

Jeffrey S. Barkin, MD
97 A Exchange Street
Suite 401
Portland, Maine 04101
(207)775-2244
Fax(207)221-1198
JSBarkin@aol.com
JeffreyBarkinMD.com

REPORT ON THE USE OF NEURONTIN FOR BIPOLAR AND OTHER MOOD DISORDERS

EXECUTIVE SUMMARY

Bipolar disorder is a potentially devastating illness, marked by serious debilitating comorbidities when left untreated. Fortunately, there exist a number of effective, indicated and FDA approved treatments for bipolar disorder. All of these treatments have demonstrated efficacy through the highest tier of medical evidence, the double-blind placebo-controlled randomized clinical trial, considered the “Gold Standard” in the practice of evidence based medicine. When such trials are present, evidence-based medicine requires that they guide treatment decisions.

Gabapentin, under the brand name Neurontin, was used extensively in the late 1990s and into the early part of this decade as a treatment for bipolar and other mood disorders. Prior to the analysis contained in this report, this use has been difficult to explain, as multiple double-blind placebo-controlled randomized trials have failed to show any efficacy of gabapentin over placebo as a treatment for bipolar disorder and other mood disorders. In fact, the scientific evidence demonstrates quite clearly that gabapentin is ineffective as a treatment of bipolar disorder and should not be used, especially given the fact that multiple, effective and FDA approved treatments exist for a disease that, when untreated or mistreated, can have devastating consequences. Given all of this evidence, recommending the use of gabapentin for the treatment of bipolar disorder, as an addition to other mood stabilizers or as a monotherapy, is unsupported, inappropriate and violates the principles of evidence-based medicine.

Yet, this is precisely what the Defendants did. Despite clear knowledge of the lack of efficacy of gabapentin, the Defendants funded numerous meetings and written material where the use of Neurontin for bipolar disorder was deceptively recommended. These programs and journal supplements consistently advocated the use of Neurontin for treating bipolar disorder and suggested that there was scientific support for this

proposition. This advocacy for Neurontin was in direct contradiction to the known lack of efficacy in the clinical trials, results which were usually not presented or were presented in an inaccurate and incomplete manner diminishing their import. These numerous presentations, which are detailed herein thanks to documents obtained in this litigation, carried a consistent message: Neurontin was a treatment which was effective for bipolar disorder and was safe and free of drug-drug interactions. The primary goal of this marketing message was to convince medical practitioners of the efficacy and safety of Neurontin in treating bipolar disorder despite the known research clearly demonstrating lack of efficacy.

As a direct result of the concealment or misrepresentation of critical Level 1 Evidence, many psychiatrists and mental health professionals became falsely convinced that Neurontin was a safe and effective treatment for bipolar disorder, and many patients were treated accordingly. However, this conclusion was based on the illusion of scientific support, directly created by the Defendants, which was in direct contradiction to the Level 1 Evidence that clearly and definitively demonstrated lack of efficacy. Owing to the fraudulent claims of efficacy, many patients were inappropriately treated with Neurontin. These prescriptions also led to a tremendous waste of precious healthcare resources. Sadly, this pattern of distortion has continued even into this litigation, as the “Expert Report” of Dr. Slaby previously submitted by Pfizer is incomplete (it fails to acknowledge the existence of all negative clinical trials) and inaccurate (it claims that the majority of clinical trials are positive when in fact they are negative).

INTRODUCTION

I have been asked to provide a report on whether gabapentin (Neurontin) is an effective treatment for bipolar disorder and whether Parke-Davis, and later Pfizer (“Defendants”), made materially false, misleading, omissive, incomplete and untruthful statements throughout their marketing materials. In addition, I have been asked to comment on the expert report provided by Dr. Andrew Slaby.

The methodology of this report includes the review of clinical trials investigating the efficacy of gabapentin for the treatment of bipolar disorder, case reports, marketing materials provided to me by counsel as well as the references cited in those marketing materials. My review also includes the report of Dr. Andrew Slaby and the references cited therein. In addition, independent PubMed searches were conducted.

My report contains a review of bipolar disorder, the treatments that exist, the importance of evidence-based medicine towards the selection of those treatments, the evidence-base surrounding gabapentin’s use for the treatment of bipolar disorder, a discussion of the Defendants’ marketing materials as well as a review of Dr. Slaby’s report.

QUALIFICATIONS

After graduating from Swarthmore College with distinction, a member of Phi Beta Kappa and Sigma Xi, I obtained my medical degree from Yale University School of Medicine. I completed residency training at Yale and have been treating psychiatric patients as an attending physician since 1991. I have been on the faculty as assistant professor of psychiatry at the University of Massachusetts Medical Center. My subspecialty of interest is in treating individuals with complex mood disorders such as treatment-resistant and refractory depression, and bipolar disorder. Additionally, I focus on critical reading and appraisal of the medical literature. I have published an article on “How to Read a Journal Article” in the February 2007 issue of The Carlat Psychiatry Report. I started and run a journal club which meets monthly in Portland, Maine. In this group, attending psychiatrists read journal articles with a focus on how a research piece was conducted, not simply on what the results are. The purpose is to be able to differentiate those studies and articles that are well supported from those that have substantial limitations. Studying methods allows us to understand just how effective various treatments may or may not be. We discuss contemporary techniques to delineate effective treatments. One example is the analysis of effect sizes, such as the number needed to treat. Here, we can calculate just how many patients need to be treated to achieve one success. A primary focus is to decipher the medical literature in an effort to make the best treatment decisions. Additionally, I am the program chair for education of the Maine Association of Psychiatry Physicians.

Attached is a list of my publications within the last 10 years. Attached is also a list of other cases where I have testified, either in a deposition or at a trial, in the last 4 years. My hourly rate in this matter is \$400/hr.

INEFFICACY OF GABAPENTIN

In this discussion, I will apply evidence-based practices to analyze the lack of efficacy of gabapentin. For a discussion of evidence-based medicine, see Clinical Epidemiology The Essentials 4th ed.

A. Background

Bipolar disorder (previously called “Manic-Depressive Disorder”) is a mood disorder affecting 1.5 % to 3.6 % of Americans. It is a cyclic disorder characterized by recurrent affective states. In particular, patients with this disorder generally present with one of the following three mood states (excluding euthymia, a “normal” mood state):

- a) Hypomania and mania describe periods of either elation or irritability. The manic state refers to mood disturbance which causes marked impairment in occupational or social functioning, can necessitate psychiatric hospitalization or presents with psychotic features. In contrast, a hypomanic mood episode is not

severe enough to cause marked impairment in social or occupational functioning, require psychiatric inpatient admission or have psychotic features. During a period of irritable or elated mood, other symptoms are manifest as well, such as inflated self-esteem or grandiosity, decreased need for sleep, increased production of speech, inappropriate and risky decision making and so on.

b) Patients may present in the depressed state. Here, the individual suffers from either profound sadness (dysphoria) or an inability to experience pleasure (anhedonia). These symptoms are typically accompanied by other symptoms such as change in sleep, appetite, energy and so on. Indeed, bipolar individuals typically experience depression for much of their lives.

c) A third mood state may be present: a so-called mixed state. Here, the patient presents with either hypomania or mania co-occurring with depression. Such mixed states are strongly associated with suicide. Individuals with bipolar disorder have higher suicide rates than the general population.

Individuals suffering from bipolar disorder have increased rates of divorce, legal problems and work-related impairment. There is substantial comorbidity with substance use disorders; prevalence rates for co-occurring substance-related disorders range from 50 – 70 %. There are notable increases in comorbid psychiatric disorders encompassing many diagnoses, anxiety disorders and attention deficit disorder being examples. Furthermore, there is substantial medical comorbidity in individuals struggling with bipolar disorder, with increased rates of both diabetes and cardiovascular diagnoses.

Bipolar disorder, like schizophrenia, is considered a major and often severe psychiatric disorder associated with deficits in numerous areas of an affected individual's life as delineated above. Accurate diagnosis leading to correct treatment is critical in preventing the devastation this disorder can create. Delaying the diagnosis and denying appropriate and efficacious treatment typically leads to worsened clinical outcomes. Given the various potential comorbidities and risk of serious impairments in various domains of personal functioning, accurate diagnosis with effective treatment is essential. There are treatments and factors that worsen the course of bipolar disorder. Antidepressant medication has the potential to induce mania when given to a bipolar patient. Similarly, bipolar persons are at increased risk of mood destabilization when taking non-psychiatric medications such as corticosteroids. Individuals suffering from bipolar disorder are at risk of clinical decompensation in the context of factors such as excessive stress and sleep deprivation. Additionally, substance use disorders have the potential for worsening the course for bipolar patients.

Bipolar patients are frequently misdiagnosed. The most common misdiagnosis is unipolar depression (major depression). The risk of this misdiagnosis encompasses potential treatment with antidepressants, which themselves may worsen the course of bipolar disorder. Misdiagnosis also leads to substantial disease burden. Slightly more than 1 in 3 bipolar patients are misdiagnosed and remain symptomatic for ten or more years.

B. The Treatment of Bipolar Disorder

The above notwithstanding, there are numerous treatments for bipolar disorder that have proven efficacy, the so-called “mood stabilizers.” The ideal mood stabilizer would demonstrate therapeutic benefit across all phases of bipolar disorder (hypomanic/manic, depressive and mixed). Furthermore, an ideal treatment would work both acutely and long term, preventing relapse. Unfortunately, such an ideal mood stabilizer does not exist. A discussion of available mood stabilizers with documented efficacy follows.

Lithium remains a cornerstone in the treatment of bipolar disorder. It demonstrates efficacy in acutely treating patients with hypomanic/manic symptoms as well as mixed states. Additionally, it has demonstrated efficacy in maintenance use, preventing recurrence. Lithium is FDA approved and has been known as an effective treatment since the 1970s.

Valproic acid represents another cornerstone in the treatment of patients suffering from bipolar disorder. It has demonstrated efficacy in the acute treatment in both manic and mixed states. FDA-approved for epilepsy, migraine prophylaxis and bipolar disorder, this agent has many years of documented use.

Carbamazepine, like valproic acid, is an anticonvulsant which has demonstrated efficacy in the acute treatment of both manic and mixed states. FDA approval for a time release form of carbamazepine occurred in early 2005 with the demonstration of efficacy in two double-blind studies.

Lamotrigine is another anticonvulsant that has efficacy in the treatment of bipolar patients. This agent helps prevent recurrence into the depressive state and may also have small efficacy in delaying relapse into the manic state. This mood stabilizer does not have efficacy in acutely treating any of the three phases of bipolar disorder and it typically is used in conjunction with another mood stabilizer to convey acute efficacy. Lamotrigine was FDA-approved in 2003 for the maintenance treatment of bipolar disorder.

A class of medications known as “atypical” (or second generation) antipsychotics all have documented efficacy in treating bipolar disorder. Olanzapine has demonstrated efficacy in the acute and chronic treatment of patients with bipolar disorder in the manic and mixed states. The combination of olanzapine and fluoxetine has demonstrated benefit in the depressive phase of bipolar disorder. Quetiapine has efficacy in all phases (manic, mixed and depressed) of bipolar disorder. Risperidone and ziprasidone have documented efficacy treating the manic and mixed phases of bipolar disorder. Aripiprazole, as well, has documented benefit in bipolar disorder. All of the above have been FDA-approved for the treatment of bipolar disorder. As a class of medications, the atypical antipsychotics, with the exception of clozapine, all have activity profiles demonstrating benefit in bipolar disorders.

C. Evidence-Based Medicine

From the discussion above, there are numerous efficacious medical treatments for this severe psychiatric disorder. As stated earlier, bipolar disorder is a severe mental illness. Early diagnosis helps prevent some of the devastating effects of this disorder. Once the correct diagnosis is arrived at, treatment with an efficacious agent or agents begins. How do we know that a given treatment works?

Medicine has adopted a model to demonstrate, among many things, which treatments work. This model is called evidence-based medicine and essentially elucidates the benefit (or lack thereof) of a given treatment, so that treatment decisions are based on scientific evidence derived from trials constructed to minimize the plethora of biases inherent in case reports and patient observation. There are many types of evidence which represent a spectrum of ability to demonstrate an effect. At the extremely powerful and useful end of the spectrum, we find double-blind, placebo-controlled randomized trials. In this experimental design, a treatment is compared against a placebo. The design mandates that (a) neither the examiner nor the subject know whether the active treatment or placebo is being administered, (b) that patients receiving the treatment be compared to a group not receiving the treatment (the placebo group) and (c) that patients be randomly assigned to either the treatment or the placebo group. The purpose of these mandates is to minimize biases, so that any difference noted between the two groups can be attributed to the treatment. Indeed, this is the “Gold Standard” by which treatments are measured and is appropriately named “Level 1 Evidence.” In contrast, at the other extreme, representing the least useful and powerful evidence, we find expert opinion typically based on clinical experience. This is graded as “Level 3 Evidence” and is of little benefit when trying to determine the usefulness of a given treatment. Also included in this lowest level of evidence are case reports and case series, reporting on one or a small number of patients. Level 3 Evidence cannot be used to determine efficacy since, without proper controls, blinding and randomization, improvement cannot be deemed due to the treatment. Nevertheless, it is not unusual for the lowest level of evidence to be considered a “clue” leading to follow-up that generates Level 1 Evidence (double-blind placebo-controlled randomized trial). Level 3 Evidence is often helpful to generate a hypothesis that can then be tested through properly designed clinical trials. In making treatment decisions where numerous options are available, we are to be guided by the Level 1 Evidence.

When there are numerous treatments with and without Level 1 Evidence, we are compelled to use those whose use is supported with the strongest evidence, i.e. those with Level 1 Evidence. Employing high quality data for decision making permits selection of treatments with the best data supporting efficacy. Indeed, in the United States a pharmaceutical company is usually required to demonstrate efficacy of a treatment based upon two randomized, double-blind, placebo-controlled trials to obtain approval from the FDA. Therefore, a threshold exists for determining efficacy of a given treatment.

There are also intermediate levels of evidence. Level 2 Evidence is comprised of cohort and non-randomized studies. In a cohort trial, two groups or cohorts, are identified. One group has been receiving the treatment under study while the other cohort has not. The groups are studied prospectively, that is forward in time, with no changes in treatment or non-treatment (i.e., the group that had been receiving the treatment continues to receive the treatment, and the group that had not continues treatment-free). An example of such a study would be the effect of antidepressants in pregnancy. Here one group of women has been receiving antidepressants, while another group has not been receiving antidepressants. Note there is no randomization, blinding or use of a placebo, and there is the possibility of selection bias. In this example, if the study showed that the women who had been receiving antidepressants had adverse pregnancy outcomes, we would be unable to conclude that this was due to exposure to the antidepressants. Instead, it is quite possible that the outcome in the group receiving antidepressants was due to the mothers having pre-existing depression. As a result, this study design is much less powerful than the randomized, placebo-controlled double-blind design.

Using an evidence-based approach to the practice of medicine allows the choice of the most efficacious treatments for either a group of patients or an individual one. In the case of bipolar disorder, a psychiatric illness with the potential of inflicting great harm to affected individuals, the choice of the most effective treatment is critical. Selection of such treatments derives from critical examination of the literature, as well as the application of evidence-based practices. Utilizing treatments which lack evidence of therapeutic benefit places the patient at great risk. Abdicating logical decision making makes little sense when numerous alternatives with proven efficacy exist. We are next poised to review the evidence-base of gabapentin treatment in bipolar disorder.

D. Level 1 Evidence for the Treatment of Bipolar Disorder with Gabapentin

In protocol 945-209, a Parke-Davis conducted study, gabapentin or placebo was adjunctively added to lithium and/or valproate to assess efficacy. This protocol covered the period of March 1996 through July 1997. Primary endpoints included change in total score on the Young Mania Rating Scale (YMRS) and the Hamilton Depression Rating Scale (HAM-D). Here, subjects with a diagnosis of Bipolar type 1, who remained symptomatic despite treatment with lithium, valproate or the combination of lithium and valproate, received either gabapentin or placebo. This protocol was a double-blind placebo-controlled randomized design involving 146 screened subjects of which 117 patients received at least one dose of study medication. In the intent to treat analysis (ITT) [1], it was noted that the group receiving adjunctive placebo had a statistically significantly greater decrease in the YMRS than those receiving active gabapentin. No differences between placebo and gabapentin were present in the HAM-D scores.

This study ultimately was published in the journal *Bipolar Disorders* [2]. The authors, Atul Pande, Jerri Crockett, Carol Janney, John Werth and Georgia Tsaroucha were all Warner-Lambert employees.

In the discussion of this paper, the authors opine that the “finding is at odds with the numerous clinical reports (on a total of nearly 200 patients) in whom gabapentin was ostensibly beneficial.” The authors then carried out additional data analyses. Here, the authors factored out non-compliance and adjustment in lithium dose. Regardless of the additional analysis, gabapentin was not statistically different than placebo. The authors also discuss the possibility that the study group was enriched with refractory patients who demonstrated a robust placebo response. The authors observe the exclusion of patients who were in the depressed phase at entry. Had this group been included, the authors opine, the outcome may have been different. The authors finally conclude that gabapentin is not superior to placebo. This double-blind, placebo-controlled trial, when held to the primary outcomes, clearly demonstrated that gabapentin was not superior to placebo in improvement in either the YMRS or HAM-D.

Protocol 945-421-291 was another Parke-Davis/Pfizer-conducted double-blind, placebo-controlled randomized trial comparing gabapentin to placebo as an add on to lithium, valproate, carbamazepine or any combination at stable doses. 80 subjects were planned, with a final total of 42 subjects randomized to gabapentin (20) or placebo (22) studied for 12 months. The primary outcome was the change in CGI severity (Clinical Global Impression of Severity - CGIS) from baseline to 12 months. This trial included numerous secondary outcomes. Only 50 % of the subjects completed the study with 21 drop outs for a number of reasons including lack of willingness to continue, lack of efficacy, non-compliance and poor tolerability. The study was designed using an Intent-To-Treat (ITT) population. However, a subpopulation of the ITT group was defined as the “Per Protocol” group. The PP group was comprised of subjects who met additional criteria including: 1) being between 18 and 75 years of age; 2) more than 1 (≥ 2) episodes in the past year and CGI score ≥ 4 at visit 1; 3) HAM-D score ≤ 8 or YMRS score ≤ 4 at visit 1; 4) received permitted concomitant medication only in the presence of an episode during the study; and 5) had adequate compliance rate of 80 % to 120 % during study period. The sample size in the ITT population was 41. The PP population was comprised of only 25 patients culled from the ITT group.

The results of the ITT population demonstrate a mean change of -0.9 in CGIS at study completion compared with study entry for the 20 subjects who received gabapentin, which was statistically significant. The subjects who received placebo had a mean change of -0.5 at study completion compared with baseline, which did not reach statistical significance. However, there was no statistical difference between the gabapentin and placebo arms. For the original ITT group, this study demonstrated no efficacy of gabapentin compared with placebo in change of CGIS from study completion to baseline.

As stated above, the PP population was a subpopulation of the ITT group. This group was enriched with both medication-compliant and healthy subjects at study entry, as evidenced by low scores on HAM-D and YMRS. The PP subjects who received gabapentin demonstrated a change of -1.9 on CGIS compared to baseline. Placebo-treated subjects showed a mean change of -0.8, which was not statistically significant. In this subpopulation, the gabapentin-treated subjects did demonstrate statistically

significant improvement in CGIS compared with placebo. The creation of a subgroup is troubling however as the PP group is a small subselection of the original ITT group. Moreover, the exclusion of patients after randomization can defeat the very purpose of randomization, thus introducing biases.

Study 945-421-291 was published by Vieta, et al. in the Journal of Clinical Psychiatry [3]. This article fails to distinguish the original ITT group from the PP subgroup. Instead, the 25 subjects in the PP subgroup are described in the absence of the original ITT group despite the fact that the authors falsely write that “all statistical analyses were done by intention to treat.” [3] The authors appear to have simply ignored the original ITT, creating an impression of efficacy from what is in reality just the PP subgroup. If the original integrity of the ITT population had been maintained, this would be a failed trial with the conclusion that “[t]he primary efficacy parameter did not show statistically significant differences between gabapentin and placebo.” [4] Culling out or “cherry picking” a subpopulation that shows efficacy in lieu of the ITT population is dishonest, unethical and a far cry from demonstrating efficacy through the randomized ITT population. Given the compromise of randomization and introduction of biases, through the creation of a subgroup, it is questionable whether this study can even be considered Level 1 Evidence.

An analysis of other double-blind randomized placebo-controlled clinical trials comparing gabapentin to placebo also fails to show efficacy in the diagnosis of bipolar disorder. Though Frye et al. presented posters at the 1997 and 1998 American Psychiatric Association (APA) annual meetings showing moderate or marked improvement for lamotrigine and gabapentin in bipolar disorder, these were interim data. Indeed at study completion gabapentin was not statistically different than placebo, and it was statistically inferior to lamotrigine [5].

Guille et al. presented a poster at the 1999 APA meeting showing lack of efficacy for gabapentin as an adjunctive treatment for acute manic and mixed states. They conclude: “This study did not find adjunctive gabapentin to be efficacious treatment for refractory mania...Enthusiastic clinical acceptance of gabapentin as a mood-stabilizing agent may be unwarranted” [6]. Pfizer and Parke-Davis were aware of this study, as they collected and retained a copy abstract in their files, as indicated by the document’s bates stamp.

Finally, in March 2008 Carey et al. performed a literature review of all published studies concerning the efficacy of gabapentin in bipolar disorders. The authors found that, of 29 published articles discussing studies of gabapentin in mood disorders, only 4 appeared to be based on Level 1 Evidence and “[t]hese four trials provided no substantial evidence of the efficacy of gabapentin in the treatment of bipolar disorder, or in preventing recurrence of symptoms” [7]. Moreover, the authors concluded that:

Cursory examination of the literature identified in this review reveals repeated references to a promising new treatment. Our more detailed examination demonstrates multiple poor quality observational studies

which collectively represent an echo chamber encouraging utilization of the medication based on minimal evidence.

It should be noted there have been positive open label case reports (Level 3 Evidence) describing the efficacy of gabapentin in bipolar disorder. Many of these were cited by Carey et al. However, in reviewing all of the double-blind, placebo-controlled trials (Level 1 Evidence), no efficacy of gabapentin is demonstrated. I conclude that the clinical trial database of Level 1 Evidence consistently shows lack of efficacy of gabapentin for the treatment of bipolar disorder. Therefore, the use of gabapentin for the treatment of bipolar disorder, as monotherapy or adjuvant therapy, is unsupported by the scientific evidence. This is a conclusion shared by Carey et al.

E. Summary of Evidence

There is little ambiguity about the results discussed above. In none of the double-blind trials did gabapentin demonstrate any efficacy over placebo as a treatment for bipolar disorder and other mood disorders. Quite the opposite, the scientific evidence clearly shows that gabapentin is ineffective as a treatment for bipolar disorder. Based on this scientific evidence, Neurontin should never have been recommended as a treatment for bipolar disorder.

DEFENDANTS FRAUDULENT MARKETING CAMPAIGN

A. Background

In order to render the best possible care for patients, medical professionals must have information on the most up-to-date and highest quality treatments. To this end, information utilized to make treatment decisions must be accurate. The potential danger of poor information can be devastating for patients. Information relating to excellent patient care starts with the medical literature. Therefore, it is imperative that the medical literature contains a complete, accurate and timely record of the scientific data relevant to a disease state. Information also arrives to physicians through continuing medical education (CME) meetings, grand rounds as well as interactions with colleagues.

Unfortunately, a substantial portion of the information that physicians receive about drug products originates from the companies that manufacture those very same products. While the use of sales representatives provides a clear cue to the presence of a marketing message, pharmaceutical companies also advertise their products less overtly through promotional presentations typically by a known expert as well as “supplements” which are published in medical journals often as an addition to an issue. These supplements are typically not peer-reviewed and offer the drug company another venue to market their products for the disorders to which the products are relevant.

Even more surreptitiously, pharmaceutical companies hire medical education and communication companies (MECCs) to present information that appears to be free from any manufacturer influence. MECCs are typically for-profit businesses that receive money from pharmaceutical companies to develop educational programs favorable to the product. Typically, these programs are offered live and/or telephonically. Physicians use these educational programs to obtain CME credits, which are a requirement for licensure. These programs discuss the disease states relevant to the product the pharmaceutical company seeks to promote, presenting information that appears less promotional than that offered through FDA-regulated promotional talks. FDA-regulated promotional talks must comply with the approval data of the product. Programs offered by MECC's present new information about a product typically representative of off-label (non-FDA approved) use of the product. Highly regarded experts in the field usually present these programs. Therefore, the information appears to be purely educational and from a trusted source, when in fact it is simply a well-disguised marketing message. Whereas the purpose of a marketing message is to increase the sales of a product, the purpose of medical education is to educate physicians. In the case of medical education activities sponsored by the Defendants, as demonstrated below, it is clear that the former goal supplanted the latter. This sort of covert implantation of a marketing message into medical education and literature is particularly dangerous, since physicians approach both with their guard down assuming the materials to be free from company bias.

B. Review of Defendants' Marketing Conduct

Before delving into specific documents, it is important to note that a balanced discussion of the evidence surrounding a drug's efficacy must include any Level 1 Evidence if such evidence is available. There is simply no situation where medical education benefits from an exclusion of Level 1 Evidence. However, this was a frequent tactic of Defendants.

A Parke-Davis memorandum dated March 10, 1998 contains a set of slides titled "Closing the Psychiatry-Neurology Divide: Emerging Uses of Anticonvulsants, presented at 50 CME dinners in numerous cities across the country as well as telephonically, throughout March and April of 1998 (WLC_CBU_012564, Pfizer_TMartin_0001795). From the set of slides, it is clear that, while the speaker might change, the message does not. Slides from this presentation list acute mania and mood changes in epilepsy as belonging to the "Therapeutic Spectrum" of gabapentin. More striking, a slide entitled "Gabapentin: Indications Summary" lists bipolar disorder. The use of the word "Indications" is misleading, as gabapentin does not and did not have an FDA approved indication for bipolar disorder. The slide falsely mentions, "early evidence suggests antimanic, antidepressant and mood stabilizing effects" but makes no mention of the negative Level 1 Evidence that was available at the time in protocol 945-209. The same presentation misleadingly concludes with a statement that "[c]ontrolled studies are needed to support open trials and case reports" even though such a study was conducted and it was negative for gabapentin. It is disconcerting that bipolar disorder is mentioned as an indication for gabapentin with neither FDA approval nor data from a Level 1 trial.

Hundreds and possibly close to 1000 physicians were exposed to this message in roughly 40 different cities (WLC_FRANKLIN_0000171583; WLC_FRANKLIN_0000081633).

“New Frontiers in Social Phobia and Bipolar Disorder”, produced by CME Inc. and supported through an unrestricted educational grant by Parke-Davis (WLC_CBU_028064) is from 1998. In this presentation, gabapentin is falsely referred to as one of the “Newer Mood Stabilizers” with reports of benefit in:

- Mania
- Bipolar depression
- Bipolar maintenance
- Rapid cycling
- Treatment resistance
- Mood instability
- Social phobia
- Chronic pain

There is no discussion of the evidence to support these claims. Moreover, there is no mention of the results of protocol 945-209 (Pande) which had already been completed and analyzed. At the same time that this event series began, Dr. Pande had already prepared a “Letter to the Investigators” that revealed the negative results of this trial. Finally, the assertions of efficacy noted above, in the face of the results from 945-209, defy the known data from the Defendants’ own Level 1 clinical trial. Unfortunately, CME Inc. is a source for CME that many physicians believe they can rely on for accurate information. Documents show that 5,600 psychiatrists were exposed to this information in 30 cities from July through October (WLC_FRANKLIN_0000036437; WLC_FRANKLIN_0000081633; CME1478-CME1748; CME0589 – CME0658).

In a teaching monograph published in *CNS Spectrums* in May 1998, sponsored by an unrestricted educational grant from Parke-Davis and entitled “Current Treatments in Bipolar Disorder” (WLC_CBU_012274), the authors concede that “the evidence supporting the effectiveness of...Neurontin is largely anecdotal.” Despite access to the results of non-anecdotal study (i.e. a Level 1 study), there is no mention of the results (nor even the occurrence) of 945-209. Instead, this statement is offered: “Studies have shown that improved mood, lower anxiety and increased sociability were nearly twice as frequent among Neurontin patients, when compared to placebo patients.” It is unclear which “studies” showed this as none are cited. Statements like this lend credence to the belief that there is an evidence-base supporting gabapentin’s efficacy for the treatment of bipolar disorder.

The monograph concludes with a discussion of gabapentin’s “tolerability” for the following reason:

“I discuss these tolerability aspects of antiepileptic drugs [only the tolerability of gabapentin is discussed], *in light of the evidence for their beneficial effects on bipolar disorder...*any physician can elect to try a

medication if it's been established as safe by the FDA for another indication if they have a reason to do so.”

Putting aside the results of 945-209, there is a clear elevation of anecdotal Level 3 Evidence in this concluding statement to create the illusion of solid evidence supporting an off-label use. In light of the results of 945-209, this statement is patently misrepresentative of the evidence-base. CNS Spectrums claims a circulation of 50,000. (<http://www.cnsspectrums.com/asp/AuthorGuidelines.aspx>).

In a Cleveland Clinic Journal of Medicine supplement containing the proceedings of a closed symposium held on July 24, 1998 entitled “New Treatment Strategies in Psychiatry” (Pfizer_TMartin_0001736), made possible through an unrestricted educational grant from Parke-Davis, gabapentin as a treatment for bipolar disorder is also discussed. An open-label trial (Young et al.) is presented as suggesting “that gabapentin may be an effective treatment for mania in bipolar patients.” Despite the fact that this symposium *post-dates* Dr. Pande’s Letter to Investigators, there is no mention of the results of 945-209. It is unclear how a presentation regarding gabapentin’s efficacy for the treatment of bipolar disorder can be complete without the disclosure of the only Level 1 Evidence investigating it. Parke-Davis had 43,000 copies of this supplement printed, 38,000 to be mailed to Cleveland Clinic Journal’s “psychiatry audience” and an extra 5,000 copies that could be handed out to physicians through Parke-Davis’s door-to-door sales force (SH_0011442).

In 1999, Parke-Davis published a supplement in *Epilepsia* authored by its employee Leslie Magnus titled “Nonepileptic uses of Gabapentin” [8]. In the section titled “Gabapentin in Psychiatric Disorders,” there is a suggestion that the data supports the use of gabapentin for bipolar disorder. Three “publications” are discussed including a series of case studies, an open-label study and a case study of *one* patient. No mention is made of either the 945-209 study or the Guille study. There is no rationale for discussing these reports over, and to the exclusion of, the results of 945-209. *Epilepsia* claims a circulation of 5,000 (WLC_CBU_167738).

Dr. Pande’s own 1999 publication entitled “Treatment of Social Phobia With Gabapentin: A Placebo-Controlled Study” [9] states that “[i]n clinical studies of patients with epilepsy, gabapentin produced improvements in mood...” Even in an article authored by the lead investigator of 945-209, the results are not disclosed. This is a pretty shocking oversight. Unfortunately, Parke-Davis distributed 25,000 copies of this publication to psychiatrists through the mail and another 125,000 to physicians through the door-to-door sales force (WLC_CBU_134928). This is on top of a circulation of 8,000 for this journal (PFIZER_LKNAPP_0026006). By contrast, Pande’s later publication of gabapentin lacking efficacy in bipolar disorder was published in a journal with a circulation of only 455 (PFIZER_LKNAPP_0026006).

The same CME Inc. slides noted above, touting gabapentin as a new mood stabilizer with reports of benefit, were used in another CME Inc. series of events from 1999, also supported by Parke-Davis, entitled “New Frontiers in Anxiety, Substance

Abuse and Bipolar Disorders (WLC_CBU_170490). Once again, gabapentin is falsely referred to as one of the “newer mood stabilizers.” The slide that lists the benefits of gabapentin is followed by one summarizing the case studies involving gabapentin. Seven case studies are listed showing improvement in the gabapentin population. Further into the presentation, a slide presents the advantages and disadvantages of gabapentin. Under disadvantages, “Need for controlled studies (under way)” is listed. In 1999, there were results from controlled studies *already available*, yet those results are not present in this lecture. It is unclear what controlled studies were “under way” in 1999, but it is indisputable that results from controlled studies already existed and therefore should have received a prominent place in any talk, including this one, that claimed to summarize the science behind gabapentin and bipolar disorder. Instead, there is simply no mention of these studies. The results of 945-209, constituting the best Level 1 Evidence to date, were known to the sponsors of this event, but had not yet been published. As previously mentioned, there is simply no valid reason for the omission of critical Level 1 Evidence. An estimated audience of 8,500 mostly psychiatrists attended all across the country and were exposed to these messages (PFIZER_NMANCINI_0011631).

In 2000, Defendants distributed a CME monograph called “Spectrum of Uses of Antiepileptic Agents: New Treatments, New Strategies.” This monograph made numerous false statements about gabapentin’s utility in bipolar disorder. First, the monograph states that “Gabapentin...has been used alone or adjunctively to treat bipolar disorder, social phobia, migraine, neuropathic pain and substance abuse,” and that the “efficacy of ...gabapentin in treating these diverse conditions may be due to overlapping mechanisms of action.” The false implication is that gabapentin is indeed effective in treating bipolar disorder. This of course is not true, and no mention is made of the negative Pande and Guille studies. Further in the monograph, it is stated that “Several small studies of bipolar disorder have shown promising results with gabapentin used as an adjunct to other psychotropic agents” (MDL_Vendors_055236). Given that this is a CME monograph, physicians reading this for CME credit expected that they were given scientifically up-to-date, reliable and relevant information. They would not have known that clinical trial results such as Pande’s and Guille’s were being withheld. The monograph doesn’t just omit Pande. It denies its existence altogether, by claiming that the “largest study of gabapentin for this indication was a retrospective analysis of 73 patients with bipolar I or II, bipolar disorder not otherwise specified, or schizoaffective disorder who failed to respond to or could not tolerate other medications.” The false and misleading implication is that gabapentin had been shown to be effective, rather than ineffective, in the “largest study” conducted to date. It should come as no surprise that the conclusion of this so-called “largest study” is that “Rapid Cycling was eliminated in all patients, and 67 (92%) had a positive response to the drug that was substantial enough to allow a return to normal activities,” a result that has never been confirmed by Level 1 Evidence. Finally, the CME post-test contains a question which, in order for physicians to correctly answer it, requires them to choose gabapentin as one of the anticonvulsants which “have also shown mood-stabilizing properties...” Parke-Davis had 6,000 copies of this monograph printed, 5,000 to be mailed to physicians and an extra 1,000 copies that could be handed out to physicians through Parke-Davis’s door-to-door sales force (SH_0064555.0012057).

In 2000, Pfizer sponsored a lecture prepared by the Institute for Continuing Healthcare Education entitled “Anticonvulsants in Psychiatry: Historical Perspectives & New Therapeutic Directions” (VOX035086). In this lecture, gabapentin is once again presented as scientifically supported therapy for bipolar disorder. In a slide entitled “Psychotropic Effects of Treatments Clinically Used for Bipolar Disorders,” gabapentin is listed as effective for both mania and depression (VOX035109). The citations on this slide point to the open-label case studies so often referenced. Of course, by 2000, the Defendants knew the results of both 945-209 and the Guille study. The Frye study would also be published in 2000. In other words, there were *three* double-blind placebo-controlled randomized trials that contained results unfavorable to gabapentin, yet this lecture, using Level 3 Evidence, claims gabapentin is effective for both mania and depression. In contrast to previous events, and *after* listing gabapentin as an effective agent for mania and depression, this lecture discloses the results from 945-209 over 13 slides, 3 of which focus on the study’s “weaknesses,” implying that the results are not reliable. No mention is made that the results are in fact confirmed by the results of Guille. It is startling to see a presentation that ignores or criticizes the available Level 1 Evidence, yet uses Level 3 Evidence to support claims of effectiveness. Simply put, flawed or not, the results from 945-209 should have been the first results presented along with the results from Guille, as they were of the most import to the scientific community.

Even more perplexing, after presenting the results of 945-209, the lecture continues with a slide “Arguments for Use of Alternative Anticonvulsants in Bipolar Disorder” that mentions “Evidence supporting the effectiveness of lamotrigine and gabapentin.” The next slide, “Arguments Against Use of Alternative Anticonvulsants in Bipolar Disorder” lists “Absence of double-blind, placebo-controlled studies.” This slide comes *after* presenting 13 slides of a double-blind placebo-controlled study. The lecture contains the same slide seen in other lectures, “Gabapentin: Advantages and Disadvantages” which still states the “Need for controlled studies (under way).” In addition, we find the same slide summarizing the case studies favorable to gabapentin.

The take home points from this presentation seem to be:

- Gabapentin is effective for both mania and depression
- There are double-blind placebo-controlled results available from only one trial that show that placebo is more effective than gabapentin, but the study is fraught with weaknesses and the results have not been confirmed
- There is an absence of double-blind placebo-controlled results
- But, these studies are under way
- There are a host of case studies showing the effectiveness of gabapentin

This program is not merely littered with misrepresentations and inaccuracies, but is a frank distortion of the science. To conclude that gabapentin was effective, and thus recommend its use for the treatment of bipolar disorder, in the face of the mounting Level

1 Evidence to the contrary is not only illogical and ludicrous, but also unethical. To state that there was an absence of quality trials is simply false. It is still unclear which studies were “under way.”

Another CME Inc. activity, supported by an unrestricted educational grant from Parke-Davis (WLC_CBU_028929) from 2000 entitled “Anxiety & Bipolar Disorders: Challenges in Current Management,” contains more of the same message. Gabapentin is still listed as a “mood stabilizer”; reports of benefits are presented, all supported by Level 3 Evidence. There is no mention of the results of any of the double-blind placebo-controlled randomized clinical trials. Gabapentin is summarized as:

- Easy to use
- Well-tolerated
- No drug interactions
- Useful adjunct
- Not primary agent for mania/rapid cycling

This theme, that gabapentin is safe and free from drug-drug interactions, is offered as a continual subtext throughout the activities supported by the Defendants. It should be noted that, while safety is of great concern to a prescriber, alone it is not a reason to prescribe a medication. As with the prior two series of CME Inc. meetings, this series was held in dozens of cities, with an audience of more than a thousand physicians (WLC_CBU_180343; WLC_CBU_108957; WLC_CBU_175353).

In October 2000, the same month that the Pande study was published, Pfizer released a CME monograph titled “Interface of Neurology and Psychiatry: Diagnostic and Treatment Issues.” This monograph contained a section called “New Options in the Management of Bipolar Disorders,” discussing the “possible efficacy of gabapentin in mood disorders.” The monograph mentions that “Reports of the use of gabapentin are primarily from open-label or retrospective studies.” This statement and the impression created by it are both false. By this point, there was a wealth of Level 1 Evidence showing that gabapentin was not effective. Moreover, the articles cited are the same favorable and unreliable reports that were recycled in the earlier marketing materials. There is no mention of Pande, Frye or Guille. Sadly, Parke-Davis distributed 7,000 copies of this CME monograph via direct mail to physicians (SH_0044769; WLC_CBU_174105).

C. Cochrane Review

The Cochrane group is an internationally known foundation that provides high quality evidence-based reviews. Indeed, they are the premiere international repository of clinical information. Sometime before November 5, 2001 Anne Stals of the Cochrane group asked Dr. Pande of Pfizer for references concerning the use of gabapentin in bipolar disorder. In an email dated November 5, 2001 Dr. Pande provides a bibliography concerning the use of gabapentin in patients with Bipolar Disorder. He states “This list

has not been updated in several months so it should not be treated as comprehensive” (PFIZER_APANDE_0005005). What is concerning is Pande’s obvious omission of the Frye study published December, 2000, which demonstrated lack of efficacy of gabapentin in Bipolar Disorder. Furthermore, Pande omitted mention of the poster by Guille et al presented at the American Psychiatric Association in 1999. The conclusion of the Guille poster states “This study did not find adjunctive gabapentin to be efficacious treatment for refractory mania...Enthusiastic clinical acceptance of gabapentin as a mood-stabilizing agent may be unwarranted.” The clinical information provided by both Frye and Guille demonstrate results unfavorable to gabapentin yet they are omitted from Pande’s bibliography. [6]

On July 8, 2003, the Cochrane group again requested information from Pfizer regarding the use of anticonvulsants in bipolar disorder. They specifically requested the published and unpublished data regarding gabapentin in bipolar disorder. Internal emails from Pfizer reveal a lack of cooperation in supplying this information. An email dated December 23, 2003 from Bruce Parsons of Pfizer states: “*I would not send unpublished Neurontin data to anyone outside of Pfizer*” (PFIZER_BPARSONS_0030122; Emphasis Added). Numerous internal emails follow which continue to show an effort to withhold this data. By February 23, 2004 an internal email from Dr. Anitra Fielding, a Senior Medical Advisor at Pfizer global Pharmaceuticals in UK notes:

They (Cochrane group) have requested specifically, unpublished data on gbp (gabapentin) in bipolar disorder and additional info on the Pande trial which was not incorporated into the publication (see below)...We appreciate everyone is busy with pregabalin activities but obviously we need to respond in a timely fashion in order to build trust with our customers – a key Pfizer initiative. If we are not willing to provide this information then we need to get back to the Cochrane team asap as this has been going on for a considerable time now and does not reflect well on Pfizer, and in particular from my point of view Pfizer UK, if we take 4 months to say sorry no. If the answer is sorry no, please can I be copied on the global response to the Cochrane team (contact details in message below also in red) and equally copied in if the answer is yes and information sent, so that I can inform the UK team the matter is closed one way or another. Either way it would be much appreciated if this could be resolved promptly. (PFIZER_BPARSONS_0098666).

On March 9, 2004, Lloyd E. Knapp, Pharm.D. of Pfizer Global Pharmaceuticals asked Dr. Macritchie of the Cochrane group if it would be possible to set up a conference call. A conference call was set up for March 23, 2004 (PFIZER_LKNAPP_0115557). However, when the collaborators from the Cochrane group called, no one from Pfizer was there (PFIZER_LKNAPP_0116131). Dr. Macritchie then again asked Dr. Knapp again for the unpublished gabapentin data on November 7, 2004 (PFIZER_LKNAPP_0104674). As of the present time, the Cochrane group has been unable to publish a review: “Due to the delay in converting this protocol to a review, it

has been withdrawn, subject to receiving the first draft of the completed review” (<http://mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD003379/frame.html>).

The emails reviewed demonstrate Pfizer’s obfuscation of the data on gabapentin as a treatment for bipolar disorder. The lack of cooperation of Pfizer with Cochrane is best seen by the withholding of data that shows lack of efficacy. Their behavior in withholding data from the Cochrane Group is fully consistent with all of Defendants’ other marketing schemes. If the data had demonstrated a beneficial effect of gabapentin on bipolar disorder, Pfizer would have shared the data with Cochrane.

D. Summary of Defendants’ Conduct

From review of these documents, it is clear that the sponsors and supporters of these medical education activities and articles had an agenda other than the full disclosure of scientific information and education of physicians. It is frightening that the Defendants could have so pervasively and comprehensively miseducated physicians. What is particularly chilling is how skillfully the message of gabapentin’s efficacy, a claim that was unsupported by evidence the entirety of which, until this litigation, the Defendants alone possessed, was presented. The use of medical education, often delivered by trusted sources to an unguarded audience prepared to learn the unbiased details of treatments and diseases, represents a particularly efficient vehicle for perpetuating a false message. Medical education, be it through a CME, grand rounds or simply physician-to-physician, cannot use a “cafeteria” approach where only select reports are used. Medical education must be inclusive. Furthermore, there is a duty, as an educator, to provide an education that is factually accurate and free of bias. Neither the sponsors, nor the creators, nor the deliverers of medical education may abdicate this duty. The Defendants completely ignored this duty, as it is clear that their motivation was to mislead physicians into believing that gabapentin’s efficacy for bipolar was scientifically supported. This was accomplished through both misrepresentations and distortions of the science. The Defendants’ use of medical education activities and scientific articles as their vehicle is deplorable.

The tactics used in these documents included (a) clear omission of Level 1 Evidence or diminishment of its import, (b) the inappropriate elevation of anecdotal evidence, and (c) the use of illogical and unsupported evidentiary conclusions. Regardless, the objective was clear: to convince medical practitioners of the efficacy and safety of gabapentin in treating bipolar disorder, despite the known research clearly demonstrating lack of efficacy. As a direct result of this, psychiatrists and other mental health professionals became convinced that gabapentin was a safe and effective treatment for bipolar disorder, and many patients were treated accordingly. However, this conclusion was in direct contradiction to the Level 1 Evidence. Owing to the fraudulent claims of efficacy, many patients were inappropriately treated with gabapentin. The omission of critical Level 1 Evidence falsely created a perception that Neurontin was safe and effective in bipolar disorder. As a result, individual patients, insurance companies, state and federal governments wasted substantial money on a product that its

manufacturer knew to be ineffective. This is money that could have been spent on the use or discovery of truly effective treatments. It appears that a further tactic included preventing outside parties like the Cochrane group from conducting a review which would have contradicted the marketing messages and undercut their marketing efforts.

In sum, the Defendants' widespread recommendation to use gabapentin, on the basis of purely anecdotal evidence and in contradiction to the Level 1 Evidence, for a severe and debilitating illness such as bipolar disorder, represents the elevation of product sales over patient care. The marketing statements used were false, misleading, deceptive, and concealed crucial information about gabapentin that would have precluded its use.

DEFENDANTS' EXPERT REPORT

In addition to my findings and opinions above, I have been asked to review the undated "Expert Report" of Dr. Slaby submitted by Defendants in this litigation. I do not need to address the entire report, as only the section on pages 11-13 of the report addresses the use of gabapentin for bipolar and other mood disorders. My initial comment is on its face, the "Expert Report" does not appear to be utilizing any particular method. Although it does cite to "studies" in published literature, nowhere does the "Expert Report" identify whether any of those so-called studies are in fact randomized, placebo-controlled, double-blind studies, nor does it segregate the studies into the levels of evidence so that they can be appropriately analyzed. Moreover, the "Expert Report" appears to be basing its conclusion on "case reports, nonrandomized clinical trials, and small case studies," and not the available randomized, placebo-controlled, double-blind clinical trials. Based on part C of my section titled "Inefficacy of Gabapentin" above, such an approach is unscientific, potentially biased and clearly inappropriate.

Second, it is clear that the author of the "Expert Report" did not receive all of the necessary Level 1 Evidence on gabapentin. He makes no reference to the negative Guille study. Moreover, he cites only Vieta's publication of the results of 945-421-291, which I demonstrated above are inaccurate, rather than citing to Pfizer's internal unpublished analysis. Assuming that the author did not in fact know about the existence of this unpublished information, the only conclusion is that Pfizer did not provide the information to the author and the author was unable to obtain the information independently.

Third, consistent with the marketing efforts of Pfizer and Parke-Davis, the "Expert Report" elevates the lower tiers of evidence such as case reports and anecdotes over the Level 1 Evidence in order to falsely suggest that the evidence supporting the efficacy of gabapentin outweighs the negative. In one paragraph, the "Expert Report" cites to 17 different publications which "clearly indicate there may be a role for Gabapentin, especially for the depressive component of bipolar disorder." Of those 17 citations, only two are in fact Level 1 Evidence, and those studies (Frye and Vieta) were negative, i.e. not supportive of the use of gabapentin in mood disorders. Missing from this paragraph is a complete discussion of the Level 1 Evidence, including the studies of

Pande and Guille, which would have rendered the conclusion of that paragraph unsupportable.

Pande and Frye are both referenced in a following paragraph as two of “[o]nly a few studies” that “have not found such promise.” However, the actual findings of Pande and Frye are never reviewed, suggesting that these citations are equivalent to citations of the favorable anecdotal case reports. Additionally, that paragraph fails to include the results of Guille and 945-421-291, suggesting that the question of gabapentin’s efficacy (or more properly inefficacy) is unsettled scientifically.

Dr. Slaby spends much of his report advocating the use of non-FDA approved treatments. This is not the issue. Rather, the issue is the purposeful and misleading withholding of Level 1 Evidence which clearly and definitively demonstrates the lack of efficacy of gabapentin in bipolar disorder.

Based on the foregoing, the undated “Expert Report” of Dr. Slaby submitted by Defendants is inaccurate, incomplete, unscientific and unreliable.

CONCLUSIONS

By late 1997, the Defendants knew full well from their own protocol 945-209 that there was no benefit of gabapentin compared to placebo in bipolar disorder. Indeed, after a thorough analysis of the results, they wrote a “letter to investigators” dated July 28, 1998. This letter stated “...placebo patients showed a greater decrease in the total YMRS score than the gabapentin patients.” Yet, they funded numerous events all around the country which falsely stated that gabapentin was a safe and promising agent for treating bipolar disorder. This message was consistently and repetitively delivered. As a direct result of this, psychiatrists and other mental health professionals became convinced that Neurontin was a safe and effective treatment for bipolar disorder and many patients were treated accordingly. However, this conclusion is in direct contradiction to the Level 1 Evidence which clearly and definitively demonstrated lack of efficacy.

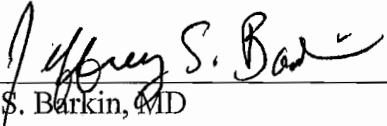
Owing to the fraudulent claims of efficacy, many patients were inappropriately treated with Neurontin. The omission of critical Level 1 Evidence falsely created a perception that Neurontin was safe and effective in bipolar disorder. Substantial money was unnecessarily spent on a product that was known by its manufacturer to be ineffective. This is money that could have been better used in other ways.

What is particularly shocking is the manner in which Parke-Davis and Pfizer exploited the supposedly independent sources of information that physicians rely on for accurate information. All physicians must participate and document ongoing continuing medical education (CME) as a basis for licensure. The marketing of gabapentin extended into such CMEs. As physicians, we are dependent on our CME in making clinical decisions, and those decisions impact patient care. Additionally, what we write with our prescription pads generates revenue for pharmaceutical manufacturers. It is startling to

what extent the makers of gabapentin were able to corrupt the CME process and conceal from us the Level 1 Evidence that they possessed. This evidence clearly and convincingly demonstrates lack of benefit of gabapentin in bipolar disorder. As physicians, we must know all the data about the treatments we utilize. Defendants' distortion and manipulation of the data (especially their failure to provide data on the lack of efficacy) led to the widespread use of gabapentin in bipolar disorder. This cost patients, insurance companies and taxpayers large amounts of money which should have been spent on truly effective treatments. Additionally, failure to share data on the lack of efficacy created a scenario where patients were prescribed gabapentin rather than another efficacious treatment. This resulted in direct harm to patients suffering from bipolar disorder, a severe and disabling illness.

Lastly, I find it unsettling that Pfizer was unconcerned that physicians were prescribing Neurontin despite the negative evidence demonstrating that such use was ineffective. We, the physicians who treat patients with bipolar and other mood disorders, should have been alerted to the full extent of this negative data. Instead, Pfizer perpetuated the myth that gabapentin was safe and effective in bipolar disorder utilizing only weak Level 3 Evidence despite the existence of known Level 1 Evidence. Pfizer could have cooperated with the Cochrane group in completing its analysis, which may have accelerated the comprehensive review of the evidence of Neurontin. Instead, Pfizer appears to have blocked access to the unpublished data that the Cochrane group was seeking, causing a delay in or possibly a withdrawal of the review. Similarly, the "Expert Report" of Dr. Slaby submitted by Pfizer in this litigation could have, but did not, set the record straight. Instead, the same omissions and distortions of the scientific record seen in the marketing documents are made.

Please note that the foregoing is based on my experience, training, education and the information I have reviewed or am generally aware of. I reserve the right to supplement this report if additional information is made available.



Jeffrey S. Barkin, MD

Date: 7/25/08

[1] Defined as the population initially randomized to treatment or placebo.

[2] Pande AC, Crockett JG, Janney CA et al. Gabapentin in Bipolar Disorder: A Placebo-Controlled trial of adjunctive therapy *Bipolar Disorders* 2000;2:249-255.

[3] Vieta E, Goikolea JM, Martinez-Aran A et al. A Double-Blind, Randomized, Placebo-Controlled, Prophylaxis Study of Adjunctive Gabapentin for Bipolar Disorder *J Clin Psychiatry* 2006;67:473-477.

[4] <http://www.clinicalstudyresults.org/documents/company-study-329-0.pdf>

[5] Frye MA, Ketter TA, Kimbrell TA et al. A Placebo-controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders *J Clin Psychopharmacology* 2000 Dec; 20(6):607-614. These results were reiterated in a follow-up publication by Obrocea et al. which discussed the same trial. It is not clear whether this publication contains analysis of new patients studied under double-blind conditions or simply a reanalysis of data from the Frye et al. study. Nevertheless, the authors of Obrocea et al. conclude that gabapentin "does not appear to be effective in acute mania or as a mood stabilizer in monotherapy." Obrocea GV, Dunn RM, Frye MA et al. Clinical Predictors of Response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002;51:253-60.

[6] Guille C. "Gabapentin versus placebo as adjunctive treatment for acute mania and mixed states in bipolar disorders." American Psychiatric Association, Annual Meeting 1999; NRJO:63.

[7] Carey TS, Williams JW, Oldham JM et al. Gabapentin in the treatment of mental illness: "The echo chamber of the case series." *J. Psychiatric Practice* 2008; 14 (suppl 1): 15-27.

[8] Magnus L. “Nonepileptic uses of Gabapentin” *Epilepsia*. 1999; 40(Suppl. 6): S66-S72.

[9] Pande AC, Davidson JRT, Jefferson JW et al. “Treatment of Social Phobia With Gabapentin: A Placebo-Controlled Study.” *Journal of Clinical Psychopharmacology*. 1999; 19(4): 341-48.

List of Documents Reviewed

Publications

1. Altshuler LL, Keck PE Jr, McElroy SL. Gabapentin in the acute treatment of refractory bipolar disorder. *Bipolar Disord.* 1999; 1: 61-65.
2. Bennett J, Goldman WT, Suppes T. Gabapentin for Treatment of Bipolar and Schizoaffective Disorders. Letter to the Editor. *J Clin Psychopharmacology.* 1997 17: 140-2.
3. Botts SR, Raskind J. Gabapentin and lamotrigine in bipolar disorder. *Am J Health-Syst Pharm.* 1999; 56: 1939-44.
4. Cabras PL, Hardoy JM, Hardoy MC et al. Clinical Experience With Gabapentin in Patients with Bipolar or Schizoaffective Disorder : Results of an Open-Label Study. *J Clin Psychiatry.* 1999; 60(4): 245-48.
5. Carey TS, Williams JW, Oldham JM et al Gabapentin in the treatment of mental illness: "The echo chamber of the case series." *J Psychiatric Practice* 2008; 14 (suppl 1): 15-27.
6. Carta MG, Hardoy MC, Dessi I et al. Adjunctive gabapentin in patients with intellectual disability and bipolar spectrum disorders. *Jour of Intellectual Disability Research.* 2001; 45(2): 139-45.
7. Carta MG, Hardoy MC, Hardoy MJ et al. The clinical use of gabapentin in bipolar spectrum disorders. *J Affect Disord.* 2003; 75: 83-91.
8. Dimond KC, Pande AC, LaMoreaux L et al. Effect of Gabapentin (Neurontin) on Mood and Well-Being in Patients with Epilepsy. *Progressive Neuro-Psychopharmacology & Biological Psychiatry.* 1996; 20: 407-417.
9. Erfurth A, Kammerer C, Grunze H et al. An open label study of gabapentin in the treatment of acute mania. *Jour Psychiatric Research.* 1998; 32: 261-264.
10. Ferrier I.N. Lamotrigine and Gabapentin Alternatives in the Treatment of Bipolar Disorder. *Neuropsychobiology.* 1998; 38: 192-197.
11. Fletcher RW, Fletcher SW Clinical Epidemiology The Essentials 4th ed. Lippincott Williams & Wilkins 2005.
12. Frye MA, Ketter TA, Kimbrell TA et al. A Placebo controlled study of lamotrigine and gabapentin monotherapy in refractory mood disorders *J Clin Psychopharmacology* 2000 Dec; 20(6)607-614
13. Ghaemi SN, Katzow JJ, Desai SP et al. Gabapentin Treatment of Mood Disorders: A Preliminary Study. *Jour Clin Psychiatry.* 1998; 59: 426-429.
14. Guille C. "Gabapentin versus placebo as adjunctive treatment for acute mania and mixed states in bipolar disorders." American Psychiatric Association, Annual Meeting 1999; NRIO:63.
15. Harden CL, Goldstein MA. Mood Disorders in Patients with Epilepsy. *CNS Drugs.* 2002; 16(5): 291-302.
16. Knoll J, Stegman K, Suppes T. Clinical experience using gabapentin adjunctively in patients with a history of mania or hypomania. [Preliminary Communication]. *Jour Affective Disorders.* 1998; 49: 229-233.
17. Marcotte D. Use of topiramate, a new anti-epileptic as a mood stabilizer. *Journal of Affective Disorders.* 1998; 50: 245-51.

18. Maurer I, Volz HP, Sauer H. Gabapentin Leads to Remission of Somatoform Pain Disorder with Major Depression. [Case Report]. *Pharmacopsychiatry*. 1999; 32: 255-57.
19. Mauri MC, Laini V, Scalvini ME et al. Gabapentin and the Prophylaxis of Bipolar Disorders in Patients Intolerant to Lithium. *Clin Drug Invest*. 2001; 21(3): 169-74.
20. McElroy SL, Keck PE Jr. Pharmacologic Agents for the Treatment of Acute Bipolar Mania. *Biol Psychiatry*. 2000; 48: 539-57.
21. McElroy SL, Soutullo CA, Keck Jr. PE et al. A Pilot Trial of Adjunctive Gabapentin in the Treatment of Bipolar Disorder. *Annals of Clinical Psychiatry*. 1997; 9(2): 99-103.
22. Obrocea GV, Dunn RM, Frye MA et al. Clinical Predictors of Response to lamotrigine and gabapentin monotherapy in refractory affective disorders. *Biol Psychiatry* 2002;51:253-60.
23. Pande AC, Crockett JG, Janney CA et al. Gabapentin in Bipolar Disorder: A Placebo-Controlled trial of adjunctive therapy *Bipolar Disord* 2000;2:249-255
24. Perugi G, Toni C, Ruffolo G et al. Clinical Experience Using Adjunctive Gabapentin in Treatment-Resistant Bipolar Mixed States. *Pharmacopsychiatry*. 1999; 32: 136-41.
25. Pollack MH, Scott EL. Gabapentin and Lamotrigine: Novel Treatments for Mood and Anxiety Disorders. *CNS Spectrums*. 1997; 2(10): 56-61.
26. Post RM, Ketter TA, Denicoff K et al. The place of anticonvulsant therapy in bipolar illness. *Psychopharmacology* 1996; 128: 115-129.
27. Rosenberg KP. Gabapentin for chronic insomnia. [Letter to the Editor]. *Am J Addict*. 2003; 12(3): 273-4.
28. Ryback R, Ryback L. Gabapentin for Behavioral Dyscontrol. [Letter to the Editor]. *Amer Jour Psychiatry* 1995; 15: 1399.
29. Ryback RS, Brodsky L, Munasifi F et al. Gabapentin in Bipolar Disorder. [Letter]. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 1997;9: 301.
30. Sachs GS, Printz DJ, Kahn DA et al. The expert consensus guideline series: medication treatment of bipolar disorder 2000. *Postgrad Med*. [Special Report]. 2000(April): 1-104.
31. Schaffer CB, Schaffer LC. Gabapentin in the Treatment of Bipolar Disorder. [Letter to the Editor]. *Amer Jour Psych*. 1997; 154: 291.
32. Sokolski KN, Green C, Maris DE et al. Gabapentin as an Adjunct to Standard Mood Stabilizers in Outpatients with Mixed Bipolar Symptomatology. *Annals of Clinical Psychiatry*. 1999; 11(4): 217-22.
33. Stanton SP, Keck Jr. PE, Mcelroy SL. Treatment of Acute Mania With Gabapentin. [Letter to the Editor]. *Amer Jour Psych*. 1997; 154: 287.
34. Sussman N. Gabapentin and Lamotrigine : Alternative Agents for the Treatment of Bipolar Disorder. *Primary Psychiatry*. 1997; Aug: 25-42.
35. Taylor CP, Gee NS, Su TZ et al. "A summary of mechanistic hypotheses of gabapentin pharmacology." *Epilepsy Research* 1998 29: 233-49.
36. Vieta E, Goikolea JM, Martinez-Aran A et al. A Double-Blind, Randomized, Placebo-Controlled, Prophylaxis Study of Adjunctive Gabapentin for Bipolar Disorder *J Clin Psychiatry* 2006;67:473-477
37. Vieta E, Martinez-Aran A, Nieto E et al. Adjunctive gabapentin treatment of bipolar disorder. *Eur Psychiatry*. 2000; 15: 433-7.
38. Wang PW, Santosa C, Schumacher M et al. Gabapentin augmentation therapy in bipolar depression. *Bipolar Disord*. 2002; 4: 296-301.

39. Yasmin S, Carpenter LL, Leon Z et al. Adjunctive gabapentin in treatment-resistant depression: a retrospective chart review. *J Affect Disord.* 2001; 63: 243-247.

Research Reports

1. 720-04174
2. Protocol 945-421-291

Web Pages

1. <http://mrw.interscience.wiley.com/cochrane/clsystrev/articles/CD003379/frame.html>
2. <http://www.cnsspectrums.com/asp/AuthorGuidelines.aspx>

Pfizer Documents

1. CME 0478
2. CME 0542
3. CME0027-CME0034
4. CME0038-CME0057
5. CME0101-CME0108
6. CME0589-CME0658
7. CME1478-CME1748
8. MDL_VENDORS_054931
9. MDL_VENDORS_054931
10. MDL_VENDORS_055236
11. MDL_VENDORS_111010
12. MDL_VENDORS_111131
13. PFIZER_APANDE_0003413
14. PFIZER_APANDE_0005005
15. PFIZER_APANDE_0005027
16. PFIZER_APANDE_0005031
17. PFIZER_APANDE_0005049
18. PFIZER_APANDE_0005053
19. PFIZER_BPARSONS_0030122
20. PFIZER_BPARSONS_0098666
21. PFIZER_CTAYLOR_0004655
22. PFIZER_EDUKES_0000057
23. PFIZER_JSU_00022639
24. PFIZER_JSU_0012780
25. PFIZER_JSU_0022591
26. PFIZER_LKNAPP_0026006
27. PFIZER_LKNAPP_0071019
28. PFIZER_LKNAPP_0071188
29. PFIZER_LKNAPP_0071199
30. PFIZER_LKNAPP_0071575
31. PFIZER_LKNAPP_0072109
32. PFIZER_LKNAPP_0104674
33. PFIZER_LKNAPP_0107849
34. PFIZER_LKNAPP_0112244

35. PFIZER_LKNAPP_0112829
36. PFIZER_LKNAPP_0115499
37. PFIZER_LKNAPP_0115557
38. PFIZER_LKNAPP_0116131
39. PFIZER_LKNAPP_0138244
40. PFIZER_LKNAPP_0142441
41. PFIZER_MDANA_0001157
42. PFIZER_MDL_0000452
43. PFIZER_NMANCINI_0011631
44. PFIZER_TMARTIN_0001736
45. PFIZER_TMARTIN_0001795
46. SH_0011442
47. SH_0064555.0012057
48. VOX034448
49. VOX035086
50. WLC_CBU_012274
51. WLC_CBU_012564
52. WLC_CBU_028064
53. WLC_CBU_028929
54. WLC_CBU_030410
55. WLC_CBU_037489
56. WLC_CBU_072207
57. WLC_CBU_074388
58. WLC_CBU_108957
59. WLC_CBU_134928
60. WLC_CBU_167738
61. WLC_CBU_170490
62. WLC_CBU_175353
63. WLC_CBU_180343
64. WLC_FRANKLIN_0000036437
65. WLC_FRANKLIN_0000047735
66. WLC_FRANKLIN_0000052703
67. WLC_FRANKLIN_0000080002
68. WLC_FRANKLIN_0000081633
69. WLC_FRANKLIN_0000081633
70. WLC_FRANKLIN_0000098315
71. WLC_FRANKLIN_0000170736
72. WLC_FRANKLIN_0000171583
73. WLC_FRANKLIN_0000199743
74. WLC_FRANKLIN_0000199997
75. Excerpts of Deposition Transcripts of Atul Pande and select exhibits

Appendix A

List of Publications:

“How to Read a Journal Article,” Carlat Psychiatry Report, Feb 2007

Book Review, Psychiatric Services, Feb 2008

Review, Psychiatric Services, March 2008

Cases:

Pare vs. Spring Harbor Hospital, 2006 (Deposition)

State of Maine vs. Janeen Miller, 2007, (Trial)

Grover vs. Spring Harbor Hospital, 2007 (Deposition and Trial)

Gutierrez vs. Gutierrez, 2008 (Deposition)

Boisvert vs. Boisvert, 2008 (Trial)