EXPERT REPORT OF JOHN ABRAMSON, MD.

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I, John Abramson, MD, hereby state, under penalty of perjury, that the following is true and correct:

INTRODUCTION

I have been asked by Plaintiffs' attorneys to discuss the sources of information typically relied upon by physicians in making prescribing decisions that are in the best interest of their patients and to explain how those traditionally independent and trusted sources of information have increasingly come under the influence, and in some cases direct control, of drug manufacturers. I have been asked to describe the effect that such influence or control can have on physicians' prescribing behaviors. I have been asked to review documents and other information concerning the drug Neurontin, and to opine as to whether Defendants influenced the information that physicians traditionally rely upon and trust in making informed prescribing decisions. Specifically, I have been asked if Defendants' actions, if established for the finder of fact substantially as set forth in the Third Amended Complaint and other court filings, impeded physician access to accurate, balanced and complete information concerning Neurontin's effectiveness in treating certain off-label conditions.

In addressing these issues, I will review the sources from which doctors and third-party payers typically receive information about new and optimal therapies. I will describe how these established patterns of information transfer were exploited by Defendants in order to create a false perception that Neurontin's use for various off-label indications was scientifically supported.

I. OPINIONS

The opinions listed below are based on my knowledge, training and experience as a medical doctor, my qualifications as set forth below, my review of documents produced by Parke-Davis, Pfizer (collectively referred to as "Defendants") and others, as well as depositions and court papers filed in this case and my knowledge and experience as a researcher and published writer in the area of pharmaceutical drug marketing. I reserve the right to continue to review documents, depositions and hearing transcripts as well as court papers, clinical studies, research articles, studies, the testimony of both Defense and Plaintiff experts and any other relevant material to supplement my opinions as this case continues to develop. Support for the

opinions listed below can be found in my full report and in the documents referenced herein. However, this report is not intended to be an exhaustive list or reference guide to all examples of evidence and testimony available to support my opinions.

Assuming the finder of fact concludes, as alleged in the Third Amended Class Action Complaint and other filings, that Parke-Davis and later Pfizer developed and executed a comprehensive campaign to increase off-label prescriptions of Neurontin for neuropathic pain, nociceptive pain, bipolar disorder, migraine headache and in doses above the maximum recommended by the FDA, I am of the opinion that, based on the evidence reviewed and detailed in my report, this campaign was effectuated by dissemination of inaccurate, incomplete or misleading scientific evidence to physicians and payers through a number of means, including:

- Control and manipulation of research design, analysis, and publication of clinical trials concerning the off-label conditions at issue;
- Withholding of material scientific evidence from physicians and payers;
- Sponsorship of continuing medical education ("CME") programs presenting inaccurate and/or incomplete scientific evidence on Neurontin's effectiveness in treating off-label conditions;
- Use of favorably disposed and paid "Thought Leaders" and Advisory Boards to promote scientifically unsubstantiated use of Neurontin;
- Use of drug representatives to promote scientifically unsubstantiated use of Neurontin;
- Manipulation of physician, payer and public opinion by the use of misleading public relations campaigns; and
- Misrepresentation of the scientific evidence and regulatory status of Neurontin in the Formulary Dossier distributed to managed care organizations and other third party payers.

The result of the above tactics was the delivery of inaccurate, incomplete and overly positive information about the efficacy of Neurontin, for the indications that are the subject of this case, to potential prescribers (as well as payers, policy makers and the public). These activities, if proven, affected the traditionally independent and trusted sources of information upon which physicians rely in making informed prescribing decisions.

II. QUALIFICATIONS

1. I am a medical doctor licensed to practice medicine in the state of Massachusetts since 1982. I have been Board Certified in Family Medicine and a Diplomate of the American Board of Family Practice since 1982. I graduated *cum laude* from Harvard College in 1970 with a degree in Social Relations. I attended Dartmouth Medical School and graduated with a degree in Medicine from Brown Medical School in 1976. I performed my internship at the University of North Carolina from 1976 to 1977. I then served as a primary care physician in the National Health Service Corps of the U.S. Public Service in Monroe County, West Virginia from 1977 to 1979. I completed my residency at Case Western Reserve University from 1979 to 1981. I also completed a Robert Wood Johnson Fellowship in Family Medicine at Case Western University from 1980 to 1982, earning a Master of Science in Family Practice degree. During this two year fellowship, which included study of epidemiology, statistics, research design and health policy, I received training in the interpretation of scientific data. Additionally, I was a Senior Research Associate on the Faculty of the Institute for Health Policy, Heller School, Brandeis University from 1992 to 1993, during which I participated in a project that explored local control of health care resources to optimize allocation and health outcomes. I served as Chair of the Department of Family Practice at Lahey Clinic in Burlington Massachusetts from 1994 to 2001. I have been a clinical instructor at Harvard Medical School since 1997.

2. In recent years, I have published on health policy and the growing commercial bias in the scientific evidence that doctors rely on to guide their clinical practice (see bibliography listed on attached CV). Based on my education, training and experience in medicine, epidemiology, statistics, research design and health policy, I am qualified to testify regarding Pfizer's manipulation of the scientific evidence about Neurontin, as well as Pfizer's deceptive and off-label marketing of Neurontin to physicians, pharmaceutical benefits managers, managed care organizations, other private and public payers and public policy officials. I am further qualified to testify regarding the sources of information physicians rely upon in formulating their opinions regarding the efficacy and safety profiles of drugs (including Neurontin) in the fulfillment (or attempted fulfillment) of their responsibility as learned intermediaries.

3. Throughout my twenty-eight years as a physician, I have had firsthand experience in multiple practice arenas that further qualifies me to render opinions in this litigation. My first experience as a primary care doctor was in a rural health clinic in Appalachia with the National Health Service Corps, then a part of the U. S. Public Health Service. From 1982 to 2002, I practiced family medicine in Hamilton, Massachusetts. As a treating physician, I was responsible for the evaluation, care and treatment of numerous patients for wellness care as well as disease diagnosis, treatment and management. I have prescribed many different drugs in the scope of my clinical practice for over two decades and have firsthand experience regarding the type and content of information a physician needs to make informed decisions about prescribing drugs to a patient, including performing risk/benefit analyses and evaluating safety and efficacy of drugs for a given patient. I carefully read medical journals both as a practicing physician, to keep up to date on the latest developments that would impact the care and treatment of my patients, and as a researcher to evaluate the quality of the scientific evidence presented therein.

4. I also have experience with the health care industry. Between 1986 and 1993, I served as Associate Medical Director of Pru-Care of Massachusetts. I am currently the Executive Director of Health Management for Wells Fargo Health Solutions. In that role, I participate in designing health benefits for self-insured companies that reflect the best scientific evidence about effective health care: integrating evidence-based medicine, epidemiologically-based health care and predictive health modeling.

5. Teaching has also been an important lens through which I have observed and experienced the changes in medicine that have taken place throughout my career. I have taught both medical students and postgraduate students and also lectured as an invited speaker regarding the growing challenge to clinicians trying to make informed decisions about optimal pharmacotherapy for their patients. My academic appointments include serving as a clinical instructor in ambulatory care and prevention at Harvard Medical School since 1997. From 1993 to 1995, I was the Chair of the Graduate Medical Education Committee (Family Practice Residency) at Beverly Hospital in Beverly, Massachusetts. I have also served as a Mentor for first year medical students in the Primary Care Mentorship Program at Harvard Medical School and also as a Preceptor in the Primary Care Clerkship Program at Harvard Medical School. I continue to serve as a tutor in the Primary Care Clerkship Program there. In these roles, I have

taught students how to critically interpret and integrate medical literature and data into a risk/benefit analysis for prescribing drugs to patients.

6. The issues of public health and health policy and how doctors process information from various sources has been of importance and interest to me throughout my career as a physician. Because of the changes I was observing in American medicine and experiencing in my own practice, I left clinical practice to devote myself full time to researching this topic, specifically in regard to the pharmaceutical industry and its impact on public health, public safety and the quality of American health care. Since the beginning of 2002, I have been researching, writing, lecturing and teaching about how the information and misinformation about drugs and other medical products available to practicing physicians impacts their medical decisions and the overall quality, effectiveness and cost of American health care.

7. As noted in my curriculum vitae, I have been invited to lecture at medical schools, hospital Grand Rounds and health insurers about the growing commercial influence on the production and dissemination of medical information available to physicians, the public and health policy makers.

8. Thus, based on my education, training, two decades of clinical practice and my independent research, I have unique knowledge and understanding and am qualified to testify regarding how pharmaceutical company sponsored research and marketing affects doctors' decisions, patients' expectations and the overall quality and effectiveness of medical care. Prior to being consulted in this litigation, I published articles and a book on this subject as listed on my curriculum vitae. A true and correct copy of that document, further outlining my education, training, publications, and experience, as well as my hourly rate, is attached as Exhibit 1.

9. The opinions expressed in this affidavit are my own and are based on my education, training, research, and experience, my review of the peer-reviewed medical literature and on corporate documents and depositions produced in this litigation by Pfizer. A list of the articles, depositions, and documents, upon which I relied in forming my opinions, are attached as Exhibit 2 and are incorporated into my opinions stated below. My opinions, as stated in this affidavit, are stated to a reasonable degree of medical probability.

10. Any testimony I have given within the past 4 years as an expert either at deposition or at trial will be listed on Exhibit 3, attached.

III. OVERVIEW

11. Neurontin was approved by the FDA in December 1993 for a single indication: "adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults with epilepsy." In October 2000, the FDA approved an expansion of the original indication for Neurontin to include "patients over 12 years of age with epilepsy" and added an indication for "adjunctive therapy in the treatment of partial seizures in pediatric patients age 3-12 years." In May 2002, the FDA approved an additional indication for Neurontin, "for the management of postherpetic neuralgia in adults." The dose recommended for this indication is 300 mg on the first day of therapy, increasing by 300 mg per day up to 900 mg/day. "The dose can subsequently be titrated up as needed for pain relief to a daily dose of 1800 mg (divided TID)…Additional benefit of using doses greater than 1800 mg/day was not demonstrated."[1]

12. During its first year on the market, Neurontin use was limited primarily to Epilepsy/Convulsions.[2] Sales for Neurontin's single FDA-approved indication peaked in 1995, after one year on the market. As of February 1996, 83% of Neurontin use was for epilepsy. The other 17% was used for off-label indications: 14% for neuropathic pain, and less than 1% for migraines, bipolar disorders or all other indications.

13. In the following two years, off-label use increased from 17% to 60% of total Neurontin usage, during which time use of Neurontin for neuropathic pain increased almost 5 fold; use for migraine increased almost 30-fold; use for bipolar disorders increased more than 6–fold; and use for all other off-label indications increased by 9-fold.[3]

14. Between 1996 and 2001, the number of patients in the U.S. taking Neurontin increased from 430,000 to 5,977,000,[4] or about 13-fold, with this growth occurring solely in Neurontin use for non-FDA approved indications. Data presented in Pfizer's 2002 Operating Plan show that, as of September 2001, only 6.5% of Neurontin being used in the U.S. was for its

[1] 2002 FDA-approved label for Neurontin
[2] NEURONTIN: Leading at the Edge—Global Operating Plan 2001. Pfizer_CGrogan_0005052
[6] Pfizer_JMarino_0002504

0	MAT/Feb 96	MAT/Feb 97	MAT/Feb 98
Epilepsy/Convulsions	462	437	464
Neuropathic Pain	76	279	444
Migraine	4	67	122
Bipolar Disorders	8	9	61
All Others	6	34	60

[4] Pfizer_Rglanzman_0164633

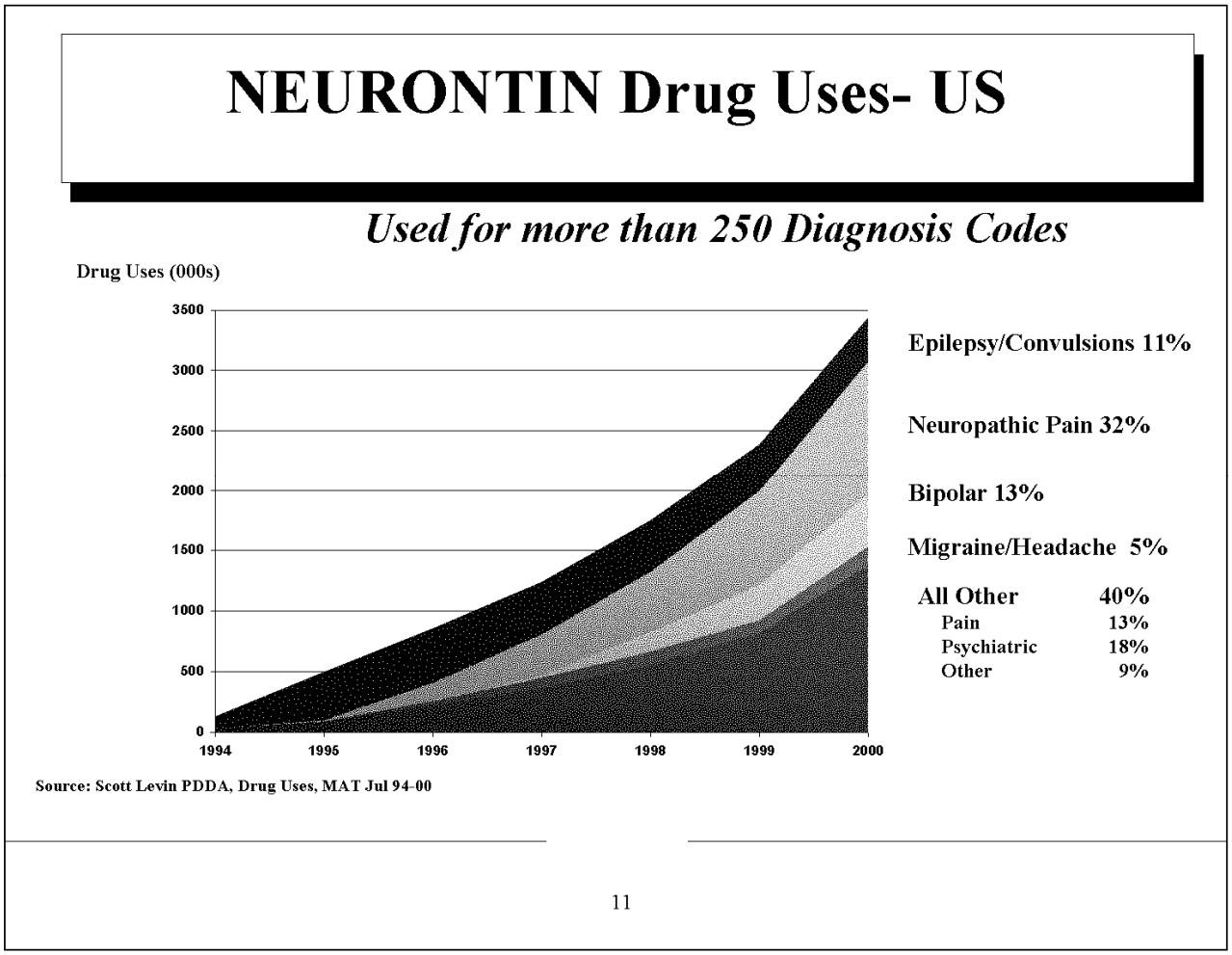
single FDA-approved indication, epilepsy.[5] The other 93.5% was being used for non-FDA approved indications.[6] Use for bipolar disorder, as just one example, increased from minimal, 8,000 prescriptions annually as of February 1996, up to approximately 402,000 annual prescriptions in November 1999.[7]

15. In 1998, 1999 and 2000, despite decreasing use for epilepsy, Neurontin sales continued to grow annually at rates of 62%, 70% and 44% respectively.[8] In 2000, despite approved use for broader indications in many other countries,[9] 88% of worldwide sales of Neurontin occurred in the United States.[10] In 2000, only 11% of Neurontin was being used for its single on-label indication.

16. According to the Pfizer's 2001 Operating Plan for Neurontin, initial sales were "somewhat sluggish and limited in the AED [antiepileptic drug] market.[11] In other words, "sluggish" sales were the result of Neurontin being used primarily for its FDA-approved indication.

17. The following graph, taken from the 2001 Global Operating Plan for Neurontin,[12] provides a visual image of the growth of Neurontin use for on and off-label indications, with the single FDA-approved indication the darkest band on top of the others. This graph shows that after its first year on the market, all growth in U.S. sales of Neurontin was for off-label indications, and that use for off-label indications went from minimal to blockbuster status in a matter of just a few years.

[5] Pfizer_BParsons_0092318
[6] Pfizer_Rglanzman_0164640
[7] WLC_CBU_040450
[8] Pfizer_SDoft_0024550
[9] Pfizer_CGrogan_0005058
[10] Pfizer_CGrogan_0005068
[11] NEURONTIN 2001 Operating Plan Executive Summary. PFIZER_JMARINO_0000688
[12] Pfizer_CGrogan_0005052



18. Pfizer's 2002 Operating Plan stated that the growth opportunities for Neurontin were "outside epilepsy," i.e. off-label, in the areas of neuropathic pain and psychiatry. Targeting of primary care physicians was specifically mentioned in order to "Grow/Protect Business."[13] Reflecting the pattern of CME, only 20% of samples and 25% of details were provided to neurologists (the one specialty most likely to be prescribing Neurontin as adjunctive therapy for seizure disorder). Psychiatrists received the most samples and detailing (55 and 43% of total, respectively), followed by PCPs and "others."[14]

19. Pfizer's 2002 Operating Plan calculated that in the unlikely event that the FDA did not approve Neurontin for any type of neuropathic pain (meaning that the only indication for Neurontin would remain adjunctive therapy for partial seizure disorder), it would lose only $45

[13] Pfizer_BParsons_00923 31
[14] Pfizer_Rglanzman_0000741

million in sales[15] out of the $1.9 billion in projected U.S. sales for 2002.[16] In other words, Pfizer calculated that the failure of the FDA to approve any indications beyond adjunctive therapy for partial seizures would decrease total Neurontin sales just 2.4% and cause a minimal decrease in off-label sales of Neurontin: from $1.77 billion to $1.72 billion per year.

20. The rapid and extensive growth of off-label use of Neurontin begs the following questions: Starting in 1996, what led doctors to believe that prescribing Neurontin for the off-label indications at issue was scientifically supported and in the best interest of their patients? What led doctors to prescribe Neurontin in doses greater than 1800 mg/day (despite a lack of FDA approval for such dosage)? Did the scientific evidence available at the time support such off-label (including high dose) use? Was the information presented to physicians accurate and balanced?

IV. SOURCES OF INFORMATION ABOUT PRESCRIPTION DRUGS RELIED UPON BY MEDICAL DECISION MAKERS

A. The Ideal

1. *Evidence-Based Medicine and the double-blind placebo-controlled randomized trial*

21. The standard upon which doctors are expected to rely when making treatment decisions for their patients is "evidence-based medicine." The Center for Evidence-Based Medicine (CEBM) provides the following definition:

> Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. [17]

22. Further, physicians are counseled that the gold standard methodology for producing such evidence is randomized trials rather than from "non-experimental approaches." When deciding whether or not a given treatment is in their patients' best interest, physicians are advised:

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[15] Pfizer_SDoft_0024606
[16] Pfizer_SDoft_0050281
[17] Sackett DL, Rosenberg WMC, Gray JAM, et al., Evidence based medicine: what it is and what it isn't: It's about integrating individual clinical expertise and the best external evidence. *British Medical Journal,* 1996;312:71-72, accessed from the Center for Evidence-Based Medicine, http://www.cebm.net/?o=1014 , July 13, 2008.

> to avoid the non-experimental approaches, since these routinely lead to false positive conclusions about efficacy. Because the randomised trial, and especially the systematic review of several randomised trials, is so much more likely to inform us and so much less likely to mislead us, it has become the "gold standard" for judging whether a treatment does more good than harm. [18]

23. Physicians' primary sources of the evidence upon which their evidence-based decisions are based are the results of gold standard double-blind randomized controlled clinical trials ("RCTs") and systematic reviews of RCTs published in peer-reviewed journals. The medical "literature" thus defines the scientific evidence that provides the foundation for "evidence-based medicine." Yet, as discussed below, much of this research and the reports summarizing it are increasingly controlled or funded by pharmaceutical manufacturers.

2. *Continuing Medical Education*

24. Doctors also keep abreast of developments in their field by participating in continuing medical education ("CME") activities. The majority of states require ongoing participation in CME activities, typically 50 hours per year, in order to maintain medical licensure. CME activities provide information about new drugs, tests and procedures, as well as optimal care for medical conditions.

25. Continuing medical education, according to the American Medical Association, consists of "educational activities that serve to maintain, develop, or increase the knowledge, skills, and professional performance and relationships a physician uses to provide service for patients, the public, or the profession."[19] As such, ongoing participation in continuing medical education plays a major role in doctors' fulfillment of the responsibility to their patients to stay current with new medical knowledge.

26. CME activities are typically provided by recognized clinical experts, referred to as "thought leaders" or "key opinion leaders," often recognized and virtually always respected by practicing physicians. Therapeutic recommendations made by such authoritative clinical experts have a major impact on attendees' beliefs about optimal therapy for their patients.

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[18] *Ibid.*

[19] Harrison RV, The Uncertain Future of Continuing Medical Education: Commercialism and Shifts in Funding, *Journal of Continuing Education in the Health Professions,* 2003;23:198-209.

27. According to the past president of the Pharmaceutical Research and Manufacturers of America ("PhRMA"):

> Industry-supported conferences, seminars, and symposia are helping physicians to provide the best, most appropriate, and most up-to-date health care to their patients. They help to ensure the widespread adoption of new medicines and technologies that save lives, cure disease, relieve pain, and allow individuals to lead longer, healthier, and more productive lives.[20]

3. *Drug Representatives*

28. Pharmaceutical companies have both in-house and third-party marketing firms to assist them in the branding and product placement of prescription drugs. Marketing, of which sales or drug representatives are only one aspect, generally includes the oversight of all printed material concerning a prescription drug, the look and feel of all advertisements, the pictures and colors used, the product message and the way that the risks and benefits of the product are described.

29. Sales or drug representatives act as a source of information for physicians. The number of drug reps making sales calls in doctors' offices tripled between the early 1990s and 2001, and now there are about 90,000 drug reps making calls on practicing physicians or one full time rep for every four and half office-based doctors.[21] Between 80-90% of office-based doctors talk to drug reps,[22] and, somewhat paradoxically, the busier a doctor is the more likely he or she is to talk to drug reps.[23] According to a 2002 survey conducted by the Kaiser Family Foundation, 74% of doctors consider the information provided by drug reps very or somewhat useful, and 81% of doctors consider the information provided by drug reps very or somewhat accurate.[24]

30. Public relations campaigns and non-profit public service organizations like the American Heart Association, the National Osteoporosis Foundation, the Arthritis Foundation,

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[20] Holmer AF. Industry strongly supports continuing medical education. *Journal of the American Medical Association.* 2001;285:2012-2014.
[21] Scott Hensley, "As Drug-Sales Teams Multiply, Doctors Start to Tune Them Out, *Wall Street Journal,* June 13, 2003.
[22] Moynihan R. Who Pays for the Pizza? Redefining the Relationships Between Doctors and Drug Companies. 1: Entanglement. *British Medical Journal*. 2003;326:1189-92.
[23] Ferguson RP, Rhim E, Belizaire W, et al., Encounters with Pharmaceutical Representatives among Practicing Internists, *Am J Med,* 1999;107:149-152.
[24] National Survey of Physicians *Part II: Doctors and Prescription Drugs,* The Kaiser Family Foundation, March 2002. http://www.kff.org/rxdrugs/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=13965 accessed 1/8/07

and the National Alliance of the Mentally Ill, also act as a source of medical information for consumers and medical providers.

B. How This System of Knowledge Production and Dissemination Actually Works

1. *Commercial Control of Design, Analysis, and Publication of Clinical Trials in Peer-Reviewed Medical Journals*

31. In today's health care market, doctors face significant time constraints in determining which drugs and treatments are in the best interest of their patients. They, along with formulary committees, purchasers, PBMs and policy makers, rely upon a variety of trusted sources for the scientific evidence upon which to base their decisions. Many of these sources are directly controlled or heavily influenced by pharmaceutical manufacturers. All of these sources contain susceptibilities that have been exploited by pharmaceutical manufacturers.

32. Physicians rely on the findings of RCTs published in respected peer-reviewed medical journals in order to make the best decisions for their patients. However, corporate influence now permeates every aspect of the research process including: the design of clinical studies (including the population included in the trial, the choice of drugs, doses, duration of the trial, and the outcome and safety measures to be tracked); control of the data and data analysis; writing the manuscripts for articles, and publication decisions (including where, or even whether the study will be published); and publicity following publication. Through these methodologies even "gold standard" double-blind randomized controlled trials can be "spun" to favor the interests of corporate sponsors, exaggerating benefits and minimizing adverse events.

a. The Changed Locus of Control of Clinical Research

33. As the National Institute of Health ("NIH") funding of clinical trials started decreasing in the late 1970s, pharmaceutical companies moved in to fill the void. Between 1977 and 1990, pharmaceutical companies increased their funding for clinical trials six-fold.[25] By 1991, approximately 70% of clinical trials were being funded by the pharmaceutical companies, but 80% of those trials were still being carried out in academic medical centers where there was a tradition of academic researchers participating in study design, data analysis and publication

[25] Dramatic Growth of Research and Development, Pharmaceutical Research and Manufacturers of America (PhRMA), *Pharmaceutical Industry Profile 2003* (Washington , DC: PhRMA, 2003). http://www.phrma.org/publications/publications/profile02/2003%20CHAPTER%202.pdf accessed 2/14/03.

decisions.[26] As the 1990s progressed, this changed dramatically, so that by 2000 only 41% of commercially funded studies were being done in universities; the rest were being done by for-profit contract research organizations. By 2004, only 26% of commercially funded studies were being performed in an academic setting.[27]

34. There is nothing inherently unethical about this change in the locale. It allows the drug companies to get their research done more quickly, with less red tape and lower overhead. But one important consequence of this transition is that it changed the locus of control of clinical research from academic researchers working in academic medical centers to the pharmaceutical companies themselves. Since pharmaceutical companies were hiring the research companies directly, they could play the primary role in designing the study and controlling the data, while at the same time denying researchers, who would author the articles to be published in medical journals (the "scientific evidence"), free access to the data. This allows the pharmaceutical companies to retain a great deal of control over publication decisions.

35. Currently, eighty to ninety percent of clinical research is commercially funded. In the ten years between 1994 and 2003, sixty-five of the seventy-seven most frequently cited clinical trials, or 84%, had commercial sponsorship. Furthermore, the percentage increased significantly during that time: since 1999, thirty-one out of thirty-two of the most frequently cited clinical trials, or 97%, had industry sponsorship.[28]

36. A study published in the *New England Journal of Medicine* ("*NEJM*") examined the standards for the arrangements between pharmaceutical companies and academic medical centers – the clinical trial contracting agreements that would be expected to maintain the highest standards of academic independence. The researchers found that more than two-thirds of the academic institutions accepted research contracts that prohibit researchers from changing the sponsor's research design. Half of the university medical centers allowed commercial sponsors to "draft manuscripts reporting the research results, with the investigators' role limited to review

[26] Bodenheimer T. Uneasy alliance – clinical investigators and the pharmaceutical industry. *New England Journal of Medicine.* 2000;342:1539-1544.
[27] Steinbrook R, Gag Clauses in Clinical-Trial Agreements, *NEJM,* 2005; 352: 2160-62
[28] Patsopoulos NA, Ionnidis JPA, Analatos AA, Origin and funding of the most frequently cited papers in medicine: database analysis, *BMJ,* 2006;332:1061-1064.

and suggestions for revision." And "24 percent of the responding institutions would grant the sponsor the right to insert its own statistical analyses into manuscripts."[29]

37. Discussing the failure of universities to defend their scientists' research independence when conducting commercially-sponsored medical studies, Drummond Rennie, MD, Deputy Editor of the *Journal of the American Medical Association* ("*JAMA*"), said that universities and scientists "are seduced by industry funding, and frightened that if they don't go along with these gag orders, the money will go to less rigorous institutions… It's a race to the ethical bottom."[30] Given the primary fiduciary responsibility of the drug companies to their shareholders rather than the public's health, this transition from public to private financing of clinical research means that – at best – studies will be designed and our medical knowledge will grow towards maximizing corporate profits rather than optimizing health most effectively and efficiently.

38. Thirteen editors of the world's most prestigious medical journals issued an alarming joint statement highlighting the extent and consequences of the commercial takeover of clinical research. In the report they stated:

> Until recently, academic, independent clinical investigators were key players in design, patient recruitment, and data interpretation in clinical trials. The intellectual and working home of these investigators, the academic medical center, has been at the hub of this enterprise, and many institutions have developed complex infrastructures devoted to the design and conduct of clinical trials. But, as economic pressures mount, this may be a thing of the past.
>
> Investigators may have little or no input into trial design, no access to the raw data, and limited participation in data interpretation. These terms are draconian for self-respecting scientists, but many have accepted them because they know that if they do not, the sponsor will find someone else who will.[31]

Unfortunately, awareness of this important statement released simultaneously in the editors' publications in the second week of September 2001 was drowned out by the tragic events of September 11th.

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[29] Mello MM, Clarridge BR, Studdert DM, Academic medical centers' standards for clinical-trial agreements with industry, *N Engl J Med*, 2005;352:2202-10.
[30] Knox RA, Boston Globe, March 30, 1999
[31] Davidoff F, DeAngelis DC, Drazen JM, et al. Sponsorship, Authorship, and Accountability, *N Engl J Med,* 2001; 345: 825-7.

39. Between two-thirds and three-quarters of the clinical studies published in even the most prestigious journals are now commercially funded.[32] Among the highest quality published studies (those deemed good enough to be included in Cochrane Reviews), the odds are 5.3 times greater that commercially funded studies will conclude that the sponsor's drug is the treatment of choice compared to non-commercially funded studies of exactly the same drugs.[33] This means that the "scientific evidence" produced by commercially sponsored studies is effectively and systematically biased in favor of the sponsor's drug. An editorial in the American Journal of Medicine noted that the "link between commercial sponsorship and the conduct and presentation of research" is difficult to minimize "because there is usually a substantial power gradient between the sponsor and the investigator."[34]

40. A rare window into the problem of authors of commercially sponsored research not having access to the data from their own study was provided by the eleven non-Merck employee authors' (including the lead author) response to the "Expression of Concern" issued by the editors of the NEJM[35] about three heart attacks that occurred in the Vioxx Gastrointestinal Outcomes Research ("VIGOR") trial that were not included in the November 23, 2000 *NEJM* article reporting the results. The non-Merck employed authors wrote: "These events were neither in the locked database used in the analysis for the VIGOR paper nor known to us during the review process."[36]

41. In other words, the non-Merck employee authors of the VIGOR article published in the *NEJM*—including the lead author—were not aware of the occurrence of the additional three heart attacks and therefore did not have the opportunity to participate in the decision about whether or not to include them in the paper they authored. That the *NEJM* editors rejected the Merck-employed authors' justification for not including the three heart attacks in the paper[37] is not the important point here. Rather, the issue is that, of the thirteen authors of the paper, only

[32] Smith R, Medical Journals Are an Extension of the Marketing Arm of Pharmaceutical Companies, *PLOS Medicine,* 2005; 2(5):e138 DOI: 10.1371/journal.pmed.0020138
[33] Als-Neilsen B, Chen W, Gluud C, Kiaergard LL, Association of Funding and Conclusions in Randomized Drug Trails, *JAMA,* 2003; 290:921-928.
[34] Landefeld CS, Commercial Support and Bias in Pharmaceutical Research, *Am J Med,* 2004;117:876-8.
[35] Curfman GD, Morrissey S, Drazen JM, Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Refecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 2000;343:1520-8. *NEJM,* 2005;353:2813-4.
[36] Bombardier C, Laine L, Burgos-Vargas R, et al., Response to Expression of Concern Regarding VIGOR Study, *NEJM,* 2006;354:1196-8.
[37] Curfman GD, Morrisey S, Drazen JM, Expression of Concern Reaffirmed, N Eng J Med, 2006;354:1193.

the two employed by Merck were given the opportunity to participate in the decision about how to handle the crucial statistical ramifications that the additional three heart attacks posed. The other authors were deprived of the opportunity to participate in this crucial decision about the data in the paper they authored.

b. Commercial Control of Publication of Clinical Trials in Peer-Reviewed Journals

42. Drug manufacturers can also bias even the most trusted "scientific evidence" by having financial relationships with researchers, funding research and coordinating research publications. A study of the effect of researchers' financial conflicts of interest and industry funding on clinical trials, published in the *American Journal of Psychiatry* in 2005, concluded: "Industry sponsorship and author conflict of interest are prevalent and do appear to affect study outcomes."[38] The study looked at clinical trials that were published between 2001 and 2003 in the four most widely cited general psychiatry journals. Forty-seven percent of the articles included at least one author with a financial conflict of interest, defined as "any report of consulting or speaking fees or honoraria, stock ownership, or employment by the study sponsor." The odds were 4.9 times higher that articles including at least one author with a conflict of interest would report positive results for the drug company's product. For those studies that had both industry sponsorship and at least one author with a conflict of interest the odds were 8.4 times higher that the study would favor the sponsor's drug.[39]

An example of the way that bias can be introduced into even the "gold standard" of clinical trials can be seen by looking at the criteria used by Merck for selection of patients to be included in the VIGOR trial, comparing the safety of Vioxx to that of naproxen. Merck scientists were concerned that allowing patients in the study to take prophylactic low-dose aspirin (to reduce risk of cardiovascular events) would neutralize the potential GI safety advantage. Yet they were also concerned that not allowing patients to use low dose aspirin would increase the risk of cardiovascular events in patients taking Vioxx (a possible consequence of either the anti-thrombotic property of aspirin or the potential prothrombotic consequence of selective COX-2 inhibition that had been raised by its own expert panel), and

[38] Perlis RH, Perlis CS, Wu Y, et al., Industry Sponsorship and Financial Conflict of Interest in the Reporting of Clinical Trials in Psychiatry, *Am J Psychiatry,* 2005;162:1957-1060

[39] $P<0.001$ for both odds ratios.

thus "kill the drug."[40] Merck's solution to this dilemma was to exclude patients for whom low dose aspirin was recommended—a perfect solution in terms of highlighting the potential GI safety of Vioxx and minimizing the cardiovascular risk (as a result of excluding people with a previous history of cardiovascular disease). There were two problems with this solution: First it weakened the quality of the Level 1 evidence by introducing selection bias,[41] rendering the safety findings applicable only to groups of people who—like those included in the study—did not have pre-existing cardiovascular disease, even though the results were clearly not intended to be applied to such a constricted population. And second, although quite a clever strategy, it didn't work. The number of excess cardiovascular complications among the patients taking Vioxx was actually greater than the number of excess serious GI complications among those taking naproxen. And overall there were twenty-one percent (21%) more serious adverse events[42] among patients taking Vioxx than among those taking naproxen (p=0.016). Merck's approach to these disadvantageous findings provides yet another window into the way that sponsor's can influence the "knowledge" produced by clinical trials. Despite the specific recommendation of the VIGOR Data Safety Monitoring Board to do a separate analysis of the rates of cardiovascular complications (because of the differences that they were seeing in the interim data), no such analysis was included in the article reporting the VIGOR results in the *NEJM.*[43] Neither was the significantly greater number of serious adverse events in those taking Vioxx included in this article. Rather, the article concluded simply that:

> rofecoxib, a selective inhibitor of cyclooxygenase-2, is associated with significantly fewer clinically important upper gastrointestinal events than treatment with naproxen, a nonselective inhibitor.[44]

(The differential rates of heart attacks were presented. However, three events that occurred in those taking Vioxx were not reported and thus allowed the article to falsely claim that Vioxx only increased the risk of MI among people with a previous history of heart disease.)[45]

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[40] Mathews AW, Martinez B, E-Mails Suggest Merck Knew Vioxx's Dangers at Early Stage, *Wall Street Journal,* November 1, 2004. Page 1.
[41] Ebell MH, Siwek J, Weiss BD, et al., Strength of Recommendation Taxonomy (SORT): A Patient-Centered Approach to Grading Evidence in the Medical Literature, *American Family Physician,* 2004;69:548-56
[42] "Serious adverse events" are defined by the FDA as those causing hospitalization, prolongation of hospitalization, permanent disability, cancer, or death.
[43] Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
[44] *Ibid.*

43. A 2003 article in the *British Journal of Psychiatry* uses the antidepressant Zoloft and studies published between 1998 and 2001 as an example to show the effect of commercial coordination of research publications.[46] Fifty-five out of a total of ninety-six articles published during this interval were coordinated by Current Medical Directions ("CMD"), a medical information company hired by Pfizer, the manufacturer of Zoloft. The raw data from the research presented in these articles was, "in almost all instances," proprietary—meaning that the authors often did not have free access to the untabulated data and, if they did, they were not free to share the data with colleagues.

44. These fifty-five articles included "a number of publications that the document suggests originated within communication agencies, with the first draft of articles already written and the authors' names listed as 'to be determined.'"[47] In other words, these articles were ghostwritten for the authors whose names later appeared on the published articles. Readers are not always informed about these relationships: only two of the fifty-five articles followed current medical journal guidelines by acknowledging "writing support from individuals not listed as authors."

45. In addition, readers of the articles often are not aware of authors' financial ties to the drug maker:

> Of the published articles, 13 of the 55 do not appear to have a company author or to have been through an agency. Four of these 13 articles involved economic models based on data provided by Pfizer, and it is assumed that these authors do not have access to raw data. Five of the 13 are review articles appearing in a company-sponsored symposium supplement [to journals]. The remaining four articles acknowledge support funding…[48]

46. Among the fifty-five CMD coordinated publications, all of the published clinical and economic analyses were favorable to Zoloft. In contrast, only eighteen of the forty-one non-CMD coordinated publications reported favorable results. In addition, there is evidence that

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[45] For a full discussion of the three omitted MIs and the statistical consequences see: Curfman GD, Morrissey S, Drazen JM, Expression of Concern: Bombardier et al., "Comparison of Upper Gastrointestinal Toxicity of Rofecoxib and Naproxen in Patients with Rheumatoid Arthritis," N Engl J Med 200, 343:1520-8, 2005; 353:2813-4
[46] Healy D, Cattell D, Interface between authorship, industry and science in the domain of therapeutics, *Br J Psych,* 2003; 183:22-27.
[47] *Ibid.*
[48] *Ibid.*

among the CMD coordinated articles, adverse events were not adequately reported: two of these studies under-report suicide and suicidal behaviors.[49] Finally, CMD coordinated articles were 5.5 times more likely to be cited in future articles (and therefore have more impact on what is perceived as the scientific evidence) than the independently published articles.[50] This is important because the CMD coordinated articles are far more likely to be favorable to Zoloft and to have greater impact on the perceived scientific evidence.

47. Commercial bias also plays a role in determining which studies get published and which ones do not. Based upon the six published studies addressing the safety and efficacy of the newer antidepressants in treating depressed children and adolescents, doctors reasonably believed that the scientific evidence clearly showed the benefits of these drugs in treating depression in this population. But the totality of scientific evidence that existed at that point showed just the opposite. In truth, through 2003 there were not six, but fifteen studies completed—nine of which remained unpublished. When all the studies were considered together, the evidence shows that these drugs are not just ineffective for depressed children and adolescents, but are also unsafe, doubling the risk of suicidal behavior. (Even among the six published studies that claimed to have documented effectiveness, three were not confirmed upon independent analysis by British and American regulatory agencies.)[51]

48. An article published in *NEJM* in January 2008 showed that of 74 studies of antidepressants that had been completed, 38 showed positive findings and 36 negative or equivocal findings. All but one of the positive studies were published in medical journals, whereas only 3 of the non-positive 36 trials were published accurately, if at all. The article concluded that the odds are 12 times greater that studies of antidepressants reaching a positive conclusion would be published accurately than studies reaching a negative or equivocal conclusion.[52] In other words, without knowing it, doctors, formulary committees and policy makers had based their decisions on a highly unrepresentative fraction of the available scientific evidence.

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[49] *Ibid.* (Healy 2003)
[50] $P \leq 0.001$
[51] Antidepressant Medications in Children and Adolescents, *Therapeutics Letter,* 2004; Issue 52. http://www.ti.ubc.ca/pages/letter52.htm accessed 1/08/07
[52] Turner EH, Matthews AM, Linardatos E, et al., Selective Publication of Antidepressant Trials and Its Influence on Apparent Efficacy, *New England Journal of Medicine,* 2008;358:252-60.

49. Dr. Richard Horton, the current editor of *The Lancet*, and Dr Richard Smith, the former editor of the *British Medical Journal,* told the new York times in 2006 that the "[medical] journals have devolved into information laundering operations for the drug companies."[53] Publication of an article in a peer reviewed journal is generally taken to mean that unbiased reviewers have deemed the article to reasonably represent the scientific evidence and doctors have been taught to trust the scientific evidence presented in peer reviewed journals. However, their faith in the ability of peer review to assure balanced interpretation of scientific evidence remains unverified as documented by a systematic review of the effect of peer review published in JAMA in 2002. The article concluded that "[e]ditorial peer review, although widely used, is largely untested and its effects are uncertain."[54]

50. Supplements published in journals are another path by which pro-drug industry material is created and disseminated to physicians, as if it had the authority of a regular peer-reviewed article (with all the reservations about those mentioned above). Supplements often include papers that are presented at industry-sponsored conferences or symposia. Sponsoring drug companies may even choose the guest editor of the supplement.[55]

2. *Review Articles*

51. The systematic bias in the results of commercially-sponsored clinical trials also appears in commercially-sponsored review articles. An article published in the *British Medical Journal (BMJ)* compared the quality and results of commercially-sponsored reviews (meta-analyses) comparing two drugs to Cochrane reviews (non-commercial, highest quality) of the same design, as well as to those with undeclared and/or non-commercial support. The study found that the estimated treatment effects of the drugs being reviewed were reported to be the same in the commercially sponsored reviews and Cochrane reviews (as would be expected because of the unambiguous nature of the results that are reported). However, the effect of commercial sponsorship was revealed in the recommendations that then followed:

> The estimated treatment effects in industry supported reviews were similar to those of Cochrane reviews, but the former had uniformly positive recommendations for the experimental drug, without

[53] Altman LK, For Science's Gatekeepers, A Credibility Gap, *New York Times,* May 2, 2006
[54] Jefferson T, Alderson P, Wagner E, Davidoff F, Effects of Editorial Peer Review, *JAMA,* 2002;287:2784-86.
[55] Brody H, Hooked: Ethics, the Medical Profession, and the Pharmaceutical Industry, New York: Rowman & Littlefield Publishers, Inc. 2007.

> reservations about methodological limitations of the trials or costs, in contrast to none of the Cochrane reviews. This suggests that the main problem with industry supported reviews lies in how conclusions are formulated.[56]

3. *Continuing Medical Education*

52. In 1998, forty-eight percent (48%) of CME activities overall were commercially sponsored.[57] Direct commercial support for continuing medical education activities increased twenty-eight percent (28%) between 1998 and 1999, to $388 million.[58] According to a survey published in *Medical Marketing & Media* in 1999, for profit medical education service suppliers ("MESSs") were playing a major role in providing commercially sponsored CME (as well as other) services, primarily for pharmaceutical companies. MESS revenues grew by nineteen percent (19%) between 1998 and 1999. The highest revenue-generating services provided by MESSs in 1999 were, in order, commercially sponsored grand rounds, symposia, coordination of advisory boards and activities related to publications.[59]

53. The largest MESS in the survey was Phase V, which included Pfizer and Lilly among its clients, whose philosophy is explained as follows:

> Through thought leaders, clinical and patient advocates, trial recruitment publicity, publication strategies, and other highly credible peer-to-peer channels, we disseminate your evidence to [predispose] target audiences toward a favorable view of your product…Collegial pressure is also a powerful influence: By understanding the often uncharted but very real professional networks that exist in every area of medicine, Phase V converts support in one quarter to influence in another.[60]

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[56] Jorgensen AW, Hilden J, Gotzsche PC, Cochrane reviews compared with industry supported meta-analyses and other meta-analyses of the same drugs: systematic review, *Br Med J,* 2006 Oct 14;333(7572):782. Epub 2006 Oct 6. Review.

[57] Harrison RV, The Uncertain Future of Continuing Medical Education: Commercialism and Shifts in Funding, *Journal of Continuing Education in the Health Professions,* 2003;23:198-209.

[58] Hensley S, When Doctors Go to Class, Industry Often Foots the Bill, *Wall Street Journal,* December 4, 2002.

[59] Ross JS, Lurie P, Wolfe SM, Medical Education Services: A Threat to Physician Education, July 19, 2000. http://www.citizen.org/publications/release.cfm?ID=7142 Accessed July 13, 2008

[60] Grey Healthcare Group. Pathways to success: medical education: Phase V Communications. Available at: http://www.ghgroup.com/pathway/content.asp?A=2&B=3&pg=11 . Downloaded on July 19, 2000. (Cited in Ross et al. above)

> Phase V never loses sight of the strategic value of Speakers Bureau programs to enhance its client's corporate image and to strengthen brands.[61]

54. According to guidelines for CME activities established by the Accreditation Council for Continuing Medical Education (ACCME), AMA, FDA and others, the content of CME programs should be directed by the CME sponsors (i.e. the medical education service suppliers, medical schools, hospitals, etc) rather than the funders (i.e. the pharmaceutical companies), the funds should be provided as unrestricted educational grants (not under the control of the funder), and the financial arrangements between sponsor and funder should be disclosed.[62]

55. Commercial sponsorship of doctors' continuing medical education increased from approximately $400 million in 1998 to approximately $700 million in 2001.[63] Commercial funding of CME activity grew from forty-eight percent (48%) of the total cost of CME in 1998 to fifty-eight percent (58%) in 2002.[64] Commercial sponsorship of CME at medical schools increased from seventeen percent (17%) in 1994 to forty percent (40%) by 2002.[65] And in 2002, the commercial investment in doctors' CME increased by another thirty percent.[66] Due to the Accreditation Council for Continuing Medical Education's changed definition of "commercial support," the percentage of CME funded by commercial interests became more difficult to track: In 2005, sixty percent (60%) of doctors' continuing education was funded directly by the drug and medical device industries. Additionally, funding was provided by non-profit organizations, which may—in turn—have been funded by commercial interests, but are not included in the sixty percent.[67] Total industry contribution of doctors' continuing medical education has been estimated to be seventy percent (70%) or higher.

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[61] Grey Healthcare Group. Pathways to success: medical education: Phase V Communications: speaker's bureau. Available at: http://www.ghgroup.com/pathway/content.asp?A=2&B=3&C=1 &pg=12 . Downloaded on July 19, 2000. (Cited in Ross et al., above)
[62] Ross et al., Op. Cit.
[63] Hensley S, When Doctors Go to Class, Industry Often Foots the Bill, *Wall Street Journal,* December 4, 2002.
[64] Op. Cit., Harrison
[65] Op. Cit., Hensley
[66] Relman A, Industry Sponsorship of Continuing Medical Education Reply to Letters, *JAMA,* 2003;290:1150
[67] Croasdale M, More dollars flow into continuing medical education, American Medical News (American Medical Association), August 21, 2006. http://www.ama-assn.org/amednews/site/free/prsb0821.htm#s1 accessed 12/24/06.

56. Drug companies exert widespread influence over the medical education activities they sponsor.[68] A review article published in *JAMA* shows that drug company-sponsored lectures are two-and-a-half to three times more likely to mention the sponsor's drug in a positive light and the competitors' drugs in a neutral or negative light than are non-commercially sponsored lectures.[69] In addition, the odds are 3.9 times greater that doctors who accepted money from drug companies for speaking at CME activities would make specific requests for addition of the sponsor's drug to the hospital formulary.[70]

57. At least as important as favoring the sponsor's drug, the growing commercial funding of continuing medical education influences the curriculum topics that are addressed.[71] Commercially funded education is more likely to be about the kinds of new information that has the greatest potential to increase the sponsor's profits rather than maximizing patients' health.

58. Among abstracts presented at the annual meeting of a professional society, the odds that the results of industry supported studies would be favorable to the sponsor's drug were far greater than for non-industry sponsored studies.[72] A result favorable to the drug studied was reported by all industry-supported studies, compared with two-thirds of studies not industry supported.[73] This is important not just because the conclusions presented in these abstracts influence attendees at the conference, but even more so because:

> evidence favorable to the sponsor of a product—perhaps its use for an indication not approved by the Food and Drug Administration (FDA), or its advantages relative to those of a rival—can be introduced easily into the professional domain as a presented abstract. Once published and presented, the abstract can be cited in talks and the literature, or offered in response to physicians' questions to pharmaceutical sales representatives. Thus, the medical professional meeting may serve as an unwitting vector of

[68] Brennan TA, Rothman DJ, Blank L, et al., Health Industry Practices that Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers, *JAMA,* 2006;295:429-433.
[69] Wazana A. Physicians and the pharmaceutical industry. *JAMA*, 2000;283:373-380
[70] Chren M-M, Landefeld CS, Physicians' Behavior and Their Interactions With Drug Companies: A Controlled Study of Physicians Who Requested Additions To a Hospital Drug Formulary, *JAMA,* 1994;271:684-689.
[71] Op. Cit. Harrison
[72] Odds ratio, 30; 95% confidence limits, 1.6 to 580.
[73] Finucane TE, Boult CE, Pharmaceutical Research at a Meeting of a Medical Professional Society, *Am J Med,* 2004;117:842–845. P_0.0007

> promotional information that otherwise could not be introduced by a pharmaceutical manufacturer.[74]

Among thirty industry-supported studies identified, commercial support of the research was explicit in only ten percent (10%) of the research abstracts presented.

59. Evidence shows that doctors are not aware of and deny that their prescribing habits are influenced by attendance at commercially sponsored CME, but in fact such attendance does increase their prescribing of sponsors' drugs in comparison to other doctors working at the same institutions who did not attend.[75]

4. *Pharmaceutical Marketing*

60. The Food and Drug Administration Modernization Act of 1997 ("FDAMA") states that if a manufacturer wishes to market or promote an approved drug for additional uses – *i.e.*, uses not listed on the approved label or so-called "off-label use" – the manufacturer must resubmit the drug for another series of clinical trials similar to those for the initial approval. Until a "supplemental new drug application" has been approved, the unapproved use is considered to be "off-label."[76] Off-label use includes treating a condition or using a dosage that is not indicated on the label, or treating a different patient population (for example, treating a child when the drug is only approved to treat adults).

61. Although physicians are allowed to prescribe drugs for off-label usage, the law prohibits drug manufacturers from marketing or promoting a drug for a use that the FDA has not approved. An off-label use of a drug can become on-label only if the manufacturer submits a supplemental new drug application and demonstrates to the satisfaction of the FDA that the product is safe and effective for the proposed new use.[77]

62. Drug manufacturers (and their drug reps) are only allowed to distribute information regarding off-label usage (for drugs without pending supplemental new drug applications) in response to an "unsolicited request from a health care

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[74] *Ibid.*
[75] Dana J, Loewenstein G, "A Social Science Perspective on Gifts to Physicians from Industry," *Journal of the American Medical Association* 290:252, 2003.
[76] 21 U.S.C. §360aaa(b), (c).
[77] 21 U.S.C. §360aaa(b), (c).

practitioner."[78] Manufacturers are, however, permitted to disseminate information concerning the off-label uses of a drug after a supplemental new drug application has been submitted to the FDA seeking approval of the drug for the off-label use; has provided the materials to the FDA prior to dissemination; and the materials themselves must be in an unabridged form and must not be false or misleading.[79]

63. Despite these rules, among the twenty-one percent (21%) of prescriptions that were written in 2001 for off-label indications, seventy-three (73%) had "little or no scientific support."[80] (This determination was based on whether the Drugdex listing for each off-label use showed that effectiveness had been demonstrated in controlled clinical trials (scientifically supported) or relied on less than the "gold standard" of clinical evidence, observational data or case reports.)

64. The confidence of marketers to overcome disadvantageous results from clinical trials was shown in the following reaction to the ALLHAT trial, which showed that the least expensive of medications to treat high blood pressure was at least as effective as the more expensive drugs in preventing hypertension-related complications. If medical practice were truly "evidence-based," these results would have been a major problem for the manufacturers of the far more expensive, but no more effective, brand name drugs. But the realities of pharmaceutical marketing were revealed by a strategic marketing consultant for the pharmaceutical industry who was quoted in the *BMJ*:

> "So you've got one study that says yes, you should [use a diuretic], then starting the day after, you've got a $10 billion industry...and 55 promotional events…for an ACE inhibitor coming back in and saying 'Here's why my ACE inhibitor is safe and here's why you should be using this.' I mean, it's promotion. Can ALLHAT stand up to that?"[81]

[78] 21 U.S.C. §360aaa-6.
[79] 21 U.S.C. §§ 360aaa(b) & (c)
[80] Radley DC, Finklestein SN, Stafford RS, Off-label Prescribing Among Office-Based Physicians, *Archives of Internal Medicine,* 2006;166:1021-26.
[81] Lenzer J. Spin Doctors Soft Pedal Data on Antihypertensives. *British Medical Journal*. 2000;326:170.

5. *Drug Representatives*

65. A common sight in doctors' offices is the pharmaceutical sales representative, commonly known as the "drug rep" bearing free samples, gifts, lunch and the latest information regarding their drug. Though most doctors find the information presented by drug reps both useful and accurate (see above), an article published in the *Journal of General Internal Medicine* shows that nearly half (forty-two percent) of the material given to doctors by drug reps made claims in violations of FDA regulations. And only thirty-nine (39%) percent of the material provided by drug reps provided scientific evidence to back up claims.[82]

66. A review published in *JAMA* shows a mostly negative effect on the quality of care of doctors' interactions with drug companies and drug reps:[83]

> Interactions with pharmaceutical representatives were also found to impact the prescribing practice of residents and physicians in terms of prescribing cost, nonrational prescribing, awareness, preference and rapid prescribing of new drugs, and decreased prescribing of generic drugs.

The more a doctor sees drug reps, the less likely the doctor is to identify false claims about the drug and the greater the doctor's tendency to prescribe more drugs overall. The odds are fifteen times greater that doctors who interact with drug companies will request that drugs manufactured by a specific company be included in hospital formularies.[84]

6. *Formulary and Health Policy Decision Makers*

67. Health policy decisions can be no better than the scientific evidence available to decision-makers. As shown above, it can no longer be assumed that the "scientific evidence" is complete, unbiased, or represents the best possible information. Accordingly,

> To the extent that this evidence is biased or misleading, health services research and policy analysis are thrown off course and become unintentionally complicit in promoting inappropriate and expensive care. Regardless, health services research and policy

[82] Stryer D, Bero LA, Characteristics of Materials Distributed by Drug Companies: An Evaluation of Appropriateness, *Journal of General Internal Medicine*, 1996;11:575-583.
[83] Wazana A, Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift? *Journal of the American Medical Association,* 2000;283:373-80.
[84] *Ibid.*

> analysis can no longer be thought of as separate from applied medical research. The game has changed. Our desire to expand access based on scientific evidence has become epistemologically naïve. The question is no longer how to provide better access, but how to determine, Access to what?[85]

V. DEFENDANTS' BUSINESS STRATEGIES RATHER THAN THE ACTUAL SCIENTIFIC EVIDENCE DETERMINED THE "KNOWLEDGE" THAT WAS PRESENTED TO PRESCRIBERS AND PURCHASERS ABOUT NEURONTIN

A. Parke-Davis's Early Off-Label Marketing Strategy

68. Almost immediately after Neurontin was approved, Parke-Davis recognized that Neurontin had a limited earnings potential, perhaps only "$500 Million" based on the "relatively short U.S. protected [patent] life."[86] The company began to consider "a strategy swerve."[87]

69. The May 19, 1995 Marketing Assessment for Neurontin in psychiatric indications outlines the Defendants strategy for selective publication bias: "The [study] results, if positive, will be publicized in medical congresses and published in peer-reviewed journals."[88] The July 31, 1995 Marketing Assessment for Neurontin in neuropathic pain and spasticity contains similar language: "The results of the recommended exploratory trials in neuropathic pain, if positive, will be publicized in medical congresses and published."[89] The July 31, 1996 Marketing Assessment for Neurontin in migraine prophylaxis proposes the same strategy: "The [study] results, if positive, will therefore be publicized in medical congresses and peer-reviewed journals."[90] The plan to skew the science in favor of Neurontin is evident from these early documents.

70. According to John Knoop, a former product manager and Director of the Epilepsy Disease Team at Parke-Davis, marketing tactics for Neurontin extended broadly into activities that are usually thought of as educational. In sworn deposition testimony, he said that CME activities, advisory boards, publications, grants, dinner meetings, mailing of journal supplements,

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[85] Op. Cit. Spitz 2005
[86] WLC_FRANKLIN_0000088763
[87] *Ibid.*
[88] WLC_FRANKLIN_0000095662
[89] WLC_FRANKLIN_0000166608
[90] WLC_FRANKLIN_0000081254

journal abstracts, teleconferences, satellite symposia, and posters at medical congresses could all be examples of marketing tactics for Neurontin.[91]

71. With all growth in Neurontin sales after 1996 coming from off-label use, the following graph, from the Neurontin 2001 U.S. Operating Plan provides a visual image of the success of Parke-Davis's off-label marketing campaign for Neurontin:[92]

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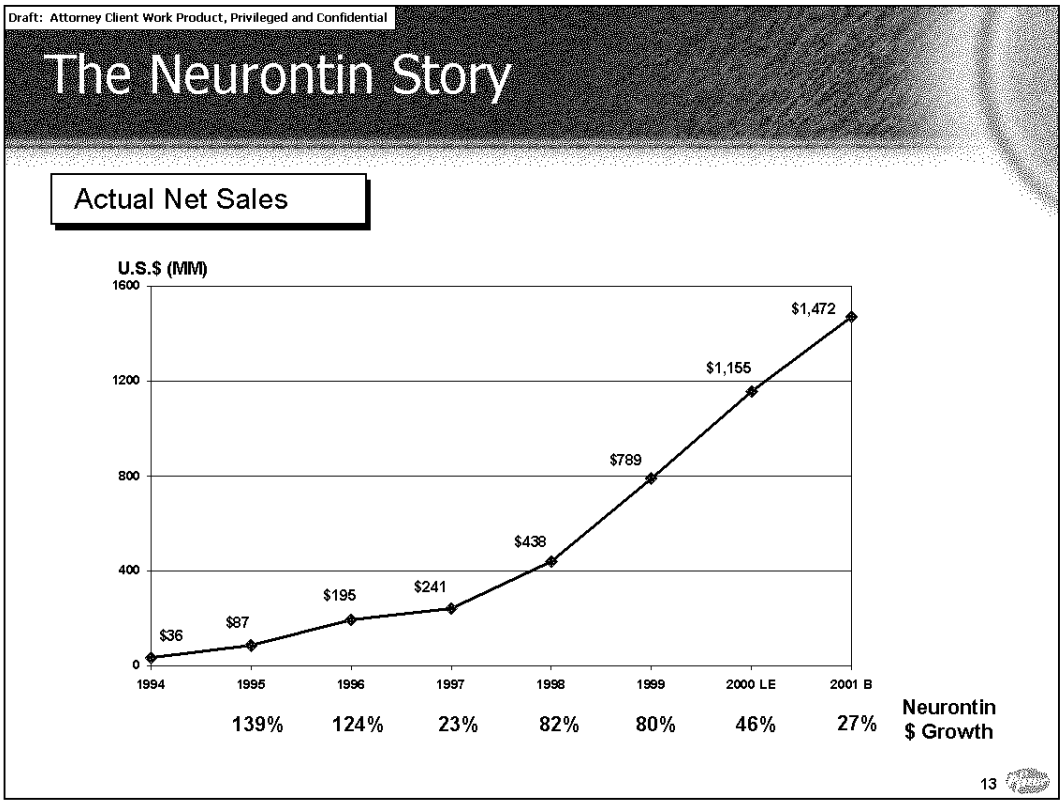
[91] Transcript of Deposition of John Knoop, Jan. 23, 2008 ("Knoop Dep.") at 18, 106-08, 122-26, 213:

Q. And does promotion mean something different than marketing?
A. Yes.
Q. Can you explain what the difference is?
A. Promotion in a sense, again, going back to our definition is typically the on-label dissemination of information through various sources for a product. Marketing has a whole broad range of tasks, I guess, that are within marketing. One of which would be promotional.
Q. So is there -- can you give me an example of non-promotional marketing?
A. Sure, sponsoring of a CME event.
Q. That, based on your experience, is marketing?
A. That falls under marketing.
Q. Any other examples that you can think of non-promotional marketing activities?
A. Providing grants, publications.
Q. These are -- I'm sorry, I didn't mean to cut you off.
A. Those are a few more examples.
Q. So grants and publications are also examples of marketing activities?
A. Advisory boards.
Q. And are these items that you just mentioned CME events, grants, publications and advisory boards, are they examples of marketing tactics?
A. They could be considered as a tactic.
Q. Well, based on your experience at Parke-Davis, were CME events used as marketing tactics?
A. Yes.
Q. Were grants, based on your experience at Parke-Davis, used as marketing tactics?
A. Yes.
Q. And based on your experience at Parke-Davis, were publications used as marketing tactics?
A. Yes.
Q. And based on your experience at Parke-Davis were advisory boards used as marketing tactics?
A. Yes, but again, these are not promotional programs.

(Knoop Dep. at 106-108 (Objections omitted)).

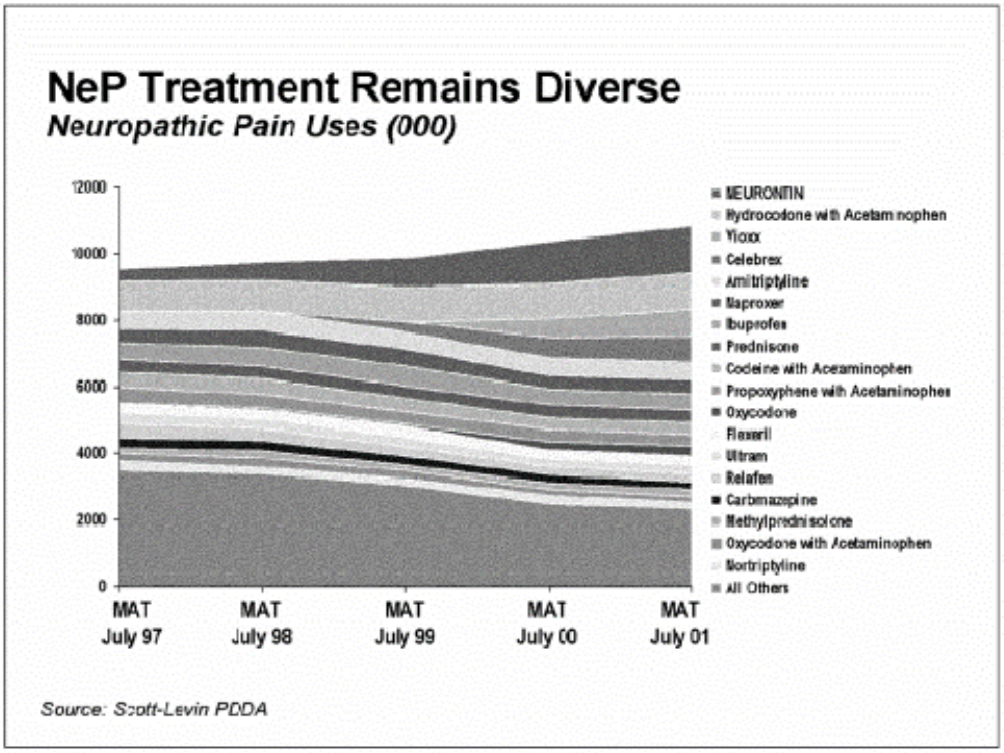
[92] Pfizer_RGlanzman_0000662



72. In 2000, among the anti-epileptic drugs (AEDs) Neurontin had the lowest percentage of use for Epilepsy/Convulsions, 11% (its single FDA-approved indication). The next lowest was Depakote at 17%, but Depakote had been approved by the FDA in 1995 for the treatment of mania in bipolar disease,[93] and approved in 1996 for the prevention of migraine headaches.[94]

73. As shown in the following graph from Pfizer's "Neuropathic Pain Advisory Board: Focus on the Specialist,"[95] between 1997 and 2001, Neurontin became the most frequently used drug for neuropathic pain (notwithstanding its lack of FDA-approval and lack of substantial scientific evidence supporting its use for this indication):

[93] http://www.nimh.nih.gov/health/publications/bipolar-disorder/complete-publication.shtml accessed 11/30/07
[94] http://www.centerwatch.com/patient/drugs/dru78.html accessed 11/30/07
[95] Pfizer_Rglanzman_0059515



74. Notwithstanding the lack of adequate supporting scientific evidence (other than for pain of postherpetic origin) and the lack of FDA approval for the use of Neurontin for neuropathic pain, such use of Neurontin in the U.S. increased from virtually zero in 1995[96] to the most frequently prescribed drug for neuropathic pain by 2000, with annual increases in use of 22 to 43% between 1997 and 2001.[97]

B. Pfizer Continued The Marketing Strategies Begun By Parke-Davis

75. At the time Pfizer took over the Neurontin franchise in 2000, Neurontin was the largest selling antiepileptic drug and had been growing faster than any other drug in this category since 1997[98]—with all sales growth coming from off-label use. In 2000, only 11% of Neurontin was being used for Epilepsy/Convulsions—its only FDA approved use.[99] Neurologists accounted for only 14% of new prescriptions, eclipsed by psychiatrists (22%) and PCPs (29%)—

[96] Pfizer_CGrogan_0005051
[97] Pfizer_AMishra_0002339
[98] Pfizer_RGlanzman_0000703
[99] Pfizer_RGlanzman_0000665

virtually all of whose prescriptions would have been for indications other than adjunctive treatment of seizures.[100]

76. A draft of "Neurontin: 2001 Situation Analysis" dated June 28, 2000 provides a window into Defendants' assessment of the current and potential market for Neurontin.[101] Despite lack of FDA approval for neuropathic pain, 33% of all Neurontin use was for this indication in 2000 and "has continued to grow."[102] "In summary," the report states:

> The neuropathic pain marketplace remains largely unsatisfied…Neurontin's use and leadership of the neuropathic pain is expected to continue to strengthen in 2001.

77. The 2001 Situation Analysis recognized bipolar disorder as the "top psychiatric use" of Neurontin, with use having "increased by 1700% from Sept 97 to Sept 99."[103] The success of Defendants' off-label marketing of Neurontin to psychiatrists for bipolar disorder is evident in the following statement from the Situation Analysis:

> The increased use [of Neurontin for bipolar disorder] comes despite the results of the "Gabapentin in Bipolar Disorder" trial (945-209) which showed no significant improvement when compared to placebo. Among psychiatric thought leaders, trial design shortcomings were responsible for the outcome.[104]

78. The 2001 Situation Analysis reported that 3.8% of Neurontin use in 2000 was for migraine prophylaxis (despite the lack of FDA approval for this indication). The report erroneously states that the results of Study 945-220 "were statistically significant in favor of Neurontin" (see below). The Situation Analysis reported that the manuscript had been rejected from *Neurology* in February 2000 and resubmitted to *Archives of Neurology,* which also did not publish the manuscript. (See below for discussion about the positive conclusions presented in the article that was eventually published in *Headache,* misrepresenting the negative results of the trial). A similar trial, 945-217, was reported in the Situation Analysis as negative acknowledging that: "The team has delayed posting or dissemination of results and they have not been presented at any scientific meetings to date,"[105] (i.e. the negative results were being quarantined, isolated

[100] Pfizer_RGlanzman_0000666
[101] Pfizer_JMarino_0002350
[102] Pfizer_JMarino_0002366
[103] Pfizer_JMarino_0002368
[104] Pfizer_JMarino_0002368-9
[105] Pfizer_JMarino_0002371

from inclusion in the scientific evidence.) The Situation Analysis reported that, because of the "mixed clinical results" (mixed only because one of Defendants' negative trials was being misrepresented as positive), the 2001 investment in education and publication in the area of migraine prophylaxis would be small, and that "growth of Neurontin's use in this area is expected to be slow but steady in 2001."[106] This growth was expected despite the lack of FDA approval for this indication and that three of the Defendants' studies showed negative results.

79. Pfizer's 2001 US Operating Plan for Neurontin, dated October 11, 2000, documented the manufacturer's plans to continue promotion of Neurontin for off-label use. It would do so by:

- offering a variety of Continuing Medical Education activities (accounting for more than half the Neurontin marketing budget for 2000 and 2001[107] aimed primarily at primary care physicians and psychiatrists for off-label indications;[108]
- developing advisory boards, diagnostic pain tools, and a relationship with the American Pain Society around the use of Neurontin for neuropathic pain;[109]
- developing "comprehensive strategic publications" that "ensure key message inclusion in all publications;"[110]
- ensuring "key data will be available of major meetings";[111]
- supporting pricing and formulary status that will encourage use of Neurontin for pain.[112]

The focus on neuropathic pain proceeded despite Pfizer being aware that its largest study of neuropathic pain, 945-224—which included three times as many patients taking Neurontin as Study 945-210 ("Backonja"), had been completed on September 7, 1999, and the report issued on February 7,200—showed no benefit of Neurontin over placebo.[113] (These studies are discussed in more detail below.) The primary marketing focus was clearly to increase the use of

[106] Ibid
[107] Pfizer_RGlanzman_0000699
[108] Pfizer_RGlanzman_0000684-5
[109] Pfizer_RGlanzman_0000690
[110] Pfizer_RGlanzman_0000694
[111] Pfizer_RGlanzman_0000694
[112] Pfizer_RGlanzman_0000695
[113] 945-224 was completed 09/07/99 and reported 02/07/2000, Kendle/CI-945 RR 720-04130 (Page 1)

Neurontin for the treatment of pain, yet the available data was not adequate to support the FDA's approval of this indication.[114] In the following year, Neurontin sales increased by 26%,[115] with on-label use declining from 11% to 6.5%.[116]

80. Prior to the 2002 Operating Plan being issued October 5, 2001, Pfizer had learned from both the FDA and a panel of its own advisors that the scientific evidence did not justify FDA-approval of Neurontin for the broad indication of neuropathic pain.

81. A meeting between Pfizer and FDA representatives to discuss the approvability of Neurontin for the treatment of neuropathic pain was held on May 14, 2001. Notes from this meeting, from both Pfizer[117] and the FDA (dated 6/13/01)[118], show that FDA stated

> The general neuropathic pain indication cannot be granted for Neurontin

The FDA went on to say that, in order to grant a general approval for neuropathic pain, Neurontin would have to be shown effective for post-herpetic neuropathy, diabetic peripheral neuropathy

> and the pain of other neuropathic disorders and/or that the drug is effective for neuropathic pain of all (or at least most) etiologies.[119]

Pfizer's notes of the meeting reflect its understanding that an application for the use of Neurontin in the "management of neuropathic pain…would be refused to file ["non-fileable"]" by the FDA. Without having fulfilled the FDA's explicit requirements for granting approval for the broad claim of Neurontin efficacy for neuropathic pain, Pfizer (as shown below) engaged in a marketing campaign that falsely presumed such efficacy had been established.

82. The purpose of the September 6, 2001 Pfizer Consultants Meeting was to prepare for an Advisory Committee Meeting at which Pfizer's sNDA for "the broad neuropathic pain indication" (meaning for all symptomatic presentations of neuropathic pain, rather than for

[114] Pfizer_RGlanzman_0000735
[115] Pfizer_BParsons_0092306
[116] Pfizer_BParsons_0092318
[117] Pfizer_LCastro_0005155
[118] Pfizer_LCastro_0005618
[119] Pfizer_LCastro_0005621

specific diagnoses such as postherpetic or diabetic neuropathy). Attendees included Paul Leber, former head of the Division of Neuropharmacologic Drug Products at FDA for many years.[120]

83. Consistent with the FDA's conclusion expressed at the May 14th, 2001 meeting, Pfizer's own consultants concluded that the scientific evidence was not sufficient to support FDA approval of Neurontin for this use:

> Expert opinion on the preclinical and clinical data to date is that the evidence is not convincing to support a broad neuropathic pain claim. Opinion on the Neurontin neuropathic pain package is that neither the FDA nor the Advisory Committee is likely to agree that adequate evidence is provided for a broad indication. New analyses/data not only do not support the broad claim, they provide evidence contrary to a broad indication.
>
> The Experts agree that the package supports PHN. Evidence for DPN is confounded by the negative DPN [unpublished 945-224] study. Advise [sic] from this panel of Experts is to file PHN and to conduct additional studies in support of the DPN claim.[121]

84. Three studies were presented at the September 6, 2001 Consultants meeting that failed to support Pfizer's goal of achieving FDA approval for the "broad indication" of neuropathic pain for Neurontin. Pfizer study 945-224 investigating the efficacy of Neurontin in diabetic neuropathy, which included three times as many people taking Neurontin as did the purportedly positive study that was published in JAMA in 1998 ("Backonja") (see below and the report of Dr. Jewell for critique of the conclusions of this study), showed no benefit of Neurontin over placebo at fixed doses (rather than forced titration[122]) of 600, 1200 and 2400 mg per day.[123] (The results of this study were reported internally on February 7, 2000, and although included in the publication strategy outlined in the 2001 U.S. operating plan for Neurontin,[124] were never published as an independent study.) Pfizer's study 945-271 ("POPP") showed no benefit of Neurontin in posttraumatic and postsurgical neuropathic pain. (The study was reportedly completed on November 30, 2001,[125] but the results were presented at Pfizer's Consultants

[120] Pfizer_JMarino_0000088
[121] Pfizer_JMarino_0000088
[122] "Forced titration" in the Backonja and Rowbotham studies referred to dose escalation up until the patient reached 3600 mg/day or developed intolerable side effects. This study design is different than titration of dose to efficacy response.
[123] RR 720-04130 (Page 11)
[124] Pfizer_RGlanzman_0000711
[125] Pfizer_LCastro_0043328

meeting on September 6, 2001, and also were never published as an independent study.) And a "new analysis" of study 945-306 ("Serpell") showed that the benefit of Neurontin was due primarily to improvement in patients with postherpetic pain, patients with other causes of neuropathic pain showed little benefit. After learning of these results, Pfizer consultant Dr. Mitchell Max said, "You're done."[126] Presumably, he meant that Pfizer could not hope to get FDA approval for a broad indication for neuropathic pain.

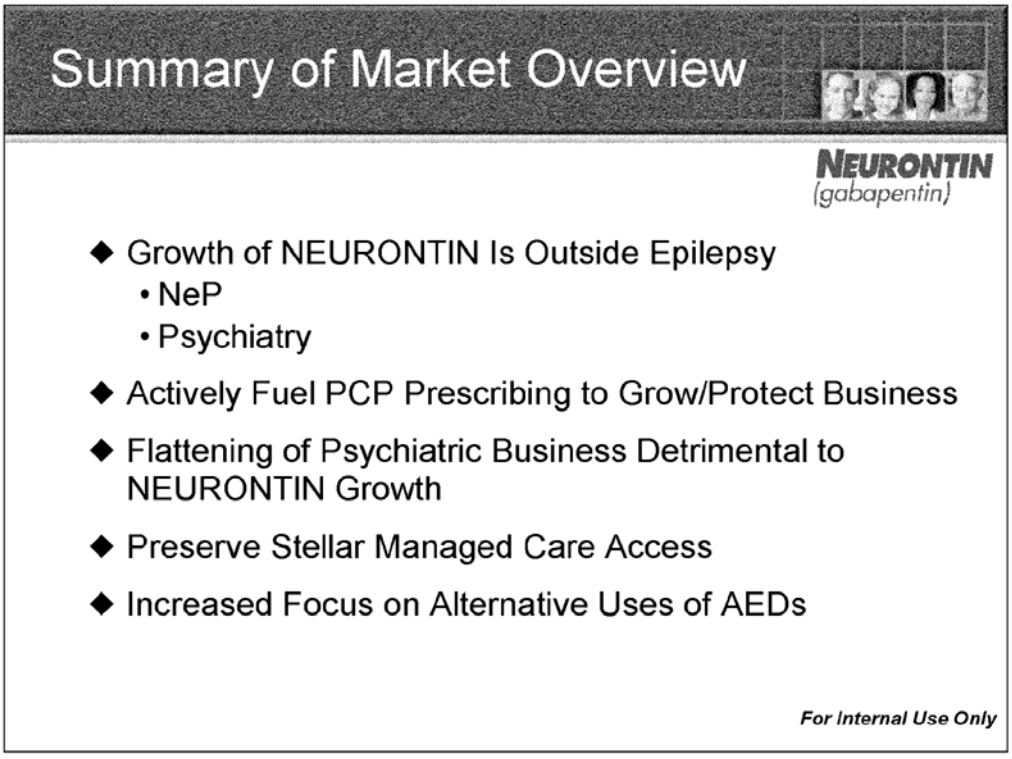
85. Ignoring both the FDA's warning in May 2001 that the sNDA for the broad indication of neuropathic pain would not be approved as well as its own expert panel's opinion that the available data did not support FDA approval, Pfizer's 2002 Operating Plan for Neurontin included preparation "for NeP launch."[127] The document presented the findings of the one purportedly positive study for DPN without mentioning the larger but still unpublished negative study, 945-224.

86. The 2002 operating plan reported that an sNDA had been filed for neuropathic pain,[128] without mention of the fact that the FDA had determined that this application would not be approved. Again, the plan showed that there was no growth in the use of antiepileptic drugs for seizure disorders,[129] but that use of this class of drugs for neuropathic pain had increased by 35%,[130] led by growth in the use of Neurontin for this off-label indication. The most rapid increase in new prescriptions for Neurontin was among primary care physicians.[131] Pfizer understood that—despite the largest of its own studies showing no benefit:

- Physicians perceive Neurontin as standard of care for neuropathic pain (NeP)
- Such use is "recognized in treatment guidelines and medical textbooks"
- "80%-90% of PCPs [who treat the majority of NeP[132]] indicate they use Neurontin to treat NeP"
- "40% of PCPs feel Neurontin is FDA approved"[133] [even though it was not]

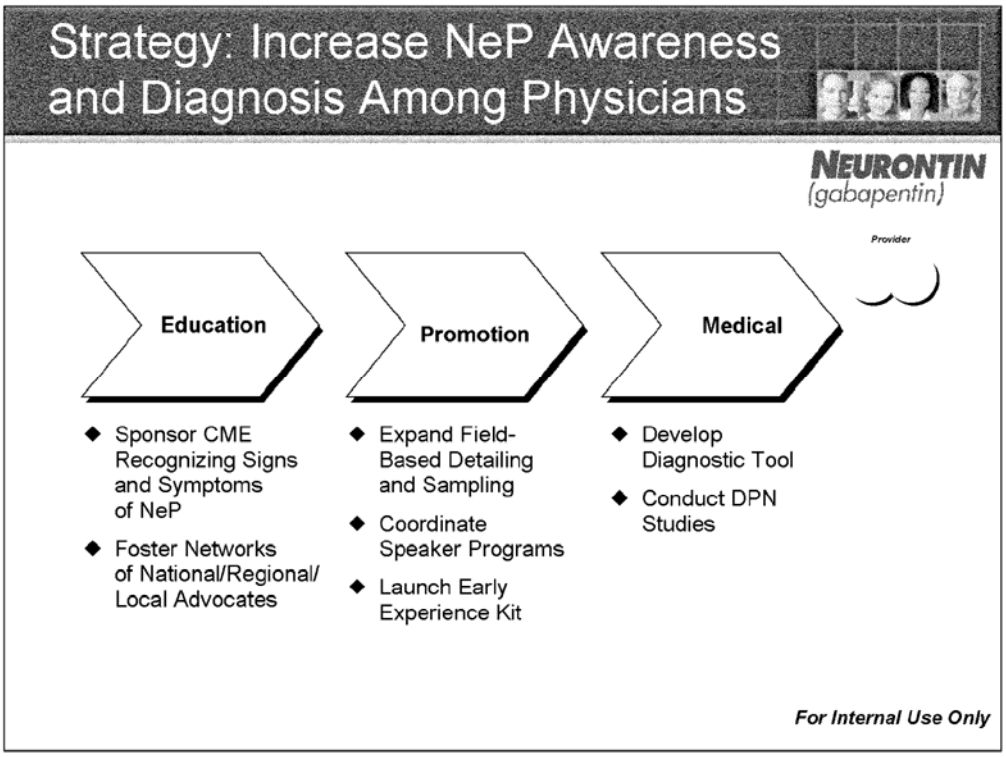
[126] Pfizer_JMarino_0000089
[127] Pfizer_BParsons_0092313
[128] Pfizer_BParsons_0092319
[129] Pfizer_BParsons_0092321
[130] Pfizer_BParsons_0092322
[131] Pfizer_BParsons_0092325
[132] Pfizer_BParsons_0092327
[133] Pfizer_BParsons_0092326

87. The following slide from the 2002 Operating Plan recognizes Neurontin's growth for neuropathic pain and psychiatric uses despite multiple negative clinical trials for both.

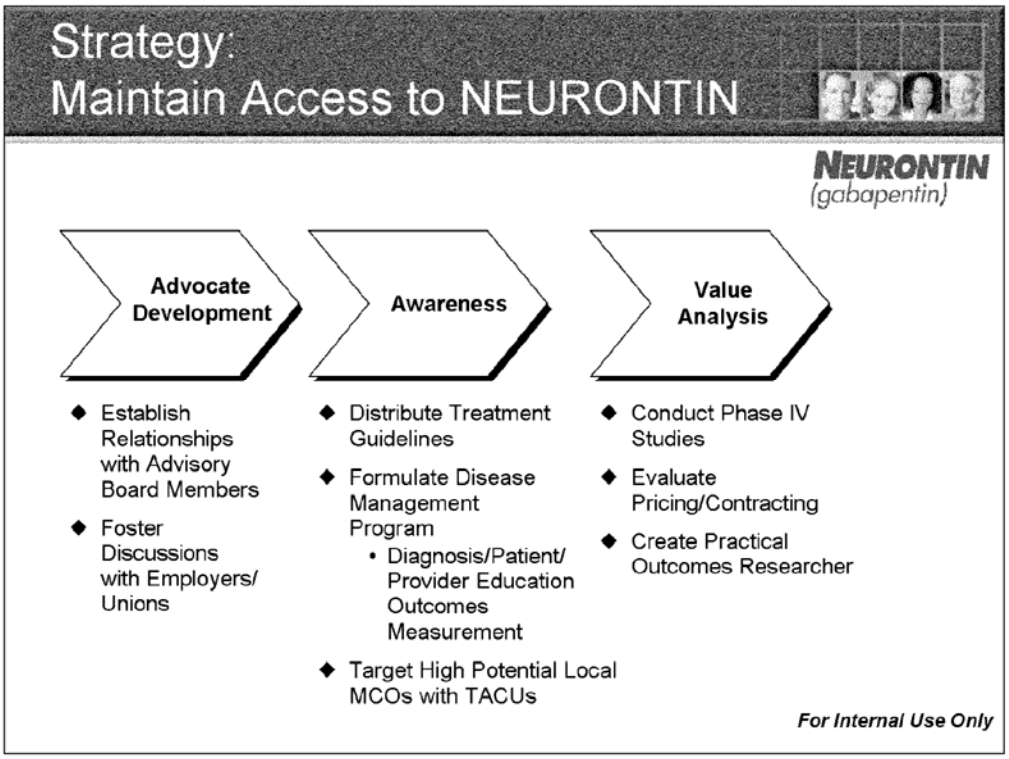


88. Pfizer's 2002 Operating Plan described the use of Neurontin for neuropathic pain as an "underdeveloped" market. A strategy for increasing the diagnosis (and therefore the prescription treatment) of neuropathic pain is outlined in the following slide, again from the 2002 Operating Plan (after Pfizer was well aware that FDA approval for this indication would not be forthcoming):[134]

[134] Pfizer_BParsons_0092339


Strategy: Increase NeP Awareness and Diagnosis Among Physicians
NEURONTIN (gabapentin)
Provider
Education
Promotion
Medical
Sponsor CME Recognizing Signs and Symptoms of NeP
Foster Networks of National/Regional/ Local Advocates
Expand Field-Based Detailing and Sampling
Coordinate Speaker Programs
Launch Early Experience Kit
Develop Diagnostic Tool
Conduct DPN Studies
For Internal Use Only

89. Sandwiched between two slides referring to the underdeveloped market for neuropathic pain, is a strategy to "maintain access to Neurontin":[135]



90. One example of the way the strategy to "foster discussions with employers" was accomplished was through two Advisory Board meetings (Millennium Hotel, NYC and Four Seasons Hotel, Scottsdale Arizona) and a monograph addressing "Neuropathic pain issues in the workplace." Both Advisory Board meetings were moderated by influential individuals representing influential organizations:[136] the New York meeting was moderated by the National Clinical Practice Leader from Towers Perin; the Scottsdale Arizona meeting was moderated by the President & CEO of the National Business Coalition on Health (representing 10,000 employers and 34 million employees. [137]) Both of the Advisory Board meetings included lectures titled "Treatment Options for Neuropathic Pain," one delivered by Leslie Tive,[138] the other by Robert Glanzman.[139]

[135] Pfizer_BParsons_0092346
[136] Pfizer_SDoft_0052469
[137] http://www.nbch.org/about/index.cfm accessed June 11, 2008
[138] Pfizer_SDoft_0010517
[139] Pfizer_SDoft_0052416

91. Comments from the New York and Arizona Advisory Board Meeting attendees included:[140]

- Treatment options for neuropathic pain was important information
- The proposed indication of Neurontin for pain was the most valuable information at the meeting
- Now realizes that Neurontin is safer, has less side effects and is more effective than he originally thought

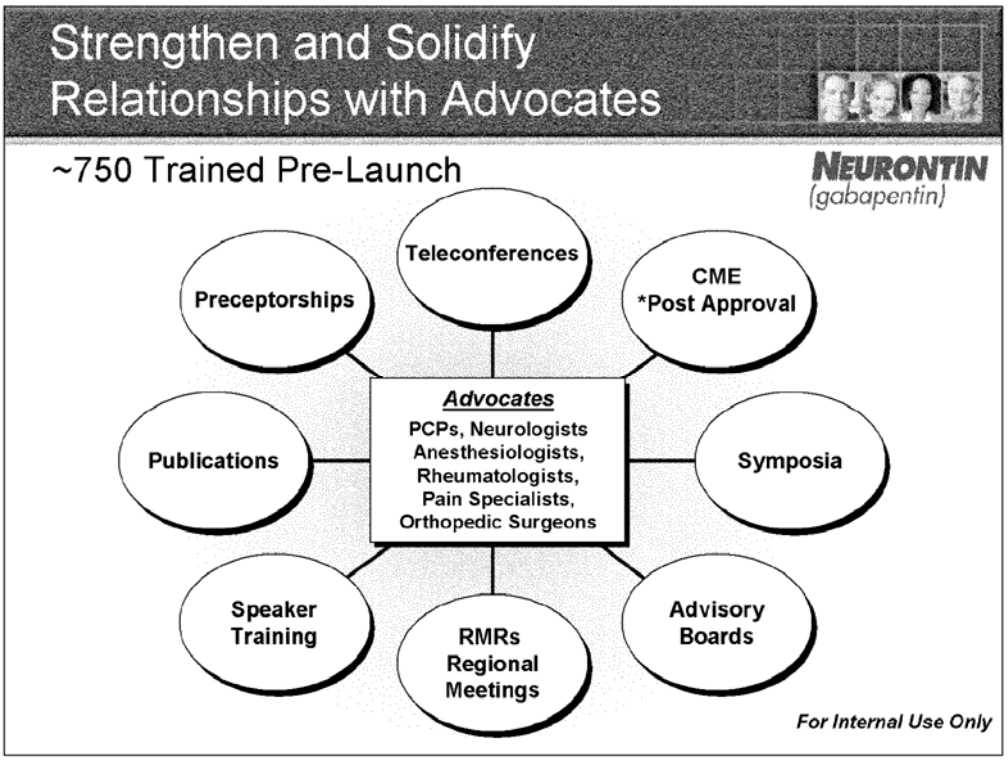
At the end of the write up of summary of the two Advisory Board meetings was a section titled Neurontin Payer Market Strategy, Next Steps:

> Educating the employer/union market on NeP and Neurontin's efficacy for treating this condition can substantially increase Neurontin's utilization in this market segment.[141]

The goal of the Advisory Board meetings and monograph is clearly articulated: to expand Neurontin use for the off-label and scientifically unsubstantiated use for neuropathic pain. Although this is marketing activity, presented as "Advisory Board" and scientific information covers the fundamental purpose: off-label marketing.

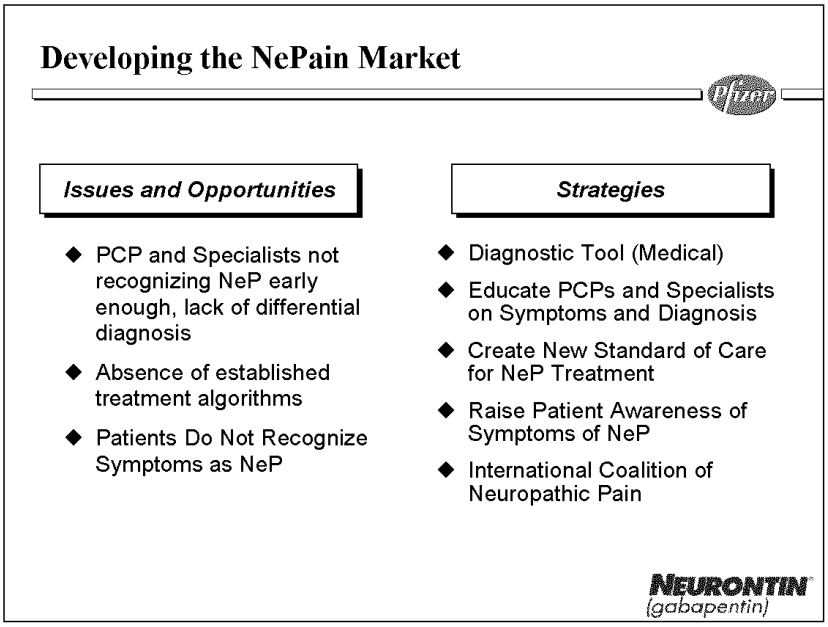
92. The 2002 Operating Plan for Neurontin also shows that approximately 750 neuropathic pain "advocates" (PCPs, neurologists, anesthesiologists, rheumatologists, pain specialists and orthopedic surgeons) had been trained during the "pre-launch period," meaning before the anticipated date for FDA approval of the broader indication of neuropathic pain. The following diagram, from the 2002 Operating Plan, shows how the manufacturer planned to use the advocates to influence all the sources of information transfer to potential prescribers:[142]

[140] Pfizer_SDoft_0052506
[141] Pfizer_SDoft_0052539
[142] Pfizer_BParsons_0092340



93. Pfizer's Global Operating Plan dated October 11, 2001 (five months after the FDA and one month after its own consultants had concluded that there was inadequate evidence to support Neurontin's use for the broad indication of neuropathic pain), presents Defendants' goal of "Making Neurontin the Standard of Treatment in NeP [neuropathic pain]."[143] Strategies to increase what Pfizer knew to be the scientifically unsubstantiated use of Neurontin for the treatment of neuropathic pain are identified in this slide from its Global Operating Plan dated October 11, 2001:[144]

[143] Pfizer_JMarino_0000111
[144] Pfizer_JMarino_0000108



Rather than accurately and completely presenting the scientific evidence (some of which remained solely in their possession, unavailable to prescribers), Pfizer chose to "educate" prescribers about recognizing neuropathic pain and provide diagnostic tools to assist physicians in making the diagnosis of neuropathic pain to increase prescribing of Neurontin. The "chronic pain screening tool" was planned to be rolled out in the US in Q4 2002, including seeking the endorsement of such off-label and unsubstantiated use by the "American Pain Society or other international body of experts."[145] (Obviously such experts would be unlikely to include the four Pfizer consultants who attended the September 6 meeting and concluded that evidence did not support this very claim.)

94. The strategy for off-label promotion didn't just include an indication for which Pfizer's own consultants had said the scientific evidence did not support the claim of efficacy, but also identified the "opportunity" to advocate doses that were not approved by the FDA: "Max efficacy with good safety is 3600mg a day."[146]

[145] Pfizer_JMarino_0000128
[146] Pfizer_JMarino_0000112

95. Based on these strategies (and others), Pfizer projected Neurontin sales to increase by $461 million between 2001 and 2002, with 83% of this growth projected to occur in the US.[147]

96. Notwithstanding the results of the Gorson study and Study 945-224, which included 3 times more patients receiving active treatment and used a fixed dose design that did not "break the blind" as did the forced titration design of study 945-210 (both discussed below), the 2001 Global Operating Plan presented a Global Neuropathic Pain Message and Positioning:

> Neurontin is the ideal first-line therapy for all types of Neuropathic Pain providing a significant improvement in quality of life due to its *proven efficacy and quick onset of action, excellent safety and tolerability, and convenient ease of use.* [Emphasis in original][148]

97. Data from 2001 showed that two-thirds of the physicians who treat neuropathic pain are primary care physicians; they see four patients with diabetic peripheral neuropathy for every patient with postherpetic neuropathy.[149] The manufacturer's market research, presented in the 2002 Operating Plan for Neurontin, showed that 80-90% of PCPs were prescribing Neurontin for neuropathic pain, and that 40% of PCPs erroneously "feel NEURONTIN is FDA Approved [for this indication]".[150]

98. The strategy outlined in the 2001 and 2002 Operating Plans would appear to have been successful. In 2001 Neurontin was the fourth fastest growing blockbuster drug worldwide,[151] with 86% of worldwide Neurontin sales occurring in the U.S.[152] While there was no U.S. growth in the use of Neurontin for seizure disorder in the years 1997 through 2001,[153] use for neuropathic pain grew rapidly, by 43% between 1999 and 2000, and by 26% the following year.[154]

99. The strategy presented in the 2003 Operating Plan shows the intention of continuing to increase off-label sales. Neurontin is identified as the "gold standard" for

[147] Pfizer_JMarino_0000133
[148] Pfizer_CGrogan_0005057
[149] Pfizer_JMarino_0000161
[150] Pfizer_BParsons_0092326
[151] Pfizer_AMishra_0002326
[152] Pfizer_AMishra_0002392
[153] Pfizer_AMishra_0002338
[154] Pfizer_AMishra_0002339

neuropathic pain in the U.S.[155] The objective of participating in the International Coalition for Neuropathic Pain 2003 is identified as adding value to the Neurontin franchise in the U.S., specifically by clarifying diagnosis and management accomplished by targeting opinion leaders and pain and non-pain specialists.[156]

100. Again in the face of their own consultants' opinions that the scientific evidence did not support a broad claim of efficacy for Neurontin in the treatment of neuropathic pain, the results of its own unpublished studies 945-224, POPP and Gorson (see below), the following slide was included in Pfizer's 2003 Operational & Tactical Plan for Neurontin:[157]

> **NEURONTIN Is an Ideal First-line Therapy for Neuropathic Pain With *Proven Efficacy, Excellent Safety and Tolerability, Favorable Onset of Action and Ease of Use*, Thereby Restoring Patients' Quality of Life**

101. The first goal identified in the 2003 Medical Operating Plan, presented by Robert Glanzman (U.S. Director), is "Grow NeP Market with Neurontin."[158] A key strategy to accomplish this goal is to use "PHN as a model for NeP." This was to include building consensus among key opinion leaders, which would then be published as a monograph and used to train primary care physicians, seeking the endorsement of the American Pain Society (for this off-label use), and "investigate building scenario of PHN being most severe form of NeP" (in other words, simply ignore the negative results of its own unpublished studies and the FDA's refusal to approve Neurontin for the broader indication of neuropathic pain).[159]

102. The Neurontin 2004 Operating Plan, dated September 30, 2003, documents the ongoing success of Pfizer's off-label marketing strategy for Neurontin. As of July 2003, 90% of Neurontin was being prescribed off-label:[160]

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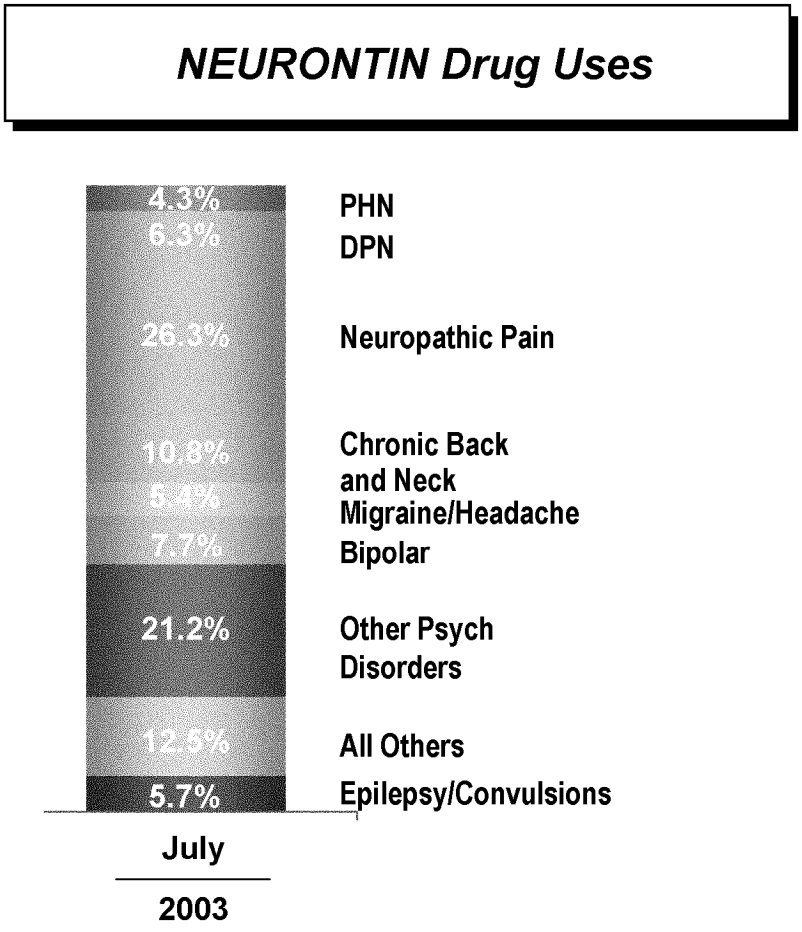
[155] Pfizer_AMishra_0002346
[156] Pfizer_AMishra_0002372
[157] Pfizer_AMishra_002350
[158] Pfizer_RGlanzman_0148327
[159] Pfizer_RGlanzman_0141302
[160] Pfizer_SPiron_0011534



103. Pfizer's 2004 Operating Plan for Neurontin identified optimal dose as "1800 mg/day and above" despite 1800 mg/day being the maximum dose approved (and deemed effective for PHN) by the FDA.[161]

104. Defendants influence over the information upon which physicians rely created the impression that Neurontin's use was scientifically substantiated for neuropathic and nociceptive pain, bipolar disorder, migraine headache and in doses greater than those approved by the FDA

[161] Pfizer_SPiron_0011550

(1800 mg/day). The misrepresentations (both affirmative and by omission) that were presented to physicians were not isolated events that resulted from unconnected individual decisions. Rather these misrepresentations were the material expression of the Defendants' well-coordinated and pervasive strategy to increase Neurontin sales by creating and manipulating the "scientific evidence" available to prescribers and purchasers.

C. Pfizer Developed "Key Messages" That Determined (Rather Than Reflected) The Scientific Evidence

105. Doctors reasonably believe that the knowledge that informs their clinical decisions and standards of care is derived from the scientific evidence published in medical journals, presented in review articles and endorsed by thought leaders and trusted organizations. Defendants' documents show, however, that they engaged in a comprehensive program to exploit physicians' trust in this process of knowledge creation and dissemination: Rather than being the product of unbiased scientific inquiry, the "scientific evidence" supporting off-label use of Neurontin was the product of the Defendants' carefully designed and orchestrated campaign to establish pre-determined marketing-favorable "key messages" as the scientific evidence, and not the other way around.

106. These key messages were not just the themes that drug reps or advertisements were to stress in their marketing messages. Rather these predetermined key messages were to determine the conclusions that would be presented in the most "upstream" source of medical knowledge, articles published in medical journals. An e-mail by Marino Garcia explained that, unlike branding guidelines, which are limited to what can be said in the present, key message targets identify what needs to be incorporated into future publications in order to lay the groundwork for the "Ideal Neurontin Story" that would enhance future sales:[162]

> We need to discuss not just how the publications strategy can support our past and current messages but how it can support what we would like to say 6-24 months from now.
>
> The publications strategy need to incorporate what we want to say in the future and how we want data and publications to support that.

[162] Pfizer_LKnapp_0035987

107. Marshalling of these key messages is shown by a Pfizer memo of April 2002, sent to all "countries/affiliates," requesting that "affiliate-driven manuscripts be forwarded to NTN PSC for review." The purpose of this was to ensure that all manuscripts are "in-line with current product messages and areas of interest."[163]

108. The target audience for these key messages identified at the "Neurontin Publication Planning Meeting held July 12, 2001 was not limited to doctors treating epilepsy, but also those treating the off-label indications for which Neurontin was being marketed: neurologists (treating migraine), primary care physicians, psychiatrists, pain specialists, psychologists and social workers, sleep experts and endocrinologists (treating diabetes).[164]

109. Notes from the July 18, 2001 meeting of the Neurontin Publications Subcommittee indicate that Medical Action Communications was to provide a list of medical congresses and journals to be used in the development of the Neurontin publication plan as well as "Key Message Development Update."[165]

110. 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."[166] Yet the efficacy of Neurontin for this indication was not proven, and – just 6 weeks later – Pfizer's own pain consultants, based on the available evidence, concluded that there was not enough evidence for the FDA to approve Neurontin for the treatment of neuropathic pain.

111. Defendants' documents show that the strategy of embedding key messages in future publications to create scientific evidence was not just hypothetical. From the Garcia e-mail of July 31, 2001

> For example, don't we want to give people a target dose in NeP and Epilepsy?
>
> One key message I would like to see supported is "1800 mg by week 2 of therapy before evaluating patient response". I know some patients will do better at lower doses, but the data (as I read it) says this is the minimum optimal effect dose in NeP as a whole…So any publication that we can provide input on should make this point clear. But this is not part of the message in the slides right now because it is still not fully clear.[167]

[163] Pfizer_AFannon_0017370
[164] Pfizer_LKnapp_0038966
[165] WLC_CBU_168005
[166] Pfizer_LKnapp_0035901
[167] Pfizer_LKnapp_0035987

112. The scientific evidence did not support the position of getting all patients up to a dose of 1800 mg/day (the Defendants' own pain consultants had concluded that the evidence was not adequate to support FDA approval for the use of Neurontin to treat neuropathic pain). Nevertheless, the strategy was to produce scientific evidence in the medical literature that would make this dosage recommendation appear as if it were the product of science rather than marketing, and thus justify the recommendation to titrate all patients to a dose of 1800 mg/day within 2 weeks of initiating therapy.

113. How did Defendants embed their pre-determined key messages into the manuscripts reporting on clinical trials that were submitted to medical journals? The draft timeline for the development of these manuscripts shows that Defendants built in their opportunity to control the message presented in its articles before the "lead author" ever had a chance to see the manuscript that he or she had supposedly written. The first and lengthiest step in manuscript development is "key message development." This is followed by first draft, revision and lead reviewer approval. Only after these stages of manuscript development had been completed, 11 weeks into the process, was the paper sent to the person euphemistically referred to as the lead author.[168]

114. Notes from an August 15, 2001 "Neurontin PSC Meeting," included people from Pfizer and Medical Action Communications. A section titled "Dosing and titration manuscripts," discussing two manuscripts reported that Angela Crespo "has mentioned [these manuscripts] as being important for the major markets: dosing and titration manuscript…." The paper, addressing neuropathic pain, was "targeted" for the journal *Clinical Therapeutics*.[169]

115. The 2003 Backonja and Glanzman review article titled "Gabapentin Dosing for Neuropathic Pain: Evidence from Randomized, Placebo-Controlled Clinical Trials"[170] (sponsored by Defendants[171]) shows that the implementation of key messages publication strategy was more than a hypothetical or a "wish list" for the results of future clinical trials. The dosing recommendations made in this article directly reflect the "key message" presented in July 2001. Leaving aside for the moment that the findings of these trials failed to support FDA approval of Neurontin for the broad indication of neuropathic pain, the dosage recommendations

[168] Pfizer_LKnapp_0038967
[169] WLC_CBU_168011-2
[170] Backonja M., Glanzman R. Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials. *Clinical Therapeutics* 2003; **25**(1): 81-104. *See also* PFIZER_LESLIETIVE_0038508
[171] Pfizer_LAlphs_0013925

presented in the review include starting with a dose of 300 mg on the first day of therapy and increasing the dose by 300 mg/day up to a dose of 900 mg/day, then

> During the following week, the dose of gabapentin should be increased to achieve the target dose of 1800 mg/d between days 9 and 14. This recommendation is based on the protocols used in the studies reviewed, although in the authors' practice and in many countries, titration to 1800 mg/d is conducted more rapidly.

116. The dosing regimen for study 945-210 (Backonja) called for increase of dose to 1800 mg in 2 weeks, but the dosing regimens of studies 945-224 (Reckless) and 945-306 Serpell called for reaching 1800 mg more slowly.[172] Even so, results of the clinical trials ought to inform dosing recommendations, rather than simply the dosing protocols of the clinical trials. The latter two studies did not show significant benefit of Neurontin for the treatment of neuropathic pain of etiology other than post-herpetic neuropathy.

117. Pfizer's goal of integrating pre-determined key messages into manuscripts submitted to medical journals was in alignment with the proposal made by Fallon Medica for "Neurontin publication planning and execution" on November 6, 2002. [173] (Slides included in an October 2004 e-mail show that Pfizer did, in fact, work with Fallon Medica on the preparation of manuscripts.[174]) Fallon Medica's standard operating procedure for manuscript creation includes addressing the following questions,[175] which unmask the illusion that the primary purpose of articles published in medical journals is to report, in as unbiased a way as possible, the scientific evidence to be learned from clinical trials and reviews of multiple clinical trials:

- What does the client want to achieve—why is the client paying for this article to be written?
- Key client messages—what must the content communicate to be a "success?" What are the positive hot-button issues?
- Key sensitivities—where must writers, editors and team tread lightly? What are the negative hot-button issues?

118. When deciding whether off-label use of a prescription medication is in the best interest of his or her patients, doctors (optimally) rely upon the scientific evidence published in medical journals. As shown in an e-mail dated October 17, 2002, Pfizer was aware that it was

[172] Study 945-271 increased the dose to 1800 mg/day within the first two weeks, but this study—with negative findings—was not included in the Backonja and Glanzman review.
[173] Pfizer_BParsons_0183188
[174] Pfizer_AFannon_0017368
[175] Pfizer_BParsons_0183199

allowed to provide off-label information in medical journals that it was not allowed to present in marketing. [176] Further, this e-mail states that

> in markets where rapid titration is promoted, physicians have adopted it…In the US, rapid titration cannot be promoted due to label restrictions. However, we can provide this information via publication.

119. This is an example of what Drs. Horton and Smith referred to as "information laundering" by the medical journals: allowing a marketing-driven key message to be integrated as the core message of a drug company written article that is published in a medical journal. Lest there be any doubt that Pfizer was aware of their end-run around marketing regulations, another e-mail of October 17, 2002 clarifies their position:

> Due to restrictions in the US label, the sales reps cannot promote [getting to 1800 mg (or higher) faster] in the US. However, this message can be communicated in publications.[177]

120. Leslie Tive responded to this e-mail saying "As long as the messages are supported by the trials and do not go beyond what has been studied I think this is fine."[178] The scientific evidence about dose and efficacy of Neurontin for neuropathic pain was not fairly and fully presented, as made very clear by Pfizer's own scientific consultants on September 6, 2001 and as described below. Acceptance of the Backonja/Glanzman review by *Clinical Therapeutics* is listed as one of the key accomplishments of the 2002 Neurontin Publication Sub-Committee (PSC).[179]

121. Physicians reading the Backonja/Glanzman review of dosing for neuropathic pain could not have been expected to independently verify the "evidence" supporting the use of and dose of Neurontin for neuropathic pain. (They had no access to the data from unpublished studies 945-224 and 945-271.) Physicians had no reason to believe that this article, recommending doses of Neurontin up to 3600 mg/day for neuropathic pain, did not accurately and fairly represent the best available scientific evidence. Yet the history and development of this article as described above show that its primary purpose was to influence "major markets." Both science and FDA regulations were sacrificed to the demands of marketing.

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[176] Pfizer_RGlanzman_0121206
[177] Pfizer_BParsons_0162576
[178] *Ibid.*
[179] Pfizer_AFannon_0003050

VI. THE SOURCES OF INFORMATION UPON WHICH PHYSICIANS RELY WERE SYSTEMATICALLY AND EFFECTIVELY MANIPULATED BY PARKE-DAVIS AND THEN PFIZER

A. Systematic Distortion Of The Scientific Evidence From Clinical Trials Of Bipolar Disorder

122. As shown in paragraph 14 above, the annual number of prescriptions written for Neurontin to treat bipolar disorder increased from 8,000 in February 1996 to approximately 402,000 in November 1999,[180] an increase of 5000% less than 4 years.

123. This dramatic increase in Neurontin use for the treatment of bipolar disorder begs the following two questions:

- Starting in 1996, what led doctors who prescribed Neurontin for patients suffering from bipolar disorder to believe that this was in their patients' best interest (despite a lack of FDA approval for this indication)?
- Did the scientific evidence available at the time support such off-label use? Was the information presented to physicians accurate and balanced?

124. Defendants' off-label marketing strategy can be seen as early as March 1995, when the decision was made at a "Neurontin Core Marketing Team" meeting "to do a 'Publication Study' in the three disorders [including bipolar disorder] since the patent situation would limit a full indication development."[181] Parke-Davis's strategy was to expand Neurontin sales, not by gaining approval for other indications from the FDA, but by performing studies that would support off-label marketing but not be submitted to the FDA. Essentially, this was an "end-run" around the FDA.

125. A document dated May 19, 1995 summarized the Marketing Assessment in Psychiatric Disorders for Neurontin.[182] After reviewing Neurontin's market potential for several different potential psychiatric indications (bipolar disorder, panic disorder and social phobia), the

> New Products Committee decisions have been incorporated, i.e., an exploratory study in bipolar disorder…The results, if positive,

[180] WLC_CBU_040450
[181] WLC_FRANKLIN_0000050315
[182] WLC_FRANKLIN_0000223121 to 80

> will be publicized in medical congresses and published in peer-reviewed journals, but there is no intention to fully develop these indications at this point.[183]

126. In other words, only positive results would be communicated to physicians. From a marketing standpoint, this is a nearly risk free strategy—heads Defendants win, tails Defendants don't lose. Positive studies would be used for marketing, but would not be subjected to independent scrutiny by submission to the FDA. Because of the company's intention to not make the results of negative studies available to physicians or the public, there was little risk of these studies compromising the marketing of Neurontin for off-label indications.

127. Dr. Franklin's Disclosure shows that in 1996 he was told "during several training sessions" to:

> tell physicians that clinical trials were in place for treatment of bipolar disease with Neurontin and that the early results from this [sic] trials indicated a 90% response rate upon administration of 300 mg of Neurontin three times a day and titrate up to 4800 mg/d.[184]

The Disclosure continues:

> It was widely acknowledged that this was not factual data, but that it would influence the physician to experiment with the drug in his or her bipolar patients.[185]

128. Dr. Franklin's Disclosure explains how he successfully "deceived" a physician "into believing" such statements, which "were false and demonstrated a reckless disregard for the truth and for the safety of Dr. [deleted]'s patients." Dr. Franklin states that he was able to convince the physician of the veracity of his statements despite the fact that:

> No data existed at all to support the use of Neurontin in bipolar disease. Any such "data" was either rumor, or outright fictitious, and designed to convince the physician that they should begin to experiment with Neurontin. No scientifically credible data supported this claim of effectiveness. Dosing data was also

[183] WLC_FRANKLIN_0000223122
[184] RELATOR00152
[185] RELATOR00152

fictitious and demonstrated a disregard for patient safety by greatly overdosing patients.[186]

129. This vignette has two key components:

- Parke-Davis intentionally communicated false information to a prescribing physician regarding clinical efficacy in the treatment of bipolar disorder and safety of doses up to 4800 mg/day.
- The physician believed Dr. Franklin's misrepresentations. (Though disturbing, the evidence is clear that doctors are influenced by "information" and "education" that is presented by authoritative sources in the formats with which they are familiar.)

130. Forty open-label studies (not blinded, not randomized and not controlled) that had been published in the medical literature were included in a 2003 review of the efficacy of Neurontin in bipolar disease.[187] Every one of the 40 open-label studies showed Neurontin to be effective in treating bipolar disorder. In stark contrast, none of the three double-blind randomized controlled trials included in this same review showed that gabapentin was superior to placebo for the treatment of bipolar disorder. Thus while the "gold standard" of evidence-based medicine failed to show benefit, the literature was dominated with positive open-label studies. How could all 40 of the open-label studies have been positive when all three of the most reliable trials, double blind randomized controlled studies, were negative?

131. A recently published literature review provides insight into the large number of articles published about the treatment of bipolar disorder with gabapentin.[188] Twenty-nine such articles were published between 1997 and 2007, most of which were published in 1998 and 1999. Of the 29 articles, 15 were uncontrolled case series and 6 were reports of single cases, i.e. Level 3 evidence. The review describes an "echo chamber" effect that was created by the publication of so much Level 3 evidence:

> The large number of case series and case reports reported encouraging results that were not confirmed by later small randomized trials. The number of reports and their distribution in a number of journals created a type of "echo chamber" effect, through which the sheer number of publications and citations may

[186] RELATOR00153
[187] Carta MG, Hardoy MC, Hardoy MJ, et al., The clinical use of gabapentin in bipolar spectrum disorders, *Journal of Affective Disorders,* 2003; 75:83-91
[188] Carey TS, Williams JW, Oldham JM, et al., *Journal of Psychiatric Practice* 2007;14(suppl 1):15–27)

> have given legitimacy to the practice of using gabapentin for bipolar disorder.

132. Dr. Franklin's Disclosure explains how the body of literature was built out of case reports that were systematically pushed forward by Defendants:

> When positive experiences were reported during this medical liaison induced experimentation, those reports would be met with support from Parke-Davis in the form of further investigation and assistance to the physician in publication of results. When reports of adverse effects were called to the attention of Parke-Davis management, medical liaisons were instructed to actively hide these reports from physicians.[189]

133. Putting these 40 positive open-label studies in perspective (generated as they were by the Defendants,) the following is a brief description of the four RCTs that were performed—all failing to show a benefit.

134. Parke-Davis's Protocol 945-209 was a double-blinded, placebo-controlled study of the efficacy of Neurontin as adjunctive therapy for bipolar disorder. The study was completed in July 1997, but the research report was not issued until March 26, 1999.[190] (Typically reports are issued about 3 months after study completion; in this case the lag time was 20 months.) The conclusion presented in the research report is:

> The results from this study do not indicate that gabapentin is effective as adjunctive therapy in bipolar disorder. However, there was no evidence that gabapentin caused a worsening of symptoms.

(Note the unusual language stating that gabapentin did not make the symptoms significantly worse.) The primary outcome measures in this study were the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HAM-D).[191] The results of this study were presented at the Third International Conference on Bipolar Disorder in Pittsburgh,[192] in June 17-

[189] RELATOR00153
[190] RR 720-04174 (Page 1)
[191] RR 720-04174 page 178
[192] as reported in: Carta MG, Hardoy MC, Hardoy MJ, et al., The clinical use of gabapentin in bipolar spectrum disorders, *Journal of Affective Disorders,* 2003;75:83-91.

19, 1999,[193] submitted for publication on July 22, 1999, and published in *Bipolar Disorders* in 2000.[194]

135. The study data presented in Table C.10 of Parke-Davis's research report show that the patients taking Neurontin did not improve in YMRS score as much as those taking placebo,[195] but – as reported in the conclusion above – the difference did not quite reach statistical significance.[196] However, the numbers for change in YMRS score presented in the *Bipolar Disorders* article were different from those presented in Parke-Davis's research report, and showed that those patients taking Neurontin actually did *significantly worse* than those taking placebo. This raises the question of the lead author, Pande (a Parke-Davis employee) having had access to data other than the data that was presented in the Research Report, and presenting the true data showing that Neurontin is significantly worse as adjunctive therapy for bipolar disorder than placebo, i.e. that Neurontin makes the symptoms worse.

136. A National Institute of Mental Health study compared lamotrigine, gabapentin and placebo for monotherapy of bipolar disorder. This study found that lamotrigine, but not gabapentin, was superior to placebo therapy. [197] Although this study wasn't published until 2000, the results had been presented in part at the 150th Annual Meeting of the American Psychiatric Association meeting on May 20, 1997 and at 151st APA meeting in June, 1998. Both of these presentations offered "interim" data. These results were also included in a review article, published in October 1998 in the journal *Neuropsychobiology,* written by the researchers who did this study:[198]

> In our double-blind study, the improvement rate on gabapentin (27%) did not exceed that of placebo (22%).

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[193] http://www.wpic.pitt.edu/Stanley/3rdbipconf/proceedings.htm accessed 11/29/2007
[194] Pande AC, Crockatt JG, Janney CA, et al., Gabapentin in Bipolar Disorder: a Placebo-Controlled Trial of Adjunctive Therapy, *Bipolar Disorders,* 2000;2:249-255.
[195] RR 720-04174 178 of 231
[196] Using the statistical tool available at "OpenEpi" to calculate significance. http://www.openepi.com/Menu/OpenEpiMenu.htm accessed 11/25/2007.
[197] Frye MA, Ketter TA, Kimbrell TA et al., A Placebo-Controlled Study of Lamotrigine and Gabapentin Monotherapy in Refractory Mood Disorders, *Journal of Clinical Psychopharmacology,* 2000;20:607-14.
[198] Post RM, Denicoff KD, Frye MA, et al., A History of the Use of Anticonvulsants as Mood Stabilizers in the Last Two Decades of the 20th Century, *Neurophsycholbiology,* 1998:152-66.

137. A small randomized controlled trial of adjunctive therapy (nine patients in each group) showed no significant improvement in those taking Neurontin compared to those taking placebo. The results of this study were presented at the APA's annual meeting in 1999.[199]

138. The fourth study ("Vieta"), performed by Pfizer, tested the efficacy of gabapentin for adjunctive therapy in bipolar disorder. The study included 42 subjects who were randomized to take gabapentin or placebo and found no significant benefit on the intent-to-treat group.[200] The per protocol population, which excluded patients originally randomized who did not meet certain compliance standards, favored gabapentin. This study was completed February 26, 2004, and the research report was issued on June 22, 2004. The results of the intent-to-treat analysis were not published. However, the results of the per protocol analysis were published in 2006[201] as if they were the results from the intent-to-treat analysis. This article claims (falsely) that "all analyses were done by intention to treat" and concluded: "despite lack of acute efficacy, treatment with gabapentin might provide some benefit on the long-term outcome of bipolar disorder." For the same reasons mentioned above, analyses on "per protocol" populations, created after randomization, are fraught with potential biases. Moreover, the reader of this article could not have known that these results were from a "per protocol" population. Since readers only could have known this if they had had access to the research report that was controlled by Defendants, Defendants thus subverted physicians' ability to function as learned intermediaries.

139. In sum, four randomized controlled clinical trials testing the efficacy of Neurontin for bipolar disorder have been done. Of the two identified as sponsored by the manufacturer, one showed that Neurontin is significantly worse than placebo, and one showed no benefit. The study done by NIMH showed no benefit. Another presented in 1999 also showed no benefit. Thus, there was no Level 1 evidence showing that Neurontin is effective in the treatment of bipolar disorder.

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[199] Guille, C., 1999. Gabapentin versus placebo as adjunctive treatment for acute mania and mixed states in Bipolar Disorders. American Psychiatric Association, Annual Meeting, NR10:63.
[200] Protocol 0945-421-291 / Page 1 of 4
[201] Vieta E, Goikolea JM, Martinez-Aran A, et al., A double-blind randomized, placebo-controlled, prophylaxis study of adjunctive gabapentin for bipolar disorder, *Journal of Clinical Psychiatry,* 2006;67:473-7

B. Systematic Distortion Of The Scientific Evidence From Clinical Trials Of Neuropathic Pain

1. *Gorson*

140. The results of the first randomized controlled trial testing the efficacy of Neurontin for the treatment of painful diabetic neuropathy were available to the Defendants no later than August 23, 1997.[202] Fifty-three patients were initially enrolled to be treated with either Neurontin 900 mg per day or placebo in this double-blind placebo-controlled randomized crossover design. After a 3 week drug free period, patients took either Neurontin or placebo for 6 weeks. There was then a 3-week washout period followed by another 6-week crossover period.[203] The primary endpoints were the changes in scores from the beginning of the six-week trial to the end in the McGill Pain Questionnaire (MPQ), the Visual Analog Scale (VAS) and the Present Pain Index (PPI) as well as a four-point global assessment of pain relief completed at the end.

141. The manuscript prepared by Gorson et al. shows that the analysis of the data was not performed according to the protocol. Rather, because two of the four outcome measures:

> did not return to baseline after the washout period for those who received the active drug in phase I, and there was an order effect for [another outcome measure]. Accordingly, analysis of treatment effects was based upon changes in the MPQ, VAS, and PPI scores between treatment periods.[204]

142. In other words, data from the second half (crossover period) of the trial was simply omitted from the report. (Note that in the Morello et al. crossover study (discussed below) comparing Neurontin and amitriptyline for the treatment of diabetic peripheral neuropathy[205] there was just a one week washout period before patients crossed over to the other therapy. Although the groups did not return exactly to baseline after this washout period, data from both periods of the trial were included in the results. In contrast, the washout period in Gorson et al. was three times longer, and the manuscript and presentations of the results described below simply stated that the Neurontin group did not return to baseline without providing any evidence.)

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[202] WLC_FRANKLIN_0000100272
[203] WLC_FRANKLIN_0000100242
[204] WLC_FRANKLIN_0000100278
[205] Morello CM, Leckband SG, Stoner CP, et al., Randomized Double-blind Study Comparing the Efficacy of Gabapentin with Amitriptyline on Diabetic Peripheral Neuropathy Pain, *Arch Intern Med,* 1999; 159:1931-7.

143. Even so, among those who completed the first half of the trial, Neurontin provided significant benefit on only one of the pre-specified four endpoints: the MPQ. In his report of the results to the manufacturer, Gorson et al. wrote:

> Gabapentin, at a dose of 900 mg/day, is probably no more effective than placebo in the treatment of painful diabetic neuropathy.[206]

144. Phil Magistro's edit of Gorson's manuscript is contained in a January 7, 1998 memorandum. While Gorson's manuscript had noted "modest improvement in the MPQ score only" and "the mean change of the VAS and PPI and the number of patients who reported pain relief as moderate or excellent were similar in gabapentin and placebo,"[207] Magistro's edit changed the author's conclusions, reporting a "substantial reduction" in the mean MPQ, VAS and PPI—a conclusion that was more advantageous from a marketing perspective, but inappropriately changed the "take-home message" from the study that would be delivered to readers. Despite Magistro's spin, the results were the same: significant improvement over placebo in only one of the four endpoints."[208]

145. Although Dr. Gorson indicated in his cover letter to Parke-Davis that accompanied the faxed manuscript his desire to publish the results as an article in *Neurology*,[209] the study was never published as a peer reviewed article in any journal. Rather, the results were presented in a poster at the 1998 Annual Meeting of the American Academy of Neurology, as an abstract in a supplement to the journal Neurology *(*albeit with a far more positive spin than in Dr. Gorson's initial communication of the results: "Gabapentin may be effective in the treatment of painful diabetic neuropathy"[210]), and as a letter to the editor in the much lower-circulation *Journal of Neurology, Neurosurgery & Psychiatry.*[211] Interestingly, the supplement and letter list the number of patients in the study as 40, not the 53 from the original draft.

146. Despite the results of the Gorson study as described above, the 2002 Diabetic Peripheral Neuropathy section of DrugDex[212] reported that the Gorson study had shown that

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[206] WLC_FRANKLIN_0000100272
[207] *Ibid*
[208] WLC_FRANKLIN_0000088375
[209] WLC_FRANKLIN_0000100272
[210] *See* 1998 Gorson Neurology.pdf and Neurontin.mdb produced by Defendants as part of the Neurontin bibliography
[211] Gorson KC. et al. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. *Journal of Neurology, Neurosurgery & Psychiatry* 1999; **66**(2): 251-2.
[212] DrugDex is one of three official drug compendia that discuss off-label uses and is the only source available online.

gabapentin was minimally effective rather than "probably no more effective than placebo", cited only the significant result in one end point and included the conclusion from Magistro's edit rather than the authors' manuscript: "[t]he authors suggest that higher doses [not *studies* investigating higher doses] of gabapentin are needed."[213]

147. In sum, despite omitting the second half of the data, this study found that Neurontin at a dose of 900 mg/day "is probably no more effective than placebo in the treatment of painful diabetic neuropathy" and was never published as a peer reviewed article.

2. *Study 945-210, "Backonja"*

148. The first published clinical trial of Neurontin for the treatment of painful diabetic neuropathy was Protocol 945-210, published in the *Journal of the American Medical Association* in December 1998.[214] This study was funded and conducted by the Defendants. Eighty-four patients were in the active treatment group and 81 in the placebo group. Those receiving Neurontin were initially treated with 900 mg/day of Neurontin and titrated on a weekly basis up to 3600 mg/day as tolerated over a four week period—whether or not they had appreciated symptom relief at a lower dose (thus the term "forced titration"). The dose for patients who experienced side effects was reduced to the previous level. During the second four weeks of the study, patients were continued on the maximum tolerated dose achieved at the end of week four.

149. Unlike the disappointing findings in the Gorson study, Backonja et al. concluded: "Gabapentin monotherapy appears to be efficacious for the treatment of pain and sleep interference associated with diabetic peripheral neuropathy and exhibits positive effects on mood and quality of life." Physicians were, however, misled in several ways by this highly publicized article.

150. The article by Backonja et al. appeared to review the relevant studies that had been done concerning the potential benefit of Neurontin for painful diabetic neuropathy. It included a review of the scientific evidence demonstrating the efficacy of Neurontin for neuropathic pain in animals. It misleadingly stated, however, that "this was the first trial to evaluate gabapentin's efficacy in this patient population." Defendants had to have known that

[213] *See* Exhibit J to Affidavit of James E. Murray in support of Defendants' Motion for Summary Judgment [Docket No. 295] filed in US ex rel. Franklin v. Pfizer et al., 96-11651-PBS (D. Mass. Apr. 14, 2003).
[214] Backonja M, Beydoun A, Edwards KR, et al., Gabapentin for the symptomatic treatment of painful neuropathy in patients with Diabetes Mellitus. *Journal of the American Medical Association*, 1998;280:1831-6.

this was not true because they had funded the unpublished Gorson study of Neurontin efficacy for painful diabetic neuropathy described above, the manuscript for which had been sent to Parke-Davis seven months before the manuscript of the Backonja study was initially submitted to JAMA.

151. The forced titration design of the study led to 23.8% of patients treated with Neurontin experiencing dizziness (compared to 4.9% of those taking placebo), and 22.6% of patients taking Neurontin experiencing somnolence (compared to 6.2 % of those taking placebo). The article raised the possibility that titration up to the point of side effects for so many patients might have had the effect of partially "unblinding" the study (because patients experiencing these side effects would have reasonably assumed that they were receiving the active treatment rather than the placebo). However, the methodology then used to determine whether this functional unblinding did bias the results was inadequate. Rather than calculating whether there was a significant correlation between the experience of *any* of the CNS side effects and the degree of pain relief achieved, the paper calculated separately whether each of the two most common side effects had a significant effect on the degree of pain relief reported. Thus, when patients experiencing dizziness were removed from the results, there was no significant impact on pain relief achieved by the remaining patients. And when these patients were put back into the mix and the patients experiencing somnolence were removed from the results, there was no significant impact on pain relief achieved by the remaining patients. Determination that pain relief was not significantly affected by removing those people experiencing single CNS side effects *one at a time* was inadequate to prove that the experience of CNS side effects *in toto* did not have a significant effect on the results.

152. Corporate e-mails show that, at least 5 months before the Backonja article was published, Defendants understood the inadequacy of this method of excluding the potential unblinding effect of CNS side effects in the forced titration study design. A Warner-Lambert e-mail dated July 1, 1998, was titled "Additional Analyses Requested for Parke-Davis Study 945-224."[215] The comments below were to apply to a fixed dose study of the efficacy of Neurontin for NeP, with the highest dose being 2400 mg per day. The potential unblinding effect of CNS side effects was much less in study 945-224 because of the lower doses and the fixed dose rather than forced titration design. Even so, when considering the possibility of unblinding as a result

[215] PFIZER_TMF_CRF_061889. (945-224 refers to the Reckless study discussed below.)

of the greater incidence of CNS side effects in those people taking Neurontin rather than placebo, Defendants' pain experts proposed:

> that we should look for a correlation of maximum CNS-related Adverse Event severity with mean pain score, assuming that patients with more severe AEs tend to believe that they are on study drug (which probably would be a good guess) and therefore tend to have better efficacy data, thus unblinding and corrupting the study.

153. No later than July 1, 1998, Defendants' pain experts suggested the proper approach to ensure that the study was not unblinded by the increased frequency of CNS-related side effects associated with Neurontin was to determine the effect of all "CNS-related Adverse Event[s]" on pain scores simultaneously. An e-mail dated July 14, 1998 shows that the methodology used in the Backonja article to determine whether the experience of CNS-related adverse events had a significant effect on subjectively reported pain scores came directly from the Defendants. Jeffrey Moore described the methodology that was later presented in the Backonja article: determine which adverse events occurred significantly more frequently in patients taking Neurontin, then:

> We proceeded to run an analysis on patients that did not experience somnolence and then another analysis on patients that did not experience dizziness. Even after removing these potentially unblinded patients we saw efficacy (means and p-values looked good) and thus we were satisfied that potential unblinding did not influence the results.[216]

154. This methodology, however, answered the wrong question: did the increased frequency of any *single* CNS-related adverse event among people taking Neurontin affect the results of the study? It failed to determine whether the more frequent experience of CNS-related adverse events *in toto* among people taking Neurontin materially affected the outcome of the study. Notes from Defendants' July 23, 1998 telephone meeting about the clinical analysis plan for study 945-224 show that Defendants were aware of the two alternative ways to test for unblinding:

> **Analysis whether the study was unblinded by the adverse events:** before using Jeff's approach (finding out by Fisher's exact test which CNS AEs could be a possible indicator of drug; then

[216] Pfizer_LLaMoreaux_0038148

> excluding all patients who has [sic] at least one of these AEs that might unblind the study and finally perform an efficacy analysis only on the remaining patients), Bruno would like to perform a stratified analysis with regard to AE and look at the interaction between strata and treatment. If there is no interaction, Bruno would leave it at this and would not proceed to Jeff's approach…[217]

155. Despite awareness of other more sensitive statistical analyses, Defendants opted to use a method less sensitive than "Jeff's approach" above. Had a more sensitive approach been used, on the results of study 945-210 (which was much more likely than 945-224 to have been unblinded by CNS-related side effects,) the manufacturer may have found (as did Dr. Jewell, as documented in his report) that in the context of forcing titration to 3600 mg (twice the FDA approved dosage limit) much of the patients' perceived efficacy of Neurontin correlated significantly with their experience of the most frequent CNS adverse events:

> Approximately 90% of the apparent total improvement in average pain scores under active treatment reported by Backonja et al. is explained by events after the onset of adverse side effects that have the potential to "unblind" treatment assignment, and are therefore subject to bias.[218]

Thus, not including those people who were essentially in an open label study design, because the blind had broken by their experience of CNS side effects, showed that, for the remaining patients, still blinded to treatment allocation, Neurontin failed to provide significant relief from the pain of diabetic neuropathy. Therefore study 945-210 was in essence a partially open label design, and instead of providing "Level 1" evidence (high quality RCT) the quality of the evidence was partially Level 2 (open-label).[219]

156. Did Defendants understand that the forced titration design was most likely to produce results that demonstrated the efficacy of Neurontin for the treatment of DPN? An e-mail dated September 7, 2001 titled "Phase IV DPN Protocol changes" shows they did. Robert Glanzman wrote to John Marino and others describing the changes made to the protocol for the upcoming DPN study, 945-1008. This study was also a forced titration study. All patients were to increase the dose of Neurontin to 3600 mg/day over the first two weeks of the study (rather than over 4 weeks as in study 945-210) and those patients who experienced side effects "will be

[217] PFIZER_TMF_CRF_062490
[218] Report of Nicholas Jewell Ph.D.
[219] Op. Cit., Ebell et al. (See Figure 1, Strength of Recommendation Taxonomy (SORT)

allowed to reduce dose 1 time at post-titration visit to 2400 mg/day. No further reductions will be allowed."[220] Dr. Glanzman stated in his introduction to this update of the protocol: "We are aware of all the issues (I hope) and feel this design is the most practical and likely to result in a positive study." [My emphasis] (In addition, this protocol incorporated a 2 week placebo run-in period designed to screen out placebo responders, also making Neurontin appear more effective.)

157. Is there evidence that Defendants understood the potential unblinding effect of the design of study 945-210 before the study was undertaken? An article published in *Neurology* (based on research supported by Parke-Davis) in 1996 (submitted April 10, 1996) shows that there was. This study examined the efficacy of Neurontin in slowing the rate of decline in patients with amyotrophic lateral sclerosis (ALS). Although the findings were not positive, the article raised the issue of a CNS-related side effect unblinding the study: "The presence of significantly more light-headedness (dizziness) in patients taking gabapentin is a potential unblinding feature of the study." The article went on to say that although the number of people experiencing this symptom was small (the dose of Neurontin in the study was 2400 mg/day), "Nonetheless, sophisticated patients may have been unblinded by these side effects."[221] If unblinding caused by CNS-related side effects was a concern in this study in which the dose of Neurontin was 2400 mg/day, then concern about the potential unblinding by CNS side effects should have been greater in study 945-210, where the dose was titrated up to 3600 mg/day. Study 945-210 was begun on July 2, 1996, three months after the manuscript for the ALS study had been submitted to *Neurology.*[222] Surely Defendants understood the potential bias in the research design of study 945-210 at the time the study was begun.

158. Besides adequately testing to see if the experience of CNS-related side effects unblinded the study and compromised the validity of the findings of study 945-210, there were two other changes to the study design that would have increased the validity of the results. The first would have been to use a fixed dose design. The Backonja article states:

> Because this was the first trial to evaluate gabapentin's efficacy in this patient population, all patients' dosages were titrated to tolerability up to 3600 mg/d regardless of any efficacy achieved at lower dosages.

[220] Pfizer_RGlanzman_0039917
[221] Miller RG, Moore D, Young LA, et al., Placebo-controlled trial of gabapentin in patients with amyotrophic lateral sclerosis, *Neurology,* 1996;47:1383-88
[222] DM_FILE/CI-0945 (KL34298a), Research Report No.: 720-03908

159. The first statement was simply not true. Though not mentioned in the *JAMA* article, Gorson was the first trial to evaluate the efficacy of Neurontin in patients with painful diabetic neuropathy. The second statement is a *non sequitur*: Especially if this had been the first trial examining the efficacy of Neurontin in patients with painful diabetic neuropathy (with plans to make positive results known as widely as possible) the logical design would have been fixed dose—like study 945-224 and the planned but not completed study 945-440. A fixed dose design would have determined not only whether Neurontin was effective for the treatment of diabetic neuropathy, but also the optimal dose.

160. The editorial that accompanied the publication of the Backonja article in *JAMA*[223] suggested two other improvements in study design. Understanding that increased CNS side effects in the group taking Neurontin "could result in unblinding," the editorial suggested an active placebo (like a benzodiazepine) instead of an inert placebo. This would have (at least partially) equalized the CNS side effects experienced by those in the Neurontin and placebo groups, thus preventing unblinding as a consequence of the CNS-related side effects experienced more frequently by those in the active treatment arm. This study design would have increased the likelihood that patient-reported improvements in neuropathic pain truly reflected the beneficial effect of Neurontin and not just the expectation of benefit created by the experience of side effects. (Seven years passed before a study using an active control was published. That study showed that morphine, but not gabapentin, was superior to active control in the treatment of neuropathic pain.[224])

161. Another modification to the study design suggested by the editorial that would have minimized unblinding caused by side effects and would also have provided information about optimal treatment would have been to use an active comparator, so-called head-to-head design:

> Moreover, it would have been desirable to compare the efficacy of gabapentin with the gold standard of amitriptyline or another tricyclic antidepressant.[225]

162. The forced titration design of study 945-210 created potential bias in favor of Neurontin as a result of the increased prevalence of CNS-related adverse events on doses

[223] Low PA, Dotson RM, Editorial: The Treatment of Painful Neuropathy, *J Am Med Assoc,* 1998;280:1863-4
[224] Gilron I, Bailey JM, Dongsheng T, et al., Porphine, Gabapentin, or Their Combination for Neuropathic Pain, *NEJM,* 2005;352:1324-34.
[225] Op. Cit., Low et al

potentially above those necessary to provide symptomatic relief. The methodology used to determine whether this did affect the outcome measures—determining the effect of individual CNS-related adverse events rather than the effect of all such side effects simultaneously—was inadequate. Defendants were aware of this potential design bias as well as the more comprehensive methodology that would have determined whether unblinding that resulted from the forced titration design had caused a substantial impact on the primary outcome measures. Biased design in manufacturer-sponsored clinical trials is not rare—the VIGOR trial described above provides another (becoming classic) example of how the manufacturer can manipulate trial design to make the results more likely to come out in favor of its drug. This in part explains why the odds are 5.3 times greater that manufacturer-sponsored trials will conclude that their own drug is the drug of choice compared to non-commercially sponsored clinical trials of exactly the same drugs.

3. *Study 945-224 ("Reckless")*

163. Study 945-224, also funded and conducted by the Defendants, was a randomized controlled trial designed to:

> evaluate the efficacy, dose-response characteristics, and safety of gabapentin by comparing dosages of 600, 1200 and 2400 mg/day gabapentin with placebo for symptomatic relief of painful diabetic peripheral neuropathy.[226]

164. This study was completed September 7, 1999 and the research report was issued February 7, 2000.[227] The study failed to show that patients taking any dose of Neurontin appreciated significant relief. As stated in Defendants' research report:

> There was no statistically significant difference between any of the gabapentin groups and the placebo group for endpoint mean pain score or at any time throughout the trial…[228]

165. Despite including three times as many patients in the active treatment groups as the Backonja article published in *JAMA* and using fixed dose groups, rather than forced titration dosing, this clinical trial was never published as an independent study. Defendant's e-mails reveal a consistent strategy of preventing these findings, which contradicted the findings of the Backonja study, from becoming available to physicians, decision makers and the public. In an

[226] Pfizer_LeslieTive_0020949
[227] RR 720-04130 (Page 1)
[228] RR 720-04130 (Page 11)

April 20th, 2000 e-mail, Sarah Wensley (Clinical Trials Monitor) stated that Dr. Reckless felt the results of study 224 "should be out in the public domain…"[229] Dr. Beate Roder (the lead Parke-Davis author on 945-224) replied: "Although I would love to publish SOMETHING about 945-224, Donna McVey [a medical director from Parke-Davis UK] made it very clear that we should take care not to publish anything that damages neurontin's marketing success. So I would rather not phone him until we have heard from Marketing what they suggest."[230] In a May 2000 e-mail, Sarah-Jane Bibby, writing about conversations with Dr. Reckless, indicated that "there were no plans at the current time to publish…"[231]

166. Sean Buckland, a Parke-Davis employee, wrote that "on balance we should write the paper up in time. We would need to have 'editorial' control, but would suggest we certainly involve Dr Reckless in the process, asking for his expert comment."[232] In response to the threat of publication, Sarah Jane-Bibby took the opportunity to remind everyone that "PD [Parke-Davis] has ownership of the data, so Dr Reckless can publish his own centre data but that would need PD approval."[233]

167. In September 2000, Michael Rowbotham (Neurontin Team Leader) wrote to Angela Crespo (a senior marketing manager): "the main investigator in the UK (Dr Reckless) is keen to publish but this will have several ramifications. The route we have all agreed to now is that we will publish the study but NOT until we have published the results of NN25 and NN26 [referring to two positive post-herpetic neuralgia studies authored by Rice and Rowbotham]."[234] Later that month, Rowbotham summarized the publication strategy of the Reckless study:

> 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. More importantly it will be more important [sic] to how WE write up the study. We are using a medical agency to put the paper together which we will show to Dr Reckless. We are not allowing him to write it up himself.[235] [Emphasis in original]

[229] PFIZER_TMF_CRF_015313
[230] *Ibid.*
[231] *Ibid.*
[232] *Ibid.*
[233] *Ibid.*
[234] *See* PFIZER_LCASTRO_0002678 (capitals in original)
[235] PFIZER_LESLIETIVE_0020985 (capitals in original)

168. On November 13, 2000 Angela Crespo wrote to Leslie Tive referring to study 945-224, "This is the negative study that we were talking about…As you can imagine, I am not in a hurry to publish it."[236] In January 2001 Dr. Usman Azam, Pain Category Medical Manager for Pfizer-UK, wrote: "Are we still in agreement that 224 should be submitted after acceptance of the above [referencing the two positive PHN studies that had just been rejected from BMJ]…"[237] Leslie Tive responded that "[her] first instinct would be to continue to wait…"[238] Notes from the July 18, 2001 meeting of the Neurontin Publications Subcommittee (PSC), indicate that Medical Actions Communications (MAC), the agency responsible for writing up the Reckless study, agrees that study 224 "…should not be pushed for publication."[239]

169. The manuscript, ostensibly authored by Reckless et al., but actually ghostwritten by MAC, was rejected by *Diabetic Medicine* in May 2002.[240] Reviewers' comments included: "quality of the statistics appears to be poor…conclusions are not justified…the trial would be considered a failure and the paper rewritten accordingly."[241] The ghostwritten study was then submitted to *Diabetologia* and again rejected in November 2002.[242] It is not hard to understand why this positive spin on a negative study would be rejected by a medical journal. Although this manuscript reported that "none of the gabapentin doses was more effective than placebo with regard to the primary outcome," multiple secondary outcome measures were reported as significantly positive. The conclusion of the submitted manuscript, following report of no effect on the primary endpoint stated:

> …statistically significant evidence for improvements in some secondary endpoints demonstrates overall benefit for patients with painful diabetic neuropathy.[243]

170. E-mails from February 2003 show that Pfizer had withdrawn support for a stand-alone publication of the Reckless study.[244] "Unfortunately, given our limited budget for Neurontin this year…the agency will not be able to take the lead in revising the manuscript

[236] PFIZER_LESLIETIVE_0020922
[237] PFIZER_LKNAPP_0053962
[238] *Ibid.*
[239] PFIZER_RGLANZMAN_0044634
[240] PFIZER_LESLIETIVE_0020880
[241] PFIZER_LESLIETIVE_0020881-3
[242] PFIZER_LESLIETIVE_0020840
[243] PFIZER_LESLIETIVE_0020849
[244] By then the review article bundling Reckless's results had been published

again. Dr. Reckless will have to take the lead this time."[245] On February 11, 2003, Dr. Roder sent Dr. Reckless the failed submissions,[246] commenting to Leslie Tive (in a later memo dated on March 31, 2003) that "Dr. Reckless decided he wanted to try and publish on his own (because Pfizer would not provide further financial and editorial support)."[247]

171. By early 2000, there were three double-blinded RCTs comparing the efficacy of gabapentin to placebo for the relief of pain from PDN. Two were negative (Gorson and Reckless) and one purportedly positive (Backonja—albeit with the potential unblinding associated with the forced titration design discussed above). A diligent doctor searching the medical literature for the scientific evidence at the time would have found only the Backonja study, published in *JAMA* and a negative letter to the editor, published in a low-circulation journal. No mention of the Reckless study, the largest of the three, could have been found until 2003 and then only briefly mentioned, with the results "bundled" into a review article (that concluded Neurontin was effective for the treatment of neuropathic pain) rather than published as an independent study. (See discussion of Backonja and Glanzman review article in *Clinical Therapeutics* below). Physicians practicing evidence-based medicine at the time were deprived of most of the scientific evidence concerning the efficacy of Neurontin for the treatment of painful diabetic neuropathy.

4. *Journal supplements*

172. A supplement to the *Clinical Journal of Pain,* titled Mechanisms of Chronic Pain, was published in September 2000.[248] The supplement was supported by an educational grant from Parke-Davis. The articles included in the supplement had been presented at a symposium August 23, 1999. The editor of the supplement, Clifford J. Woolf, M.D., Ph.D., listed affiliations with Massachusetts General Hospital and Harvard Medical School.

173. Contrary to the general orientation of this supplement, the FDA-approved label for Neurontin (updated in 2002) stated "The mechanism by which gabapentin exerts its analgesic action is unknown." For example, one of the articles in the supplement, titled "Chronic Neuropathic Pain: Mechanisms and Treatment" states:

[245] PFIZER_LESLIETIVE_0020835
[246] *Ibid.*
[247] *See* PFIZER_LESLIETIVE_0020834
[248] Pfizer_AFannon_0008126

> Recently, particular attention has been paid to newer antiepileptics, specifically gabapentin, lamotrigine, and topiramate, in the treatment of neuropathic pain…These agents have additional mechanisms of action compared with current antiepileptics, which may account for broader spectrum of efficacy. Gabapentin, a cyclic GABA analogue, has multiple sites of action, some of which may explain its analgesic effects, most notably an increase in GABA potentiation (without interaction with GABA receptors) and binding on a subunit of calcium channels, the alpha-2-delta subunit, common to all calcium channels.[249]

174. An article in the supplement by Attal about the mechanisms and treatment of chronic neuropathic pain included just 2 studies—both positive—about Neurontin, which were the two published in *JAMA*. (Additionally, the Gorson article was cited, but just in support of the position that doses of Neurontin higher than 900 mg/day were needed. The overall negative findings of the study were not presented.) Study 945-224, with three times more patients in active treatment than the study by Backonja et al., was completed 12 months before this supplement was published, yet its results are not included. The Attal article makes unsubstantiated off-label claims of efficacy—using a Defendant-sponsored journal supplement as if it were an arm of marketing:

> Gabapentin is now largely used in clinical practice in various pain conditions because of its favorable side-effect profile and possible broad-spectrum analgesic activity in various neuropathic pain conditions, including central pain.[250]

5. *Neutralizing Negative Studies*

175. Although I have been informed by Plaintiffs counsel that the details of the other neuropathic pain trials will be presented in a separate expert report by Dr. Perry, a brief look at the Morello and Dallacchio studies shows how the Defendants sponsored their own study to offset negative findings from an independent study. Like the Morello study, the Dallocchio study[251] compared the efficacy of Neurontin to amitriptyline for the treatment of painful diabetic neuropathy. The studies differed in one critically important way: instead of being a "gold standard" double-blind RCT like the Morello study, the Dallocchio study was *open-label*

[249] Attal N, Chronic Neuropathic Pain: Mechanisms and Treatment, *Clinical Journal of Pain,* 2000;16:S118-S130
[250] *Ibid.*
[251] Dallocchio C.et al. Gabapentin vs. amitriptyline in painful diabetic neuropathy: an open-label pilot study. *Journal of Pain and Symptom Management* 2000:20:280-5.

(patients and doctors knew which drug was being administered). Despite the fact that the Dallocchio study was published 13 months after the Morello study, it made no mention of the Morello findings or conclusion: that Neurontin "should be reserved as an alternative to patients in whom a less costly agent fails, such as amitriptyline, or for whom tricyclic antidepressants are contraindicated."[252] Dr. Elizabeth Mutisya (a Pfizer medical director) explained Parke-Davis's strategy to neutralize the effect of the Morello study: "When the negative UCSD gabapentin-amitriptyline paper [Morello] was published, Parke-Davis had a two-pronged approach. Attack the flaws in the study, and sponsor another study which ultimately provided more favorable results (the Dallocchio study)."[253] Though there was no apparent scientific benefit to repeating the Morello study in an open-label design, there was potential marketing value.

176. Analogous to the Defendant-sponsored Dallacchio article's lack of mention of the disadvantageous findings and conclusions of the Morello study, the independent study of Neurontin for adjunctive therapy of refractory bipolar disorder by Guille was not cited in subsequent Defendant-sponsored publications on this issue. An abstract presented at the 1999 American Psychiatric Association Annual Meeting reported the results of the Guille study, a double-blind RCT testing the efficacy of Neurontin vs. placebo, performed at the Massachusetts General Hospital Department of Psychiatry. The abstract concluded "This study did not find adjunctive gabapentin to be efficacious treatment for refractory mania…Enthusiastic clinical acceptance of gabapentin as a mood-stabilizing agents [sic] may be unwarranted.[254]

C. Systematic Distortion Of The Scientific Evidence From Clinical Trials Of Migraine Prophylaxis

177. The Mathew study (945-220) was published in *Headache* in 2001.[255] The results of the published study show that Neurontin is significantly superior to placebo in decreasing the frequency of migraine headache:

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[252] Morello, CM, Leckband SG, Stoner CP, et al. Randomized Double-blind Study Comparing the Efficacy of Gabapentin With Amitriptyline on Diabetic Peripheral
Neuropathy Pain, *Arch Intern Med.* 1999;159:1931-1937
[253] PFIZER_RGLANZMAN_0040034
[254] Pfizer_JSu_0022640
[255] Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache,* 2001;41:119-28.

> At the end of the 12-week treatment phase, the median 4-week migraine rate was 2.7 for the gabapentin-treated patients maintained on a stable dose of 2400 mg/day and 3.5 for the placebo-treated patients (*P*=.006), compared with 4.2 and 4.1, respectively, during the baseline period. Additionally, 26 (46.4%) of 56 patients receiving a stable dose of 2400 mg/day gabapentin and 5 (16.1%) of 31 patients receiving placebo showed at least a 50% reduction in the 4-week migraine rate (*P*=.008).

The article in *Headache* concluded:

> Gabapentin is an effective prophylactic agent for patients with migraine. In addition, gabapentin appears generally well tolerated with mild to moderate somnolence and dizziness.

These results were presented 1998 American Pain Society and the 1999 American Association for the Study of Headache.[256]

178. There are, however, several problems with the study design and the way that the results of study 945-220 were presented in the article published in *Headache*. First, a basic study design issue: those patients who met the initial criteria for participation in the study were entered into a 4 week single-blind placebo phase. Because previous studies had shown that 27 to 30% of people with migraine headaches generally respond to placebos, the single-blind placebo phase of the study was specifically designed to identify and remove placebo responders from the study population. Of the 201 patients who met the screening criteria 56 (28%) were not randomized after the 4 week single blind placebo phase of the trial. No other exclusion criteria at this stage of the study were offered except positive response to placebo treatment. Such exclusion limited the generalizability of the results of study 945-220 to people suffering from migraine headaches who do not respond to placebos. Thus, the result of the study would, at best, determine the efficacy of Neurontin in placebo non-responders, but would not be applicable to the actual patient population to which the results were to be applied (like the population that met the initial screening criteria for this study and were entered into the single-blind placebo phase).

179. Second, the design of the study increased the dose of Neurontin to 2400 mg/day for all patients, allowing a return to 1800 mg/day for those unable to tolerate the higher dose. This design is similar to the forced titration design in the Backonja study discussed above. The

[256] Pfizer_JMarino_0002371

frequency of somnolence and dizziness in the study participants was similar to that experienced in the Backonja study. The manuscript for the Mathew article was submitted to *Headache* October 2, 2000, and therefore Defendants were well aware (as described above) of the potential unblinding effect of the increased frequency of CNS-related side effects in those taking Neurontin and the statistical steps that would have determined whether or not the increased frequency of side effects effectively unblinded the trial and confounded the results. But potential unblinding was neither mentioned nor corrected for in the *Headache* article.

180. Third, the "primary efficacy variable" presented in the article published in *Headache* was the migraine headache rate during SP2, or weeks 8-12 of the study, experienced not by those in the intent-to treat population, but by a subset of the ITT population called the "modified intent-to-treat (MITT) population." The MITT population was defined as including:

> any patient who was randomized, took at least one dose of study medication during SP2 [i.e. stabilization period 2, meaning weeks 8-12 of the study], maintained a stable dose of 2400 mg/day during SP2, had baseline migraine headache data, and at least 1 day of migraine headache evaluations during SP2.

181. This MITT population differed materially, however, from the group originally identified in the Defendants' study report issued August 24, 1999. This *post hoc* change in primary analyses led to opposite conclusions in the Defendants' study report and the article published in *Headache*. In the Defendants' study report, the primary efficacy analyses were not conducted on the MITT population, but on a subset of the MITT population: the "efficacy evaluable population." The "Modified Intention-to-Treat Population" was defined in Defendants' study report as presented above from the article in *Headache*.[257] The "efficacy evaluable population" was defined as a further subset of the Modified Intention-to-Treat Population that: met compliance thresholds in taking the study medication, provided complete diary information, had at least 25 days in the single blind placebo phase of the study, and participated in at least 25 of the 28 days of the final 4 weeks of the study (or discontinued due to treatment failure).[258]

182. According to Defendants' research report, "Primary efficacy was measured by the 4-week migraine headache rate at stabilization period 2 (Weeks 8-12) and the change from

[257] RR 995-00074 p. 15
[258] RR 995-00074 p. 16

baseline at stabilization period 2."[259] And the primary analysis "was performed using the efficacy evaluable population."[260] According to Defendants' research report, the larger patient population included in the MITT population "was defined to provide supportive analysis."[261] The primary efficacy outcome results presented in Defendants' research report, dated August 24, 1999 (more than a year before the final manuscript was accepted by *Headache)* could not have been more different from the conclusion published in the *Headache* article:

> **Efficacy:** For efficacy evaluable patients, no statistically significant differences were seen at any study period between the placebo and Neurontin groups with respect to 4-week migraine headache rates of proportion of patients with reduction of 50% or greater in migraine headache rates.[262]

183. To summarize, the article in *Headache* provided scientific evidence in a peer-reviewed journal that Neurontin "is an effective prophylactic agent for patients with migraine." Readers of this article (including the authors of the Cochrane review on migraine prophylaxis and other review articles, as shown below) had no way of knowing that this was not the primary outcome measure identified in Defendants' research report. As reported, according to the pre-specified outcome measure: "In the efficacy evaluable population, no statistically significant differences were seen at any study period between the placebo and Neurontin groups with respect to 4-week migraine headache rates."[263] In other words, this was a negative trial, yet the scientific record, because of the noted manipulations, reflected a positive trial.

184. Finally, besides excluding placebo responders and changing the population upon which the primary outcome measure was calculated, the study design was flawed from the beginning because of its reliance upon the "efficacy evaluable population," which was a subset of the MITT population, which was in turn a subset of the intention-to-treat (ITT) population. Level 1 evidence from RCTs demands that analyses be conducted on the intention-to-treat population as a whole. The purpose of randomizing patients in the gold standard RCT study design is to eliminate to the greatest degree possible any systemic difference between the treatment and control groups. Modification of the ITT population diminishes the likelihood that

[259] RR 995-00074 p. iv
[260] *Ibid.*
[261] *Ibid.*
[262] RR 995-00074 p. v
[263] RR 995-00074 p. vi

significant differences in outcome measures between the study groups were due to actual effect of the active drug. Relying upon any subset of the ITT population allows factors that might systematically skew patient outcomes after randomization to distort the results of the study.[264]

185. The design of Defendants' study 945-217 (completed January 25, 1999 and reported January 20, 2000—note the delay) was similar to 945-220, except that the maximum dose of Neurontin was 1800 vs. 2400 mg/day, respectively. The primary efficacy measure was similar: "4-week migraine headache rate at the stabilization period 2 (Weeks 9-12) and the change from baseline at stabilization period 2 in efficacy evaluable patients."[265] The outcome was also the same:

> For efficacy evaluable patients, no statistically significant differences were seen at any study period between the placebo and Neurontin groups with respect to 4-week migraine headache rates.[266]

This study was completed January 25, 1999. As of the 2001 Neurontin Situation Analysis, the results had not been presented at any meetings, and there were no plans for publication.[267]

186. Defendants' also completed a double-blind RCT of Neurontin for prophylaxis of migraine headache in May 1988, Study CT 879-200 that was reported in June 1990. Like studies 945-217 and 945-220, the first of the RCT studies also found no significant advantage for Neurontin (but was not published):

> There was no statistically significant difference in the adjusted mean reduction in migraine attack frequency between placebo (0.7) and gabapentin (1.4) treatment groups, or in the response ratio…
>
> …these data are not sufficient to permit conclusions regarding efficacy. [268]

187. Not only were the results of studies 879-200 and 945-217 not published, but data from both studies were available in ample time to be included in the Mathew et al. article

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[264] Op. Cit., Ebell
[265] RR 995-00085 p. 4, Pfizer_LCastro_0044833
[266] RR 995-00085 p. 5, Pfizer_LCastro_0044834
[267] Pfizer_JMarino_0002371
[268] RR 4301-00066 pp. ii-iii

published in *Headache* in 2001, yet neither were. Thus, physicians reading the misrepresented results of study 945-220 in a peer-reviewed journal were further misled by the Defendants' withholding of the rest of the scientific evidence in their possession showing that Neurontin was not effective for the prophylaxis of migraine headache.

D. Cochrane Review Articles

188. Cochrane Reviews are important to consider from two different perspectives. First, busy physicians have neither the time nor the resources to exhaustively search the scientific evidence to determine what the weight of evidence suggests is the best treatment for a given condition. Subscription services such as "The Medical Letter" and "Up To Date" provide reviews of published literature. The Cochrane Collaboration is a non-profit organization that provides systematic reviews of healthcare interventions, trusted for their lack of commercial influence and probing for data beyond the published medical literature. These reviews are published quarterly in the Cochrane Library along with updates of past reviews when relevant.[269] Evidence incorporated in Cochrane reviews represents the totality of acceptable quality evidence reasonably available to prescribers and payers, and is presented independent of regulatory authorities' approval or lack of approval for the indications reviewed. For all of these reasons, physicians trust that the conclusions presented in Cochrane reviews present a fair distillation of all the scientific evidence.

189. Cochrane reviews must, however, rely upon manufacturers to provide results of studies that have not been published and details of studies that have been published to verify that the results presented are accurate and consistent with the pre-specified outcome measures identified in manufacturers' study protocols. If there is scientific evidence that is not available to Cochrane reviewers, it is very unlikely that practicing physicians—even if they made the effort to search the medical literature—would have access to this information.

1. *Migraine*

190. In March 2002, Cochrane requested from Pfizer information about the use of Neurontin for prophylaxis of migraine headache.[270] On April 5, 2002 Elizabeth Mutisya suggested sending "a general letter on migraine prophylaxis and the published literature on

[269] http://www.cochrane.org/reviews/clibintro.htm#library Accessed July 21, 2008
[270] Pfizer_RGlanzman_0140657

Neurontin."[271] Importantly, Ms. Mutisya added, "We would not be able to provide them with our databases which is what they ultimately are interested in."[272] Leslie Tive responded, "I don't understand why Cochrane can't do a search to find the literature they want. If they are looking for unpublished data, I would be reluctant to send it."[273] Marino Garcia added "We definitely will not supply any internal data, we all agree on that."[274]

191. The Cochrane Review titled "Anticonvulsant drugs for migraine prophylaxis" was first published in July 2004.[275] Among the 14 placebo-controlled RCTs included in the 2004 Cochrane review were two RCTs that had evaluated the efficacy of gabapentin, Di Trapani 2000 and Mathew 2001. The review recommends gabapentin—but not other anticonvulsant medications, albeit with reservations:

> The evidence derived from trials of gabapentin suggests a beneficial effect in migraine prophylaxis, but this drug needs further evaluation. Although two clinical trials of reasonable size have been reported, the interpretation of both is hampered by some aspects of their method or data analysis. In the meantime, it may be advocated with some reservation that gabapentin may be used for those cases that are difficult to manage with other currently available strategies, since it has a reasonable tolerability and safety profile.

192. Pfizer's strategy of withholding unpublished studies and internal data from Cochrane reviewers was successful. Neither of the Defendants' two negative RCTs is mentioned in the Cochrane review. Furthermore, the fact that study 945-220 was negative for the pre-specified outcome measures remained invisible—it was presented in the Cochrane review as a positive study, as it was originally published in *Headache.* The evidence from clinical trials presented in the Cochrane review of migraine prophylaxis about Neurontin is positive—and differentiates Neurontin from other AEDs. With access to the Defendants' documents, it is clear that the weight of evidence from clinical trials is overwhelmingly negative, yet physicians a) are misled by the Cochrane review because evidence has been withheld and misrepresented, b) don't

[271] Pfizer_RGlanzman_0140656
[272] *Ibid.*
[273] *Ibid.*
[274] Pfizer_RGlanzman_0140655
[275] Chronicle E, Mulleners W, Anticonvulsant drugs for migraine prophylaxis (Review), *The Cochrane Library,* 2005, Issue 4

have access to any more evidence than the Cochrane reviewers could get, and c) cannot be expected to distrust one of their most trustworthy sources of information or engage in independent searches for unknown missing or misrepresented evidence.

2. *Neuropathic pain*

193. The first Cochrane review of anticonvulsant drugs for acute and chronic pain was issued in April 2000.[276] The review was not favorable:

> There is no evidence that anticonvulsants are effective for acute pain. In chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried. While gabapentin is increasingly being used for neuropathic pain the evidence would suggest that it is not superior to carbamazepine.

194. Commenting on the Backonja and Rowbotham articles in *JAMA,* about Neurontin for painful diabetic neuropathy and post-herpetic neuralgia, the review states that there was significant benefit in both studies, but that both "used doses significantly higher than the maximum licensed dose of 2.4 grams." [1.8 grams per day in the U.S.] Although Defendants' report of study 945-224, showing no benefit of Neurontin for painful diabetic neuropathy, was issued on January 20, 2000, the May 23, 2000 update does not contain Defendants' unpublished data.

195. A review of anticonvulsants and antidepressants by Collins et al. (from the Pain Research Group in Oxford) was published in the *Journal of Pain Symptom Management* in December 2000. The review was not favorable to Neurontin, concluding:

> No difference in efficacy was demonstrated between gabapentin…and the older anticonvulsants phenytoin and carbamazepine. This result provides little to recommend a first-line drug choice for neuropathic pain.[277]

[276] Wiffen P, Collins S, McQuay, et al., Anticonvulsant Drugs for Acute and Chronic Pain (Cochrane Review) , *The Cochrane Library,* Issue 1, 2002.
[277] Collins SL, Moore RA, McQuay HJ, Wiffen P, Antidepressants and anticonvulsants for Diabetic Neuropathy and Postherpetic Neuralgia: A Quantitative Systematic Review, *Journal of Pain Symptom Management,* 2000;20:449-58

196. Defendants' consistent strategy of withholding negative information (study 945-224 was not included in the review) and promoting positive information is shown in a "field letter for our reps" drafted in response to the publication of this review:[278]

> - Whilst a welcome addition to the evidence based analysis of clinical studies in neuropathic pain this study does not include data that is soon to be published.
>
> - Whilst for the purposes of a systematic review this study appropriately looked at PHN and PDN alone we have a wealth of data in **ALL** neuropathic pain conditions that is available in the public domain. [279] [Emphasis in original]

197. Just one week after this draft written, Defendants received word that the "soon to be published" articles referenced above had been rejected by the *British Medical Journal.* The reviewer at *BMJ* who recommended rejection was Dr. Henry McQuay[280] (from the Pain Research Group in Oxford). Defendants then undertook a strategy, outlined in an attachment to a January 10, 2001 e-mail, to "aim for publication in *Pain*" and to contact Dr. McQuay:

> We have very good relationships with this individual and we can reassure him that most of his comments will be incorporated [in the rewrite and resubmission]. This action is important as it is highly likely that he will review these papers in his capacity as the world authority on pain and clinical methodology.[281]

198. An e-mail 3 weeks later documented that a plan to perform "an individual patient meta-analysis of the Neurontin randomized controlled trials in neuropathic pain has been agreed and is currently being commissioned."[282] The lead investigator of this meta-analysis was to be Dr. Henry McQuay, who had just rejected two papers about Neurontin from *BMJ* and was expected to be the reviewer for *Pain,* the journal to which the articles were to be resubmitted. Another e-mail of the same day articulates the Defendants' desire to put the scientific cart before the horse:

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[278] Pfizer_CGrogan_0012128
[279] Pfizer_CGrogan_0012131
[280] Pfizer_WSigmund_0000241-2
[281] Pfizer_LeslieTive_0020632
[282] Pfizer_DProbert_0007533

> We also need to get some idea from Henry [McQuay] and Andrew [Moore] about what is a good outcome – and where the results of the analysis will lead us in the future. In other words, we need to start with the end in mind![283]

199. This strategy of commissioning a review from an influential expert evidently was not a novel approach—as described in this e-mail of January 31, 2001:

> What research questions are currently being discussed with McQuay for the commissioned work? Will this work include unpublished study reports that we provide?...We recently went down this path with the Celebrex NICE [National Institute for Clinical Excellence of the U.K.] submission that Matthew Bradley contracted to John Deeks at Oxford and I'm just trying to get a sense of whether we're using the same approach.[284]

200. A March 2, 2001 e-mail reiterates the need "to be very clear about what is a good outcome!" re: the planned meta-analysis with Dr. McQuay. A suggestion is made that the quality of life "angle will give us the most leverage."[285] And a March 20, 2001 e-mail is even more direct about the commissioned meta-analysis: "Obviously we need to be very clear what we want to get out of the analysis and why."[286]

201. A review of neuropathic pain, authored by Dr. McQuay and titled "Neuropathic pain: evidence matters" was published in a supplement of the *European Journal of Pain* in 2002.[287] No financial disclosure or commercial support is presented. The article is primarily a presentation of the review published in 2000 by Collins et al. (including Dr. McQuay). The article does conclude with suggestions for "three important methodological considerations for future trials": (a) neuropathy scales may underestimate pain relief, (b) duration of study is important with shorter studies showing less relief and (c) differential placebo responses rates for different conditions. Like the 2000 review article, Dr. McQuay's review does not include the negative results of the largest study of painful diabetic neuropathy, Defendants' study 945-224.

[283] Pfizer_DProbert_0007543
[284] Pfizer_DProbert_0007548
[285] Pfizer_RGlanzman_0001383
[286] Pfizer_LeslieTive_0035819
[287] McQuay HJ, Neuropathic pain: evidence matters, *European Journal of Pain,* 2002; 6 (Suppl. A): 11-18

202. In 2004, Dr. McQuay was a co-author on a meta-analysis addressing the efficacy and safety of another of the Defendants' drugs, Bextra (valdecoxib), for which "financial support was provided by Pfizer Ltd, UK."[288] This review included 9 studies of Bextra in patients with osteo- and rheumatoid arthritis. At the time of publication, the risk of increased cardiovascular complications, and heart attacks in particular, was a threat to selective COX-2 inhibitor sales (Vioxx, Celebrex and Bextra). The review presented reassuring data about the comparative risk of MI associated with taking Bextra vs. a non-selective anti-inflammatory drug (NSAID):

> Myocardial infarction occurred in 14 patients, in 3/2733 (0.1%) with valdecoxib compared with 11/1846 (0.6%) with NSAID. This was statistically significant, but not robust because of the small number of events.

203. The European Medicines Agency had presented a review of valdecoxib and parecoxib data in 2003.[289] The EMEA review included all nine studies in the Edwards et al. review, plus one more study. Curiously, the Edwards study reports 11 heart attacks among the patients taking NSAIDs in the 9 studies included in the review, while the EMEA report (Table 6) shows that, when one more study is included, the number of MIs is not 11, but 7.[290] As a result, the Edwards study reports that Bextra is significantly less likely to cause heart attacks than non-selective NSAIDs, whereas the EMEA report finds no such diminution in risk. .

204. A Cochrane review of "Gabapentin for acute and chronic pain"[291] and an updated review of "Anticonvulsants for acute and chronic pain" were issued in 2005.[292] Note that two of the three authors of the 2004 Bextra review, funded by Pfizer, were also authors of these Cochrane reviews. In both of the 2005 Cochrane reviews, potential conflicts of interest are listed as "None Known."

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[288] Edwards JE, McQuay HJ, Moore A, Efficacy and safety of valdecoxib for treatment of osteoarthritis and rheumatoid arthritis: systematic review of randomised controlled trials, *Pain,* 2004;111:286-96
[289] Bass R, Abadie E, Lyons D, Medicinal Products Containing COX-2 Selective Inhibitors, Article 31 Referral, EMEA/H/A-31/503 on Valdecoxib and Parecoxib, EMEA, 2003
[290] *Ibid.*
[291] Wiffen P, McQuay H, Edwards JE, Moore RA, Gabapentin for acute and chronic pain (Review), *The Cochrane Library,* 2005, Issue 4
[292] Wiffen P, Collins S, McQuay H, et al., Anticonvulsants for acute and chronic pain (Review), *The Cochrane Library,* 2005, Issue 4

205. The "Gabapentin for acute and chronic pain" review concludes that there is evidence "to show that gabapentin is effective for neuropathic pain" and there is "limited evidence to show that gabapentin is ineffective for acute pain." Four clinical trials of gabapentin for the treatment of diabetic neuropathy are considered. Backonja et al. accounts for about two-thirds (63.2%) of the weight of evidence for this indication. The potential unblinding as a result of the increased frequency of CNS-related side effects experienced as the dose of Neurontin was increased to 3600 mg/day ("forced titration") is not considered. The Gorson study is presented as showing a significant benefit for Neurontin over placebo, even though the primary outcome measure was negative and Gorson's original manuscript concluded: "gabapentin is probably ineffective or is only minimally effective for the treatment of painful diabetic neuropathy at a dosage of 900 mg/day."[293] (See above). The "Reckless" study, 945-224, which had three times as many patients on active treatment as the study by Backonja et al. and used fixed doses, was never published and was not included. The "POPP" study, 945-271, was never published and was not included. The bottom line is that if the authors of the Cochrane review were not aware of studies 945-224 (Reckless) or 945-271 (POPP), and Defendants were not informing physicians of the Level 1 scientific evidence from their own studies, there is no possibility that practicing physicians could be informed about or consider all the evidence in their clinical decision making.

3. *Bipolar Disorder*

206. The inability of the Cochrane Collaboration to conduct a thorough review of gabapentin treatment for bipolar disorder provides another example of the extent to which Defendants' prevented independent analysis of their research data. The protocol for the Cochrane review was first published in April 2001.[294] On October 22, 2001 Dr. Karine Macritchie wrote to Pfizer requesting references pertaining to the use of gabapentin in patients with bipolar disorder (original not available) for the upcoming Cochrane review.

207. Atul Pande responded to this request in an e-mail dated November 5, 2001.[295] The list included the study on which he was the lead author, which failed to show that gabapentin

[293] *See* WLC_FRANKLIN_0000100272
[294] Macritchie KA, Geddes JR, Young A, Gabapentin in the treatment of acute affective episodes in bipolar disorder: efficacy and acceptability (Protocol), *The Cochrane Library* 2008, Issue 3 http://www.thecochranelibrary.com
[295] Pfizer_APande_0005005

is effective as adjunctive treatment of bipolar disorder in outpatients. Defendants' response to Cochrane did not, however, include the other two randomized controlled trials of gabapentin for the treatment of bipolar disorder that had been completed at the time: Frye et al. (2000) showed that lamotrigine, but not gabapentin, is effective as adjunctive therapy for bipolar disorder.[296] Guille failed to show that gabapentin is effective for the adjunctive therapy of refractory mania in bipolar disease.[297]

208. Dr. Macritchie wrote again on July 8, 2003 to Dr. Pande and other experts in the field for information about trials "published or unpublished, complete or ongoing, which would meet our inclusion criteria."[298] Defendants' Study 945-291, begun May 14, 1999 and completed February 26, 2004 was ongoing at the time.[299] On December 15, 2003 Dr. Macritchie requested access to "the original data and the overall results of any published or unpublished studies on gabapentin in bipolar disorder, which have been conducted by your company for the purposes of our [Cochrane] Review."[300] In response, Bruce Parsons, a Pfizer medical director wrote an internal e-mail stating "I would not send unpublished Neurontin data to anyone outside Pfizer."[301] On January 13, 2004, Dr. Macritchie sent the same request to Ellen Dukes of Pfizer.[302] An e-mail dated February 10, 2004 contains Dr. Macritchie's request for unpublished data from the Pande study.[303] Anitra Fielding wrote on February 23, 2004 that numerous e-mails have addressed but none have responded to Cochrane's request for data from Defendants' bipolar studies, the requests for which began in October 2003. [304] Pfizer failed to participate in a scheduled conference call with Dr. Macritchie and Prof. Young about the Cochrane review of gabapentin use for bipolar disorder.[305] On April 14, 2004, Dr. Macritchie wrote to Lloyd Knapp (of Pfizer) referring to their recent phone conversation and reiterating the request for original

[296] Frye MA, Ketter TA, Kimbrell TA et al., A Placebo-Controlled Study of Lamotrigine and Gabapentin Monotherapy in Refractory Mood Disorders, *Journal of Clinical Psychopharmacology*, 2000;20:607-14.
[297] Op. Cit., Guille, C.
[298] Pfizer_APande_0003413
[299] Research Report 945-291
[300] Pfizer_LKnapp_0071020
[301] Pfizer_LKnapp_0071019
[302] Pfizer_EDukes_0000057
[303] Information requested: "Are you able to provide us with the baseline and end-point scores on YMRS, HAM-D and CGIS and the numbers of patients who were in remission by the end of the study?" Pfizer_LKnapp_0112830
[304] Pfizer_LKnapp_0112829
[305] Pfizer_LKnapp_0116131

data from the Pande study.[306] Lloyd Knapp then wrote to Angela Dwyer: "Let's discuss." Dr. Macritchie's final request for unpublished information from the Pande study was made on November 7, 2004.[307] On April 18, 2007 the Cochrane protocol for a review of the use of gabapentin in bipolar disease was withdrawn "due to delay in converting this protocol to a review…"[308] Without Pfizer's cooperation, the Cochrane reviewers were unable to complete their review of the efficacy of gabapentin for bipolar disorder.

E. Other Review Articles

209. Two review articles evaluating the scientific evidence in support of the use of Neurontin for migraine prophylaxis came from two respected non-profit organizations. They include the evidence that was available to researchers who sought to provide a comprehensive review of the available evidence. Certainly no practicing physician could be expected to perform a more comprehensive evaluation of the scientific literature than the authors of these review articles.

1. *Mack, Journal of Managed Care Pharmacy, 2003*

210. An article published in the *Journal of Managed Care Pharmacy* (the journal of the Academy of Managed Care Pharmacy) in 2003 evaluated the available scientific evidence pertaining to off-label use of gabapentin for 10 non-FDA approved indications, including migraine prophylaxis, neuropathic pain and bipolar disease.[309] The article concludes that off-label use of Neurontin should be restricted to the specific indications for which there is "solid research support (e.g., diabetic neuropathy and prophylaxis of frequent migraine headaches)."

211. On what basis does this review conclude that the scientific evidence was solid enough to recommend managed care coverage for prophylaxis of frequent migraine headaches? The review cites two clinical trials: the Mathew et al. article (discussed above) published in *Headache* in 2001, and the Di Trapani article (published in *La Clinica Terepeutica* in 2000).[310] In addition, two other review type articles are cited. One was an article about the cost-

[306] Pfizer_LKnapp_0107849
[307] Pfizer_LKnapp_0104674
[308] Op. Cit., Macritchie et al
[309] Mack A, Examination of the Evidence for Off-Label Use of Gabapentin, *J Man Care Pharm,* 2003;9:559-68
[310] Di Trapani G, Mei D, Marra C, et al., Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study, *La Clinica Terepeutica*, 2000;151:145-8

effectiveness of AEDs for migraine prophylaxis by Adelman et al.[311] that relied solely on the Mathew et al. study published in *Headache* (with the misrepresentations described above), concluding that the cost of preventing one migraine headache with Neurontin is $138 higher than the other two AEDs considered (topiramate and divalproex sodium) and that:

> The use of AEDs makes little clinical or economic sense in the migraine population in which they are currently being studied.

212. The other review cited in the *Journal of Managed Care Pharmacy* article was published in a supplement to *Headache* in 2001,[312] written by Mathew, the lead author of the 2001 article in *Headache* that reported the results of Defendants' study 945-220 as described above. In this review, Mathew stated that the "only double-blind, placebo-controlled study of gabapentin for migraine prevention" was the trial for which he was the lead author. No mention is made of the other two Defendant-sponsored RCTs, both of which had shown—like the Mathew et al. article should have shown—that Neurontin is not effective for migraine prophylaxis. Because the Defendants' two negative trials were not included in Mathew's review, and because the Defendants' third negative trial was misrepresented as positive, Mathew's review article comes to an erroneous conclusion: "The double-blind trials of divalproex, gabapentin, and topiramate demonstrate their effectiveness in migraine prevention." (In the review article, Mathew did not disclose any financial relationship with the Defendants.)

213. With regard to gabapentin for the treatment of neuropathy, the review article cites three positive RCTs: Serpell (2002), Backonja (1998), and Rowbotham (1998). The results of the Serpell study were dominated by improvement in post-herpetic neuralgia (as identified by Defendants' pain experts).[313] The Rowbotham study included post-herpetic neuralgia patients only. Backonja is the only RCT included in the review that examined the effect of gabapentin on painful diabetic neuropathy (see discussion above for problems related to the forced titration methodology). Based on the positive results from this one study, the review in the *Journal of Managed Care Pharmacy* concluded that diabetic neuropathy is one of the two off-label indications for which there is "solid research support." The author did not report the results of

[311] Adelman JU, Adelman LC, Von Seggern R, Cost-Effectiveness of Antiepileptic Drugs in Migraine Prophylaxis, *Headache,* 2002;42:978-983
[312] Mathew NT, Antiepileptic /drugs in Migraine Prevention, *Headache,* 2001; 41 Suppl 1:S18-24.
[313] Pfizer_JMarino_0000089

two of Defendants' unpublished RCTs that showed no benefit for diabetic neuropathy (Gorson and Reckless). Thus, relying upon the best available scientific evidence the author concluded that gabapentin is effective for treatment of diabetic neuropathy, without being aware of Defendants' two other studies that had reached the opposite conclusion.

214. Finally, showing the importance of making scientific evidence available by publication in the medical literature, the review article cited two published RCTs that failed to find gabapentin efficacious in the treatment of bipolar disorder. To be fair, one of these published studies was done by Defendants.[314]

215. The conclusion presented in the *Journal of Managed Care Pharmacy* review—that there is solid research support for the use of gabapentin in painful diabetic neuropathy and migraine prophylaxis—shows how Defendants' control of most of the scientific evidence biased the "knowledge" available to clinicians and medical decision makers. There are two important conclusions to be drawn. First, the author sought the best available scientific evidence evaluating the efficacy of Neurontin for migraine prophylaxis and diabetic neuropathy, but did not have access to the results of the Defendants' unpublished studies, nor could she find the results of Gorson's study (published only as a letter, see above). And without access to the Defendants' research reports, the author was not able to determine whether published conclusions were consistent with prespecified research protocols and outcome measures. If the author of this review article couldn't find unpublished scientific evidence or the Defendants' research report showing that the pre-specified outcome measure in study 945-220 was changed in the published article, there is no way that practicing physicians and decision makers could reasonably be expected to function as learned intermediaries, i.e. to integrate these findings into their determinations of optimal treatment.

216. Second, this review article shows that positive information available to physicians was dominated by Defendants' misrepresented study 945-220. The only other positive study, Di Trapani et al., was published in an Italian language journal, though the abstract is available on PubMed.

[314] Pande AC, Crockatt JG, Janney CA, et al., Gabapentin in Bipolar Disorder: a Placebo-Controlled Trial of Adjunctive Therapy, *Bipolar Disorders,* 2000;2:249-255.

2. *Pappagallo, Clinical Therapeutics, 2003*

217. Another review article, published in *Clinical Therapeutics in 2003,* was titled "Newer Antiepileptic Drugs: Possible Uses in the Treatment of Neuropathic Pain and Migraine."[315] A single study, 945-220, Mathew et al. was cited as evidence of the efficacy of Neurontin in migraine prophylaxis. Without access to Defendants' research report, the author of this review article failed to inform doctors that the primary outcome measure had been misrepresented in the *Headache* article and that Neurontin was actually ineffective as determined by the pre-specified outcome measures. This sort of propagation of misinformation demonstrates how misrepresentation of original research has a "ripple effect," reappearing in the sources of medical information trusted by physicians.

3. *Backonja and Glanzman, Clinical Therapeutics, 2003*

218. A review article titled "Gabapentin Dosing for Neuropathic Pain: Evidence from Randomized, Placebo-Controlled Clinical Trials" co-authored by Miroslav Backonja and Pfizer employee Robert Glanzman was published in *Clinical Therapeutics* in January 2003.[316] This review stated the "manufacturer provided additional unpublished data [the Reckless data]." E-mails from the Medical Director of Medical Action Communications, the company that assisted Pfizer with the preparation of the manuscript for this review, to Pfizer show the evolution of this review. On August 21, 2002 David Cooper wrote to Pfizer expressing concern about "deciding how to justify only reviewing 4 of the 6 randomized studies…" (Actually there were 7 randomized studies: the 3 unpublished studies were Reckless, 945-224, POPP, 945-271 and Gorson.) Dr. Cooper raised concern that if data from one or more unpublished studies were included there would have to be an explanation for how Dr. Backonja, not a Pfizer employee, had access to Pfizer's unpublished data.[317] An e-mail dated August 28, 2002 provided the solution to this dilemma. After the journal in which the article was to be published granted an extension of the deadline to submit changes to October 1, 2002, changes to the article were made

[315] Pappagallo Marco, Newer Antiepileptic Drugs: Possible Uses in the Treatment of Neuropathic Pain and Migraine, *Clinical Therapeutics,* 2003,;25:2506-38
[316] Backonja M., Glanzman R. Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials. *Clinical Therapeutics* 2003; **25**(1): 81-104. *See also* PFIZER_LESLIETIVE_0038508
[317] MAC_004074

that included adding in data from the Reckless study and adding Robert Glanzman as a Pfizer-employed author to explain how the data was obtained.[318]

219. As will be shown below, the issue of explaining access to unpublished data was a charade. The article was conceived, written, distributed, publicized and used in continuing education by Defendants. The façade that the article was based on "disinterested" and independent research was maintained to maximize the effectiveness of the delivery of the key messages.

220. The fact that there was no significant difference between the gabapentin and placebo group in the primary endpoint of the Reckless study (the largest of the studies addressed other than post-herpetic neuralgia included in the review) is not mentioned until the ninth page. Even then, the positive findings in the secondary outcome measures were accentuated in a way that was criticized by reviewers of the twice rejected manuscript (see above). The review article failed to include the results from the Gorson study, which had been known to the Defendants four years earlier. The article concluded:

> At doses of 1800 to 3600 mg/d, gabapentin was effective and well tolerated in the treatment of adults with neuropathic pain.[319]

221. The authors stated that the review included studies with "100 per treatment arm," but meant 100 total patients in all treatment arms, given that the Backonja study had a total 165 patients. (Defendants' research report states, "A total of 165 patients were randomized to treatment: 84 received gabapentin and 81 received placebo." Analyses were performed on the ITT population "defined as all randomized patient who received at least one dose of study medication.") The threshold requiring at least 100 patients randomized excluded the Gorson trial, but should not have excluded the POPP trial, the report for which stated that 120 patients had been randomized.

222. The manuscript for the Backonja Glanzman review was accepted for publication on October 14, 2002, presenting the results of 5 trials that had been completed. At Pfizer's pain consultants' meeting on September 6, 2001 the results of studies 945-224 and 945-271 had both

[318] MAC_0003929

[319] Backonja M., Glanzman R. Gabapentin dosing for neuropathic pain: Evidence from randomized, placebo-controlled clinical trials. *Clinical Therapeutics* 2003; **25**(1): 81-104. *See also* PFIZER_LESLIETIVE_0038508

been presented. Based on both of these studies being negative and the positive findings in study 945-306 representing mostly improvement in people with post-herpetic neuralgia:

> The Experts did not feel that this indication [peripheral neuropathic pain] could be supported by the Neurontin package given the negative DPN study and the contrary new data summarized in the following.

223. The Backonja/Glanzman review recommends that when initiating treatment for neuropathic pain (which, except for post-herpetic neuralgia, is off-label) a target of reaching a Neurontin dose of 1800 mg per day after 2 weeks

> appears to be a reasonable choice for converting from the somewhat artificial study goal of ≥ 50% response to the ideal clinical practice goal of as close to 100% improvement (freedom from pain) as possible.

224. Though switching the goal to 100% pain relief in the clinical (rather than the research) context makes sense on the face of it, the evidence from the clinical trials showed that this could not be achieved by increasing the dose. Commenting on study 945-224, Pfizer's own pain experts had concluded at their meeting in September 2001 that:

> 2400 mg/day appearing worse than 120[0] mg/day in this dose-response study (600, 1200, 2400 mg/day) was viewed as particularly problematic.[320] [Emphasis in original]

225. The Backonja and Rowbotham studies published in *JAMA*, and the Serpell study all failed to show a greater improvement compared to placebo at higher doses than at doses of half or less of the 3600 mg/day recommended in this article. Thus, there is scant evidence to support and much evidence to refute the conclusions and recommendations made in the review article:

> In many patients, further dose escalation of gabapentin up to 3600 mg/day may be necessary to reach an individualized effect dose…

And

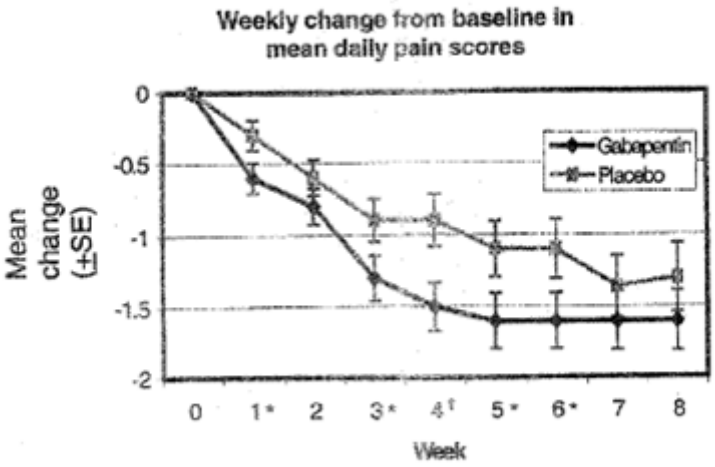
> Thus, doses between 1800 and 3600 mg/day have been found to be effective in achieving ≥ improvement in pain scores…

[320] Pfizer_Lknapp_0024969

226. The following is one example of the review's cherry-picking of data to support the conclusion that higher doses of Neurontin are more effective. The review article cites results from the Serpell article that:

> noted a markedly greater improvement when doses of 1800 mg/d were achieved after 3 weeks at 900 mg/d. Thus, in most patients, the maximal improvement with concomitant tolerability may be achieved at a gabapentin dose of 1800 mg/d. However, dose > 1800 mg/d have been effective and well tolerated in other patients.

227. But the data presented in the Serpell article tell a different story, and show that the review article picked two data points *post hoc* to provide evidence for the claim of a dose response relationship:



The above graph shows that significant improvement occurred after the first week of therapy (at 900 mg/d), that the difference in pain scores between gabapentin and placebo were significant on weeks 1 (900 mg/day), 3 and 4 (1800 mg/d), 4 and 5 (2400 mg/d) but not weeks 7 and 8 (2400 mg/d). Visually, the separation between gabapentin and placebo is as great in week 1 on 900 mg/day as it was in weeks 7 and 8 on 2400 mg/day.

228. The Rice study showed no greater improvement with 2400 than 1800 mg/d. Reckless showed better improvement with 1200 than 2400 mg/day. Serpell (above), Backonja and Rowbotham show no better response compared to placebo at higher doses than at lower doses. (The flaw in the Backonja and Glanzman review article is that in all studies, the placebo arm continues to improve, and therefore the treatment arm would be expected to continue to improve–with or without dosage increases.)

229. The one thing that did increase with increasing doses was side effects. In the Serpell study "All reported cases of dizziness and 91% of cases of somnolence occurred during the titration phase." With between 40 and 50% of the patients taking Neurontin in these studies experiencing dizziness or somnolence, the issue of effective unblinding must be considered as a possible confounder to the subjective assessment of improvement in pain.

230. The review article states that combining the results of studies 945-210, 945-224, and 945-306 shows that patients taking ≥ 1800mg/d appreciated significantly more relief than those taking placebo, whereas this was not true for doses < 1800 mg/d. Yet when the time/dose response curves are examined for each of those trials, the separation of gabapentin from placebo is no greater at higher than at lower doses. The effect of unblinding due to increased incidence of CNS-related side effects in the increasing dose studies 945-210 and 945-306 could well explain some of this *post hoc* claim that doses at or above 1800 mg/d are more effective for painful diabetic neuropathy

231. After re-iterating that the studies reviewed show that a dose of 3600mg/d can be used when required and tolerated, the review article misrepresents the FDA's approved dosage:

> This recommendation is consistent with the 1800 to 3600 mg/d range of gabapentin approved by the FDA for the treatment of PHN.

In fact, the FDA-approved product label states clearly that no benefit is shown for PHN in doses above 1800 mg/d:

> In clinical studies, efficacy was demonstrated over a range of doses from 1800 mg/day to 3600 mg/day with comparable effects across the dose range. Additional benefit of using doses greater than 1800 mg/day was not demonstrated.[321]

232. The final conclusion of the Backonja Glanzman review article directly contradicts the FDA-approved package insert for the single cause of neuropathic pain that is an FDA-approved indication. The article states that once the dose of gabapentin has been titrated up to 1800 mg/d

> gabapentin can be titrated up to 3600 mg/d as required over the following weeks to achieve a maximal response with good tolerability.

[321] http://www.fda.gov/cder/foi/label/2005/20235s029,20882s015,21129s016lbl.pdf accessed July 27, 2008

233. Defendants' documents show that this review article was not the work of researchers systematically evaluating the scientific evidence for the purpose of bringing the most accurate and balanced information to practicing physicians. Key messages were developed before the author was involved.[322] Among those key messages were:

- Gabapentin is an anticonvulsant that has proven effective in the treatment of neuropathic pain [Notwithstanding Defendants' own consultants' conclusions to the contrary.[323]]
- Gabapentin doses up to 3600 mg/d have been proven well tolerated and effective in clinical studies. [This is in direct violation of the approved dosage range on the package insert.]
- Based on these findings, it is recommended at [sic], after a 3-day titration to 900 mg/d, additional titration is performed to 1800 mg/d. Doses up to 3600 mg/d may be necessary in some patients, depending on tolerability and efficacy. [These are the recommendations that were included in the final article.]

234. A Pfizer e-mail dated January 16, 2003 was titled "Neurontin: NeP Dosing Manuscript Published; Public Relations Materials attached. Importance: High" The promotional messages identified are commercially advantageous: dose should be increased to 1800 mg/day within two weeks; 600 and 800 mg tablets should be used to simplify dosing escalation; and reinforcement of the "efficacy message of gabapentin in DPN, PHN, and in treating neuropathic pain of many causes with onset of pain relief within 1-2 weeks."[324]

235. This same e-mail indentified the promotional use of this review article:

> Because this is a key publication for NEURONTIN, information from this study should be used in all neuropathic pain initiatives subject to your local regulations.

Such initiatives were to include promotional detail aids, speakers programs, regional promotional and scientific meetings, and public relations programs. [325]

236. In sum, the key messages for the Backonja/Glanzman review article about dosing for neuropathic pain were developed before either author was "on board." The purpose of the article was commercial not scientific. The article presented a biased view of the science in order

[322] Pfizer_LKnapp_0023646
[323] Pfizer_JMarino_0000088
[324] Pfizer_LAlphs_0013850
[325] Pfizer_LAlphs_0013850

to convince readers of the efficacy of Neurontin for neuropathic pain—a conclusion that Defendants' own consultants and the FDA had recently rebuked. The article also presented a biased view of the science to justify recommendations for higher than FDA-approved doses. And finally, the plan to capitalize on the commercial opportunity created by the publication of this review is clearly articulated in Defendants' e-mails.

237. As late as 2007, an independent review of the effects of treatments for painful diabetic neuropathy published in the *BMJ* included only the positive Backonja study, not the negative and unpublished Gorson and Reckless studies.[326] Even so, the article concluded that tricyclic antidepressants, traditional anticonvulsants (sodium valproate and carbamazepine) and opioids provide better pain relief than "newer generation anticonvulsants," meaning gabapentin and pregabalin. Specifically, the odds ratio for achieving greater than 50% pain relief was greater for the older anticonvulsants than for gabapentin and pregabalin. In terms of side effects that were significant enough to cause withdrawal from the study, gabapentin and pregabalin had the highest rate, with tricyclic antidepressants next; older anticonvulsants had the lowest rate of withdrawals (these differences are not statistically significant). This review also shows, contrary to the claims made in the Formulary Dossier (see below), that Neurontin does not have an advantage over tricyclic antidepressants in causing a lower rate of side effects. Thus, even without access to data from the two studies that were negative, this (apparently) unbiased review provides a very different view of optimal treatment for diabetic neuropathy than the Pfizer-generated review by Backonja and Glanzman.

F. Manufacturer-Sponsored CME / Academic Meetings

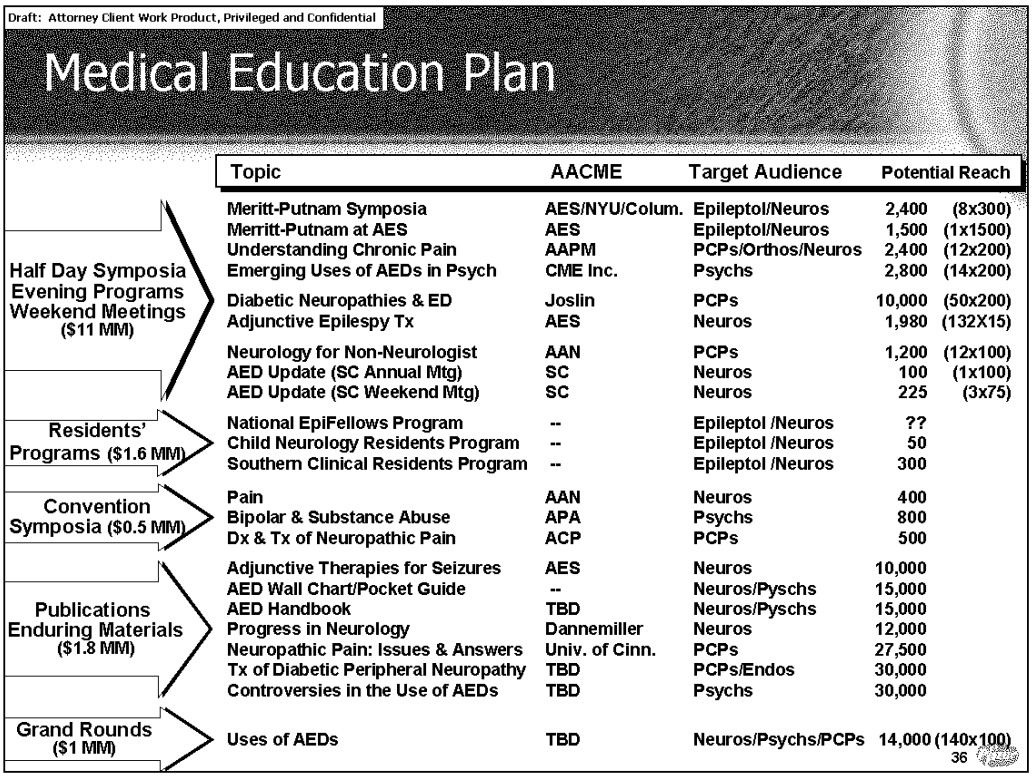
238. In addition to original scientific evidence and systematic reviews, continuing medical education is one of the, if not the, most important source of information about evolving therapies for practicing physicians. Most states require that doctors participate in 50 hours of accredited CME each year to maintain their medical license. But more than the requirement, physicians are busy and want to learn as efficiently as possible about new therapies that will allow them to provide the best possible care to their patients. Physicians are taught during their

[326] Wong M, Chung JW, Wong, Effects of treatments for symptoms of painful diabetic neuropathy: systematic review, *British Medical Journal,* 2007; 335: 87-96.

many years of training to trust and learn from the hierarchy of medical authority. Continuing medical education programs generally are presented by such trusted authorities or experts with academic credentials. When talking to a drug rep or reading marketing material, physicians are, at least, alerted to the fact that commercial bias may be coloring the information. (See earlier discussion on Drug Representatives). When physicians attend CME activities they are in a receptive mode, poised to learn new material from trusted authorities. The last thing most physicians want to do (or should have to do) after attending a CME activity is to spend hours trying to verify whether the information that was presented by the expert was an accurate and balanced review of the best available scientific evidence. For all these reasons, the content of medical education is not expected to be driven by commercial concerns, especially when trusted authorities provide reviews of data that lead to clinical recommendations. But, as shown below, this is exactly what the Defendants did in the medical education that they provided for what was, in truth, scientifically unsubstantiated off-label use of Neurontin for pain, bipolar disorder and migraine headache and in doses higher than those that are FDA-approved.

239. In 2000, Pfizer offered a total of 764 Medical Education programs about Neurontin that were attended by 37,600 physicians. 85% of these events were about pain (never an FDA-approved indication, outside of PHN after 2002) and 75% of the attendees went to the programs on pain.[327] The Medical Education Plan outlined in Pfizer's 2001 Operating Plan for Neurontin, dated October 11, 2000, shows the overwhelming predominance of topics that are for non-FDA approved indications. The "potential reach" for events advocating probable off-label use is approximately 139,000 compared to 17,000 for probably on-label use (with 12,000 unclear).[328]

[327] Pfizer_RGlanzman_0000727
[328] Pfizer_RGlanzman_0000685



240. In 2000, Pfizer spent $38 million on Medical Education about Neurontin and budgeted $28.3 million for Medical Education in 2001.[329] According to the 2001 U.S. Operating Plan for Neurontin, the majority of educational activities were aimed at primary care doctors and psychiatrists.[330]

241. A window into the core purpose of Defendant-funded CME is provided by a "situation analysis" written in response to less positive than intended presentation about the off-label use of Neurontin for painful diabetic neuropathy.[331] Proworx had been hired by Defendants to present an "ADA Satellite Symposium." Proworx contacted Defendants for recommendations about appropriate speakers at this symposium. Based on one of the speaker's proposed abstract, Proworx determined that "she was clearly not planning on presenting what had originally been agreed upon" and considered the options to "counteract a possible 'negative' presentation." The approach agreed upon was to present pre-written questions at the Q &A session that would "lead Dr. Bril to address some of the positive aspect of anticonvulsants and of

[329] Pfizer_Rglanzman_0000699
[330] Pfizer_RGlanzman_0000685
[331] WLC_CBU_131223

Neurontin." Reportedly, this approach was successful. The following comments from the situation analysis demonstrate Proworx' commitment to ensuring that a positive message is delivered about the sponsor's product at future CME events:

> Proworx must take responsibility for not following up with a more in depth investigation of those physicians suggested by the research team in Ann Arbor.
>
> In other situations, such as the APA [American Psychiatric Association] Advisory Board meeting, it is Proworx policy to complete a literature search to determine who authors favorable on the topics outlined…
>
> In summary, we would like to take this opportunity to assure you that additional guidelines have been set to ensure that this type of situation does not occur again. There will be in depth research into all selected faculty members, regardless of whom the recommendations come from. We look forward to working with you in the future and turning this unfortunate situation into a positive one.

242. The ADA satellite symposium was then turned into a written CME monograph, dated December 1997. The cover letter states that the monograph provides an "overview of painful syndromes in diabetes and three case studies which detail treatment options and the use of anticonvulsants in the treatment of diabetic neuropathy."[332] Readers are informed that the program "is accredited by Medical Education Resources Inc (MER)," but nowhere is the reader informed that Parke-Davis funded this CME activity. The results of the Backonja study were presented in this CME monograph—a full year before they were published in the *JAMA* and before the research report was issued (contrast this with the delay in communicating the negative results of the much larger study 945-224). The Gorson study, completed no later than August 1997, had shown no benefit of Neurontin for painful diabetic neuropathy but was not included in this monograph.

243. In December 1999 The Institute of Continuing Healthcare Education requested a "grant" of $157,000 from Parke-Davis in order to update the current lecture curriculum on the use of anticonvulsants in psychiatry, train faculty presenters for future continuing medical

[332] WLC_FRANKLIN_0000195502

education activities and create approximately 60 slides and lecture notes to be used by faculty members.[333]

244. A memo from Intramed provides insight into the funding of Neurontin CME activities. The memo suggests that a grant request for $1,518,000 be sent to solicit funds for a series of CME programs to be held in multiple U.S. cities. The programs were to include lectures on the treatment of low back pain, migraine, diabetic and other painful neuropathies, and the treatment of neuropsychiatric comorbidities.[334]

245. A letter from Marilyn Abel, Manager of CME Programs for IntraMed to Ruth Tiernan of the American Academy of Pain Medicine dated August 8, 2000 explained that "IntraMed is the intermediary between the CME provider [AAPM in this case] and the pharmaceutical company [Pfizer]."[335] The letter instructs the AAPM: "If the Academy wishes to proceed, the next step in the process would be that you would need to submit a formal grant request to Pfizer, Inc." The letter went on to offer assistance in writing this letter. The proposal was for half-day CME programs on treating intractable pain: lower back pain, migraine, and diabetic and other neuropathies–all off-label indications for Neurontin—to be presented in 22 U.S. cities.

246. Another memo, dated November 28, 2000, reported that IntraMed suggested to the American Academy of Pain Medicine that it apply to Pfizer for a grant to sponsor half day CME programs about the treatment of chronic pain (including low back, migraine and neuropathic pain—all off-label indications), targeted toward primary care physicians. The grant was approved by Pfizer.[336]

247. Of the 37,600 physicians who attended medical education programs sponsored by the Defendants in 2000, only 20% went to programs about epilepsy. Three quarters of attendees went to programs about the off-label indication of pain treatment, and 4% attended programs about treatment of psychiatric problems.[337] Pfizer identified the following opportunities to

[333] WLC_CBU_028648
[334] MDL_VENDORS_101127
[335] MDL_VENDORS_068601
[336] MDL_VENDORS_068595
[337] Pfizer_RGlanzman_0000727

"meet customer education demand": industry supported symposia, publications support in journals, CME accredited medical education programs, grand rounds and medical grants.[338]

1. *CME for neuropathic pain*

248. In 1998 the Dannemiller Memorial Education Foundation was awarded a CME grant by Defendants to present CME symposia, a published article, and an internet site to provide continuing education to physicians about the treatment of neuropathic pain. Other CME activities included a full day seminar at the American Academy of Pain Medicine 1998 review course and a 16 page supplement in *Neurology Reviews* that would reach 10,000 neurologists and 3500 members of the American Pain Society.[339]

249. The 2001 US operating plan indicated Defendants' intention to expand off-label and unsubstantiated use of Neurontin through "education":

Continuously present neuropathic pain data at key conferences.[340]

As identified in the 2000-2001 Neurontin Situation Analysis (dated June 28, 2000), manufacturer-sponsored CME activities were employed to expand off-label use of Neurontin for pain. Multiple "Pain CME" events are described therein, attended by 17,910 physicians. In addition, attendance was not reported at the following additional CME Pain activities: 75 Grand Rounds, 16 half day CME programs for PCPs and symposia at the congresses of the American Academy of Neurology, the American Pain Society, the American Geriatric Society, the American Society of Addiction Medicine and the American Physician Assistants Association.[341]

250. The 2000-2001 Neurontin Situation Analysis also identified the publication of "Major CME Pain" materials that were sent out to 77,500 physicians plus all US neurologists. In addition five monographs were produced, the total distribution of which is not reported.[342]

251. The Neurontin Situation Analysis: 2000-2001 included the following recommendation to increase off-label prescribing for neuropathic pain:

[338] Pfizer_RGlanzman_0000742
[339] Pfizer_JMarino_0002508-9
[340] Pfizer_RGlanzman_0000666731
[341] Pfizer_JMarino_0002375
[342] Pfizer_JMarino_00023754

> Among PCPs, Neurontin is becoming more widely known and thus more popular as a first line agent…Sponsorship of medical education initiatives in neuropathic pain for PCPs will continue to grow Neurontin's use in this area.[343]

252. One example of these CME events was titled "New Directions in the Understanding & Treatment of Chronic Pain," presented in Coral Gables, FL on June 2, 2001. Included among the notes for this event was an article by Ahmad Beydoun titled "Clinical Success Factors in Managing Neuropathic Pain."[344] Gabapentin is listed among the pharmacotherapy options for the treatment of neuropathic pain, with the Backonja and Rowbotham articles published in *JAMA* in 1998 introduced as "two recent large clinical trials."[345] Defendants' study 945-224 had been completed in September 1999 and the report issued February 7, 2000. The studies published in *JAMA* had a total of 197 patients on active treatment with Neurontin, whereas Study 945-224 alone had 248 patients on active treatment with Neurontin in fixed dose groups that were far less subject to unblinding problem as discussed previously. Yet the results of 945-224 were neither shared with participants of this CME event nor with practicing physicians as Defendants purposely stalled publication of this negative study.

253. Strategies to "grow NeP market with Neurontin" identified in the 2003 Medical Operating Plan include the education of physicians on the diagnosis and treatment of neuropathic pain. This strategy would be accomplished by training speakers on neuropathic pain, creating regional advisory boards, presenting at an American Pain Society Symposium, executing a publication strategy (see above publications),[346] field force training,[347] increasing average daily dose[348] and creating a medical economic analysis for patients with neuropathic pain [see National Business Coalition on Health Publication] for this off-label use.[349]

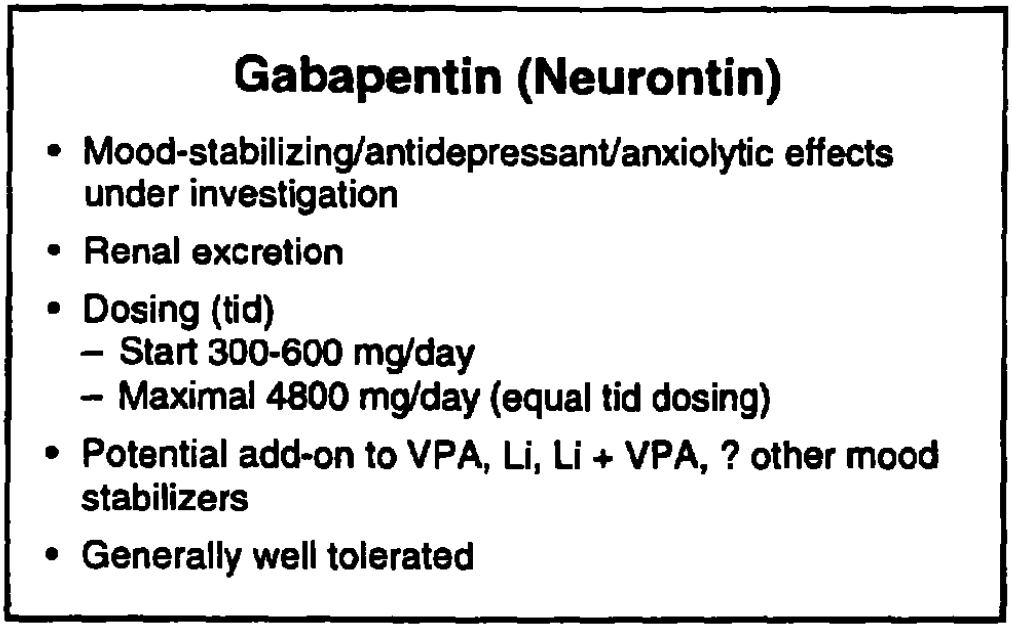
2. *CME for bipolar disorder*

254. "Educational" programs sponsored by Parke-Davis informing doctors of the efficacy of gabapentin for the off-label treatment of patients with bipolar disorder are presented

[343] Pfizer_JMarino_0002367
[344] MDL_Vendors_094799
[345] MDL_Vendors_094821
[346] Pfizer_RGlanzman_0148328
[347] Pfizer_RGlanzman_0148329
[348] Pfizer_RGlanzman_0148330
[349] Pfizer_RGlanzman_0148331

in the following paragraphs. The absence of Level 1 evidence demonstrating the efficacy of gabapentin for the treatment of bipolar, despite several double-blind RCTs, has already been discussed.

255. A seminar titled "New Frontiers in Social Phobia and Bipolar Disorders, Supported in part by an *unrestricted* educational grant from Parke-Davis" was presented at the 10th Annual U.S. Psychiatric & Mental Health Congress in Orlando FL on November 15, 1997. The symposium was advertised as being of benefit to "psychiatrists, general practitioners, family doctors, neurologists, and clinicians."[350] The lecture titled "New Options for Bipolar Disorders" was presented by John Zajecka, M.D. Assistant Professor of Psychiatry, Rush-Presbyterian-St. Luke's Medical Center. The lecturer identified Neurontin as a "Treatment for Bipolar Disorder" without informing the audience that it had not been approved by the FDA for this indication, nor in doses above 1800 mg/day.[351] The use of gabapentin for bipolar disorder is presented in the following slide from this CME seminar:[352]



256. Note in the above slide:

-Lack of FDA approval for bipolar disorder is not included.

[350] CME 0481
[351] WLC_FRANKLIN_0000080355
[352] WLC_FRANKLIN_0000080364

-Efficacy is indicated as "under investigation" without informing the audience that a double-blind randomized controlled trial had already been completed that showed Neurontin was not effective in the treatment of bipolar disorder. Parke-Davis's own study, completed July 1997 had shown that Neurontin was significantly worse than placebo as "add-on" therapy for bipolar disorder. [353]

-Doses up to 4800 mg/day are recommended, though the FDA had never approved doses greater than 1800 mg/day for any indication.

-Neurontin is presented as "generally well tolerated," but Parke-Davis's own study of Neurontin for bipolar disorder showed that of those taking Neurontin 24.1% developed somnolence (versus 11.9% for placebo) and 19% developed dizziness (versus 5.1% for placebo).[354]

257. In the five weeks between March 16 and April 8, 1998, Parke-Davis sponsored 50 "CME Psychiatry Dinners" in expensive restaurants around the country.[355] All of the lecturers held prestigious academic positions.[356] During this time period, Parke-Davis also held 16 hour and a half Psychiatry teleconferences.[357] The lectures appear to have shared a common set of slides,[358] titled "Closing the Psychiatry-Neurology Divide: Emerging Uses of Anticonvulsants." Bipolar disorder was said to be responsive to gabapentin,[359] although Parke-Davis's own study (completed July, 1997) had shown this not only not to be true, but had actually shown that placebo is significantly more effective as adjunctive therapy for bipolar disease than is Neurontin. Impressive, although completely unproven, pharmacological mechanisms are presented by which Neurontin might be beneficial. After listing partial seizures as the indication for Neurontin, the slides then present additional uses including: acute mania, episodic dyscontrol, neuropathic pain, radiation myelopathy, migraine, periodic leg movements, and mood changes in epilepsy.[360] The next two slides are then titled "Gabapentin: Indications Summary"[361] and include bipolar disorder (without reporting Parke-Davis's negative study that

[353] Pande AC, Crockatt JG, Janney CA, et al., Gabapentin in Bipolar Disorder: a Placebo-Controlled Trial of Adjunctive Therapy, *Bipolar Disorders,* 2000;2:249-255.
[354] Pande AC, Crockatt JG, Janney CA, et al., Gabapentin in Bipolar Disorder: a Placebo-Controlled Trial of Adjunctive Therapy, Bipolar Disorders, 2000;2:249-255.
[355] WLC_CBU_037638-40
[356] WLC_CBU_037642-47
[357] WLC_CBU_037641
[358] WLC_CBU_037642-74
[359] WLC_CBU_037650
[360] WLC_CBU_037658-59
[361] WLC_CBU_037659

had been completed in July of 1997[362]) and neuropathic pain (both non-FDA approved indications).

258. In May 1998, MBL Communications published a teaching monograph titled "Current Treatments in Bipolar Disorder" funded by an unrestricted educational grant from Parke-Davis.[363] This supplement was listed in the Quarterly Brand Review for Neurontin dated 4/98.[364] The abstract states:

> The US Food and Drug Administration has extended the use of anticonvulsants beyond the treatment of epilepsy, to include wide-reaching neuropsychiatric illnesses such as mania, migraine, panic disorder, and trigeminal neuralgia…Depakote and Tegretol have been joined by Neurontin and Lamictal as agents shown to be useful in the treatment of bipolar, and possibly unipolar depression.
>
> Recently, both clinical and research attention has focused specifically on the use of Neurontin and Lamictal as alternatives to standard agents for the treatment of mood and anxiety disorders.

The implication here, through clever wording, is that Neurontin has been FDA-approved.

259. The content was created by Parke-Davis and the existence of negative studies was not disclosed in this monograph. At the conclusion of this monograph, off-label prescribing of Neurontin is actively encouraged:

> One reason I discuss these tolerability aspects of antiepileptic drugs, in light of the evidence for their beneficial effects on bipolar disorder, is any physician can elect to try a medication if it's been established as safe by the FDA for another indications, if they have reason to do so.[365]

To be clear, the best "evidence" (Defendants' own 945-209 study, completed July 1997) was neither presented nor available to prescribers.

260. Within a 10 week period from July 11 to September 27, 1998, seminars titled "New Frontiers in Social Phobia and Bipolar Disorders," supported by Parke-Davis, were held in 21 American cities. The brochure that was sent out for these half-day seminars, presumably to a

[362] DM_FILE/CI-0945 (GM03599a) RR 720-04174 (Page 1)
[363] WLC_CBU_012274 to 81
[364] Pfizer_JMarino_0002515
[365] WLC_CBU_012278

large number of physicians, was itself misleading when considered in the context of being a prelude to presenting the use of Neurontin for bipolar disorder:

> …powerful new techniques and treatments are emerging for [bipolar illness and social phobia]…you will hear top experts discuss the latest research discoveries and breakthroughs in both of these crippling disorders. At the same time, you'll easily earn 4 hours of Category 1 credit just by attending…These programs will give you new therapeutic tools that will help you treat both of these common and debilitating disorders.[366]

261. Parsing this brochure, the message is that (a) there are breakthrough treatments for bipolar disease, (b) that you will learn how to treat this debilitating disorder and (c) that you will earn 4 hours of Category 1 continuing education credits for free. However, the completed randomized controlled trials, discussed above, showed that Neurontin is not effective for bipolar disorder.

262. Between November 7 and November 15, 1998, seminars title "New Frontiers in Social Phobia and Bipolar Disorders" were held in seven more cities.[367]

263. A letter from CME Inc. Senior Sales Director, Chris Prifte, to Parke-Davis points out two "programs of particular interest to you" at the 11th Annual U.S. Psychiatric & Mental Health Congress, to be held November 18-22 in San Francisco. Both of these programs related to off-label use of Neurontin: Advances in Treating Depression, and New Frontiers in Social Phobia and Bipolar Disorders.[368] These two presentations were made on November 21, 1998.

264. At this event, James W. Jefferson, M.D., Distinguished Senior Scientist Madison Institute of Medicine[369] presented a CME lecture titled "New Options in Bipolar Disorders." The abstract presented with the lecture notes introduces the use of gabapentin for bipolar disease, doesn't inform participants that it is not FDA-approved for treatment of bipolar disorder and creates the false impression that there is "some substantial research support of efficacy, particularly in treatment-resistant situations."[370]

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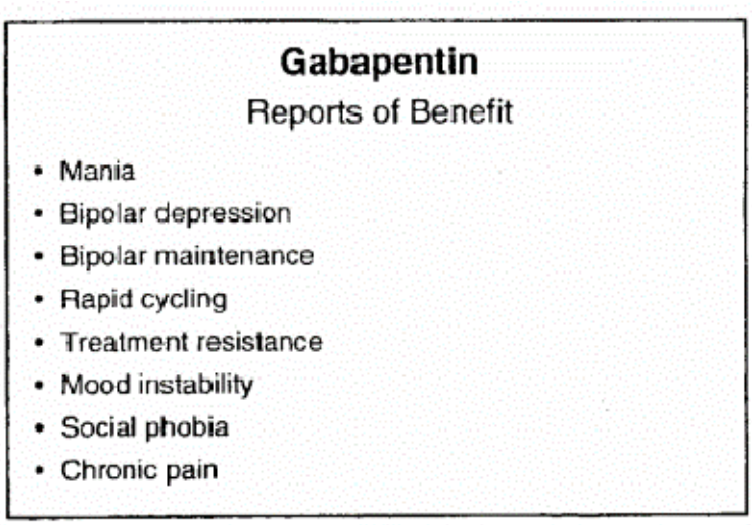
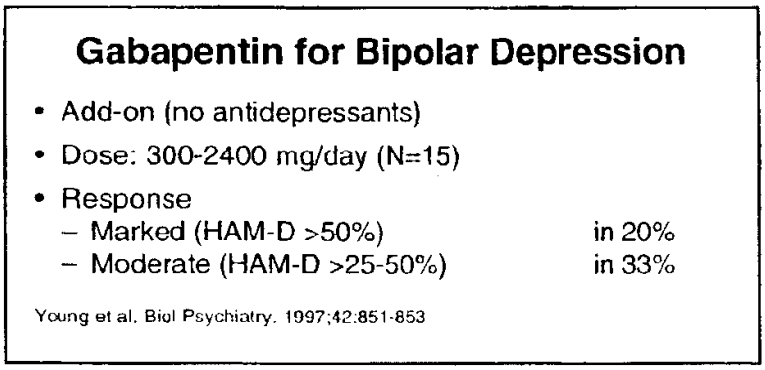
[366] CME 0665
[367] CME 0229
[368] CME 0458
[369] CME 0483
[370] CME 0484

265. The following slide was presented, listing indications for which there were "reports of benefit," but failing to inform participants that none of the indications listed, including bipolar disorder, is an FDA-approved use of Neurontin:[371]



266. The following slide was presented as evidence supporting the efficacy of Neurontin (generic gabapentin was not available until 2004):[372]



267. The "Young et al." study was an open label (patients and clinicians knew that patients were being treated with Neurontin) series of 15 patients (Level 3 evidence) not having nearly the scientific value of the "gold standard" double-blind randomized controlled trials (Level 1 evidence). No mention was made in any of the slides included in this lecture that the "Young et al." study was not a randomized controlled trial. More important, no mention is made of Parke-Davis's own study of 117 patients with bipolar disease that had been completed in July

[371] CME 0489
[372] CME 0490

1997 (16 months before this lecture),[373] which showed (in the words of Parke-Davis's research report), "The results from this study do not indicate that gabapentin is effective as adjunctive therapy in bipolar disorder."[374] In fact, as written in the published article (but not until 2000), the study didn't simply fail to show benefit of gabapentin, the study showed that patients treated with gabapentin did significantly worse that those treated with placebo.[375]

268. To enhance the aura of scientific credibility to the off-label recommendation for the physician audience, one slide proposed four possible mechanisms of action ("How It May Work"),[376] although the FDA-approved label states that the mechanism of "anticonvulsant action is unknown."[377] The dosage range recommended was "900-3600 mg (sometimes higher),"[378] although the dosage range recommended in the FDA-approved label was only up to 1800 /day. In a slide titled "New Options for Bipolar Disorders"[379] doctors are actually encouraged to make treatment decisions without adequate supporting scientific evidence:

- Treatment need often exceeds data availability
- The skillful combination of art and science will prevail

269. Another set of "key slides" from a syllabus prepared by CME Inc. with the same title, "New Frontiers in Social Phobia and Bipolar Disorders" (copyright date 1998), contained many of the same slides recommending the use of Neurontin in bipolar disorder without reporting the single RCT done by the manufacturer, which had shown no benefit.[380] Neurontin's lack of FDA approval for use in bipolar is not mentioned, although carbamazapine's lack of approval for bipolar disorder is reported.[381]

270. CME Inc.'s Outcomes Report on the 1998 series of seminars sponsored by Parke-Davis stated that "The *New Frontiers in Social Phobia and Bipolar Disorders* was a remarkably successful program in both attendance and quality ratings." Total registration at the 30 seminars

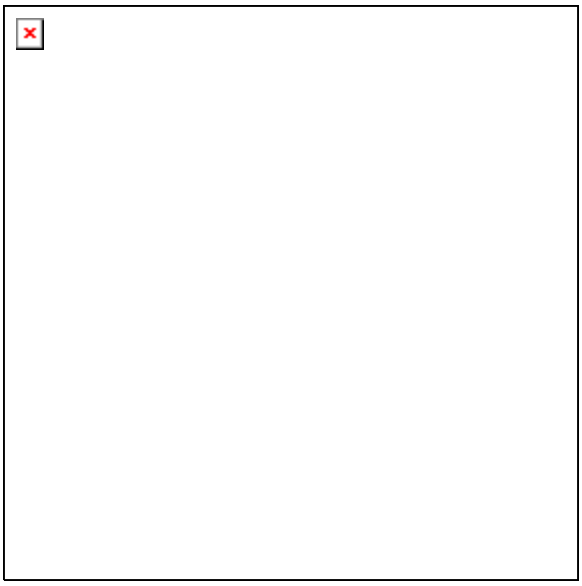
[373] DM_FILE/CI-0945 (GM03599a) RR 720-04174 (Page 4)
[374] DM_FILE/CI-0945 (GM03599a) RR 720-04174 (Page 6)
[375] Pande AC, Crockatt JG, Janney CA, et al., Gabapentin in Bipolar Disorder: a Placebo-Controlled Trial of Adjunctive Therapy, *Bipolar Disorders,* 2000;2:249-255.
[376] CME 0490
[377] FDA-approved label for Neurontin 1998.
[378] CME 0491
[379] CME 0494
[380] WLC_CBU_028076 to 79
[381] WLC_CBU_028074

held nationwide was more than 11,000 with an average of attendance of 188 people at each meeting.[382]

271. A letter from CME, Inc. to Parke-Davis dated December 22, 1998 outlined a request for a $2.5 million "*unrestricted* educational grant" to present another 30 national and 23 regional meetings, designed to fulfill psychiatrists' interest in "new treatment strategies for bipolar disorders and social phobia."[383] In other words, this was a grant to "educate" mental health prescribers about the benefits of Neurontin for off-label treatment of psychiatric disorders. One hundred and fifty attendees were projected for each of the 30 National Meetings and 75 attendees for each of the 23 Regional Meetings (a total of 6225 attendees). Each meeting was to include "[t]wo world-class faculty members," "[d]ignified promotion to attract a large and enthusiastic audience," and "[p]rominent identification as "[s]upported by an unrestricted educational grant from Parke-Davis." The agreement to provide these seminars was signed on February 5, 1999.[384] At this point two randomized controlled trials had been completed: Parke-Davis's study was completed July 1997 and showed that Neurontin is worse than placebo as adjunctive therapy for bipolar disorder, and the final results of the NIMH study (which had been presented in 1997 and 1998 at the American Psychiatric Association meetings as interim data[385]) showed that Neurontin was not effective for monotherapy in bipolar disorder.

272. The following graph (modified from the 2002 operating plan for Neurontin) shows that the number of new prescriptions for Neurontin written by psychiatrists increased 168% in 1999 and 88% in 2000[386]—dramatic growth for a drug that had been on the market since 1994 and for which there were no FDA-approved psychiatric indications:

[382] CME 1478 to 85
[383] CME 0039
[384] CME 0048
[385] Post RM, Denicoff KD, Frye MA, et al., A History of the Use of Anticonvulsants as Mood Stabilizers in the Last Two Decades of the 20th Century, *Neurophsycholbiology,* 1998:152-66.
[386] Pfizer_JMarino_0000204



Growth of new prescriptions for Neurontin by psychiatrists (depicted by diamonds) can be seen to be much greater than growth for any of the other anti-epilepsy drugs. As Neurontin use was increasing (with no FDA-approved psychiatric indication), Depakote use was decreasing, despite having been approved in 1995 by the FDA for use in bipolar disorder.[387]

273. A continuing education monograph, sponsored by Parke-Davis, a Warner-Lambert Division, was released in April 2000. A general "disclosure of drug use" was included in the introduction, informing readers that "use of antiepileptic drugs in treating conditions for which they are not approved by the US Food and Drug Administration" would be presented. The section on psychiatric uses of anticonvulsants states:

> • Gabapentin, a newer AED, has a favorable side-effect profile and does not interact with other anticonvulsants. Several small studies of bipolar disorder have shown promising results with gabapentin used as an adjunct to other psychotropic agents.[388]

The monograph presents results from three open-label trials supporting the efficacy of Neurontin in bipolar disorder. It states "The largest study of gabapentin for this indication was a retrospective analysis of 73 patients," 92% of whom had a positive response to Neurontin.[389] The monograph makes no mention of the three double-blind randomized controlled trials that had been completed at the time, two showing that Neurontin was no more effective than placebo

[387] http://www.nimh.nih.gov/health/publications/bipolar-disorder/complete-publication.shtml accessed 11/29/07.
[388] MDL_Vendors_055302
[389] MDL_Vendors_055306

as monotherapy and the other (the Defendants') showing it to be significantly worse than placebo as adjunctive therapy.

274. Sixteen months after submission of the Pande manuscript to *Bipolar Disorders* containing the results of research protocol 945-209 on the use of Neurontin for adjunctive therapy in bipolar disease (showing that patients taking placebo did significantly better than patients taking Neurontin), the Neurontin Situation Analysis: 2000-2001 stated:

> Parke-Davis plans to continue to support educational initiatives in the psychiatric arena that will discuss the broad utility of AEDs in a range of medical conditions such as bipolar disorders…[390]

275. Notwithstanding the three randomized controlled trials showing that Neurontin was ineffective as both mono- and adjunctive therapy for the treatment of bipolar disease, the Neurontin Situation Analysis: 2000-2001 listed, under the heading of "Psychiatry CME" meetings and symposia planned at the Psychiatric Times Weekend Congress and half day courses that included the treatment of bipolar disorder."[391]

3. *CME for migraine*

276. Proworx, working for Defendants, coordinated the creation and dissemination of CME material regarding the prevention of migraine. Approximately 77,000 invitations to participate in teleconferences were given to physicians by drug reps. The teleconferences were held in May and June 1999.[392] A continuing medical education monograph produced in conjunction with the teleconferences titled "Advances in the Preventive Treatment of Migraine," was released May 15, 1999.[393] The monograph was supported by an unrestricted educational grant from Parke-Davis. The author of the monograph and narrator of the accompanying audio tape was Ninan Mathew MD, President of the International Headache Society and the lead non-Parke-Davis investigator listed on Defendants' report of study 945-220.

277. The results of this study are presented in the CME monograph as showing that Neurontin is effective at preventing migraine headaches:[394]

[390] Pfizer_JMarino_0002368
[391] Pfizer_JMarino_0002376
[392] MDL_Vendors_008418
[393] CDM0022376
[394] CDM0022388

> The mean 4-week migraine headache rate at the end of the 12-week treatment phase was 2.9 for the gabapentin patients and 3.4 for the placebo-treated patients, compared with 4.5 and 4.2, respectively, during the single-blind baseline period. In addition, 36.4% of patients receiving gabapentin and 13.9% receiving placebo demonstrated a 50% or greater reduction in a 4-week migraine headache rate.

However, the conclusion presented in Defendants' research report for study 945-220 (completed March 10, 1998 and report issued August 24, 1999)—again, with the lead investigator being the author of the monograph—left a very different impression:

> **Efficacy:** For efficacy evaluable patients [the pre-specified primary analysis], no statistically significant differences were seen at any study period between placebo and Neurontin groups with respect to 4-week migraine headache rates or proportion of patients with reduction of 50% or greater in migraine headache rates.[395]

278. One might argue that the results of study 945-220 couldn't be known before the research report was issued, but Defendants had presented these results to the American Pain Society meeting in San Diego in November 1998—between the completion of the study and the issuing of the research report.[396] Similarly, study 945-217 had been completed in January 1999 and also failed to show efficacy for Neurontin in the prevention of migraine headaches.[397] The results of this study were not included in CME activities described above, and were never published as an independent study. And yet another of Defendants' RCT studies failing to show a benefit of Neurontin for prophylaxis of migraine headache had been completed in May 1988, Study CT 879-200, but was not presented in this CME activity. [398]

279. Physicians participating in the teleconferences, reading the monograph or listening to the tape presented by a recognized expert in the field could not have known that the results presented were not statistically significant because the research report had not yet been issued (and even after it was issued the results were not released to the public). Nor could physicians have known that two other of Defendants' RCT studies showed lack of efficacy of Neurontin for migraine prophylaxis. Nor could physicians have known that instead of the scientific evidence justifying the recommendation presented in this CME activity of Neurontin as

[395] RR 995-0074 p. v
[396] MDL_VENDORS_026390-1
[397] RR 995-00085 p. 5, Pfizer_LCastro_0044834
[398] RR 4301-00066 pp. ii-iii

a first-line drug for migraine prophylaxis, it had repeatedly failed to provide scientific evidence of efficacy at all.

280. Further compounding the misrepresentation, the monograph actually presents advantages of Neurontin over divalproex sodium as first-line therapy, even though the former had not shown efficacy and was not FDA-approved for this indication and the latter had shown efficacy and was FDA-approved for this indication.[399]

281. Another CME program titled "New Treatment Options for the Management of Pain: The Role of Anticonvulsants" was presented on June 10, 2000.[400] The section on migraines stated that "gabapentin has been shown to be effective in migraine prophylaxis," followed by the statement that, unlike valproic acid, gabapentin does not have side effects of "weight gain, hair loss, and tremor." In addition, unlike valproic acid, monitoring of blood tests is not necessary. The only citation that substantiates the claim of Neurontin efficacy in the prevention of migraine headache is an abstract of an open-label trial that was published in 1996.[401] There is no mention of the three RCTs that Defendants had completed and reports issued at the time of this CME program. All three RCT studies had shown lack of efficacy of Neurontin for migraine prophylaxis, yet participants in this CME activity were told only of a positive open-label study from 1996.

282. Another CME program on chronic pain, presented June 2, 2001, included a talk titled "Effective Management of the Hard-to-treat Migraine," One of the slides presented in this lecture, labeled "Preventive Drugs" listed gabapentin among the preventive drugs recommended, at doses of 900-4800 mg/day.[402] No mention was made of Defendants' three negative trials of migraine prophylaxis with Neurontin, all of which had been completed at the time of this lecture.

4. *Advisory Boards*

283. Among the points identified in the "2001 Neurontin Medical Strategic Plan" contained in the 2001 US Operating Plan for Neurontin (dated October 11, 2000) were[403]

[399] CDM0022389
[400] MDL_Vendors_056827
[401] Mathew NT, Gabapentin in migraine prophylaxis, *Cephalalgia,* 1996;16:367
[402] MDL_Vendors_094797
[403] Pfizer_RGlanzman_0000731

- Develop and Publish a Diagnostic Tool for Neuropathic Pain to Be Used by PCPs
- Continuously Present Neuropathic Pain Data at Key Conferences
- Engage key consultants and advisors to help train PCPs and field forces.

Although this strategy looks perfectly sensible on the face, the presentations to physicians –both as CME and to Advisory Board members—did not include the most important data. Defendants' study 945-224 had been completed September 7, 1999 and the study report issued on February 7, 2000. The study (as described above) included 3 times more patients in active treatment than study 945-210 (Backonja), was a fixed dose trial providing better information about dose-response relationships, and was less likely to be confounded by unblinding that resulted from forced titration to twice the FDA-approved maximum dose. Defendants' controlled the data from this study and did not include the results with the other studies that were presented when following the strategies outlined above, depriving physicians access to all of the Defendants' scientific evidence—positive and negative.

284. In the 2002 Operating Plan for Neurontin, dated October 5, 2001, a slide titled "2002 US Controllables" included the following budget item: "Advisory Boards for NeP (PCP, MCOs [Managed Care Organizations], etc)."[404] Not only were these Advisory Boards to promote Neurontin use for the non-FDA approved indication of neuropathic pain (in general), but they would do so (as shown below) by withholding negative information that Defendants alone controlled. As indicated by the following bullet points from the same slide, these Advisory Boards were part of a larger strategy to increase scientifically unsubstantiated use of Neurontin for the unapproved indication of neuropathic pain (in general):

- Grants Expanding to NeP and Neurology
- Convention Coverage Expanding to NeP and PCP
- Preceptorships for NeP (2002)

[404] Pfizer_BParsons_0092372

This report was issued almost 5 months after the FDA had indicated that Defendants' application for approval of Neurontin for the broad indication of neuropathic pain was "non-fileable," [405] and one month after Defendants' own pain consultants had advised that the scientific evidence did not justify approval of Neurontin for this indication. The 2002 Operating Plan also identified Advisory Boards as a subset of the 750 "Advocates" who had been trained "pre-launch," meaning prior to the launch of Neurontin for the broad indication of neuropathic pain, which——as known by Defendants—was not going to happen.[406]

285. In November 1999, Advisory Board Meetings entitled "Anticonvulsants in the Treatment of Psychiatric Disorders" were held at the Ritz-Carlton on Amelia Island, FL and Kingsmill Resort in Williamsburg, VA. The purpose of these meetings, as stated in the invitation letter, was to promote the use of Neurontin for (non-FDA approved) psychiatric indications:

> The purpose of this meeting is to bring together a select group of experts to review and discuss the latest clinical data regarding the treatment of psychiatric disorders. The program will include didactic presentations as well as group discussion regarding clinical practice and experience.[407]

Participants were reimbursed for all travel expenses and received honoraria of $1000. The post-meeting survey included the following question: "How can Parke-Davis further help you in the management of psychiatric disorders?"[408] Responses included:

- Speakers training meetings so we can take the message back to our colleagues
- Continue to provide reprints for off-label uses

Another question in the survey was "Is there a particular [psychiatric] patient type in which you find Neurontin specifically useful?" Like the first question, participants were being encouraged to consider Neurontin for off-label use (no psychiatric indications had been approved by the FDA).[409]

[405] Pfizer_LCastro_0005618
[406] Pfizer_BParsons_0092340
[407] MDL_Vendors_026378
[408] MDL_Vendors_026381
[409] MDL_Vendors_026383

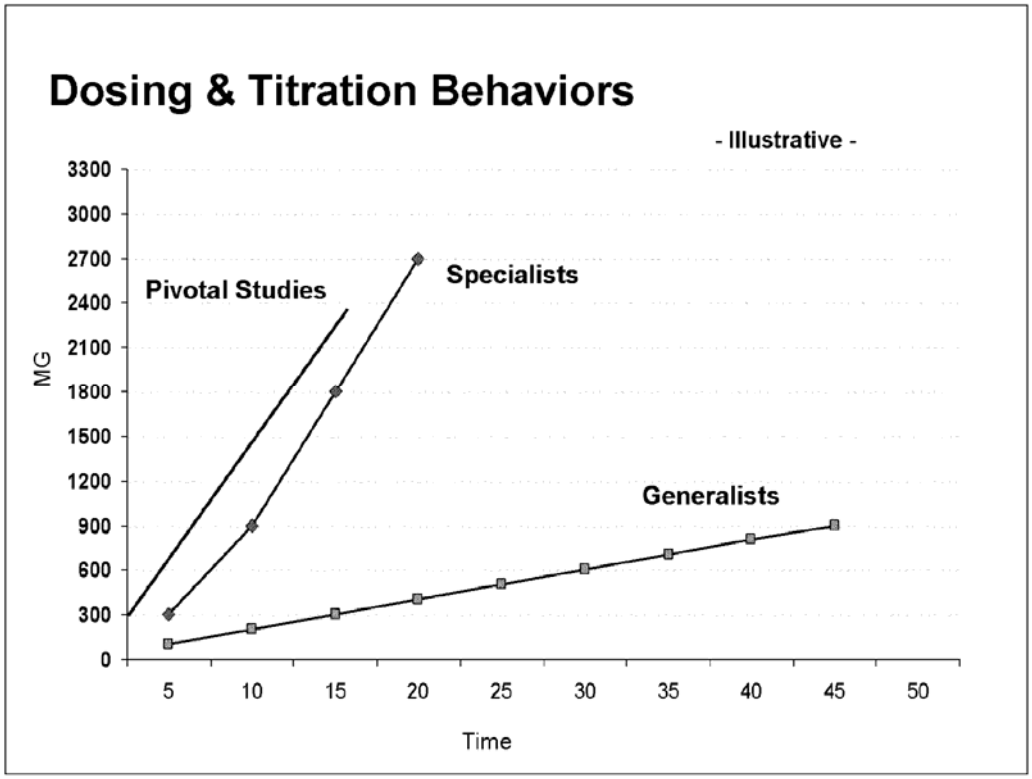
286. A "Neuropathic Pain Management Issues in Primary Care and Neurology Advisory Board" meeting was held on November 8, 2001.[410] Data from four of Defendants' RCTs, all of which had produced positive results, were presented. This Advisory Board meeting took place about 8 weeks after the September 6, 2001 meeting of Defendants' pain expert consultants. At that meeting the results of two other RCTs had been presented, 945-224 (Reckless) and 945-271 (POPP), which had failed to demonstrate efficacy of Neurontin for diabetic neuropathy and post-surgical neuropathy, respectively. Advisory board members at the November meeting had no way of knowing that they were being presented a skewed sample of the scientific evidence. Nor could they have known that Defendants' experts looking at all the data had recently opined that there was not adequate evidence of efficacy to make the case to the FDA that Neurontin should be approved for the broad indication of neuropathic pain—exactly the opposite of the impression of Neurontin efficacy for neuropathic pain presented to this Advisory Board meeting. And even more important than misinforming the Advisory Board members themselves is the logarithmic amplification of this skewed message about the efficacy of Neurontin for neuropathic pain when the Advisers assume the roles for which they were being "educated": as speakers and advocates who would—unbeknownst to themselves—become purveyors of the misinformation that they were receiving.

287. The same set of slides—including the Defendants' four positive studies and omitting the two negative studies (945-224 and 945-271)—was presented at an Advisory Board Meeting titled "Neuropathic Pain: Focus on the Specialist."[411] Though the date of this meeting is unclear, one of the slides has drug utilization data from September 2001, so it was certainly after the results of studies 945-224 and 945-271 had been presented to Defendants' pain consultants.

288. The same slide set was also used at a PBM Managed Care Advisory Board meeting held on March 4, 2002, titled "Treatment Options for Neuropathic Pain." Once again the four positive studies were presented, but no data from the two negative RCTs, 945-224 and 945-271, were presented.[412]

[410] Pfizer_RGlanzman_0049084
[411] Pfizer_RGlanzman_0059497
[412] Pfizer_Leslietive_0074344

289. Misinformation about off-label dosing was also provided to the advisers. One slide stated "Few physicians are titrating up to the maximum dose of 3600 mg, as outlined in the new product profile."[413] The maximum dose of 3600 mg/day had not been approved by the FDA, though this language might be interpreted as meaning such. The following "illustrative" graph was presented at the specialists' advisory board meeting,[414] creating the visual impression that PCPs were treating their patients with inappropriately low doses. In fact it was the PCPs who were dosing appropriately and it was the specialists who were dosing their patients too high based on the totality of scientific evidence in Defendants' possession.



290. The advisers attending this meeting were not just manipulated by the Defendants' withholding of their own two negative trials, they were then unwittingly enlisted as purveyors of this misrepresentation of the scientific evidence as shown in a slide labeled "Objectives for Today, Work Together to:

- Provide Optimal Treatments to Patients Suffering from NeP [based only on Defendants' positive studies]

[413] Pfizer_RGlanzman_0059594
[414] Pfizer_RGlanzman_0059598

- Determine Ways to Educate and Disseminate Data to Physicians on Use of NEURONTIN to treat NeP [but not to educate with a fair and complete presentation of Defendants' scientific evidence]
- Develop Strategies to Best Position NEURONTIN for Launch in NeP [Defendants' knew there would be no launch in NeP in the foreseeable future—the FDA had found the application "non-fileable."]

The advisers were simply being shown incomplete and one-sided scientific evidence and being trained to promulgate the misinformation to colleagues who trusted them.

291. At the "Neuropathic Pain Advisory Board: Focus on the Specialist" meeting, held January 11-12, 2002 the following causes of neuropathic pain were presented: alcoholism, amputation, back/leg/hip problems (sciatica), cancer chemotherapy, diabetes, facial nerve problems (trigeminal neuralgia), HIV infection or AIDS, multiple sclerosis, shingles (herpes zoster virus infection) and surgery.[415] Not one of these was an FDA-approved indication for Neurontin at the time of this meeting, and postherpetic neuropathy was the only indication for which there was substantial scientific evidence and that later became an FDA-approved indication. According to data presented at the Advisory Board meeting of November 8, 2001, post-herpetic neuralgia (the only indication for which the FDA found Neurontin effective) was the cause of less than one out of six cases of neuropathic pain.[416]

G. Drug Reps And Marketing

292. In September 1997, there were zero or close to zero "details" (i.e. visits by drug reps) to psychiatrists. By February 1999, despite there being no FDA-approved indication for any psychiatric illness or symptoms, there were about 7,300 calls from drug reps to psychiatrists to discuss Neurontin use.[417]

[415] Pfizer_RGlanzman_0059513
[416] Pfizer_RGlanzman_0049091
[417] PFIZER_AFANNON_0008586

293. Use of Neurontin in bipolar disease increased from minimal (12,000 "uses") in May 1997 about 23-fold over the next 21 months, to 275,000 "uses" in February 1999.[418] According to the "2001: Neurontin Situation Analysis":

> Neurontin's use in bipolar disorder has increased by 1700% for Sept 97 to Sept 99 (QTR Sept 99, Scott Levin PDDA). Currently bipolar disorder represents over half of all psychiatric drug uses for Neurontin.[419]

294. Despite the lack of FDA approval for any psychiatric indications, Neurontin was marketed more heavily to psychiatrists in 2000 than any other specialists: 43% of "details" and 55% of samples were given to psychiatrists. Neurologists were next with 25% and 20%, respectively.[420] Similarly, 17% of details and 5% of samples went to PCPs, whose use of Neurontin would also be off-label.

H. Public Relations

295. Defendants' ability to control the impact of scientific evidence—both positive and negative—to its own business advantage is exemplified by the different impact that Studies 945-210 (Backonja) and 945-224 had on physicians' and the public's understanding of the benefit of Neurontin in treating painful diabetic neuropathy. From an objective point of view, the scientific evidence produced by study 945-224 should have had far more "weight" than study 945-210: the latter had 84 patients in the active treatment arm and, as shown by Dr. Jewell, the results were confounded by the potential unblinding effect of forced titration to 3600 mg/day. In contrast, study 945-224 had three active treatment arms, each with as many patients receiving Neurontin as the entire study 945-210 and was a fixed dose study, with far less risk of unblinding as a result of side effects.

296. Suggesting "A Tale of Two Trials," the impact of the evidence from the two trials could hardly have been more different. As described above, study 945-210 was published in *JAMA*, while study 945-224 was never published independently (the results were "bundled" into the Backonja/Glanzman review article the overall message of which was positive). The results of Study 945-210 were prominently presented at continuing medical education activities and

[418] PFIZER_AFANNON_0008581
[419] Pfizer_JMarino_0002368
[420] Pfizer_Rglanzman_0000741

advisory board meetings, whereas the results of study 945-224 were rarely if ever brought up in these Defendant-sponsored activities and remained essentially invisible to physicians.

297. Defendants used public relations to amplify positive results (rather than present balanced and accurate scientific information) and extend their influence on "knowledge" about the efficacy of Neurontin beyond the medical community—turning the volume way up when it suited their business goals and turning the volume way down when it did not.

298. Notes of minutes from a conference call dated October 1, 1998[421] show how the manufacturer planned to optimize the impact of the two forthcoming articles in *JAMA* about Neurontin use in diabetic and post-herpetic neuropathy. The strategy was to include

- $2.5 million in increased spending in 4Q'98 to pay for the "Neurontin expanded program in 4Q98";
- implementation of Advisory Boards for PCPs and specialists;
- development of core faculty to present at CME teleconferences and Dinner meetings; submission of "five potential thought leaders for the core faculty from the specialties of Neurology (pain management), Anesthesiology, Endocrinology and Immunology";
- submission of 50 potential faculty members for the teleconferences and dinner meetings by each CBU; hiring of IntraMed to develop a consensus conference to "discuss the development of AED guidelines for pain";
- development of "leave behind information package for physicians" including reprints of the JAMA articles; and
- agreement "to have hospital reps begin promoting Neurontin" (which would constitute off-label marketing by drug reps).

299. One hundred and thirty thousand copies of *JAMA* reprints, costing $50,000, were purchased "for representatives without direct mail." Another $200,000 was allocated for the cost of the DPN article alone and direct mailing. And another $20,000 was allocated to purchase 30,000 more reprints.

300. An extensive public relations campaign was suggested, designed to "leverage study publications in *JAMA* to generate interest in and coverage of gabapentin's efficacy in

[421] WLC_CBU_000221

chronic pain management."[422] The scope of the planned PR campaign (the actual results of which are described below) can be seen in the widespread coverage of press releases planned for "key trade publications":[423]

301. In December 1998, Parke-Davis retained the Public Relations firm Makovsky & Company to carry out a PR initiative to "educate both consumers and medical professionals" about the results of the two studies about Neurontin published in JAMA that month.[424] This media campaign achieved more than "85 million impressions," meaning that at least that many times Americans were informed that of the benefit of Neurontin for the treatment of diabetic and post-herpetic neuropathy. These "impressions" were accomplished by the following activities:

- Press releases targeting "trade publications catering to medical professionals in the fields of diabetes and pain management," as well as "consumers that could benefit from knowledge of these studies."[425]
- Video news releases that were distributed to TV stations in all key US markets
- Radio news releases distributed to key stations across the country
- Radio health journal: a one minute spot designed to "air unedited," on stations around the country during the six weeks between December 13, 1998 and January 17, 1999.
- Airline video news release to be shown to passengers on several airlines shortly after take-off.
- "Mat release": an article designed to run unedited in daily and weekly newspapers around the country.

302. The impact of this campaign is described by the PR firm in its program overview, dated February 23, 1999:

> Through the use of these publicity tools, Makovsky placed the Neurontin story in some of the most prestigious consumer and trade publications in the U.S., including *Business Week, the Washington Post, Los Angeles Times & Chicago Tribune.* We were also able to place the story on some of the most watched television stations including CNN, WCBS &WNBC and news

[422] WLC_CBU_000231
[423] WLC_CBU_000233
[424] WLC_CBU_092879
[425] WLC_CBU_092885

> wires – including AP and Reuters. In all Makovsky's campaign reached all key U.S. markets, generating in excess of **85 million impressions.** [Emphasis in original][426]

303. In addition, "aggressive pitches" were planned for key patient group magazines, newsletters and websites to reach target audiences. These organizations included: Diabetes Research Institute Foundation, American Academy of Pain Management, American Pain Society, American Chronic Pain Society, International Association for the Study of Pain, and Dannemiller Memorial Education Foundation (www.pain.com).[427] "Core Strategies" directed at MDs, RNs, and RPhs outlined in this document included maximizing "clinical trials data to increase use of Neurontin for pain."[428]

304. Of course Defendants have the right to accurately publicize good news. The problem is that Defendants' controlled the impact of (from their point of view) good and bad news about Neurontin, and their control led to misrepresentation of the scientific evidence in order to maximize sales. In striking contrast to the Backonja study—which was published in *JAMA*, publicized through a large public relations campaign that produced up to 85 million "audience impressions" [429] and was included prominently in CME courses—the Reckless study remained virtually invisible to practicing physicians. Physicians attending the above CME events that touted the benefits of Neurontin for diabetic neuropathy, were deprived of the data contained in the Reckless study which was material to their accurate appraisal of Neurontin's efficacy. Moreover, even if they had searched, the results of the Reckless study were simply not available.

VII. FORMULARY DOSSIER

305. The Academy of Managed Care Pharmacists (AMCP) formatted Formulary Dossier titled "Neurontin (gabapentin) Submission: for the Management of Postherpetic Neuralgia and Painful Diabetic Neuropathy"[430] was attached to an e-mail dated May 19, 2003.[431]

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[426] *Ibid.*
[427] WLC_CBU_000237
[428] WLC_CBU_000246
[429] WLC_CBU_092888
[430] PFIZER_SDOFT_0023146 to 319
[431] PFIZER_SDOFT_0023144

306. At the beginning of the document in the brief description of the sections therein, "Place of Product in Therapy" states:

> A brief overview of the management of chronic pain including neuropathic pain and rationale for the development and use of Neurontin.[432]

Recommendation of such off-label and scientifically unsubstantiated use of Neurontin would have violated FDA regulations if included in unsolicited marketing material, but could be made within the context of a formulary dossier. Even so, Defendants still had an obligation not to provide false or misleading information in the dossier.[433] Defendants' failure to include results from the Gorson study of gabapentin for diabetic neuropathy (funded by Defendants), the Morello study comparing gabapentin to amitriptyline for the treatment of diabetic neuropathy and study 945-271 ("POPP," funded by Defendants) rendered the scientific evidence presented in the dossier incomplete and biased. Reference in the dossier to a review article by Johnson et al published in *Contemporary Reviews of Pharmacotherapy*[434]—a publication not listed on PubMed—does not constitute presentation of the results of any of the studies mentioned therein.

307. In the introduction of the dossier, under the heading "Clinical Efficacy Studies,"[435] two studies pertaining to diabetic neuropathy are listed: Protocol No. 945-210 (published as Backonja 1998, Backonja 1999[436] (which presented the same data as Backonja 1998)) and Protocol No. 945-224. In addition, one study in "patients with neuropathic pain of diverse etiology," Protocol No. 945-306, is listed as a study of "patients with neuropathic pain of diverse etiology." Absent from this list are Gorson (completed in 1997), Morello (published in the Archives of Internal Medicine in 1999[437]) and protocol 945-271 ("the POPP-study," not published[438]) completed November 30, 2001. The Gorson and POPP studies failed to show a benefit of Neurontin in comparison to placebo for diabetic neuropathy. The Morello study

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[432] PFIZER_SDOFT_0023149
[433] Neumann PJ, Evidence-Based And Value-Based Formulary Guidelines, *Health Affairs,* 2004;23:124-134
[434] PFIZER_SDOFT_0023146
[435] PFIZER_SDOFT_0023149
[436] Backonja MM, Gabapentin Monotherapy for the Symptomatic Treatment of Painful Neuropathy: **A** Multicenter, Double-blind, Placebo-controlled Trial in Patients With Diabetes Mellitus, *Epilepsia,* 4O(Suppl. 6):S57-S59, 1999.
[437] Morello CM, Leckband SG, Stoner CP, et al., Randomized Double-blind Study Comparing the Efficacy of Gabapentin With Amitriptyline on Diabetic Peripheral Neuropathy Pain, *Archives of Internal Medicine,* 1999; 159:1931-37.
[438] Pfizer_LCastro_0043325

showed no benefit of Neurontin compared to amitriptyline for the treatment of diabetic neuropathy and no fewer side effects experienced than in patients taking the tricyclic antidepressant amitriptyline. In addition, although Study 945-306 did show a significant benefit of Neurontin compared to placebo, Pfizer was aware that virtually all of the benefit was in patients suffering from post-herpetic neuralgia, with little benefit appreciated by those suffering from diabetic peripheral neuropathy.

308. Listed under the heading "Indications" are "*Unlabeled Uses: Tremors, pain associated with multiple sclerosis; neuropathic pain other than PHN; bipolar disorder; migraine prophylaxis."*[439] And listed under "Indications Currently Under Study" is "*Management of neuropathic pain associated with diabetic neuropathy."* Nowhere in the dossier is the reader informed that the FDA had found that the application for this indication was "non-fileable" because there was inadequate scientific evidence supporting efficacy.

309. The Pharmacology section of the dossier begins: "Gabapentin is an anti-epileptic and anti-neuropathic pain agent."[440] This is misleading because, based on the available evidence, the FDA and Pfizer's own consultants had determined that the evidence from clinical trials failed to support such a claim.

310. The dossier offers claims of efficacy and reduced risk of side effects as a rationale for using Neurontin to treat non-malignant neuropathic pain rather than tricyclic antidepressants.

> Antiepileptic drugs (AEDs) have been recognized as effective in the management of neuropathic pain, while exhibiting fewer side effects than TCAs. In particular, a number of recent studies have demonstrated the effectiveness of gabapentin in treating neuropathic pain.[441]

311. Neurontin is reported to be considered by many pain physicians as "a first-line therapy for chronic neuropathic pain.[442] Pfizer was aware that, by May 2001, Neurontin was the most frequently used drug for neuropathic pain,[443] despite the FDA and Pfizer's own consultants conclusion that the clinical trials didn't provide efficacy of Neurontin for this indication. The dossier fails to present the conclusions of the 2000 Cochrane report on the use of anticonvulsant drugs for acute and chronic pain, which concluded:

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[439] PFIZER_SDOFT_0023152
[440] *Ibid.*
[441] Pfizer_SDoft_0023166
[442] Ibid
[443] Pfizer_JMarino_0000218

> There is no evidence that anticonvulsants are effective for acute pain. In chronic pain syndromes other than trigeminal neuralgia, anticonvulsants should be withheld until other interventions have been tried. While gabapentin is increasingly being used for neuropathic pain the evidence would suggest that it is not superior to [the less expensive anticonvulsant] carbamazepine.[444]

In 2001, Neurontin was, however, being used many times more frequently than carbamazepine for the treatment of neuropathic pain.[445]

312. The section of the dossier titled "Pain Associated with Diabetic Neuropathy" provides the reader with no indication that an sNDA had been filed with, but not approved by, the FDA to add this indication for Neurontin.

313. While the section titled "Pain Associated with Diabetic Neuropathy" does cite Collins et al., 2000 (gabapentin no better than carbamazepine and more expensive), and Morello (Neurontin not superior to amitriptyline and more expensive), it does not include 945-224 and 945-271 both of which are manufacturer-sponsored and fail to show efficacy of Neurontin against placebo in patients with neuropathic pain.

314. The final section, "Clinical Value and Overall Cost," fails to include study 945-271 and makes the false claim of significant pain relief with gabapentin compared to placebo for patients with diabetic neuropathy—a claim that had not been accepted by the FDA. The single study presented in the dossier claiming that treatment of neuropathic pain with Neurontin was associated with a decrease in health care costs had not been published.[446]

VIII. CONCLUSION

Assuming the finder of fact concludes, as alleged in the Third Amended Class Action Complaint and other filings, that Parke-Davis and later Pfizer engaged in a strategy to exert control and influence over the sources of information upon which physicians relied when prescribing Neurontin for non-FDA approved, scientifically unsubstantiated indications and doses, I am of the opinion that this strategy was begun when there was insufficient evidence to support claims of efficacy and was continued in the face of either ongoing lack of evidence or the existence of good evidence that Neurontin was not effective for such uses. This strategy was

[444] Pfizer_LeslieTive_0026463 to 64
[445] Pfizer_JMarino_0000218
[446] Pfizer_SDoft_002320

designed in such a way as to exploit physicians' trust in the sources from which they typically assimilate new knowledge, including selective publication of the results of clinical trials, use of Advisory Boards and thought leaders, sponsorship of extensive continuing medical education designed to encourage off-label prescribing and the use of detailing by drug reps and sales-oriented efforts of medical liaison personnel to encourage off-label use of Neurontin.

In many cases, information that would have been relevant to prescribers remained (and in some cases, still remains) the sole property of the Defendants such that it was unavailable to physicians making prescribing decisions for their patients. In many other cases, information was distorted in order to elevate less rigorous scientific evidence and create a perception that there existed a scientifically-based rationale for prescribing Neurontin for the various indications discussed. Because the lack of balanced, accurate, and reasonably complete information related to Neurontin's use for bipolar disorder, pain, migraine and dosages above 1800 mg/day was disguised, prescribing physicians had no reason to doubt the veracity of the information they were receiving about Neurontin's effectiveness for the off-label uses at issue. Prescribers needed—but were not provided—balanced, accurate and reasonably complete information, critical and material to their determination of Neurontin's efficacy for the off-label uses at issue, in order to adequately fulfill their role as learned intermediaries.

Dated: August 11, 2008 John Abramson MD

John Abramson, M.D.

EXHIBIT 1

John Abramson, MD

Professional Address: 39 Spring Street, Ipswich, MA 01938

Email: john_abramson@hms.harvard.edu Phone: 978-312-1225

Place of Birth: Cambridge, MA

Education:

1970	BA cum laude	Harvard College	Social Relations
1971-2		Harvard College	Premedical courses
1974	BMS	Dartmouth Medical School	Medicine
1976	MD	Brown Medical School	Medicine

Postdoctoral Training:

1982	MS	Case Western Reserve University	Family Medicine
1976-77	Internship	Memorial Hospital, Chapel Hill, NC	Family medicine
1979-81	Residency	University Hospitals of Cleveland, OH (Case Western Reserve University)	Family practice
1980-82	Fellow	Case Western Reserve University	Robert Wood Johnson Fellow in Family Medicine

Licensure and Certification:

1982	Massachusetts Board of Registration in Medicine. License No. 49182
1982	Diplomate, American Board of Family Practice 1982, recertified 1989, 1995, 2001, 2007

Academic Appointments:

1992-3	Senior Research Associate, Institute for Health Policy, The Heller School, Brandeis University
1997-School	Clinical Instructor, Dept. of Ambulatory Care and Prevention, Harvard Medical

Hospital or Affiliated Institution Appointments:

1982-2002	Medical Staff	Beverly Hospital
1994-2002	Medical Staff	Lahey Clinic

Other Professional Positions and Major Visiting Appointments:

1977-9	National Health Service Corps, US Public Health Service
1982-2002	Family physician, Hamilton-Wenham Family Practice, Hamilton, MA
1986-1993	Associate Medical Director, Pru-Care of MA
1994-2001	Chair, Department of Family Practice, Lahey Clinic, Burlington MA
2005-present	Executive Director of Health Management, Wells Fargo Health Solutions

Hospital and Health Care Organization Service Responsibilities:

1989-1991	Member, Board of Trustees, Beverly Hospital

Major Committee Assignments:

1993-5	Chair, Graduate medical Education Committee (Family Practice Residency), Beverly Hospital

Professional Societies:

1982-2002	Massachusetts Medical Society

1982 American Academy of Family Practice

Awards and Honors:

1996, 1999 Community Newspapers “Readers’ Choice Award for Best Doctor”, Beverly, Hamilton, Wenham
1999 Center for the Study of Services “Guide to Top Doctors”
2000 Castle Connolly/Town and Country’s Guide to Primary care Physicians
2001 Castle Connolly/AOL-Digital City “Guide to Top Doctors”
2002 Selected to be included in Lady’s Home Journal: The Best Family Doctors in America (had left practice to write book so name did not appear in magazine)
2003 Profiled in Harvard Magazine article: “Doctored Research?” Nov-Dec issue

Part II:
Research, Teaching, and Clinical Contributions

A. Primary Care Clerkship and mentorship program: Harvard Medical School, preceptor of third-fourth year student for the next eight years. Teaching activities have also included the elective course and independent study in “Healing and Spirituality” as listed below.

D. Report of Teaching
1. Local Contributions

1992-1994 Harvard Medical School
Two years
Primary Care Mentorship Program
Mentor
One first-year medical student per year

1994-2001 Harvard Medical School
Eight years (One student per year)
Primary Care Clerkship
Preceptor

1999-2001 Harvard Medical School
Three years (average 12 students per year)
Healing and Spirituality in Medicine
Elective
Faculty 1999, Course Co-director 2000 and 2001

2002 Harvard Medical School
Independent Study
Healing and Spirituality

2002-2007 Harvard Medical School
Ongoing
Primary Care Clerkship
Tutor

2003 Harvard Medical School
Independent Study
Healing and Spirituality

2. Presentations:

1981	A prepaid primary care network for private and AFDC patients: an alliance between the private and public sectors. National Governor's Association Conference on Primary Care Networks, New Orleans, LA.
1982	Participation of a residency based family practice center in an innovative case management program. Society of Teachers of Family Medicine, Chicago, IL.
1983	The economic impact ofa primary care network on primary care physicians and Medicaid costs. Robert Wood Johnson Foundation, Princeton, NJ.
1984	Primary care of de-institutionalized retarded adults in the community. HCFA Meeting of Federal Surveyors of Intermediate Care Facilities, Portland, ME.
1991	The role of physicians in the Michigan Comprehensive Community Health Models Project. Pew Health Policy Annual Meeting, Cambridge, MA
1999	The role of the physician/patient relationship in the healing process. Topics in Internal Medicine (Lahey Clinic), Portsmouth, NH
2002-5	Healing our Critically Ill Health Care System. Clinical Training in Mind/Body Medicine. Mind/Body Medical Institute/Harvard Medical School Continuing Education, Boston, MA
2004	The Quality of Our Medical Knowledge: Vioxx and Statins. Heller School for Social Policy NCEP Recommendations: Preventing Heart Disease or Pushing Drugs?. Encino-Tarzan Regional Medical Center, CA. Grand Rounds, Beverly Hospital Beverly MA: NCEP Recommendations: Preventing Heart Disease or Pushing Drugs?
2005	Williams College; Lessons from Vioxx: Misinforming Doctors, Harming Patients and Making money, 1/11/05 New York City Department of Public Health, Chronic Disease Grand Rounds, 2/4/05 Bellevue Hospital Medical Seminar 2/9/05 Denver Forum, Denver CO 2/10/05 Woman's National Democratic Club, Washington DC, 3/3/05 Congressional Task Force on Prescription Drugs, Washington DC, 3/3/05 Mind Body Medical Institute Harvard Medical School 3/23/05 San Diego City Club 4/8./05 Alternative Therapy Conference, San Francisco, Keynote Address: "Overdosed America." 4/9/05 University of Michigan (Undergraduate course in health policy) 4/05/05 Health Care Benefits Forum, Chicago Hyatt Regency, Keynote Address: 4/7/05 City Club of San Diego, 4/08/05 Alternative Health Conference, San Francisco CA 4/9/05 Harvard Medical School, Cabot Lecture Series, 4/25/05 Drug Therapy Conference, British Columbia 4/16/05 Lutheran Medical Center, Brooklynn NY, 4/27/05 Cooley Dickinson Hospital, Northampton MA 4/29/05 Harvard School of Public Health, 5/02/05 Southern Vermont Area Health Education Center, 5/07/05 Chilten Club of Boston, 05/26/05 Hiram B. Curry Memorial Lecture, University of S. Carolina Dept Family Practice, 6/6/05 Harvard Medical School, Mind/Body Medical Institute Continuing Medical Education 6/15/05 Vermont Citizens Campaign for Health 6/16/05 Medical Foundation of Boston, 6/21/05 Harvard Club of Boston, 6/22/05 Hamilton Wenham Public Library 6/23/05 World Pension Forum, Chatham MA, 7/12/05 Boulderfest, Boulder CO, 7/14/05

Center for Popular Economic, Amherst MA, 8/1/05
Public Policy Virginia, Roanoke VA, 9/17/05
Fletcher Allen Hospital, Burlington Vermont 9/26/05
University of Vermont Medical School 9/26/05
Central Vermont Hospital 9/27/05
Vermont Medical Society 9/27/05
Cayuga Medical Center of Ithica, 9/30/05
Michigan State Medical Society Bioethics Conference, 10/08/05
Harvard Medical School, Mind/Body Medical Institute Continuing Education Course 10/17/05
U Mass Med School, Community Medicine 10/19/05
Massachusetts Medical Society/Medical students 10/19/05
Rotary Club, Charleston, WV, 10/21/05
National Legislative Association on Prescription Drug Prices, Charleston, WV 10/21/05
League of Women Voters, Hamilton, MA, 10/30/05
Sharp Medical Center, San Diego, CA 11/04/05
Pacific College Symposium, San Diego CA 11/05/05
Allegheny General Hospital, Pittsburgh, PA 12/7/05

2006

LA Country Employee Pension Association 1/26/06
West Virginia House and Senate 2/1/06
George Washington Medical School panel about Drug reps on campus 2/9/06
HealthFirst Conference 2/22/06
Cambridge Health Alliance Family Medicine Grand Rounds 2/24/06
Harvard Medical School Pharmacology Patient Safety Session "The Vioxx example" 2/28/06
Nieman Journalism Fellowship 3/1/06
Sudbury League of Women Voters 3/5/06
Bentley College, Business Ethics Lecture 3/7/07
Northwest Pharmacy Benefits Managers-Medical Directors Conference, Seattle WA 3/10/06
Harvard Medical School Continuing Medical Education, Mind Body Medicine 3/13/06
Association of Health Care Journalists, Houston TX, 3/17/06
North Shore Seminars, Beverly MA 3/19/06
New England Biolabs, Ipswich MA 3/23/06
Florida State University Medical Grand Rounds, Tallahassee FL 3/30/06
Hampden County [MA] Medical Society 4/25/06
Boston Medical Center, Family Medicine Grand Rounds 4/25/06
Cooley Dickinson Hospital Northampton MA, Grand Rounds 5/1/06
University of Colorado Family Medicine Grand Rounds 5/3/06
American College of Lifestyle Medicine, Loma Linda CA 5/24/06
Harvard Medical School Lecture to students: Statins 5/30/06
The Regence Group Pharmacy Managers, Portland OR 6/14/06
Alta Bates Hospital, Berkeley CA, Grand Rounds 6/13/06
Harvard Medical School Mind/Body Medical Institute Continuing Medical Education 6/21/06
Tufts Family Medicine Residency 6/23/06
Forum for Behavioral Science in Family Medicine 9/17/06
Biomedical Research and the Law, Hofstra Law School 10/4/06
Sharp Community Medical Group CME Conference 10/8/06
Harvard Medical School, Course on Mind/'Body Medicine 10/20/06
Idaho State University Family Practice Residency 10/26/06
Idaho State University Conference on Health Care 10/26/06

American Public Health Association, panelist : “Drug manufacturers, the FDA, and U.S. health care,” Boston, MA 11/7/06

Loma Linda University, School of Pharmacy 11/3/06
Sharp Rees-Steely Community Group CME 11/4/06
Rollins College, Winter Park, FL, 11/13/06
Capital Health Plan, Tallahassee, FL, 11/15/06
National Federation of Women Legislators, Bachelor’s Gulch, CO, 11/18/06
University of New Hampshire, Masters in Public Health Program Grand Rounds, Durham, NH, 11/28/06
Washington University, “Pharm-Free Day,” St. Louis, MO, 11/30/06

2007

Panelist at George Washington University: Relations with the Pharmaceutical Industry, Washington, D.C., 1/25/07
Prescription Access Litigation Dinner, Keynote Speech, Washington D.C., 1/25/07
McDougall Program Health Conference, Santa Rosa, CA, 2/2-4//07
Sutter Medical Center, Family Medicine Grand Rounds, Santa Rosa, CA 2/5/07
Renown Medical Center, Grand Rounds, Reno NV., 2/6/07
Gila River Health Indian Community Health Center: “The Growing Gap Between Evidence-Based Medicine and Good Health Care,” Sacaton AZ., 2/8/07
Harvard Medical School: “Why Primary Care Don’t Get No Respect.” 2/13/07
Indian Health Services, National Combined Councils: “Can We Trust the Evidence in Evidence-Based Medicine,” San Diego CA. 2/25/07
Harvard Medical School Continuing Education: Mind/Body Medicine Clinical Training, Boston MA. 2/28/07
University of Michigan, Family Medicine Grand Rounds, Ann Arbor, MI 3/14/07
University of Texas, Medical Branch, Galvaston TX, 3/15/07
Puerto Rican Third Annual Public Health Conference, San Juan PR, 5/8/07
Harvard Medical School Continuing Education: Mind/Body Medicine Clinical Training, Boston MA. 6/25/07
International Academy of Law and Mental Health, Padua Italy, 6/29/07
Lee Memorial Health System, Continuing Education Conference, Sanibel Harbor, FL, 7/15/07
Orlando Regional Medical Center, Continuing Education Conference, Orlando FL, 7/16/07
American Association of Naturopathic Medicine Annual Meeting, Palm Springs, CA 8/25/07
Dept. of Psychiatry Grand Rounds, Massachusetts General Hospital, Boston, MA 10/5/07
North Atlantic Health Sciences Libraries, When the Facts Aren’t True, What’s a Librarian to Do?, Woodstock VT, 10/29/07
Canadian Coalition for Health: Is Free Speech more Important than your Health, Toronto, CA March 4, 2008
Benson-Henry Institutre for Mind Body Medicine/Harvard Medical School Coninuing Medical Education Program. Understanding our Critically Ill Health Care System and Offering a Real Alternative, Boston, MA, March18, 2008
Northwest Naturopathic Physicians Convention, Can We Trust the Evidence in Evidence-Based Medicine? Vancouver, British Columbia, April 5, 2008
Therapeutics Initiative, University of British Columbia , Lookin’ For Health in All the Wrong Places: The Commercial Distortion of Efforts to Reduce the Burdent of Heart Disease, Vancouver, British Columbia,
April 7, 2008

Direct to Consumer Perspectives National Convention, What's Wrong with the American Healthcare System (and How to Make it Right), Washington DC, April 16, 2008

E. Report of Clinical Activities

1982-2002 Family Physician, Hamilton-Wenham Family Practice
1997-2001 Hamilton-Wenham School District Physician

Bibliography

Original Articles

1987 Competition, capitation, and case management: barriers to strategic reform. Milbank Quarterly 1987;65:3: 348-370

2003 Medical Reporting in a Highly Commercialized Environment: A family doctor prescribes eight guiding principles for accurate and fair coverage of research findings. Nieman Reports. 2003; Summer: 54-57

2003 Comments on the MRC/BHF Heart Protection Study. Correspondence. The Lancet. 2003; 362: 745-746

2005 When Health Policy is the Problem (with Bruce Spitz). Journal of Health Politics, Policy and Law, 2005; 30(2):327-366.

2005 The Effect of Conflict of Interest on Biomedical Research and Clinical Practice Guidelines: Can We Trust the Evidence in Evidence-Based Medicine? (With Barbara Starfield, MD, MPH). Journal of the American Board of Family Practice, 2005; 18:414-418.

2007 Are Lipid-lowering guidelines evidence-based? (With James M. Wright MD, PhD). The Lancet, 2007: 369:168-169.

The Reliability of Our Medical Knowledge as a Product of Industry Relationships. Hofstra Law Review, 2007; 35: 691-704.

Book

2004 Overdosed America: The Broken Promise of American Medicine. How the Pharmaceutical Companies Distort Medical Knowledge, Mislead Doctors, and Compromise Your Health (HarperCollins, Sept. 2004)

OP-EDS (Major Newspapers)
LA Times Drug Guidelines Fatten Bottom Line 7/25/04
NY Times Information is the Best Medicine 9/18/04
LA Times Physician Know Thy Patient 10/24/04
LA Times Drug Profits Infect Medical Studies 1/7/06
LA Times Healthcare Code Blue 11/3/06
Atlanta Journal Constitution Cold-hearted tug fails women 2/2/07

Partial list of National Media Appearances:
9/30/04 CBS Evening News
Lou Dobbs
CNN Headline News
NPR Radio: All Things Considered
10/1/04 The Today Show
CNN American Morning
10/18/04 FOX News Linda Vester: Bush and Kerry Health Plans
11/04/04 ABC News Vioxx article and editorial in Lancet
11/06/04 CNN "In the Money" DTC advertising

11/18/04 CNN HEADLINE NEWS Vioxx Hearings:
11/19/04 CNN AMERICAN MORNING Vioxx Hearings: Why didn't Doctors know?
11/22/04 FOX LINDA VESTER Merck's role in funding Vioxx research
11/29/04 Lou Dobbs Are We A Nation of Hypochondiracs?
12/05/04 C-Span BookTV: From Collected Works, Brattleboro, VT (Recorded 11-05-04)
12/14/04 (taped)TV Ontario, What to do after Vioxx?
12/17/04 CNN with Betty Nguyen
CNN Wolf Blitzer (interviewed by Mary Snow)
CNBC Closing Bell with Tyler Mathisen
Lou Dobbs Tonight
CNN Headline News
12/18/04 Ron Insana Show (radio)
NBC Nightly News
12/20/04 Fox News: Neil Cavuto
WBUR Radio: On Point
News Night with Aaron Brown
CNN Headline News
NPR Radio: All Things Considered
12/21/04 CNN American Morning
CNN Live
MSNBC Market Wrap with Ron Insana
MSNBC Ron Insana: The Death of a Wonder Drug
12/22/04 The Today Show
CNN Live From
12/26/04 WSJ Report with Maria Bartiromo
1/13/05 MSNBC (Over the Counter Statins)
1/24/05 CBS Evening News: Celebrex
2/18/05 MSNBC Bull's Eye
2/19/05 CNN In the Money
Fox News
CNN Headline News
2/25/05 CNN Prime News
2/28/05 CNN Lou Dobbs LIve
5/27/05 CNN Lou Dobbs Live
CNN Judy Woodruff Inside Politics
5/28/05 Fox with Bob Sellers
7/27/05 Fox and Friends, National
8/15/05 Fox 25, Boston
3/22/06 CNBC Live interview FDA, ADHD drug labeling
6/23/06 CNBC Morning Call: Zocor pricing

Expert Witness consulting and testifying fee: $550/hr

Testimony in the past 4 years:
August 3, 2006: Deposition Vioxx Products Liability Litigation, Robert G. Smith Versus Merck & Co., Inc. Attorney: Larry Wright, Watts Law Firm, One Congress Plaza, Suite 1000, 111 Congress, Austin, TX 78701. (512) 479-0500

April 30, 2007: Deposition, Zyprexa Products Liability: MDL No 1596 Litigation Zyprexa. Attorney: Jayne Conroy, Naly, Controy, Bierstein, Sheridan, Fisher & Hayes LLP. 112 Madison Mavenue, New York, New York 10016. 212-784-6400

May 18, 2007: Deposition, Estratest, Susannah K. Alexander Versus Solvay Pharmaceuticals, Inc., et al. Attorney: Ed Notargiacomo, Hagens Berman Sobol Shapiro
One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

December 12, 2007: Deposition, TriCor, Joe Lukens, Hangley Aronchick Segal & Pudlin One Logan Square, 18th & Cherry Streets, 27th Floor, Philadelphia, PA 19103-6933

December 18, 2007: Deposition, Nexium, Ed Notargiacomo, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

March 4, 2008: Deposition, CanWest Media Inc, vs. Attorney General of Canada (re restraint of CanWest's freedom of commercial speech due to the ban on direct-to-consumer advertising of prescription drugs.

March 18, 2008: Phone Deposition, Kathleen R Skiles vs. Richard M. Fruehling MD, Richard K Waggoner, PA, and Family Practice of Grand Island. Attorney: Mark A. Weber, Walentine O'Toole McQuillan & Gordon, 11240 Davenport Street, P.O. Box 540125, Omaha, NE 68154-0125

March 24-25, 2008: Deposition, Bextra Marketing, Sales Practices and Product Liability Litigation, MDL No. 1699

April 1, 2008: Hearing before Judge Jack Weinstein: Multiple plaintiffs vs. Eli Lilly re: Marketing and Sales of Zyprexa, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

July 24, 2008: Deposition, Vioxx, Consumer Plaintiff's Renewed Motion for Class Certification, Tom Sobol, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

Exhibit 2

Testimony in Past Four Years

August 3, 2006: Deposition Vioxx Products Liability Litigation, Robert G. Smith Versus Merck & Co., Inc. Attorney: Larry Wright, Watts Law Firm, One Congress Plaza, Suite 1000, 111 Congress, Austin, TX 78701. (512) 479-0500

April 30, 2007: Deposition, Zyprexa Products Liability: MDL No 1596 Litigation Zyprexa. Attorney: Jayne Conroy, Naly, Controy, Bierstein, Sheridan, Fisher & Hayes LLP. 112 Madison Avenue, New York, New York 10016. 212-784-6400

May 18, 2007: Deposition, Estratest, Susannah K. Alexander Versus Solvay Pharmaceuticals, Inc., et al. Attorney: Ed Notargiacomo, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700
December 11, 2007: Deposition, Tricor Direct Purchaser Antitrust Litigation

December 11, 2007: Deposition, TriCor, Joe Lukens, Hangley Aronchick Segal & Pudlin One Logan Square, 18th & Cherry Streets, 27th Floor, Philadelphia, PA 19103-6933

December 18, 2007: Deposition, Nexium, Ed Notargiacomo, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

March 4, 2008: Deposition, CanWest Media Inc, vs. Attorney General of Canada (re restraint of CanWest's freedom of commercial speech due to the ban on direct-to-consumer advertising of prescription drugs

March 18, 2008: Phone Deposition, Kathleen R Skiles vs. Richard M. Fruehling MD, Richard K Waggoner, PA, and Family Practice of Grand Island. Attorney: Mark A. Weber, Walentine O'Toole McQuillan & Gordon, 11240 Davenport Street, P.O. Box 540125, Omaha, NE 68154-0125

March 25-26, 2008: Deposition, Bextra Marketing, Sales Practices and Product Liability Litigation, MDL No. 1699, Jayne Conroy, Hanly Conroy Bierstein Sheridan Fisher & Hayes LLP 112 Madison Avenue, New York, New York 10016

April 1, 2008: Hearing before Judge Jack Weinstein: Multiple plaintiffs vs. Eli Lilly re: Marketing and Sales of Zyprexa, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

July 24, 2008: Deposition, Vioxx, Consumer Plaintiff's Renewed Motion for Class Certification, Tom Sobol, Hagens Berman Sobol Shapiro, One Main Street, 4th Floor Cambridge, MA, 02142-1531 Tel. (617) 482-3700

Exhibit 3

List of Documents Reviewed

Publications

1. Radley DC, Finklestein SN, Stafford RS, Off-label Prescribing Among Office-Based Physicians, *Archives of Internal Medicine,* 2006;166:1021-26.

2. Harrison RV, The Uncertain Future of Continuing Medical Education: Commercialism and Shifts in Funding, *Journal of Continuing Education in the Health Professions,* 2003;23:198-209.

3. Sackett DL, Rosenberg WMC, Gray JAM, et al, Evidence based medicine: what it is and what it isn't: It's about integrating individual clinical expertise and the best external evidence. *British Medical Journal,*1996;312:71-72, accessed from the Center for Evidence-Based Medicine, http://www.cebm.net/?o=1014 , July 13, 2008.

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6. Moynihan R. Who Pays for the Pizza? Redefining the Relationships Between Doctors and Drug Companies. 1: Entanglement. *British Medical Journal.* 2003;326:1189-92.

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106.WLC_CBU_046363

107.WLC_CBU_092879

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133. Metadata extracted from the Merlin database

Other

1. 2002 FDA-approved label for Neurontin.
2. FDA-approved label for Neurontin 1998.
3. 21 U.S.C. §360aaa(b), (c).
4. 21 U.S.C. §360aaa-6.
5. 1998 Gorson Neurology.pdf and Neurontin.mdb produced by Defendants as part of the Neurontin bibliography
6. Exhibit J to Affidavit of James E. Murray in support of Defendants' motion for summary judgment [docket no. 295] filed in US ex rel. Franklin v. Pfizer et al., 96-11651-PBS