minimizing abuses, the establishment of penalties that eliminate the profit to be gained through illegal marketing, and the independent public funding of peer-reviewed pharmaceutical research through a National Institute for Pharmaceutical Research that might be funded by a tax on all drug sales.⁵

Will our profession soon feel compelled to advocate for such actions to preserve our integrity, our social contract, and ultimately our privileges? Neurontin’s most important legacy may be promoting our discussion of these issues and perhaps pushing us beyond the tipping point to action.

Drs. Landefeld and Steinman report serving as unpaid consultants to the plaintiff’s attorney in *United States of America ex rel. David Franklin vs. Pfizer, Inc., and Parke-Davis Division of Warner-Lambert Company* and participating in the creation of the Drug Industry Document Archive by the University of California, San Francisco, Kalmanovitz Library, an effort that was funded in part by Thomas Greene, whose law firm represented David Franklin in the case. Dr. Steinman also reports receiving support from an educational grant funded by the Attorney General Settlement Fund that arose from the Franklin case. No other potential conflict of interest relevant to this article was reported.

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GLOBAL HEALTH

Toward the Elimination of Schistosomiasis

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Related article, p. 121

 An interactive graphic on schistosomiasis is available at NEJM.org

Schistosomiasis remains one of the world's most prevalent diseases. Despite more than a century of control efforts and the introduction of highly effective antischistosomal drug therapy in the 1980s, the disease just will not go away. More than 207 million of the world's poorest people are currently infected with schistosomiasis, which is often a decades-long, chronic inflammatory disorder that is associated with disabling anemia and undernutrition as well as poor performance in school and at work.¹

Schistosomiasis, also known as bilharziasis, results from long-lived infection by multicellular intravascular parasites of one of five trematode species — *Schistosoma japonicum*, *S. mansoni*, *S. haematobium*, *S. intercalatum*, or *S. mekongi*. Parasite transmission and the consequent risk of human infection are strongly linked to specific geographic locations, because the parasite goes through several developmental stages that must occur in fresh water, including a period of growth within partic-

ular species of intermediate host snails (see diagram and interactive graphic).

Even after infection ends, disease persists. In some patients, especially those with intestinal schistosomiasis (see photo), the late fibrotic complications of schistosomiasis-associated inflammation lead to portal hypertension, which conveys a substantial risk of death due to variceal gastrointestinal bleeding. In patients with urinary schistosomiasis, late complications include irreversible urinary tract obstruction with an associated risk of renal failure and inflammation-induced bladder cancer. Arguably, the Asian form of intestinal schistosomiasis caused by the species *S. japonicum*, reported on by Wang et al. in this issue of the *Journal* (pages 121–128), carries the highest risks of infection-related inflammation and other complications.

In the 1980s, after the introduction of the highly effective antischistosomal drug praziquantel, it was believed that large-scale drug delivery through school-based or community-based

programs could solve the problem of schistosomiasis transmission and, in so doing, eliminate the risk of parasite-associated disease. Although such mass-treatment campaigns substantially reduced the infectious burden and the parasite-associated morbidity, they often failed to curb parasite transmission in high-risk communities. Since these efforts failed to prevent immediate reinfection itself, they also did not do a very good job of reducing the substantial rates of illness associated with reinfection.

Why didn't mass treatment stop transmission? As it turns out, the very complexity of the parasite's life cycle helps to ensure that its transmission continues within local ecosystems. Whereas public health planners had assumed that a treatment-related reduction in the excretion of parasite eggs by humans would stem the transmission of the parasite, the process of infection is, in fact, more complicated, being abetted by "superspreaders" (especially untreated children who do not attend school) and by social and hydrologic linkages