

Report on gabapentin (Neurontin®) for migraine prophylaxis: evaluation of efficacy, effectiveness and marketing

Expert consultant's report

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## **Executive Summary**

As a health services researcher experienced in the evaluation of clinical trials on migraine, I have been asked to review all available clinical trial reports, published and unpublished, on the effectiveness of gabapentin for migraine prophylaxis and to review Parke-Davis/Pfizer marketing materials. In addition to materials provided to me, I conducted my own independent search of the published literature. As part of my assessment, I performed some quantitative meta-analyses of the individual trial results.

Based on my assessment of the published and unpublished reports from 4 unique double-blind, placebo-controlled randomized trials of gabapentin for migraine prophylaxis, in my opinion, the total evidence does not meet the generally established criteria for efficacy. A single positive study is small, with a questionable analysis, and has failed to be replicated in several other larger better designed studies. The most notable studies are two negative trials performed by Parke-Davis, the primary analyses of which fail to reach statistical significance and have remained unpublished. Although some statistically significant findings have been reported among secondary analyses involving multiple outcomes, multiple time points and multiple populations, there is little consistency among the findings of these exploratory analyses.

A meta-analysis of headache frequency data from 4 trials fails to show a statistically significant effect of gabapentin compared with placebo for migraine prophylaxis. In comparison with other widely used migraine preventive drugs, the estimated effect size for gabapentin not only fails to reach statistical significance, but also has a much lower magnitude of effect.

My evaluation of the marketing materials points to a pattern of suppressing the results of negative randomized double-blind, placebo-controlled clinical trials. At the same time, lower level, uncontrolled data were used to promote the off-label use of gabapentin for migraine prophylaxis, and generate interest in conducting new double-blind placebo-controlled clinical trials, which Parke-Davis undertook with the hope of demonstrating favorable results. When both of these trials failed to show significant benefit in the primary outcome measures, Parke-Davis misrepresented one of these studies in a published manuscript manipulated to achieve statistically significant results favoring gabapentin over placebo. Furthermore, Parke-Davis and then Pfizer undertook substantial efforts to promote the favorable published results in the medical community.

In summary, Parke-Davis/Pfizer has engaged in deceptive marketing by disseminating information known to be both incomplete and misleading, in an effort to promote gabapentin for migraine prophylaxis.

## **Introduction**

I have been asked to provide a report on whether gabapentin is an effective treatment for the prevention of migraine headache and whether Parke-Davis, and later Pfizer, made false, misleading, or incomplete statements in their marketing materials. In addition, I have been asked to comment on the expert report provided by Dr. Alan Rapoport.

This report is based on (a) my education, training and experience, (b) documents and information of which I am generally aware, and (c) documents and information that are listed in this report. I reserve the right to supplement this report if I am presented with or review new documents or information relevant to my assessment.

For my work in preparing this report, I will bill \$300 per hour. I have not testified as an expert in any lawsuits in the last 4 years.

## **Qualifications**

After graduating *magna cum laude* from Duke University in 1982, I obtained my medical degree from the University of Miami School of Medicine in 1986. I completed an internal medicine residency at the Medical College of Virginia Hospitals in Richmond, Virginia, followed by a fellowship in General Internal Medicine and Ambulatory Care at Duke University, leading to a Master of Health Science degree in biometry. I am currently a tenured Associate Professor of Medicine in the Division of General Medicine and Research Fellow in the Center for Clinical Health Policy Research at Duke University and a Research Associate in the Center for Health Services Research in Primary Care at the Durham Veterans Affairs Medical Center. My research interests primarily revolve around systematic reviews and synthesis of existing evidence as well as clinical practice guideline development. I have been co-director of the AHRQ-designated Evidence-based Practice Center (EPC) at Duke University for the past 10 years. Under my direction, the EPC has developed operational procedures for conducting systematic reviews and successfully produced a wide variety of evidence reports and technology assessments through the EPC program.

I have used evidence syntheses in guideline development through collaborations with several organizations. These include the American College of Chest Physicians (acute exacerbations of COPD, cough, lung cancer, and pulmonary hypertension); the American College of Physicians (stroke prevention), and the US Headache Consortium (migraine), among others. I also regularly teach classes in meta-analysis in the Department of Medicine Clinical Research Training Course and the School of Medicine's master's level Clinical Research Training Program.

The topics of migraine and headache care has been of long-standing interest to me in both clinical care and research. One of the major projects early in my career was the synthesis of clinical trial and other evidence in support of a planned clinical practice guideline on headache. (Gray, et al., 2000) Furthermore, in the Cochrane Collaboration, I am the lead

editor for headache reviews in the Collaborative Review Group on Pain, Palliative and Supportive Care (PaPaS). I have published several articles relating to research in headache. A list of these and other publications is attached.

## **Part 1: Evaluation of scientific evidence for the effectiveness of gabapentin for prevention of migraine**

### **Introduction**

Migraine headache is a chronic disease characterized by episodes of disabling head pain often associated with other symptoms. Persons suffering with episodes of migraine often treat each episode with medications to provide short term relief from the attack (acute treatment); persons who suffer frequent episodes or get inadequate relief from such acute treatments may use a preventive medication. Preventive medications are taken regularly during migraine-free periods with the goal of reducing migraine attacks (primarily the frequency of attacks, but may also affect the intensity or duration).

Preventive drug treatments are used by a small percentage of migraineurs – 3% to 5% of patients in various studies (Clarke, et al., 1996; Edmeads et al., 1993; Rasmussen et al 1992). It is not known whether patients in these studies had never been offered preventive therapy or had tried it and found it ineffective or intolerable.

Many different drugs have been shown to have some efficacy as migraine preventive treatments including certain beta blockers (propranolol, metoprolol, atenolol), amitriptyline, and several anticonvulsants. (Kaniecki and Lucas, 2004; Ramadan et al., 2000) Among anticonvulsants, topiramate and valproic acid, for example, have received FDA-approval for marketing this indication.

A Cochrane review evaluated randomized controlled trials of various anticonvulsant drugs for treatment of migraine. (Chronicle and Mulleners, 2004) This review concluded that “The evidence derived from trials of gabapentin suggests a beneficial effect in migraine prophylaxis.” However, it noted that only two clinical trials of reasonable size have been reported, and that the interpretation of both is hampered by some aspects of their method or data analysis. They concluded that this drug needs further evaluation.

Additional unpublished data from clinical trials conducted or sponsored by Parke-Davis/Pfizer is now available. In this part of the report, I will examine the new unpublished evidence along with previously published evidence for the efficacy of gabapentin for the preventive or prophylactic treatment of migraine headache.

## Methods

In order to ensure that all relevant studies are considered, I conducted a new search for relevant trials. I searched the Ovid MEDLINE® database for the period 1950 to July Week 1 2008 using the following search strategy:

- 1 gabapentin.mp. (2656)
- 2 (neurontin or gabapentin).mp. (2660)
- 3 migraine disorders/ or migraine with aura/ or migraine without aura/ (18127)
- 4 2 and 3 (57)

I reviewed the 57 citations and identified relevant controlled trials of gabapentin for migraine.

In addition, I examined the reference lists of comprehensive systematic reviews known to me including the Cochrane review (Chronicle and Mulleners, 2004) and AHRQ Technical Report (Gray et al., 2000).

Finally, I received the following unpublished research reports:

Study 945-220

-Research report No RR 995-00074/unpublished (later published as Mathew et al., 2001)

Study 879-200

-Research report 4301-00066/unpublished (later published as Wessely et al., 1987)

Study 945-217

-Research report 995-00085/unpublished

I also reviewed other published literature

Di Trapani, et al., 2000

Jimenez-Hernandez et al., 2002

Wessely et al., 1987

Because the natural history of outcomes in migraine is fairly variable over time (there is a large potential for change in migraine frequency even without treatment) it is important to use a concurrent comparison group when evaluating the effect of drug treatment. This is usually accomplished by randomizing subjects to a placebo group and a treated group. For this report, I considered any randomized clinical trials for migraine prevention that compared gabapentin with a comparison group, which could include placebo, no treatment, an alternative treatment or another dose of gabapentin.

### *Efficacy versus effectiveness*

Distinguishing between the closely related concepts of efficacy and effectiveness is important. Efficacy is defined as the measure of benefit (or harm) caused by the use of an intervention, considering the balance between benefits and harms.

Efficacy studies are usually conducted in a highly selected and homogeneous population, free of comorbid medical conditions. They are tightly controlled in terms of fidelity of the intervention such as dosage, etc.

In contrast, effectiveness refers to the expected benefit of a policy of putting an intervention into general use in a population. Effectiveness studies are designed using inclusion criteria that are less strict; they may include a wider variety of ages, allow patients with comorbid conditions, and perhaps even allow a greater variation in dosing.

*Trial analysis – intention to treat versus efficacy analysis*

Even within a particular study, several different analyses may be planned. The efficacy analysis, sometimes called on-treatment or per-protocol analysis generally refers to an analysis that considers patients who receive the intervention as planned, but excludes from analysis patients who may have dropped out due to side effects or other reasons. In contrast, an intention-to-treat (ITT) analysis, considers all patients from the point of randomization forward. Dropouts would still be included in an analysis, and a conservative approach is used to adjust for missing data, such as last value carried forward. This analysis is considered to be a better approximation of “effectiveness” as it analyses all comers.

The modified intention to treat (mITT) is a recently coined term that is not widely used or defined in a standard way. Le Hananff (2006) used the definition that a mITT excludes patients who never received the treatment. The key principle is that mITT excludes fewer patients than the efficacy, per-protocol, or on-treatment analysis, but excludes more patients than the intention-to-treat analysis.

Finally, I considered the analyses planned in terms of study population and outcome variable. For the purposes of comparison, I will assemble data according to conventions of clinical trial design in migraine as specified in guidelines from the International Headache Society (IHS, 1991; Tfelt-Hansen, 2000). In particular, the preferred outcome measures compare between treatment and placebo groups, first, headache frequency (as the number of headaches per month or 28-days) and, second, the responder rate (50% improvement – the proportion of patients with a 50% or greater reduction in headache frequency from baseline to on-treatment).

## **Results**

The following studies were identified and used as the basis for this report:

- 1) Study 879-200  
-Research report 4301-00066/unpublished
- 2) Wessely et al., 1987/published (abstract)
- 3) Study 945-217  
-Research report 995-00085/unpublished
- 4) Study 945-220  
-Research report No RR 995-00074/unpublished (later published as Mathew et al., 2001)
- 5) Di Trapani, et al., 2000/published
- 6) Jimenez-Hernandez et al., 2002/published

## **Findings of the studies regarding efficacy of gabapentin**

### **RR4301-00066**

#### **Feuerstein T, 1990**

#### **Periods covered: 11/85-5/88**

This was a study comparing gabapentin at 300mg three times a day (900mg/d) versus placebo. The primary efficacy measure was the reduction of the number of migraine attacks from the retrospective 3-month baseline to treatment. The study found no statistically significant difference in the adjusted mean reduction in migraine attack frequency (primary efficacy measure) between the placebo (0.7) and gabapentin (1.4) treatment groups, or in the response ratio (difference in attack frequency from a retrospective three-month baseline to treatment divided by the sum of attacks during baseline and treatment) between the placebo (-0.093) and gabapentin (-0.170) groups. In an intent-to-treat analysis, the mean response ratio was -0.109 for the placebo group and -0.242 in the gabapentin group which was statistically significant ( $p=0.04$ ).

Baseline HF was based on a retrospective 3 month reporting period: there was no prospectively measured baseline as recommended in IHS guidelines. Therefore, the validity of the baseline HF measurements is questionable, and, since this is used to calculate the change in HF from baseline to treatment, this measure too is not optimally measured.

A large number of patients ( $n=26$ ) were excluded from the efficacy analysis because the patients had taken other prophylactic migraine medications during the study or had not stopped taking such drugs at least 1 month. Disallowed drugs included flunarizine,



pizotifin, propranolol, methysergide, amitriptyline, and metoprolol. Of the 26 patients excluded for this reason, 7 were from the placebo group but 19 were from in the gabapentin arm, comprising nearly half of the patients randomized to receive gabapentin. Since these patients are included in the ITT analysis, this contamination with proven effective migraine preventive drugs (which was greater in the gabapentin group) could explain the significant finding in the ITT analysis while no significant difference was found in the efficacy analysis.

Another unusual feature of this study was the inclusion criteria: while most of the centers participating in this study required patients to have 2 or more attacks per month, one of the centers required patients to have a minimum of 8 attacks per month. This is in contrast the IHS guidelines which recommend including patient with between 2 and 6 attacks per month in migraine prophylactic trials (IHS, 1991).

In summary, this trial suffers from several deficiencies.

- it is small with only 53 subjects in the efficacy analysis
- it suffers from differential contamination of the gabapentin arm with known effective cointerventions; furthermore the degree of contamination is of sufficient magnitude to explain the observed positive findings in the ITT analysis
- poorly designed and executed
  - one center had different inclusion criteria with excessively high baseline headache frequency
  - no prospective baseline headache frequency recording (a component of the primary efficacy criterion)
- the dose of gabapentin is the lowest used among the studies reviewed at 900mg/d

### **Wessely et al., 1987**

Wessely et al. (1987) reported a randomized control trial of gabapentin 900 mg daily (divided doses; 300mg x 3) versus placebo. The main outcome measure was headache frequency compared between a baseline presumably obtained prospectively during a 3-month washout period with an on-treatment headache frequency obtained during a 3 month treatment period. The results, published in abstract form only, lack some detail about the methods used in the study. The study randomized 45 patients, but only 33 were analyzed (14 gabapentin and 19 placebo). HF reduced from 6.5 to 4.1 per month in the gabapentin group and from 4.3 to 4.0 in the placebo group; no standard deviations were reported. The statistical analysis was based on the cumulative distribution of the percentage reduction in migraine attacks; this is reported to show a trend, but no exact p-value was reported. Figure 1 in Wessely et al. (1987) does permit an estimation of the number of patients who have a 50% or greater reduction in migraine attacks (6/14 [43%] in gabapentin-treated patients and 5/19 [26%] placebo-treated patients). The abstract refers to this report as an interim analysis; however, no later report by these authors was identified. According to my analysis of these results, the difference between gabapentin and placebo is not statistically significant (p=0.32).

Close similarities in the design of the trial and the fact that there are several names in common between the authors of this abstract and the outside investigators listed in RR4301-00066 (which both include Wessely, Saltuari, Klingler, and Schutt), lead me to conclude that this abstract reports an interim analysis of Study 879-200. Some differences between this abstract and the Research Report in the results and numbers of patients are likely because this abstract is an interim report (before completion) while the Research Report represents a final report (after completion).

**RR995-00085**

**Magnus-Miller L, et al., 2000**

**Periods covered: 3/97-1/99**

This study is a randomized controlled trial comparing gabapentin at a daily dose of 1800 mg versus placebo. 157 patients were randomized in a 2:1 ratio to gabapentin or placebo after a prospective 4- week single-blind baseline period and followed by a 4-week titration period and two 4-week stabilization periods. While 55 patients were randomized to placebo, there were 46 who took at least one dose of study medication in SP2 and thus met the definition of the mITT population, and 37 who completed the study and met the definition of the efficacy population. Similarly, among the 102 patients randomized to gabapentin, 76 remained in the mITT population and 65 in the efficacy population. The primary outcome variable was the HF at SP2 and change in HF from baseline to SP2, with the primary analysis considering the efficacy population. Secondary analyses considered the mITT population and additional outcome variables including HF change from baseline to SP2, HF at SP1, HF at SP1 and 2 combined, and the proportion of patients with more than 50% reduction in HF at SP1, SP2 or SP1 and 2 combined, and several others.

The primary outcome variables did not show any statistically significant difference between gabapentin and placebo in either the efficacy population or the mITT population. Among additional secondary analyses involving multiple different outcome variables there were 5 findings that reached statistical significance at the  $p=0.05$  level (without adjustment for multiple testing) out of approximately 22 separate tests: median 4-week migraine rate at SP1 and median change from baseline at SP1, and more than 50% reduction from baseline in 4-week migraine headache rate for efficacy population at SP1 and for mITT population at SP1 and at SP1 and SP2 combined.

According to my reading, there does not appear to be any systematic difference between the mITT population and the efficacy population with regard to potential predictors of response. I interpret the study as a negative study, since the analysis of the primary outcome variable in both the efficacy population and the mITT population failed to achieve statistical significance. The few findings of significance among many comparisons of secondary outcome variables suggests that there may be a potential effect of gabapentin, but that would need to be confirmed in further studies.

**RR995-00074****Magnus-Miller 1999****Periods covered: 11/96 – 3/98**

This study is a randomized controlled trial comparing gabapentin at a daily dose of 1800-2400 mg versus placebo. 145 patients were randomized in a 2:1 ratio to gabapentin or placebo after a prospective 4- week single-blind baseline period and followed by a 4-week titration period and two 4-week stabilization periods (SP1 and SP2). While 46 patients were randomized to placebo, there were 36 who took at least one dose of study medication in SP2 and thus met the definition of the mITT population, and 33 who completed the study and met the definition of the efficacy population. Similarly, among the 99 patients randomized to gabapentin, 77 remained in the mITT population and 62 in the efficacy population. The primary outcome variable was the HF at SP2 and change in HF from baseline to SP2, with the primary analysis considering the efficacy population. Secondary analyses considered the mITT population and additional outcome variables including HF change from baseline to SP2, HF at SP1, HF at SP1 and 2 combined, and the proportion of patients with more than 50% reduction in HF at SP1, SP2 or Sp1 and 2 combined, and several others. Except for the higher dosage of gabapentin, this study is essentially the same design as that of the study described in RR995-00085.

The actual steady dosage of gabapentin that was tolerated by patients remaining in the study was 2400mg for 75% of the gabapentin group and 1800mg for 17.9%.

The results showed no significant difference between gabapentin and placebo in the primary outcome measures HF at SP2 or change in HF from baseline to SP2 in the efficacy population. However, there was a significant difference in HF at SP2 in the mITT population (3.1 versus 3.5;  $p=0.045$ ), while the change in HF from baseline to SP2 was not significantly different. One of the secondary outcomes showed a statistically significant difference between gabapentin and placebo: proportion of patients with greater than 50% reduction in HF from baseline to SP2 (40% versus 19%;  $p=0.033$ ). Similar to my conclusions from the study reported in RR995-00085, I would characterize this as a negative trial with some interesting findings in secondary analyses that might deserve clarification in further study, but on their own, are inconclusive.

**Discrepancy between reports of Study 945-220****-Research report No RR 995-00074 versus Mathew, et al., 2001**

Mathew et al. (2001) is a published report of Study 945-220. I am familiar with this report as the largest of two published studies comparing gabapentin and placebo that were described in the Cochrane Review (Chronicle and Mulleners, 2004), the other being Di Trapani et al. (2000). In this section, I will describe the content of the Mathew et al. (2001) report, and comment specifically on how this report of Study 945-220 deviates from the Research Report (RR995-00074). My interpretation of these discrepancies is predicated on two assumptions: 1) that Mathew et al. (2001) is, in fact, a report of Study 945-220 and 2) that the Research Report (RR995-00074) is accurate and true description of the study's design, conduct, results and analysis.

Mathew et al. (2001) describe a randomized controlled trial comparing gabapentin and placebo. The study recruited 145 patients from 7 participating centers, randomized participants in a 2:1 ratio with 99 assigned to gabapentin and 46 assigned to placebo. The study design described in Mathew et al. (2001) is nearly identical to that described in the research report, with one important difference. Mathew et al. (2001) describes “the primary outcome measure was the 4-week migraine rate during stabilization period 2 ([SP2] the last 4 weeks of the stable-dosing period) *for patients who had received a stable dose of 2400 mg/day*” (italicization added). Similarly, Mathew et al. (2001) describe “secondary outcome measures assessed for SP2 included a responder analysis, defined as the proportion of patients *receiving a stable dose of 2400 mg/day gabapentin* with at least a 50% reduction in the 4-week migraine headache rate from baseline to SP2” (italicization added). However, the Research Report makes no such restriction regarding the dose when describing the primary and secondary outcome measures. It defines the primary outcome measures as “the 4-week migraine headache rate during stabilization period 2 and change from baseline to stabilization period in the 4-week migraine headache rate *in efficacy evaluable patients*” (italicization added). Efficacy evaluable patients were defined as a *subset* of the mITT population as follows:

- Included in the mITT population,
- Took at least 75% of study medication during participation in stabilization period 2 or discontinued the study during stabilization period 2 due to treatment failure,
- Took at least 50% of study medication during stabilization period 1,
- Did not use concomitant migraine prophylactic medication,
- Provided complete diary data for at least four days/week during the baseline period (i.e., the 28 days prior to baseline visit),
- Provided complete diary data for at least four days/week during stabilization period 2 or discontinued due to treatment failure,
- *Achieved a stable dose of 1800-2400 mg/day* during stabilization periods 1 and 2,
- Had a baseline period of at least 25 days on placebo, and
- Had at least 25 days in stabilization period 2 or discontinued due to treatment failure.

The research report describes the definition of the mITT population as follows: “patients who met all of the following criteria were included in the mITT population:

- Randomized into trial;
- Completed the titration period;
- Took at least one dose of study medication during stabilization period 2;
- Provided complete diary data for at least one day during the baseline period (i.e., the 28 days prior to baseline visit), and
- Provided complete diary data for at least one day during stabilization period 2.”

According to this definition, the mITT population consisted of 113 patients, 77 in the gabapentin group and 36 in the placebo group.

Table 1 summarizes the patient flow in Study 945-220 and identifies the relevant populations of interest including the safety evaluable population, the efficacy population and the modified intention-to-treat population. Note that the mITT populations defined

in the Research Report differs markedly from that analyzed in Mathew et al. (2001). What is curious about the additional mITT population described in Mathew et al. (2001), is that it has *fewer* patients than in the efficacy analysis. In Mathew et al. (2001), the mITT population was reported to consist of only 87 patients, 56 on gabapentin and 31 on placebo, which is fewer even than the efficacy or on-treatment population, which had 95 patients, 62 and 33 patients, respectively. In contrast, the mITT population in the Research Report has 113 patients, or 77 and 36, respectively. This is clearly a consequence of the additional criterion of “*patients receiving a stable dose of 2400 mg/day*” required by Mathew et al. (2001) in their re-analysis of the data from Study 945-220.

**Table 1. Patient flow in Study 945-220 as described in RR995-00074 and Mathew et al. (2001)**

	Gabapentin	Placebo	
Approached	201 (176)		Discrepancy between Research Report and Mathew et al. (2001)
Consented	Not reported		
Randomized	145		
	99	46	True intention-to-treat population
Began treatment	98	45	Safety evaluable population
Completed titration to 1800-2400 mg	74	36	
Completed stabilization period 1	77	36	mITT population defined in research report
	74	36	?Completed study (Mathew et al., 2001)
Stable dose of 2400 mg	63	33	
Completed stabilization period 2	62	33	Efficacy population defined in research report
	56	31	Subpopulation analyzed in Mathew et al. (2001) described as mITT

The results described in the Research Report for efficacy evaluable patients are as follows: “no statistically significant differences were seen at any study period between the 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.” This includes the primary outcome measures (based on the efficacy population and concerns the 2<sup>nd</sup> 4-week treatment period HA frequency and change from baseline in headache frequency) as well as secondary outcome measures. The only positive findings in the research report come from the analysis of mITT population, which showed a lower migraine headache rate in gabapentin than placebo group at SP2 (p=0.045), a larger proportion of patients in gabapentin group (40%) than placebo group (19%) with a 50%

or greater reduction in migraine headache rate during SP2 ( $p=0.033$ ) as well as differences in duration, functional ability and headache days.

In contrast to the results reported in the Research Report, the main results reported in Mathew et al. (2001) are as follows “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 (16.2%) of 31 patients receiving placebo showed at least a 50% reduction in the 4-week migraine rate ( $P=.008$ ).” These results, quoted from the abstract, correspond to the primary and secondary outcomes described in the methods section.

The contrast between the Research Report, for which the results for the primary outcomes were not statistically significant, and the Mathew et al. (2001) paper, for which the results for both primary and secondary outcomes are both highly statistically significant could not be more vivid. Further statistically significant results are reported by Mathew et al. (2001) as follows: “The average number of days per 4 weeks with migraine was also statistically significant and favored gabapentin ( $P=.006$ ) during stabilization period 2. The median change in 4-week headache rate was statistically significant as well ( $P=.013$ ).”

How did this difference occur? I have already disclosed the mechanism: this appears to have been achieved by redefining the study population by limiting it to those patients on a stable 2400mg daily dose. This population included “56 (72.7%) of 77 gabapentin-treated patients and 31 [86.1%] of 36 placebo-treated patients” who received study medication during SP2.

Why did this difference occur? A clue to this comes from the memo of Wed Oct 3, 2001 from John Marino to Lloyd Knapp and others, which contains an earlier correspondence from Michael Vinegra, which notes in a previous report of the Mathew study in abstract form “he reported the ITT, where 36% of Px experienced a 50% reduction in HA frequency, which was not significant. I think the dropout rate was the problem.” This suggests to me that the data were reanalyzed in comparison with an earlier analysis, such as that in the Research Report.

Naming the analyzed population a modified intention-to-treat population is misleading because it is in fact a subgroup analysis. There was no mention of a planned subgroup analysis based on dose received in the Research Report. Therefore, I conclude that this was an unplanned or post hoc subgroup analysis.

Why then was this post hoc subgroup analysis presented as the primary analysis of Study 945-220 by Mathew et al. (2001)? I believe this subgroup analysis was reported as the primary analysis in order to give the false impression that this was a positive study supporting the claim that gabapentin is effective. Calling this post hoc subgroup analysis a mITT analysis seems designed to give the impression that the intention-to-treat

principle was being followed; however, this analysis considers a smaller, more select population than even the original efficacy population, not a broader population more like those initially randomized as the mITT language implies. There is an enormous misrepresentation of the study in the which portrays this as a positive study by presenting the few positive secondary analyses as if they were the primary end points and major findings.

### **Di Trapani et al., 2000**

Di Trapani et al. (2000) reported the results of a randomized controlled trial comparing gabapentin 1200mg daily with placebo. 63 patients were randomized (35 gabapentin; 28 placebo) and underwent a 1-week dose escalation followed by a 4-week treatment phase followed by an 8-week stable dosing phase. The main outcome was HF reduction from screening to follow-up. Baseline HF was measured during a 1-month screening period; HF was measured during the 3<sup>rd</sup> month follow-up period after the 8-week stable dosing phase.

The main outcomes were HF and headache intensity and considered baseline and post-treatment time periods, comparing means among three groups: placebo, gabapentin-treated patients with migraine without aura, and gabapentin-treated patients with migraine with aura. Note that while the statistical analysis considered the gabapentin-treated patients in two strata (with aura and without aura), it considered all placebo patients as one group, despite the fact that the placebo group also consisted of some patients who had migraine with aura (n=14) and some who had migraine without aura (n=14). It is unclear why aura was not used as another factor in the repeated-measures multivariate analysis of variance (MANOVA) analysis. This choice would obscure potential differences in efficacy of gabapentin between migraine patients with aura or without aura.

No patients dropped out, so the efficacy population is the same as the intention-to-treat population, according to the report.

HF declined in the placebo group from 5.41 at baseline to 4.7 at follow-up, in the gabapentin-treated patients with migraine without aura from 5.08 to 3.13, and in the gabapentin-treated patients with migraine with aura from 5.14 to 2.47. All three groups showed significant declines in HF from baseline to follow-up, but the gabapentin-treated patients had greater reductions in HF than placebo (without-aura  $p < 0.001$ ; with aura  $p < 0.0001$ ). Reporting of the results was not complete; no mean and variance was provided for the gabapentin-treated patients as a whole, only for the subgroups by with or without aura. (Incidentally, the reported variance statistics associated with the reported means in this paper are not labeled; while the authors of the Cochrane review assumed that they were standard deviations (SD), I believe that they are instead standard error of the mean (SEM). My conclusion is based on the magnitude of the SD reported in the preceding research reports and my estimation of the efficacy analysis described below). In order to produce an analysis comparable to that of the other studies, I used the reported mean and SEM for each subgroup and estimated the mean and SEM for the follow-up HF

for a combined gabapentin-treated group using Fast\*Pro software. This results in a mean of 2.68 with SEM of 0.75. Using this estimate results in a standardized difference in means of 0.359 (-0.141 to 0.860;  $p=0.16$ ) which is a slightly larger effect size than the other studies (see Figure 2); while the  $p$ -value is slightly greater than the 0.045 reported by Di Trapani, et al. (2000), this is expected because my re-analysis is less statistically powerful when compared to the RM-MANOVA reported in the article. I believe that this study supports the conclusion that gabapentin results in a statistically significant reduction on migraine frequency with a point estimate of a difference on the order of 1.6 fewer headaches per month associated with gabapentin compared with placebo; however, I am concerned that the statistical analysis was improperly designed by comparing a post-hoc subgroup (with and without aura) in the main analysis. Furthermore, the distinction between patient with and without aura was not considered in the placebo group, although this would clearly be both possible and preferable. This leads me to suspect that the reported analysis was not planned a priori, but rather a post hoc re-analysis; alternatively, it could be that the authors, whose native language is clearly not English, did a poor job of explaining their analysis and the reasons behind it. Even taking the analysis as true, the study is rather small, and the magnitude of the effect, which is the largest of those reported among all of these studies, might have been exaggerated by this analysis.

#### **Jimenez-Hernandez, et al. (2002)**

This is the only randomized controlled trial without a placebo comparison; it is also the only one with a planned randomized dose comparison. The article is written in Spanish but with an English abstract. My assessment is based mostly on the English-language abstract. Patients were randomized to take gabapentin at either 1200 mg daily or 2000 mg daily at a 2: 1 ratio. The study found no statistically significant differences between the 1200 and 2000 mg dosage in headache frequency, intensity, or duration. Headache frequency declined from 5.3 to 2.7, 2.3, and then 2.1 (at baseline, 4, 10 and 16 weeks, respectively) in the 1200 mg group and from 4.4 to 2.4, 1.6 and 1.6 in the 2000 mg group. The proportion of patients with at least 50% reduction from baseline headache frequency was 42.6%, 52.6% and 65.3% at 4, 10 and 16 weeks in the 1200mg group and 26.8%, 62.0% and 62.5% in the 2000mg group. The authors concluded that “gabapentin can be considered an effective and safe drug in the preventive treatment of migraine.” However, this study had important limitations that threaten the validity of this conclusion. The lack of a placebo comparison is the main drawback which makes conclusions about the efficacy of gabapentin impossible from these data; the authors conclusions about effectiveness are not supported by the randomized comparison within this study design, so rather than this study comprising Level 1 data in support of this conclusion, it is essentially supported by a before-after prospective comparison (case series) or Level 4 data. As such, this study is of little relevance to the assessment of the efficacy of gabapentin for migraine prevention given that there are better designed studies available as described previously. Considering the value of this study, a more robust level of evidence could be assigned to the conclusion that there is no statistically significant difference between the reduction in headache frequency from 200mg compared with 1200mg of gabapentin (level 1b).

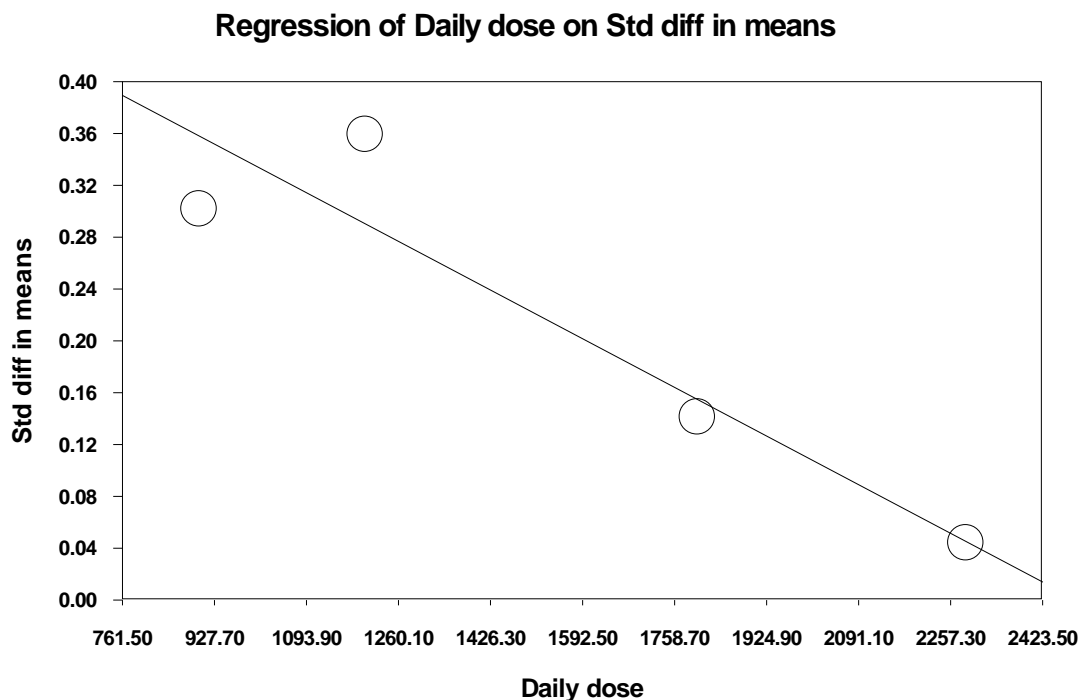


### Summary of the findings of placebo clinical trials of gabapentin versus placebo

Based on the placebo-controlled randomized trials conducted, gabapentin showed statistical superiority to placebo in only one relatively small study of 1200mg/day (Di Trapani), but failed to demonstrate effectiveness for primary analyses in all of the other studies performed. Mathew et al. (2001), the only other published article reporting positive findings, appears to have presented a positive post hoc subgroup analysis as if it was the primary planned analysis; an unpublished research report.

A variety of doses ranging from 900 mg/day to 2400 mg/day have been tested, but there does not appear to be a positive dose-response gradient across this range (Figure 1). Differential drop out appears to be an explanation for positive findings in mITT population in at least one study (RR4301-00066).

**Figure 1. Meta-regression of daily gabapentin dose on effect size, efficacy analyses**

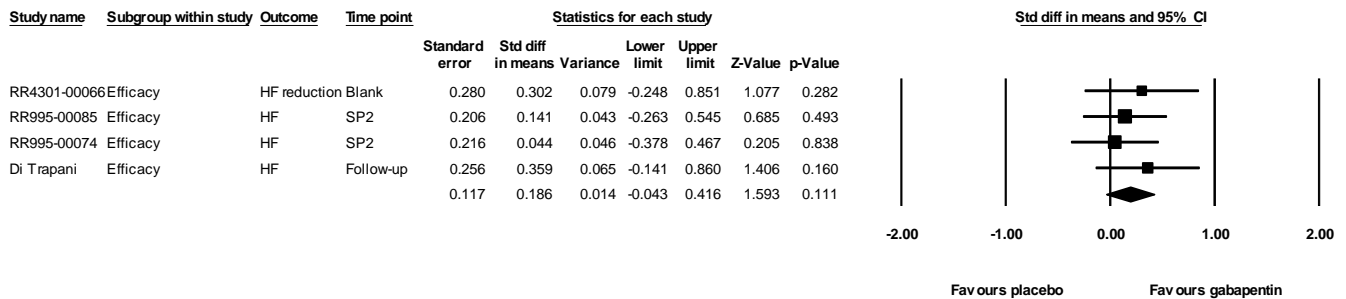


In my opinion, the total evidence from placebo controlled trials comparing gabapentin with placebo for migraine prophylaxis does not meet the generally established criteria for efficacy. A single positive study is small, with a questionable analysis, and has failed to be replicated in several other larger better designed studies. Statistically significant findings have been reported among analyses involving multiple outcomes and multiple time points and multiple populations; however, there is little consistency among the findings of these exploratory analyses. The most notable studies are unpublished negative trials performed by Parke-Davis.

The unpublished data provide valuable information that help to interpret the published data. For example, they clearly show that the analysis presented in the Mathew et al. (2000) article is a post hoc subgroup analysis presented as if it were an a priori planned primary analysis. Second, they suggest that unlabeled variance statistics in Di Trapani are SEM rather than SD, and that the Cochrane analysis has overestimated the treatment effect for that study. However, access to these valuable unpublished data has been denied by Pfizer, even when such data were requested by research scientists. Furthermore, Pfizer has permitted one study (Study 945-220) to be reported in such a way that exaggerates the effect of gabapentin making a negative study appear to be positive (Mathew et al., 2001).

These data do not show that gabapentin is inert or totally inactive in migraine prophylaxis. Although most individual trials did not demonstrate efficacy of gabapentin, it is possible that inadequate statistical power precluded finding a small true effect. To explore this idea, I evaluated all the studies of 900-2400mg/d gabapentin versus placebo and attempted to combine results using meta-analysis of HF data using Comprehensive Meta Analysis version 2.2.034. Four trials provided sufficient data on HF to calculate an effect size or standardized difference in means. There was no significant heterogeneity ( $p=0.774$ ). Even under assumptions favorable to finding an effect of gabapentin (e.g. fixed effects model) a meta-analysis of HF data fails to show that gabapentin is efficacious for migraine prophylaxis (Figure 2).

**Figure 2. Meta-analysis of studies reporting headache frequency, efficacy population**



To put this estimate of the effect of gabapentin relative to placebo into perspective, Table 2 presents effect size estimates calculated for other migraine preventive drugs from a systematic review of preventive treatment for migraine headache that used comparable methods. (Gray et al., 2000) In comparison with other widely used migraine preventive drugs, the estimate for gabapentin is not only fails to reach statistical significance, but also has a much lower estimated effect size. Effect sizes are difficult to interpret in clinical terms; I repeated the analysis using the difference in number of days per month with headache. This yields an estimate of 0.4 days with 95% confidence intervals of -0.16 to 0.94 days representing the difference between the number of days per month with

headache for gabapentin-treated compared with placebo-treated patients. In other words if placebo treated patients have post-treatment HF of 4 migraines per month, then gabapentin-treated patients would be expected to have 4-0.4 or 3.6 migraines per month; however, this difference is not statistically significant.

**Table 2. Effect size associated with gabapentin in comparison with other migraine preventive drugs with at least moderate efficacy (except for gabapentin, data from Gray et al., 2000)**

<b>Drug</b>	<b>Effect size estimate (95% confidence interval)</b>
Divalproex sodium#	0.93 (0.39 to 1.5)
Pizotifen*	0.91 (0.50 to 1.3)
Timolol#	0.69 (0.18 to 1.2)
Amitriptyline	0.62 (0.15 to 1.1)
Propranolol#	0.55 (0.42 to 0.69)
Flunarizine*	0.52 (0.24 to 0.80)
Naproxen sodium	0.29 (0.01 to 0.57)
Gabapentin	0.19 (-0.04 to 0.42)

\*not licensed in US

#FDA approved indication for migraine prophylaxis

A similar analysis was conducted using the proportion of patients with at 50% or more reduction in HF (Figure 3).

**Figure 3. Unique studies reporting at least 50% reduction in HF, efficacy population**

While none of these studies found a statistically significant effect when considered alone, neither does a combined estimate of effect reach statistical significance.

In summary, the randomized double-blind, placebo-controlled trials of gabapentin versus placebo, considered together, fail to consistently or convincingly demonstrate that gabapentin is effective for migraine prophylaxis. A summary estimate of available data suggests that an estimate of the effect of gabapentin is lower than that of other approved or widely used migraine prophylactic drugs. Furthermore, selective reporting of positive secondary analyses in the published literature has contributed to a misperception that gabapentin is effective for migraine prophylaxis.

**Part 2: Review of Defendants’ Marketing Conduct**

In my review of marketing materials made available to me, I evaluated specific statements, claims or messages based on scientific information from published and unpublished clinical trials that were available at the time. I considered the context of the claim, in terms of the type of audience, purpose of the meetings and the venue.

**Evaluation of various internal Pfizer communications regarding the Cochrane data request through Pfizer Netherlands for unpublished data on gabapentin for migraine prevention**

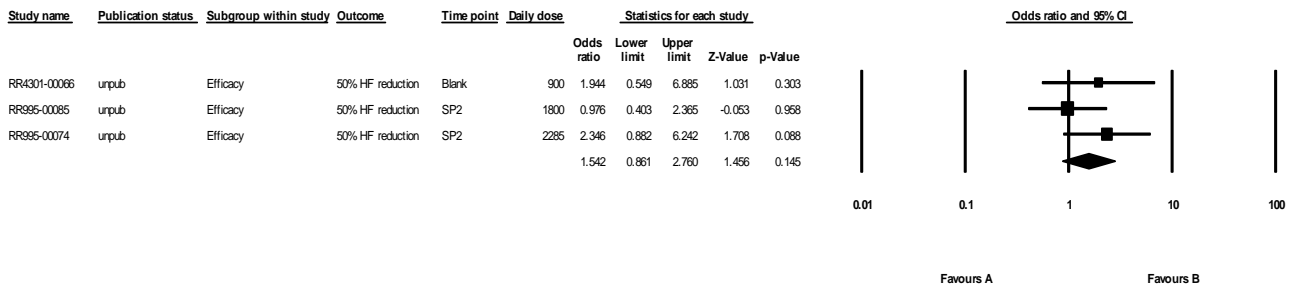
Statements from Wim Mulleners, Dutch headache researcher and co-author of Cochrane Review on anticonvulsants for migraine (Chronicle and Mulleners, 2004)

I contacted Dr. Mulleners to find out whether and how he sought unpublished data from pharmaceutical companies related to his Cochrane review on anticonvulsants for migraine prevention. The following is a summary of what he told me.

In 2002, one the authors of the Cochrane systematic review on anticonvulsants for migraine prevention, Wim Mulleners, sent out a letter to all companies known to have a product for migraine in the Netherlands requesting any and all data on the efficacy of anticonvulsants for migraine prevention. Among the companies to whom the letter was sent is Pfizer Netherlands. Dr. Mulleners reported to me that he received a reply from the Dutch representative from Pfizer who said he had forwarded the request the US headquarters. Dr. Mulleners never received any further reply or any of the requested data.

Angela Crespo response and history

The request from Dr. Mulleners seems to be the impetus for several e-mail exchanges among Pfizer Marketing staff. Angela Crespo describes the request is for “any papers of abstracts published on Neurontin in migraine prophylaxis” A reply from Elizabeth



Mutisya states “We would not be able to provide them with our databases which is what they ultimately are interested in.” And Leslie Tive notes “If they are looking for unpublished data, I would be reluctant to send it.” The intent to deny the existence of relevant unpublished trials is clearly evident in the comment of Marino Garcia who wrote “have someone from medical just tell them ...that we are only aware of two double-blind placebo controlled trials done independently of Pfizer and which we had no involvement and send them the reference.” Angel Crespo responded “I totally agree. Who from

Medical will do it?” in an e-mail to which are attached what appear to be electronic versions of the Mathew et al. (2001) and Di Trapani et al. (2000) articles.

### **Evaluation of Various Other Marketing Materials**

A Parke-Davis memorandum dated 9/29/1995 describes the proceedings of a Consultants Meeting on 9/28/1995 in Boston, MA, with the objective of planning for researching and marketing gabapentin for use in treatment of pain.(WLC\_FRANKLIN\_0000087284). Ninan Mathew described preliminary work in headache patients and suggested “Ideally monotherapy GBP, plc controlled.” Later in these minutes (WLC\_FRANKLIN\_0000087289) one of several options for promoting GBP is “Sponsor publications of seeding trials ‘A drumbeat in the literature’”; further noted in “Remember ‘Prozac factor’ – successful because family care MD feel comfortable with the med. – Could easily be the same for GBP.” This memo suggests that as early as 1995, a plan was being formulated to develop a marketing strategy for gabapentin in various chronic pain conditions using publications in the peer review literature. Furthermore, other options for communicating to physicians the idea to recommend gabapentin for pain are listed including CME events, Speakers bureau, and “conferences, symposia – with invited [sic] MDs” (WLC\_FRANKLIN\_0000087289)

At a regional consultants Meeting during November 16-19 called Mastering Epilepsy (WLC\_FRANKLIN\_0000015499) a part of the agenda presented new clinical uses of gabapentin. Migraine was noted as one of 6 new clinical uses. The outline of this section describes anecdotal reports of use in migraine, improvement in frequency, duration and severity of headache and dose ranges of 1200-2400mg/day. It is noted that there is a need for clinical trials in this area, however, the title of the session as “New Clinical Uses for Gabapentin” suggests that this is proposed to the regional consultants as information that can be shared. Despite the fact that Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al. (1987) was published in 1987, this clinical trial was not discussed.

A Parke-Davis memo from Edda Guerrero to John Knoop dated 12/12/1995 summarizes “the consultants were enthusiastic about the potential for Neurontin in this market...The group suggested controlled multicenter trials in ...migraine headaches. Once Neurontin is proven effective in a controlled trial, its use will likely spread to other pain syndromes.” (WLC\_FRANKLIN\_0000015522). This memo brings forward a key point in Parke-Davis’ marketing strategy, acknowledging that there was a plan to use clinical trial data for one indication to promote use in other pain syndromes, even in the absence of well-designed controlled clinical trials demonstrating definite efficacy. In the same memo, a plan is articulated as an Action Step to develop a CME Home Study Program on the use of anticonvulsants for the treatment of neuropathic pain and migraine headaches. The memo states “The program will be mailed to neurologists 1<sup>st</sup> QTR 1996. The mailing will be followed by a series of dinner meetings to be conducted 2<sup>nd</sup> QTR 1996.” Despite the fact that a double-blind, placebo-controlled trial of gabapentin had been performed (Study 879-200 had already been completed and described in RR 4301-00066, and an

interim analysis in abstract by Wessely et al., (1987) was published in 1987), this clinical trial was not discussed. This plan to market gabapentin for migraine treatment in the absence of clinical trial data supporting its efficacy is misleading and deceptive.

A report entitled “Emerging applications for anticonvulsant therapy” prepared by Professional Postgraduate Services for the Parke-Davis Epilepsy Disease Management Team dated 11/20/1995 described in more detail the planned Home Study Program and Study Group Sessions #2 and #3. (WLC\_FRANKLIN\_0000032930) The content of Study Group Session #3 – Use of Anticonvulsants in Treatment of Pain includes the case of a patient with migraine headaches (WLC\_FRANKLIN\_0000032937) which follows a 15 minute “presentation of new clinical data, trials in progress update, etc.” The report goes on to describe faculty recruitment and training, as well as participant recruitment. The educational program seems clearly designed to promote the off-label use of gabapentin for migraine among other on- and off-label indications. Since there is no supportive placebo control clinical trial data available at this time, this plan is designed to mislead and deceive the participants.

A case study appears in the Study Group Program Faculty Guide (WLC\_FRANKLIN\_0000068820). The outlined management steps for the case study involve prescription of acute analgesics and prophylactic medications amitriptyline and propranolol, which are dismissed as being of no value in this case study (WLC\_FRANKLIN\_0000068822). A trial of divalproex is successful at reducing headache frequency, but is discontinued because of an adverse effect (WLC\_FRANKLIN\_0000068823). The next step in the case study presentation involves a successful trial of gabapentin at 300 mg/day titrated up to 600 mg/day. The discussion points presented in the faculty guide (WLC\_FRANKLIN\_0000068824) include the following points (F1) related to the use of gabapentin: “There is now good evidence that divalproex is useful as a migraine preventive. There are also studies suggesting that both divalproex and gabapentin are helpful in chronic daily headaches.” What is not disclosed is the fact that a double-blind, placebo-controlled trial of gabapentin had been performed but did not show gabapentin to be effective (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987). To present a successful outcome associated with gabapentin in this case study suggests that it has been proven to be efficacious for migraine. This case study is misleading and deceptive.

A series of presentation slides includes one describing published abstracts on gabapentin for migraine prophylaxis (WTC\_FRANKLIN\_0000016168). The slide lists an abstract presented at the 1996 American Academy of Neurology meeting (Mathew NT, Lucker C. Neurology 1996; 46:A169) describing it as an “open-label, 3-month trial of gabapentin 900 to 1800 mg/day in patient with migraine with or without aura. Furthermore, the results are described as “gabapentin reduced severity and frequency of headaches and was well tolerated.” This study is uncontrolled; the conclusion that it reduced the severity and frequency of headaches is based on a comparison of post-treatment to baseline data, not a comparison of the response in gabapentin-treated with placebo-treated or control patients. As such, these data do not rise to the level generally required to

conclude that a drug is effective. Therefore, I believe the inclusion of these data on gabapentin is misleading.

The above-referenced abstract by Mathew and Lucker (WLC\_CBU\_018761) lacks details regarding the design, conduct, results and analysis of the study. The abstract does not report any data on the magnitude of any of the claimed effects in reducing severity and frequency of headaches. Two groups are referred to in the abstract, but it is unclear whether they represent different dosage levels of gabapentin. There is also no mention of any statistical hypothesis testing related to the conclusion that severity and frequency are reduced. Other abstracts on the same page include up to twice as many lines of text, so the lack of detail cannot be ascribed to word limits. The abstract is so poorly written that it seems designed to obscure the detail necessary to critically appraise the study and its conclusions. The conclusion that “double-blind, placebo-controlled studies are indicated” seems to acknowledge that these data alone are insufficient to conclude that gabapentin is efficacious. It also fails to acknowledge that at least one such study had already been conducted, and was negative (Study 879-200/Wessley, 1987).

A more complete description of the Mathew and Lucker study appears in Novel Applications of AEDs: Current Research, a Medi-Fax Report from data presented at the AAN 48<sup>th</sup> Annual Meeting (WLC\_FRANKLIN\_0000041546). This summary of data presented at the AAN meeting confirms that the two groups referred to in Mathew and Lucker’s abstract comprise two different patient populations distinguished by headache type (35 patients with episodic migraine and 30 patients with transformed migraine) rather than by treatment. The description of the outcome measures and results along with statistical testing confirms that post-treatment headache frequency was significantly reduced when compared with baseline among migraine patients; however, no statistically significant changes are noted for patients with transformed migraine.

Parke-Davis memo dated 3/22/96 from John Knoop to Larry Perlow describes “Proceedings of AES Annual Meeting will be mailed to 10,000 neurologists” as one goal that was met during January. This suggests that dissemination of the Mathew and Lucker study, despite the low level of evidence, was an important goal within the context of marketing gabapentin. Because this evidence was of such poor quality, its use in marketing gabapentin for this use suggests the intent to mislead physicians by exaggerating data about the effectiveness of gabapentin for migraine prophylaxis.

In the transcript of a meeting entitled “Mastering Epilepsy” on 4/19/1996 held at Marriott’s Vail Mountain Resort, Ninan Mathew delivered a presentation entitled “Clinical and Scientific Reports on Other Uses for Neurontin: Migraine” (WLC\_FRANKLIN\_0000015735). After discussing the neurophysiology of migraine, Dr. Mathew turns his discussion to describe the open-label study (Mathew and Lucker, 1996) and gives the following caveat “I would warn that this is an open study. This is not a double-blind, placebo-controlled study. This is just a preliminary observation. So you have to – the conclusions are not conclusive.” Toward the end of his presentation he states that “gabapentin appears to be an effective, well-tolerated prophylactic agent in migraine and in transformed migraine. Double-blind, placebo-controlled studies are being

planned to confirm this preliminary observation.” (WLC\_FRANKLIN\_0000015753) He further adds “I want to emphasis [sic] again, nothing can be concluded without a double-blind study, and we are going to undertake that soon.”

(WLC\_FRANKLIN\_0000015754) Dr. Mathew fails to describe the randomized double-blind placebo controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987), which would clearly have been relevant. The average dosage in the Mathew and Lucker study was described as “1,050 with a range of 600 to 1,800” (WLC\_FRANKLIN\_0000015752) which compares favorably with the 900 mg/day used in Study 879-200. While it is encouraging that Dr. Mathew notes the importance of basing conclusion about efficacy on double-blind, placebo controlled studies, the failure to disclose the earlier study, which he should have been aware of, suggests that the existence of those data had not been disclosed to him or that he was intentionally omitting it.

At a Regional Consultants Meeting in April 19-21, 1996 entitled “Advances in Anticonvulsants,” Steven Schachter mentioned the then recent approval of Depakote for prophylactic therapy against migraine headache. (WLC\_FRANKLIN\_0000064355) He continues by noting that “a fairly astounding percent of all Neurontin prescriptions are written for off-label uses, and the vast majority of that is for pain” By juxtaposing the mention of Depakote’s approval for migraine prophylaxis with a discussion of off label uses for gabapentin, Dr. Schachter seems to be suggesting promoting off-label use of gabapentin for migraine prophylaxis; however, this is despite a lack of level 1 evidence showing efficacy.

On a later portion of the transcript from the same meeting the Mathew and Lucker abstract is again recapped in the context of a discussion of several other studies of gabapentin for other off-label indications (WLC\_FRANKLIN\_0000064365). The presentation, noted as unidentified male speaker, but whom I suspect is Dr. Schachter, concluded with a statement that “I think we’d all agree that double-blind placebo-controlled studies are indicated at this time to really formally assess the efficacy and safety of gabapentin in pain syndromes.” (WLC\_FRANKLIN\_0000064367) Again, there is a failure to describe the already existing randomized double-blind placebo controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987), which would clearly have been relevant. The failure to disclose this earlier negative trial suggests Dr. Schachter either wasn’t aware of it (it hadn’t been disclosed by Parke-Davis) or was intentionally omitting it.

On a subsequent part of the transcript dated 4/21/1996 an unidentified man asks “Is there data using it [gabapentin] as a prophylactic agent?” (WLC\_CBU\_157311). The reply, presumably from the speaker is “I think right now, there’s ... I don’t know of any ... any properly controlled studies on that yet.” Again, there is a failure to describe the already existing randomized double-blind placebo controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987), which would clearly have been relevant.



The discussion continued with a lengthy exchange of anecdotal observations about the lack of efficacy of Depakote, despite its FDA approval for migraine prophylaxis. Then an unidentified man describes the permissibility of discussing data on off-label indications: “In a CME event, there are two sets of rules. One set of rules is as a CME event, we can talk about anything we want amongst physicians. And the other rule is that if it’s an open CME event, you can only talk about those things that are well-established. And so it really ties your hands. That’s one of the reasons why in a forum like this, you can say whatever you want to say and share experiences because that’s really how we change our practices.” (WLC\_CBU\_157317) This speaker echoes the strategy described in the Parke-Davis memorandum dated 9/29/1995. (WLC\_FRANKLIN\_0000087289)

On another transcript from the same meeting, 11:50am Breakout session in Room 221, an unidentified man asks “Is there any experience with Neurontin in ...in migraine...any experience with migraine” To which the response is “There are a fair number of anecdotal reports, and they say the Neurontin does occasionally work in migraine ...” Again, there is a failure to describe the already existing randomized double-blind placebo-controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987) which was clearly relevant. The failure to describe results from Study 879-200, suggests that it had been suppressed by Parke-Davis, or that the speaker was intentionally omitting it.

In a 5/4/1996 Anticonvulsants Consultant Meeting, an unidentified presenter describes data on a variety of off-label uses for gabapentin in various pain syndromes, and again brings up only the Mathew and Lucker open-label three-month trial when discussing the topic of migraine prophylaxis (WLC\_FRANKLIN\_0000064229). . The failure to describe results from Study 879-200, suggests that it had been suppressed by Parke-Davis, or that the speaker was intentionally omitting it. The omission of these data is clearly misleading the participants to think 1) that gabapentin is effective based on the lower quality of evidence provided in the Mathew study and 2) that no better evidence to the contrary exists.

In a document prepared for Edda Guerrero, Product Manager, entitled Neurontin in the Management of Migraine: A Proposal for an Advisory Board, the stated objectives for the proposed Advisory Board include advising Parke-Davis on protocols for studies of the safety and efficacy of gabapentin for treatment of migraine and to generate “case-based publications regarding migraine treatment” (WLC\_FRANKLIN\_0000073830) A transcript of an Advisory Board Meeting held on 5/25/1996 begins with an introduction by Dr. Mathew, which concludes with a statement to motivate why a clinical trial of gabapentin should be undertaken, as follows

“And also, there are a number of reports about the effectiveness of gabapentin in several neuropathic pains like diabetic, like post-herpetic neuralgia, and sympathetic dystrophy and so on. So, because of all that reasons, because of some link between migraine pain and other kinds of pain, it may be worthwhile studying this drug. Our, one of the preliminary

open studies showed that the results are encouraging, that we need probably a double-blind study to prove that.”  
(WLC\_FRANKLIN\_0000116906)

While Dr. Mathew mentioned his open-label uncontrolled clinical study, he fails to describe the already existing randomized double-blind placebo-controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987) which was clearly relevant. The failure to describe results from Study 879-200, suggests that it had been suppressed by Parke-Davis, or that the speaker was intentionally omitting it.

Later in this meeting, Ms Guerrero, Parke-Davis Product Manager for Neurontin, describes a variety of background marketing data regarding use of gabapentin to the Advisory Board. Dr. Moskowitz asks Ms. Guerrero whether, given the high comorbidity between epilepsy and migraine, there was “any attempt to address the issue of headache either as a potential side effect or headache as a potential therapeutic action for the gabapentin? In other words, you may have that data already in house.”  
(WLC\_FRANKLIN\_00000116919)

She refers the question to Dr. Magnus-Miller, who answers the question without mentioning the already existing randomized double-blind placebo-controlled trial (Study 879-200 had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessely et al., (1987) was published in 1987) which was clearly relevant. Instead, she seemed to limit her response to epilepsy studies where headache is “among one of the top side effects seen”... but “if you aren’t specifically looking at that, you don’t capture was it migraine or was it just headache.”

(WLC\_FRANKLIN\_00000116920) The failure to describe the directly relevant results concerning the effect of gabapentin on migraine from Study 879-200, suggests that it had been suppressed by Parke-Davis, or that the speaker was intentionally omitting it. As a Parke-Davis researcher involved with research on gabapentin, I find it hard to believe that she would have been unaware of the study.

In a Parke-Davis memorandum from John T. Boris dated 7/31/1996 (WLC\_FRANKLIN\_0000081255) about Neurontin® marketing, he notes that a decision was reached to "conduct only publication study(ies) in the U.S. due to the current patent situation in the U.S., limited use of anticonvulsants in the EC, and favorable pre-clinical results in analgesia seen with CI-1008. The results, if positive, will therefore be publicized in medical congresses and published in peer reviewed journals." This presumably refers to the decision that led to undertaking nearly simultaneously Study 945-220 and Study 945-217. Furthermore, this states clearly that there is intent to disseminate the results of these studies only if they report positive findings, favorable to gabapentin.

A marketing brochure collated three poster presentations selected from the American Pain Society Annual Meetings of 1997 and 1998 concerning Gabapentin Use in neuropathic Pain and Migraine. The brochure included a reproduction of a poster

presentation by Mathew, Saper, Magnus-Miller, et al. which is presumably interim data from 945-220 based on the similarity of authorship between the poster and RR 995-00074. (WLC\_CBU\_107311) The promulgation of a marketing brochure containing the favorable open-label study by Mathew, when better quality double-blind, placebo-controlled randomized data are available and omitted, is misleading.

A review article entitled Nonepileptic Uses of Gabapentin by Leslie Magnus (*Epilepsia* 1999; 40(Suppl 6): S66-S72), Table 5 describing gabapentin in migraine prophylaxis lists only the single open label study by Mathew and Lucker, (Pfizer\_NMancini\_0024608) but fails to list the two extant randomized double blind placebo-controlled clinical trials (Study 879-200 or Study 945-220) despite the fact that both had been published in abstract form (like the Mathew and Lucker abstract cited). This failure to include a complete reckoning of the extant studies suggests that these negative studies are being deliberately suppressed. As an author of RR 995-00074, Leslie Magnus-Miller certainly was aware of at least Study 945-220.

In a review article entitled Diagnosis and Modern Treatment of Migraine, Dr. Mathew, in a section on gabapentin, states that “gabapentin has been shown to be effective in a randomized double-blind placebo-controlled trial for migraine prophylaxis” (WLC\_CBU\_014215) and cites an abstract from the American Pain Society annual meeting of 1998 authored by Magnus-Miller, Podolnick, and himself. He fails to describe the already existing randomized double-blind placebo-controlled trial (Study 879-200, which had already been completed and described in RR 4301-00066, and an interim analysis in abstract by Wessley et al., (1987) was published in 1987) which was clearly relevant. The failure to describe results from Study 879-200, suggests that it had been suppressed by Parke-Davis, or that the author was intentionally omitting it.

A slide set entitled Neurontin® (gabapentin) for prophylactic Treatment of migraine headache by Mathew, Saper, Rapoport et al., describe the data from Study 945-220 (WLC\_CBU\_008134) however, it considers only the mITT population (113 patients; 36 placebo and 77 gabapentin) when describing the baseline characteristics and primary and secondary outcome measures. The Research Report, in contrast, based the primary analysis on the efficacy population. By presenting only the results from the mITT population in the slide set, Mathew has selectively reported the only positive findings from this study. This misrepresentation of the primary efficacy measures of the study is a misrepresentation of the results of the study and seems calculated to mislead the reader, by selectively reporting the positive results. (WLC\_CBU\_008146)

In the physician education program entitled Advances in the Preventive Treatment of Migraine authored by Dr. Mathew with assistance from Proworx medical writer Debra Hughes (MDL\_Vendors\_008417), gabapentin is listed as a first-line option for migraine prophylaxis among beta blocker, tricyclic antidepressants and divalproex sodium (MDL\_Vendors\_02386). All of the other first-line options besides gabapentin have multiple well-designed placebo-controlled double-blind trials providing support for efficacy. Including gabapentin on this list despite its lack of positive placebo-controlled double-blind trials providing support for efficacy is misleading.

Later in this program, Mathew cites the open-label trial (Mathew and Lucker) as an “initial” study. (MDL\_Vendors\_026390) Using the word initial to characterize this study denies the existence of the earlier placebo-controlled double-blind Study 879-200. He also cites the Magnus-Miller abstract presented at the American Pain Society annual meeting 1998, (MDL\_Vendors\_026391) and quotes the mITT data from that study despite the fact that he efficacy population was clearly the primary analysis. This misrepresents this study as positive.

In a tactical meeting on Neurontin on 5/12/1999, the Annenberg CME program “New Advances in the Treatment of Migraine” is discussed and described as follows “The monograph *very favorably* mentions NEUROTIN.” (WLC\_CBU\_030392) [emphasis as in original]

A status report dated 6/22/1999 reports that “Over 20,000 invitations were mailed to neurologists and primary care physicians. We have received approximately 1,800 requests for the monograph and audiotape kit thus far.” (WLC\_CBU\_013057) On the next page, it is noted that “Proworx would be available to work with Parke-Davis to research and track prescriptions for those physicians who completed the program. This additional investment could be worthwhile to track the ROI [return on investment] for the program” (WLC\_CBU\_013058) This comment suggests that the goal of the program is clearly to market the use of gabapentin for migraine prophylaxis, through misrepresentation of gabapentin as a highly effective treatment.

In the slide set describing the planned teleconference, the Study 945-220 is characterized as follows: “Dr. Mathew and colleagues recently completed a clinical trial on the use of gabapentin for migraine headaches that produced favorable results” This characterization of Study 945-220 is at odds with the Research Report RR 995-00074; characterizing this study as favorable is misleading.

The development costs for the teleconference are shown and include \$82,450 for monograph development, \$31,350 for audiotape development, (WLC\_CBU\_013070) and \$30,850 for teleconference development, (WLC\_CBU\_013071) for a total development cost of \$160,400.(WLC\_CBU\_01372). This represents a large financial incentive for the developer of the program.

In describing the role of gabapentin in migraine prophylaxis, the audiotape master reads “What is the place of gabapentin and valproex in migraine prophylaxis? While beta blockers remain first-line drug of choice, gabapentin and valproex may be considered as first line under many circumstances.” (MDL\_Vendors\_008539). By describing valproex (which has an FDA-approved indication for migraine prophylaxis) and gabapentin together, the audiotape erroneously implies that the evidence for these two drugs for migraine prevention is of similar quality. Furthermore, the situations described as for their use first include patients with contraindications to beta blockers or patients with depression as a side-effect of beta blocker treatment; however in both of these situations, tricyclic antidepressants might be a more reasonable alternative.

The misleading comparison between valproex and gabapentin is continued when the audiotape discussed which drug to use when there is co-morbid epilepsy, stating “Valproex may be considered the drug of choice. However, recent anecdotal evidence also suggests that Gabapentin may be equally effective in patients with bipolar illness, migraine and epilepsy, as in the case of valproex.”(MDL\_Vendors\_008540)

At a Parke-Davis Advisory Board meeting on Neurontin on 3/15/2000 in Denver, CO, the use of gabapentin for migraine prophylaxis was described citing only the open-label study by Mathew and Lucker and the double blind study 945-220, which is once again described misrepresenting the mITT population as the primary efficacy analysis. (WLC\_CBU\_164390).

At a Parke-Davis Speakers Bureau meeting 1/21-23/2000 in Scottsdale, AZ, the double blind study 945-220 is again described by misrepresenting the mITT population as the primary efficacy analysis. (WLC\_CBU\_164424) Furthermore, in responding to a question about the dose of gabapentin for migraine headache, Gelblum responds “Higher doses are necessary.” (WLC\_CBU\_164429) This assertion does not seem to be based on any data reported in the Research Report RR995-00074.

In a CME monograph entitled “Spectrum of uses of antiepileptic drugs: new treatments, new strategies,” an article by Michael J. McLean, MD, PhD, entitled “Understanding the Mechanisms of Action of Anticonvulsant Agents” asserts that gabapentin has “significant efficacy in the treatment of ...migraine” citing “N. Mathew and the Gabapentin Migraine Prophylaxis Study Group, unpublished data, Parke-Davis data on file). (MDL\_Vendors\_055255) Later in the same article the same reference is provided. (MDL\_Vendors\_055260)

A Pfizer sponsored CME program entitled “Antiepileptic Drugs and Neurobehavioral Disorders: Emerging Concepts, Shared Solutions” includes in the slide set a list of antiepileptic drugs as options for migraine prophylaxis. (MDL\_Vendors\_052660) Gabapentin is listed along with divalproex sodium. Lecture notes accompanying the slide cites the Di Trapani et al., (2000) and the Mathew et al., (2001) study published in *Headache* in support of the listing of gabapentin.(MDL\_Vendors\_052661) The Mathew et al., (2001) study, which exaggerates the effectiveness of gabapentin compared with the Research Report RR 995-00074 is cited extensively after appearing in the peer-review journal *Headache*. Slide 32 suggests that antiepileptic drugs by virtue of their similar mechanisms of action, may share similar efficacy (MDL\_Vendors\_052663). In particular, the lecture notes accompanying the slide notes divalproex is FDA approved for migraine prophylaxis and lists gabapentin among several “second-generation AEDs” that “show promise as new therapeutic options for migraine prophylaxis. The implication is that clinicians may expect similar efficacy in migraine prophylaxis from gabapentin compared to divalproex, an assumption that has not been shown in clinical trials.

The Review article entitled “Newer antiepileptic drugs: possible uses in the treatment of neuropathic pain and migraine by Marco Pappagallo cites only one trial in discussing the efficacy of gabapentin in migraine prophylaxis: that of Mathew et al. (2001) published in

*Headache*. (FAL000751) At the end of his discussion of these data, he writes “these results have yet to be confirmed by other trials.” While I suspect he was not aware that other trials had in fact been conducted but failed to replicate the favorable results reported in Mathew et al. (2001), his remark is oddly prescient. It demonstrates to what extent a well placed, publicized article can dominate the attention of the clinical audience.

In summary, my evaluation of the marketing materials points to a pattern of suppressing the results of negative randomized double-blind, placebo-controlled clinical trials. At the same time, lower level, uncontrolled data were used to promote the off-label use of gabapentin for migraine prophylaxis, and generate interest in conducting new double-blind placebo-controlled clinical trials, which Parke-Davis undertook with the hope of demonstrating favorable results. When both of these trials failed to show significant benefit in the primary outcome measures, they misrepresented one of these studies in a manuscript manipulated to achieve statistically significant results favoring gabapentin over placebo. Furthermore, Parke-Davis and then Pfizer undertook substantial efforts to promote the favorable published results in the medical community.

### **Part 3: Review of Expert Report Submitted by Pfizer**

I have reviewed the report of Alan M. Rapoport, M.D., dated December 1, 2006. Dr Rapoport describes data from only "The Mathew Paper" in his section summarizing the clinical trial evidence supporting the use of gabapentin for treatment of migraine. In his discussion of this study, he cites the analysis described in Mathew et al. (2001), which includes only the subgroup of patients in the mITT population who achieved a stable dose of 2400 mg/day. As I described earlier, this is a misrepresentation of Study 945-220 because it has redefined the study population according to a post hoc reanalysis and selectively reports only positive findings. Dr. Rapoport does state in his report that he "reviewed several published studies" and fails to cite any unpublished data.

He characterizes the published studies as showing "the value of gabapentin as a daily preventive medication for migraine. Patients on this medication have fewer migraine attacks, fewer days of severe headache, more pain free days, less use of rescue medication and better quality of life than patients on placebo." This assessment of the published literature is perhaps overly optimistic, but the main failure of Dr. Rapoport's assessment is the failure to include unpublished data, which have uniformly negative findings for primary efficacy criteria.

Dr. Rapoport notes that he "helped to design" the study described in "The Mathew Paper" implying that he should be familiar with the analysis plan described in Research Report RR 995-00074. In the Research Report, the primary analysis is based on the efficacy population which include patient regardless of whether they achieved a stable dose of 1800 mg/day or 2400 mg/day. However, he does not mention the discrepancy between the design of the study and the ultimate reporting in the published article.

Dr. Rapoport states that he is "second author" on the Mathew paper; however, other than noting that he helped to design the study, he, in this report and the published article, fails

to describe his contributions in terms of 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. As an author, he should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Given his role in helping to design the study (as he states in his report) and as an investigator (as listed on the cover page of the Research Report), I believe that he should take public responsibility for the discrepancies between the design described in the Research Report and discrepancies with the reporting in the published article.

In his report, he states that "the primary efficacy variable was reduction in migraine attack rate"; however, the p-value of 0.006 he quotes is for the median 4-week migraine headache rate during stabilization period 2 rather than the change from baseline in the 4-week migraine headache rate during stabilization period 2 as his statement would imply. In fact, the median change from baseline to SP2 is reported in Table 3 of "The Mathew Paper" with a p-value of 0.013. However, this analysis is limited to the subset of patients on a stable 2400 mg/day dose from the mITT population. Were he to quote from the efficacy population as defined in the Research Report, the corresponding p-values would be  $p=0.332$  for change in migraine headache rate from baseline to SP2, and, for the mITT population the p-value would be  $p=0.339$ , neither of which represents a statistically significant difference between gabapentin-treated and placebo-treated patients.

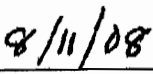
Similarly, Dr. Rapoport quotes a responder rate of 46% on gabapentin and 16% for placebo significant at the  $p<0.01$  level; however, these figures relate to the subgroup of patients on a stable dose of 2400 mg/day gabapentin from the mITT population. The main analysis from the Research Report for this outcome variable referred to the efficacy population, where 39% of gabapentin-treated patients and 21% of placebo-treated patients achieved a reduction of at least 50% in 4-week migraine headache rate ( $p=0.097$ ), a difference that is not statistically significant. The secondary or supportive analysis in the mITT population from the Research Report found 40% of gabapentin-treated patients and 19% of placebo-treated patients had a reduction of at least 50% in 4-week migraine headache rate ( $p=0.033$ ).

Dr. Rapoport was also listed as an investigator on Research Report RR 995-00085, therefore he should be aware of this study, too. However, he does not mention this study or the findings which are negative for the primary efficacy endpoints of the efficacy analysis (4-week migraine headache rate during SP2 and change from baseline to SP2 in 4-week headache rate). I think he is obliged to refer to these data in formulating his assessment, rather than limiting his assessment to the published or publically available reports.

In summary, Dr. Rapoport's assessment of the evidence on the effectiveness of gabapentin for the preventive treatment of migraine is based primarily on selectively quoting positive findings from a secondary analysis of Study 945-220. Given his roles in the design of this study and as an investigator, he should be aware of these discrepancies and should have had access to the data in the research report. Furthermore, he neglects to

mention Study 945-217, despite the fact that he was an investigator on this study. His characterization of the effectiveness of gabapentin is at odds with the unpublished results of the two studies he was involved in. I conclude that he is deliberately omitting the unpublished data of which he is undoubtedly aware.

  
Douglas C. McCrory, MD, MHS

  
Date

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1. Research Report 4301-00066
2. Research Report 995-00074
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151. Expert Report of Alan Rapoport, M.D.

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### **In Press**

Provenzale JM, **McCrorry DC**, Shah K, Patel U. Systematic review of CT and MR perfusion imaging for assessment of acute cerebrovascular disease. American Journal of Neuroradiology. In press.

### **Submitted**

Hartman ME, **McCrorry DC**, Schulman SR. Sedation to facilitate mechanical ventilation in the pediatric intensive care unit: A systematic review. Pediatric Critical Care Medicine. Submitted.

## **2. Non-refereed publications:**

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## **3. Chapters in books:**

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#### 4. Books:

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#### 5. Other:

##### a. Published scientific reviews

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#### **b. Selected abstracts**

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